Supporting Information 1. Description of the chemical synthesis depicted in Scheme 1.

2-((12-Bromododecyl)oxy)tetrahydro-2H-pyran (2). To a solution of **1** (5.2 g, 19.61 mmol, commercial) and 2,3-dihydro-2H-pyran (2.47 g, 29.4 mmol) in DCM (35 mL) was added pyridinium *p*-toluenesulfonate (PPTS) (0.74 g, 2.94 mmol) at RT. The mixture was stirred for 18 hr at RT. The mixture was concentrated. The residue was taken up in hexanes and purified by a silica gel column (5% EtOAc in hexanes) to give **2** (6.8 g, 99%) as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 4.58 (dd, J = 4.5, 2.7 Hz, 1H), 3.87 (ddd, J = 11.1, 7.4, 3.4 Hz, 1H), 3.73 (dt, J = 9.5, 6.9 Hz, 1H), 3.55 - 3.47 (m, 1H), 3.45 - 3.33 (m, 3H), 1.90 - 1.78 (m, 3H), 1.76 - 1.68 (m, 1H), 1.64 - 1.47 (m, 6H), 1.46 - 1.23 (m, 16H).

2-((13-Cyclobutyltridecyl)oxy)tetrahydro-2H-pyran (3). To a mixed solution of **2** (3.64 g, 10.42 mmol) in THF (30 mL) and Li_2CuCl_4 (0.1 M solution in THF, 5.2 mL, 0.522 mmol) at 0^{o}C was added Grignard reagent cyclobutylmethyl)magnesium bromide which was made from (bromomethyl)cyclobutane (4.0 g, 26.8 mmol) and grinded magnesium turnings (1.31 g, 53.7 mmol) in Et_2O (25 mL). After the addition completed, stirred at 0^{o}C for 30 min and then at RT for 16 hr. The reaction was quenched by NH_4Cl at 0^{o}C. Stirred at RT for 20 min. Then the mixture was treated with hexanes and water. Organic phase was washed by brine, dried over Na_2SO_4, and concentrated to give **3** (3.5 g, 99%) as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 4.58 (dd, J = 4.5, 2.7 Hz, 1H), 3.87 (ddd, J = 11.0, 7.4, 3.4 Hz, 1H), 3.73 (dt, J = 9.6, 6.9 Hz, 1H), 3.58 - 3.45 (m, 1H), 3.38 (dt, J = 9.6, 6.7 Hz, 1H), 2.23 (dt, J = 15.5, 7.8 Hz, 1H), 2.01 (dddd, J = 13.6, 6.7, 5.2, 3.0 Hz, 2H), 1.91 - 1.66 (m, 4H), 1.62 - 1.49 (m, 9H), 1.40 - 1.11 (m, 21H).

13-Cyclobutyltridecan-1-ol (4). To an emulsion of **3** (3.45 g, 10.2 mmol) in Methanol (20 mL) was added *p*-toluenesulphonic acid monohydrate (97 mg, 0.51 mmol). The mixture was stirred at 40^{o}C for 48 hr. Most of the methanol was removed under reduced pressure. Water (20 mL) was added to the residue and the mixture was extracted with hexane (2 x

40 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give **4** (2.42 g, 93%) as an wax-like solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 3.64 (t, J = 6.6 Hz, 2H), 2.22 (h, J = 7.8 Hz, 1H), 2.08 - 1.92 (m, 2H), 1.80 (tddd, J = 14.8, 11.4, 9.3, 6.4 Hz, 2H), 1.57 (dtd, J = 11.2, 7.4, 6.2, 2.3 Hz, 4H), 1.42 - 1.06 (m, 23H).

13-Cyclobutyltridecyl methanesulfonate (5). Compound **4** (2.4 g, 9.43 mmol) and triethylamine (1.15 g, 11.32 mmol) were dissolved in DCM (30 mL) and the solution was cooled to 0^{o}C. Methanesulfonyl chloride (1.30 g, 11.32 mmol) was added dropwise. The reaction was stirred at RT for 3 hr, quenched with 0.5 N aq HCl and extracted two times with hexanes. The organic layer was then washed with H_2O, $NaHCO_3$, brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give **5** (3.0 g, 96%) as an wax-like solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 4.22 (t, J = 6.6 Hz, 2H), 3.01 (s, 3H), 2.23 (p, J = 7.8 Hz, 1H), 2.07 - 1.93 (m, 2H), 1.87 - 1.68 (m, 4H), 1.61 - 1.52 (m, 2H), 1.42 - 1.12 (m, 22H).

3-((13-Cyclobutyltridecyl)thio)propan-1-ol (6). Under nitrogen, to a solution of **5** (3.0 g, 9.02 mmol) and 3-mercaptopropan-1-ol (1.25 g, 13.53 mmoL) in acetone (30 mL) was added potassium carbonate (2.49 g, 18.04 mmol). The suspension was stirred at 30^{o}C for 16 hr. The mixture was evaporated and the residue was partitioned between water and hexane. The organic phase was washed with 1 N sodium hydroxide, water, brine, dried over sodium sulfate, and the volatiles was removed under vacuum to give **6** (2.9 g, 98%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 3.77 (q, J = 5.4 Hz, 2H), 2.64 (t, J = 7.0 Hz, 2H), 2.53 (dd, J = 8.1, 6.8 Hz, 2H), 2.28 - 2.19 (m, 1H), 2.07 - 1.95 (m, 2H), 1.92 - 1.72 (m, 4H), 1.65 - 1.48 (m, 5H), 1.47 - 1.07 (m, 22H).

3-((13-Cyclobutyltridecyl)sulfonyl)propan-1-ol (7). To a solution of **6** (2.85 g, 8.67 mmol) in AcOH (65 mL) was added 30% H_2O_2 (17.7 mL, 30%, 173 mmol). The solution

was stirred in the dark at RT for 16 h. The solvent was evaporated under reduced pressure. The white solid residue was treated with DCM and sat. $NaHCO_3$. The organic phase was washed by brine, dried over Na_2SO_4, and evaporated to afford **7** (2.98 g, 95%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 3.82 (d, J = 5.6 Hz, 2H), 3.17 - 3.07 (m, 2H), 3.00 (d, J = 8.2 Hz, 2H), 2.27 - 2.19 (m, 1H), 2.16 - 2.07 (m, 2H), 2.04 - 1.98 (m, 2H), 1.88 - 1.73 (m, 4H), 1.56 - 1.47 (m, 1H), 1.43 (q, J = 7.3 Hz, 2H), 1.38 - 1.10 (m, 22H).

3-((13-Cyclobutyltridecyl)sulfonyl)propyl methanesulfonate (8). Compound **7** (2.95 g, 8.18 mmol) and triethylamine (0.99 g, 9.82 mmol) were added in DCM (40 mL) and cooled to 0^{o}C. Methanesulfonyl chloride (1.12 g, 9.82 mmol) was added dropwise via syringe to the stirred solution over 2 min. The reaction was stirred at RT for 3 hr, quenched with 0.5 N aq HCl, and extracted 2 times with DCM. The organic layer was then washed with H_2O, $NaHCO_3$, brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give **8** (3.3 g, 92%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 4.41 (t, J = 5.9 Hz, 2H), 3.16 - 3.08 (m, 2H), 3.05 (s, 3H), 3.02 - 2.96 (m, 2H), 2.41 - 2.28 (m, 2H), 2.28 - 2.19 (m, 1H), 2.05 - 1.95 (m, 2H), 1.92 - 1.69 (m, 4H), 1.59 - 1.50 (m, 4H), 1.45 (d, J = 7.3 Hz, 1H), 1.29 (d, J = 35.3 Hz, 19H).

4-Amino-1-(((5S)-2-(3-((13-cyclobutyltridecyl)sulfonyl)propoxy)-2-oxido-1,4,2-dioxaphosphinan-5-yl)methyl)pyrimidin-2(1H)-one (9). To a suspension of cCDV-DCMC (cyclic cidofovir-dicyclohexylmorpholinocarboxamindine salt, prepared from cidofovir as described in *ANTIMICROBIAL AGENTS AND CHEMOTHERAPY*, (2002), p. 991-995) (0.270 g, 0.487 mmol) in dry DMF (10 mL) was added **8** (0.534 g, 1.22 mmol) and the mixture was stirred and heated at 80^{o}C for 16 hr. The reaction mixture was then concentrated in vacuo and the soft solid residue was dissolved in 6 ml of 9:1 DCM/MeOH mixed solvent and purified by silica gel preparative TLC plate (9:1 DCM/MeOH) to give **9** (0.147 g, 50%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.28 (dd, J = 7.3, 5.6 Hz, 1H), 5.97 (d, J = 7.2 Hz, 1H), 4.39 (dd, J = 11.5, 6.1 Hz, 1H), 4.33 - 4.11 (m, 2H), 4.09

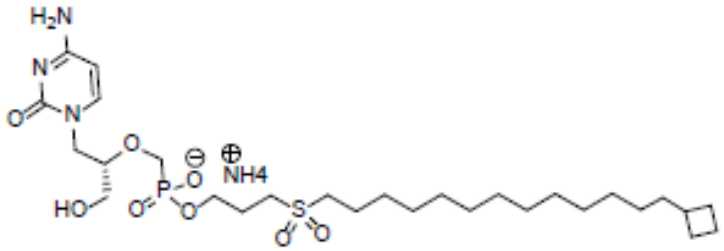
- 4.03 (m, 1H), 3.89 (dd, J = 14.8, 3.0 Hz, 1H), 3.77 (s, 2H), 3.45 (s, 2H), 3.15 (t, J = 7.6 Hz, 1H), 3.07 - 2.96 (m, 2H), 2.25 (dt, J = 15.4, 8.7 Hz, 2H), 2.01 (dt, J = 9.7, 3.8 Hz, 1H), 1.91 - 1.76 (m, 9H), 1.64 - 1.49 (m, 3H), 1.43 (d, J = 7.2 Hz, 1H), 1.37 - 1.15 (m, 20H). ^{31}P NMR (162 MHz, Chloroform-d) δ 12.52, 11.12. MS: m/z 604.3185 $(M+H)^+$, m/z 602.3011 $(M-H)^-$.

Ammonium 3-((13-cyclobutyltridecyl)sulfonyl)propyl hydrogen ((((S)-1-(4-amino-2-oxopyrimidin-1(2H)-yl)-3-hydroxypropan-2-yl)oxy)methyl)phosphonate (10). Compound **9** (0.135 g, 0.224 mmol) was put into a screw-cap reaction tube. Concentrated NH_4OH (28-30%, 15 mL) was added. The reaction tube was screw capped. The suspension mixture was then stirred at 80°C for 18 h. The reaction mixture was then cooled to room temperature and evaporated under reduced pressure at 55°C. The soft solid residue was triturated with acetone, collected by filtration, washed by a small amount of acetone and DCM, and dried under vacuum to give **10** (76 mg, 53%) as white solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.82 (d, J = 7.5 Hz, 1H), 5.95 (d, J = 7.4 Hz, 1H), 4.13 (dd, J = 14.0, 3.2 Hz, 1H), 3.99 (q, J = 6.2 Hz, 2H), 3.88 - 3.48 (m, 6H), 3.21 (dd, J = 9.6, 6.1 Hz, 2H), 3.16 - 3.04 (m, 2H), 2.24 (dt, J = 16.6, 8.3 Hz, 1H), 2.14 - 1.97 (m, 5H), 1.96 - 1.72 (m, 3H), 1.60 (qd, J = 8.8, 2.5 Hz, 2H), 1.46 (q, J = 7.3 Hz, 2H), 1.40 - 1.09 (m, 20H). ^{31}P NMR (162 MHz, Methanol-d4) δ 16.13. MS: m/z 622.3294 $(M+H)^+$, 620.3132 $(M-H)^-$. HPLC: 97.57%. It is NPP-669.

Supporting Information 2. NPP-669 Certificate of Analysis.

Chemical Name: 3-((13-cyclobutyltridecyl)sulfonyl)propyl (S)-(((1-(4-amino-2-oxopyrimidin-1(2H)-yl)-3-hydroxypropan-2-yl)oxy)methyl)phosphonate ammonium (aka. NPP-669)

Structure:



NPP-669

Formula: C28H51N3O8PS

Molecular Weight: 638.31

Amount: 3.23 g

Date Prepared: 3/29/2021

Purity: 96.7 %

Analyst: Caitlin Tan

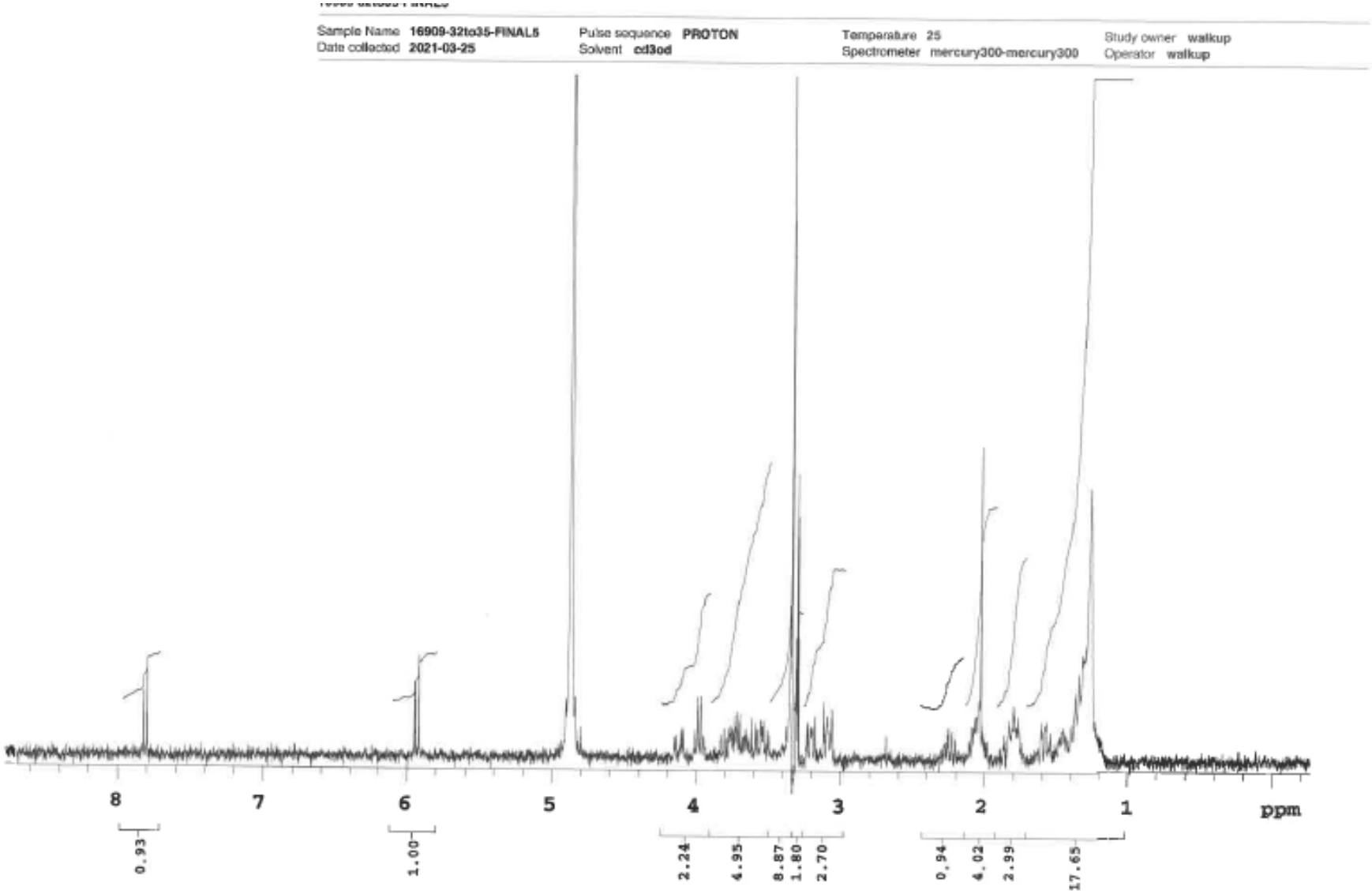
Appearance: White solid

^{1}H NMR: (300 MHz, CD_3OD) δ 7.68 (d, J=7.0 Hz, 1H), 5.94 (d, J=7.0 Hz, 1H), 4.07 (d, J=10.5 Hz, 1H), 3.97 (q, J=J=6.0 Hz, 2H), 3.82-3.48 (m, 6H), 3.19 (m, 2H), 3.07 (m, 2H), 2.24 (m, 1H), 2.06-1.98 (m, 4H), 1.86-1.77 (m, 4H), 1.74-1.54 (m, 2H), 1.40 (m, 2H), 1.45-1.18 (m, 20H).

^{31}P NMR: (300 MHz, CD_3OD): 16.16 ppm (H_3PO_4, -0.81 ppm).

MS: (ESI positive ion mode) M+1: Calc. 622.2, Found: 622.03.

HPLC: Waters XBridge C18 5um, 4.6x250 mm, gradient: 5-95% of acetonitrile (0.1% TFA) in H_2O with 0.1 % TFA, UV 286 nm. Rf=17.42 min., Purity:96.7 %.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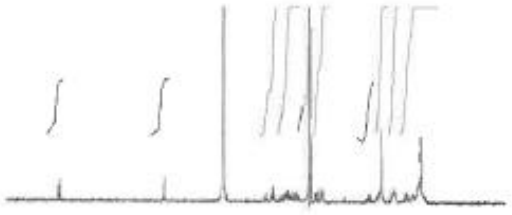
Date collected 2021-03-25
Pulse sequence PROTON
Solvent cd3od
Temperature 25
Spectrometer mercury300-mercury300
Study owner walkup
Operator walkup
8
7
6
5
4
3
2
1
ppm
0.93
1.00
2.24
4.95
8.87
1.80
2.70
0.94
4.02
2.99
17.65

16909-32to35-FINAL5

Sample Name **16909-32to35-FINAL5** | Pulse sequence **PROTON** | Temperature **25** | Study owner **walkup**
Date collected **2021-03-25** | Solvent **cd3od** | Spectrometer **mercury300-mercury300** | Operator **walkup**



16909-32to35-FINAL5

SAMPLE

date	Mar 25 2021
solvent	cd3od
file	/home/walkup/vnmrsys/data/16909-32to35-FINAL5_20210325_01/PROTON_01

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np	16384
fb	2600
bs	32
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nt	1024
ct	1024

TRANSMITTER

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tof	263.5
tpwr	63
pw	5.650

DECOUPLER

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dof	0
dm	nnn
decwave	W40_HCNSmm
dpwr	37
dmf	13100

PRESATURATION

satmode	n
wet	n

SPECIAL

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gain	38
spin	20
hst	0.008
pw90	11.300
alfa	10.000

FLAGS

il	n
in	n
dp	y
hs	nn

PROCESSING

fn	not used

DISPLAY

sp	-78.2
wp	2708.1
rfl	600.3
rfp	0
rp	92.8
lp	-87.9

PLOT

wc	234
sc	8
vs	18487
th	4
ai cdc ph	

PEAK FREQUENCIES

index	freq(ppm)	intensity
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2	7.79709	16.5191
3	5.95116	13.6783
4	5.92577	18.4543
5	4.90807	10.7935
6	4.87486	1668.07
7	4.8397	11.0724
8	4.80649	5.86805
9	4.1404	4.30745
10	4.10524	5.36072
11	4.09547	5.68908
12	4.01147	5.49465
13	3.99194	11.2209
14	3.97045	11.4708
15	3.94897	4.26333
16	3.83762	4.38842
17	3.81223	5.64663
18	3.76535	6.25154
19	3.73605	7.95592
20	3.71847	8.67323
21	3.7048	8.24266
22	3.66377	5.58995
23	3.6208	7.56144
24	3.58955	6.65847
25	3.57783	5.69973
26	3.55243	7.07347
27	3.54071	7.12452
28	3.51337	5.40117
29	3.49969	4.538
30	3.34342	440.344
31	3.31412	16.4596
32	3.30826	22.011
33	3.30436	51.5758
34	3.2985	43.8496
35	3.29264	21.9226
36	3.23013	5.79576
37	3.20864	6.07735
38	3.17934	7.8499
39	3.11488	10.4505
40	3.09144	7.88186
41	3.06214	9.16525
42	2.691	4.44145
43	2.2554	6.10212
44	2.23196	5.41083
45	2.09132	6.18731
46	2.03076	56.5756
47	1.86473	4.79023
48	1.83738	7.46057
49	1.80417	10.0981
50	1.77292	8.02435
51	1.60884	7.01148
52	1.57367	7.1973

PEAK FREQUENCIES(CONTINUED)

index	freq(ppm)	intensity
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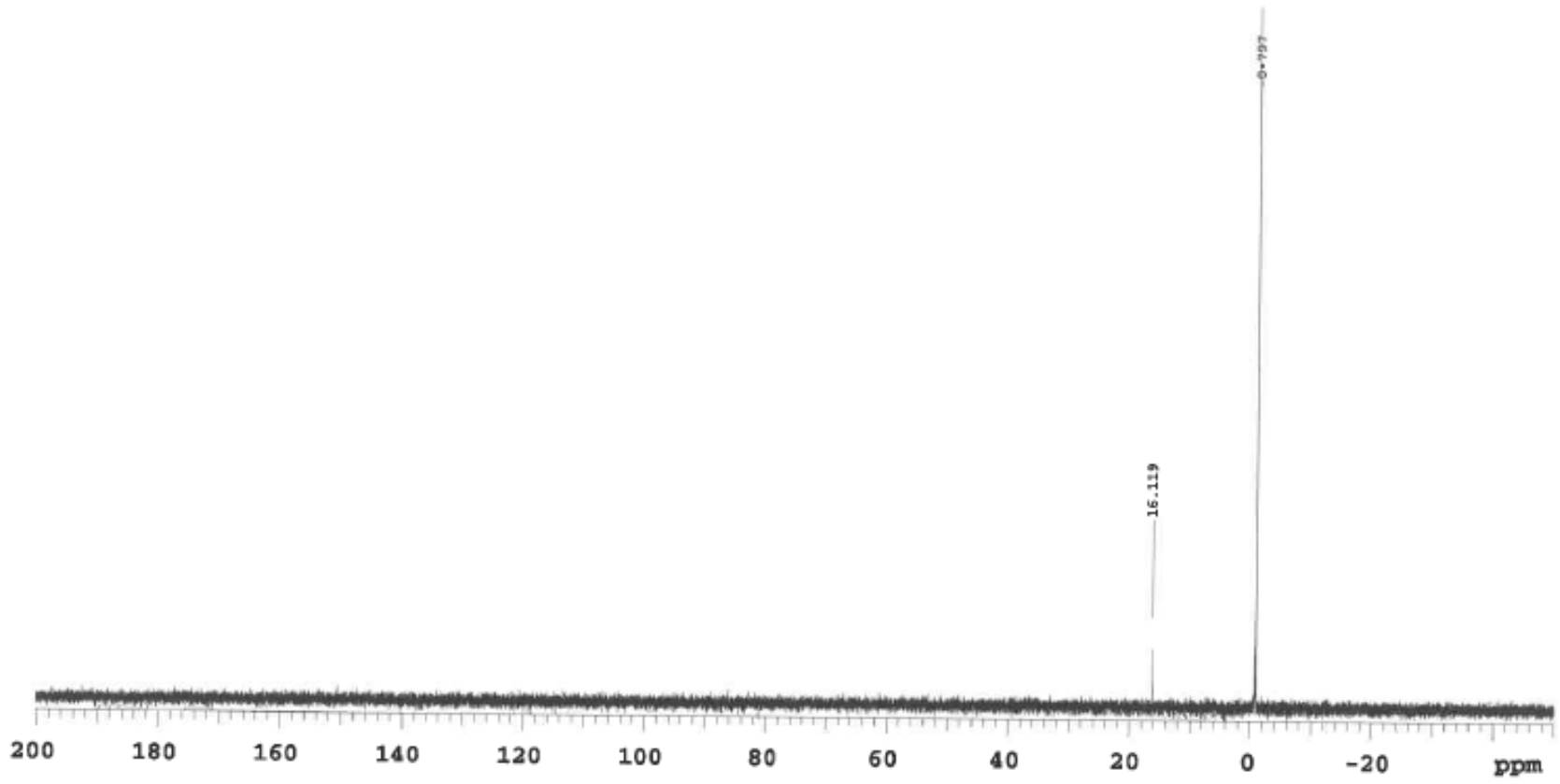
55	1.37639	12.4669
56	1.35294	15.6518
57	1.27872	49.2554

16909-32to35-FINAL-P31

Sample Name	**16909-32to35-FINAL-P31**	Pulse sequence	**PHOSPHORUS**	Temperature	**25**	Study owner	**walkup**
Date collected	**2021-03-26**	Solvent	**cd3od**	Spectrometer	**mercury300-mercury300**	Operator	**walkup**



Millennium HPLC Information

Sample: B-15-FINAL

Operator: Caitlin

Column: Phenom Synergi Fusion C18 4u 4.6 x 250 mm

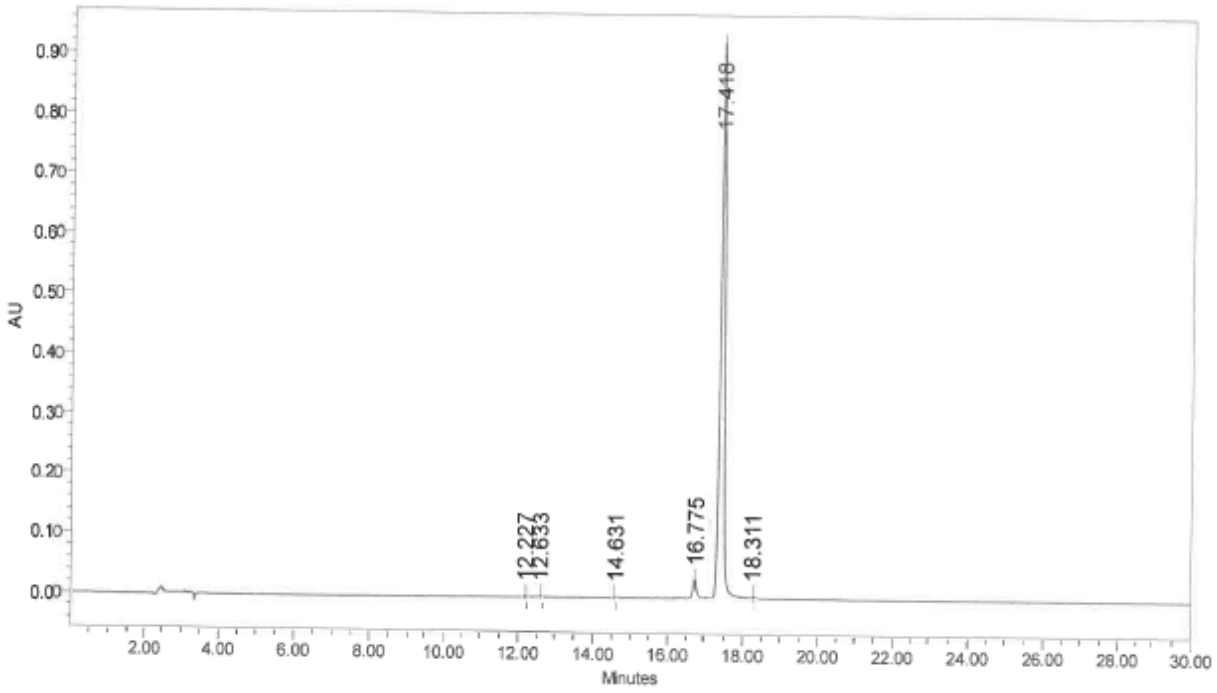
Flow Rate: 1.0 ml/min

Run Time: 30.00 Minutes

Solvent System:

Channel Description: PDA 286.0 nm

Date: 3/25/2021 1:40:12 PM PST



Peak Results

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3	14.631	1107	3743	0.05
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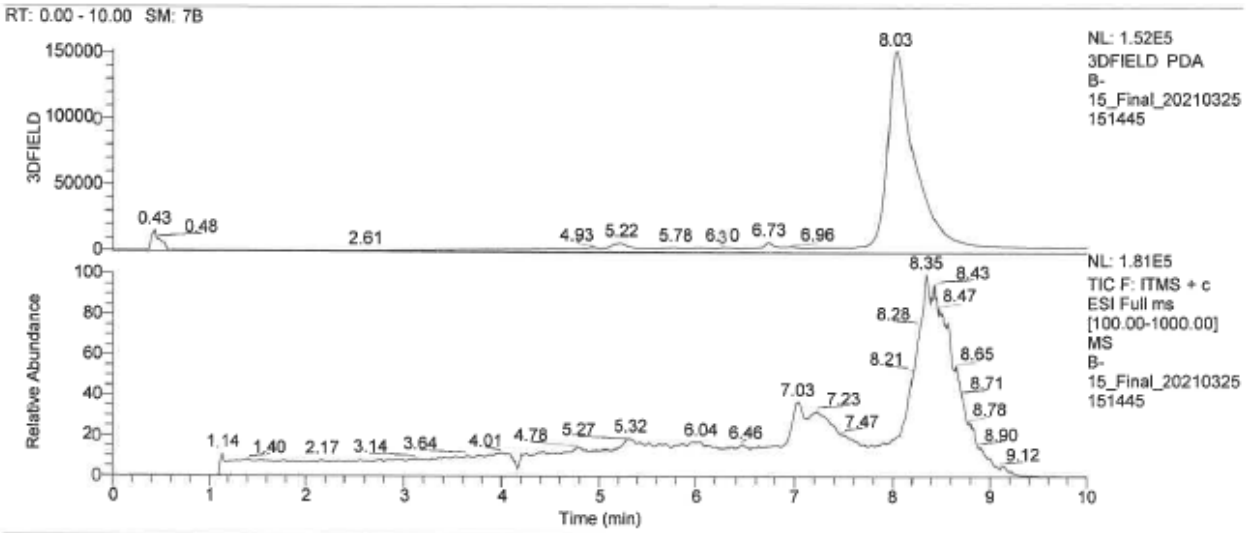
5	17.418	918575	7168714	96.71
6	18.311	2195	12190	0.16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3DFIELD
Relative Abundance
Time (min)
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3DFIELD PDA
B-
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NL: 1.81E5
TIC F: ITMS + c
ESI Full ms
[100.00-1000.00]
MS
B-
15_Final_20210325
151445
8.03
0.43
0.48
2.61
4.93
5.22
5.78
6.30
6.73
6.96
8.35
8.43
8.47
8.28
8.21
8.65
8.71
8.78
8.90
9.12
7.03
7.23
7.47
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4.78
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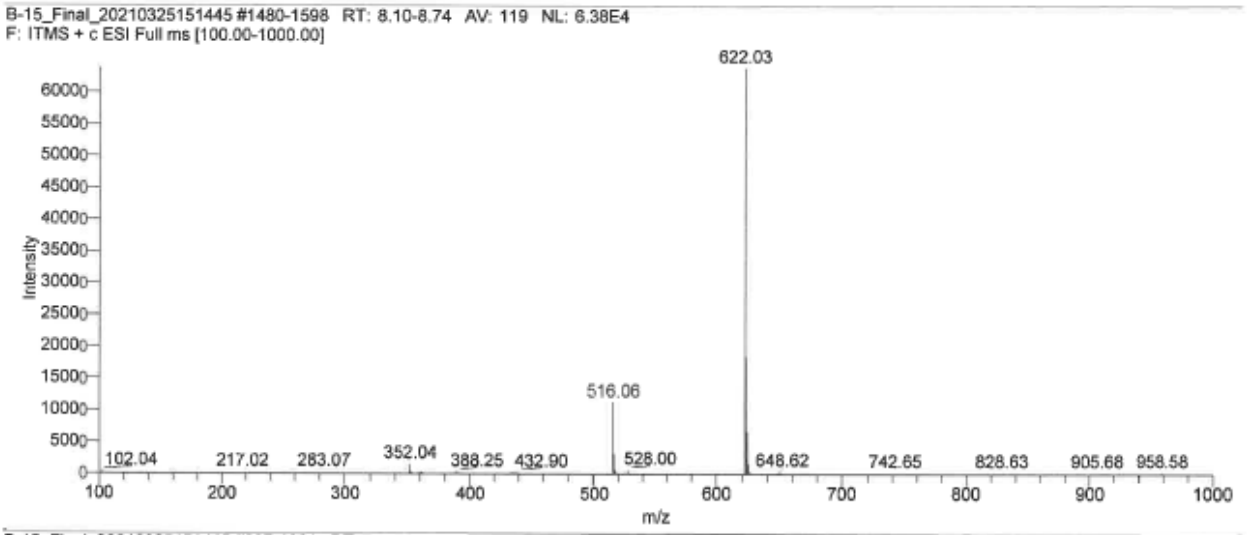
6.46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F: ITMS + c ESI Full ms [100.00-1000.00]
Intensity
m/z
622.03
516.06
102.04
217.02
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352.04
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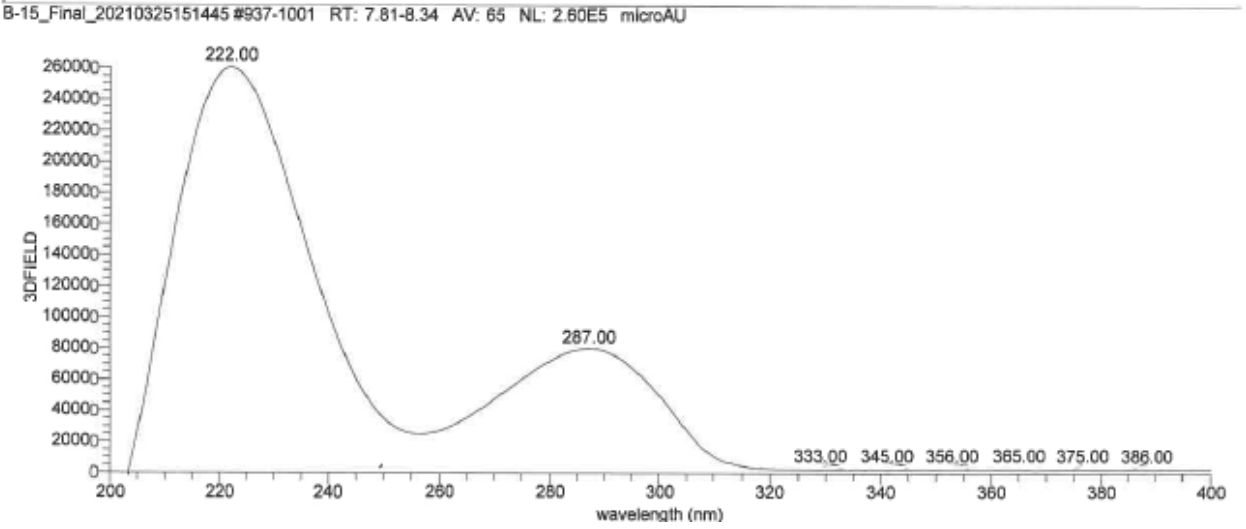
432.90
528.00
648.62
742.65
828.63
905.68
958.58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365.00
375.00
386.00