FIG. 1

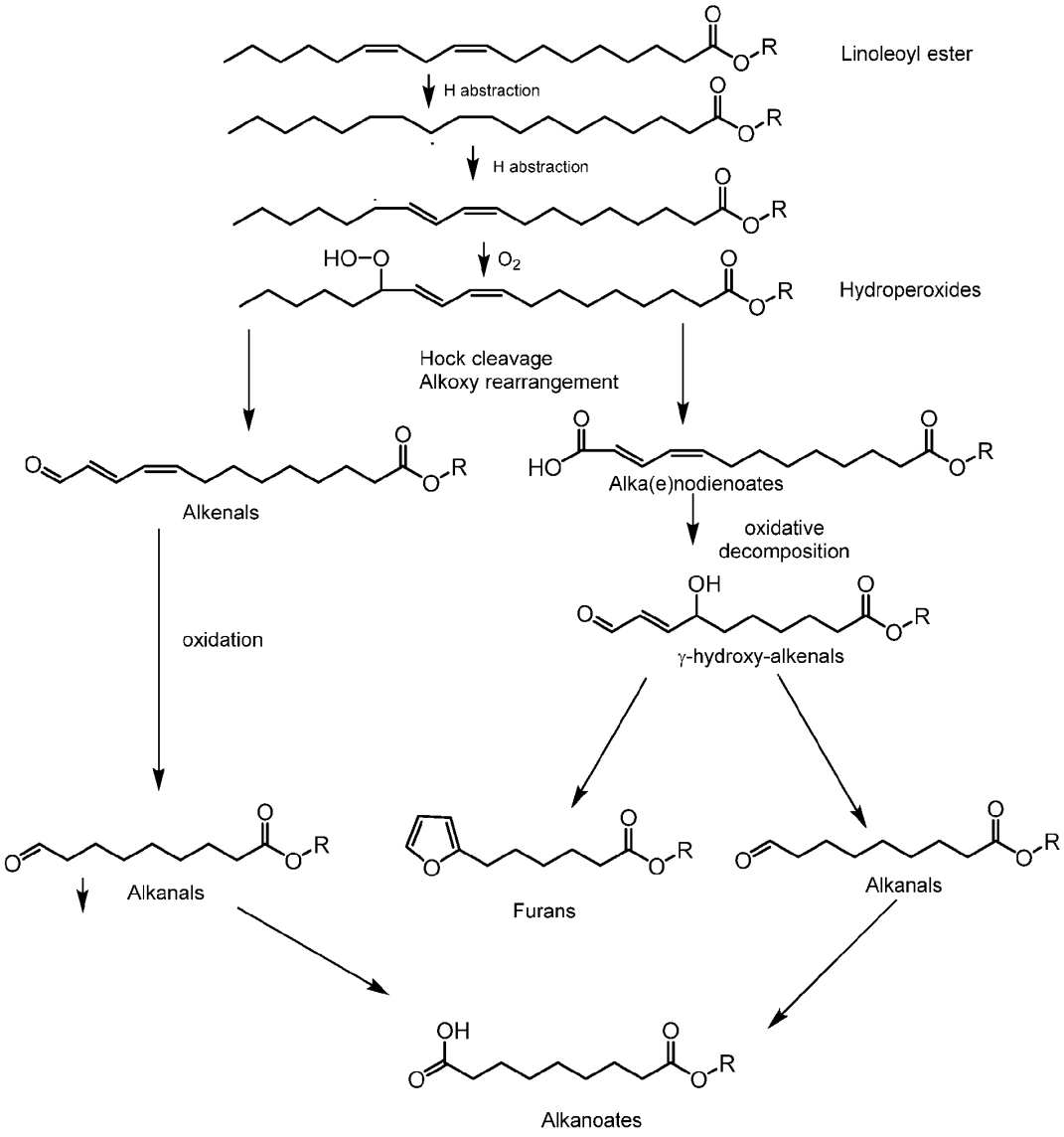

Linoleoyl ester
H abstraction
H abstraction
HO–O
O_2
Hydroperoxides
Hock cleavage
Alkoxy rearrangement
Alkenals
Alka(e)nodienoates
oxidative
decomposition
oxidation
γ-hydroxy-alkenals
Alkanals
Furans
Alkanals
Alkanoates

FIG. 2

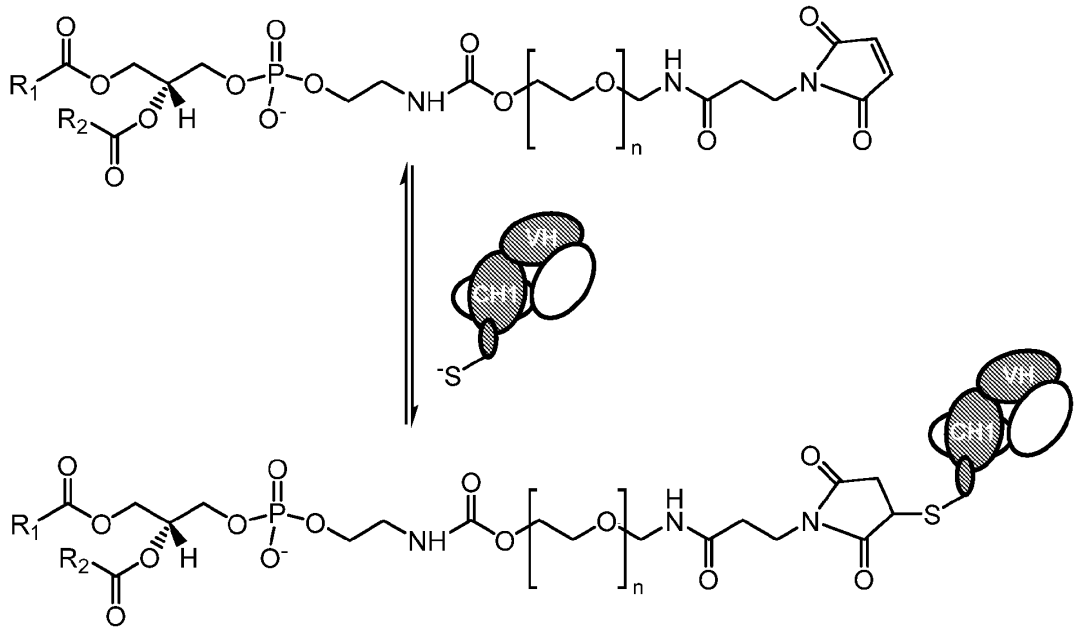


FIG. 3A (Example 12)

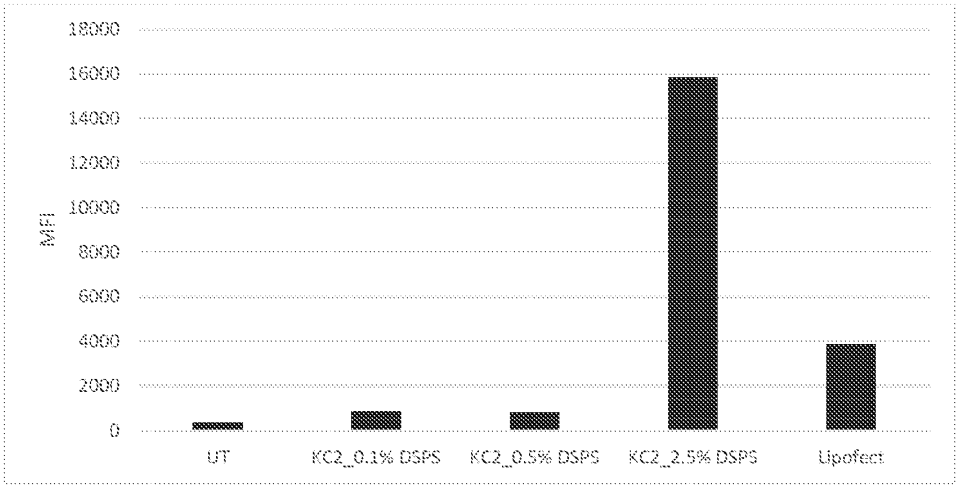


FIG. 3B (Example 12)

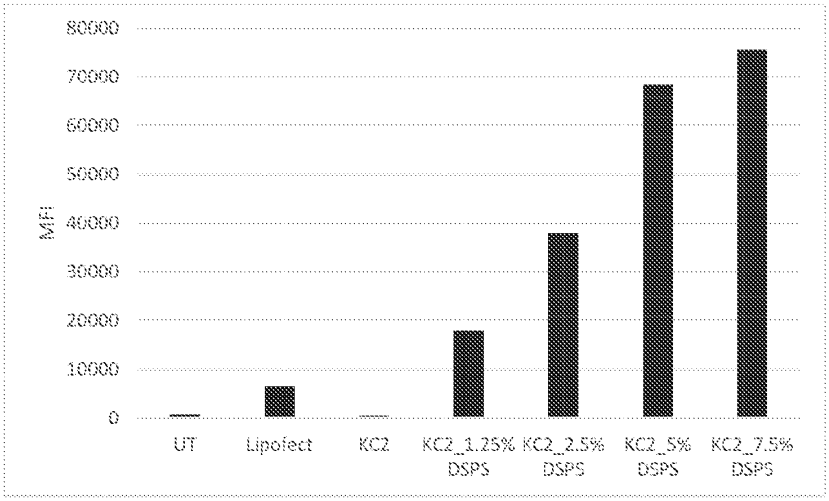


FIG. 3C (Example 12)

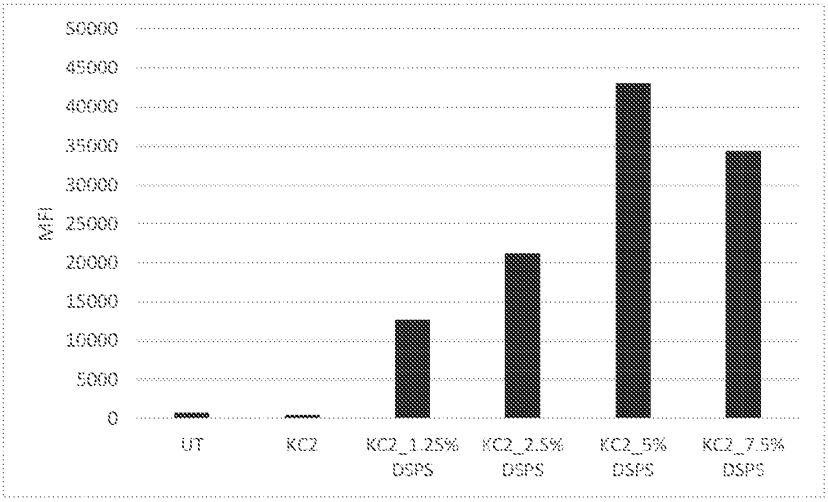


FIG. 3D (Example 12)

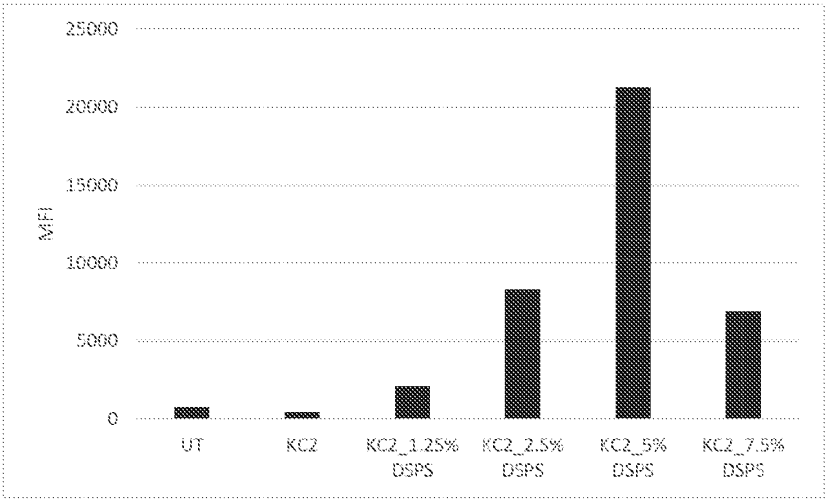


FIG. 4 (Example 13) – SM102 comparison with KC series

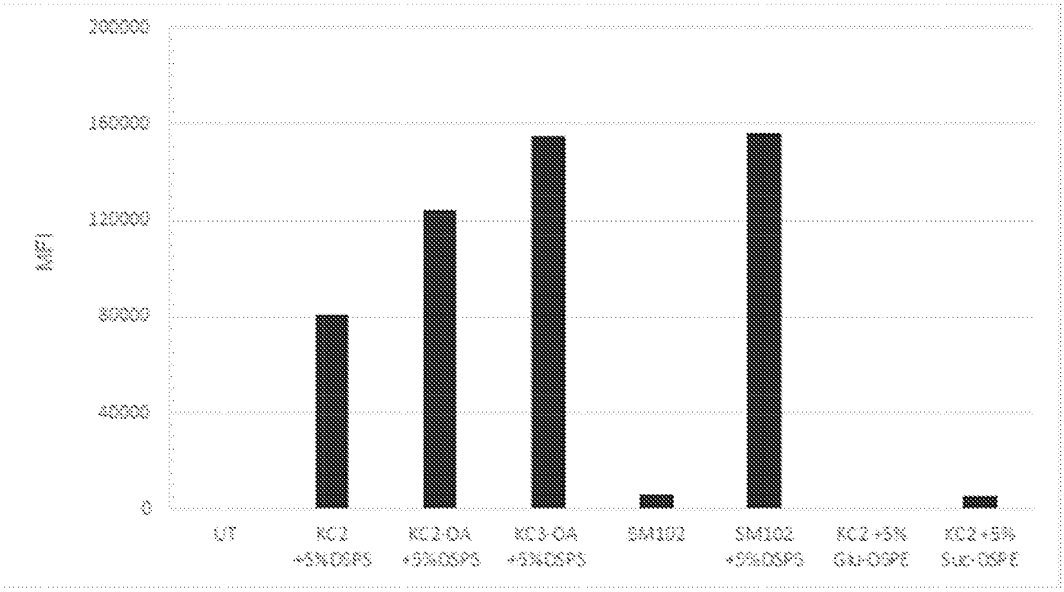


FIG. 5 (Example 14) – PS targeting KC series

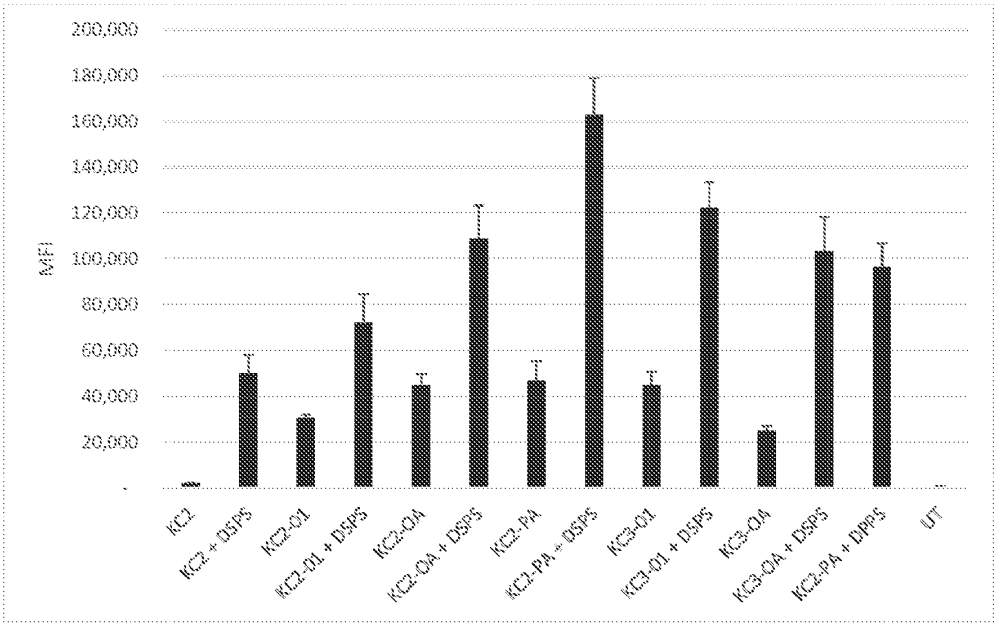


FIG. 6A (Example 15)

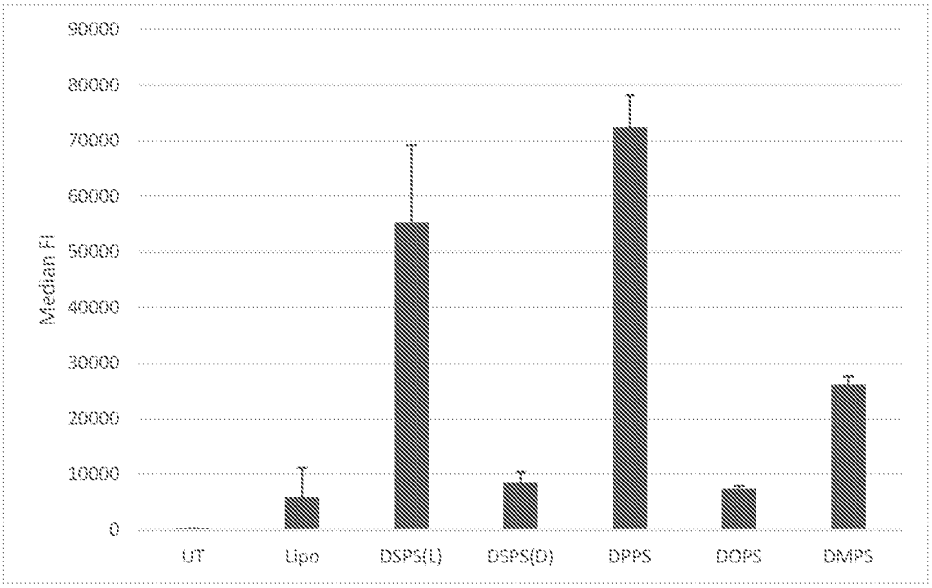


FIG. 6B (Example 15)

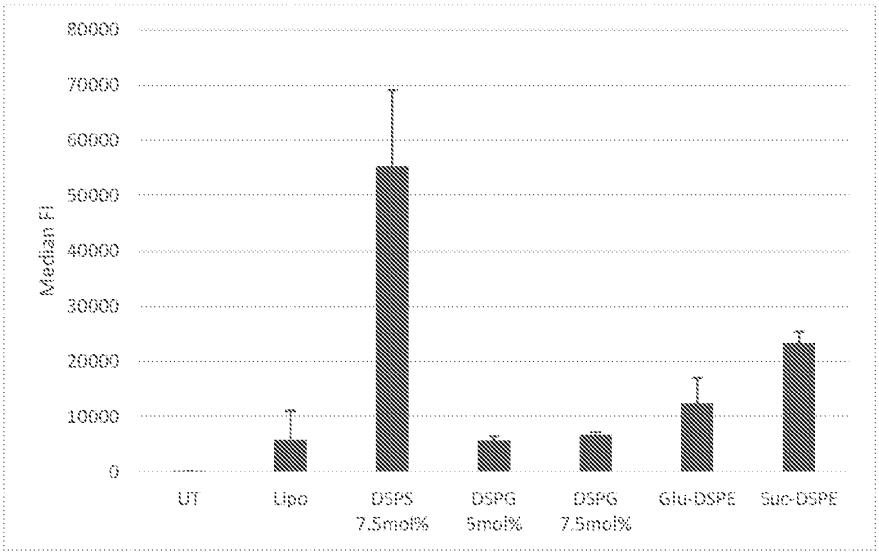


FIG. 7 (Example 16)

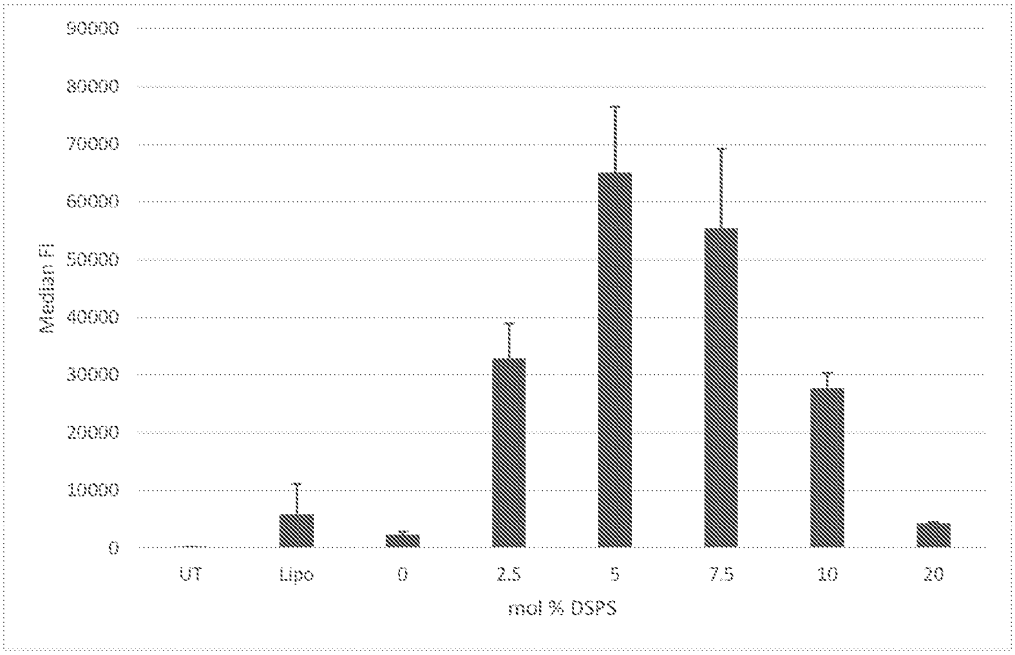


FIG. 8 (Example 17)

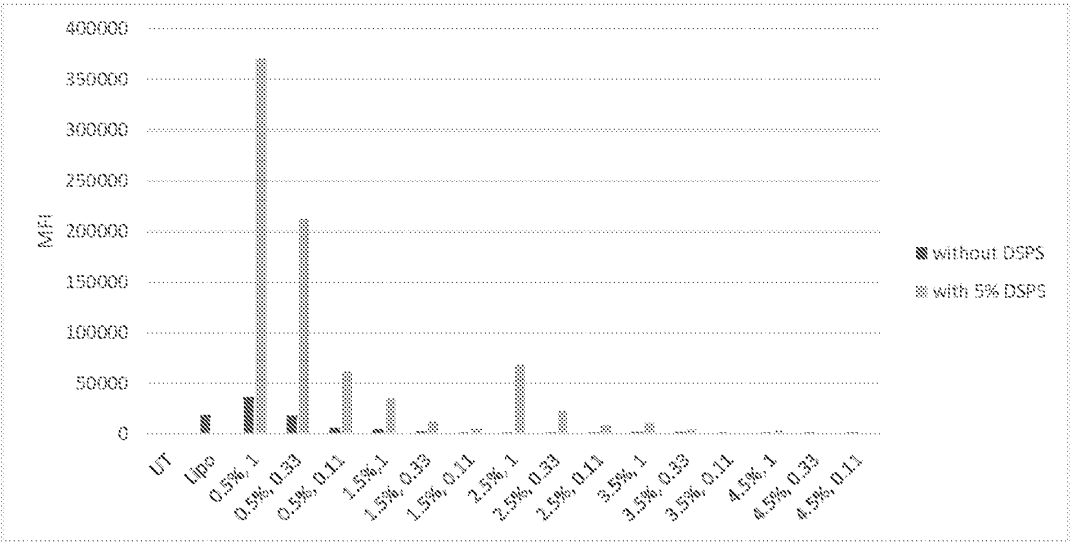


FIG. 9A (Example 18)

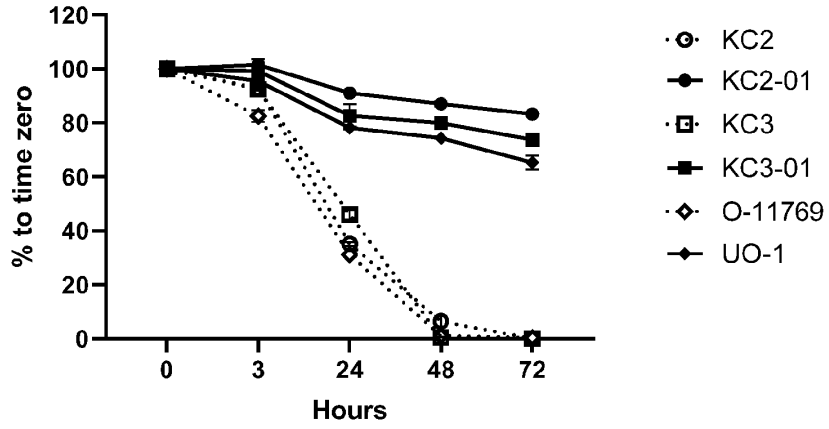


FIG. 9B (Example 18)

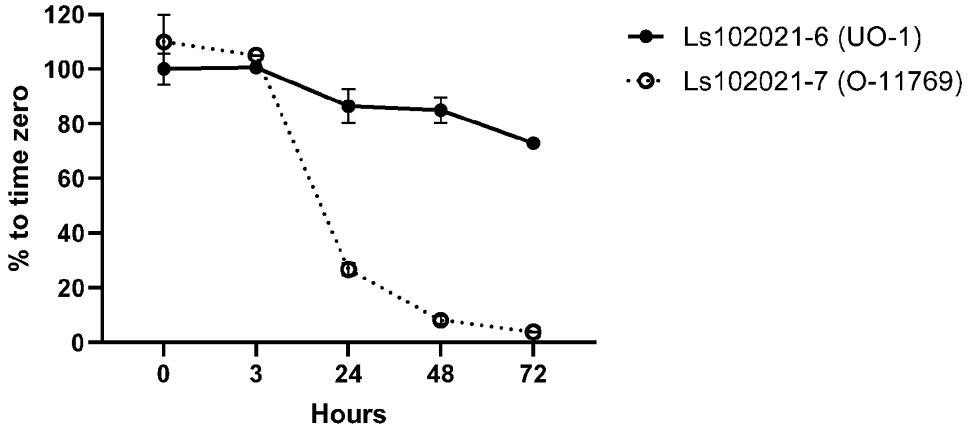


FIG. 10A (Example 19)

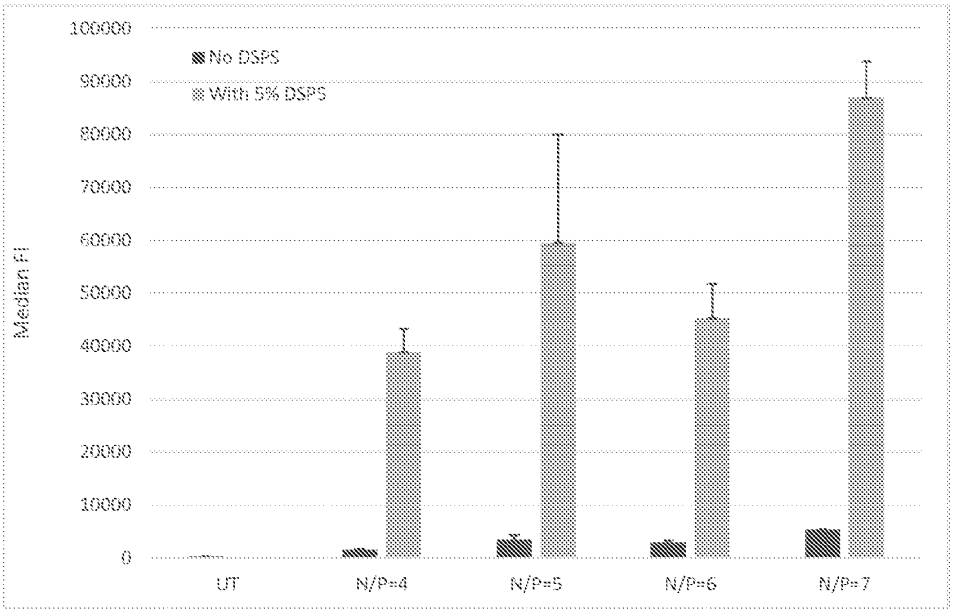


FIG. 10B (Example 19)

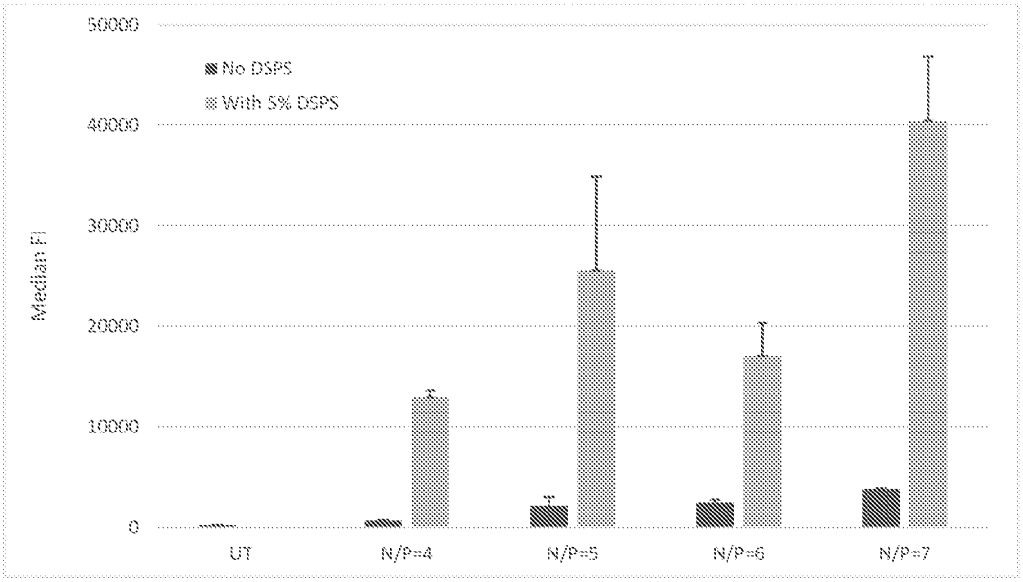


FIG. 11 (Example 20)

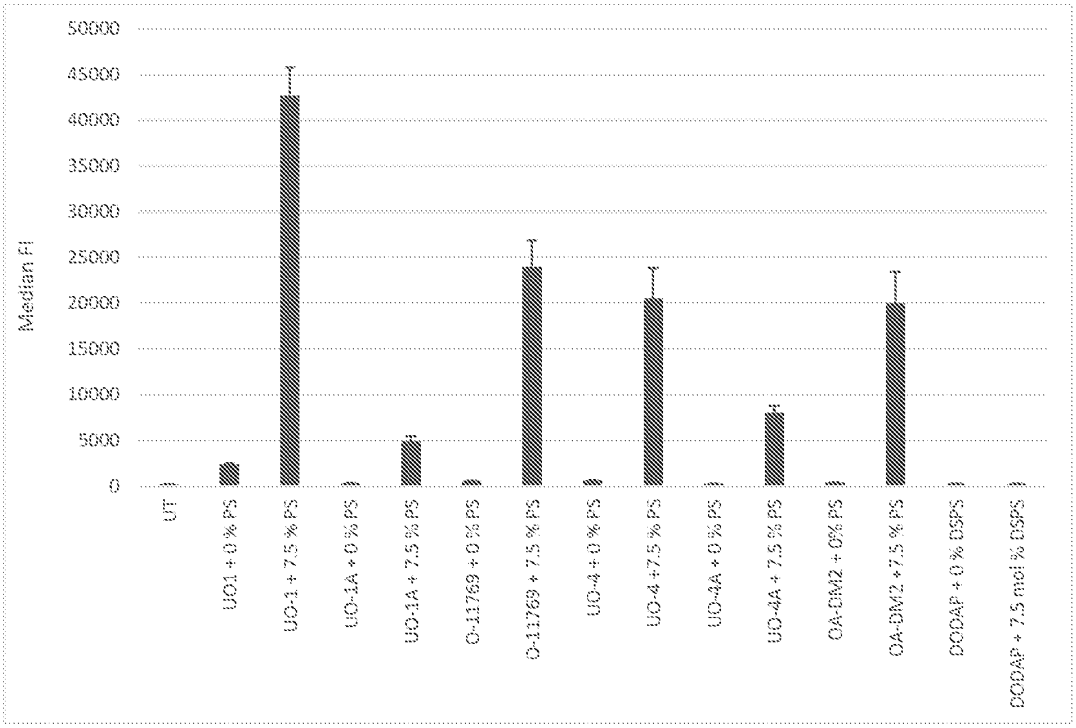


FIG. 12 (Example 21)

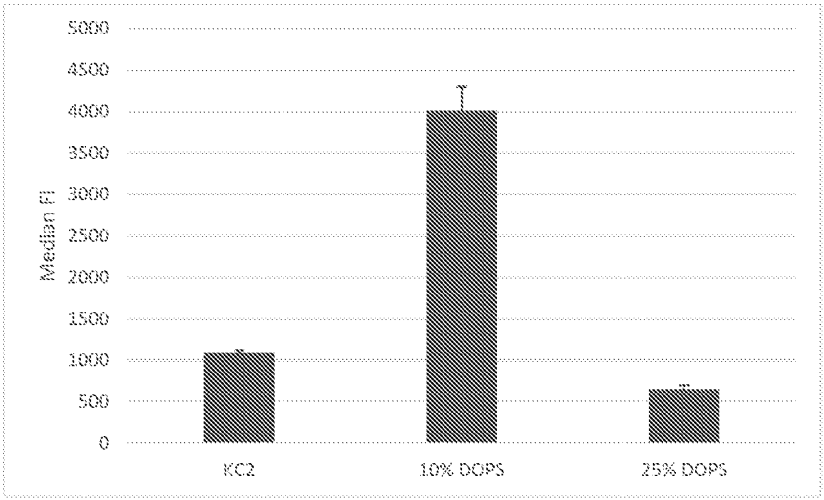


FIG. 13A (Example 22)

mVRN029 (SEQ ID NO: 2)

GGGAATAAACTAGTATTCTTCTGGTCCCCACAGACTCAGAGAGAACCCGCCACCATGTTCGTGTTCCTGG
TGCTGCTGCCTCTGGTGTCCAGCCAGTGTGTGAACCTGACCACCAGAACACAGCTGCCTCCAGCCTACAC
CAACAGCTTTACCAGAGGCGTGTACTACCCCGACAAGGTGTTCAGATCCAGCGTGCTGCACTCTACCCAG
GACCTGTTCCTGCCTTTCTTCAGCAACGTGACCTGGTTCCACGCCATCCACGTGTCCGGCACCAATGGCA
CCAAGAGATTCGACAACCCCGTGCTGCCCTTCAACGACGGGGTGTACTTTGCCAGCACCGAGAAGTCCAA
CATCATCAGAGGCTGGATCTTCGGCACCACACTGGACAGCAAGACCCAGAGCCTGCTGATCGTGAACAAC
GCCACCAACGTGGTCATCAAAGTGTGCGAGTTCCAGTTCTGCAACGACCCCTTCCTGGGCGTCTACTACC
ACAAGAACAACAAGAGCTGGATGGAAAGCGAGTTCCGGGTGTACAGCAGCGCCAACAACTGCACCTTCGA
GTACGTGTCCCAGCCTTTCCTGATGGACCTGGAAGGCAAGCAGGGCAACTTCAAGAACCTGCGCGAGTTC
GTGTTTAAGAACATCGACGGCTACTTCAAGATCTACAGCAAGCACACCCCTATCAACCTCGTGCGGGATC
TGCCTCAGGGCTTCTCTGCTCTGGAACCCCTGGTGGATCTGCCCATCGGCATCAACATCACCCGGTTTCA
GACACTGCTGGCCCTGCACAGAAGCTACCTGACACCTGGCGATAGCAGCAGCGGATGGACAGCTGGTGCC
GCCGCTTACTATGTGGGCTACCTGCAGCCTAGAACCTTCCTGCTGAAGTACAACGAGAACGGCACCATCA
CCGACGCCGTGGATTGTGCTCTGGATCCTCTGAGCGAGACAAAGTGCACCCTGAAGTCCTTCACCGTGGA
AAAGGGCATCTACCAGACCAGCAACTTCCGGGTGCAGCCCACCGAATCCATCGTGCGGTTCCCCAATATC
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AGCGGATCAGCAATTGCGTGGCCGACTACTCCGTGCTGTACAACTCCGCCAGCTTCAGCACCTTCAAGTG
CTACGGCGTGTCCCCTACCAAGCTGAACGACCTGTGCTTCACAAACGTGTACGCCGACAGCTTCGTGATC
CGGGGAGATGAAGTGCGGCAGATTGCCCCTGGACAGACAGGCAAGATCGCCGACTACAACTACAAGCTGC
CCGACGACTTCACCGGCTGTGTGATTGCCTGGAACAGCAACAACCTGGACTCCAAAGTCGGCGGCAACTA
CAATTACCTGTACCGGCTGTTCCGGAAGTCCAATCTGAAGCCCTTCGAGCGGGACATCTCCACCGAGATC
TATCAGGCCGGCAGCACCCCTTGTAACGGCGTGGAAGGCTTCAACTGCTACTTCCCACTGCAGTCCTACG
GCTTTCAGCCCACAAATGGCGTGGGCTATCAGCCCTACAGAGTGGTGGTGCTGAGCTTCGAACTGCTGCA
TGCCCCTGCCACAGTGTGCGGCCCTAAGAAAAGCACCAATCTCGTGAAGAACAAATGCGTGAACTTCAAC
TTCAACGGCCTGACCGGCACCGGCGTGCTGACAGAGAGCAACAAGAAGTTCCTGCCATTCCAGCAGTTTG
GCCGGGATATCGCCGATACCACAGACGCCGTTAGAGATCCCCAGACACTGGAAATCCTGGACATCACCCC
TTGCAGCTTCGGCGGAGTGTCTGTGATCACCCCTGGCACCAACACCAGCAATCAGGTGGCAGTGCTGTAC
CAGGACGTGAACTGTACCGAAGTGCCCGTGGCCATTCACGCCGATCAGCTGACACCTACATGGCGGGTGT
ACTCCACCGGCAGCAATGTGTTTCAGACCAGAGCCGGCTGTCTGATCGGAGCCGAGCACGTGAACAATAG
CTACGAGTGCGACATCCCCATCGGCGCTGGAATCTGCGCCAGCTACCAGACACAGACAAACAGCCCTCGG
AGAGCCAGAAGCGTGGCCAGCCAGAGCATCATTGCCTACACAATGTCTCTGGGCGCCGAGAACAGCGTGG
CCTACTCCAACAACTCTATCGCTATCCCCACCAACTTCACCATCAGCGTGACCACAGAGATCCTGCCTGT
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TTCAACAAAGTGACACTGGCCGACGCCGGCTTCATCAAGCAGTATGGCGATTGTCTGGGCGACATTGCCG
CCAGGGATCTGATTTGCGCCCAGAAGTTTAACGGACTGACAGTGCTGCCTCCTCTGCTGACCGATGAGAT
GATCGCCCAGTACACATCTGCCCTGCTGGCCGGCACAATCACAAGCGGCTGGACATTTGGAGCAGGCGCC
GCTCTGCAGATCCCCTTTGCTATGCAGATGGCCTACCGGTTCAACGGCATCGGAGTGACCCAGAATGTGC
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CAGCACAGCAAGCGCCCTGGGAAAGCTGCAGGACGTGGTCAACCAGAATGCCCAGGCACTGAACACCCTG
GTCAAGCAGCTGTCCTCCAACTTCGGCGCCATCAGCTCTGTGCTGAACGATATCCTGAGCAGACTGGACC
CTCCTGAGGCCGAGGTGCAGATCGACAGACTGATCACAGGCAGACTGCAGAGCCTCCAGACATACGTGAC
CCAGCAGCTGATCAGAGCCGCCGAGATTAGAGCCTCTGCCAATCTGGCCGCCACCAAGATGTCTGAGTGT
GTGCTGGGCCAGAGCAAGAGAGTGGACTTTTGCGGCAAGGGCTACCACCTGATGAGCTTCCCTCAGTCTG
CCCCTCACGGCGTGGTGTTTCTGCACGTGACATATGTGCCCGCTCAAGAGAAGAATTTCACCACCGCTCC

FIG. 13A (Example 22) Continued

AGCCATCTGCCACGACGGCAAAGCCCACTTTCCTAGAGAAGGCGTGTTCGTGTCCAACGGCACCCATTGG
TTCGTGACACAGCGGAACTTCTACGAGCCCCAGATCATCACCACCGACAACACCTTCGTGTCTGGCAACT
GCGACGTCGTGATCGGCATTGTGAACAATACCGTGTACGACCCTCTGCAGCCCGAGCTGGACAGCTTCAA
AGAGGAACTGGACAAGTACTTTAAGAACCACACAAGCCCCGACGTGGACCTGGGCGATATCAGCGGAATC
AATGCCAGCGTCGTGAACATCCAGAAAGAGATCGACCGGCTGAACGAGGTGGCCAAGAATCTGAACGAGA
GCCTGATCGACCTGCAAGAACTGGGGAAGTACGAGCAGTACATCAAGTGGCCCTGGTACATCTGGCTGGG
CTTTATCGCCGGACTGATTGCCATCGTGATGGTCACAATCATGCTGTGTTGCATGACCAGCTGCTGTAGC
TGCCTGAAGGGCTGTTGTAGCTGTGGCAGCTGCTGCAAGTTCGACGAGGACGATTCTGAGCCCGTGCTGA
AGGGCGTGAAACTGCACTACACATGATGACTCGAGCTGGTACTGCATGCACGCAATGCTAGCTGCCCCTT
TCCCGTCCTGGGTACCCCGAGTCTCCCCCGACCTCGGGTCCCAGGTATGCTCCCACCTCCACCTGCCCCA
CTCACCACCTCTGCTAGTTCCAGACACCTCCCAAGCACGCAGCAATGCAGCTCAAAACGCTTAGCCTAGC
CACACCCCCACGGGAAACAGCAGTGATTAACCTTTAGCAATAAACGAAAGTTTAACTAAGCTATACTAAC
CCCAGGGTTGGTCAATTTCGTGCCAGCCACACCCTGGAGCTAGCAGCGGCCGCGGCCGCAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIG. 13B (Example 22)

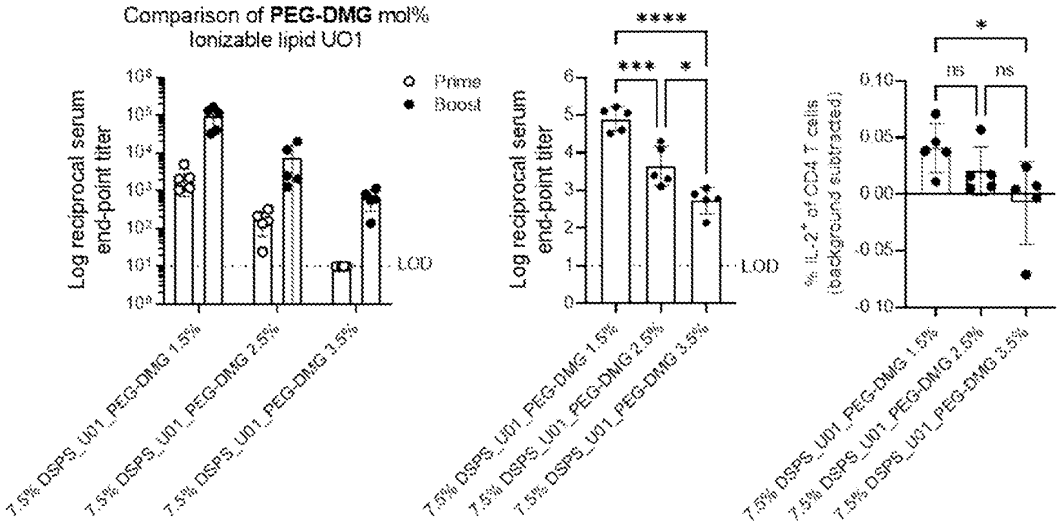


FIG. 13C (Example 22).

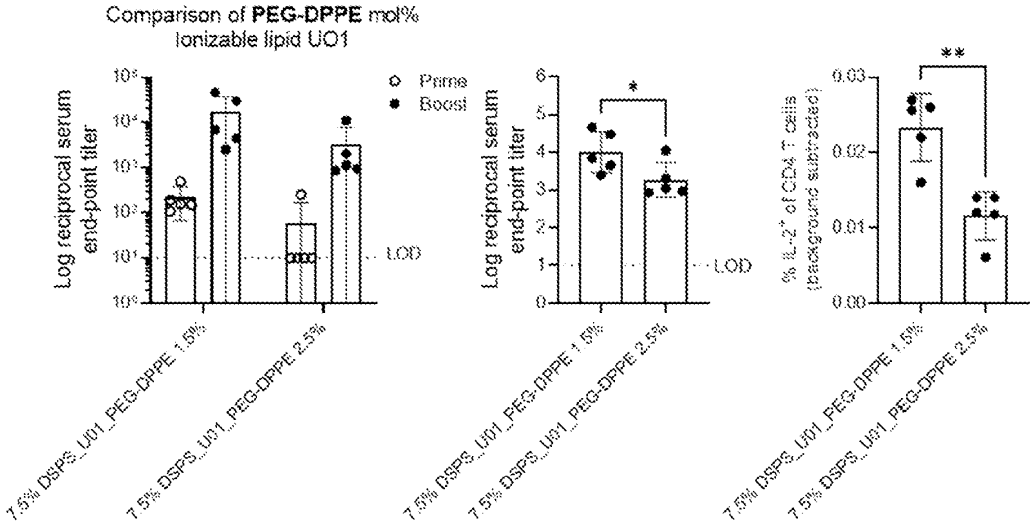


FIG. 13D (Example 22).

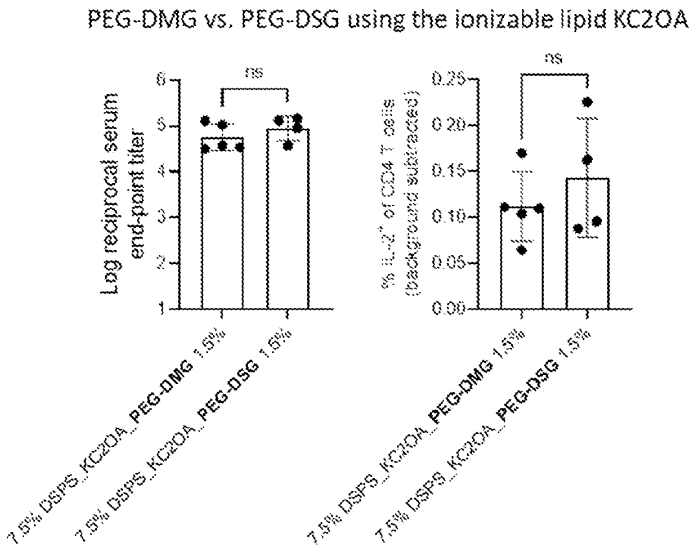


FIG. 13E (Example 22).

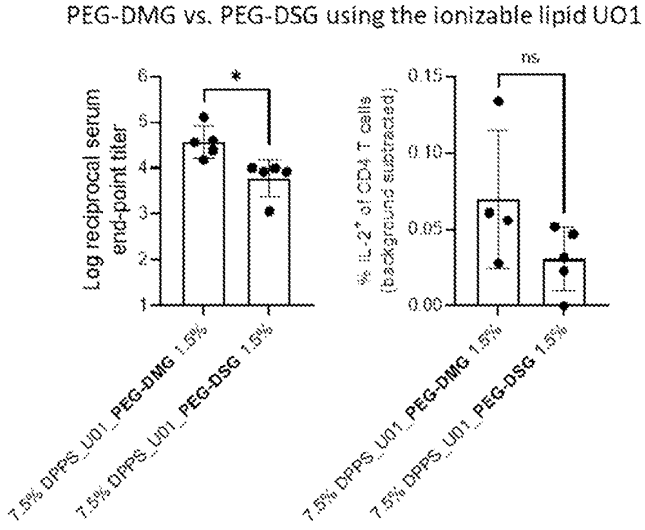


FIG. 13F (Example 22).

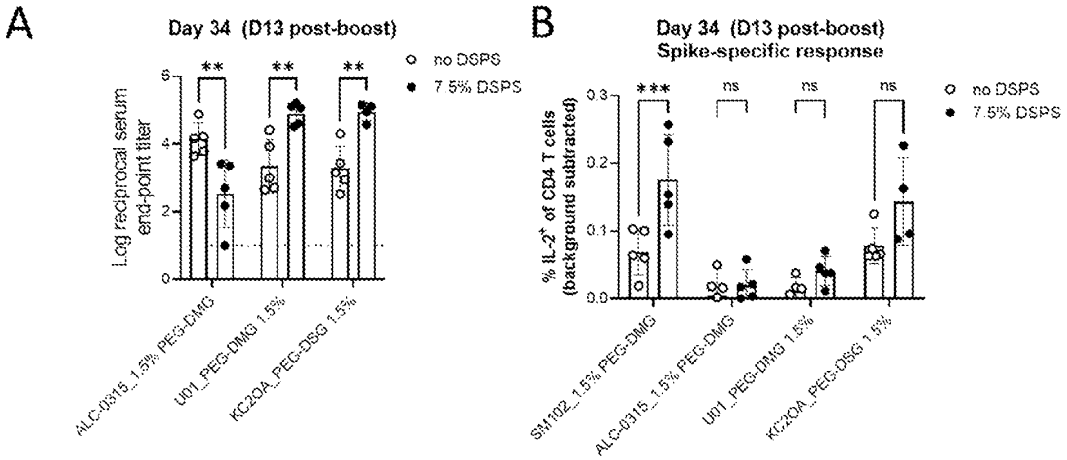


FIG. 13G (Example 22).

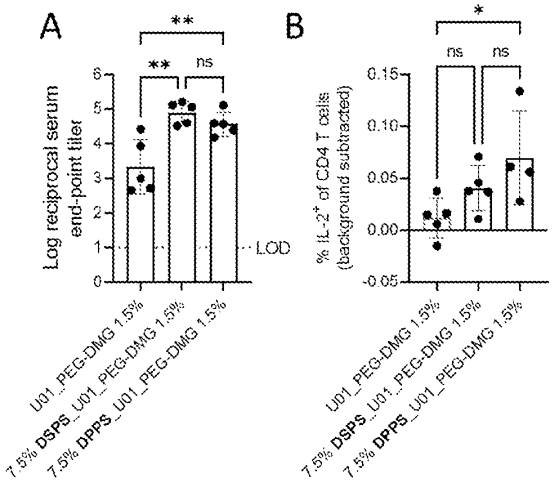


FIG. 14A (Example 23).

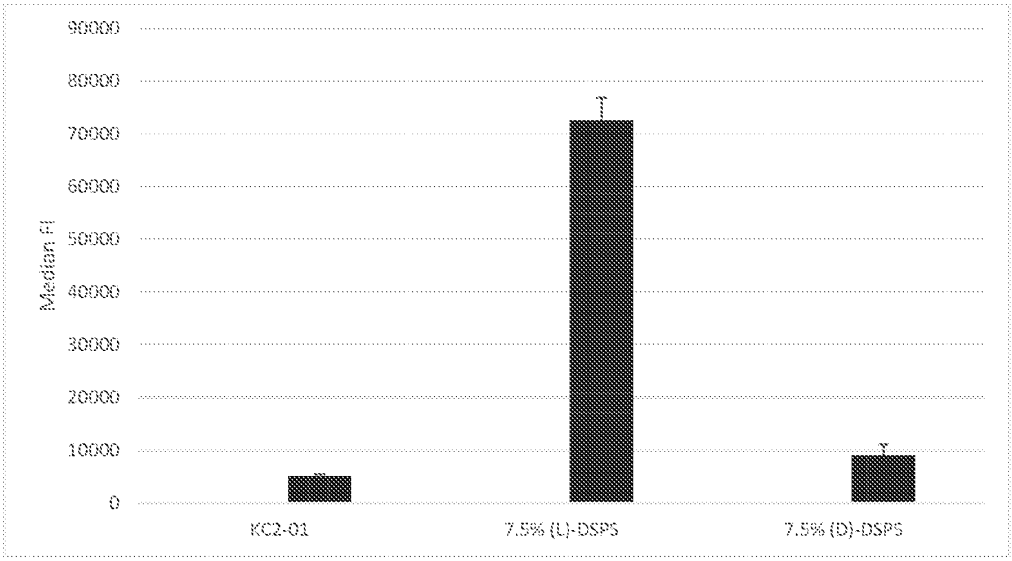


FIG. 14B (Example 23).

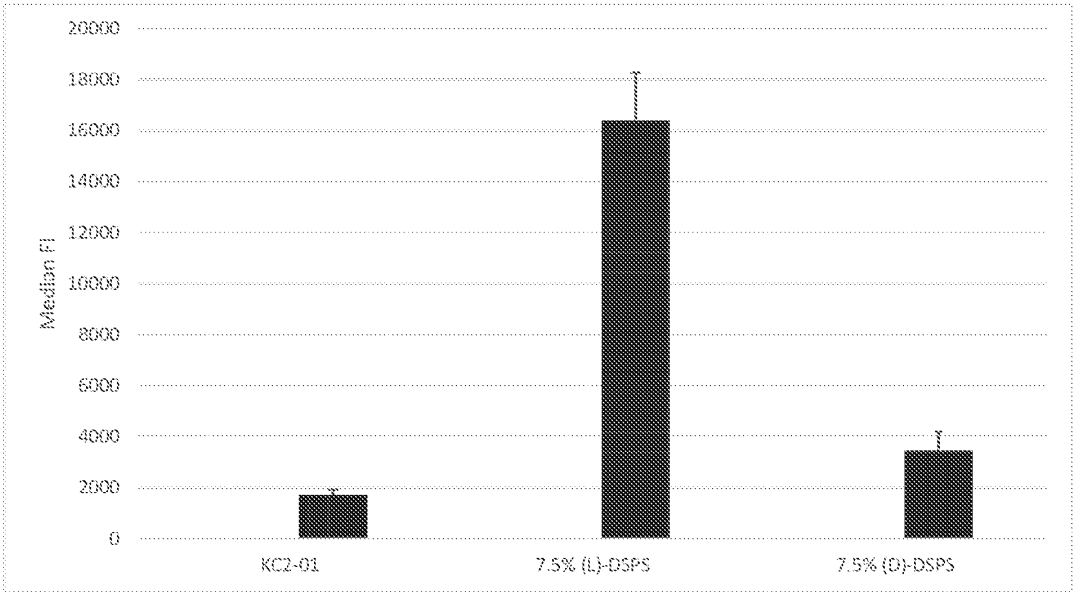


FIG. 15 (Example 24).

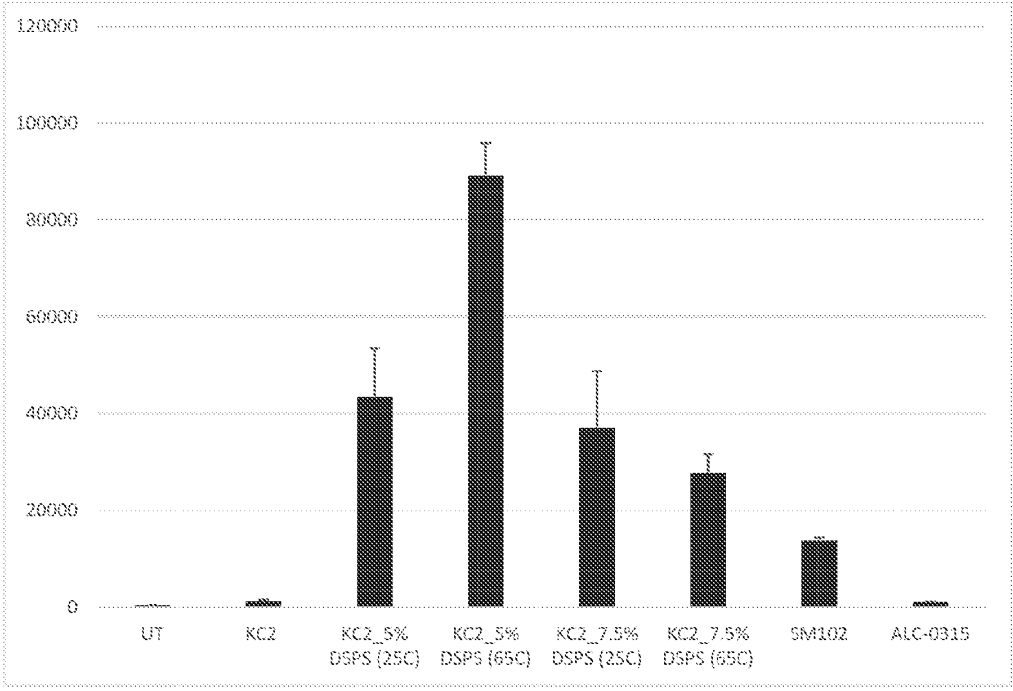


FIG. 16 (Example 25).

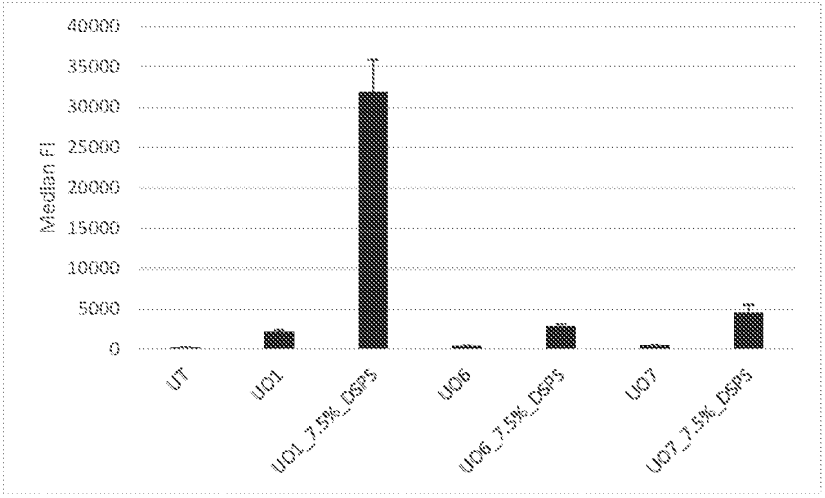


FIG. 17 (Example 26).

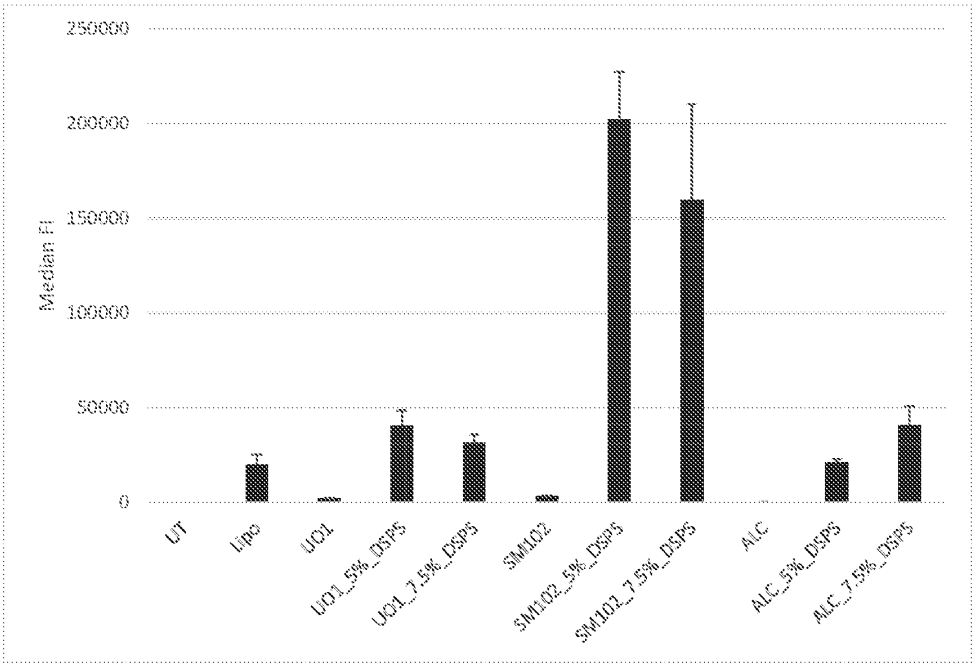


FIG. 18 (Example 29)

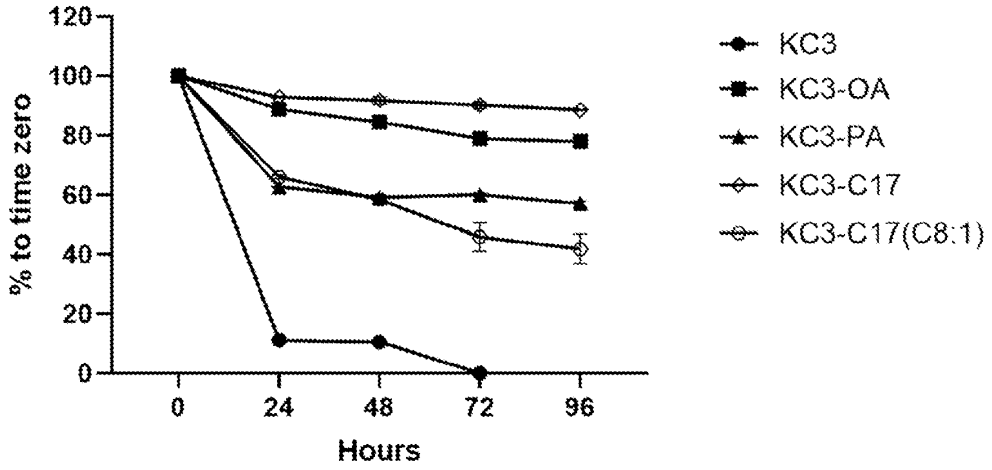


FIG. 19 (Example 30)

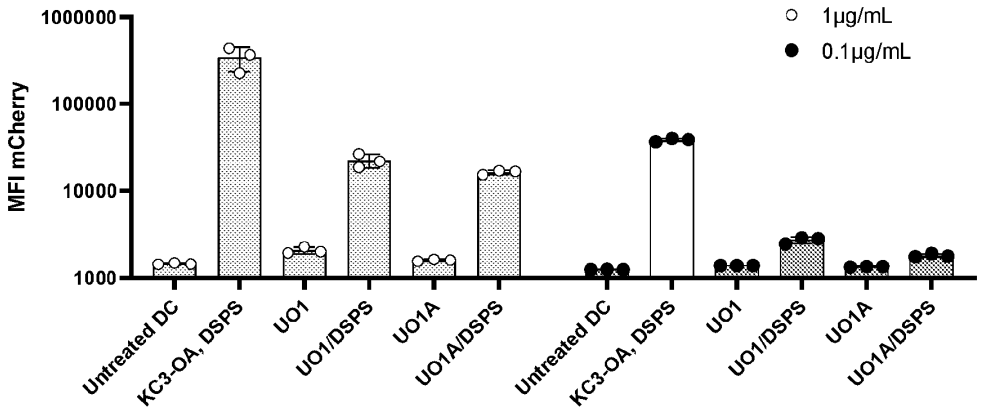


FIG. 20 (Example 31)

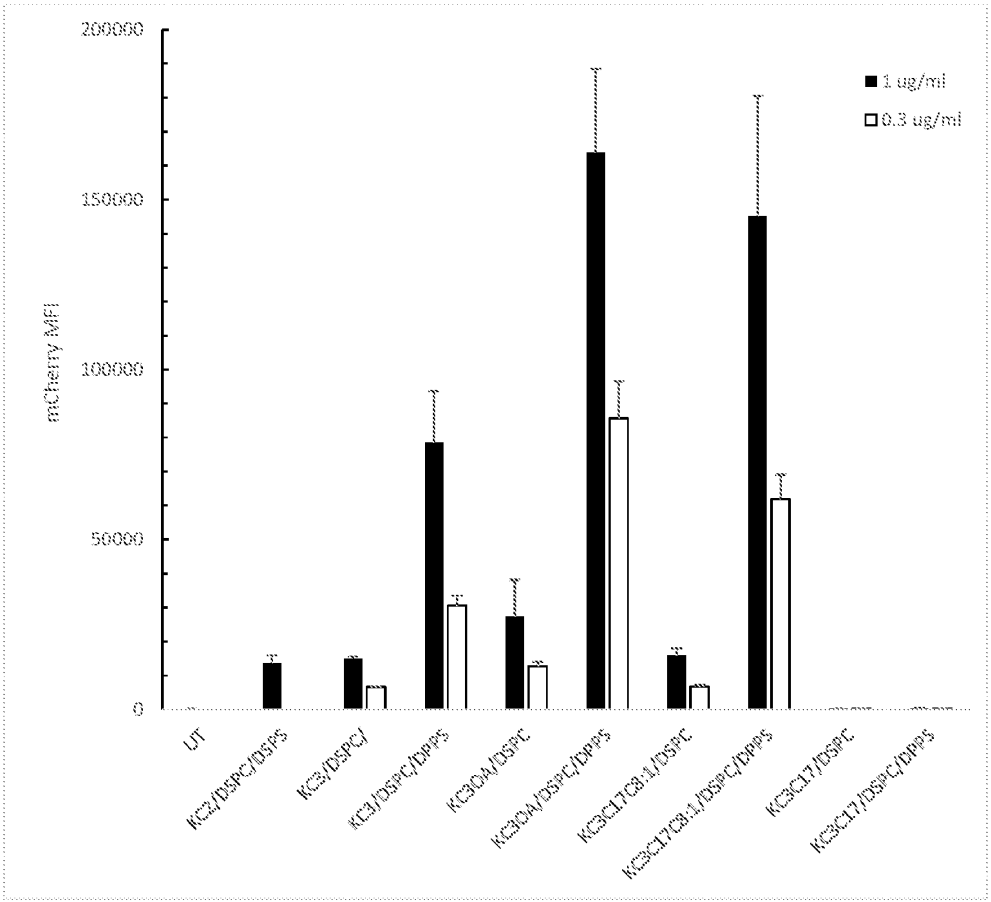


FIG. 21 (Example32)

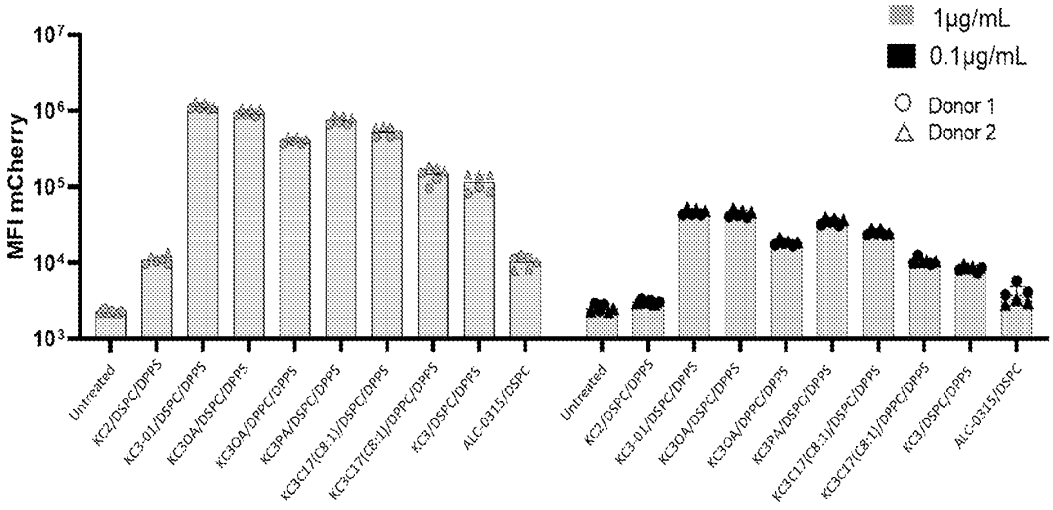


FIG. 22 (Example 33)

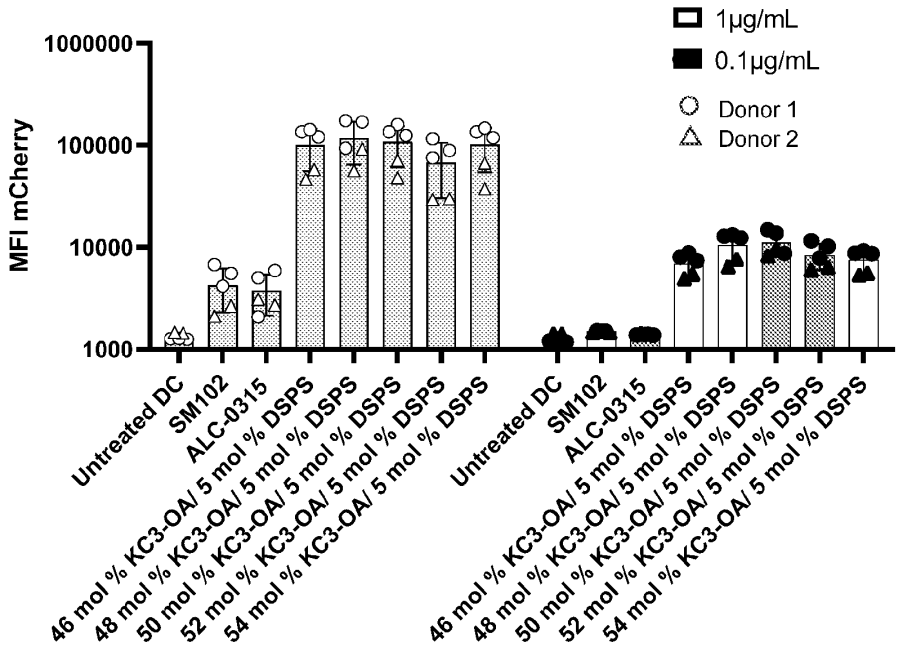


FIG. 23 (Example 34)

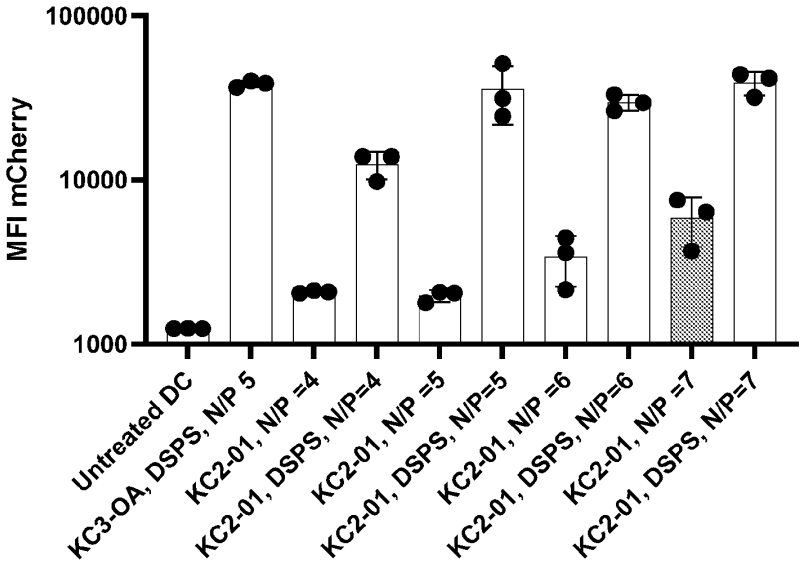


FIG. 24A (Example 35)

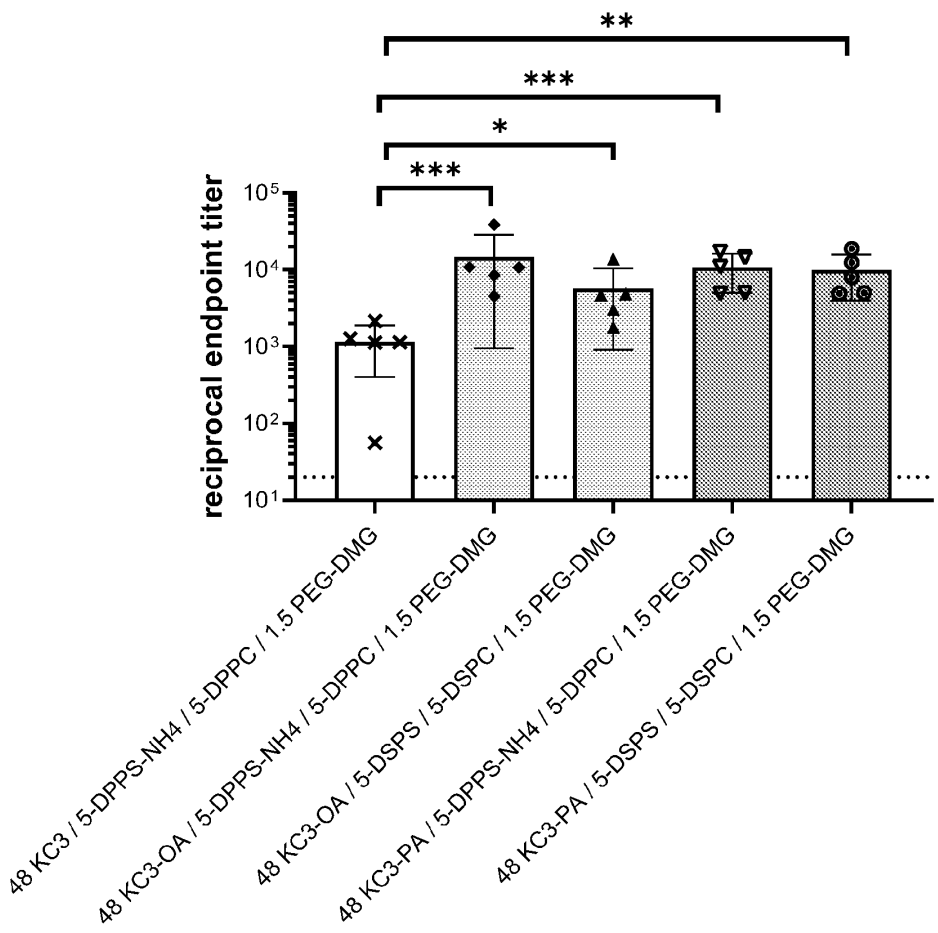


FIG. 24B (Example 35)

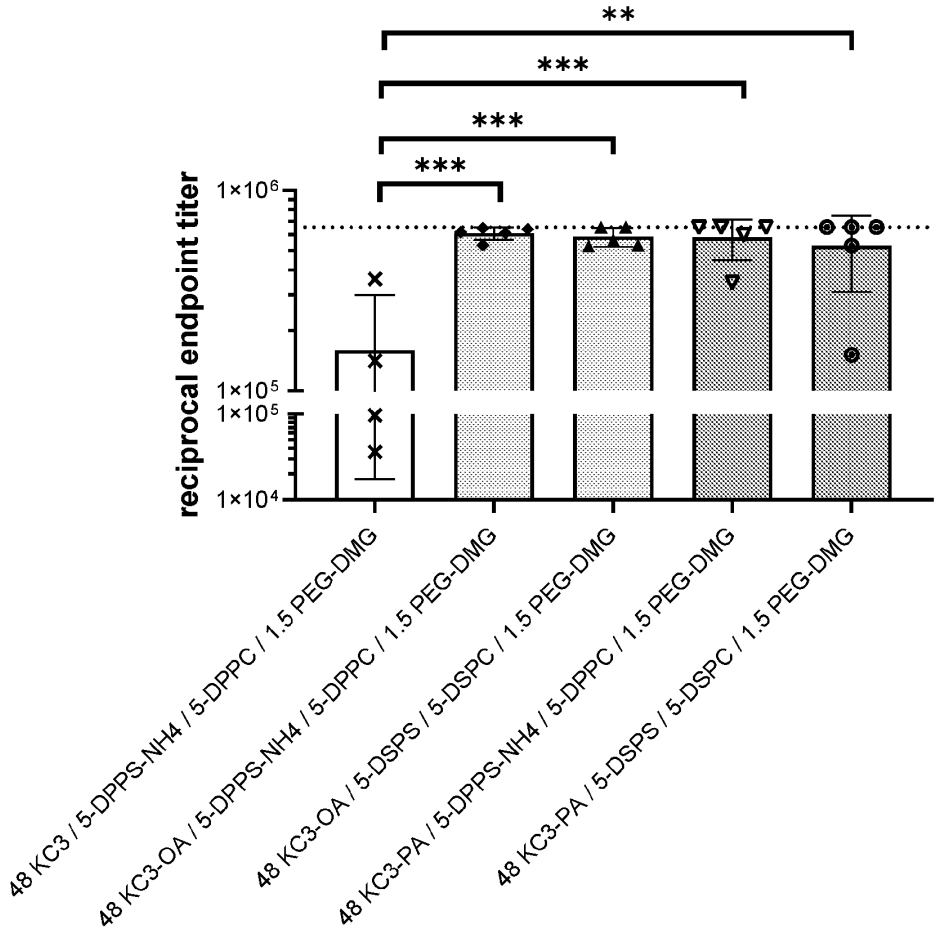


FIG. 25A (Example 38)

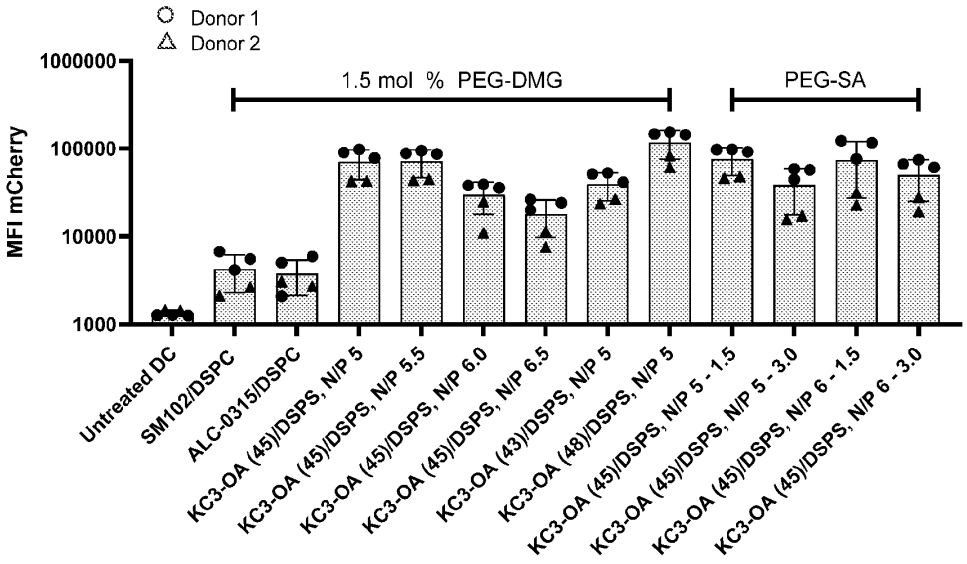


FIG. 25B (Example 38) – MS 148-152

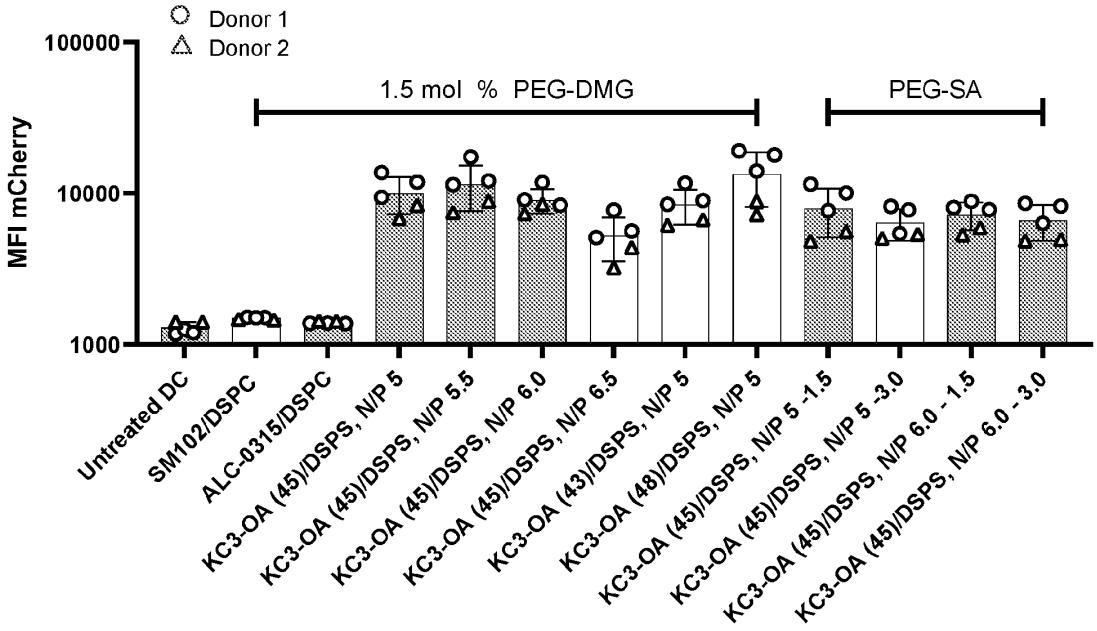


FIG. 26A (Example 39)

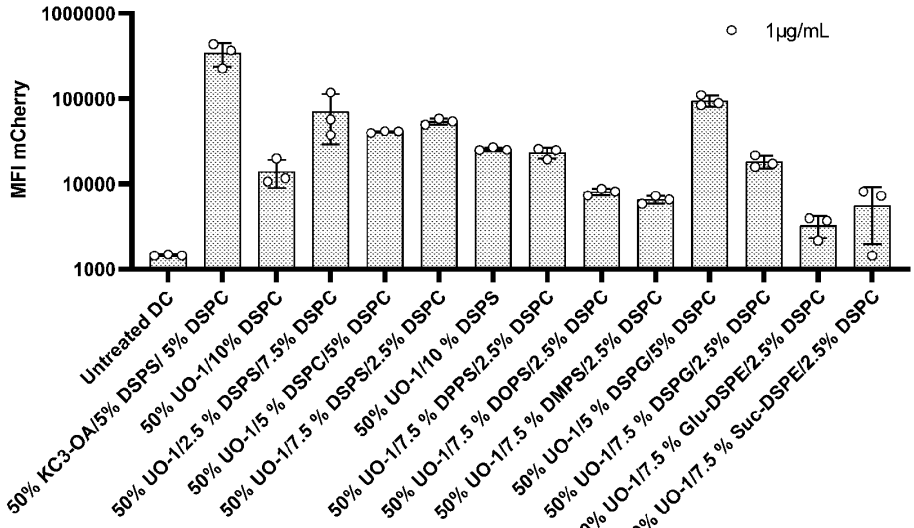


FIG. 26B (Example 39)

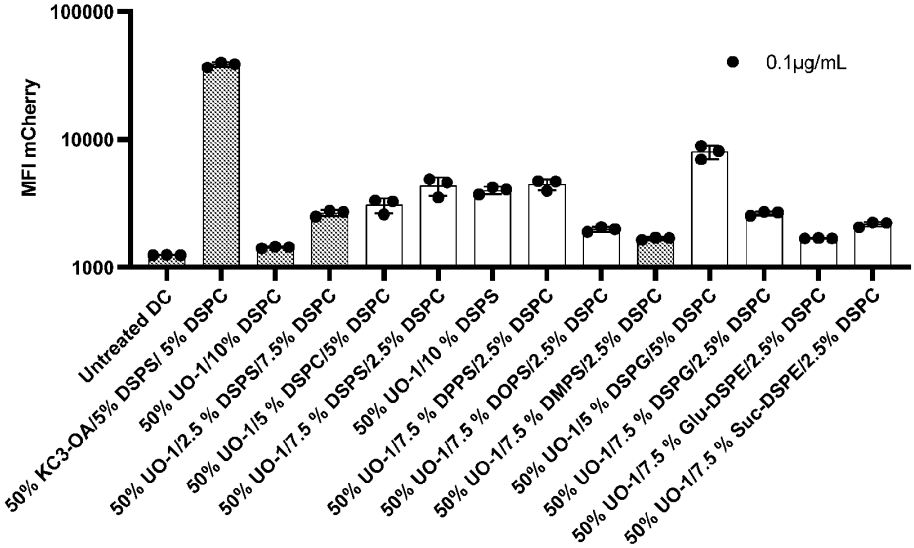


FIG. 27A (Example 40)

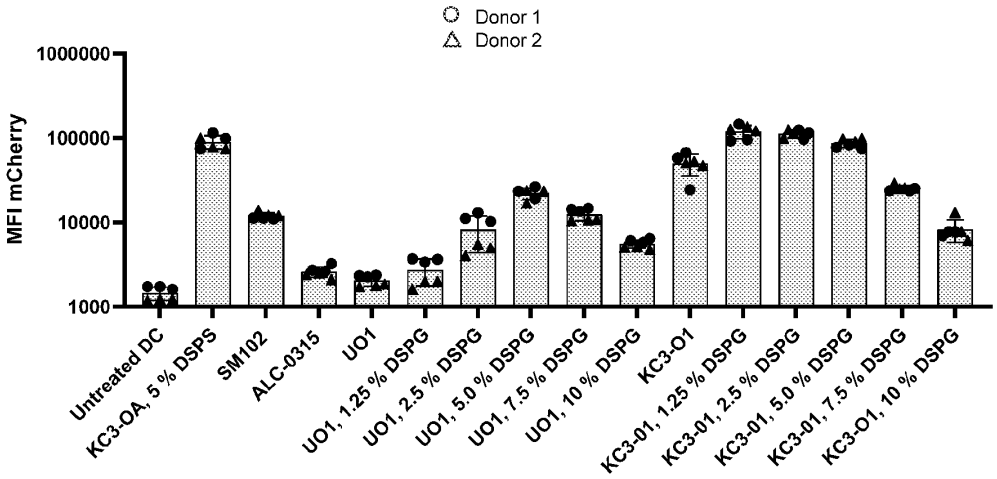


FIG. 27B (Example 40)

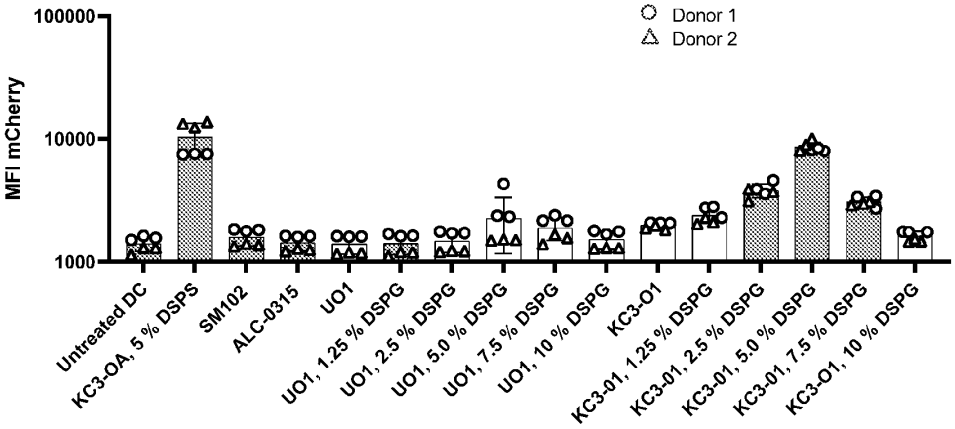


FIG. 28 (Example 42)

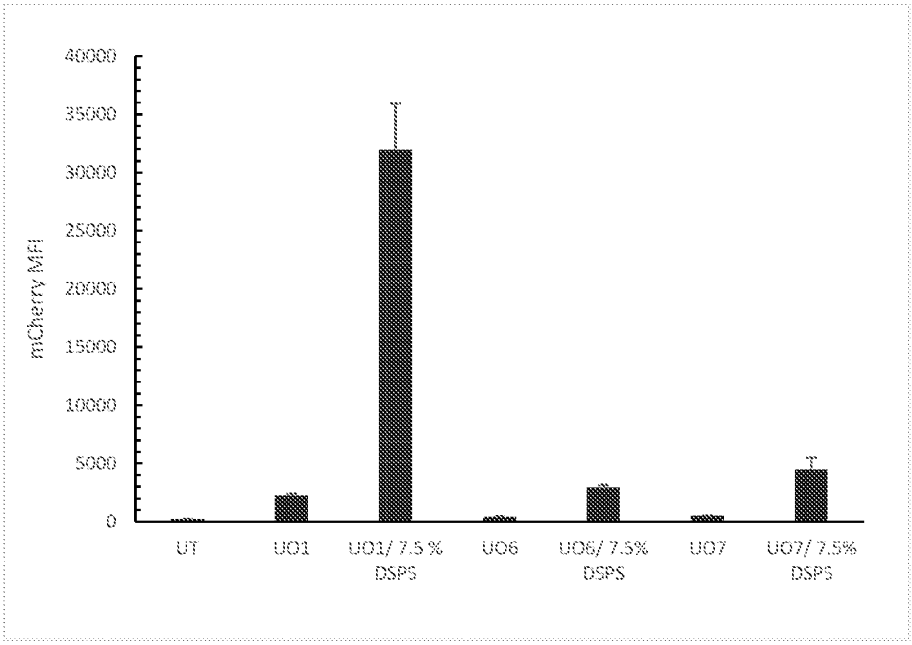


FIG. 29 (Example 43)

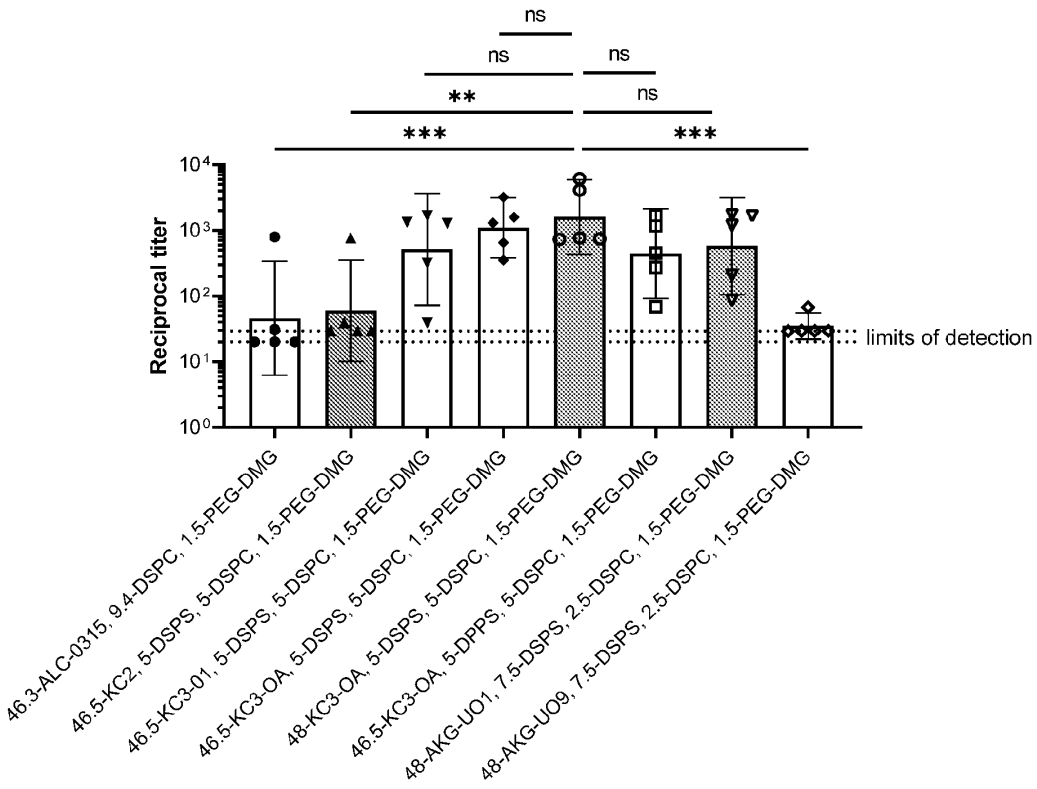


FIG. 30A (Example 44)

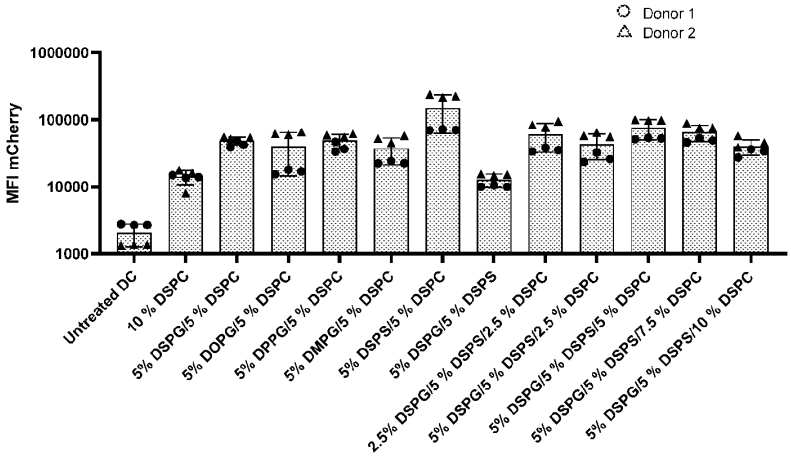


FIG. 30B (Example 44)

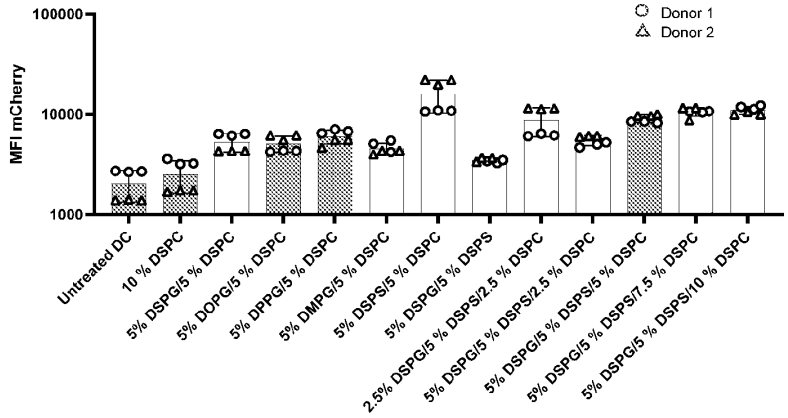


FIG. 31 (Example 45)

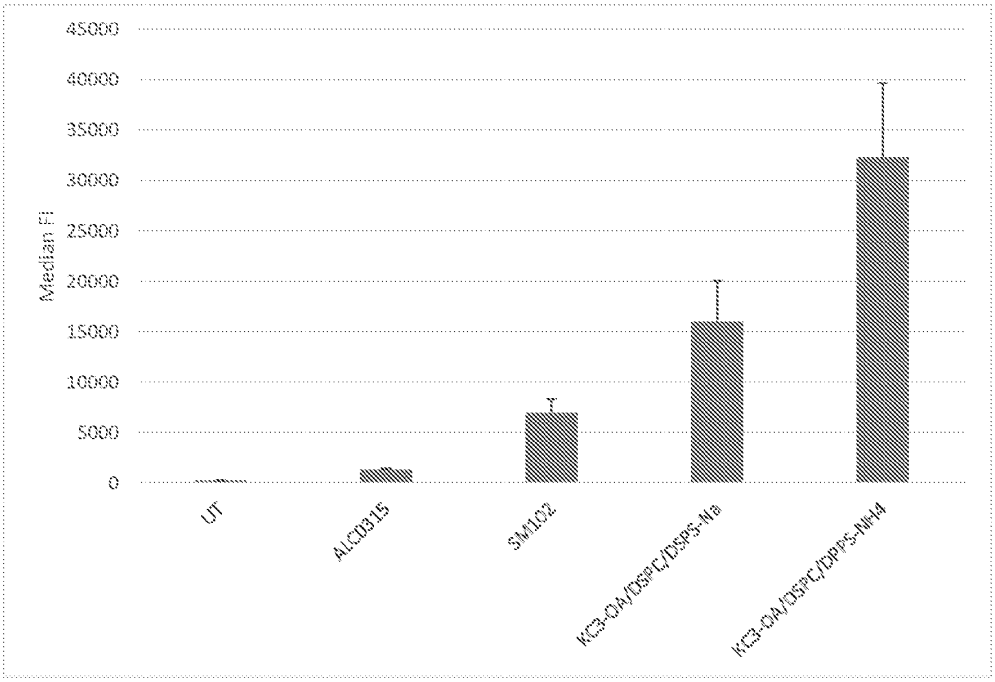


FIG. 32

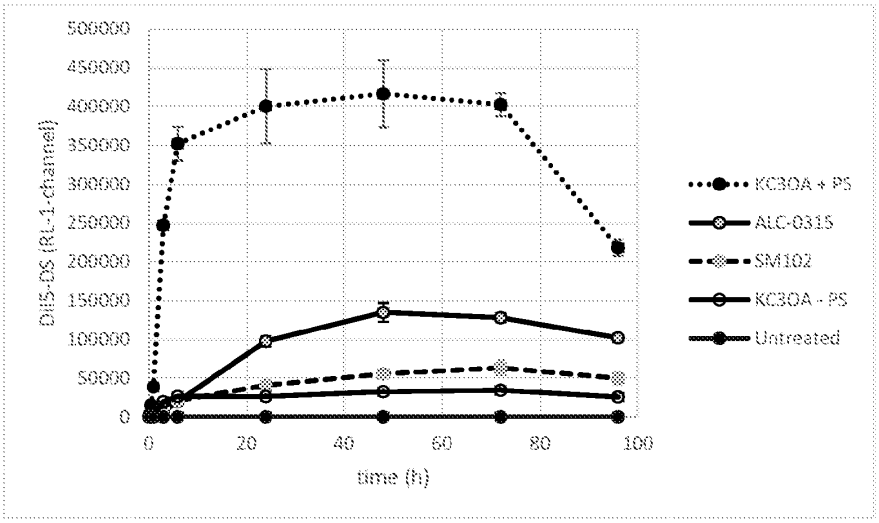

500000
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
DiI5-DS (RL-1-channel)
0
20
40
60
80
100
time (h)
KC3OA + PS
ALC-0315
SM102
KC3OA - PS
Untreated

FIG. 33

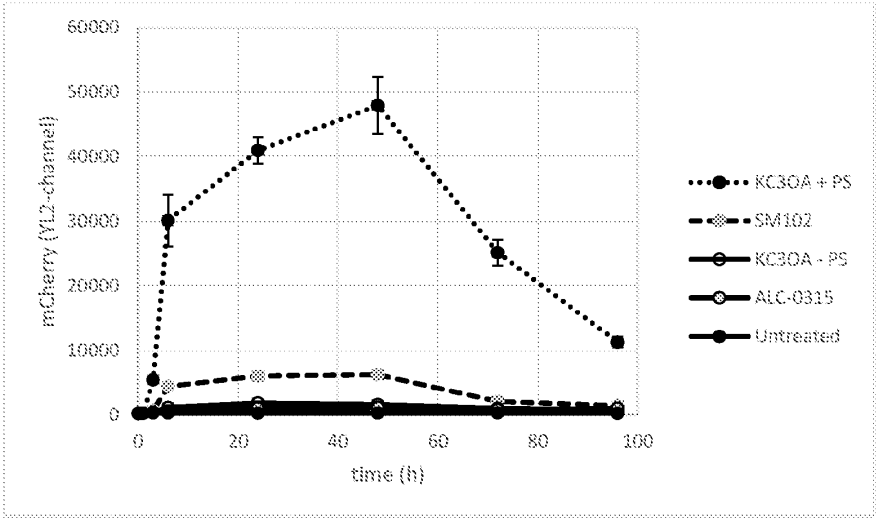

60000
50000
40000
30000
20000
10000
0
mCherry (YL2-channel)
0
20
40
60
80
100
time (h)
KC3OA + PS
SM102
KC3OA - PS
ALC-0315
Untreated

FIG. 34

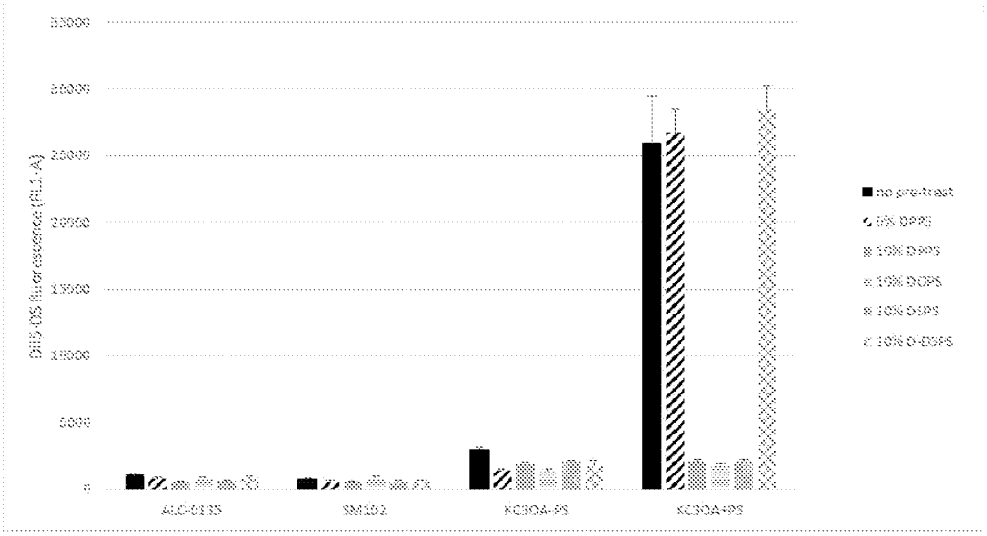


FIG. 35


3h mCherry Expression
mCherry fluorescence (YL2-A)
3500
3000
2500
2000
1500
1000
500
0
UT
NT
DPPS
DSPS
D-DSPS
ICL/PS
UO-1
KC2
KC3OA

FIG. 36

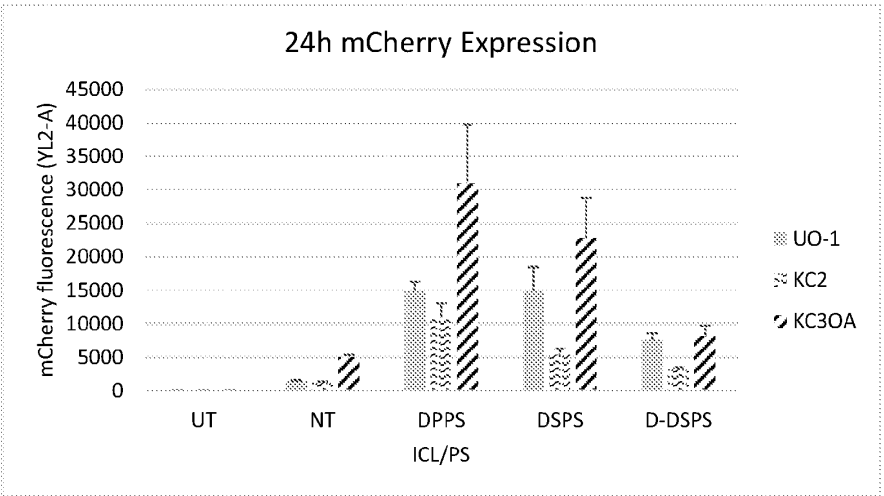

24h mCherry Expression
mCherry fluorescence (YL2-A)
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
UT
NT
DPPS
DSPS
D-DSPS
ICL/PS
UO-1
KC2
KC3OA

FIG. 37

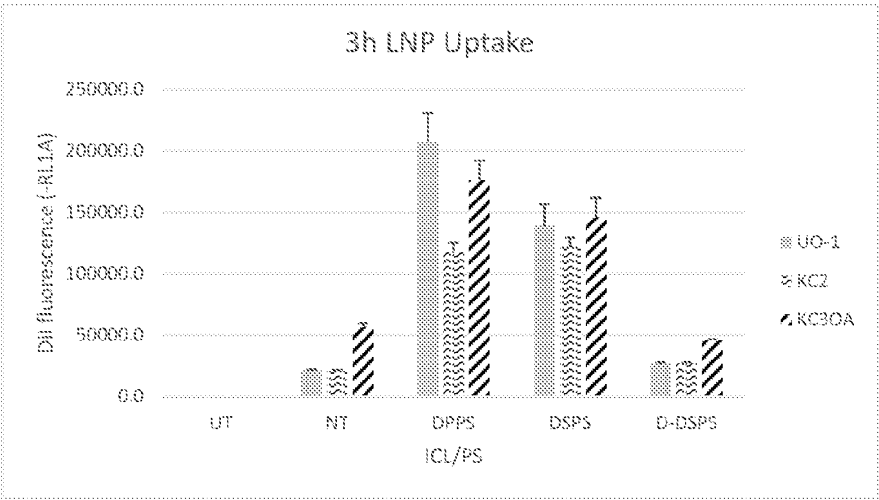

3h LNP Uptake
250000.0
200000.0
150000.0
100000.0
50000.0
0.0
Dil fluorescence (-RL1A)
UT
NT
DPPS
DSPS
D-DSPS
ICL/PS
UO-1
KC2
KC3OA

FIG. 38

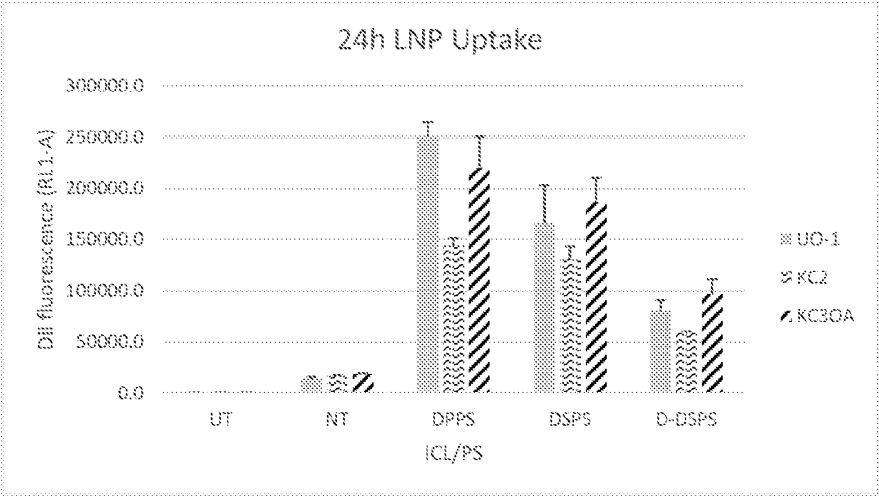

24h LNP Uptake
300000.0
250000.0
200000.0
150000.0
100000.0
50000.0
0.0
Dil fluorescence (RL1-A)
UT
NT
DPPS
DSPS
D-DSPS
ICL/PS
UO-1
KC2
KC3OA

FIG. 39

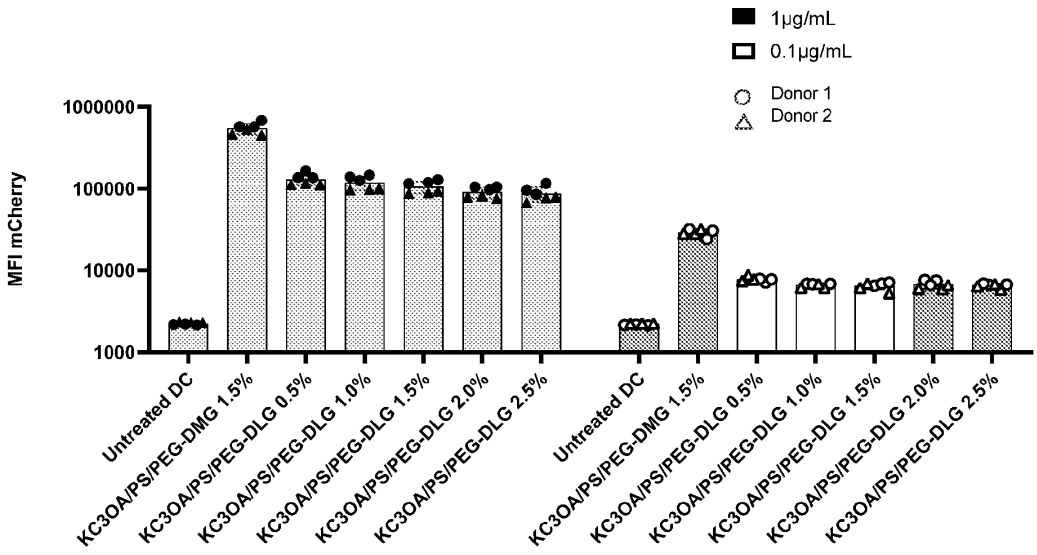

1µg/mL
0.1µg/mL
Donor 1
Donor 2
MFI mCherry
1000000
100000
10000
1000
Untreated DC
KC3OA/PS/PEG-DMG 1.5%
KC3OA/PS/PEG-DLG 0.5%
KC3OA/PS/PEG-DLG 1.0%
KC3OA/PS/PEG-DLG 1.5%
KC3OA/PS/PEG-DLG 2.0%
KC3OA/PS/PEG-DLG 2.5%
Untreated DC
KC3OA/PS/PEG-DMG 1.5%
KC3OA/PS/PEG-DLG 0.5%
KC3OA/PS/PEG-DLG 1.0%
KC3OA/PS/PEG-DLG 1.5%
KC3OA/PS/PEG-DLG 2.0%
KC3OA/PS/PEG-DLG 2.5%

FIG. 40 (After boost)

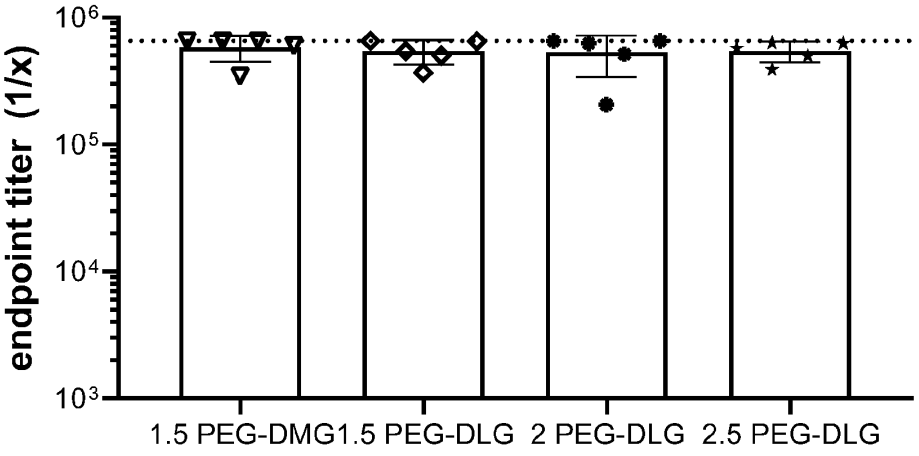


FIG. 41A (all KC3-OA/5 % DPPS and 1 ug dose)

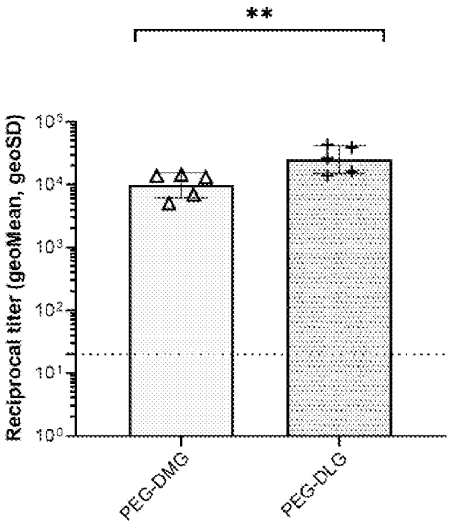


FIG. 41B (2 weeks post boost)

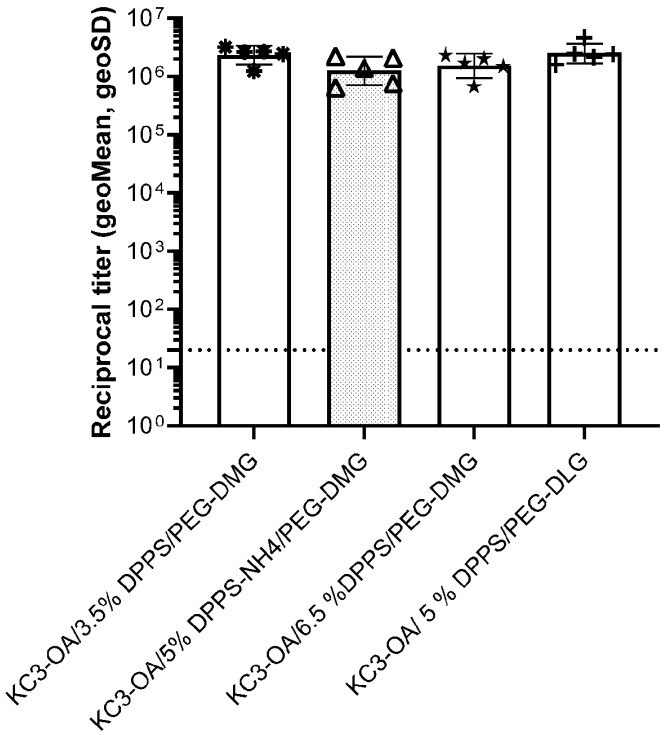


FIG. 42

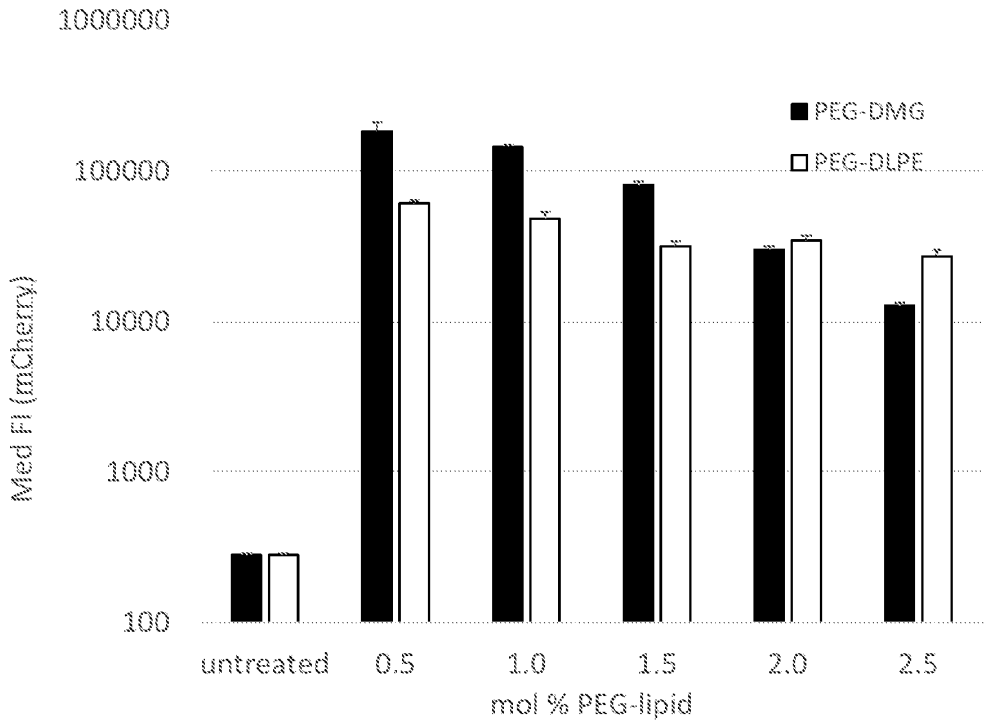

1000000
100000
10000
1000
100
Med FI (mCherry)
PEG-DMG
PEG-DLPE
untreated
0.5
1.0
1.5
2.0
2.5
mol % PEG-lipid

FIG. 43A

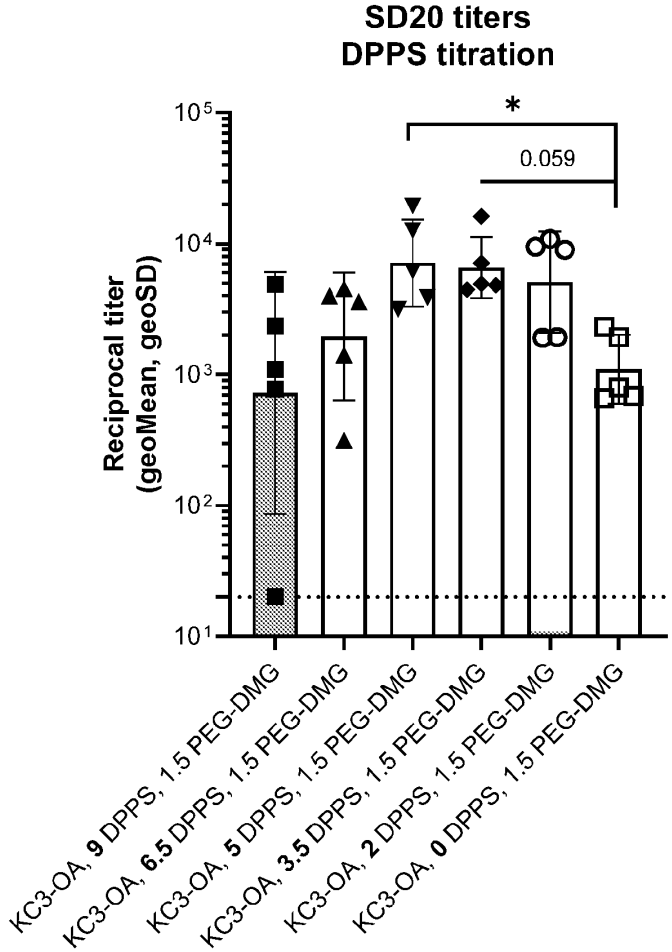

SD20 titers
DPPS titration
Reciprocal titer
(geoMean, geoSD)
10^5
10^4
10^3
10^2
10^1
*
0.059
KC3-OA, 9 DPPS, 1.5 PEG-DMG
KC3-OA, 6.5 DPPS, 1.5 PEG-DMG
KC3-OA, 5 DPPS, 1.5 PEG-DMG
KC3-OA, 3.5 DPPS, 1.5 PEG-DMG
KC3-OA, 2 DPPS, 1.5 PEG-DMG
KC3-OA, 0 DPPS, 1.5 PEG-DMG

FIG. 43B

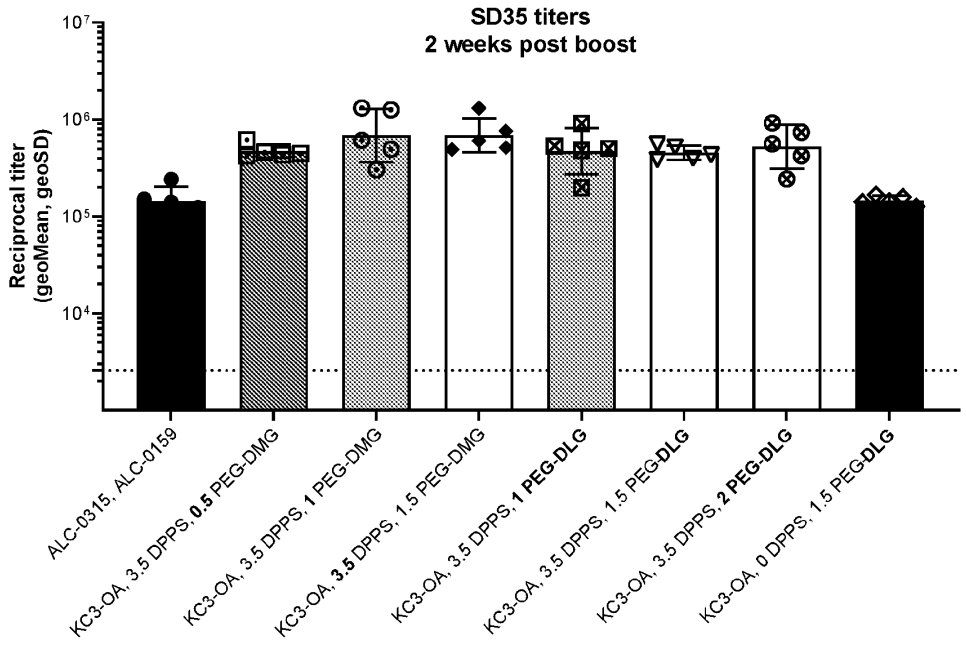


FIG. 43C

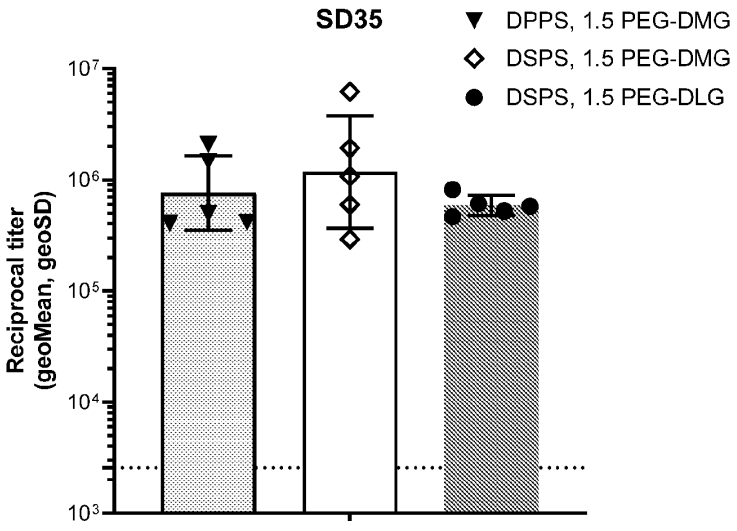


FIG. 44

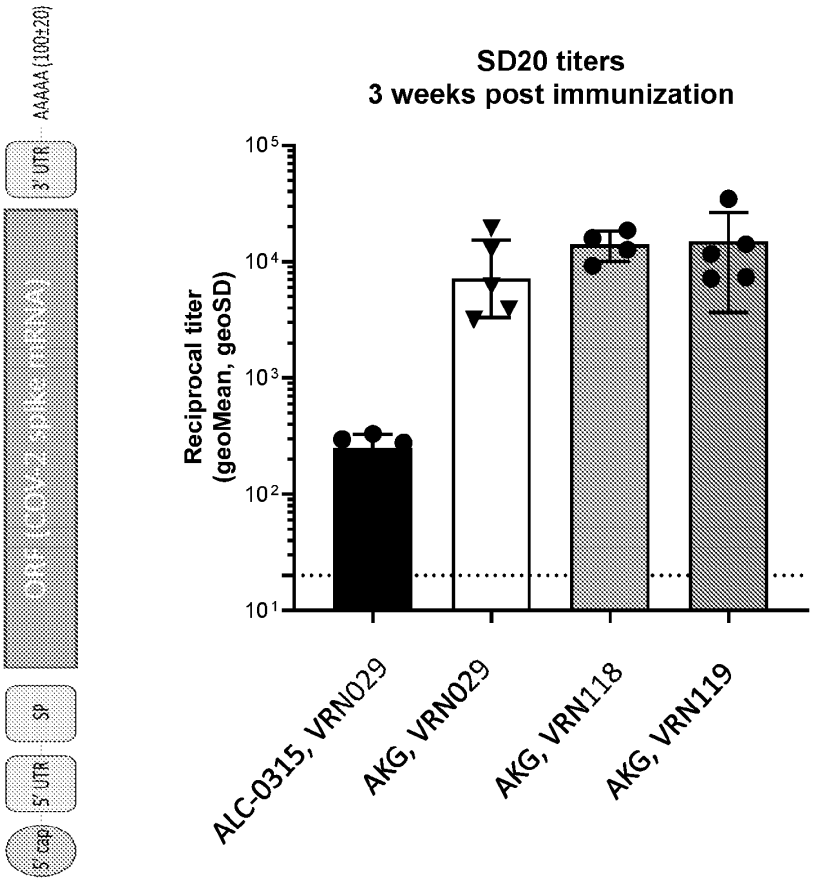

AAAAA (100±20)
3' UTR
ORF (COVID-19 RBD mRNA)
SP
5' UTR
5' cap
SD20 titers
3 weeks post immunization
Reciprocal titer
(geoMean, geoSD)
10^5
10^4
10^3
10^2
10^1
ALC-0315, VRN029
AKG, VRN029
AKG, VRN118
AKG, VRN119

FIG. 45A

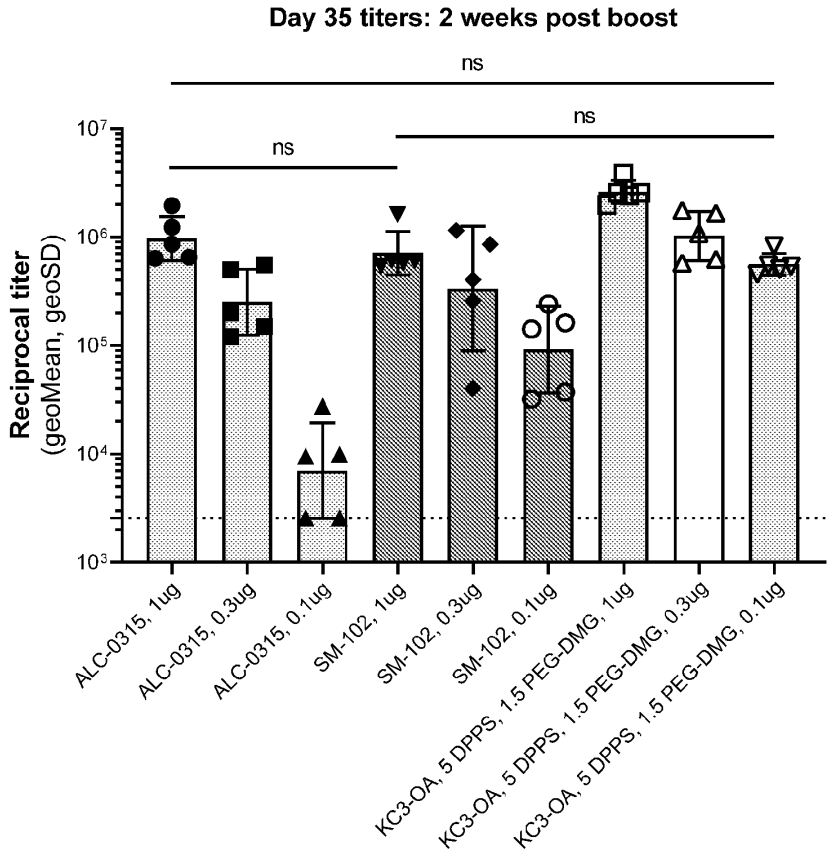

Day 35 titers: 2 weeks post boost
ns
ns
ns
Reciprocal titer
(geoMean, geoSD)
10^7
10^6
10^5
10^4
10^3
ALC-0315, 1ug
ALC-0315, 0.3ug
ALC-0315, 0.1ug
SM-102, 1ug
SM-102, 0.3ug
SM-102, 0.1ug
KC3-OA, 5 DPPS, 1.5 PEG-DMG, 1ug
KC3-OA, 5 DPPS, 1.5 PEG-DMG, 0.3ug
KC3-OA, 5 DPPS, 1.5 PEG-DMG, 0.1ug

FIG. 45B

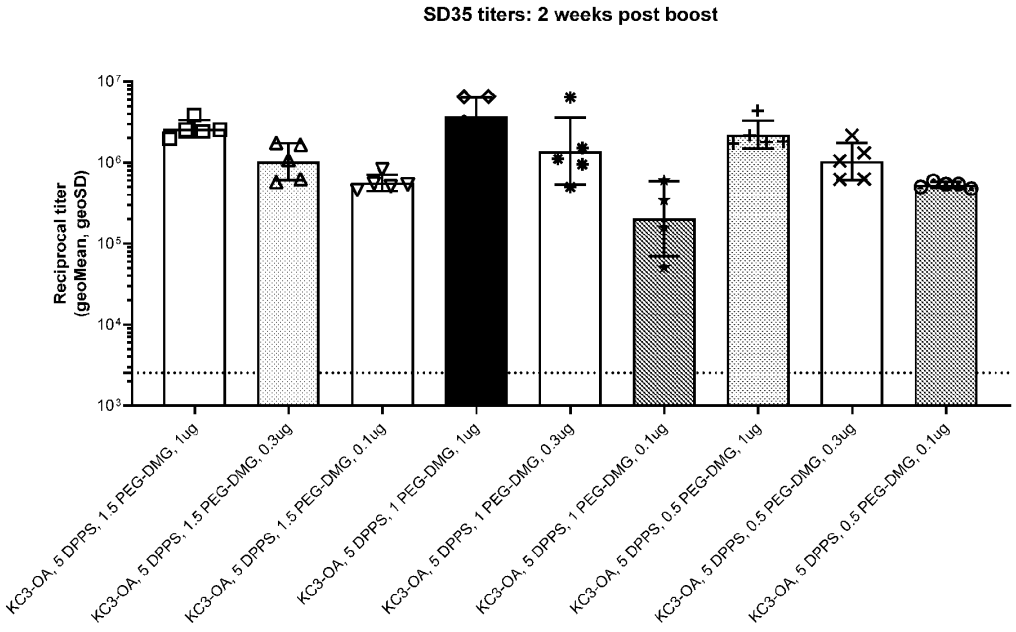

SD35 titers: 2 weeks post boost
Reciprocal titer (geoMean, geoSD)
10^7
10^6
10^5
10^4
10^3
KC3-OA, 5 DPPS, 1.5 PEG-DMG, 1ug
KC3-OA, 5 DPPS, 1.5 PEG-DMG, 0.3ug
KC3-OA, 5 DPPS, 1.5 PEG-DMG, 0.1ug
KC3-OA, 5 DPPS, 1 PEG-DMG, 1ug
KC3-OA, 5 DPPS, 1 PEG-DMG, 0.3ug
KC3-OA, 5 DPPS, 1 PEG-DMG, 0.1ug
KC3-OA, 5 DPPS, 0.5 PEG-DMG, 1ug
KC3-OA, 5 DPPS, 0.5 PEG-DMG, 0.3ug
KC3-OA, 5 DPPS, 0.5 PEG-DMG, 0.1ug

FIG. 46A

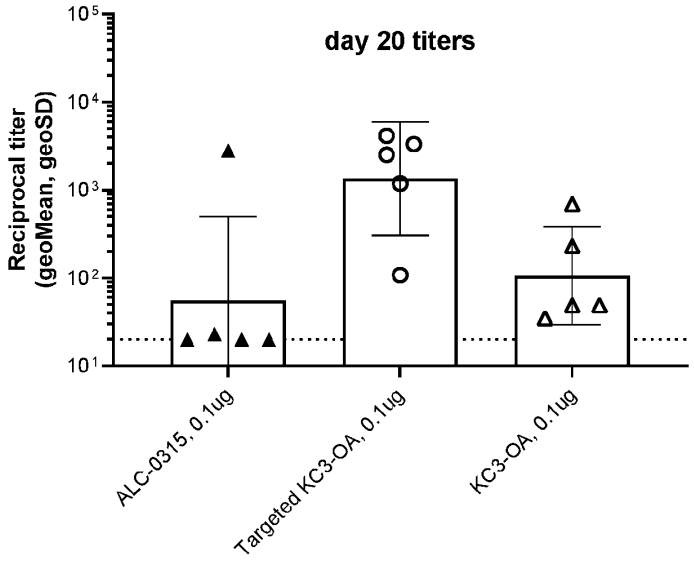
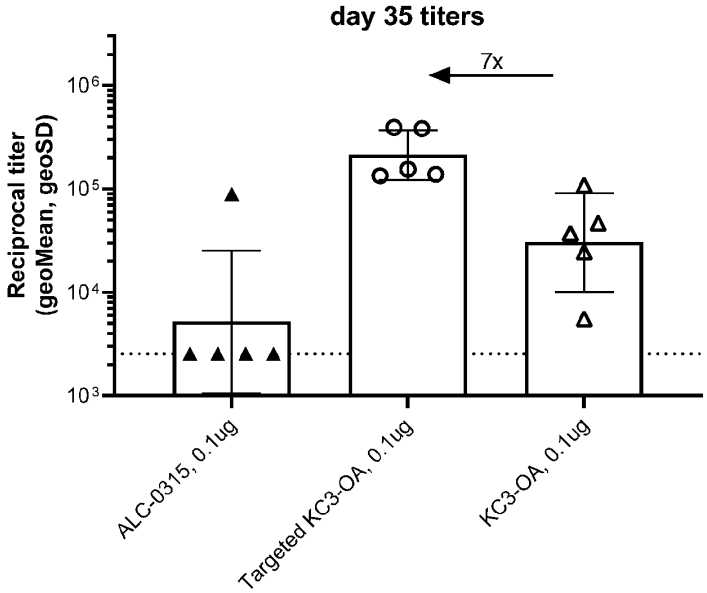


FIG. 46B



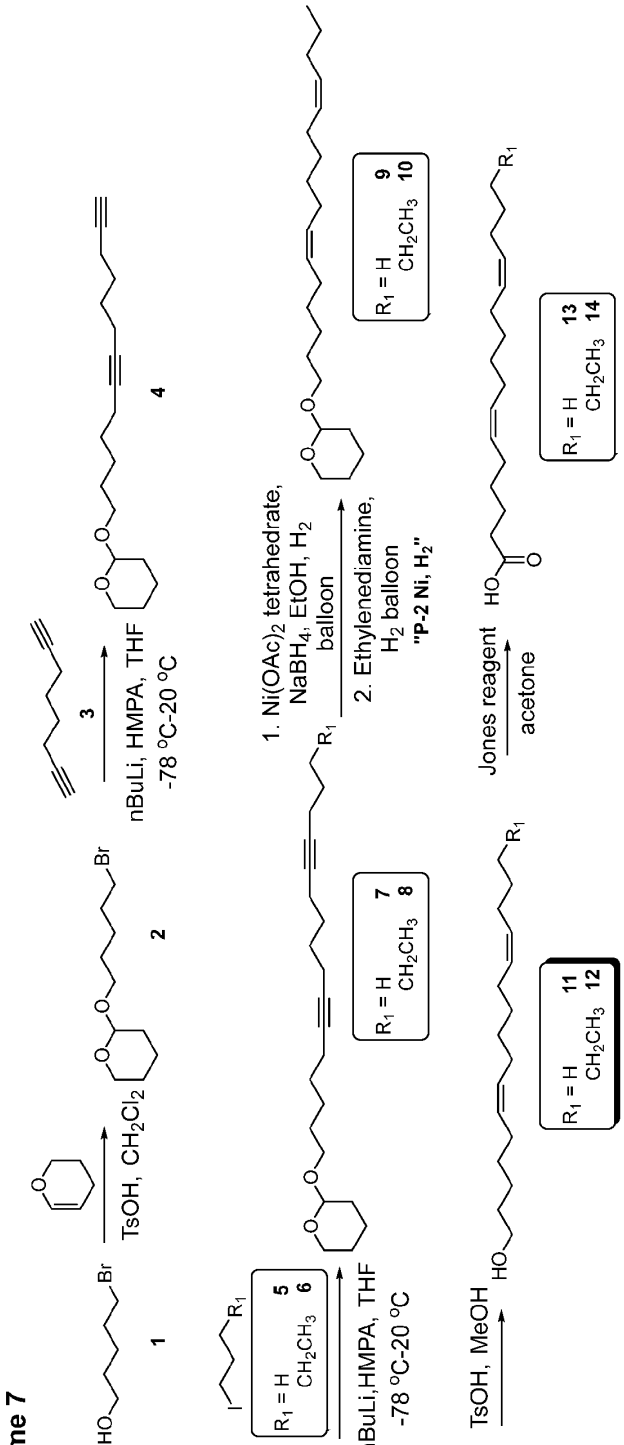
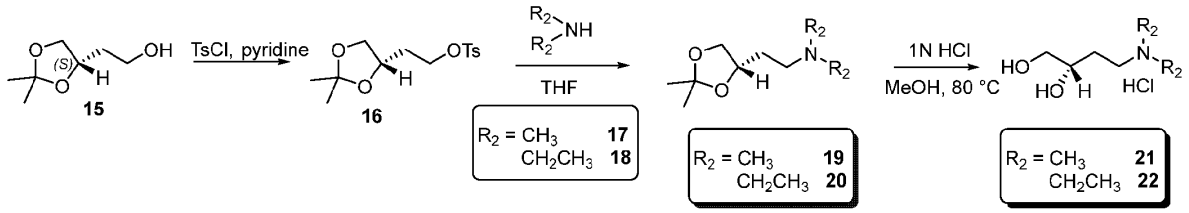
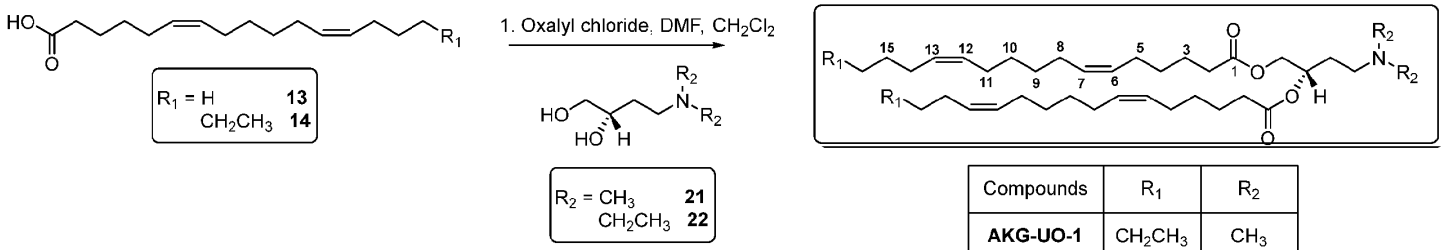

Scheme 7
HO
Br
1
TsOH, CH_2Cl_2
2
nBuLi, HMPA, THF
-78 °C-20 °C
3
4
I
R_1
R_1 = H 5
CH_2CH_3 6
nBuLi,HMPA, THF
-78 °C-20 °C
R_1 = H 7
CH_2CH_3 8
1. $Ni(OAc)_2$ tetrahedrate,
$NaBH_4$, EtOH, H_2
balloon
2. Ethylenediamine,
H_2 balloon
"P-2 Ni, H_2"
R_1 = H 9
CH_2CH_3 10
TsOH, MeOH
R_1 = H 11
CH_2CH_3 12
Jones reagent
acetone
R_1 = H 13
CH_2CH_3 14

FIG. 47A

Scheme 8



Scheme 9



Compounds	R_1	R_2
AKG-UO-1	CH_2CH_3	CH_3
AKG-UO-1A	CH_2CH_3	CH_2CH_3
AKG-UO-4	H	CH_3
AKG-UO-4A	H	CH_2CH_3

FIG. 47B

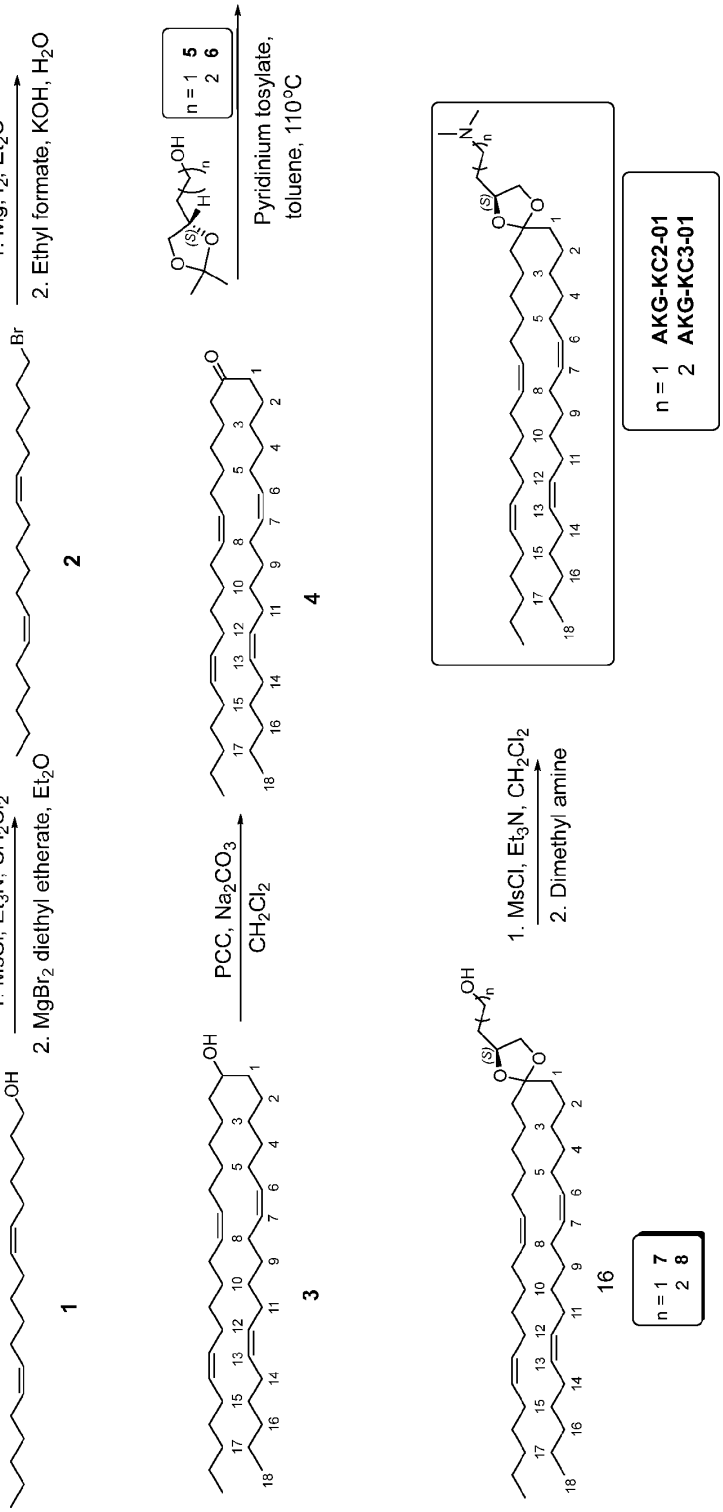
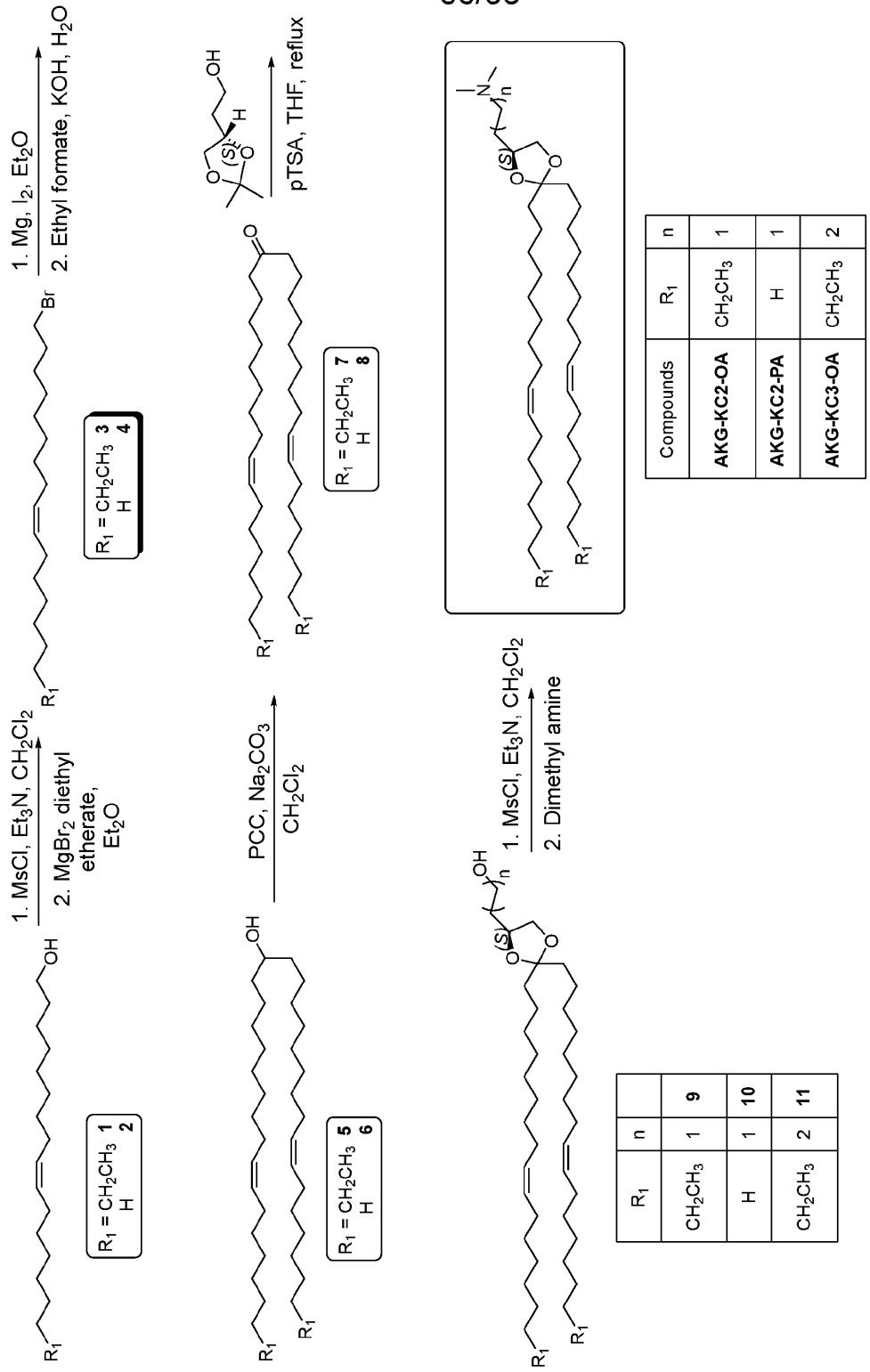

1. MsCl, Et3N, CH2Cl2
2. MgBr2 diethyl etherate, Et2O
1. Mg, I2, Et2O
2. Ethyl formate, KOH, H2O
PCC, Na2CO3
CH2Cl2
Pyridinium tosylate,
toluene, 110°C
n = 1 5
2 6
1. MsCl, Et3N, CH2Cl2
2. Dimethyl amine
n = 1 AKG-KC2-01
2 AKG-KC3-01
n = 1 7
2 8
1
2
3
4
16

FIG. 48



R_1	n	
CH_2CH_3	1	**9**
H	1	**10**
CH_2CH_3	2	**11**

Compounds	R_1	n
AKG-KC2-OA	CH_2CH_3	1
AKG-KC2-PA	H	1
AKG-KC3-OA	CH_2CH_3	2

FIG. 49

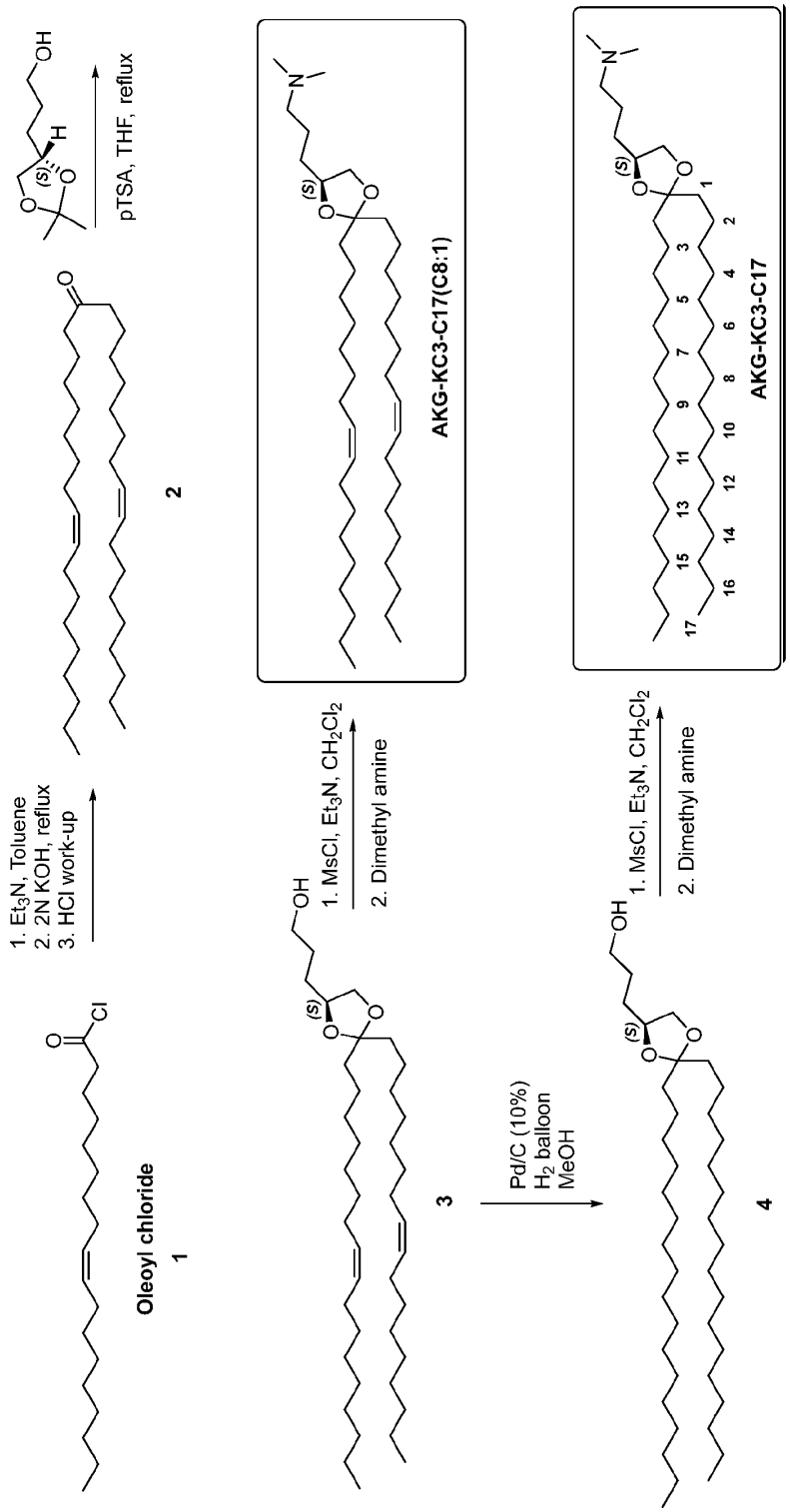

1. Et3N, Toluene
2. 2N KOH, reflux
3. HCl work-up
Oleoyl chloride
1
2
pTSA, THF, reflux
1. MsCl, Et3N, CH2Cl2
2. Dimethyl amine
AKG-KC3-C17(C8:1)
3
Pd/C (10%)
H2 balloon
MeOH
4
1. MsCl, Et3N, CH2Cl2
2. Dimethyl amine
AKG-KC3-C17

FIG. 50

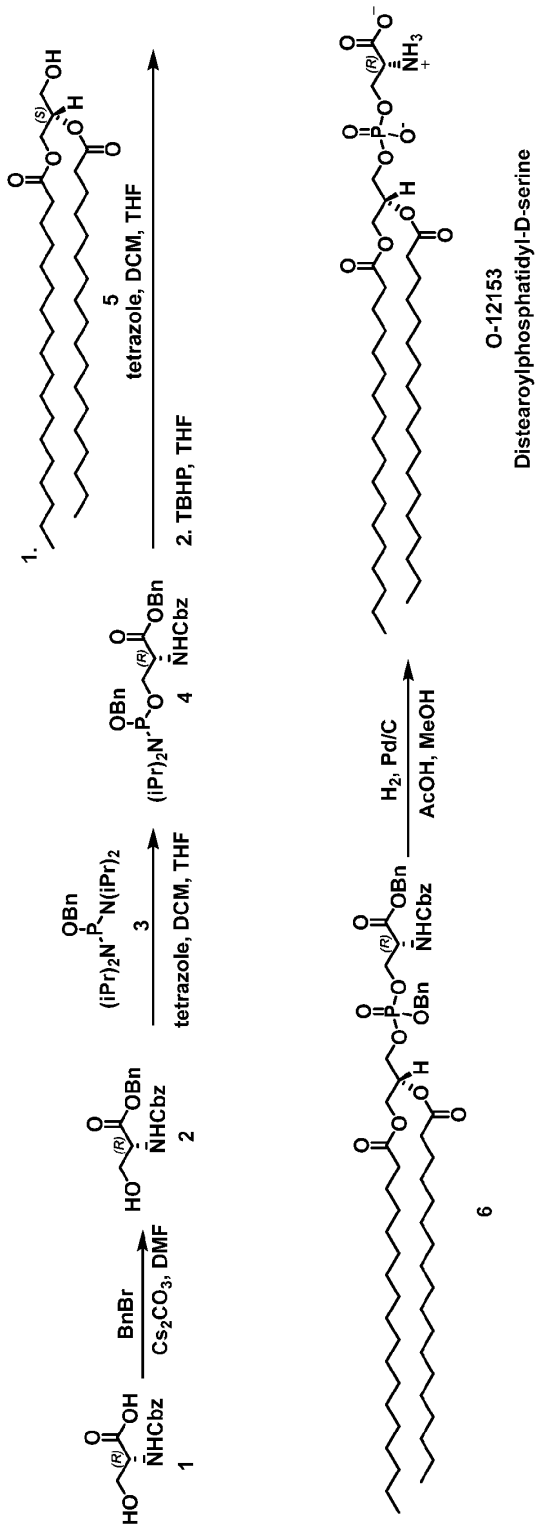

BnBr
Cs_2CO_3, DMF
1
2
tetrazole, DCM, THF
3
4
1.
5
tetrazole, DCM, THF
2. TBHP, THF
6
H_2, Pd/C
AcOH, MeOH
O-12153
Distearoylphosphatidyl-D-serine

FIG. 51