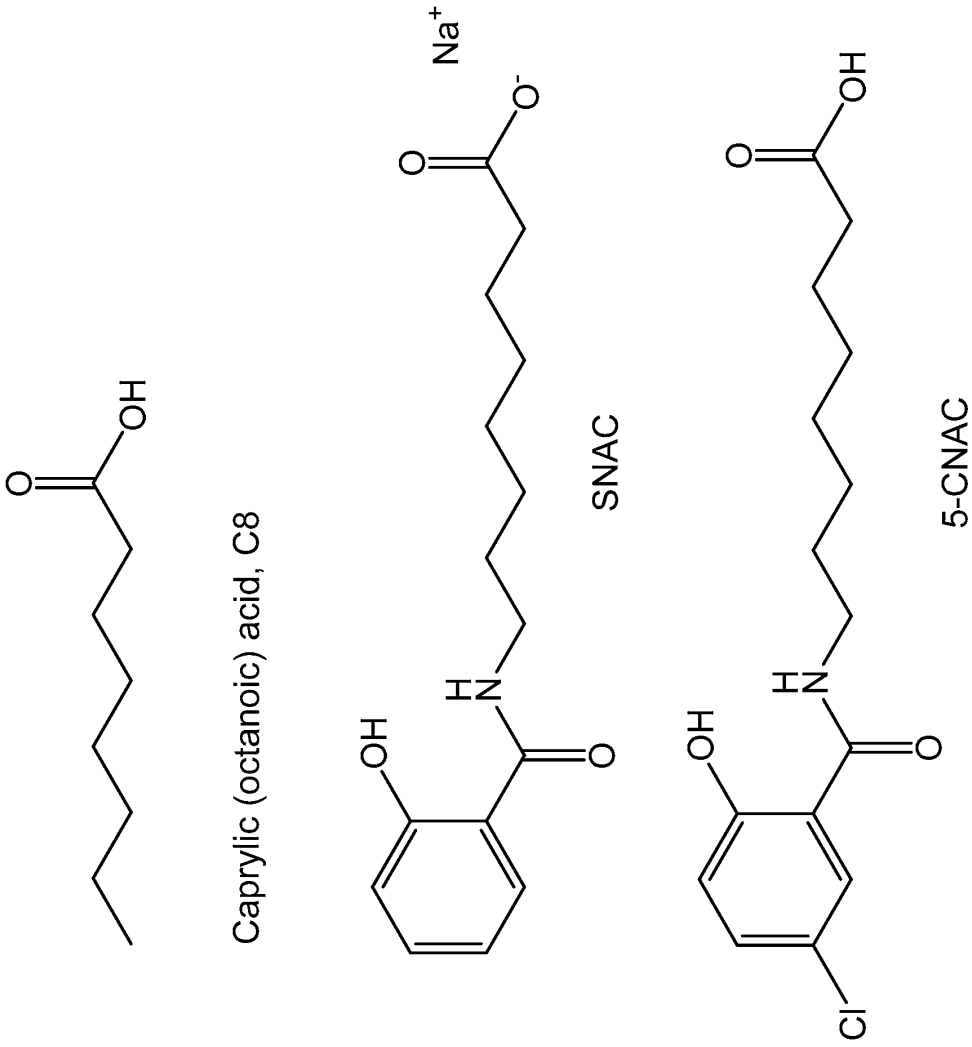
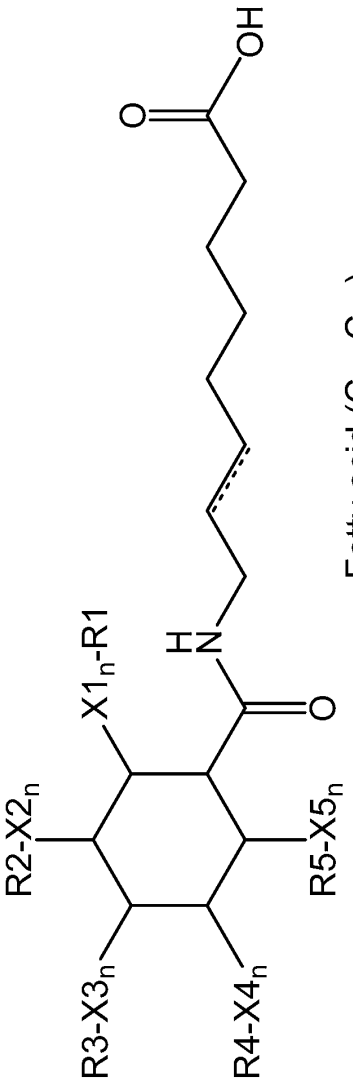


FIG. 1A



- The ring comprises at least one fatty acid substituent between C_6 and C_{12}, e.g., C_8, and at least two polar group substituents, wherein:
  - At least one of R1..R5 comprises or consists of a halogen group (e.g., F, Cl, or Br)
  - At least one of R1..R5 comprises or consists of an OH group
- At least two of R1..R5 are not H
- X1 to X5 are alkyl spacers, e.g., CH_2, wherein n is independently between 0 and 5

FIG. 1B

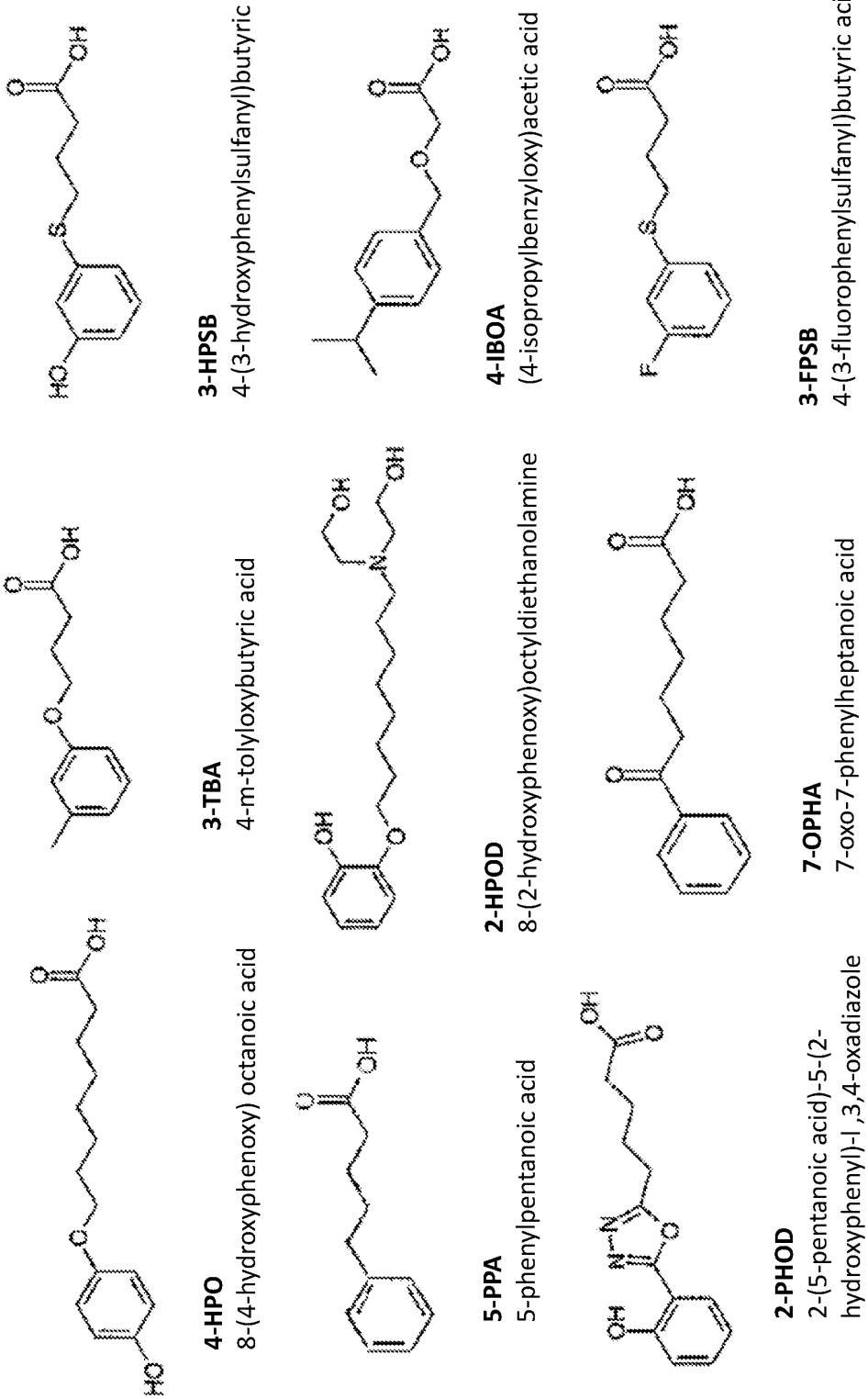
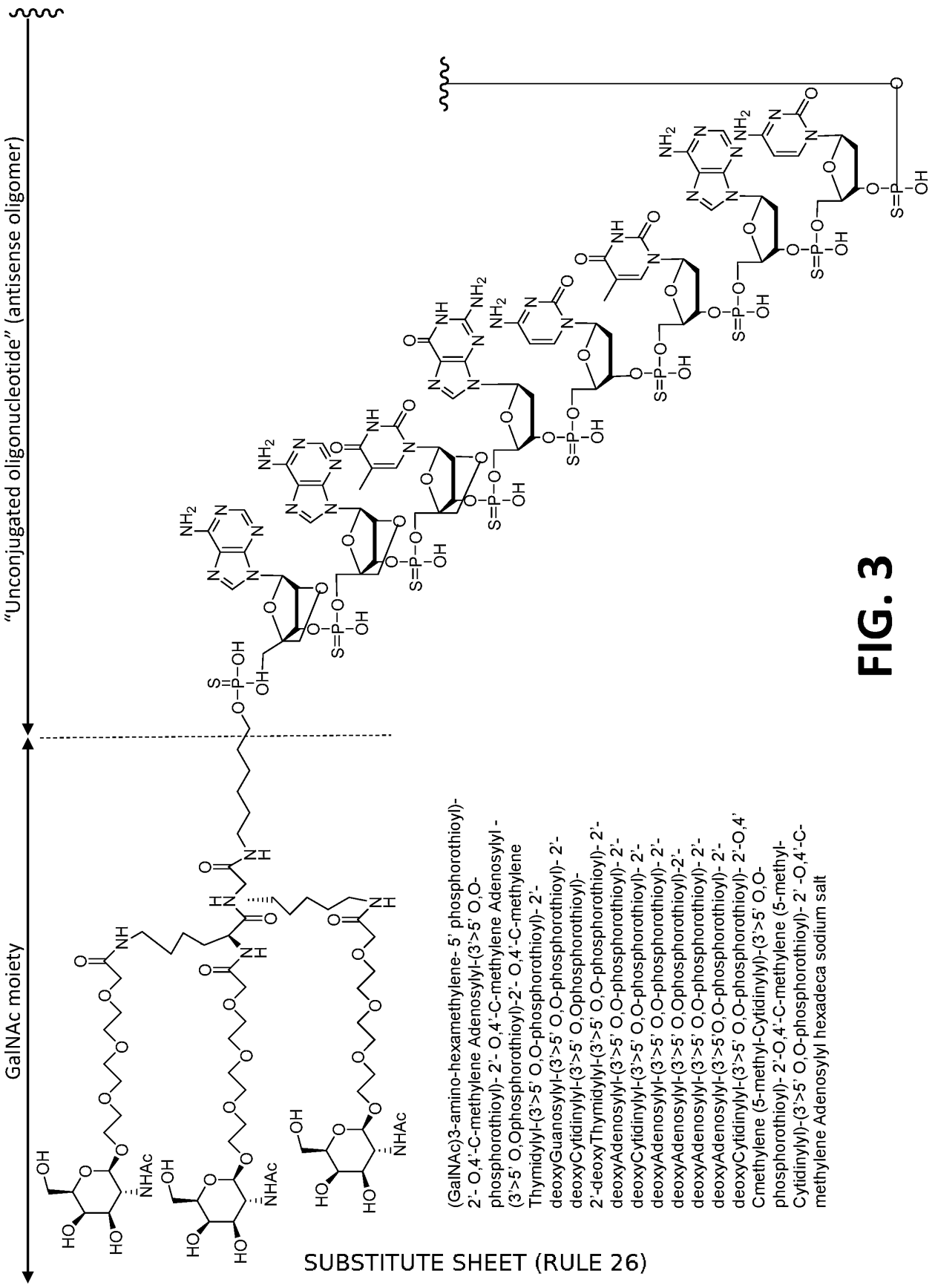

4-HPO
8-(4-hydroxyphenoxy) octanoic acid
3-TBA
4-m-tolyloxybutyric acid
3-HPSB
4-(3-hydroxyphenylsulfanyl)butyric acid
5-PPA
5-phenylpentanoic acid
2-HPOD
8-(2-hydroxyphenoxy)octyldiethanolamine
4-IBOA
(4-isopropylbenzyloxy)acetic acid
2-PHOD
2-(5-pentanoic acid)-5-(2-hydroxyphenyl)-l ,3,4-oxadiazole
7-OPHA
7-oxo-7-phenylheptanoic acid
3-FPSB
4-(3-fluorophenylsulfanyl)butyric acid

FIG. 2



(GalNAc)3-amino-hexamethylene- 5' phosphorothioyl)-2'- O,4'-C-methylene Adenosylyl-(3'>5' O,O-phosphorothioyl)- 2'- O,4'-C-methylene Adenosylyl -(3'>5' O,Ophosphorothioyl)-2'- O,4'-C-methylene Thymidylyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyGuanosylyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyCytidinylyl-(3'>5' O,Ophosphorothioyl)-2'-deoxyThymidylyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyAdenosylyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyCytidinylyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyAdenosylyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyAdenosylyl-(3'>5' O,Ophosphorothioyl)-2'-deoxyAdenosylyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyAdenosylyl-(3'>5'O,O-phosphorothioyl)- 2'-deoxyCytidinylyl-(3'>5' O,O-phosphorothioyl)- 2'-O,4' Cmethylene (5-methyl-Cytidinylyl)-(3'>5' O,O-phosphorothioyl)- 2'-O,4'-C-methylene (5-methyl-Cytidinylyl)-(3'>5' O,O-phosphorothioyl)- 2' -O,4'-C-methylene Adenosylyl hexadeca sodium salt

FIG. 3

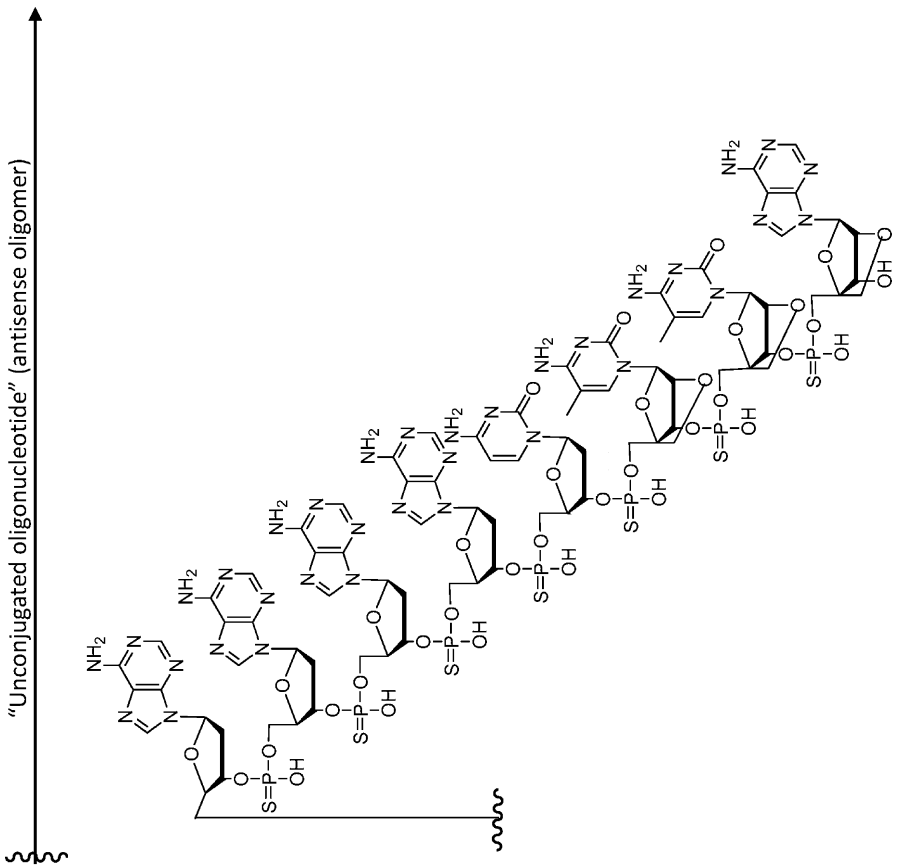
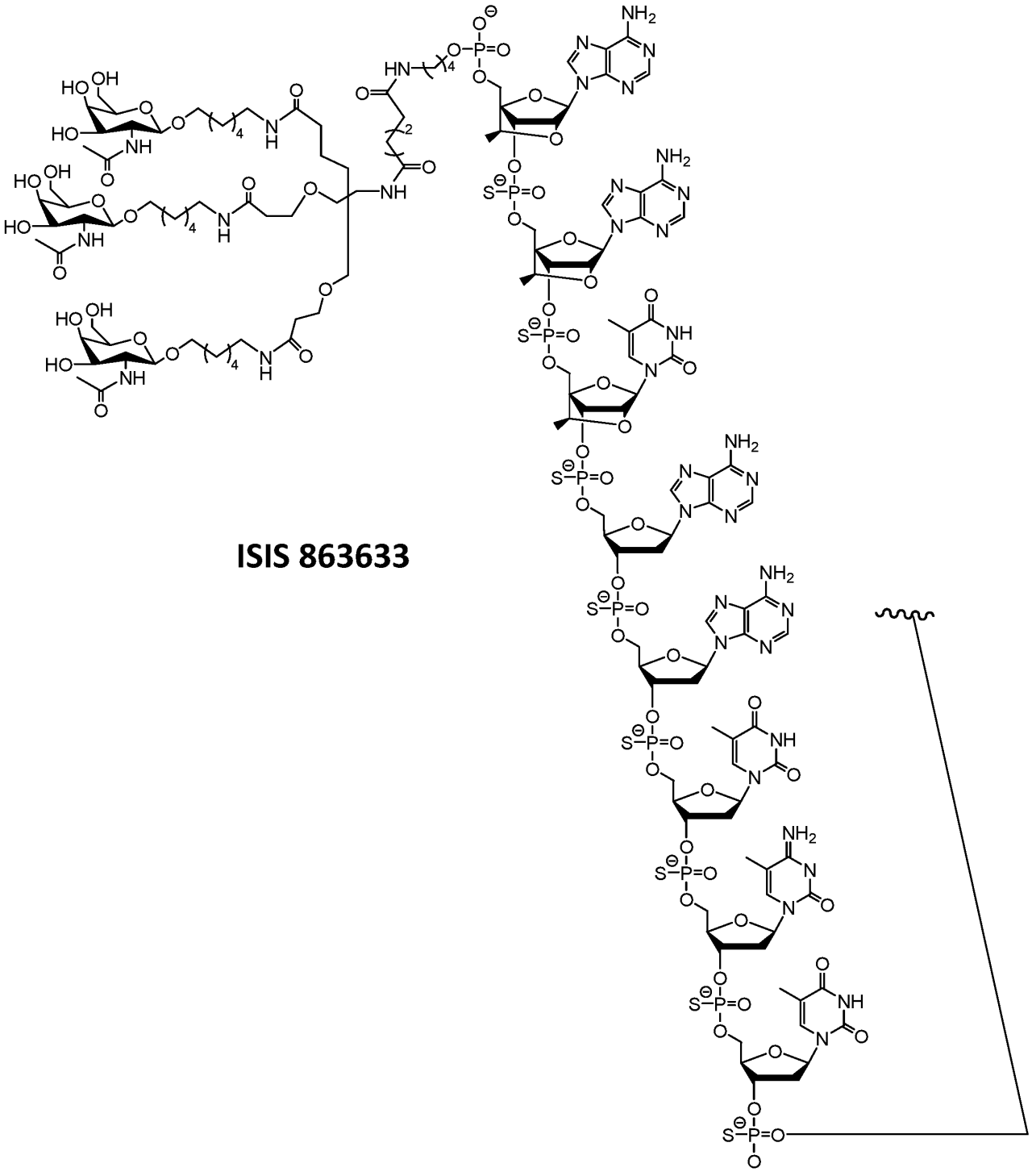

"Unconjugated oligonucleotide" (antisense oligomer)
Cepadacursen

FIG. 3



ISIS 863633

FIG. 4

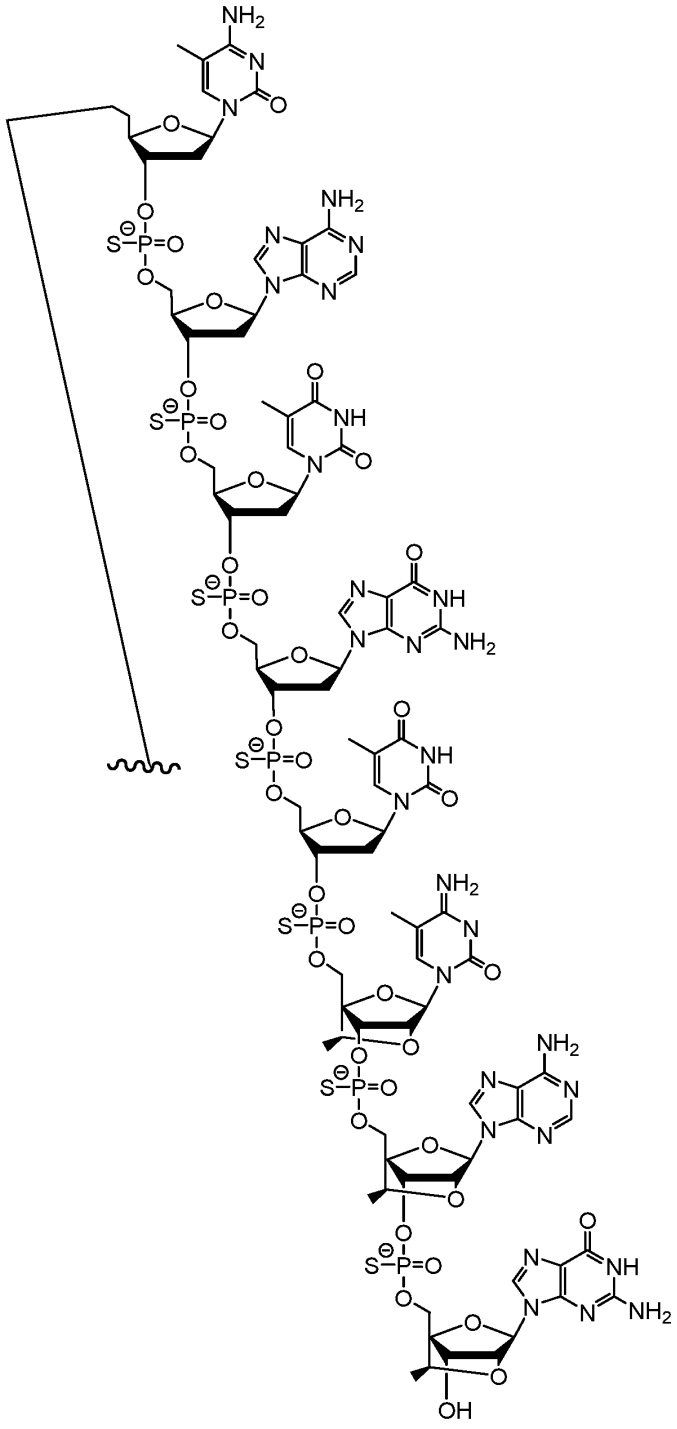


FIG. 4

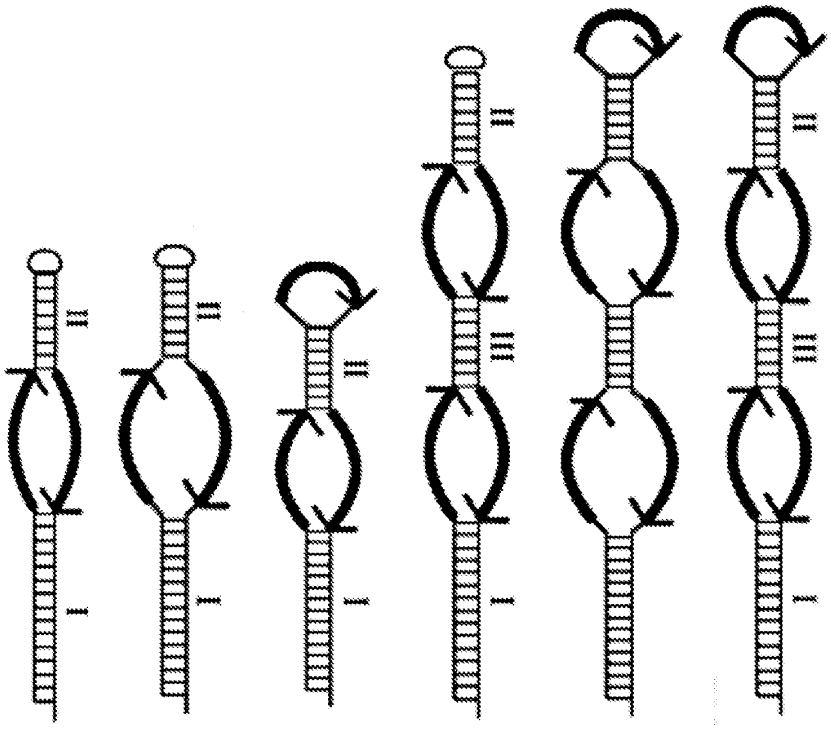
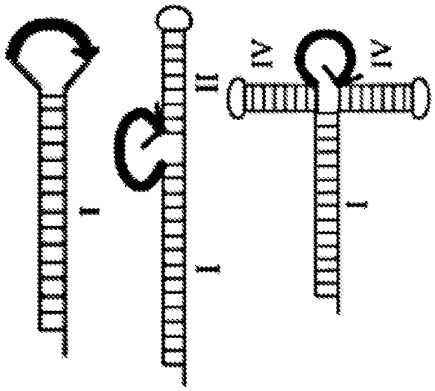


FIG. 5



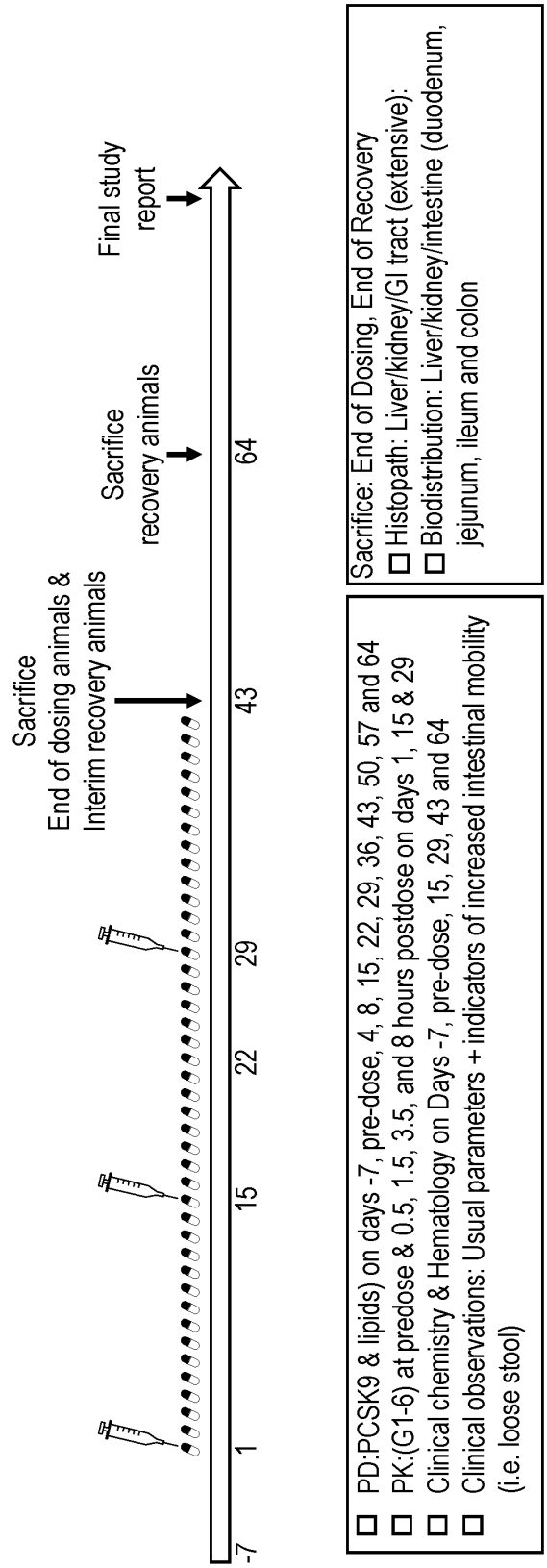

Sacrifice
End of dosing animals &
Interim recovery animals
Sacrifice
recovery animals
Final study
report
-7
1
15
22
29
43
64
PD:PCSK9 & lipids) on days -7, pre-dose, 4, 8, 15, 22, 29, 36, 43, 50, 57 and 64
PK:(G1-6) at predose & 0.5, 1.5, 3.5, and 8 hours postdose on days 1, 15 & 29
Clinical chemistry & Hematology on Days -7, pre-dose, 15, 29, 43 and 64
Clinical observations: Usual parameters + indicators of increased intestinal mobility (i.e. loose stool)
Sacrifice: End of Dosing, End of Recovery
Histopath: Liver/kidney/GI tract (extensive):
Biodistribution: Liver/kidney/intestine (duodenum, jejunum, ileum and colon

FIG. 6

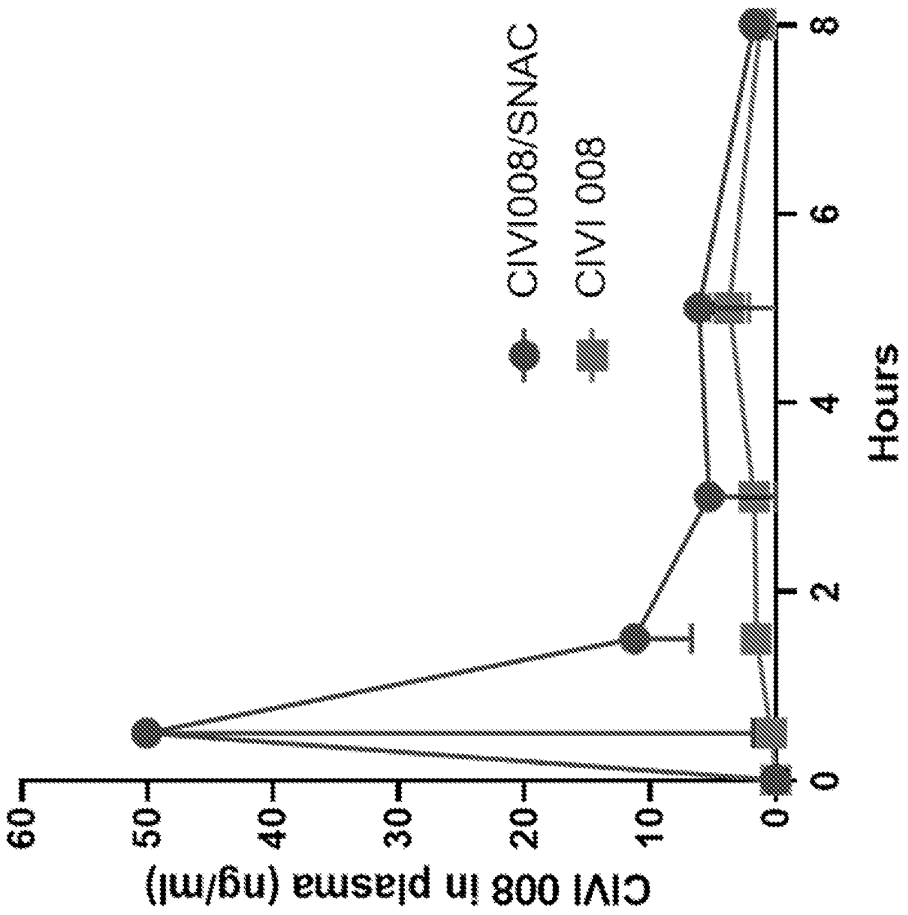

CIVI008/SNAC
CIVI 008
CIVI 008 in plasma (ng/ml)
0
10
20
30
40
50
60
0
2
4
6
8
Hours

FIG. 7

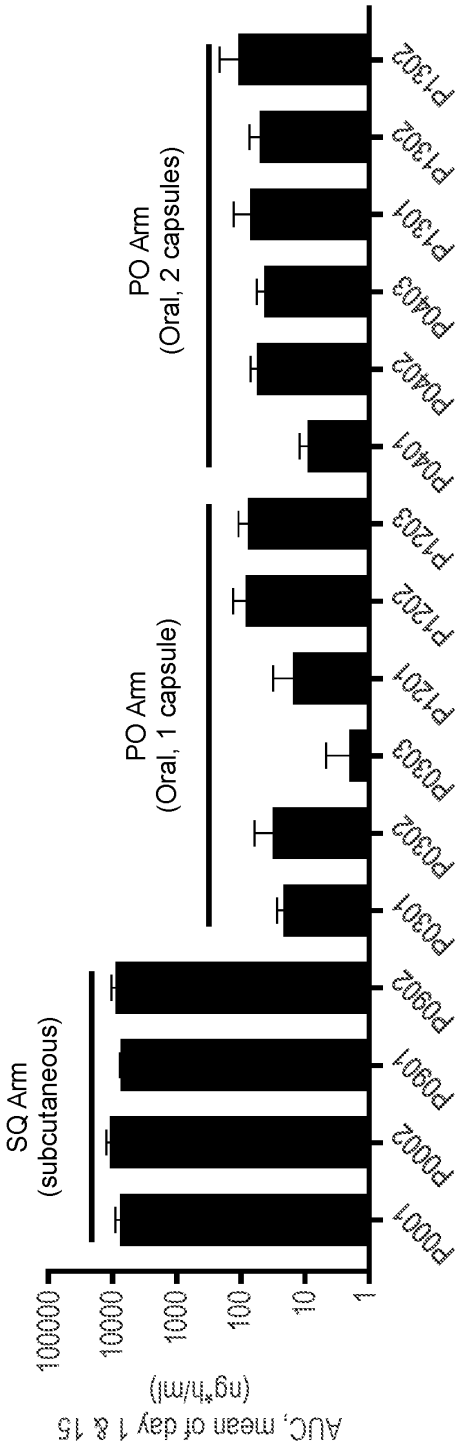

AUC, mean of day 1 & 15
(ng*h/ml)
100000
10000
1000
100
10
1
SQ Arm
(subcutaneous)
PO Arm
(Oral, 1 capsule)
PO Arm
(Oral, 2 capsules)
P0001
P0002
P0901
P0902
P0301
P0302
P0303
P1201
P1202
P1203
P0401
P0402
P0403
P1301
P1302
P1302

FIG. 8

Dose group	End of dosing (µg/gram tissue)	End of recovery (µg/gram tissue)
SQ Q2W x 3	33.8 (19.1)	N.A.
1 capsule QD x 42	2.3 (1.2)	0.6 (0.2)
2 capsules QD x 42	4.0 (1.6)	0.9 (0.7)

FIG. 9

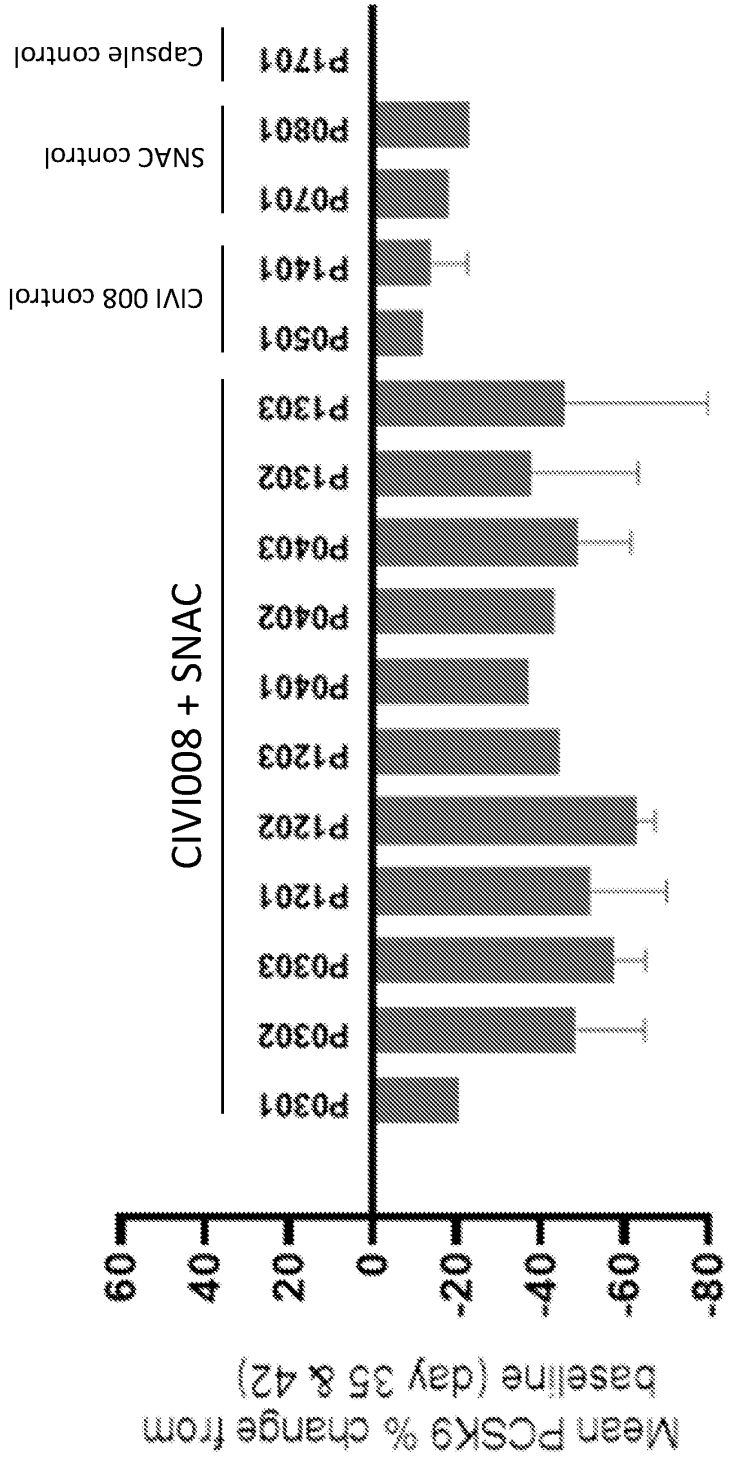

Mean PCSK9 % change from baseline (day 35 & 42)
60
40
20
0
-20
-40
-60
-80
CIVI008 + SNAC
P0301
P0302
P0303
P1201
P1202
P1203
P0401
P0402
P0403
P1302
P1303
CIVI 008 control
P0501
P1401
SNAC control
P0701
P0801
Capsule control
P1701

FIG. 10

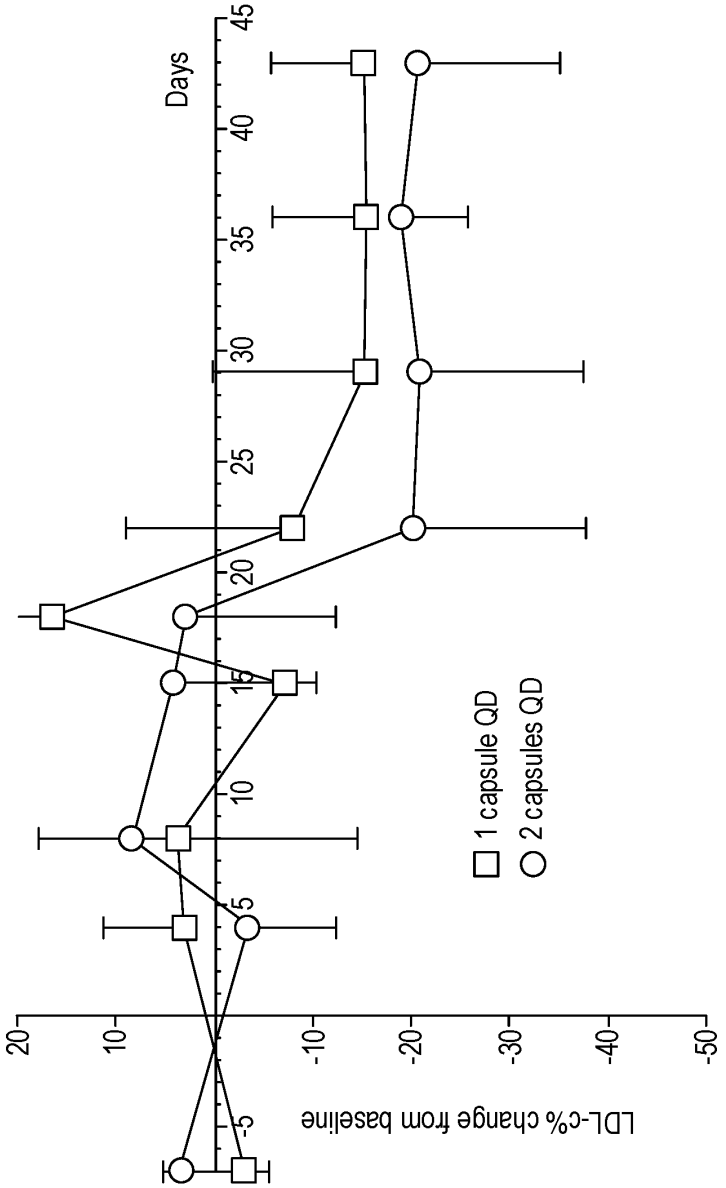

Days
45
40
35
30
25
20
15
10
5
20
10
-5
-10
-20
-30
-40
-50
LDL-c% change from baseline
1 capsule QD
2 capsules QD

FIG. 11A

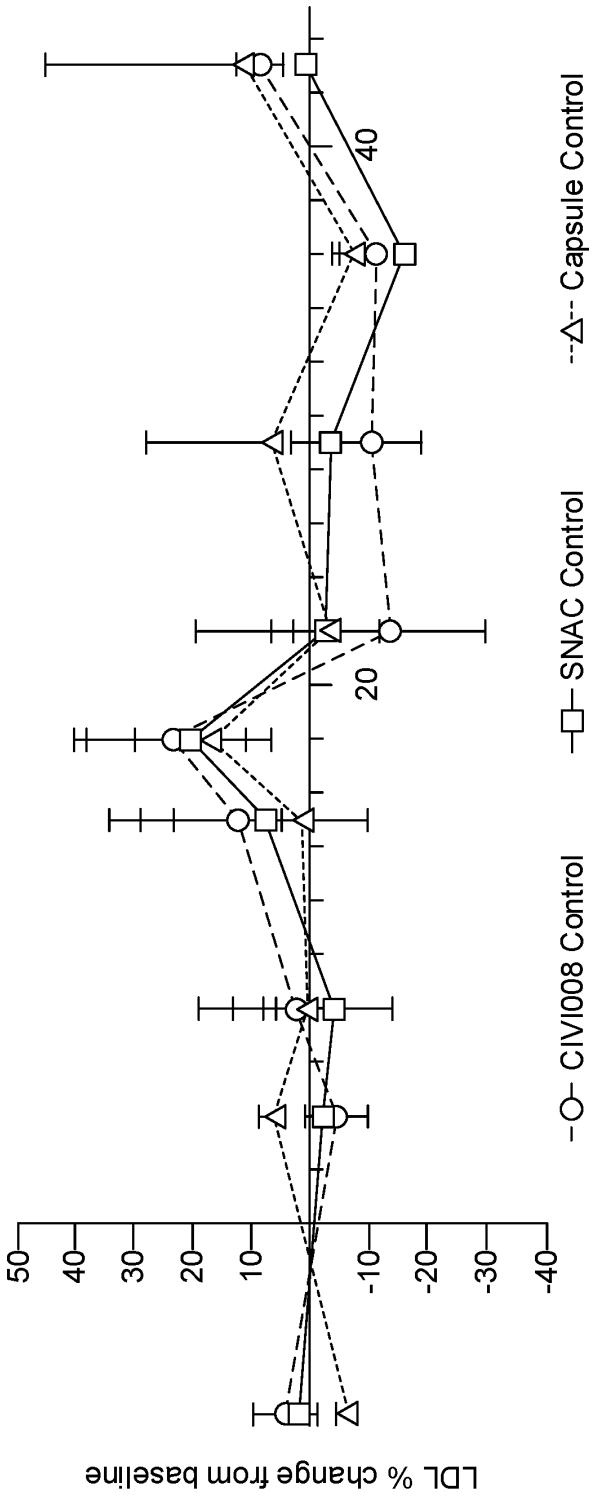

LDL % change from baseline
50
40
30
20
10
-10
-20
-30
-40
20
40
CIVI008 Control
SNAC Control
Capsule Control

FIG. 11B

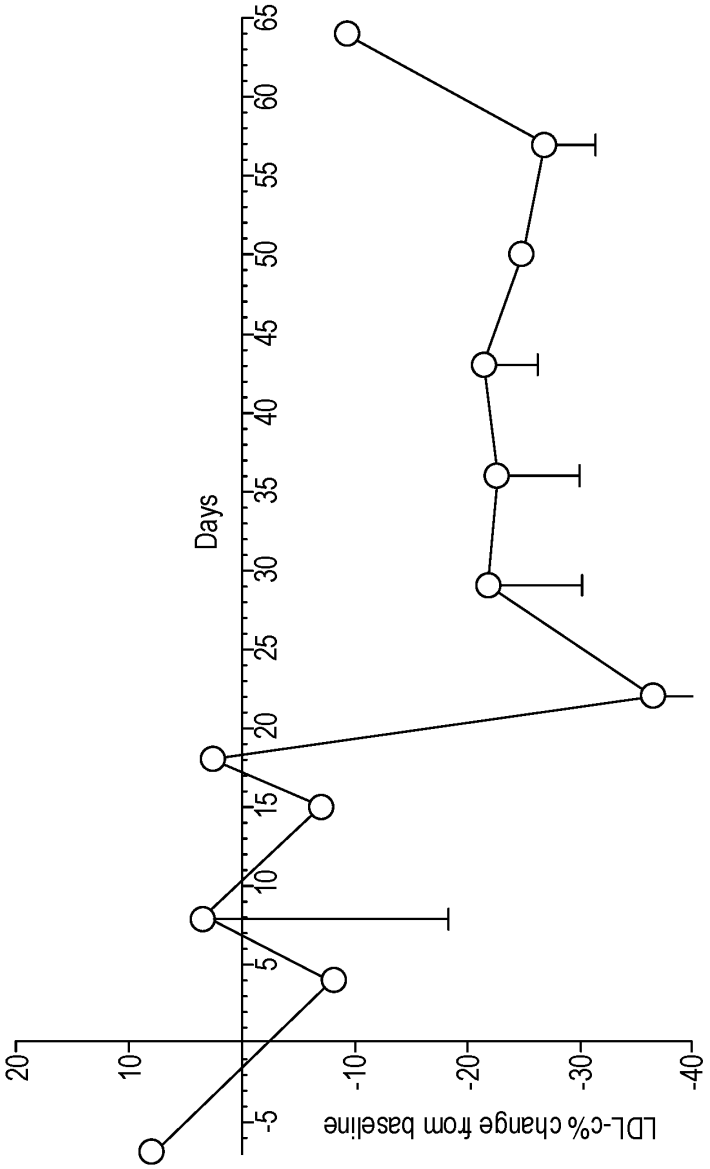

LDL-c% change from baseline
20
10
-5
-10
-20
-30
-40
Days
5
10
15
20
25
30
35
40
45
50
55
60
65

FIG. 12

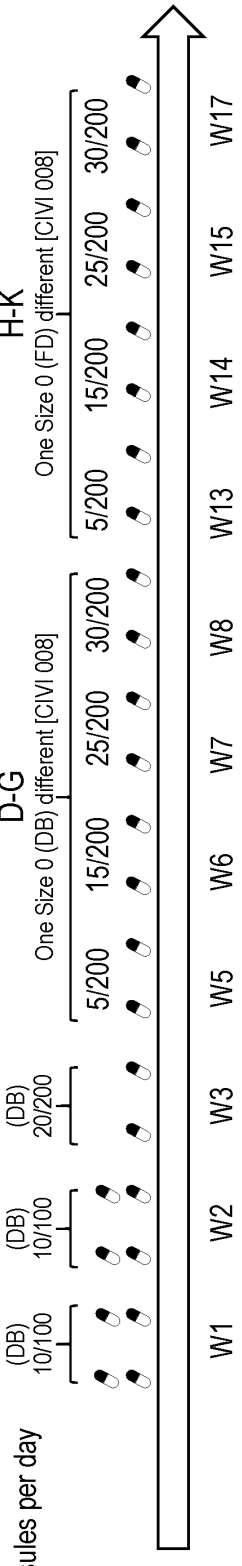

A
Two Size 4 (DB) 10/100
B
Two Size 0 (DB) 10/100
C
One Size 0 (DB) 20/200
D-G
One Size 0 (DB) different [CIVI 008]
5/200
15/200
25/200
30/200
H-K
One Size 0 (FD) different [CIVI 008]
5/200
15/200
25/200
30/200
Capsules per day
W1
W2
W3
W5
W6
W7
W8
W13
W14
W15
W17
Animals: 10 non-naive HNPs (5m/5F)
PK: at pre-dose & 0.5, 1.5, 3 and 5 hours post dose on dosing days
Clinical observations: Twice weekly
Clinical chemistry: days -7 and end of dosing

FIG. 13

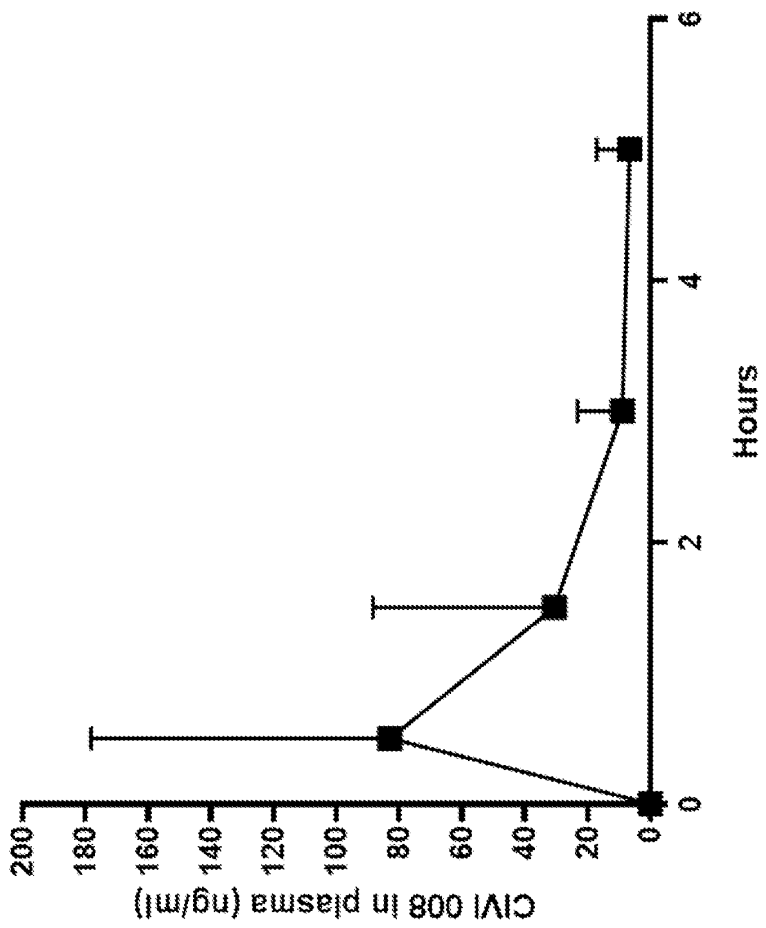
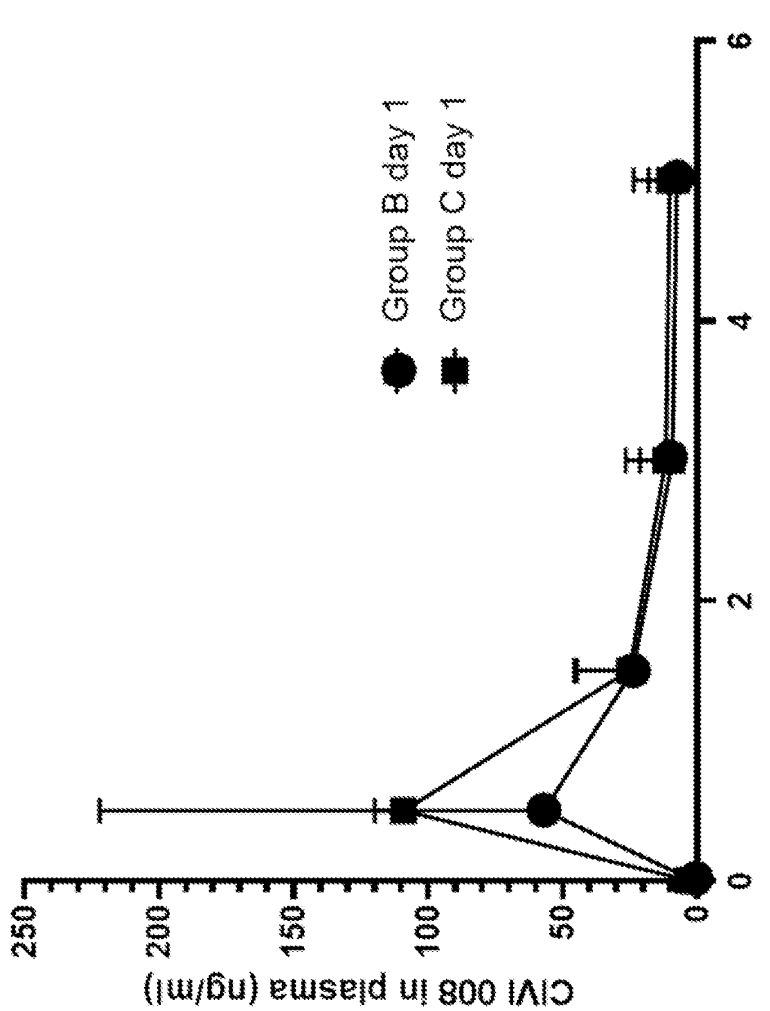

CIVI 008 in plasma (ng/ml)
200
180
160
140
120
100
80
60
40
20
0
0
2
4
6
Hours

FIG. 14

	No. animals	Mean AUC_{0-5} (ng*ml*h)	SD	Mean C_{max} (ng/ml)	SD
CIVI008/SNAC	6	67.1	50.7	50,7	52,3
CIVI008/5-CNAC	10	122,5	98.6	106.9	91.2

FIG. 15



	No. Capsules	No. Animals	Mean AUC_{0-5} (ng*ml*h)	SD	Mean C_{max} (ng/ml)	SD
Group B	2	10	97.0	87.9	60.8	64.6
Group C	1	10	144.8	101.2	116.9	114.1

FIG. 16

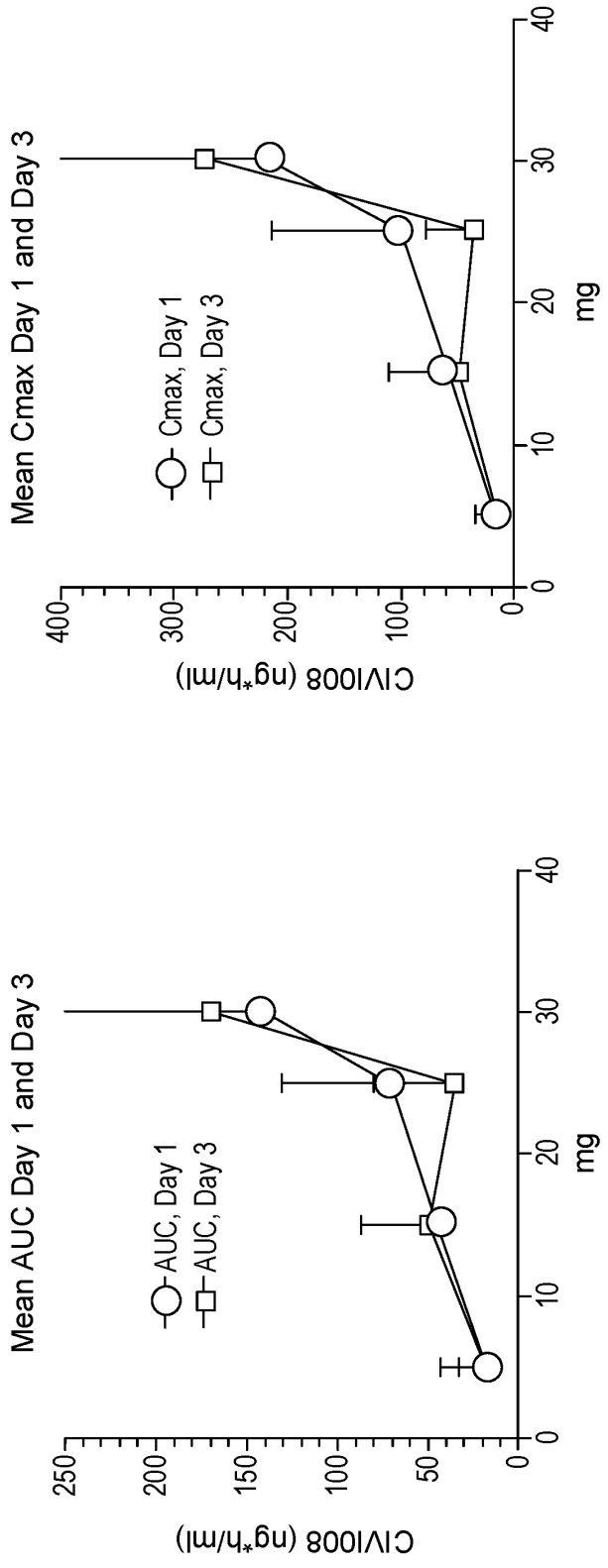

Mean AUC Day 1 and Day 3
AUC, Day 1
AUC, Day 3
CIV1008 (ng*h/ml)
mg
0
50
100
150
200
250
0
10
20
30
40
Mean Cmax Day 1 and Day 3
Cmax, Day 1
Cmax, Day 3
CIV1008 (ng*h/ml)
mg
0
100
200
300
400
0
10
20
30
40

FIG. 17

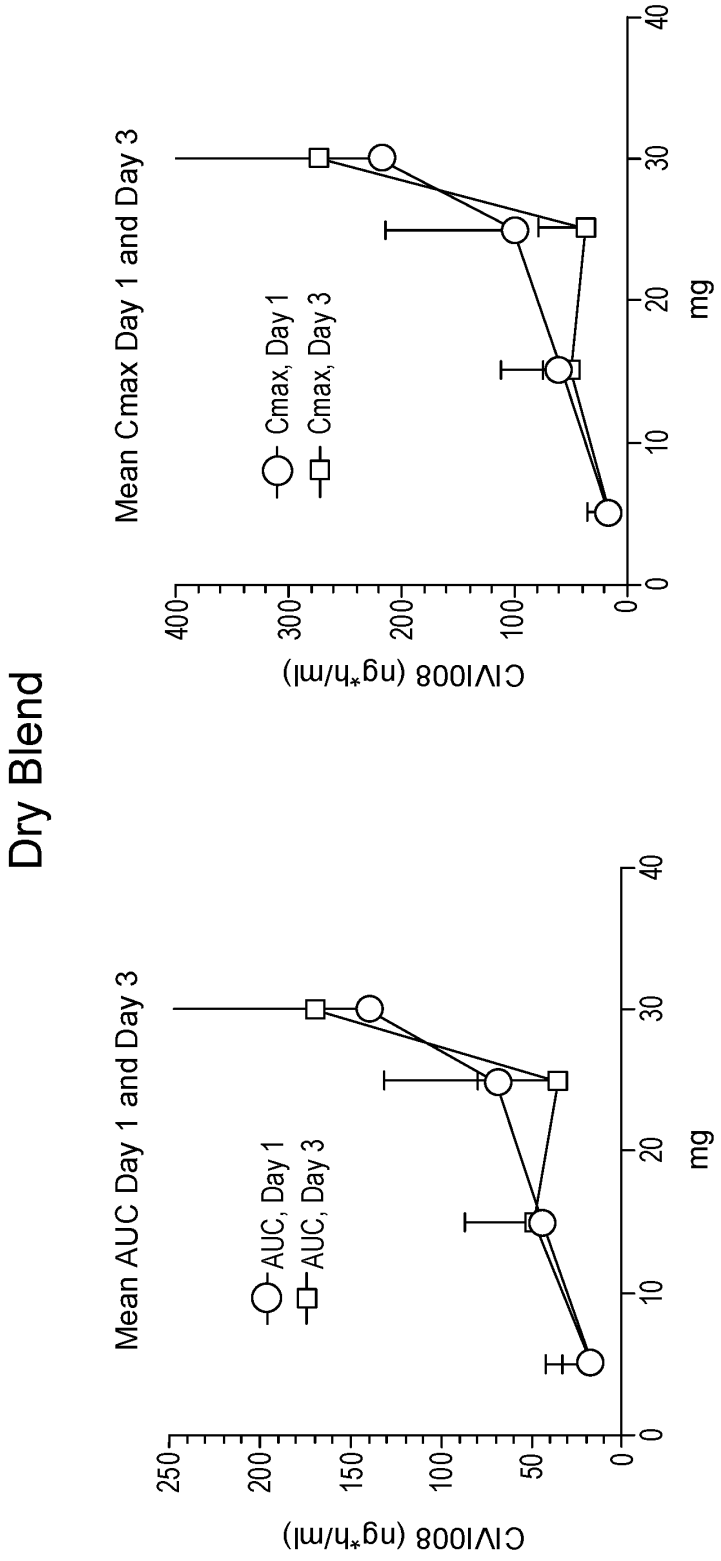

Dry Blend
Mean AUC Day 1 and Day 3
AUC, Day 1
AUC, Day 3
CIVI008 (ng*h/ml)
mg
Mean Cmax Day 1 and Day 3
Cmax, Day 1
Cmax, Day 3
CIVI008 (ng*h/ml)
mg

FIG. 18A

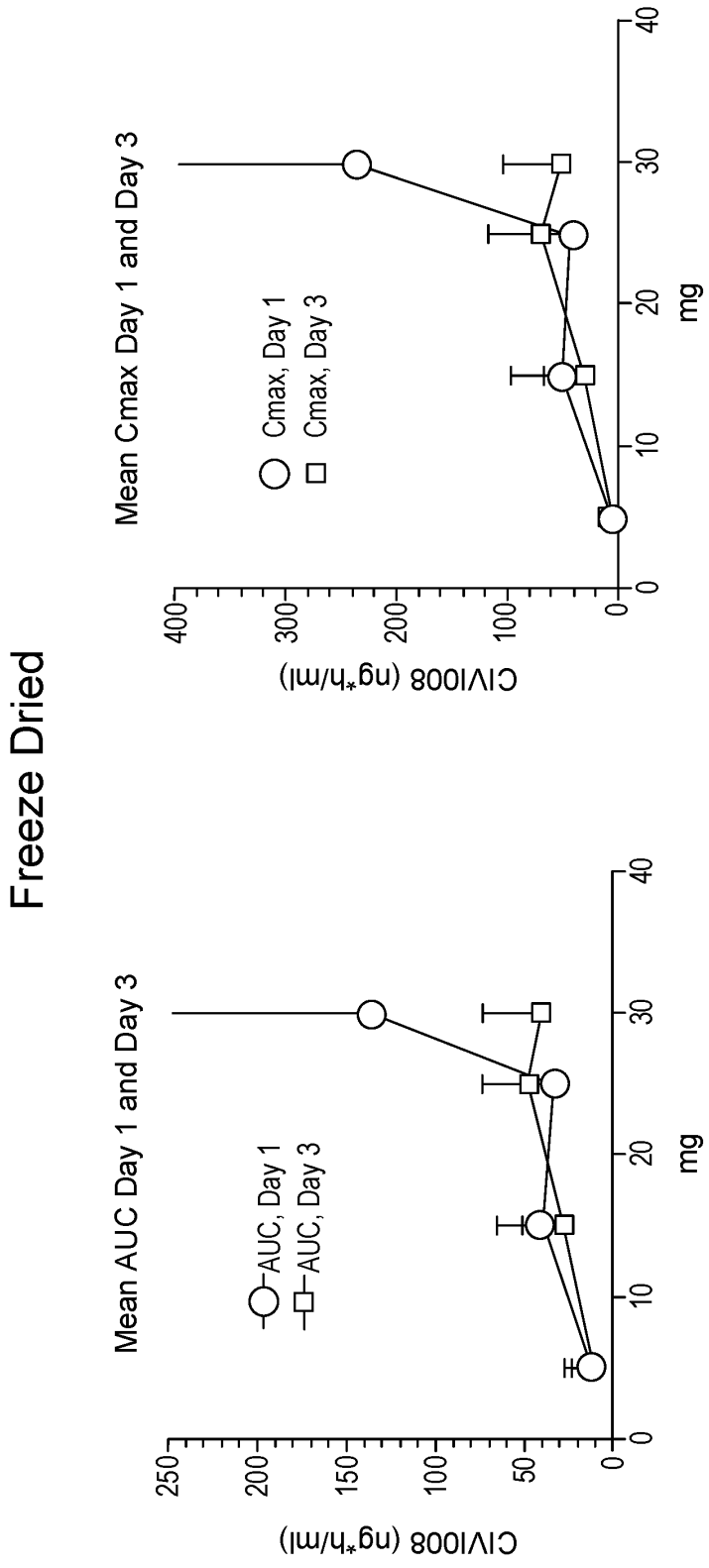

Freeze Dried
Mean Cmax Day 1 and Day 3
Cmax, Day 1
Cmax, Day 3
CIV1008 (ng*h/ml)
0
100
200
300
400
0
10
20
30
40
mg
Mean AUC Day 1 and Day 3
AUC, Day 1
AUC, Day 3
CIV1008 (ng*h/ml)
0
50
100
150
200
250
0
10
20
30
40
mg

FIG. 18B

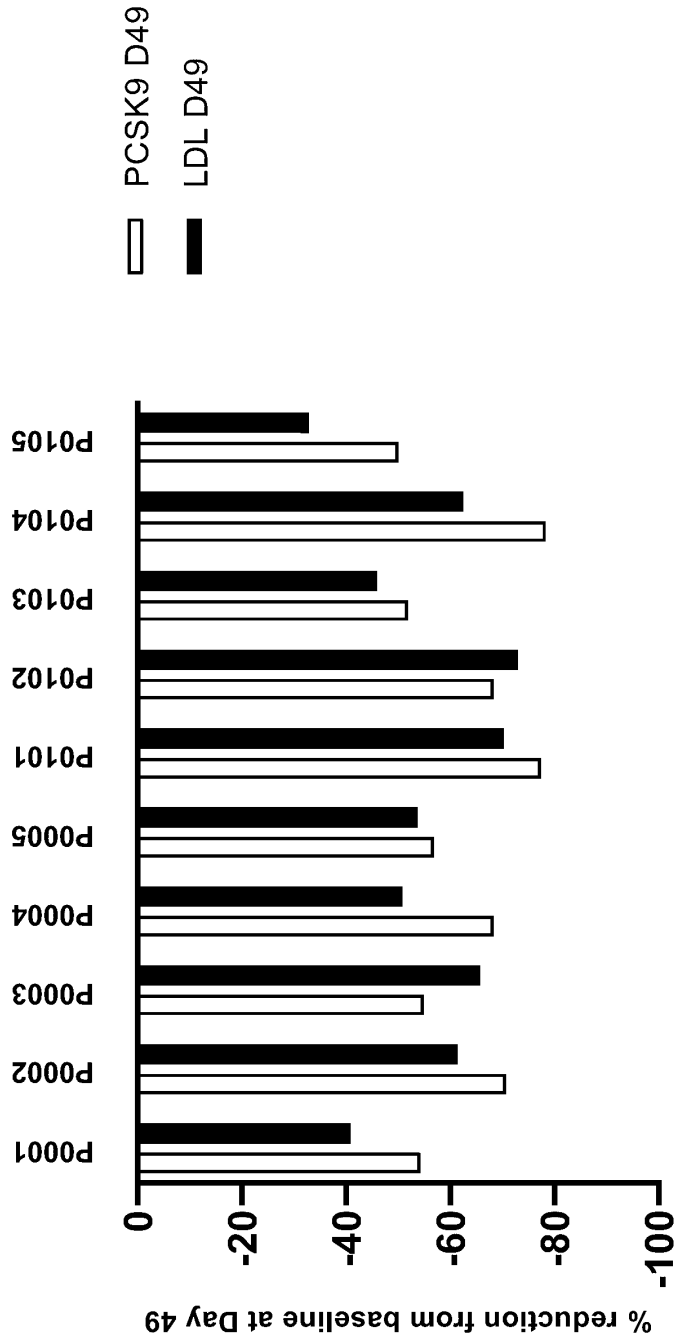

PCSK9 D49
LDL D49
P0105
P0104
P0103
P0102
P0101
P0005
P0004
P0003
P0002
P0001
0
-20
-40
-60
-80
-100
% reduction from baseline at Day 49

FIG. 19

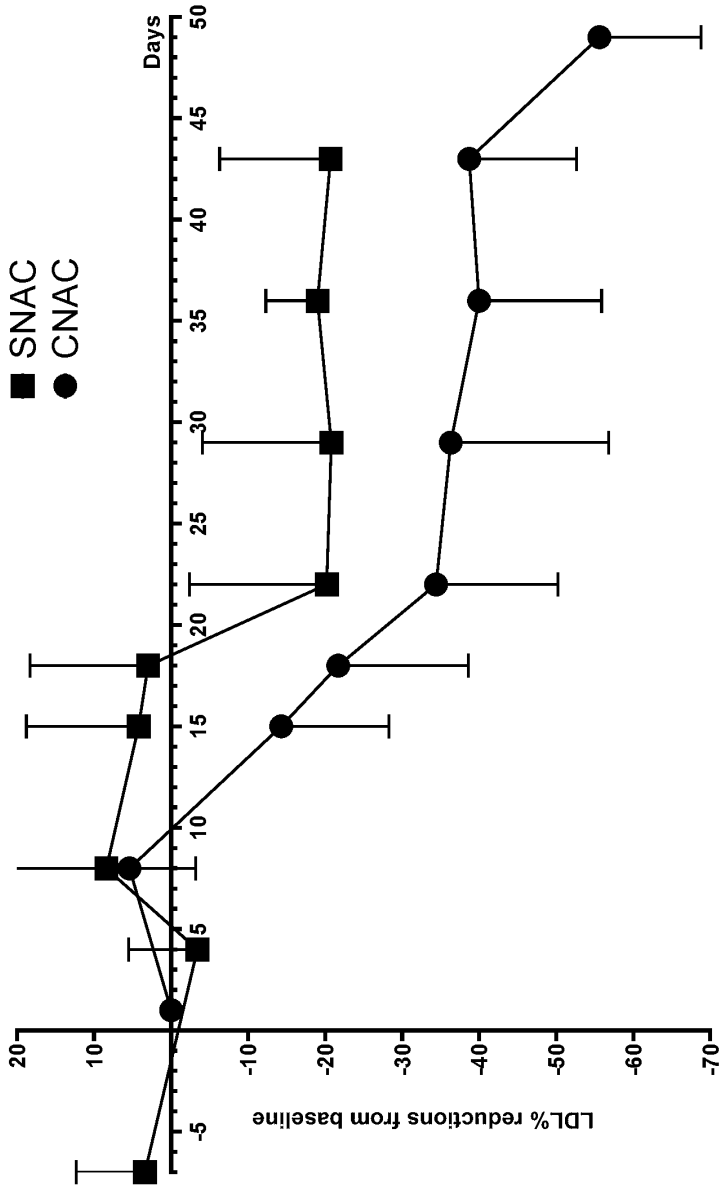
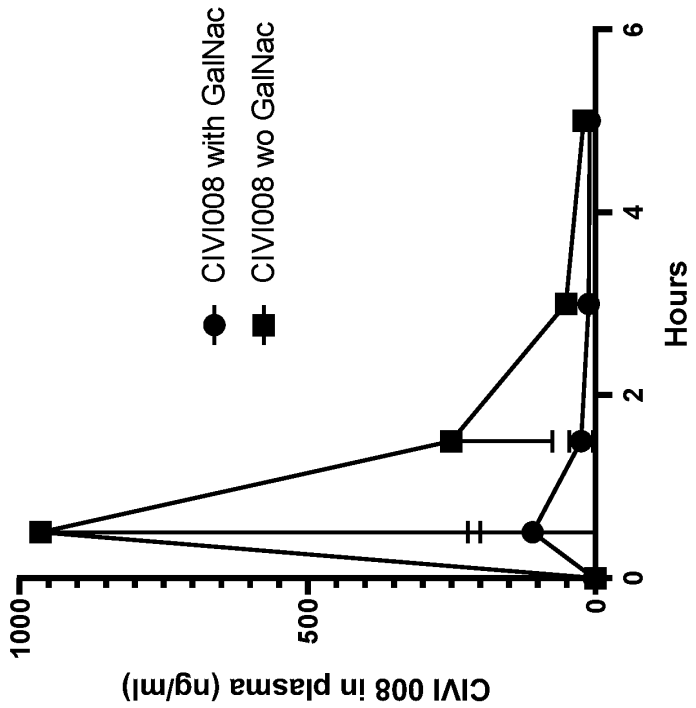
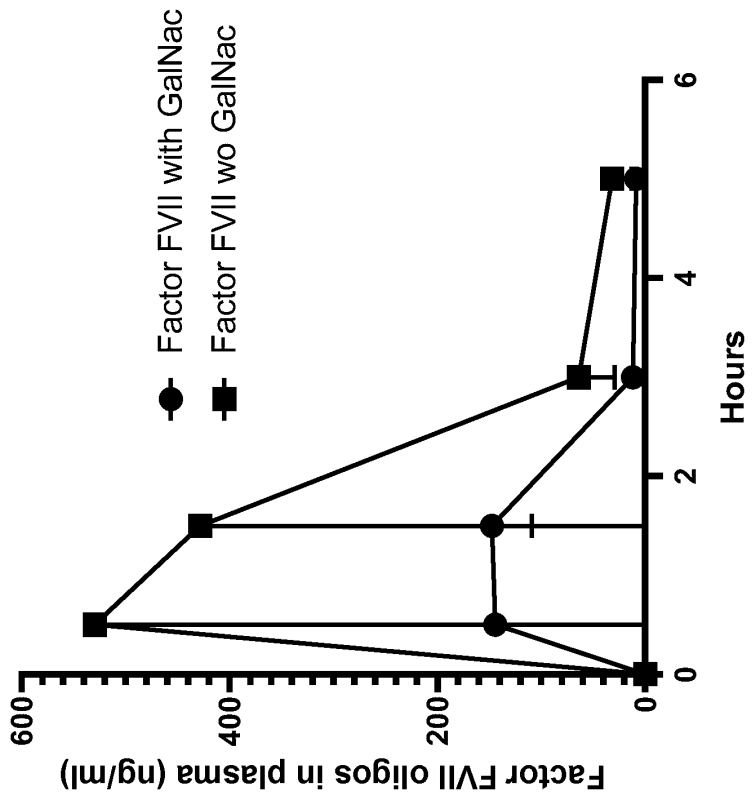

SNAC
CNAC
Days
50
45
40
35
30
25
20
15
10
5
20
10
-5
-10
-20
-30
-40
-50
-60
-70
LDL% reductions from baseline

FIG. 20



	No. animals	Mean AUC_{0-5} (ng*i*h),	SD	Mean Cmax (ng/ml)	SD	Tmax (hours)
CIVI 008 with GalNac	10	144.8	101.2	116.9	114.1	0.5-1.5
CIVI 008 wo GalNac	10	1147.7	756.3	968.0	760.4	0.5-1.5

FIG. 21



	No. animals	Mean AUC_{0-5} (ng*i*h),	SD	Mean Cmax (ng/ml)	SD	Tmax (hours)
Factor FVII with GalNac	10	322.5	358.6	184,9	179.2	0.5-1.5
Factor FVII wo GalNac	8	1109.5	811.1	743.3	646.4	05-1.5

FIG. 22

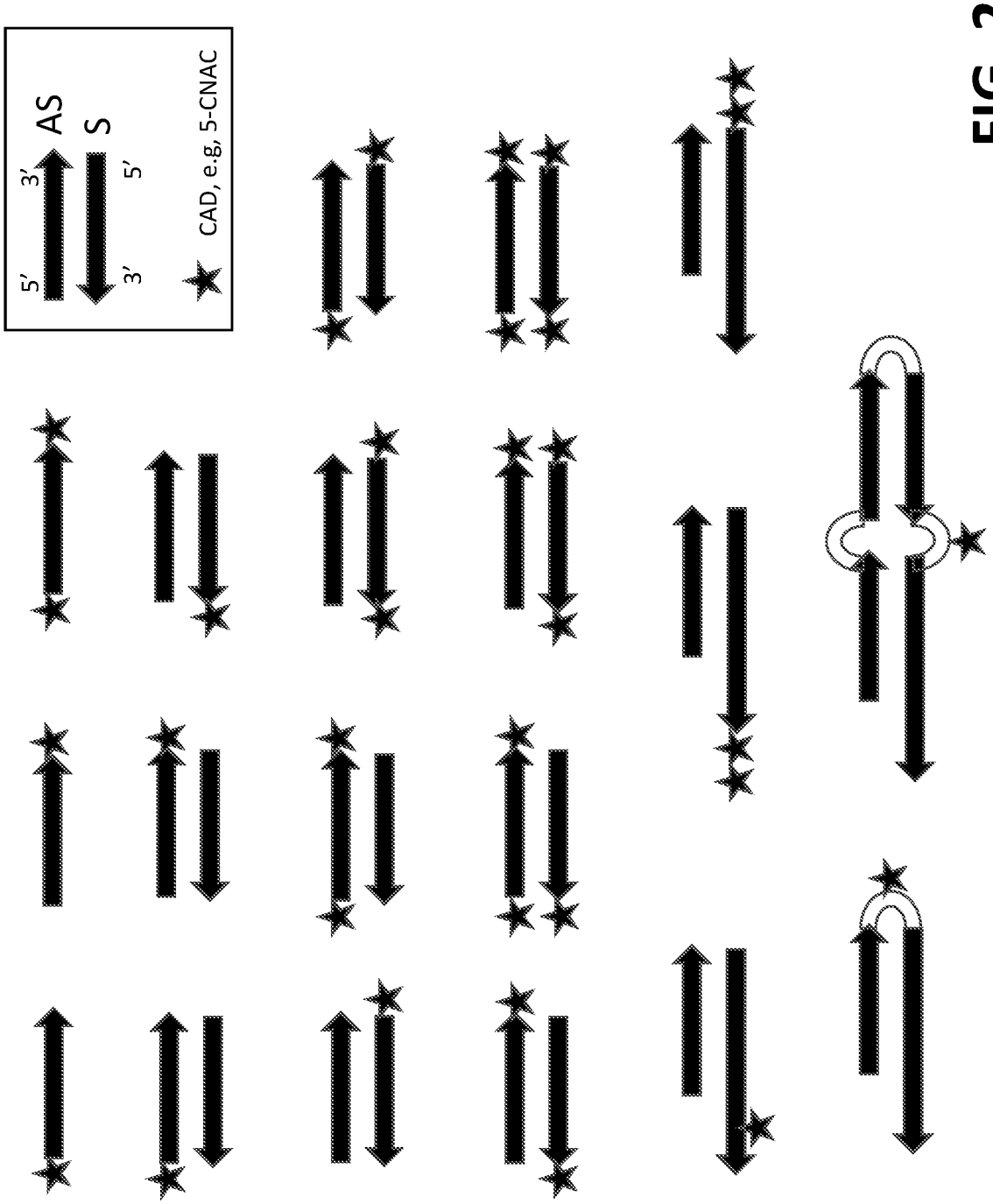


FIG. 23