Figure 1

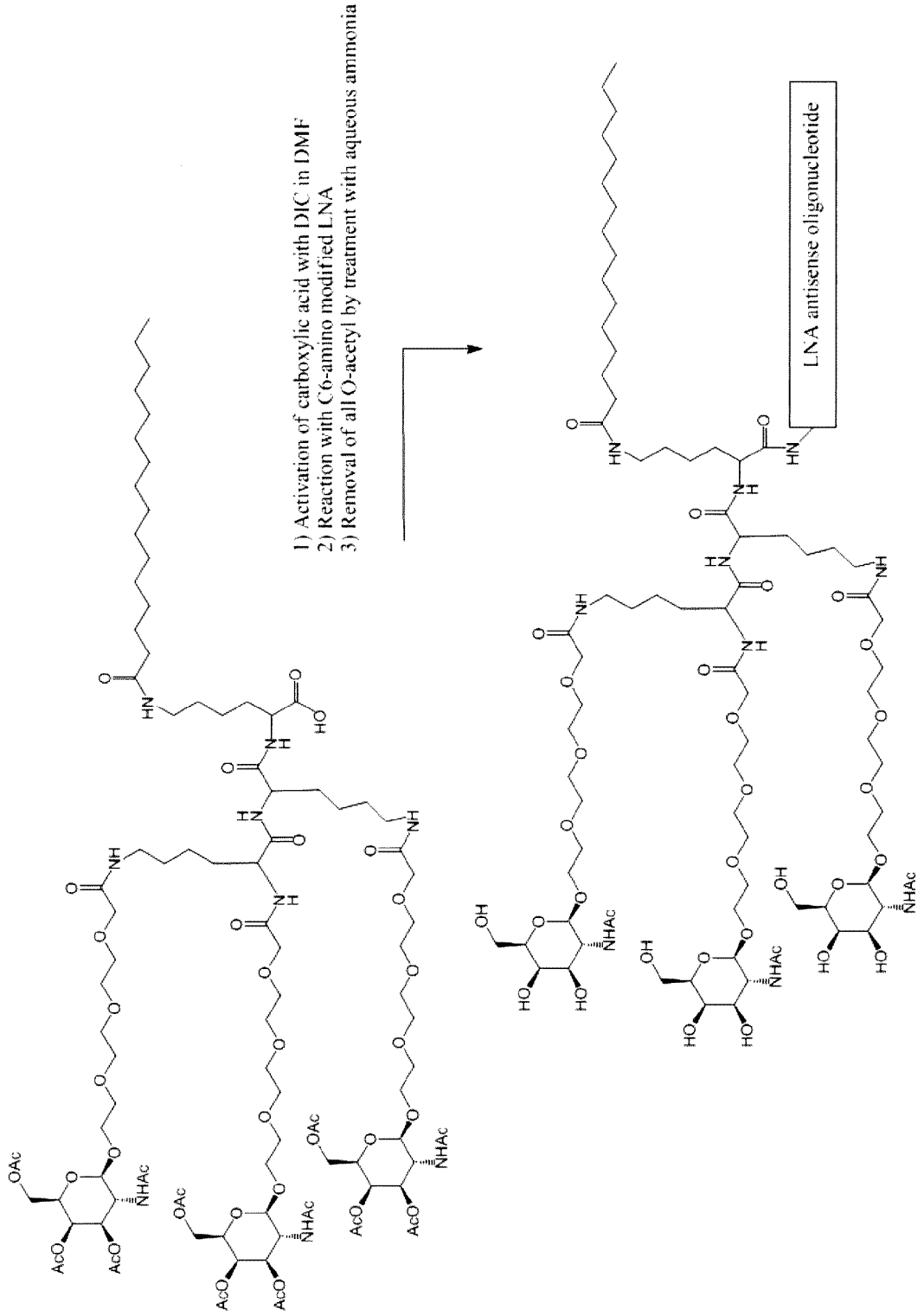

1) Activation of carboxylic acid with DIC in DMF
2) Reaction with C6-amino modified LNA
3) Removal of all O-acetyl by treatment with aqueous ammonia
LNA antisense oligonucleotide

Figure 2

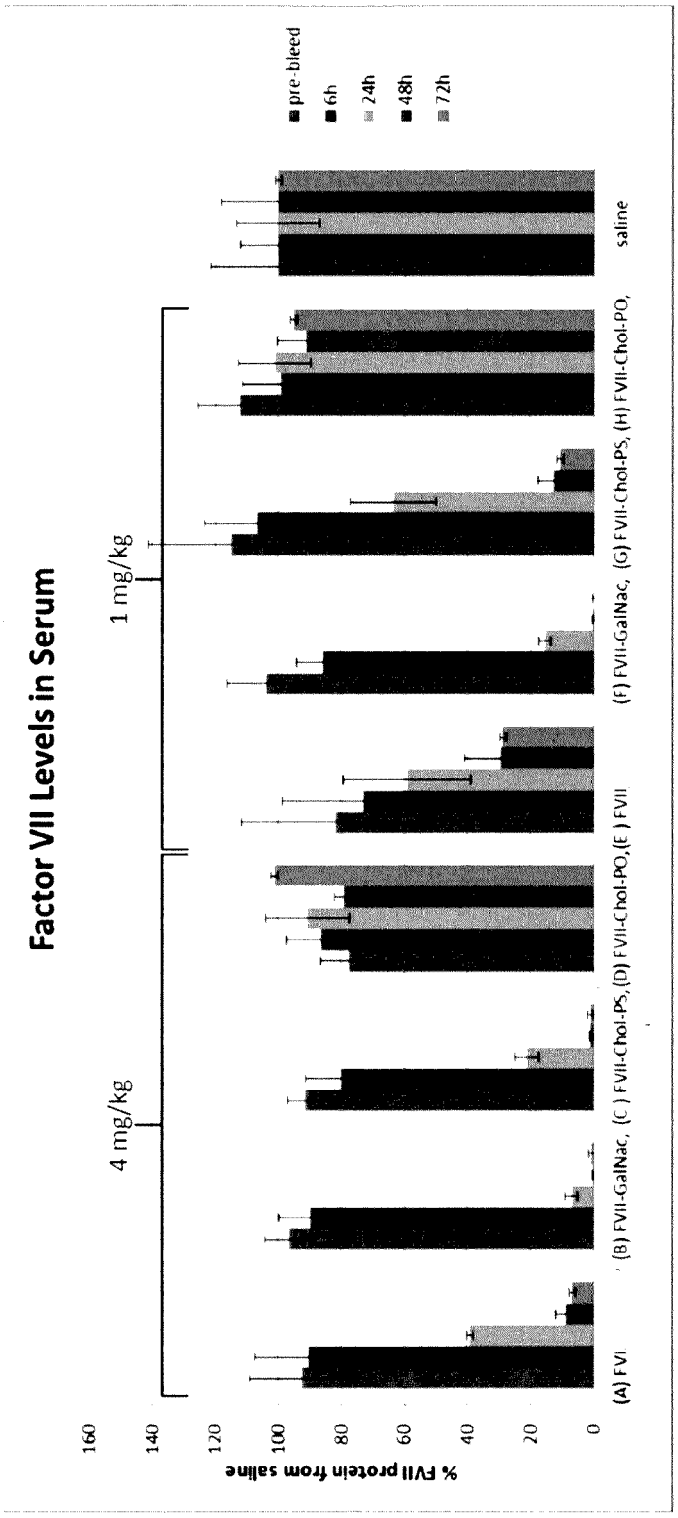

Factor VII Levels in Serum
% FVII protein from saline
0
20
40
60
80
100
120
140
160
4 mg/kg
1 mg/kg
pre-bleed
6h
24h
48h
72h
(A) FVI
(B) FVII-GalNac,
(C) FVII-Chol-PS,
(D) FVII-Chol-PO,
(E) FVII
(F) FVII-GalNac,
(G) FVII-Chol-PS,
(H) FVII-Chol-PO,
saline

Figure 3

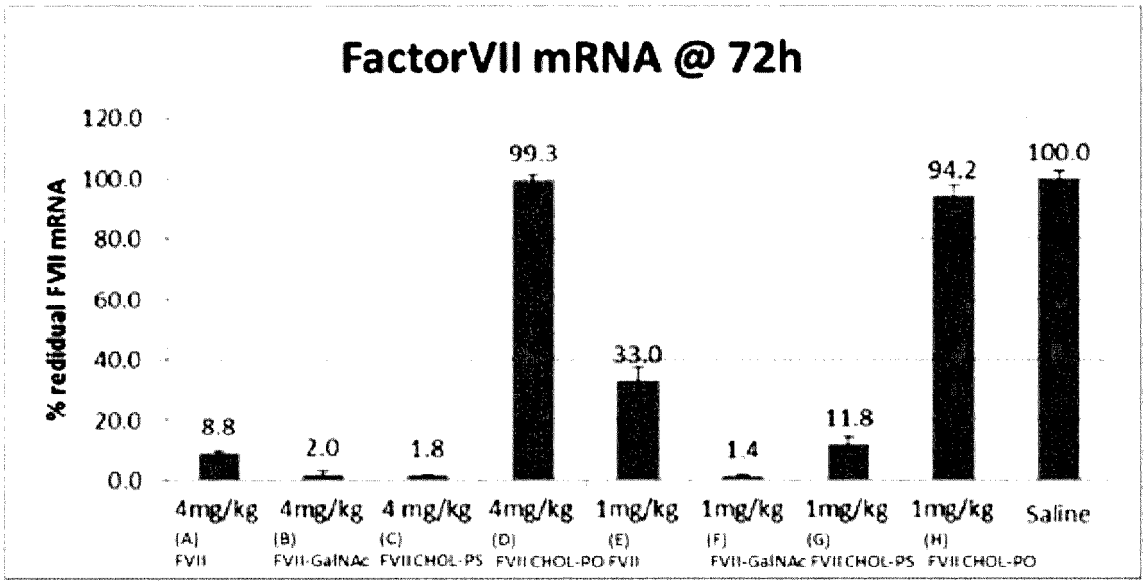


Figure 4 a)

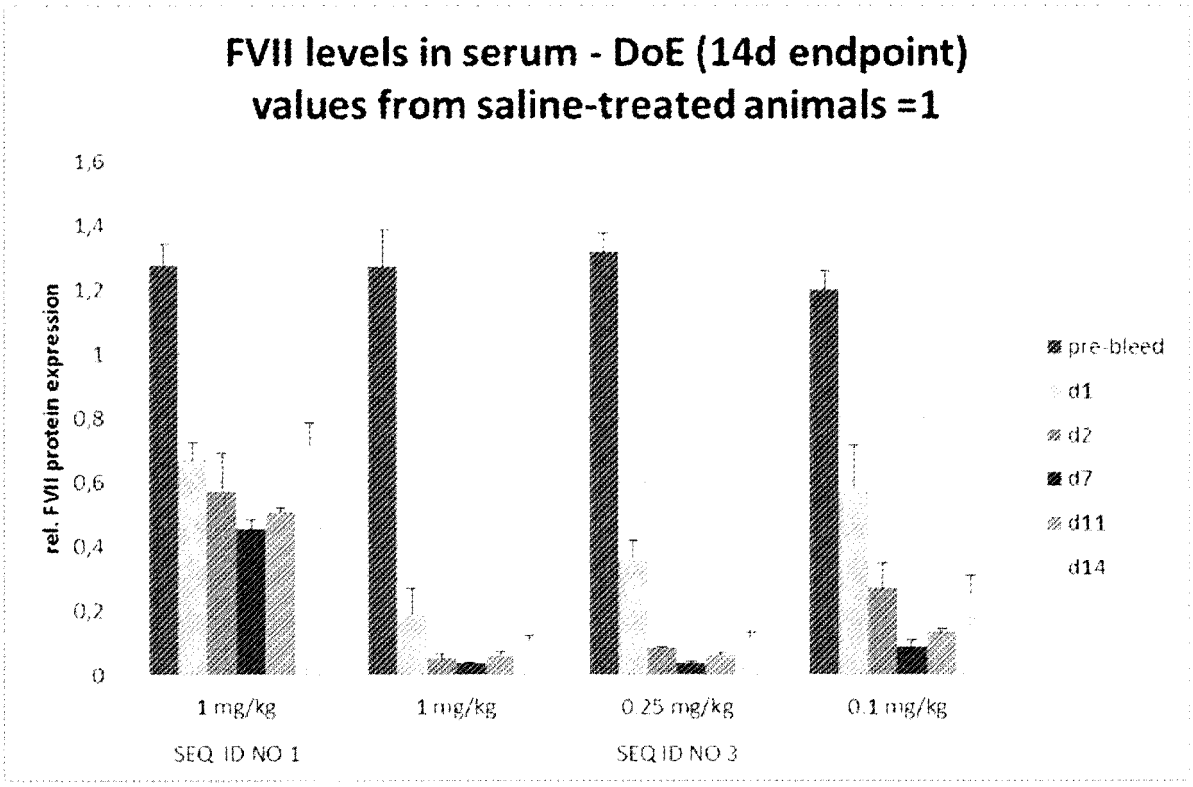


Figure 4 b)

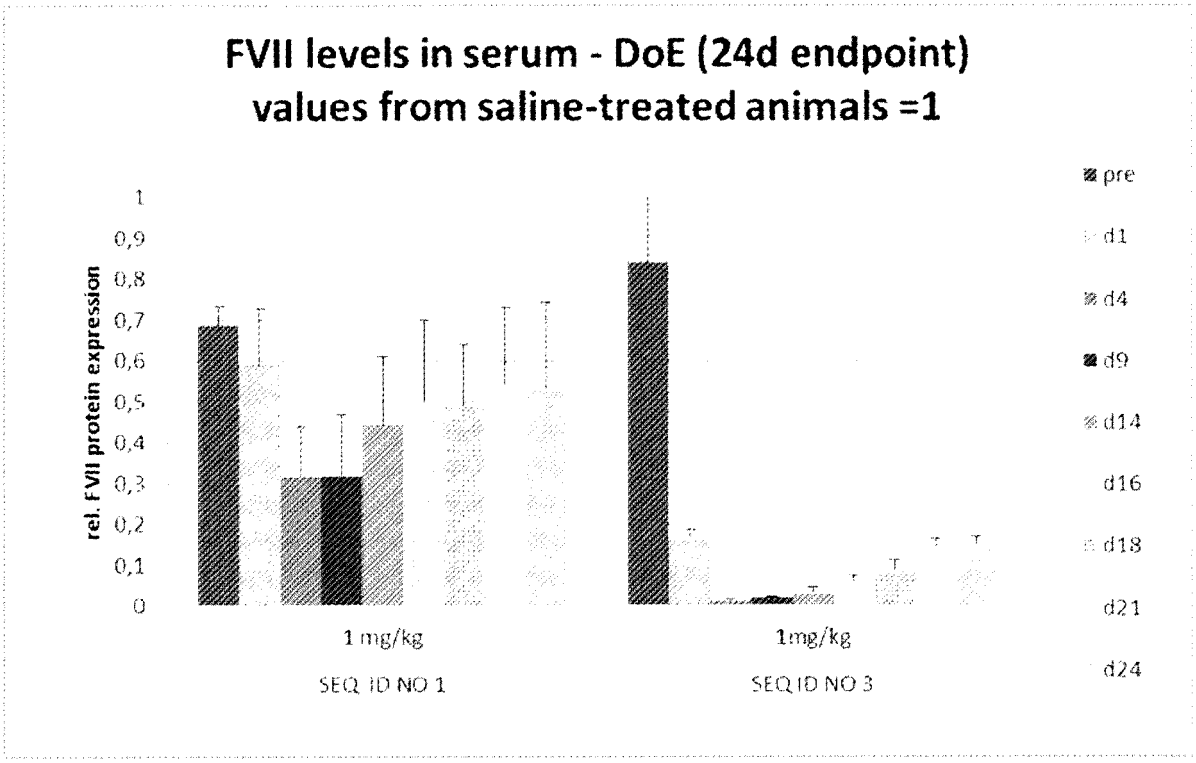


Figure 4 c)

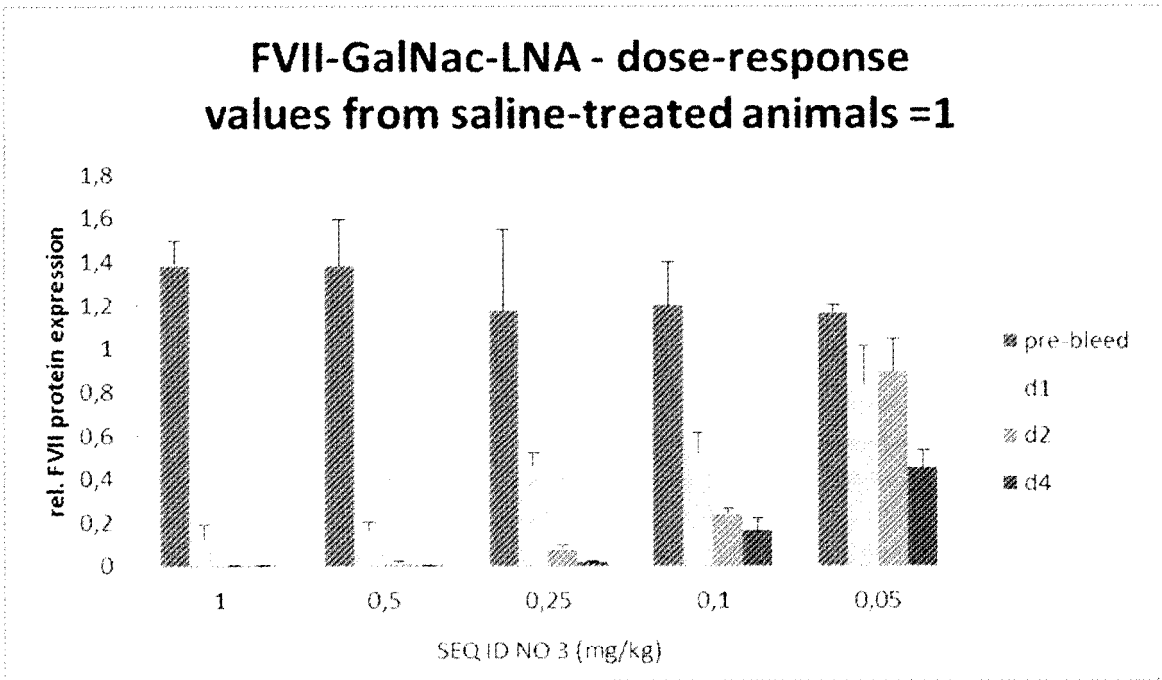


Figure 4 d)

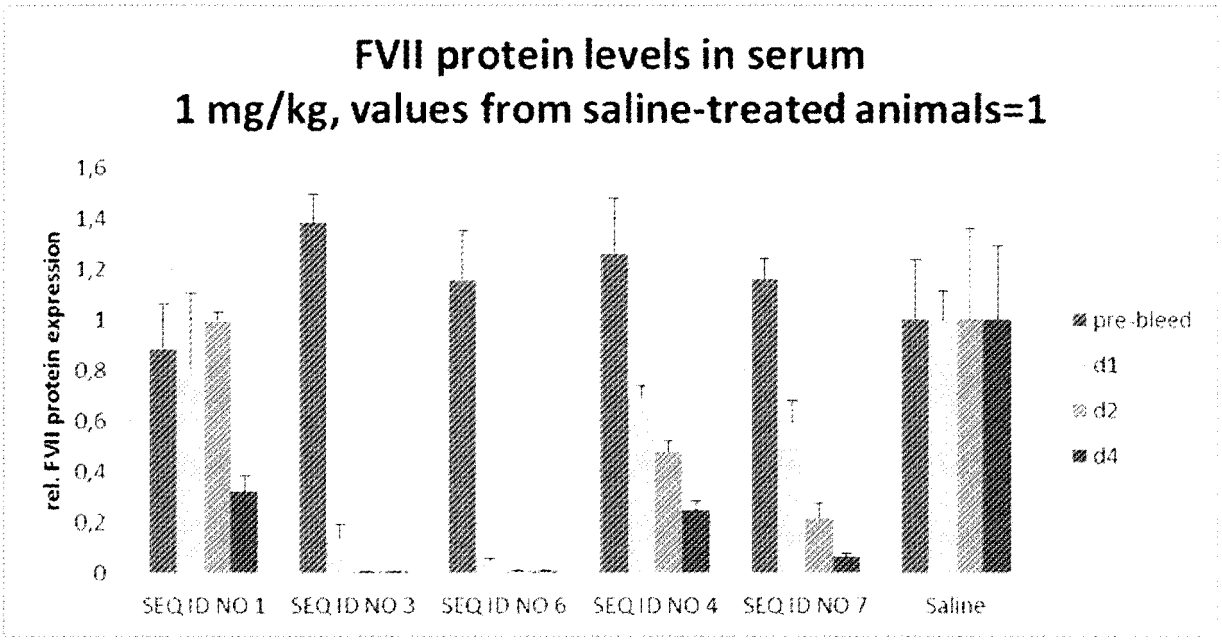


Figure 5 a)

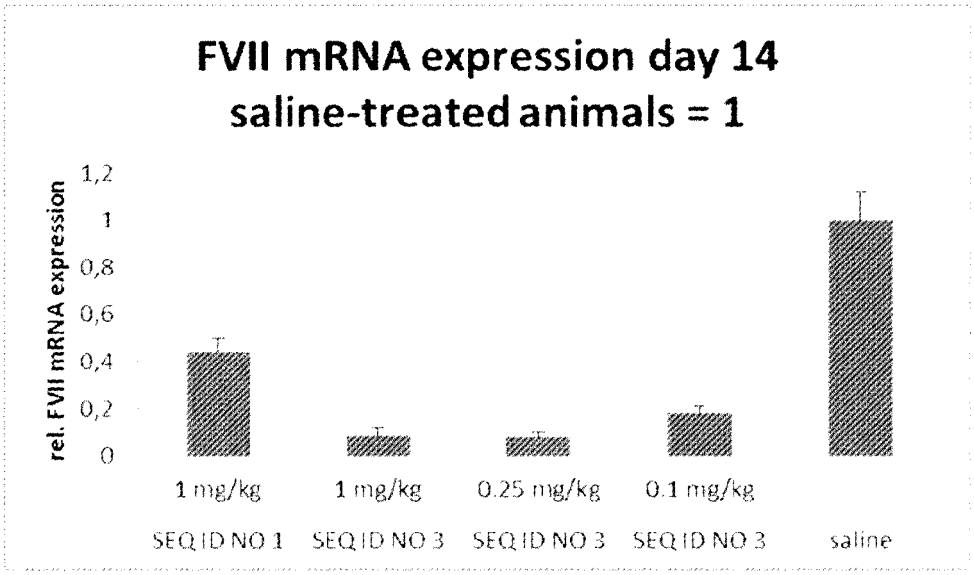


Figure 5 b)

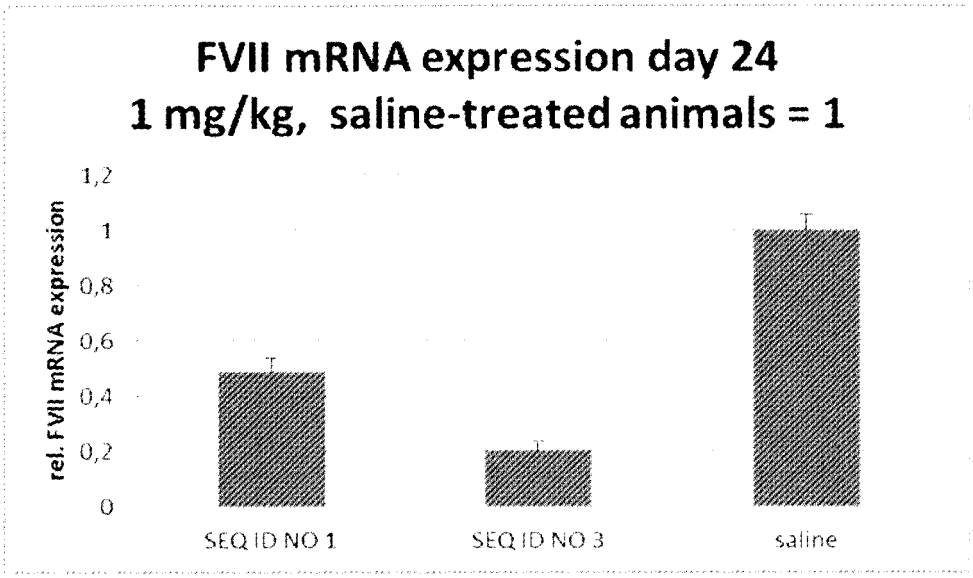


Figure 5 c)

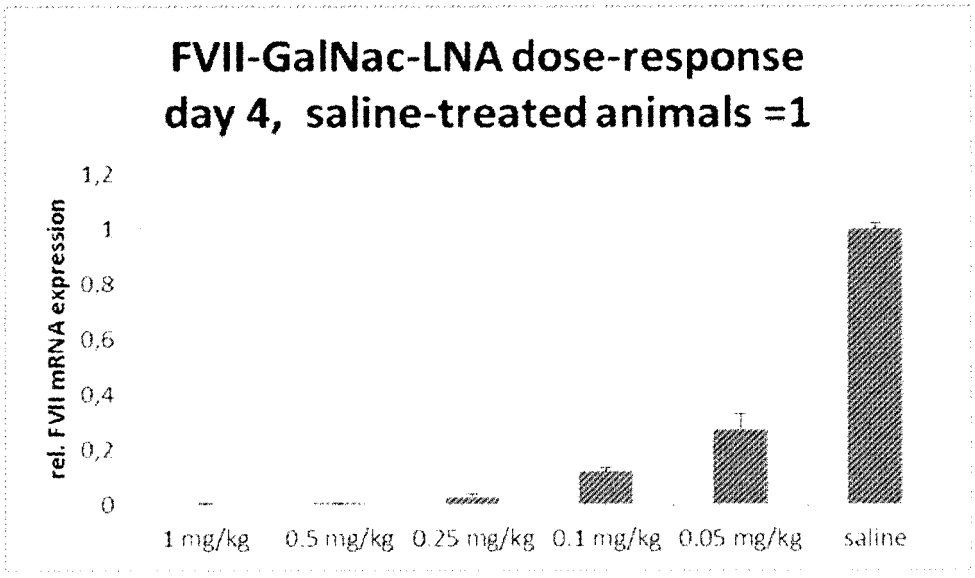


Figure 5 d)

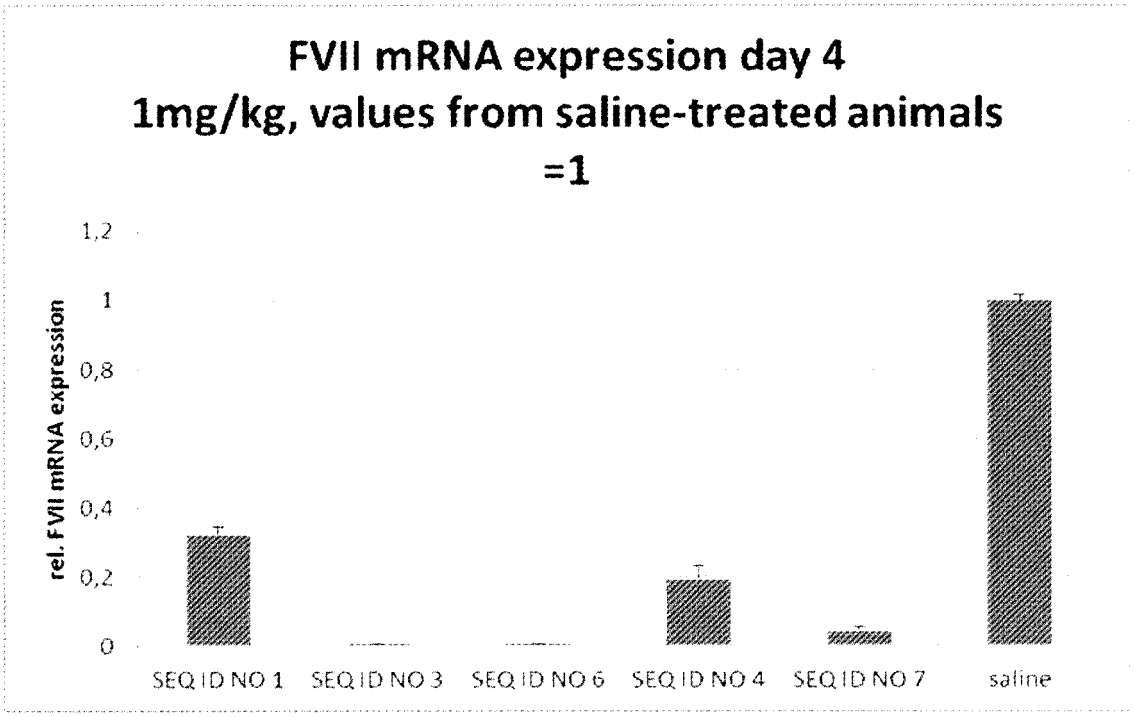


Figure 6

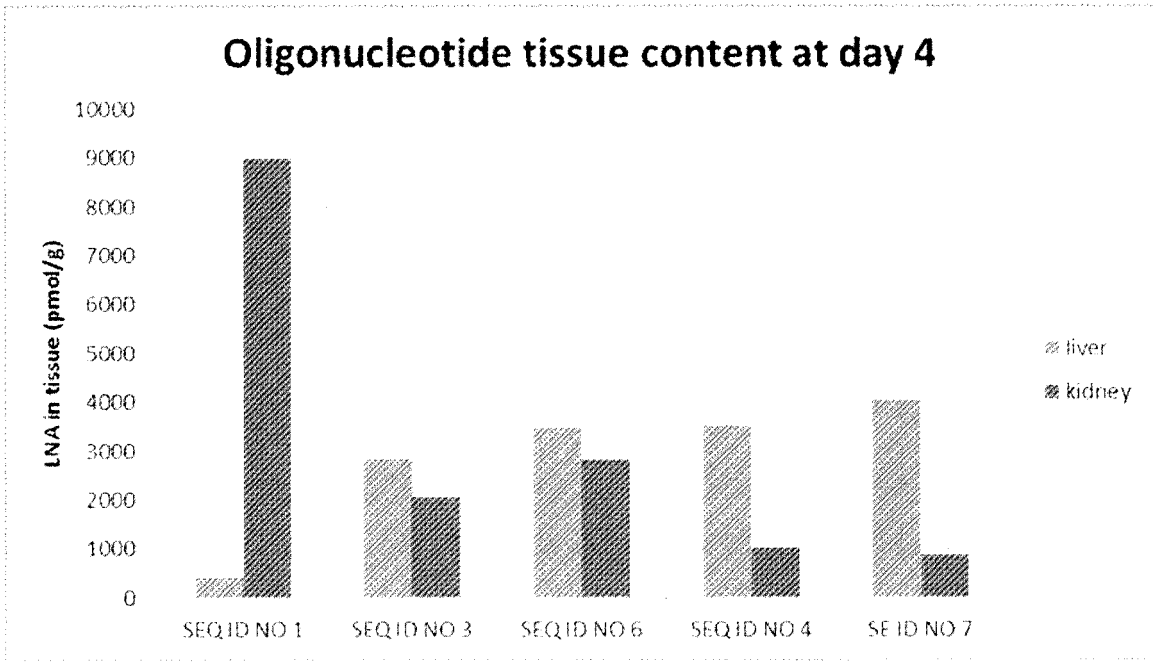
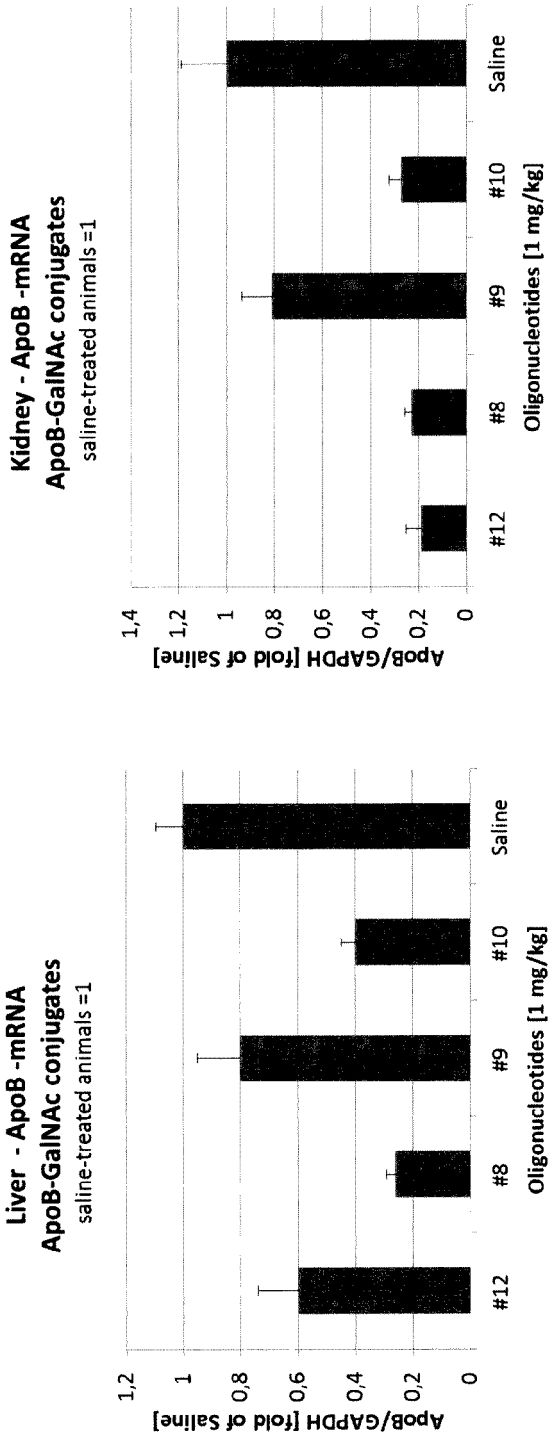
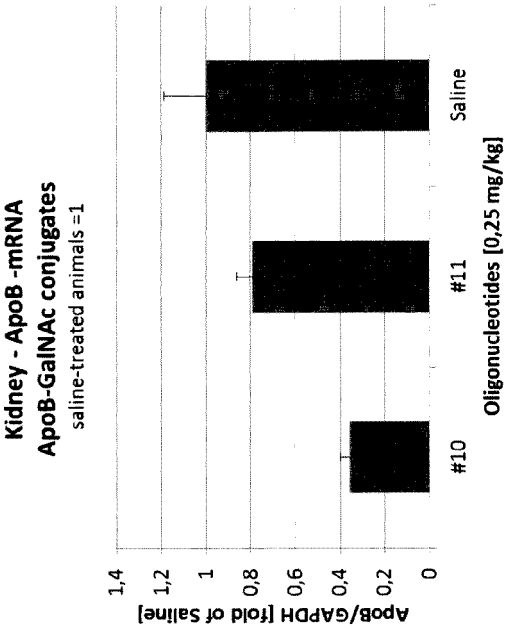


Figure 7

A


Kidney - ApoB -mRNA
ApoB-GalNAc conjugates
saline-treated animals =1
ApoB/GAPDH [fold of Saline]
1,4
1,2
1
0,8
0,6
0,4
0,2
0
#12
#8
#9
#10
Saline
Oligonucleotides [1 mg/kg]
Liver - ApoB -mRNA
ApoB-GalNAc conjugates
saline-treated animals =1
ApoB/GAPDH [fold of Saline]
1,2
1
0,8
0,6
0,4
0,2
0
#12
#8
#9
#10
Saline
Oligonucleotides [1 mg/kg]

B


Kidney - ApoB -mRNA
ApoB-GalNAc conjugates
saline-treated animals =1
ApoB/GAPDH [fold of Saline]
1,4
1,2
1
0,8
0,6
0,4
0,2
0
#10
#11
Saline
Oligonucleotides [0,25 mg/kg]

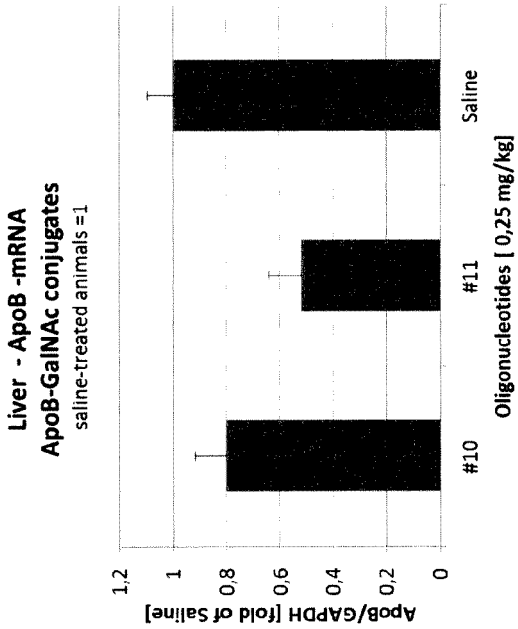

Liver - ApoB -mRNA
ApoB-GalNAc conjugates
saline-treated animals =1
ApoB/GAPDH [fold of Saline]
1,2
1
0,8
0,6
0,4
0,2
0
#10
#11
Saline
Oligonucleotides [0,25 mg/kg]

Figure 8

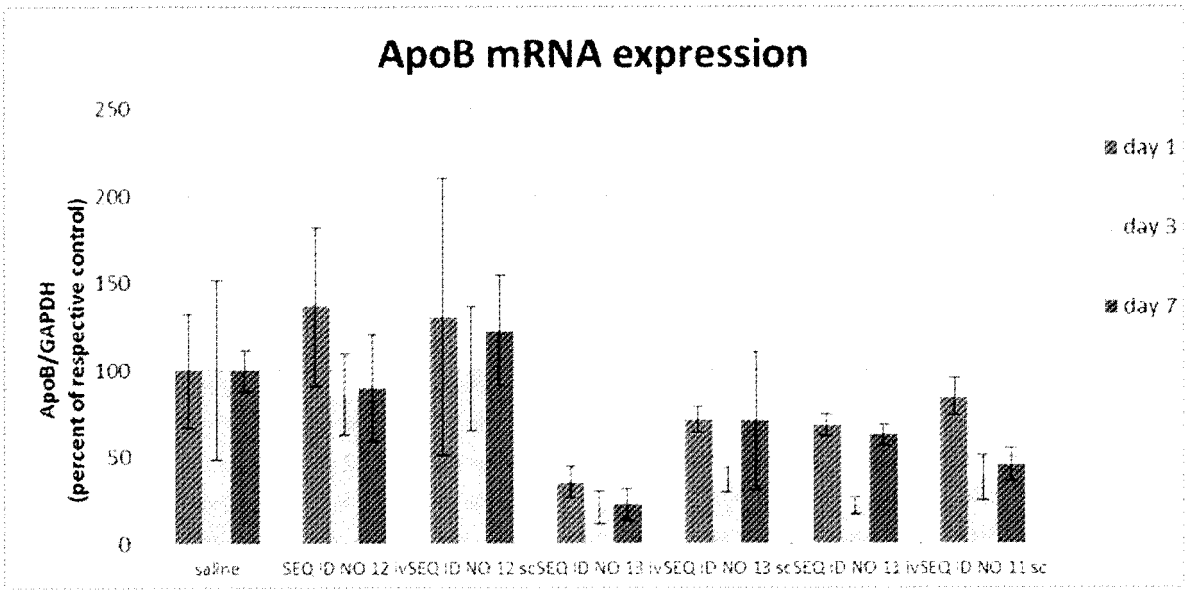


Figure 9 a)

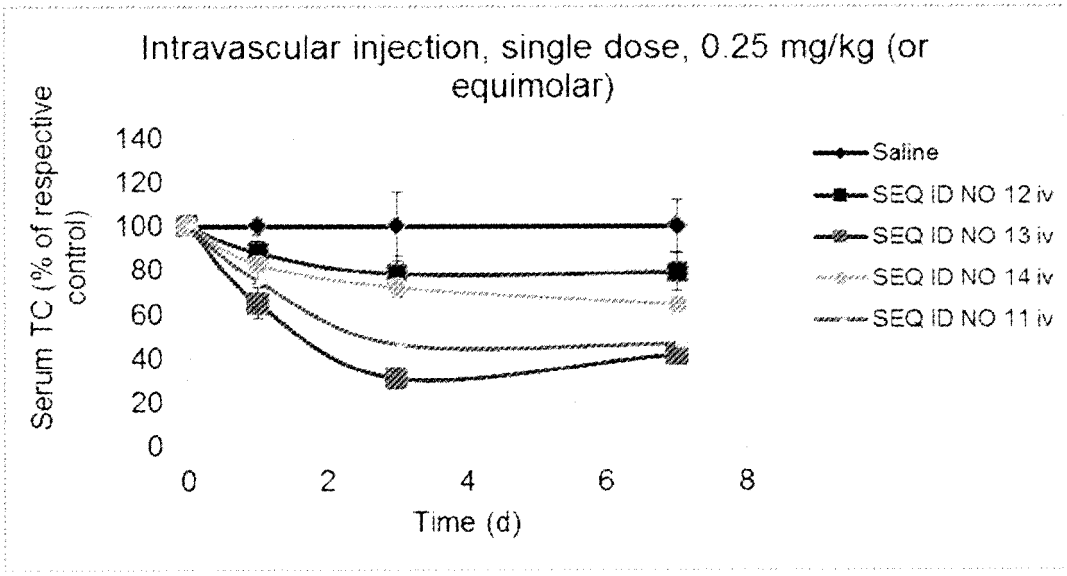


Figure 9 b)

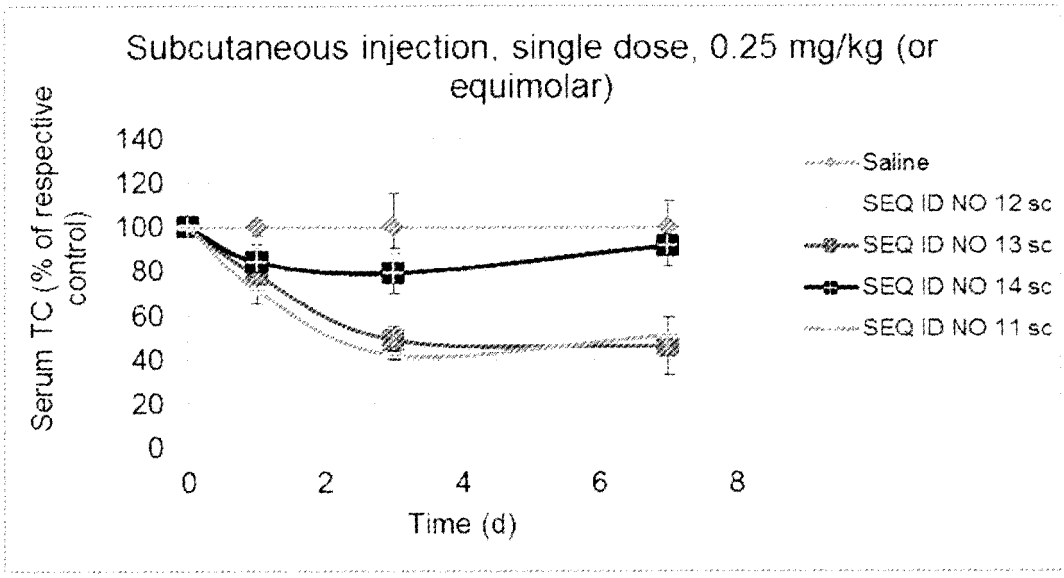


Figure 10 a)

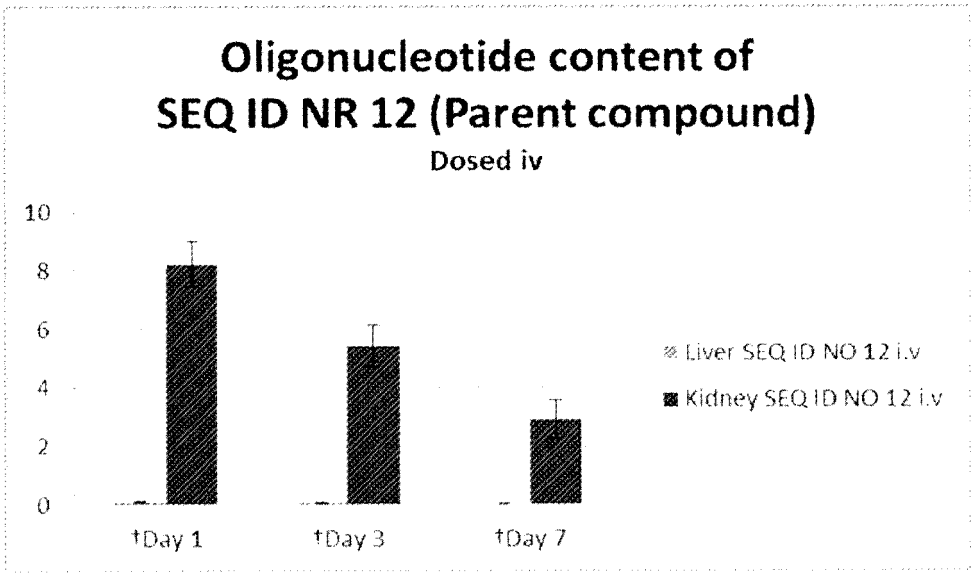


Figure 10 b)

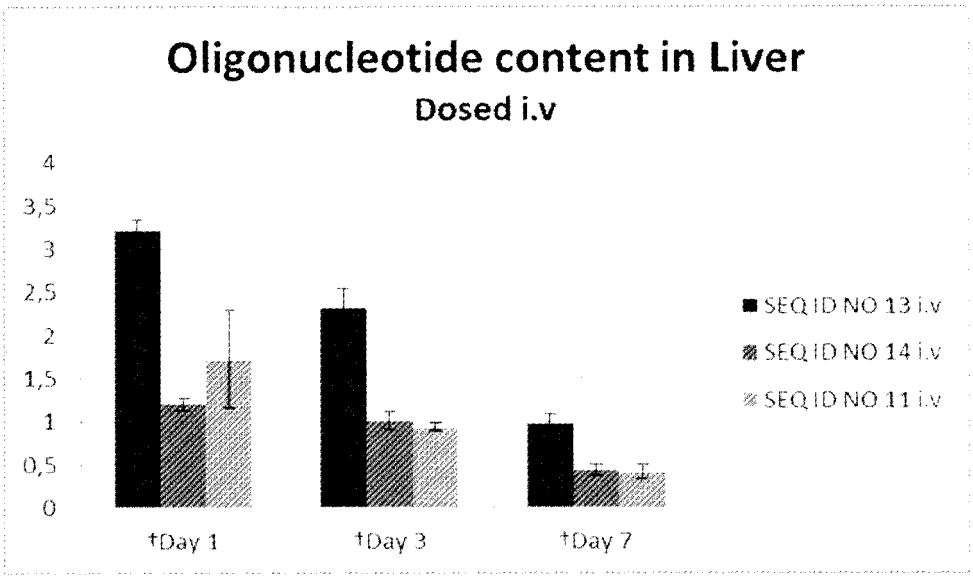


Figure 10 c)

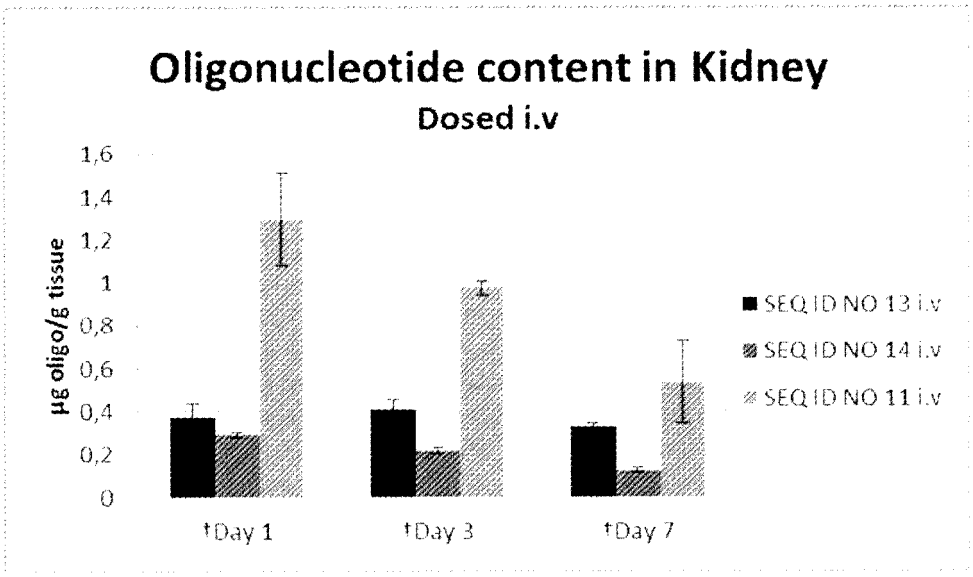


Figure 10 d)

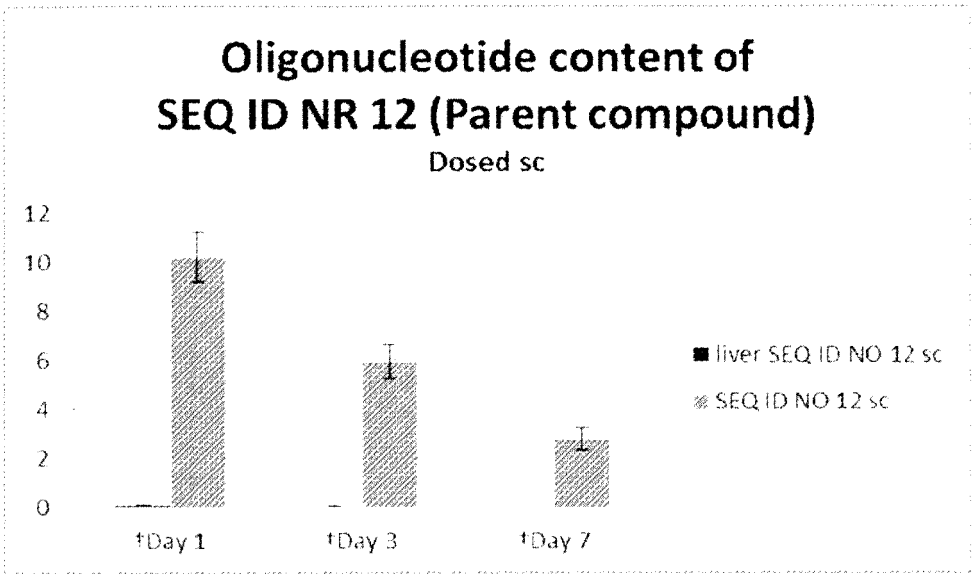


Figure 10 e)

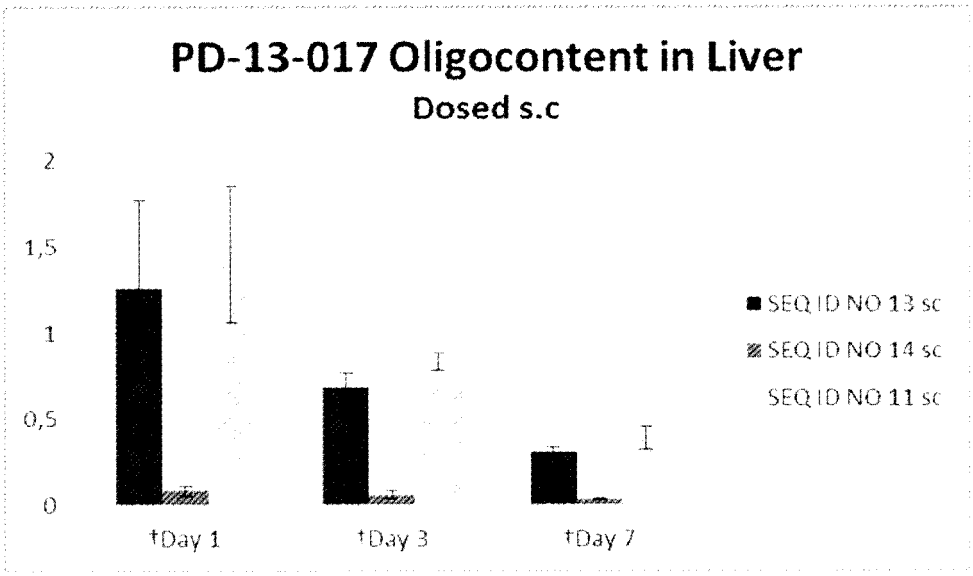


Figure 10 f)

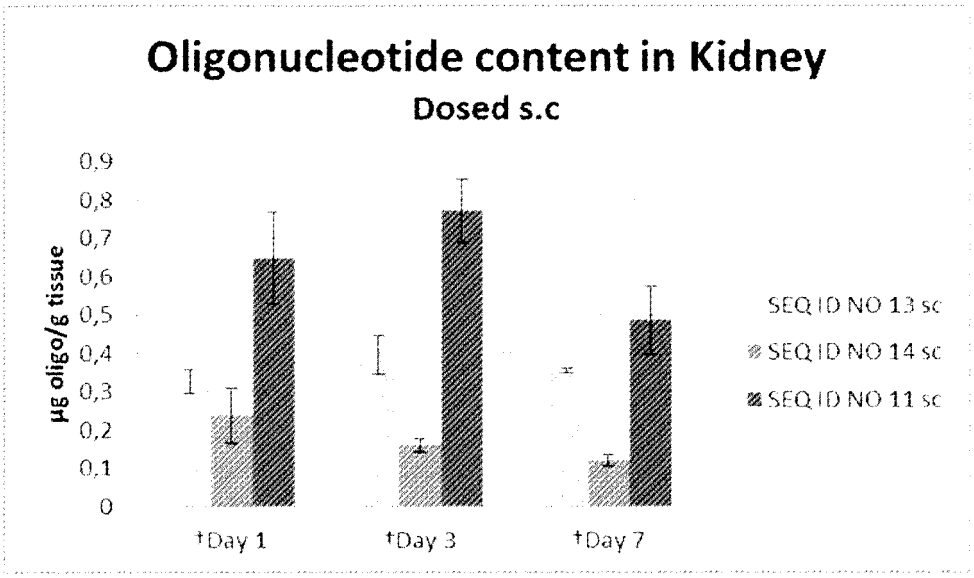


Figure 11

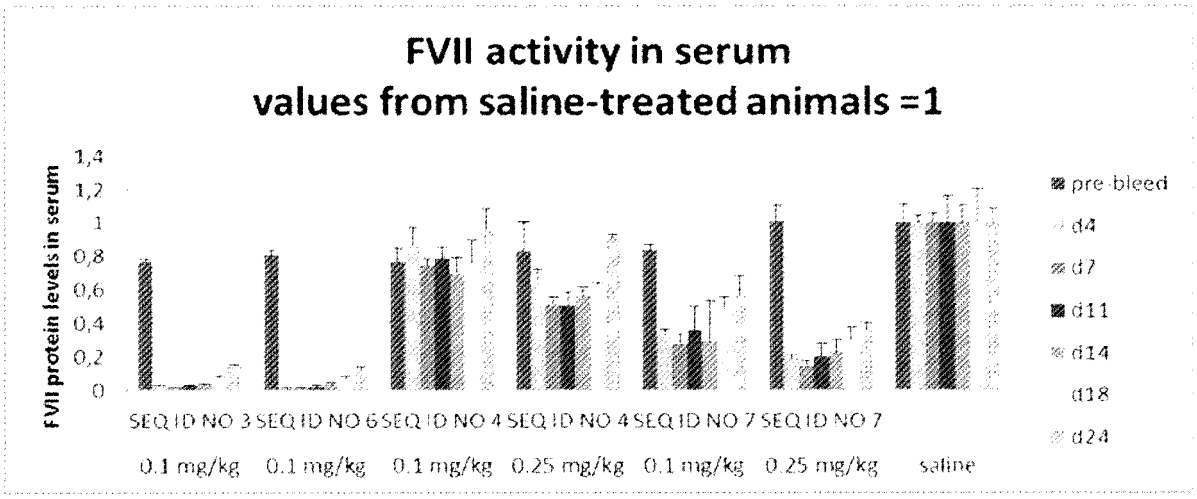


Figure 12

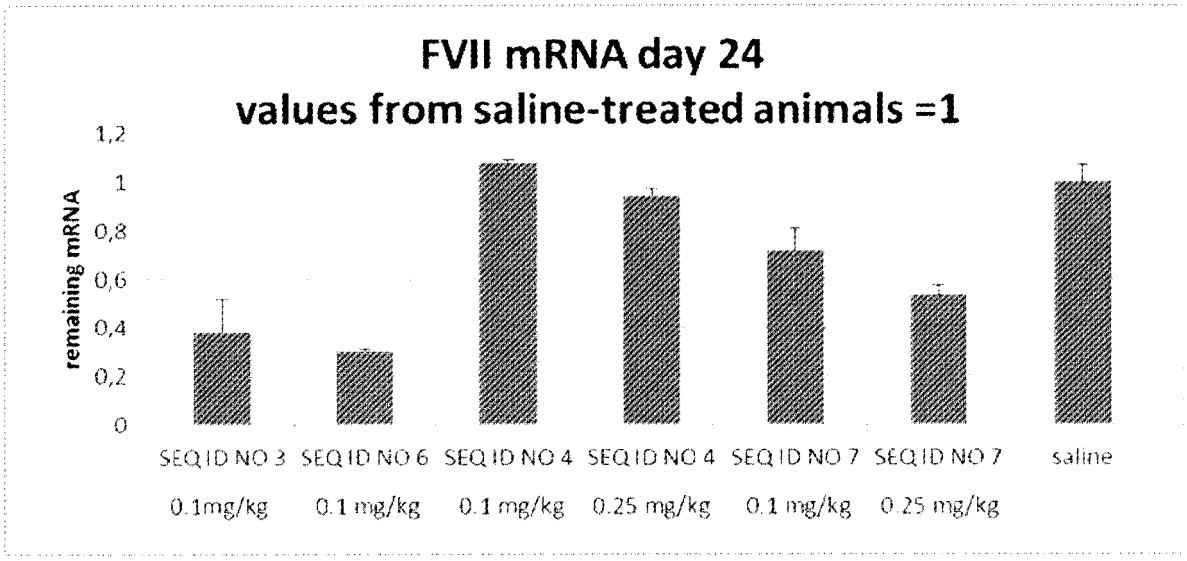

FVII mRNA day 24
values from saline-treated animals =1
remaining mRNA
1,2
1
0,8
0,6
0,4
0,2
0
SEQ ID NO 3 0.1mg/kg
SEQ ID NO 6 0.1 mg/kg
SEQ ID NO 4 0.1 mg/kg
SEQ ID NO 4 0.25 mg/kg
SEQ ID NO 7 0.1 mg/kg
SEQ ID NO 7 0.25 mg/kg
saline

Figure 13

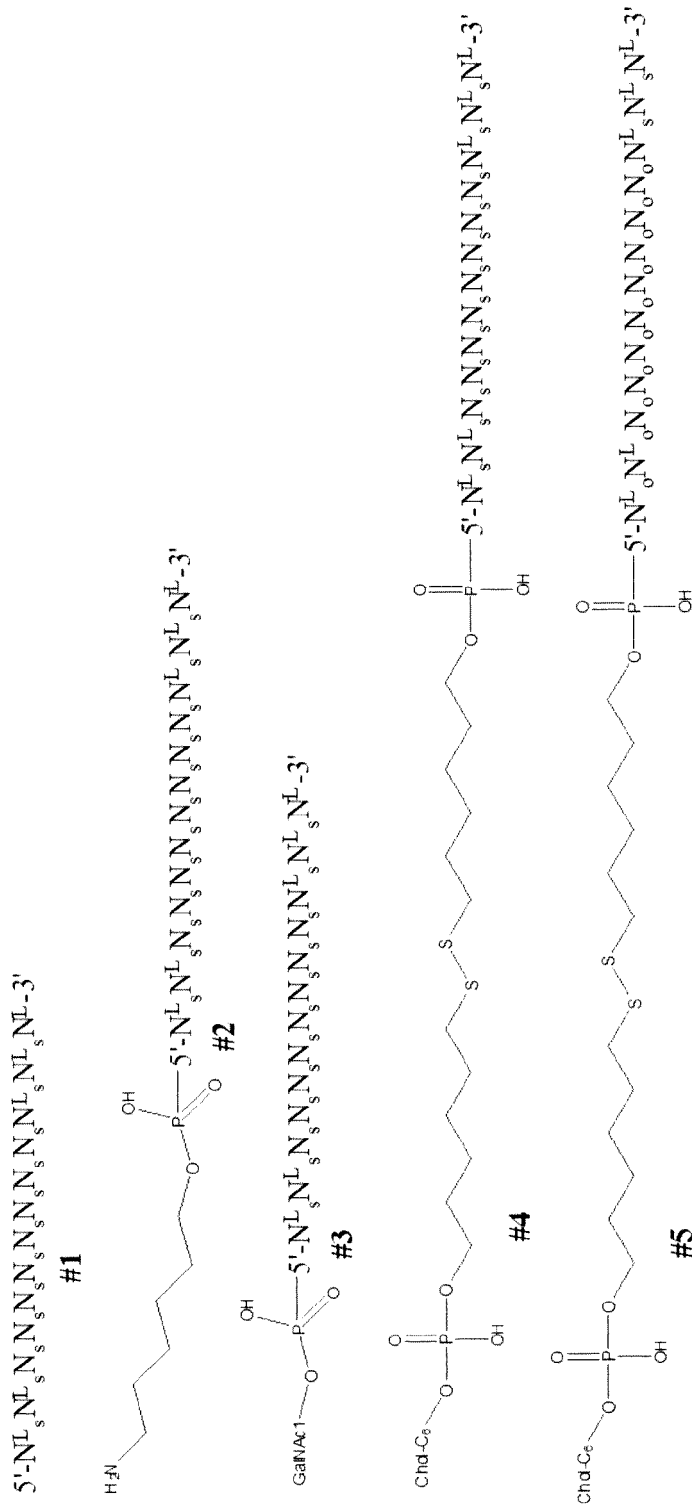

5'-NL sNL sN sN sN sN sN sN sN sN sNL sNL sNL sNL-3'
#1
H2N
5'-NL sNL sN sN sN sN sN sN sN sN sN sN sNL sNL sNL sNL-3'
#2
GalNAc1
5'-NL sNL sN sN sN sN sN sN sN sN sNL sNL sNL-3'
#3
Chd-C6
5'-NL sNL sN sN sN sN sN sN sN sN sN sN sN sNL sNL sNL-3'
#4
Chd-C6
5'-NL oNL oN oN oN oN oN oN oN oN oN oN oN oNL oNL oNL-3'
#5

Figure 13 (continued)

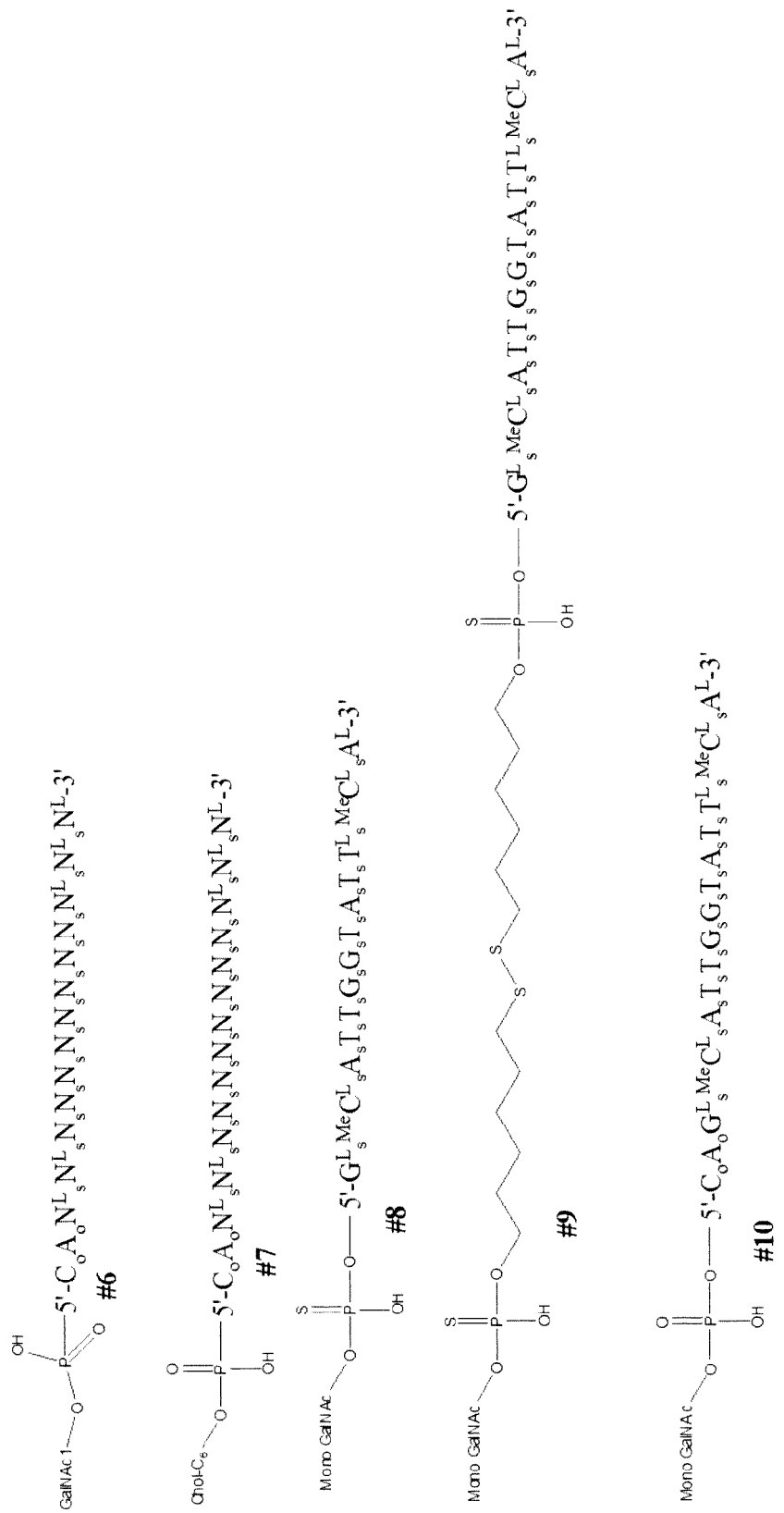
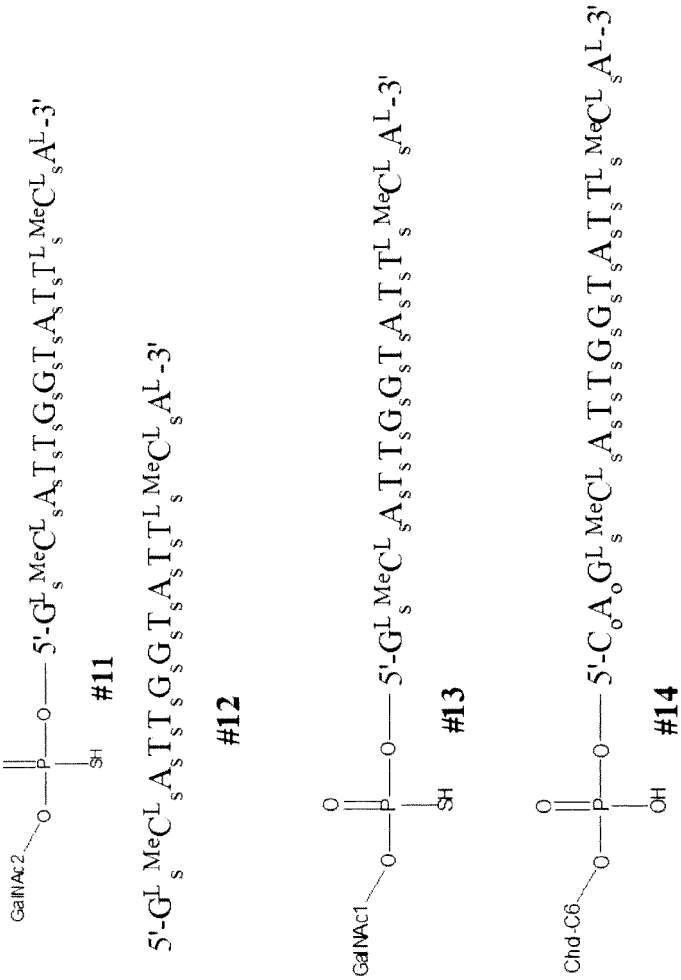


Figure 13 (cont)



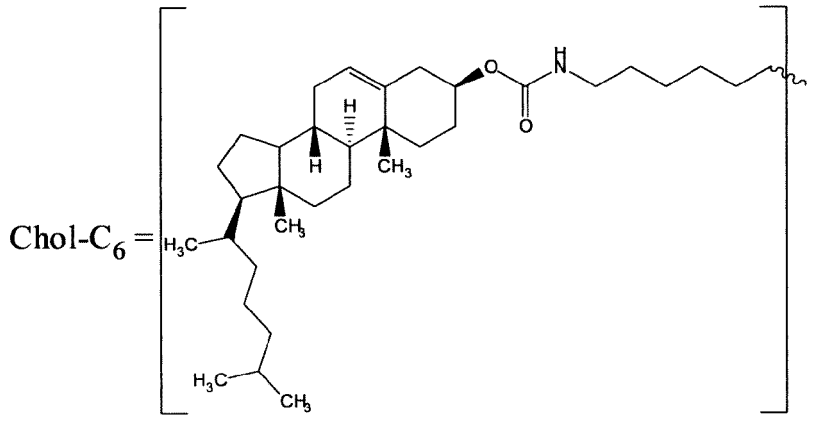
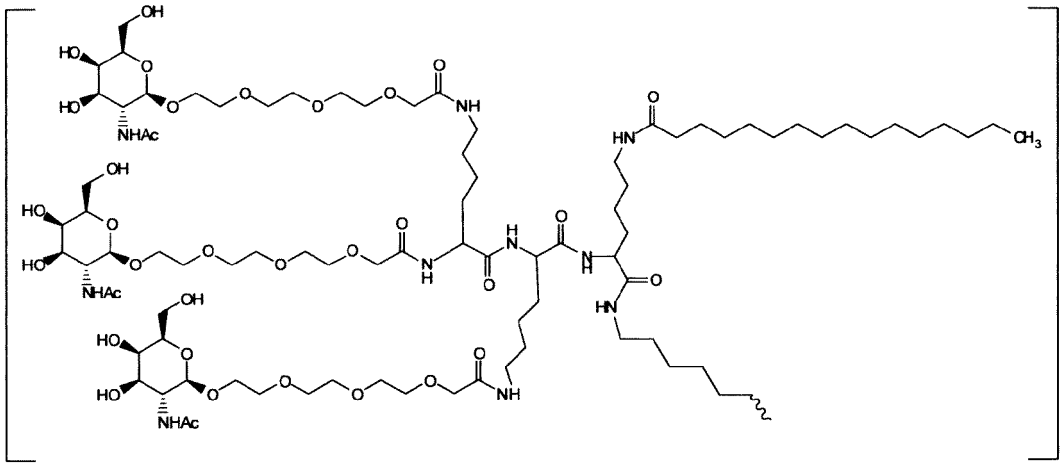
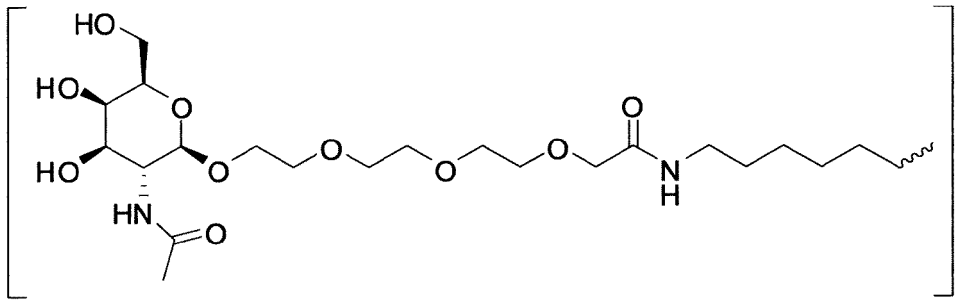


Figure 13 (cont)

GalNAc 1=



Mono GalNAc=



GalNAc2=

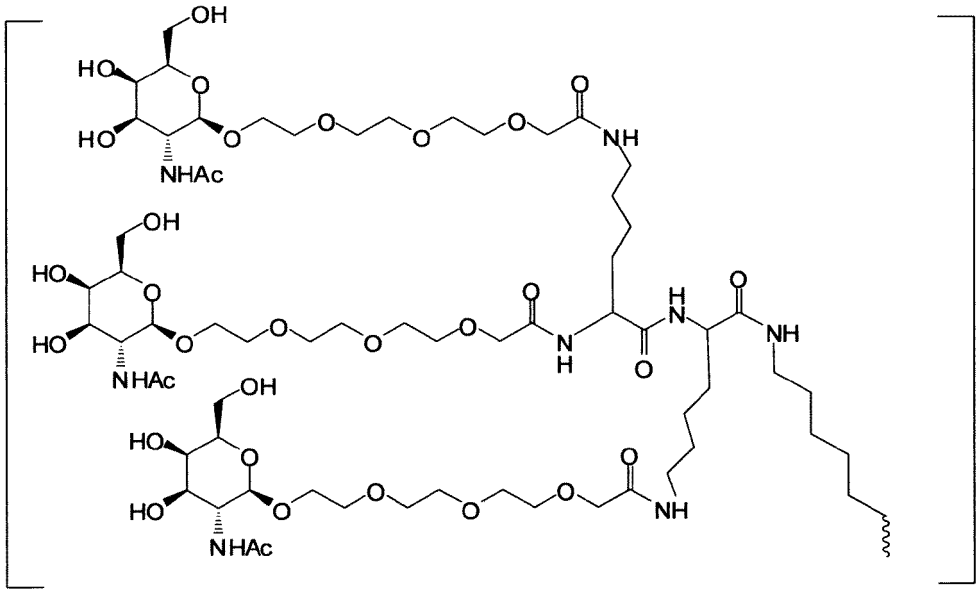
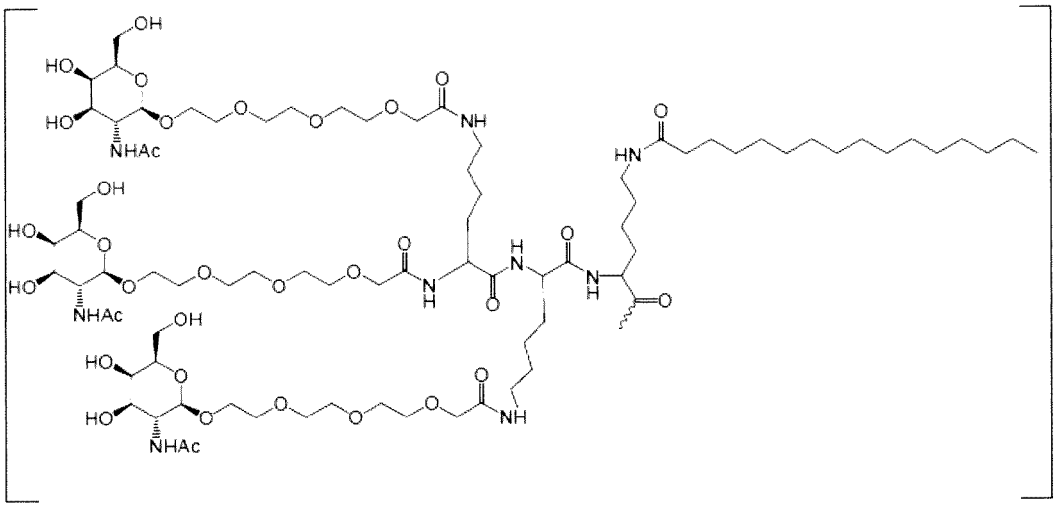
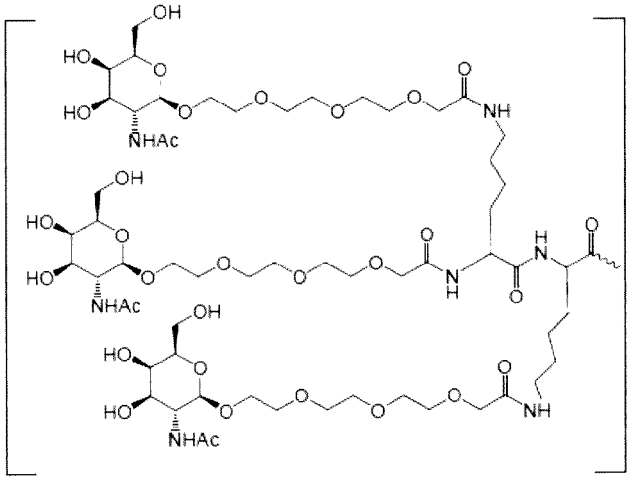


Figure 14

Conj 1=



Conj 2=



Conj 3=

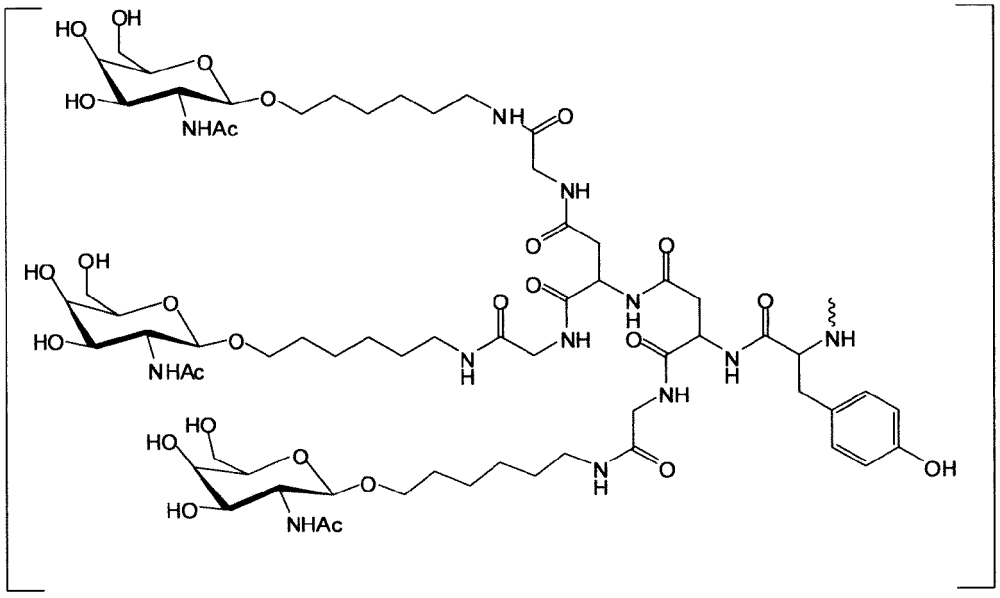


Figure 14 (cont)

Conj 4=

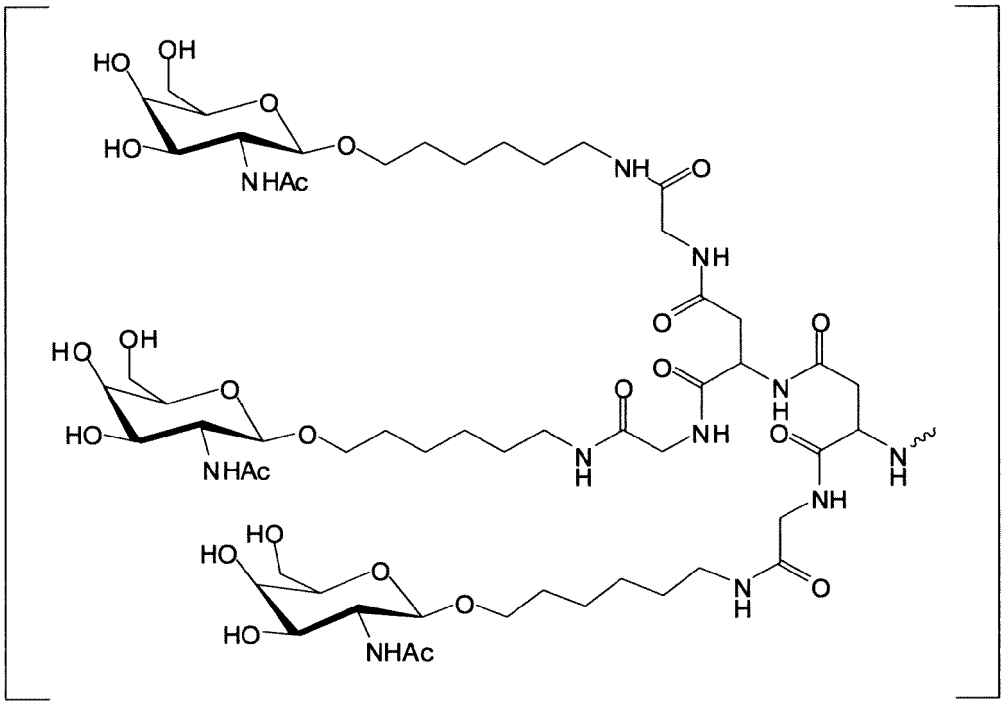
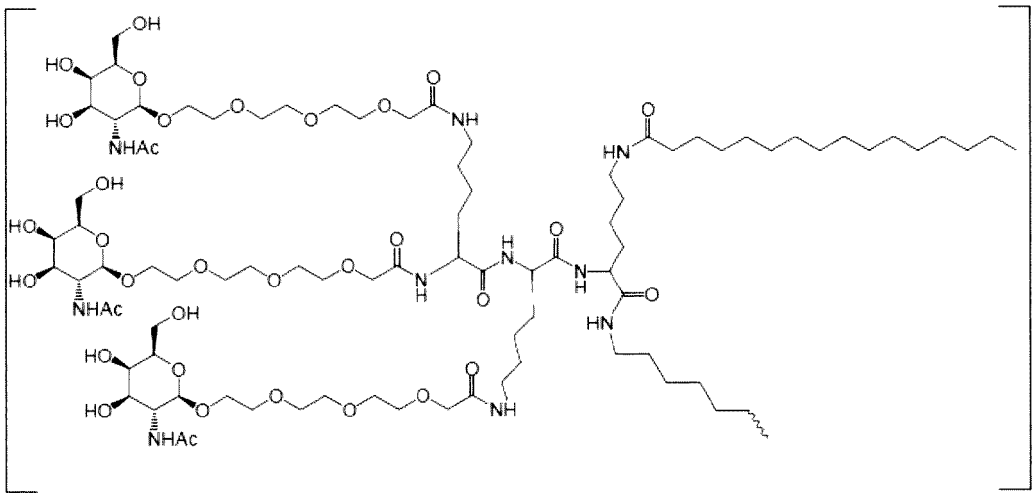
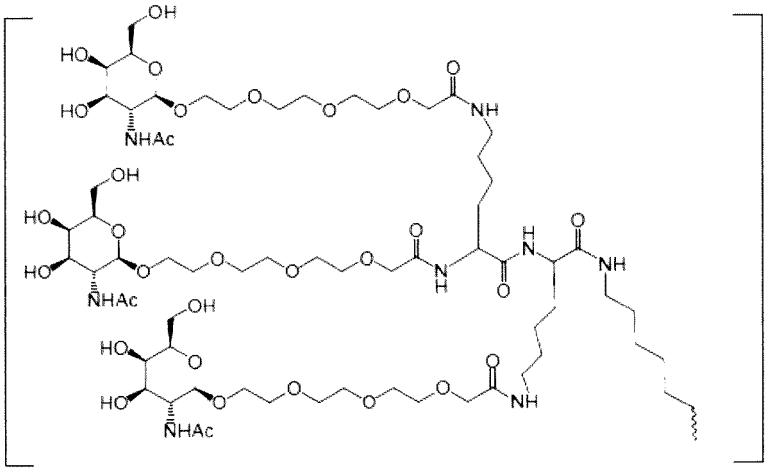


Figure 14 (cont)

Conj 1a=



Conj 2a=



Conj 3a=

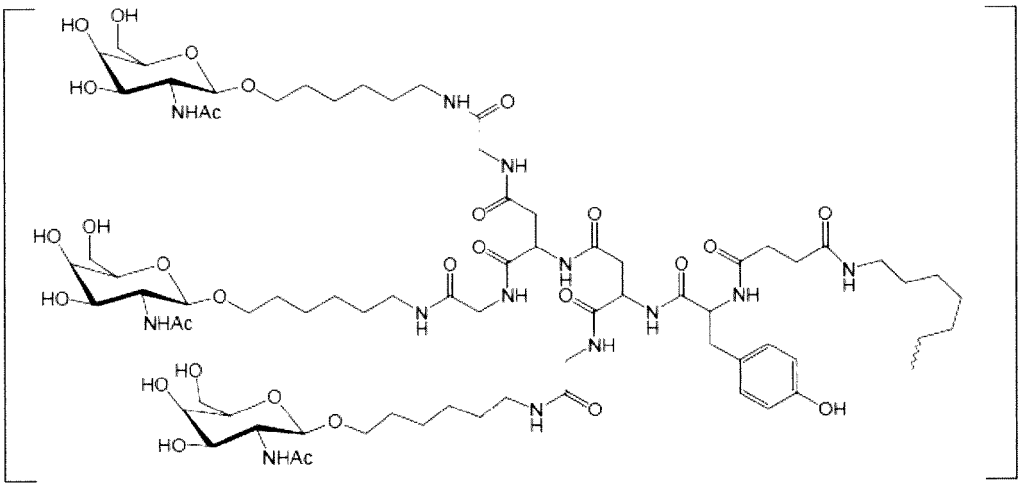


Figure 14 (cont)

Conj 4a=

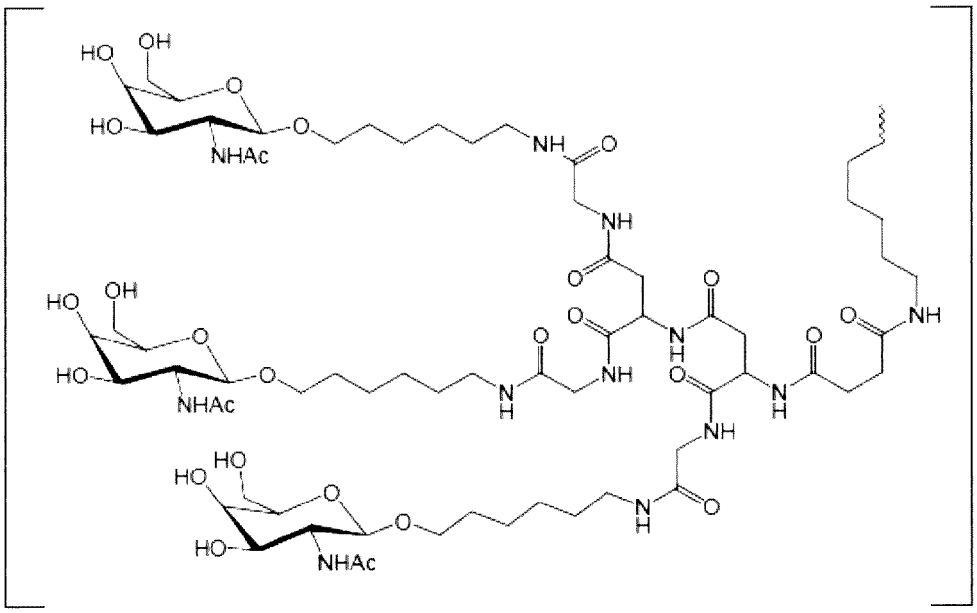


Figure 15

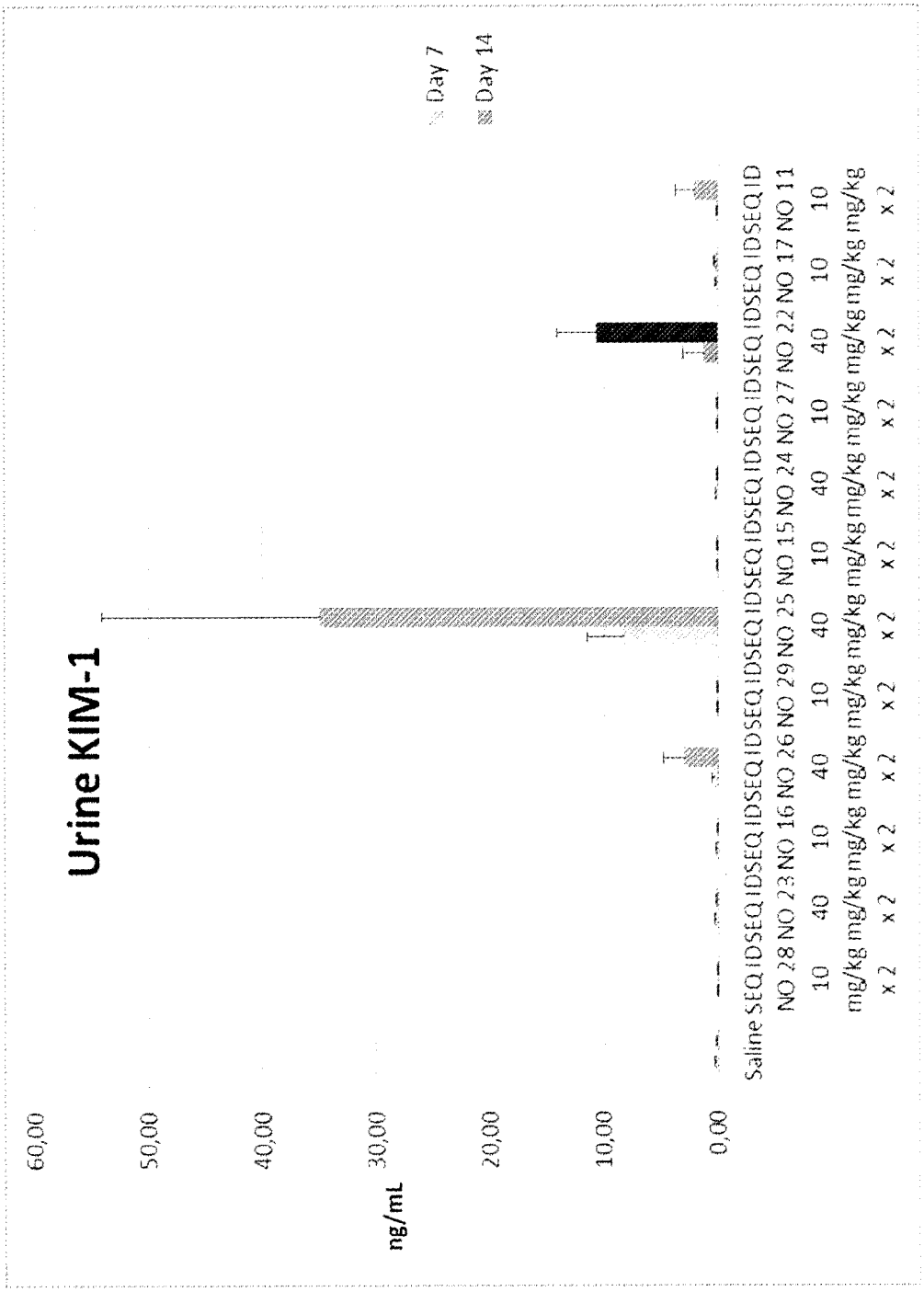
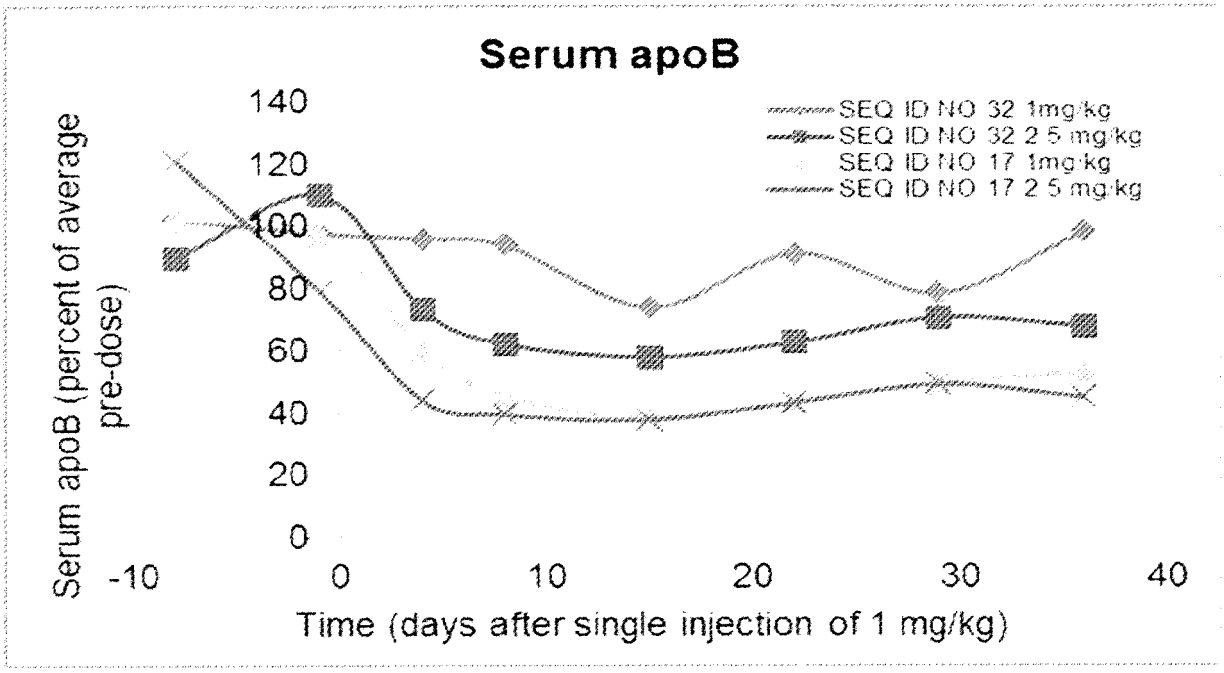

Urine KIM-1
ng/mL
60,00
50,00
40,00
30,00
20,00
10,00
0,00
Day 7
Day 14
Saline SEQ ID NO 28 x 2
SEQ ID NO 23 10 mg/kg x 2
SEQ ID NO 16 40 mg/kg x 2
SEQ ID NO 26 10 mg/kg x 2
SEQ ID NO 29 40 mg/kg x 2
SEQ ID NO 25 10 mg/kg x 2
SEQ ID NO 15 40 mg/kg x 2
SEQ ID NO 24 10 mg/kg x 2
SEQ ID NO 27 40 mg/kg x 2
SEQ ID NO 22 10 mg/kg x 2
SEQ ID NO 17 40 mg/kg x 2
SEQ ID NO 11 10 mg/kg x 2

Figure 16


Serum apoB
SEQ ID NO 32 1mg/kg
SEQ ID NO 32 2 5 mg/kg
SEQ ID NO 17 1mg/kg
SEQ ID NO 17 2 5 mg/kg
Serum apoB (percent of average pre-dose)
140
120
100
80
60
40
20
0
-10
0
10
20
30
40
Time (days after single injection of 1 mg/kg)

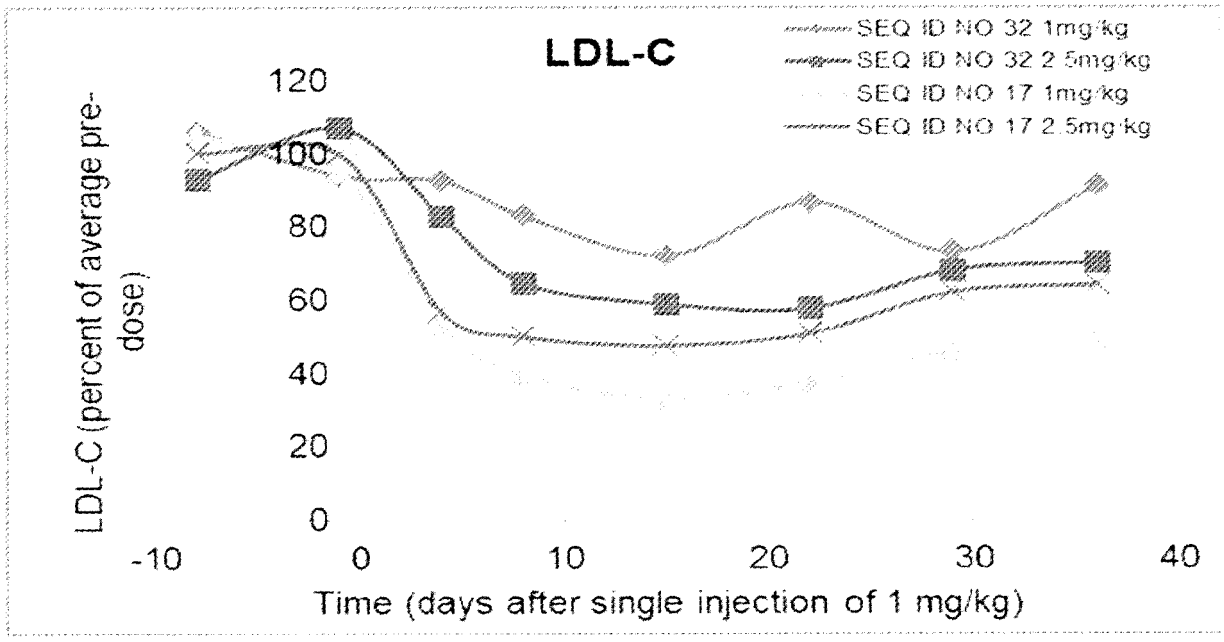

LDL-C
SEQ ID NO 32 1mg/kg
SEQ ID NO 32 2 5mg/kg
SEQ ID NO 17 1mg/kg
SEQ ID NO 17 2 5mg/kg
LDL-C (percent of average pre-dose)
120
100
80
60
40
20
0
-10
0
10
20
30
40
Time (days after single injection of 1 mg/kg)

Figure 17

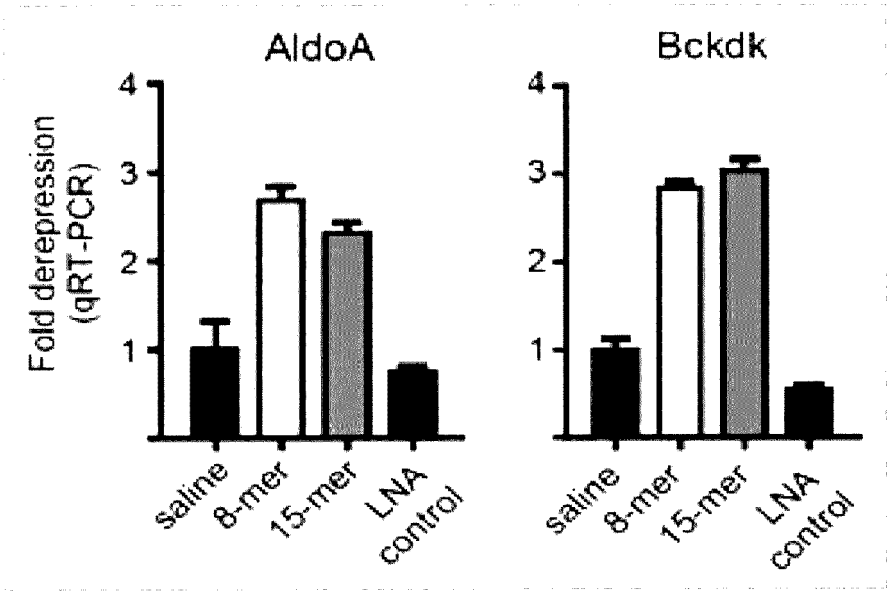

AldoA
Bckdk
Fold derepression (qRT-PCR)
4
3
2
1
saline
8-mer
15-mer
LNA control

Figure 18

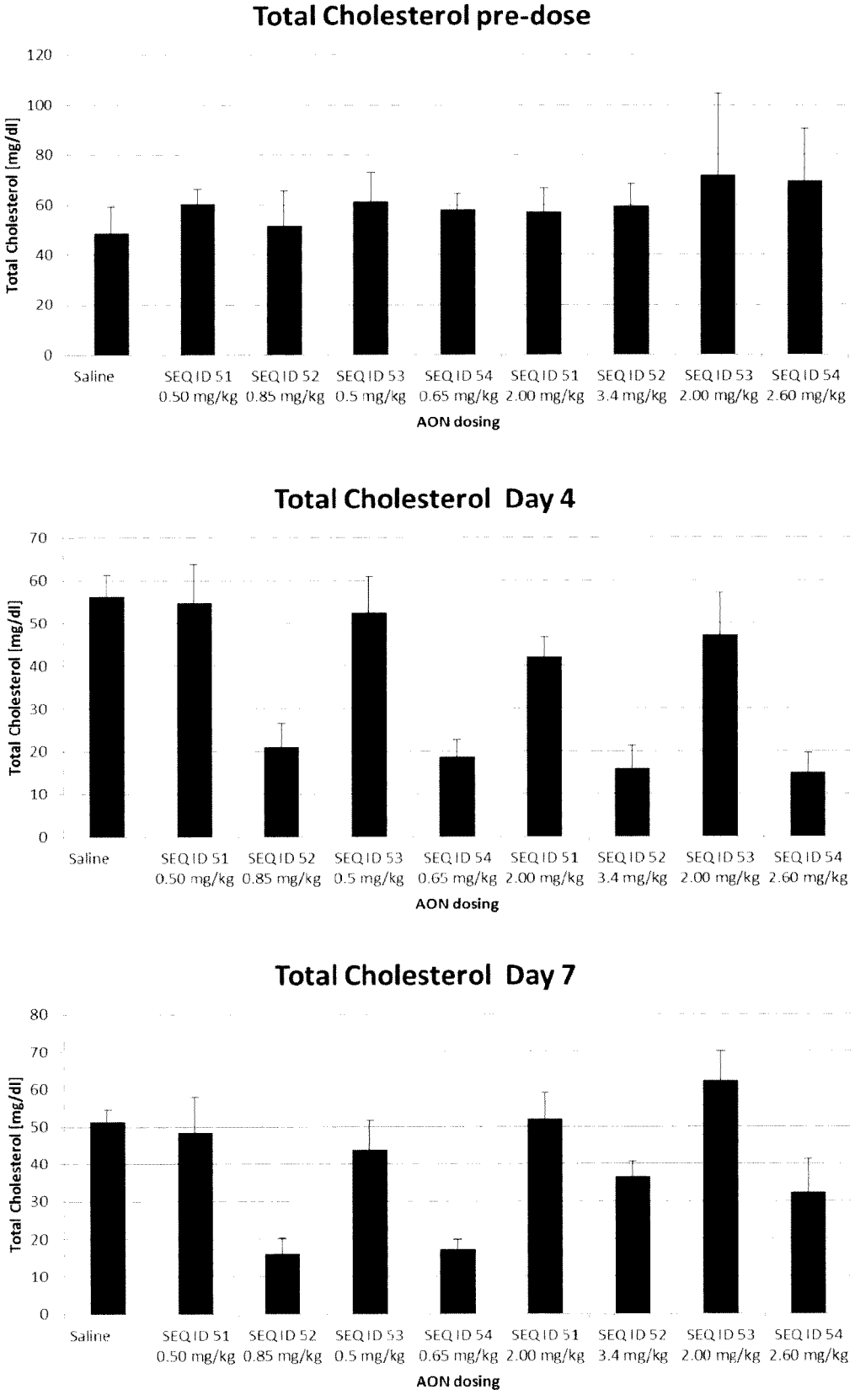

Total Cholesterol pre-dose
Total Cholesterol [mg/dl]
120
100
80
60
40
20
0
Saline
SEQ ID 51 0.50 mg/kg
SEQ ID 52 0.85 mg/kg
SEQ ID 53 0.5 mg/kg
SEQ ID 54 0.65 mg/kg
SEQ ID 51 2.00 mg/kg
SEQ ID 52 3.4 mg/kg
SEQ ID 53 2.00 mg/kg
SEQ ID 54 2.60 mg/kg
AON dosing
Total Cholesterol Day 4
Total Cholesterol [mg/dl]
70
60
50
40
30
20
10
0
Saline
SEQ ID 51 0.50 mg/kg
SEQ ID 52 0.85 mg/kg
SEQ ID 53 0.5 mg/kg
SEQ ID 54 0.65 mg/kg
SEQ ID 51 2.00 mg/kg
SEQ ID 52 3.4 mg/kg
SEQ ID 53 2.00 mg/kg
SEQ ID 54 2.60 mg/kg
AON dosing
Total Cholesterol Day 7
Total Cholesterol [mg/dl]
80
70
60
50
40
30
20
10
0
Saline
SEQ ID 51 0.50 mg/kg
SEQ ID 52 0.85 mg/kg
SEQ ID 53 0.5 mg/kg
SEQ ID 54 0.65 mg/kg
SEQ ID 51 2.00 mg/kg
SEQ ID 52 3.4 mg/kg
SEQ ID 53 2.00 mg/kg
SEQ ID 54 2.60 mg/kg
AON dosing

Figure 19

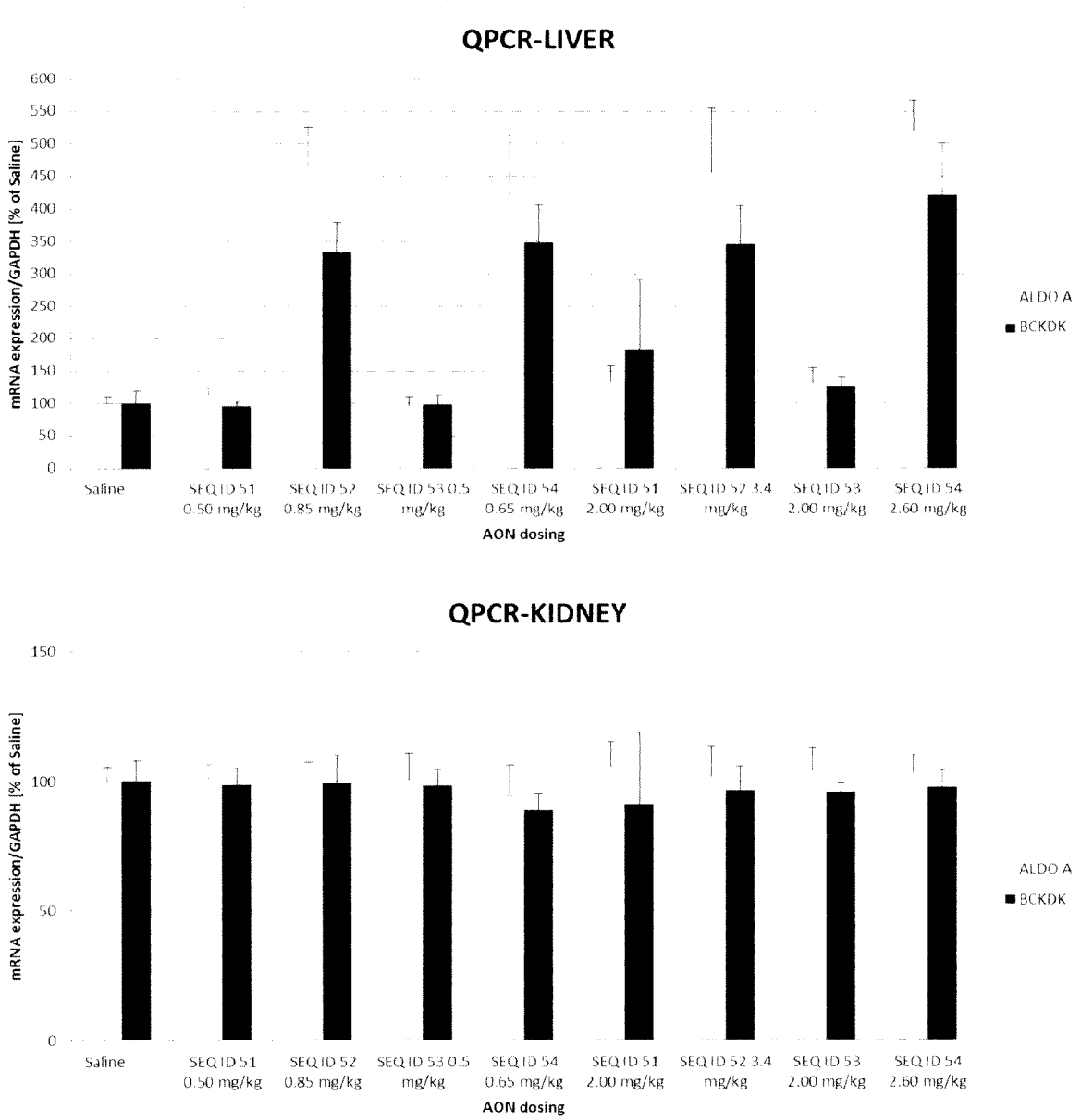

QPCR-LIVER
mRNA expression/GAPDH [% of Saline]
600
550
500
450
400
350
300
250
200
150
100
50
0
Saline
SEQ ID 51 0.50 mg/kg
SEQ ID 52 0.85 mg/kg
SEQ ID 53 0.5 mg/kg
SEQ ID 54 0.65 mg/kg
SEQ ID 51 2.00 mg/kg
SEQ ID 52 3.4 mg/kg
SEQ ID 53 2.00 mg/kg
SEQ ID 54 2.60 mg/kg
AON dosing
ALDO A
BCKDK
QPCR-KIDNEY
mRNA expression/GAPDH [% of Saline]
150
100
50
0
Saline
SEQ ID 51 0.50 mg/kg
SEQ ID 52 0.85 mg/kg
SEQ ID 53 0.5 mg/kg
SEQ ID 54 0.65 mg/kg
SEQ ID 51 2.00 mg/kg
SEQ ID 52 3.4 mg/kg
SEQ ID 53 2.00 mg/kg
SEQ ID 54 2.60 mg/kg
AON dosing
ALDO A
BCKDK

Figure 20

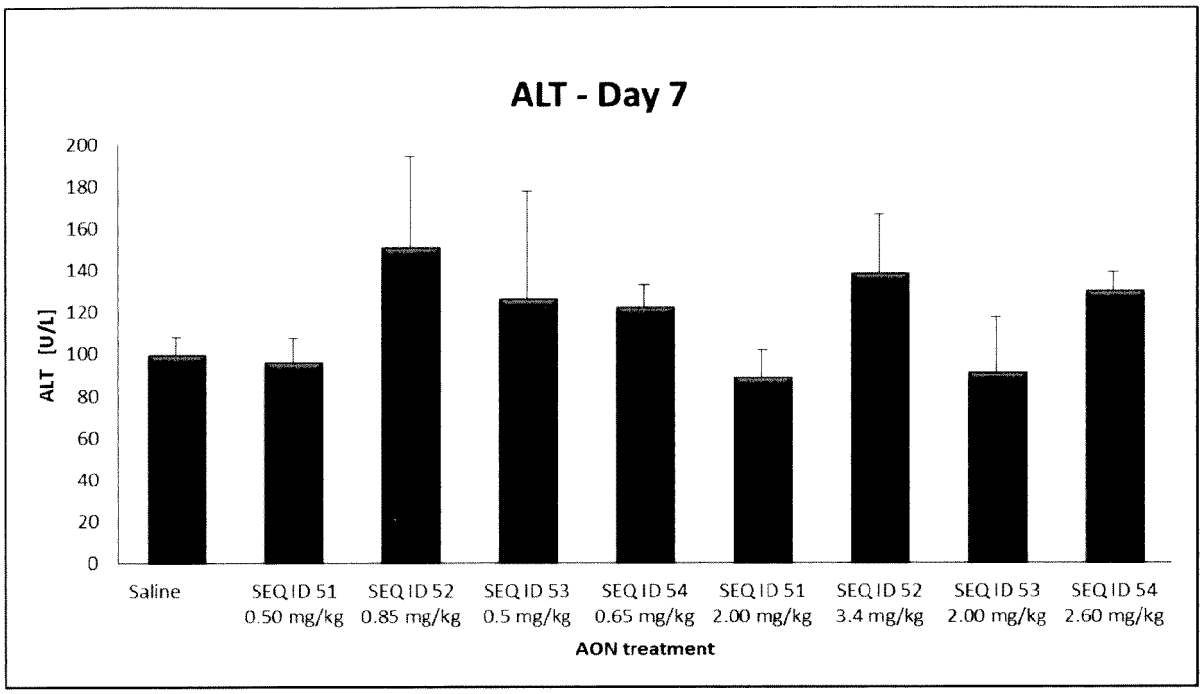


Figure 21

