FIGURES

Figure 1

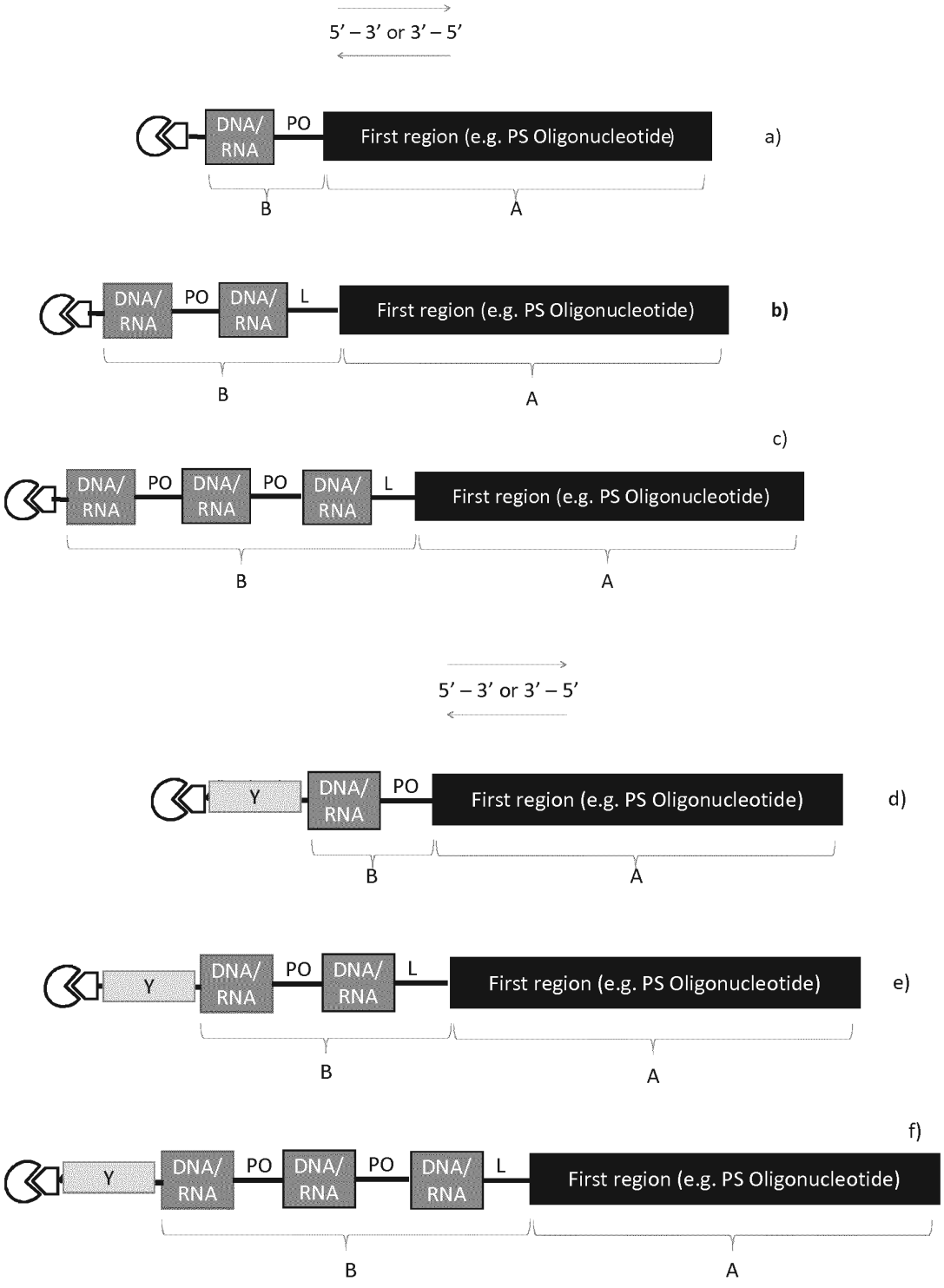


Figure 2

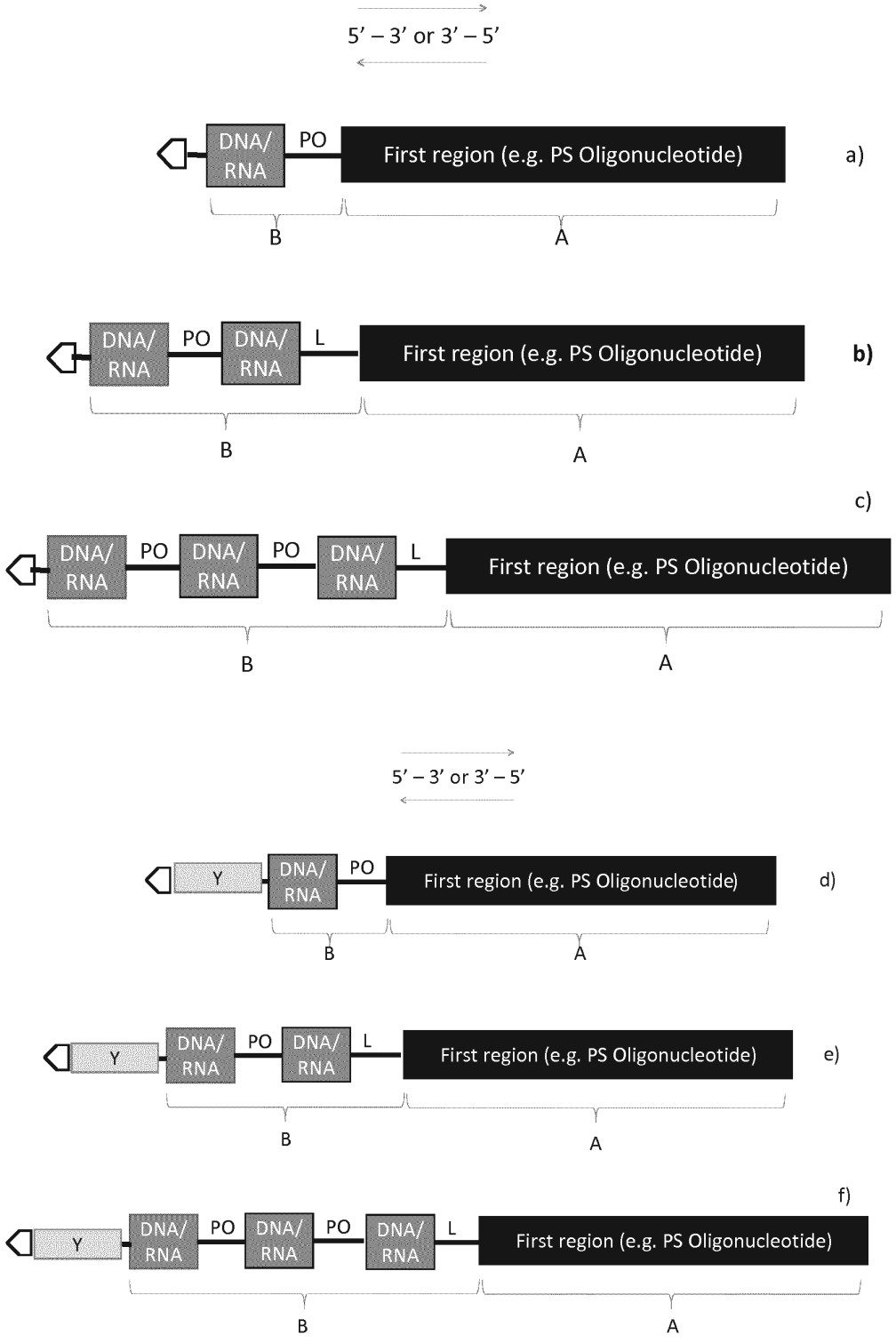

5' – 3' or 3' – 5'
DNA/ RNA
PO
First region (e.g. PS Oligonucleotide)
a)
B
A
DNA/ RNA
PO
DNA/ RNA
L
First region (e.g. PS Oligonucleotide)
b)
B
A
c)
DNA/ RNA
PO
DNA/ RNA
PO
DNA/ RNA
L
First region (e.g. PS Oligonucleotide)
B
A
5' – 3' or 3' – 5'
Y
DNA/ RNA
PO
First region (e.g. PS Oligonucleotide)
d)
B
A
Y
DNA/ RNA
PO
DNA/ RNA
L
First region (e.g. PS Oligonucleotide)
e)
B
A
f)
Y
DNA/ RNA
PO
DNA/ RNA
PO
DNA/ RNA
L
First region (e.g. PS Oligonucleotide)
B
A

Figure 3

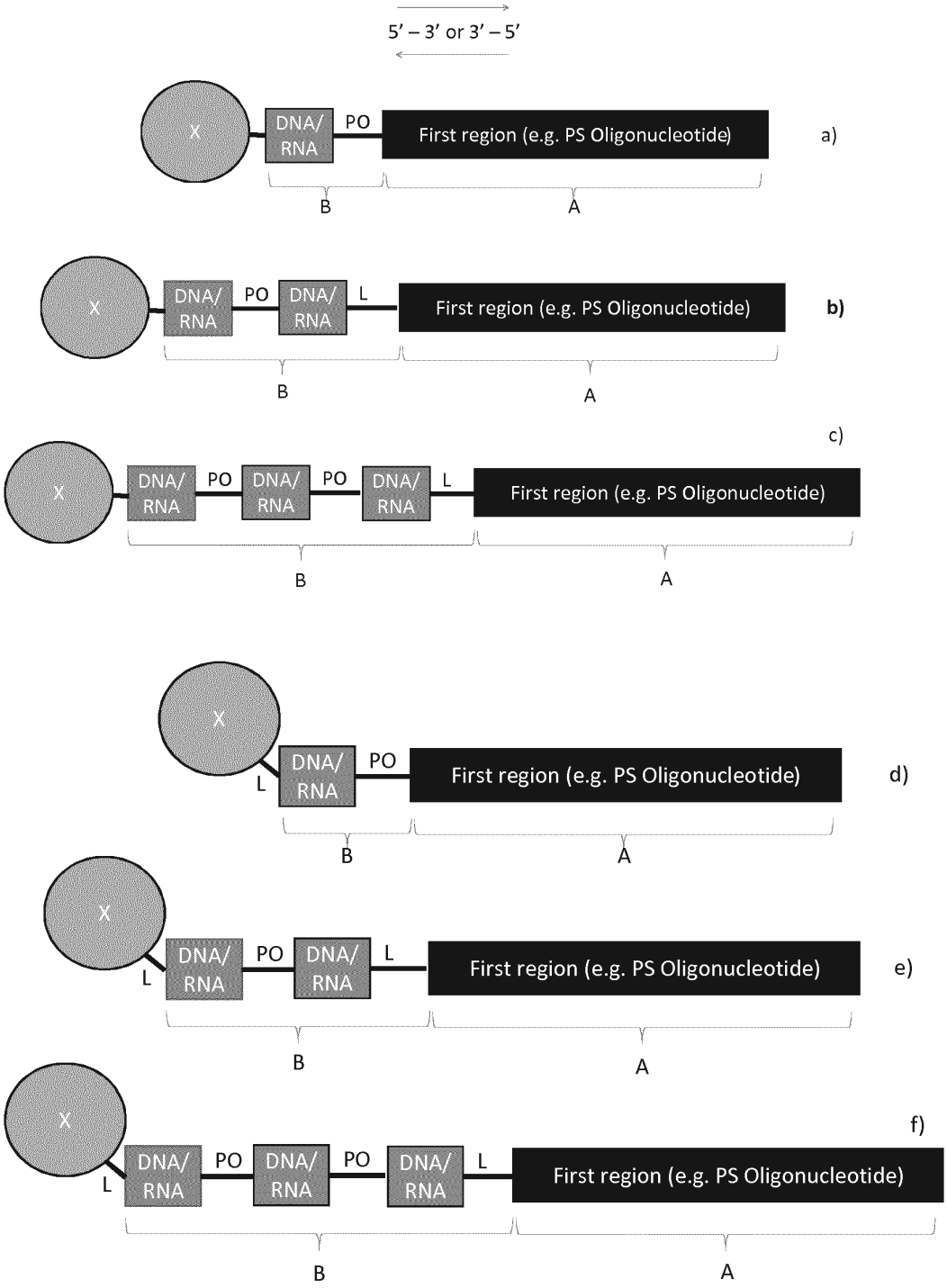

5' – 3' or 3' – 5'
X
DNA/ RNA
PO
First region (e.g. PS Oligonucleotide)
a)
B
A
X
DNA/ RNA
PO
DNA/ RNA
L
First region (e.g. PS Oligonucleotide)
b)
B
A
c)
X
DNA/ RNA
PO
DNA/ RNA
PO
DNA/ RNA
L
First region (e.g. PS Oligonucleotide)
B
A
X
L
DNA/ RNA
PO
First region (e.g. PS Oligonucleotide)
d)
B
A
X
L
DNA/ RNA
PO
DNA/ RNA
L
First region (e.g. PS Oligonucleotide)
e)
B
A
X
L
DNA/ RNA
PO
DNA/ RNA
PO
DNA/ RNA
L
First region (e.g. PS Oligonucleotide)
f)
B
A

Figure 4

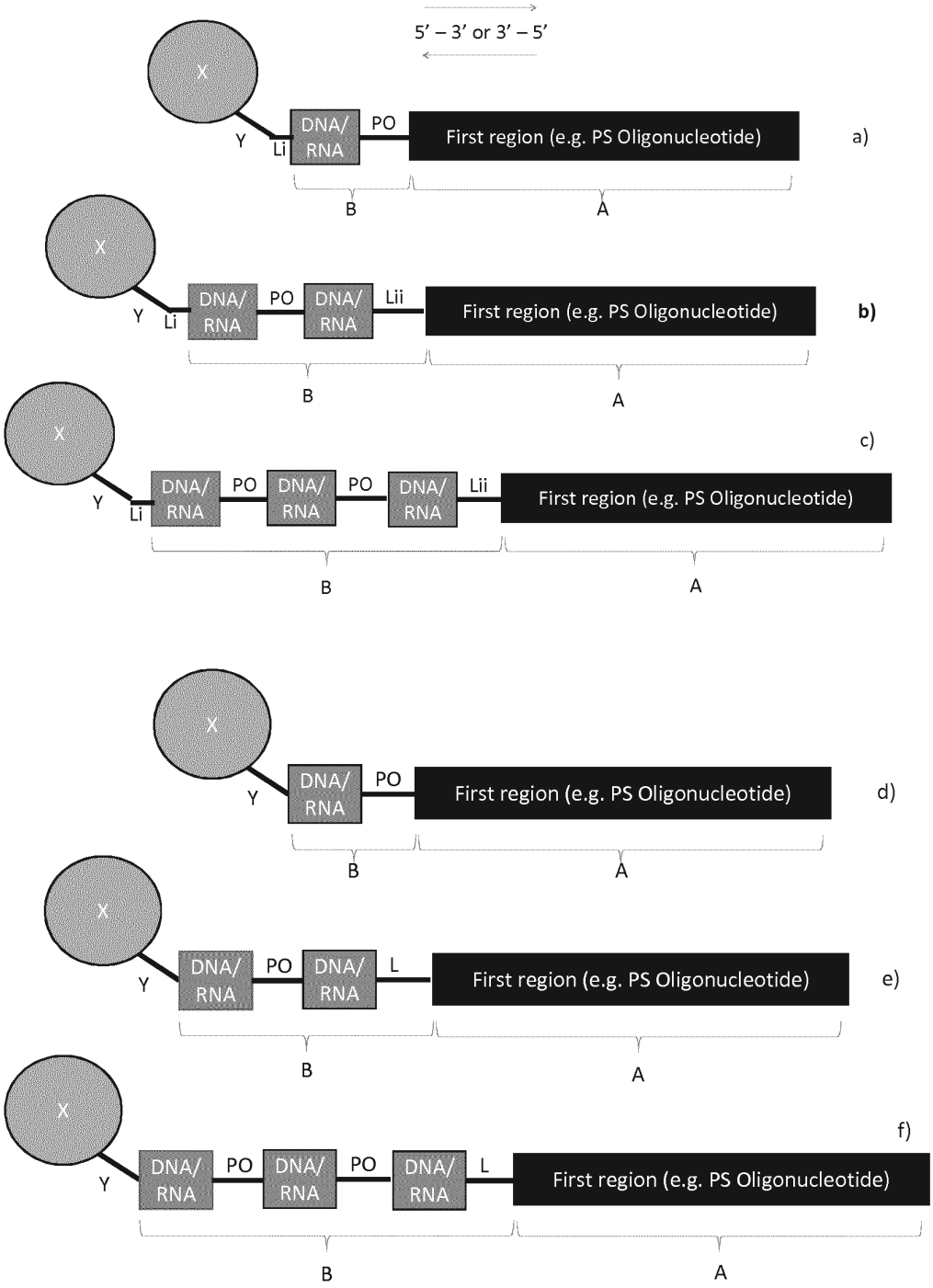

5' – 3' or 3' – 5'
X
Y
Li
DNA/ RNA
PO
First region (e.g. PS Oligonucleotide)
a)
B
A
Lii
b)
c)
d)
L
e)
f)

Figure 5a

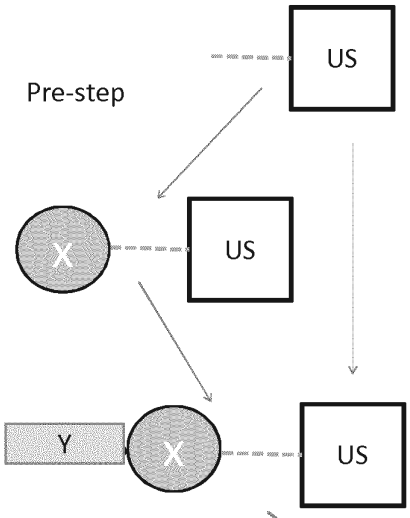


Figure 5b

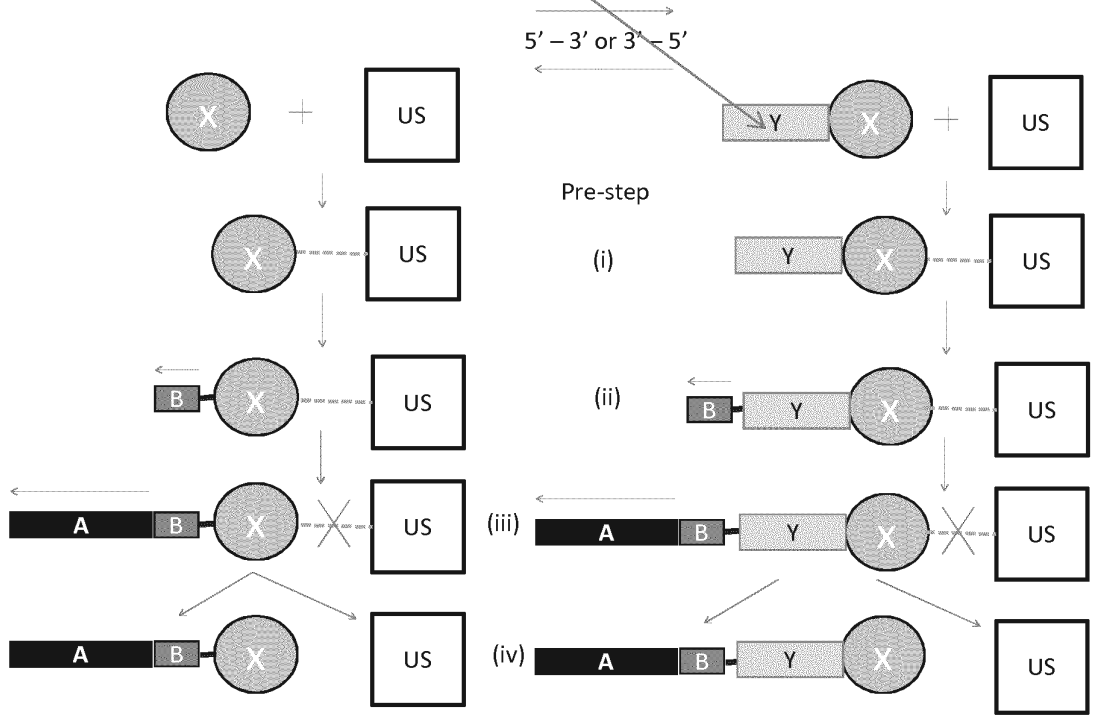


Figure 6

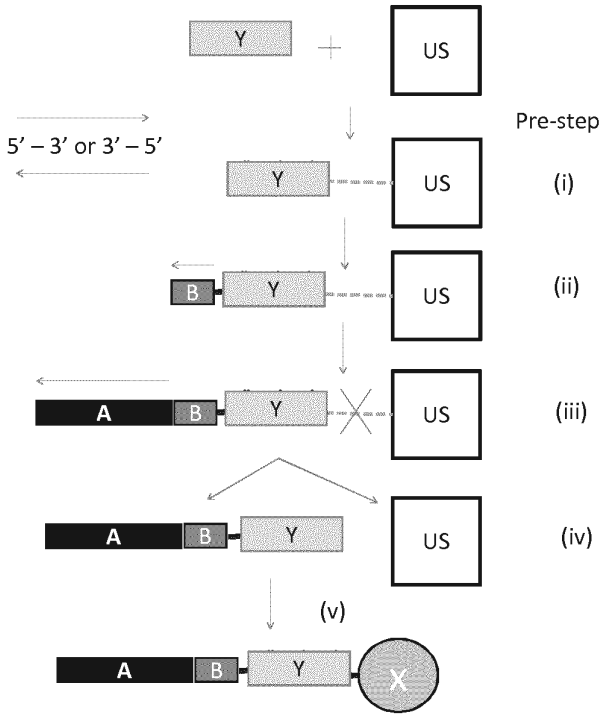


Figure 7

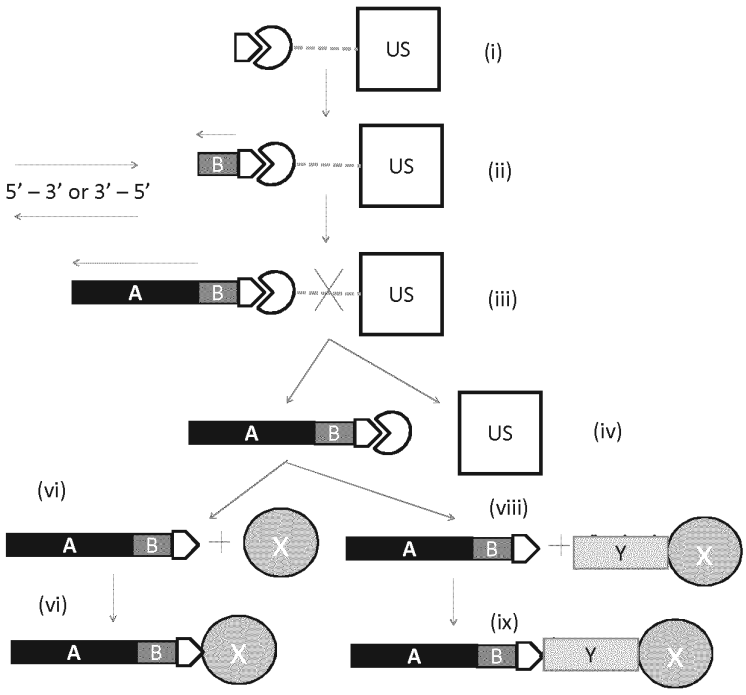


Figure 8

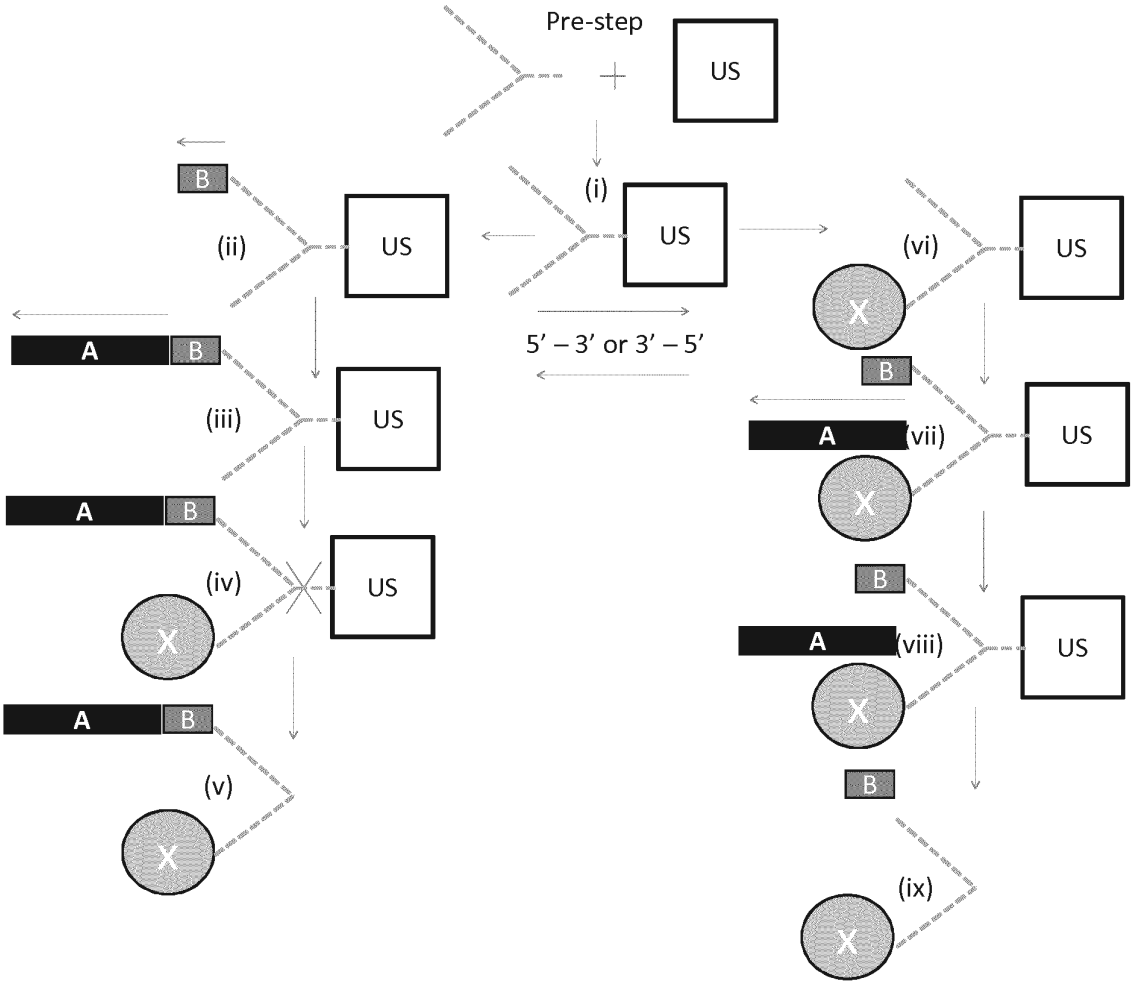

Pre-step
US
(i)
US
5' – 3' or 3' – 5'
B
(ii)
US
A
B
(iii)
US
A
B
(iv)
US
X
A
B
(v)
X
(vi)
US
X
B
A
(vii)
US
X
B
A
(viii)
US
X
B
(ix)
X

Figure 9

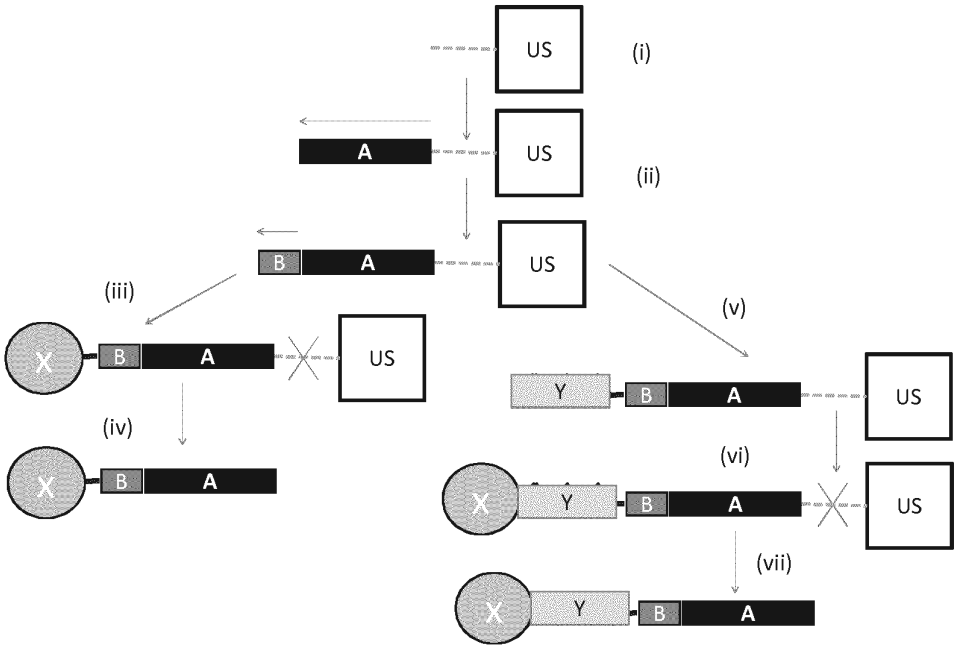


Figure 10

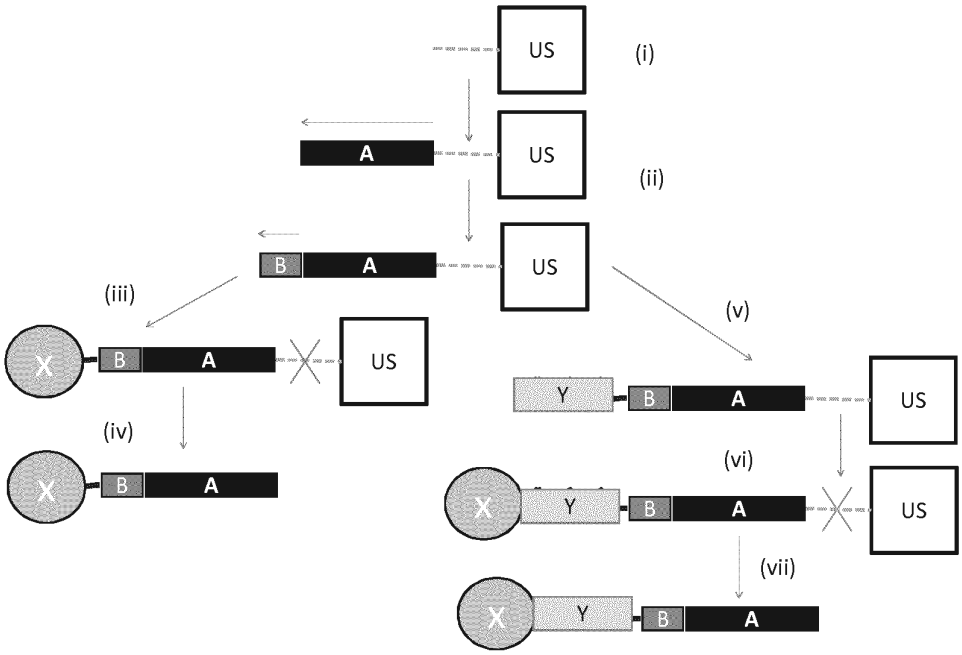
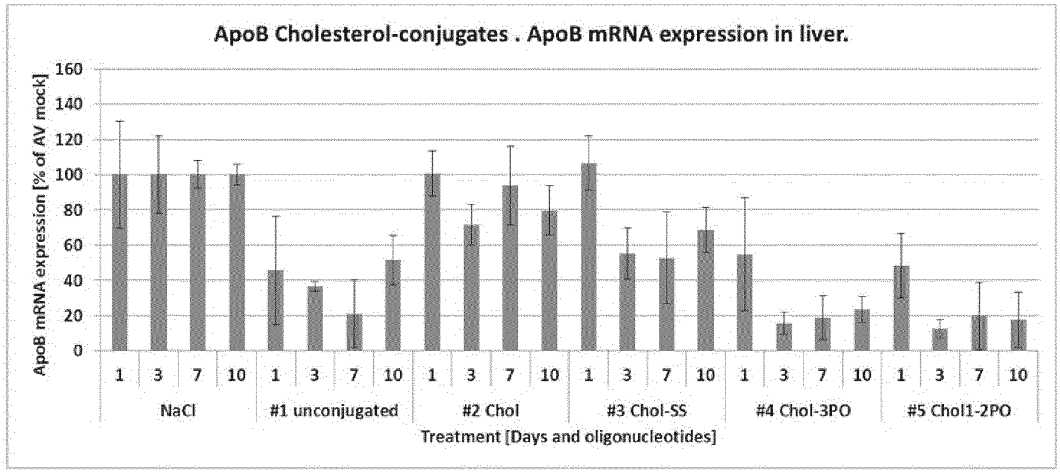


Figure 11

A


ApoB Cholesterol-conjugates . ApoB mRNA expression in liver.
ApoB mRNA expression [% of AV mock]
0
20
40
60
80
100
120
140
160
1 3 7 10 1 3 7 10 1 3 7 10 1 3 7 10 1 3 7 10 1 3 7 10
NaCl
#1 unconjugated
#2 Chol
#3 Chol-SS
#4 Chol-3PO
#5 Chol1-2PO
Treatment [Days and oligonucleotides]

B

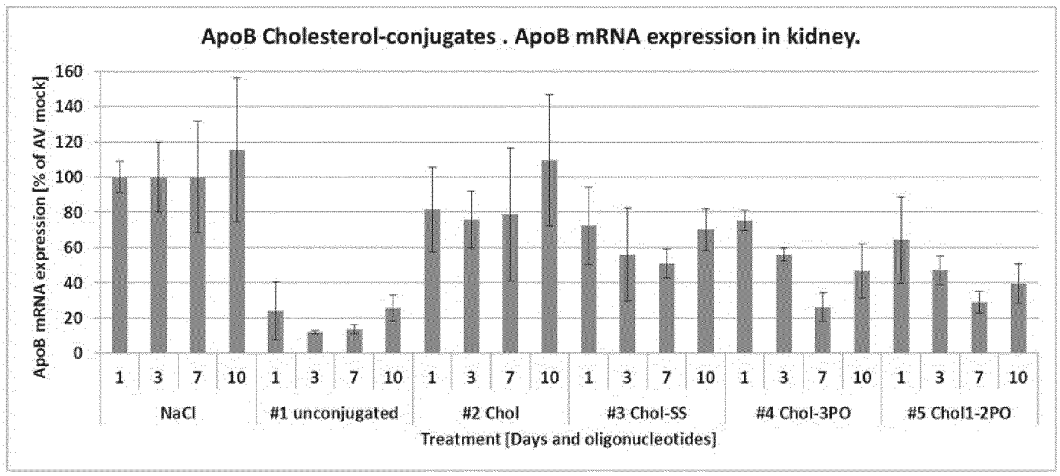
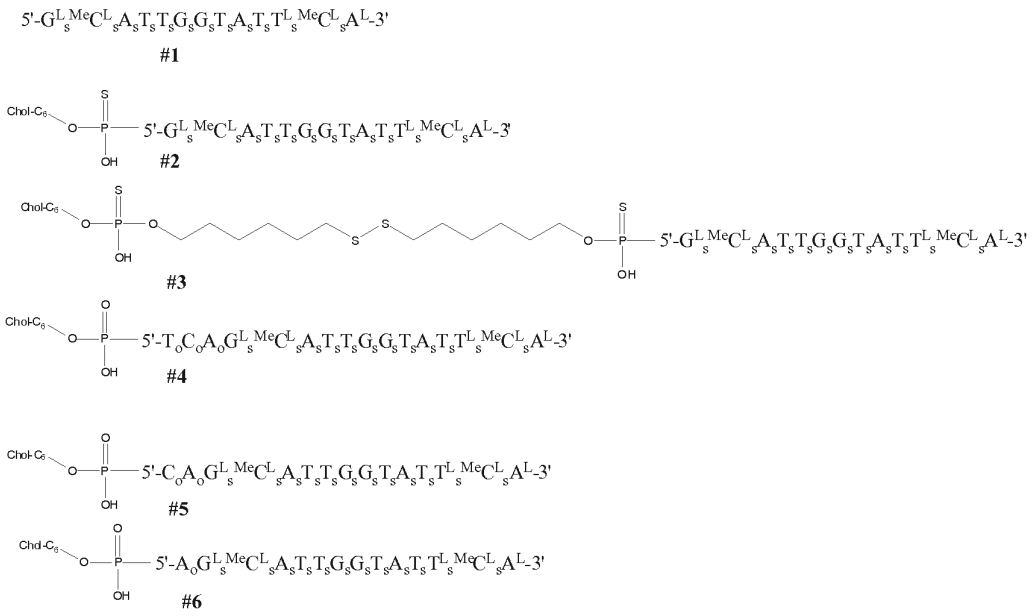

ApoB Cholesterol-conjugates . ApoB mRNA expression in kidney.
ApoB mRNA expression [% of AV mock]
0
20
40
60
80
100
120
140
160
1 3 7 10 1 3 7 10 1 3 7 10 1 3 7 10 1 3 7 10 1 3 7 10
NaCl
#1 unconjugated
#2 Chol
#3 Chol-SS
#4 Chol-3PO
#5 Chol1-2PO
Treatment [Days and oligonucleotides]

Figure 12


5'-G^L_s^MeC^L_sA_sT_sT_sG_sG_sT_sA_sT_sT^L_s^MeC^L_sA^L-3'
#1
Chol-C6
5'-G^L_s^MeC^L_sA_sT_sT_sG_sG_sT_sA_sT_sT^L_s^MeC^L_sA^L-3'
#2
Chol-C6
5'-G^L_s^MeC^L_sA_sT_sT_sG_sG_sT_sA_sT_sT^L_s^MeC^L_sA^L-3'
#3
Chol-C6
5'-T_oC_oA_oG^L_s^MeC^L_sA_sT_sT_sG_sG_sT_sA_sT_sT^L_s^MeC^L_sA^L-3'
#4
Chol-C6
5'-C_oA_oG^L_s^MeC^L_sA_sT_sT_sG_sG_sT_sA_sT_sT^L_s^MeC^L_sA^L-3'
#5
Chol-C6
5'-A_oG^L_s^MeC^L_sA_sT_sT_sG_sG_sT_sA_sT_sT^L_s^MeC^L_sA^L-3'
#6



#7



#8



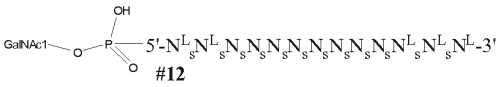
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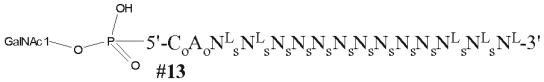
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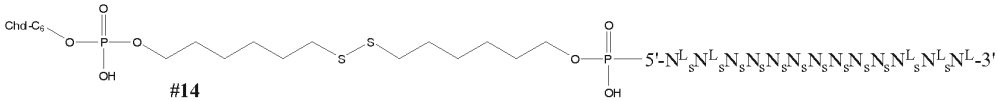
#11



#12



#13



#14



#15



#16



#17



#18



#19



#20

5'-$N^L_sN^L_sN^L_sN_sN_sN_sN_sN_sN_sN_sN_sN^L_sN^L_sN^L_oN_oN_oN_oN_sN_sN_sN_sN_sN^L_sN^L_sN^L_sN^L$-3'
#21

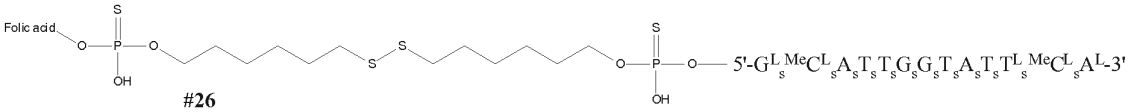
5'-$N^L_sN^L_sN^L_sN_sN_sN_sN_sN_sN_sN_sN_sN_sN^L_sN^L_sN^L_sN_sN_sN_sN_sN_sN_sN_sN_sN^L_sN^L_sN^L_sN^L$-3'
#22

5'-$N^L_sN^L_sN^L_sN_sN_sN_sN_sN_sN_sN_sN_sN_sN^L_sN^L_sN^L_oN_oN_oN_oN_sN_sN_sN_sN_sN^L_sN^L_sN^L_sN^L$-3'
#23

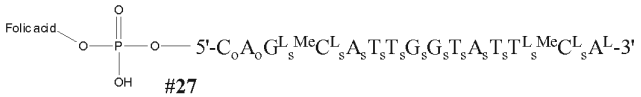
5'-$N^L_sN^L_sN^L_sN_sN_sN_sN_sN_sN_sN_sN_sN_sN^L_sN^L_sN^L_sN_sN_sN_sN_sN_sN_sN_sN_sN^L_sN^L_sN^L_sN^L$-3'
#24



#25



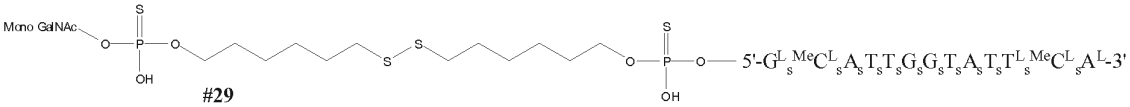
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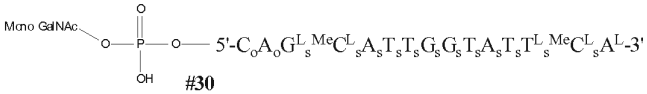
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#28



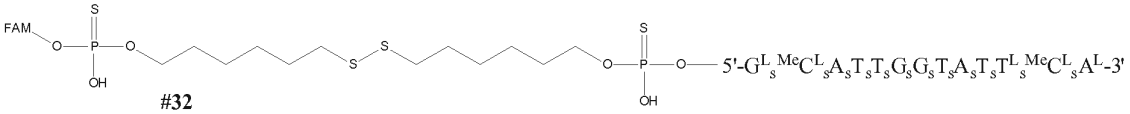
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#30



#31



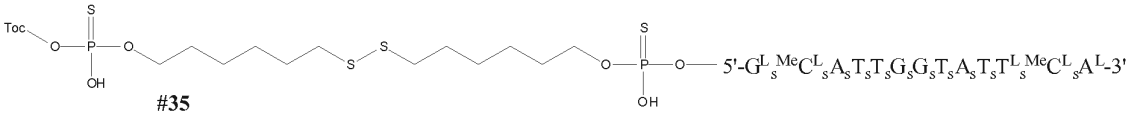
#32



#33



#34



#35



#36

5'-TLsGLsMeCLsTsAsCsAsAsAsAsCsMeCLsMeCLsALs-3'
SEQ ID 37

5'- ALsALs TLsGsCsTsAsCsAsAsAsAsMeCLsMeCLsMeCLsALs-3'
SEQ ID 38

5'-ALsALsTLsGsCsTsAsCsAsAsAsAsCsMeCLsMeCLsALs-3'
SEQ ID 39

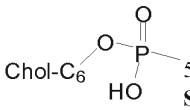
5'-GLsMeCLsTsGsTsGsTsGsAsGsCsTsTsGLsGL-3'
SEQ ID 40

5'-TLsGLsCsTsGsTsGsTsGsAsGsCsTsTLsGLsGL-3'
SEQ ID 41

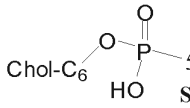
5'-TLsGLsMeCLsTsGsTsGsTsGsAsGsCsTsTLsGLsGL-3'
SEQ ID 42

5'-TLsMeCLsMeCLsTsGsGsTsCsTsGsTsGsTsTLsMeCLsMeCL-3'
SEQ ID 43

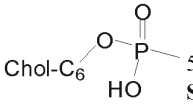
5'-TLsMeCLsMeCLsTsGsGsTsCsTsGsTsGsTsTsMeCLsMeCL-3'
SEQ ID 44



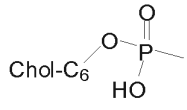
5'-CoAoTLsGLsMeCLsTsAsCsAsAsAsAsCsMeCLsMeCLsALs-3'
SEQ ID 45



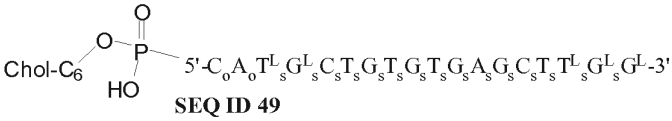
5'- CoAoALsALs TLsGsCsTsAsCsAsAsAsAsMeCLsMeCLsMeCLsALs-3
SEQ ID 46



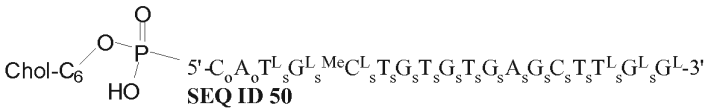
5'-CoAoALsALsTLsGsCsTsAsCsAsAsAsAsCsMeCLsMeCLsALs-3'
SEQ ID 47



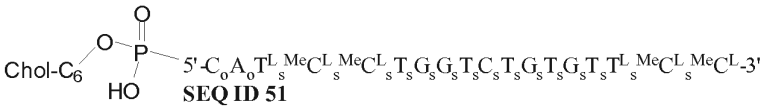
5'-CoAoGLsMeCLsTsGsTsGsTsGsAsGsCsTsTsGLsGL-3'
SEQ ID 48



SEQ ID 49



SEQ ID 50



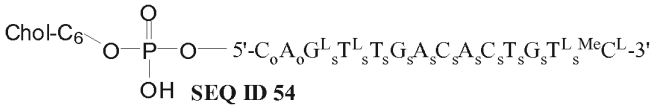
SEQ ID 51



SEQ ID 52



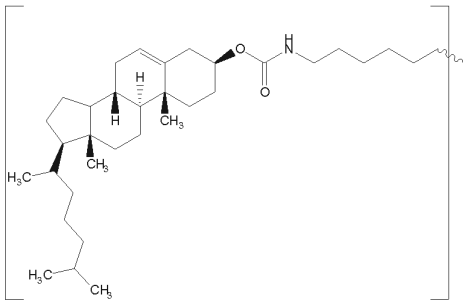
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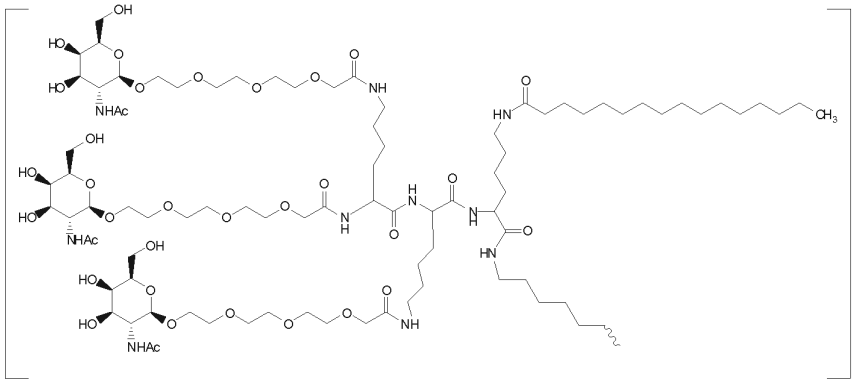
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Figure 13

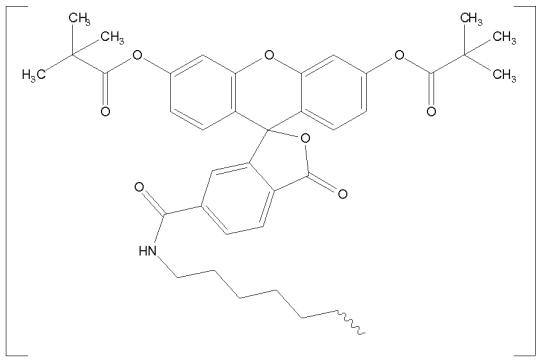
Chol-C_6 =



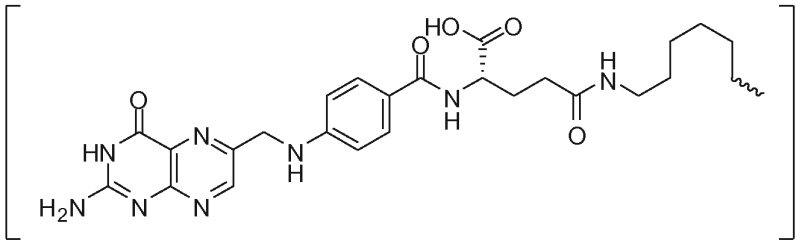
GalNAc 1=



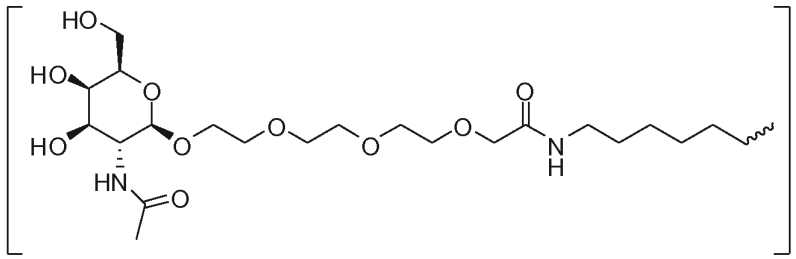
FAM=



Folic acid=



Mono GalNAc=



Toc=

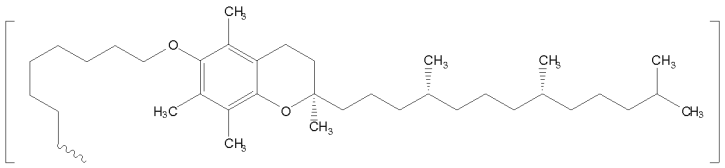
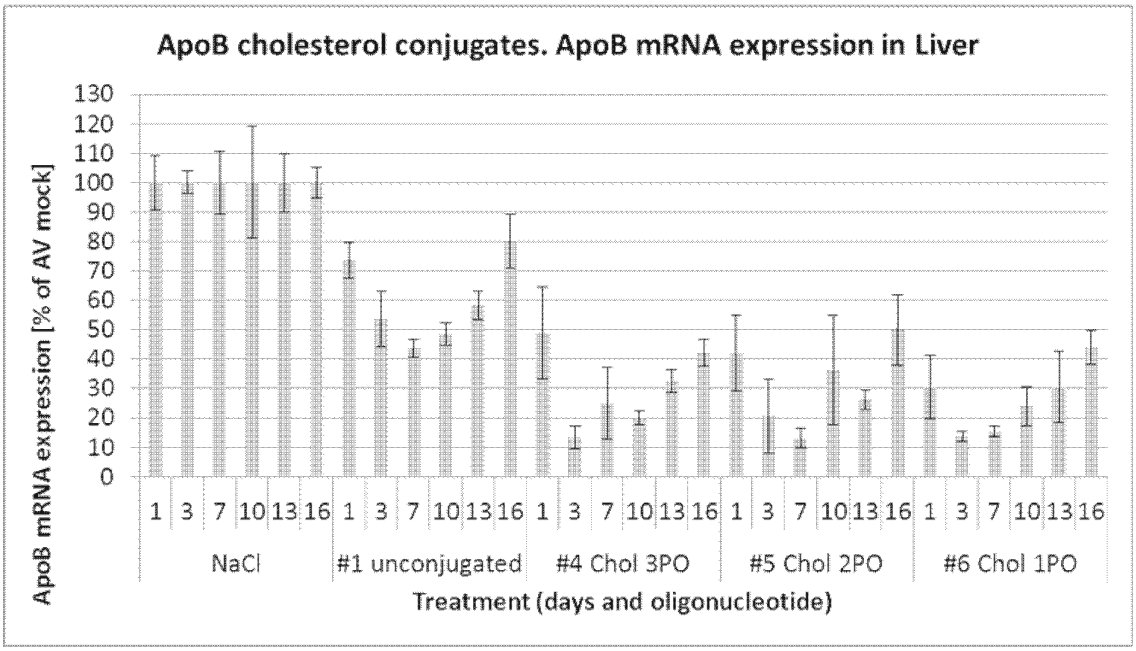


Figure 14

A


ApoB cholesterol conjugates. ApoB mRNA expression in Liver
ApoB mRNA expression [% of AV mock]
130
120
110
100
90
80
70
60
50
40
30
20
10
0
1 3 7 10 13 16 1 3 7 10 13 16 1 3 7 10 13 16 1 3 7 10 13 16 1 3 7 10 13 16
NaCl
#1 unconjugated
#4 Chol 3PO
#5 Chol 2PO
#6 Chol 1PO
Treatment (days and oligonucleotide)

B

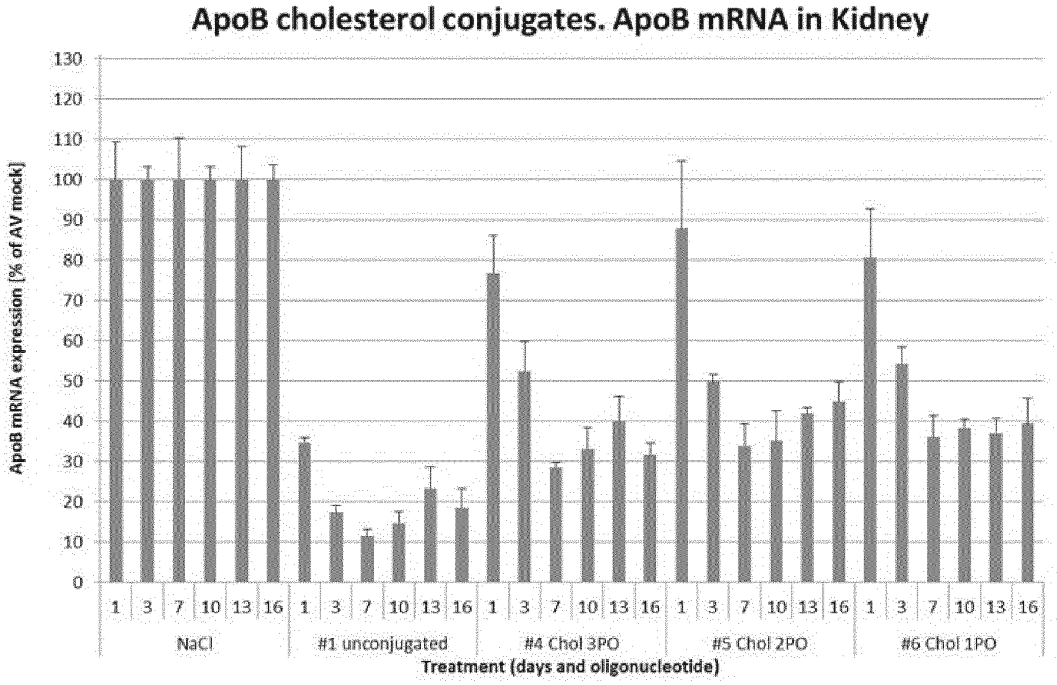
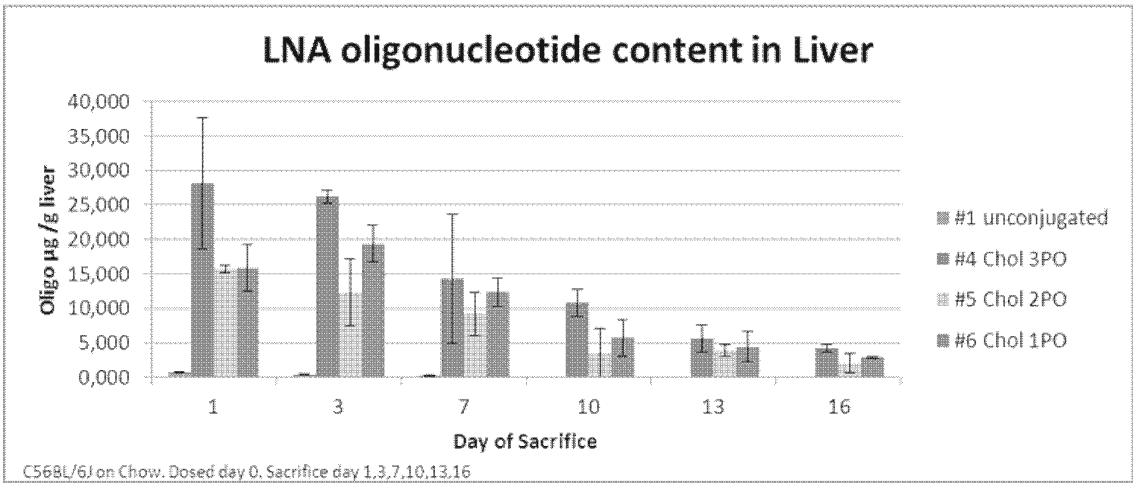

ApoB cholesterol conjugates. ApoB mRNA in Kidney
ApoB mRNA expression [% of AV mock]
130
120
110
100
90
80
70
60
50
40
30
20
10
0
1 3 7 10 13 16 1 3 7 10 13 16 1 3 7 10 13 16 1 3 7 10 13 16 1 3 7 10 13 16
NaCl
#1 unconjugated
#4 Chol 3PO
#5 Chol 2PO
#6 Chol 1PO
Treatment (days and oligonucleotide)

Figure 15

A


LNA oligonucleotide content in Liver
Oligo µg /g liver
40,000
35,000
30,000
25,000
20,000
15,000
10,000
5,000
0,000
1
3
7
10
13
16
Day of Sacrifice
#1 unconjugated
#4 Chol 3PO
#5 Chol 2PO
#6 Chol 1PO
C56BL/6J on Chow. Dosed day 0. Sacrifice day 1,3,7,10,13,16

B

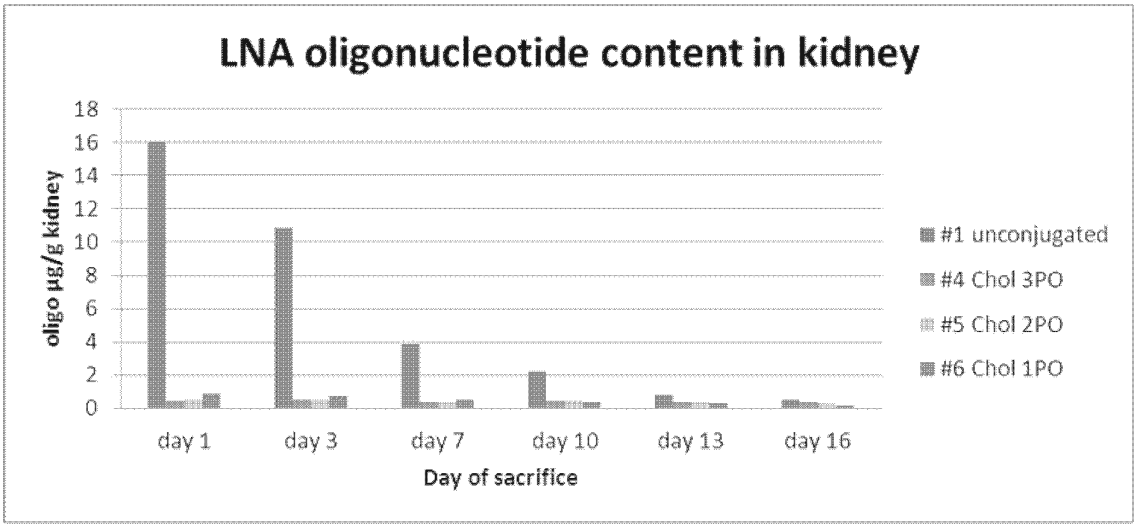
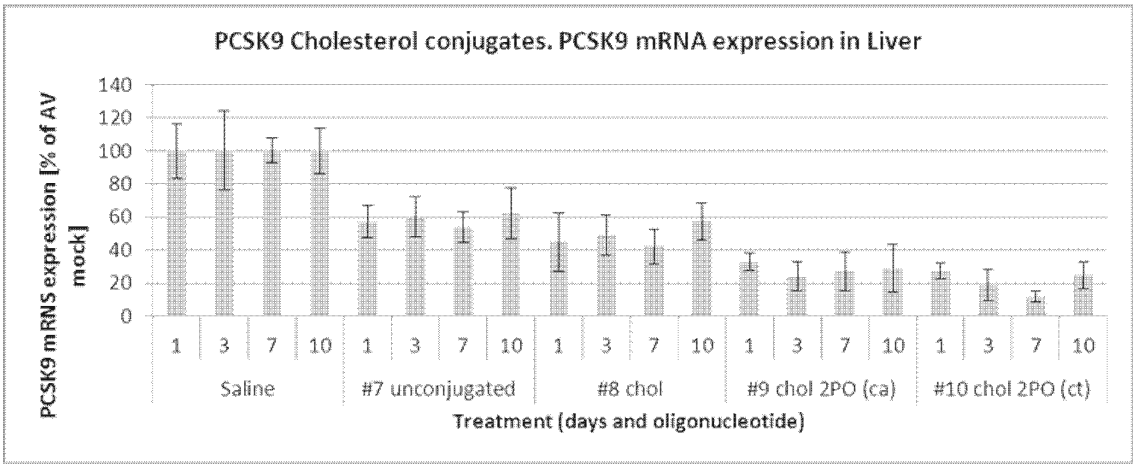

LNA oligonucleotide content in kidney
oligo µg/g kidney
18
16
14
12
10
8
6
4
2
0
day 1
day 3
day 7
day 10
day 13
day 16
Day of sacrifice
#1 unconjugated
#4 Chol 3PO
#5 Chol 2PO
#6 Chol 1PO

Figure 16

A


PCSK9 Cholesterol conjugates. PCSK9 mRNA expression in Liver
PCSK9 mRNS expression [% of AV mock]
140
120
100
80
60
40
20
0
1 3 7 10 1 3 7 10 1 3 7 10 1 3 7 10 1 3 7 10
Saline
#7 unconjugated
#8 chol
#9 chol 2PO (ca)
#10 chol 2PO (ct)
Treatment (days and oligonucleotide)

B

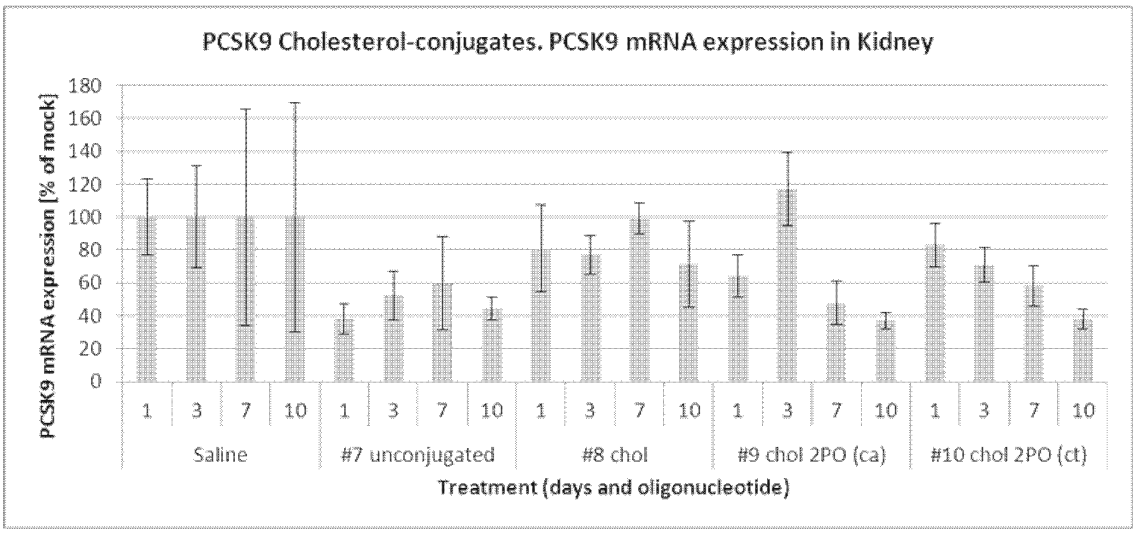
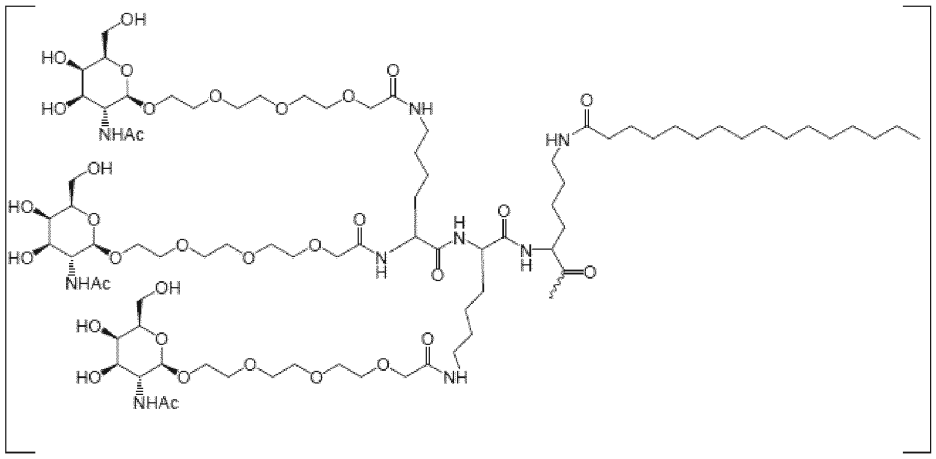
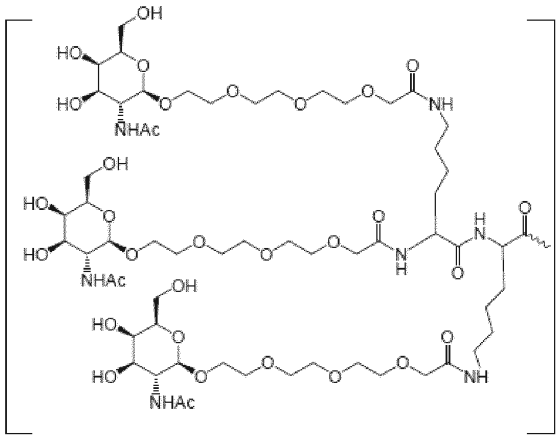

PCSK9 Cholesterol-conjugates. PCSK9 mRNA expression in Kidney
PCSK9 mRNA expression [% of mock]
180
160
140
120
100
80
60
40
20
0
1 3 7 10 1 3 7 10 1 3 7 10 1 3 7 10 1 3 7 10
Saline
#7 unconjugated
#8 chol
#9 chol 2PO (ca)
#10 chol 2PO (ct)
Treatment (days and oligonucleotide)

Figure 17

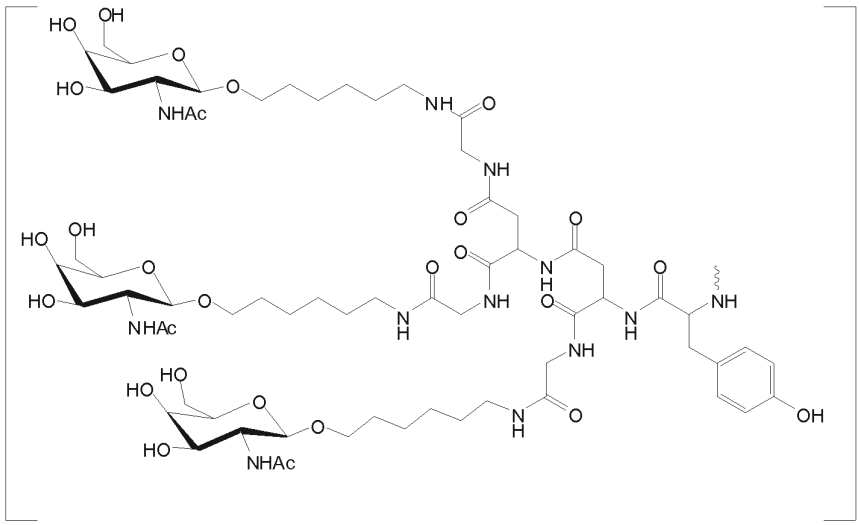
Conj 1=



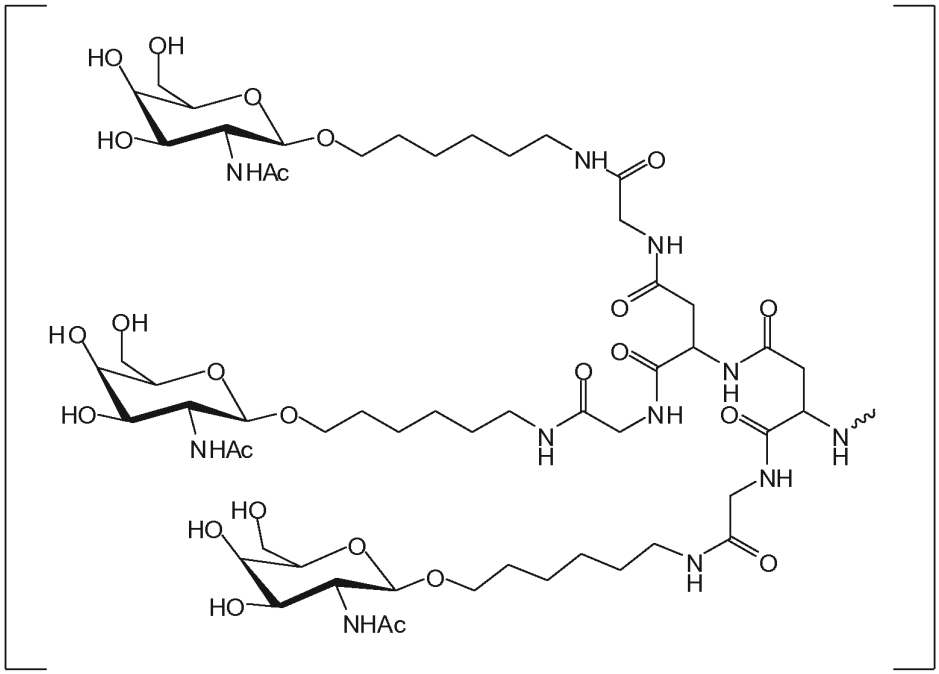
Conj 2=



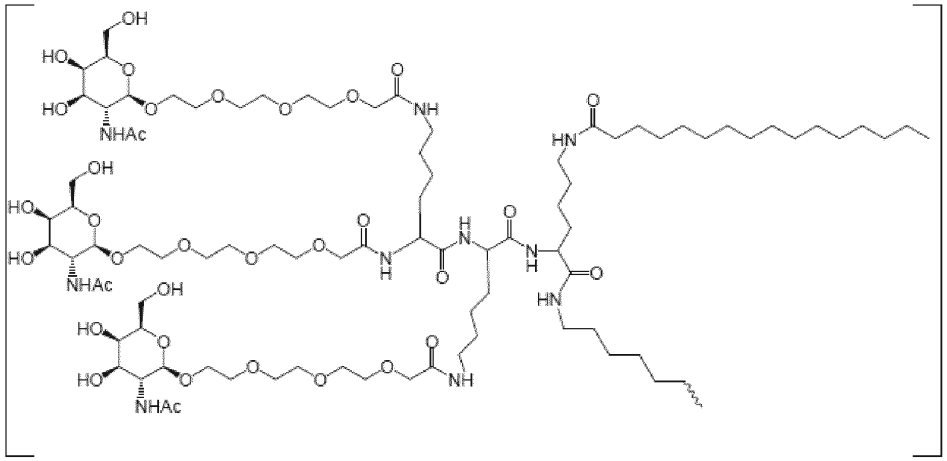
Conj 3=



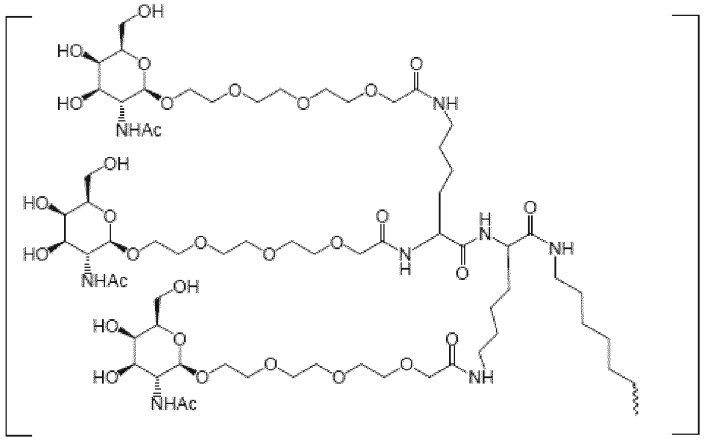
Conj 4=


HO
OH
O
HO
NHAc
O
NH
O
NH
O
O
N
H
O
HO
OH
O
HO
NHAc
O
N
H
O
NH
O
N
H
NH
HO
HO
O
HO
NHAc
O
N
H
O

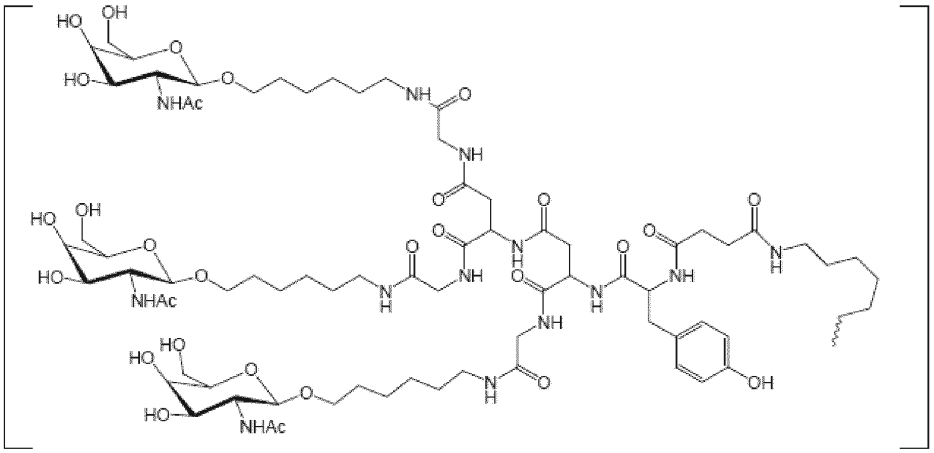
Conj 1a=



Conj 2a=



Conj 3a=



Conj 4a=

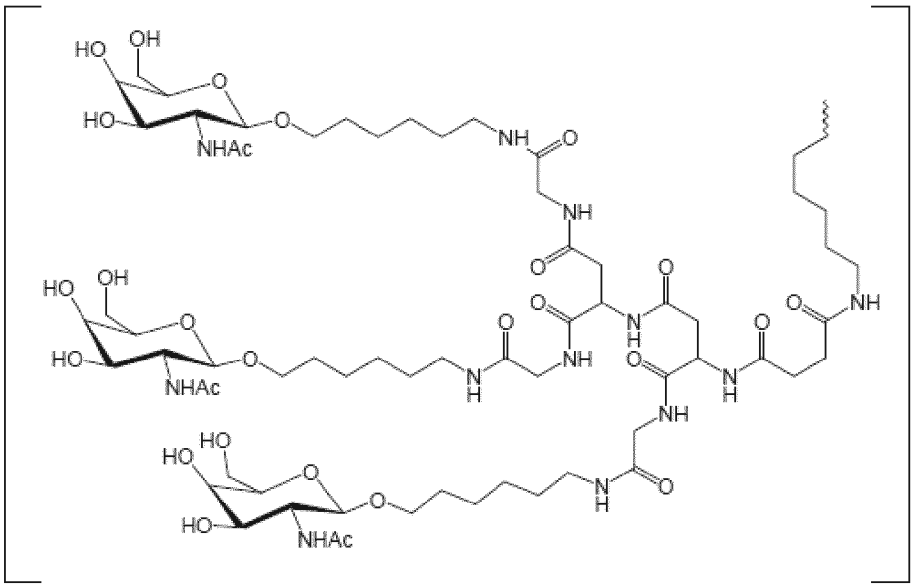

HO
OH
O
HO
NHAc
O
NH
O
NH
O
O
NH
O
N
H
O
O
NH
HO
OH
O
HO
NHAc
O
N
H
NH
O
O
N
H
NH
HO
HO
O
HO
NHAc
O
N
H
O

Figure 18

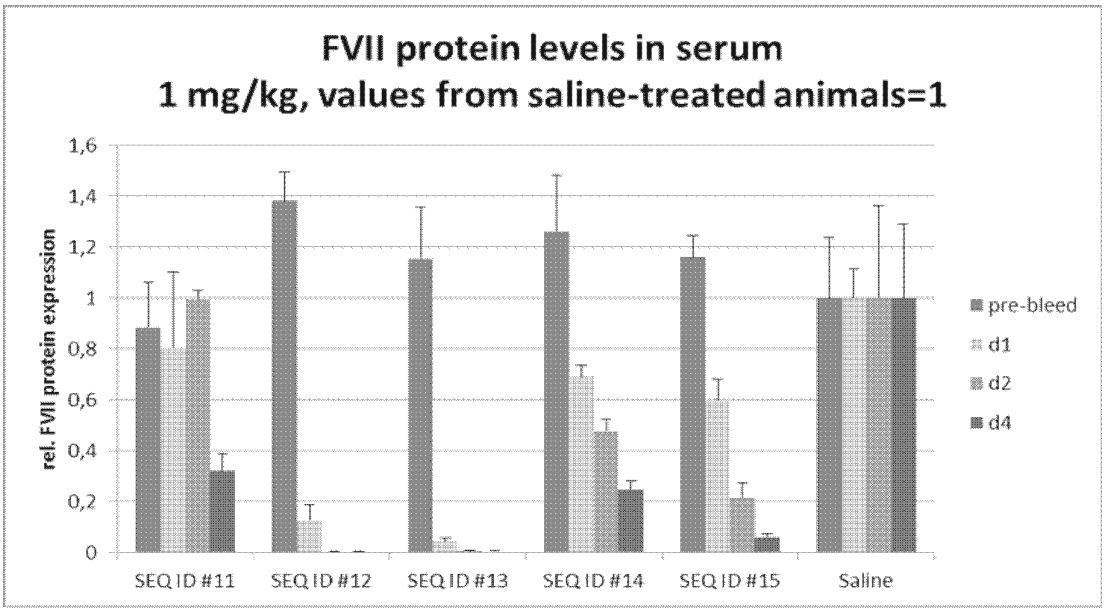


Figure 19

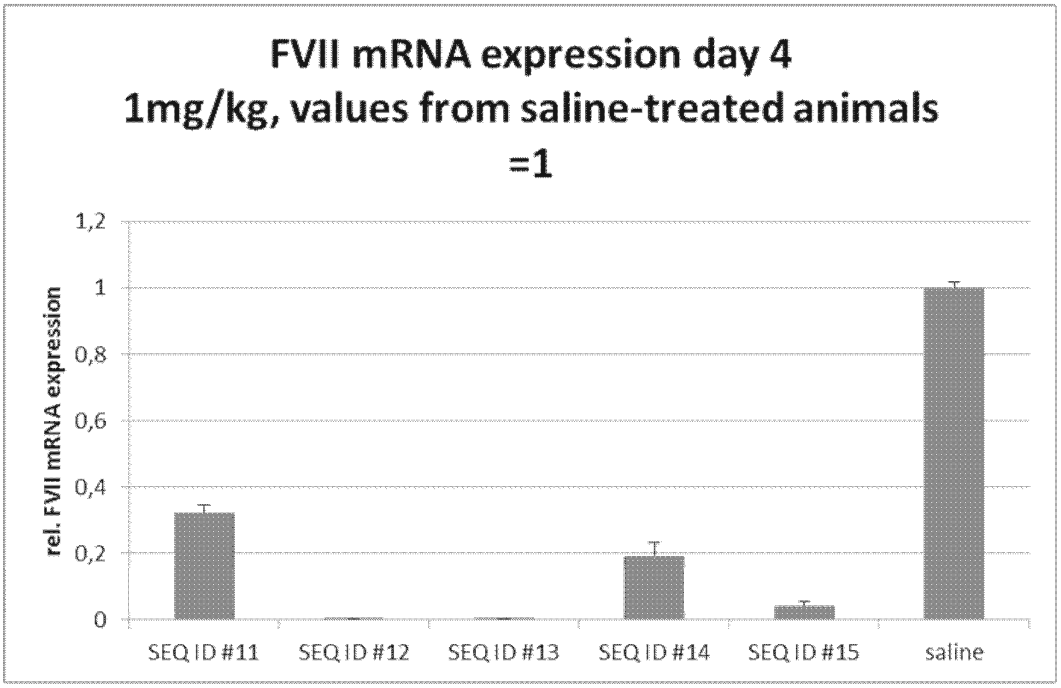


Figure 20

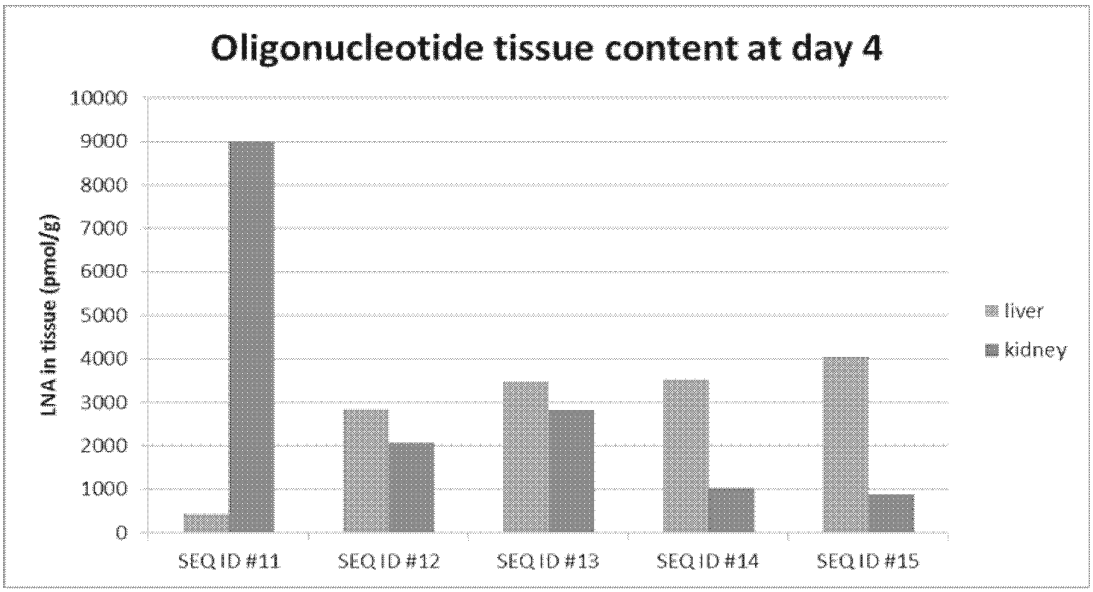


Figure 21

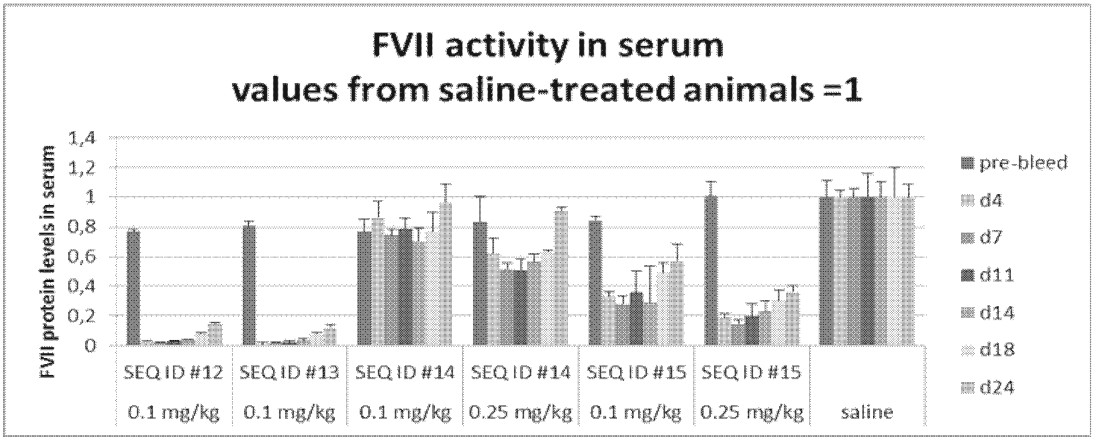


Figure 22

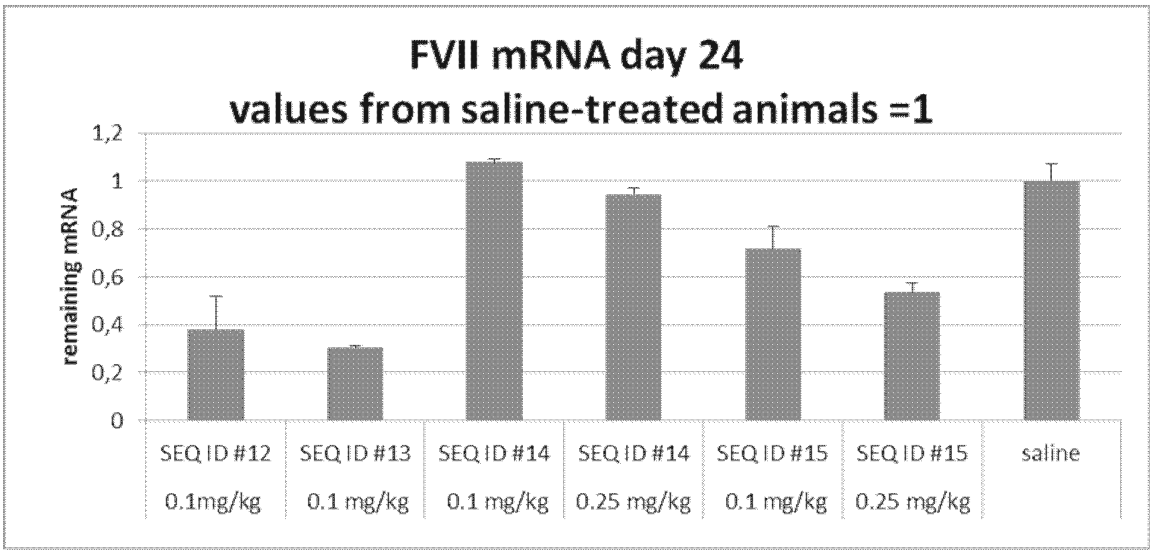


Figure 23

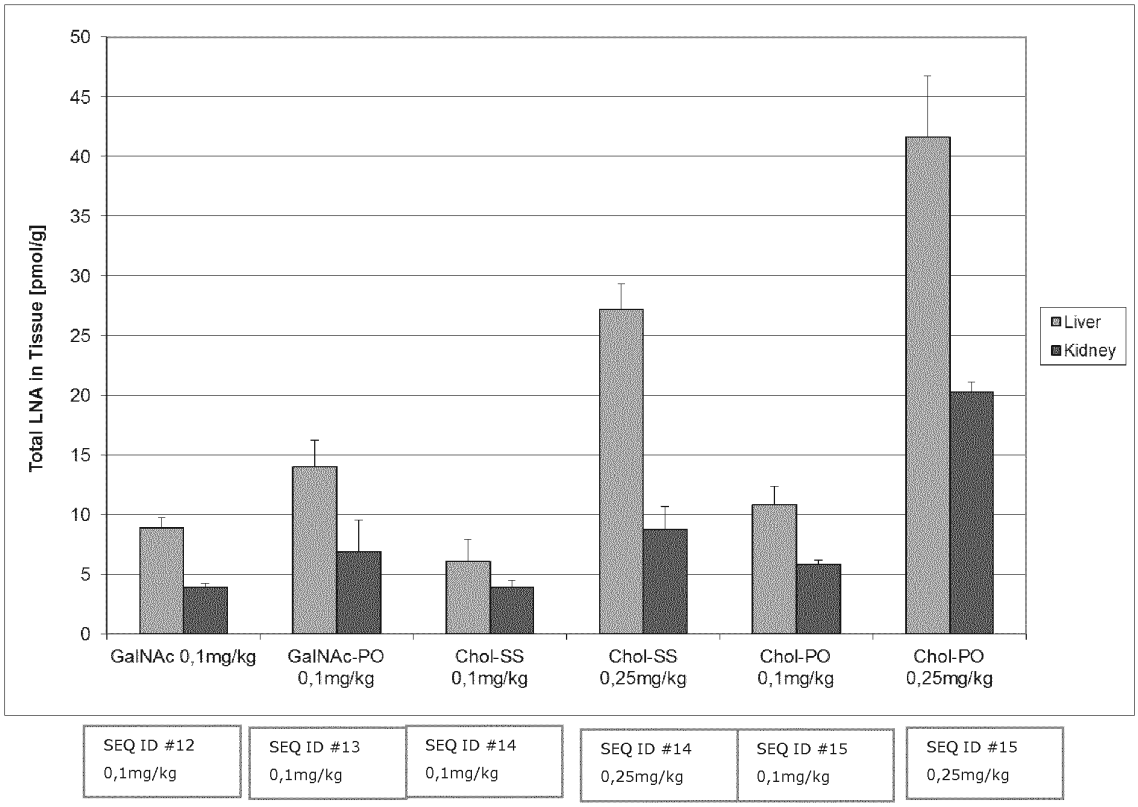
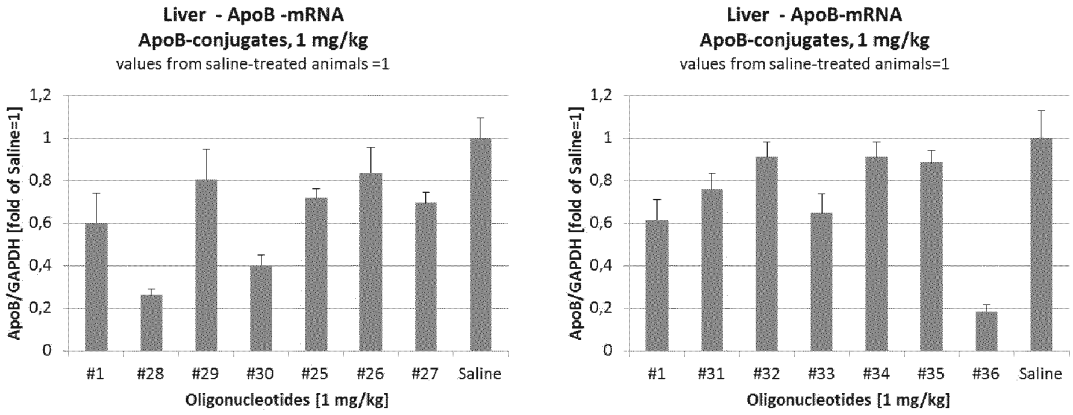


Figure 24

A


Liver - ApoB -mRNA
ApoB-conjugates, 1 mg/kg
values from saline-treated animals =1
ApoB/GAPDH [fold of Saline=1]
1,2
1
0,8
0,6
0,4
0,2
0
#1 #28 #29 #30 #25 #26 #27 Saline
Oligonucleotides [1 mg/kg]
Liver - ApoB-mRNA
ApoB-conjugates, 1 mg/kg
values from saline-treated animals=1
ApoB/GAPDH [fold of Saline=1]
1,2
1
0,8
0,6
0,4
0,2
0
#1 #31 #32 #33 #34 #35 #36 Saline
Oligonucleotides [1 mg/kg]

B

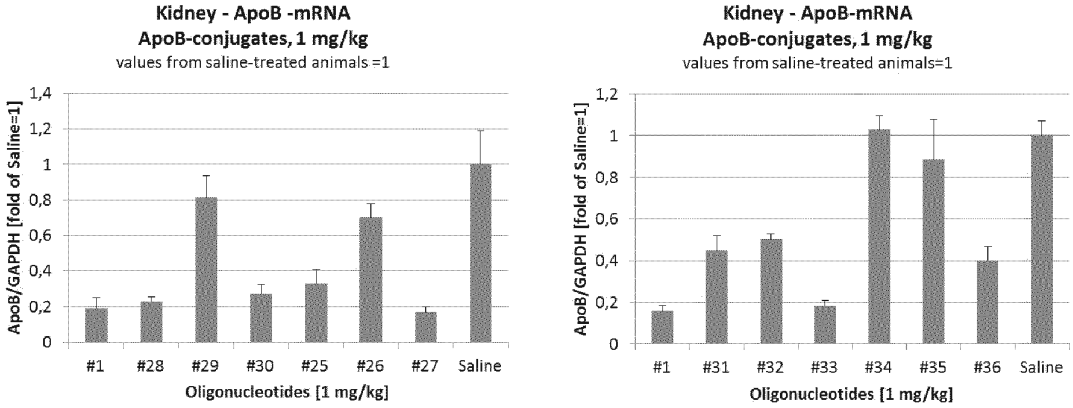
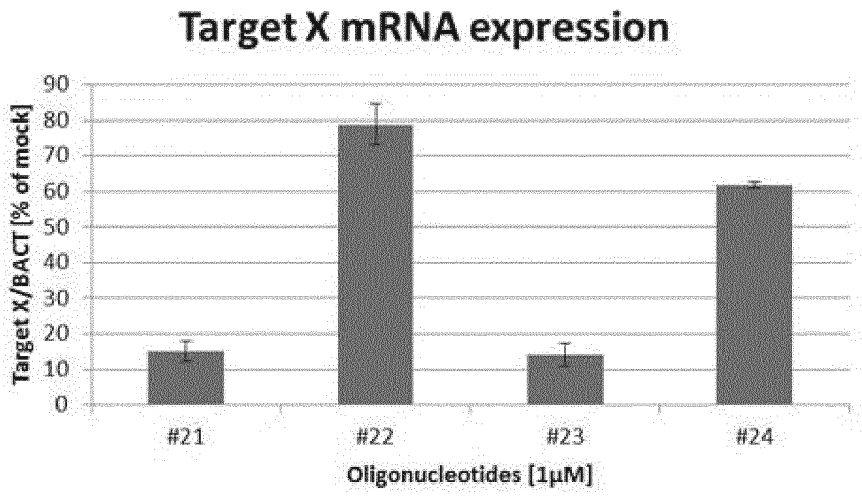

Kidney - ApoB -mRNA
ApoB-conjugates, 1 mg/kg
values from saline-treated animals =1
ApoB/GAPDH [fold of Saline=1]
1,4
1,2
1
0,8
0,6
0,4
0,2
0
#1 #28 #29 #30 #25 #26 #27 Saline
Oligonucleotides [1 mg/kg]
Kidney - ApoB-mRNA
ApoB-conjugates, 1 mg/kg
values from saline-treated animals=1
ApoB/GAPDH [fold of Saline=1]
1,2
1
0,8
0,6
0,4
0,2
0
#1 #31 #32 #33 #34 #35 #36 Saline
Oligonucleotides [1 mg/kg]

Figure 25


Target X mRNA expression
Target X/BACT [% of mock]
90
80
70
60
50
40
30
20
10
0
#21
#22
#23
#24
Oligonucleotides [1µM]