**Figure 1**

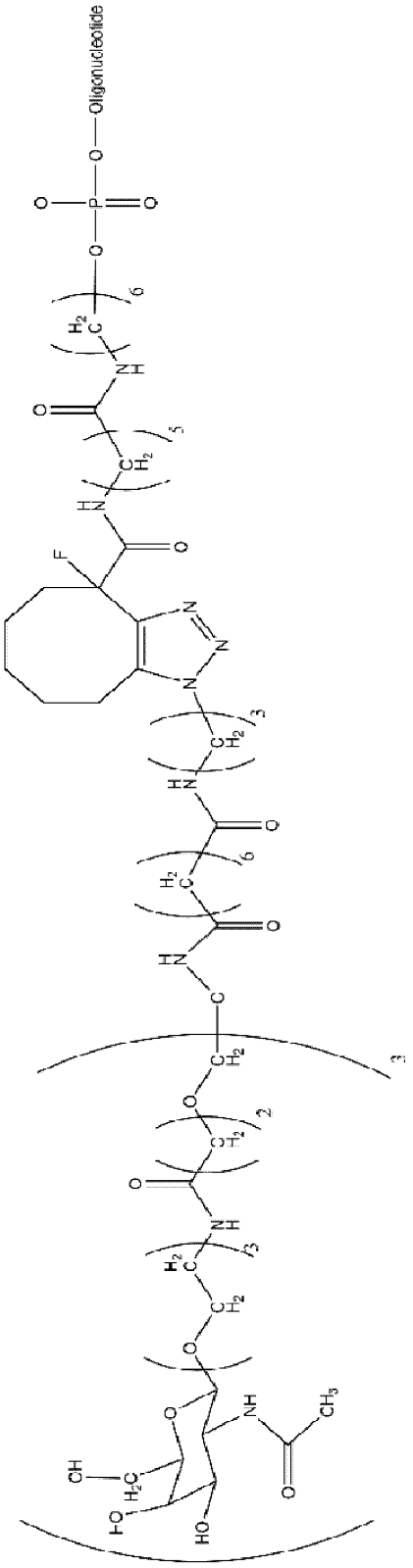


**Figure 2**

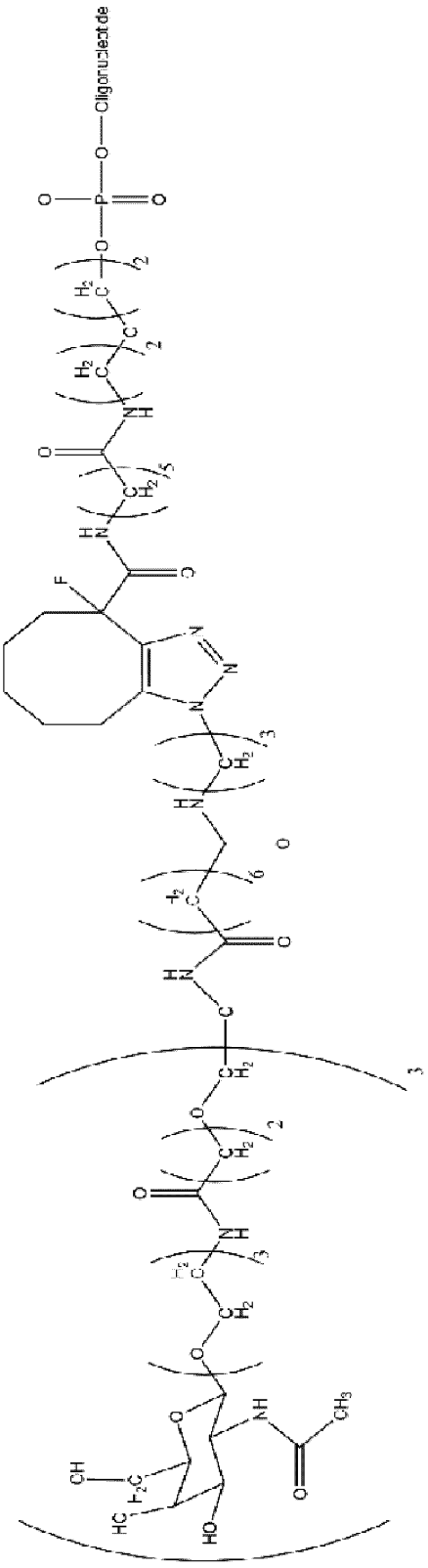


**Figure 3**

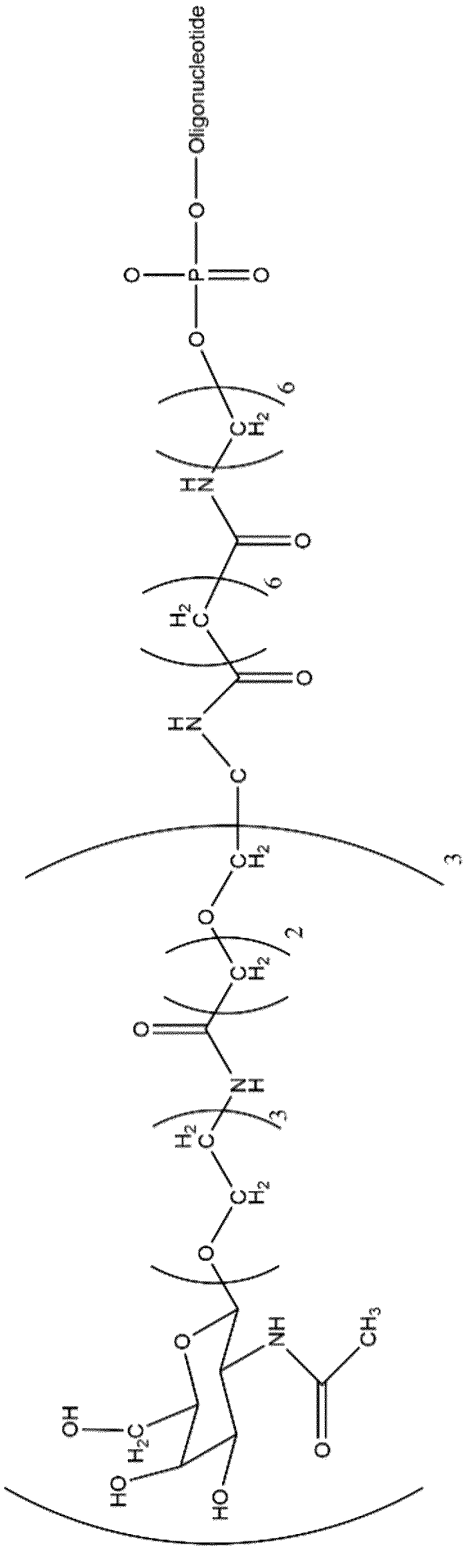

Oligonucleotide
O
P
O
O
O
6
H2
C
N
H
O
6
H2
C
O
N
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C
3
H2
C
O
2
H2
C
O
N
H
3
H2
C
H2
C
O
NH
CH3
O
OH
H2C
HO
HO

**Figure 4**

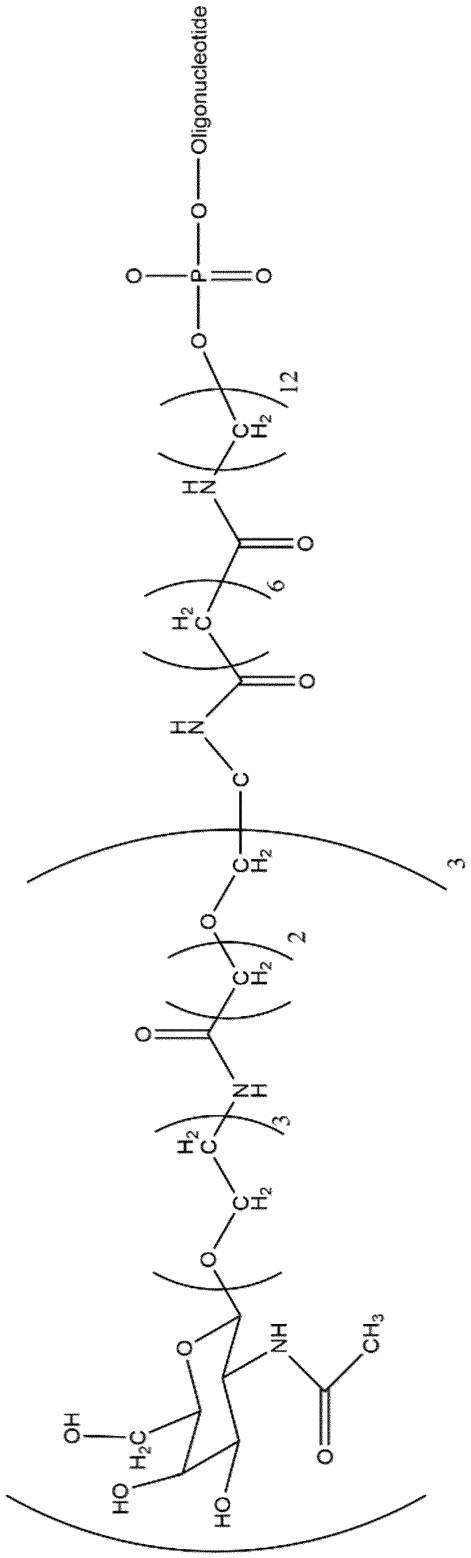
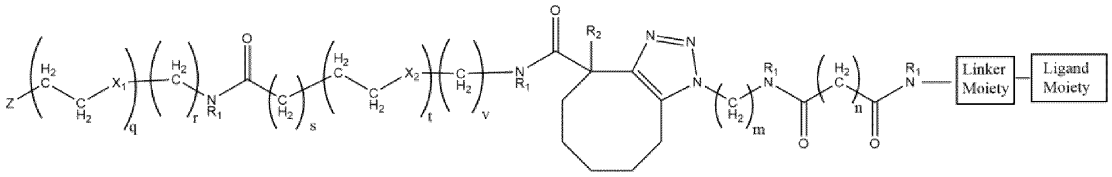
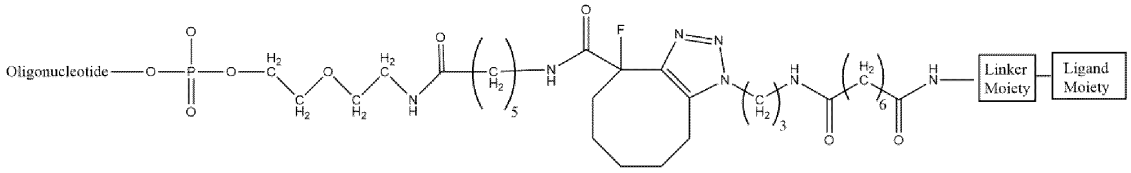

Oligonucleotide
O
P
O
O
O
12
H2C
N
H
O
6
H2C
O
N
H
C
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H2C
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O
OH
H2C
HO
HO

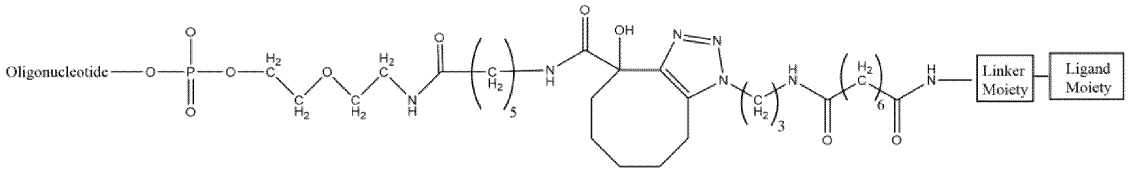
**Figure 5 (from Sentences 1 – 101)**



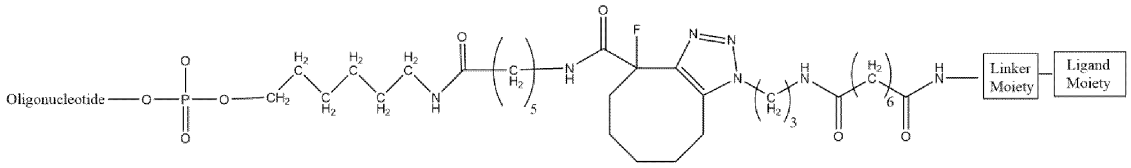

Formula (I)




Formula (II)

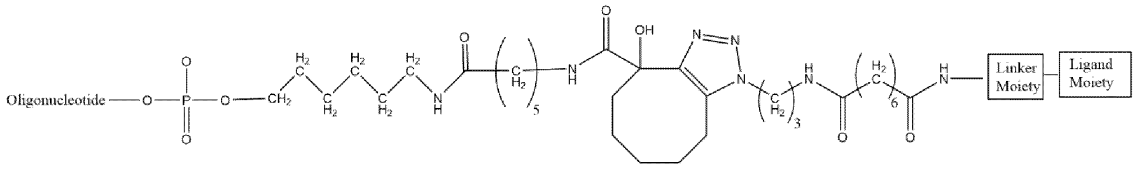



Formula (III)

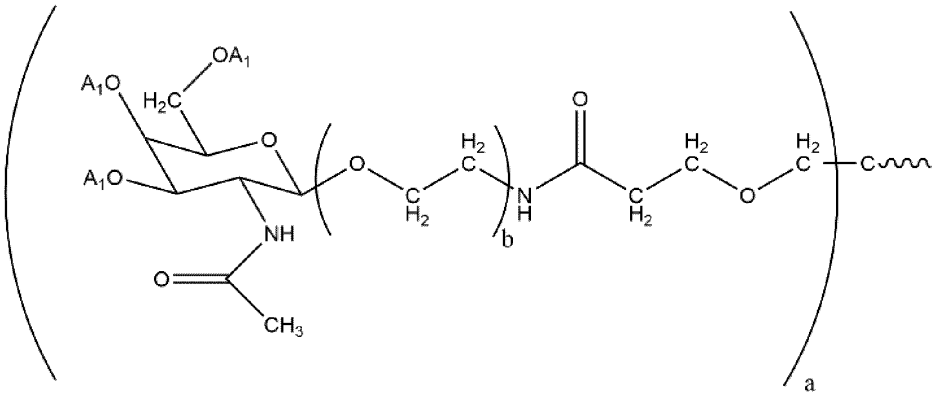



Formula (IV)

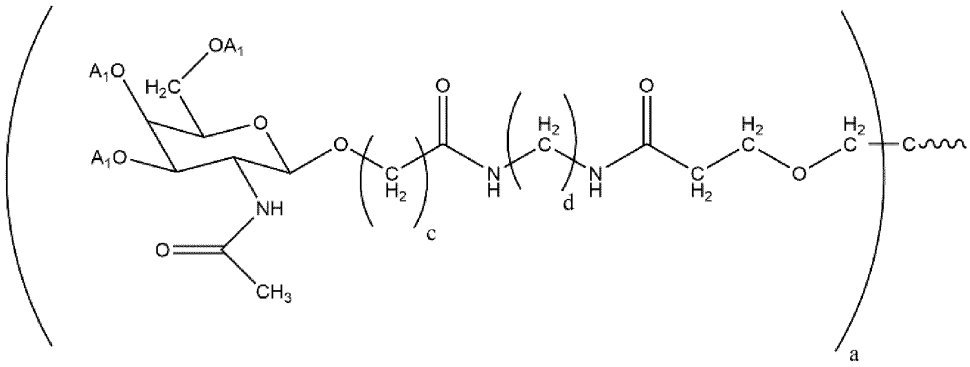
**Figure 5 cont.**




Formula (V)

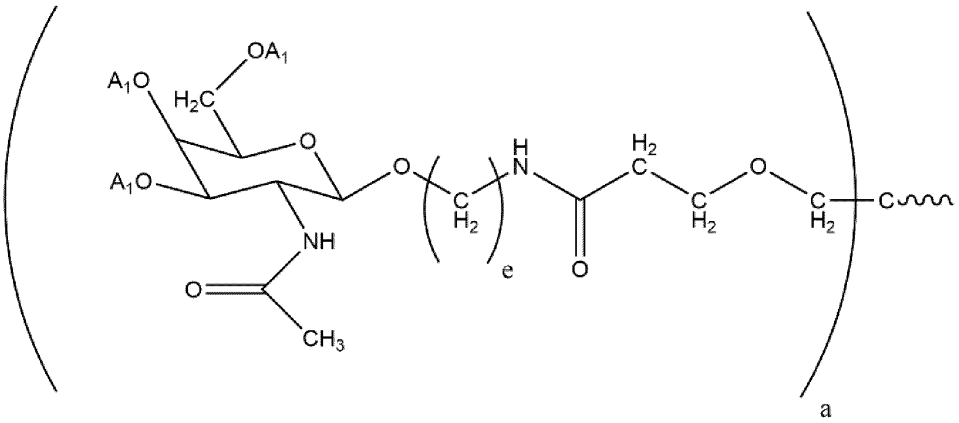


Formula (VIa)

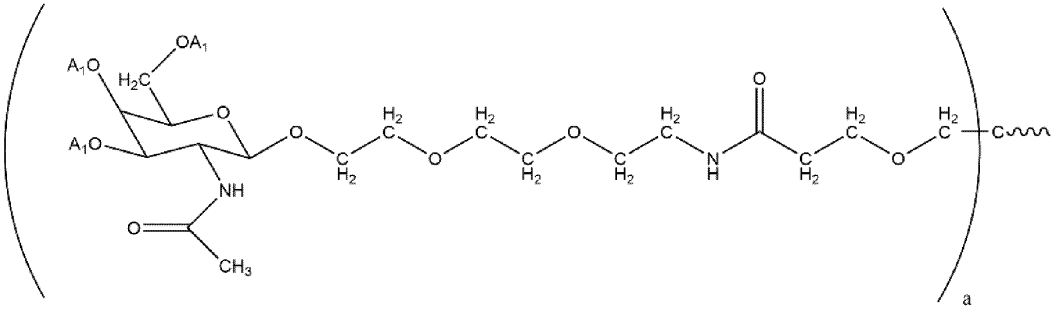


Formula (VIb)

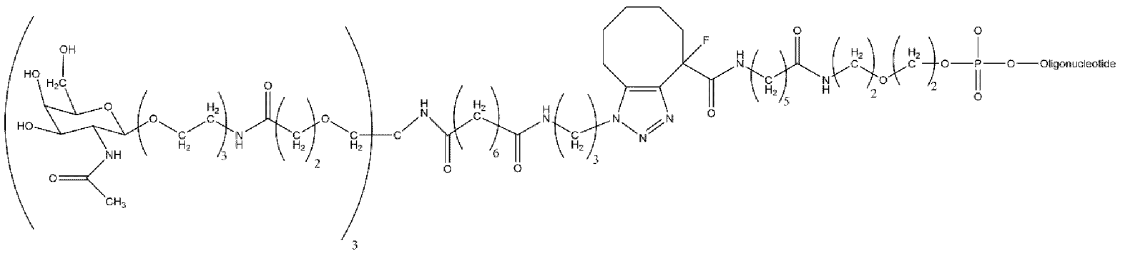
**Figure 5 cont.**



Formula (VIc)

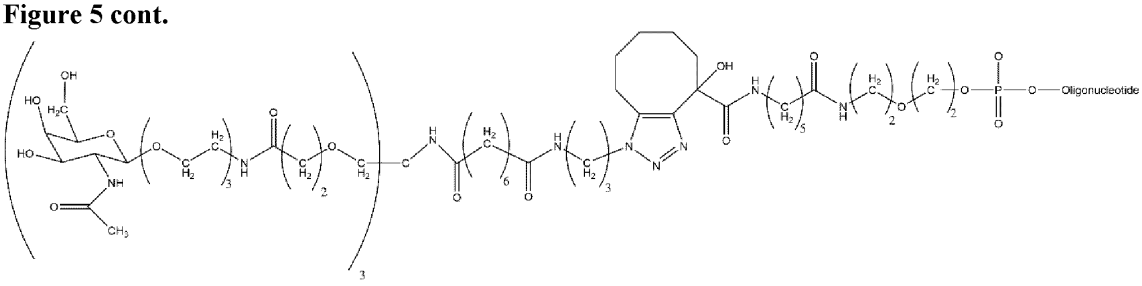


Formula (VII)

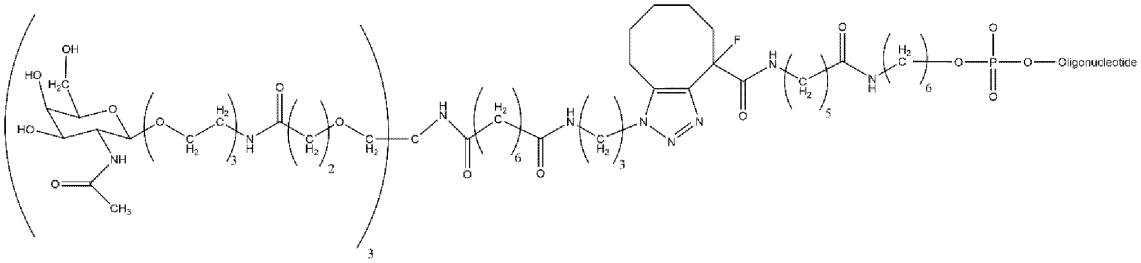


Formula (VIII)

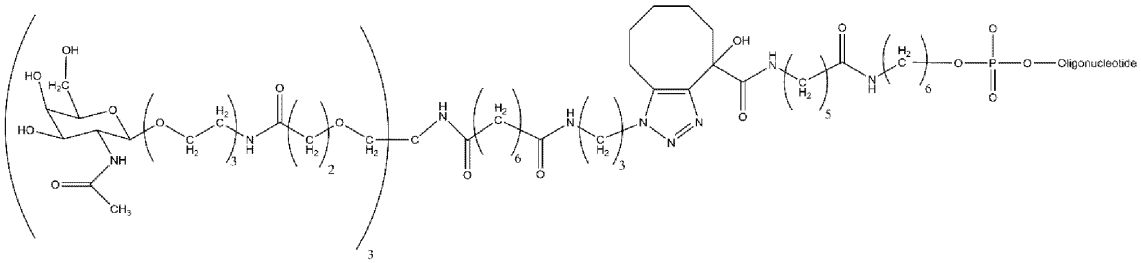
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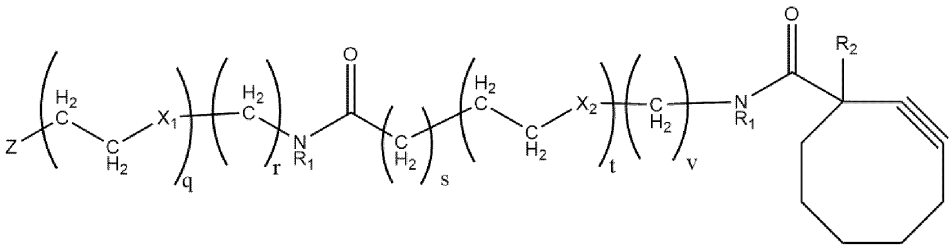

Formula (IX)




Formula (X)

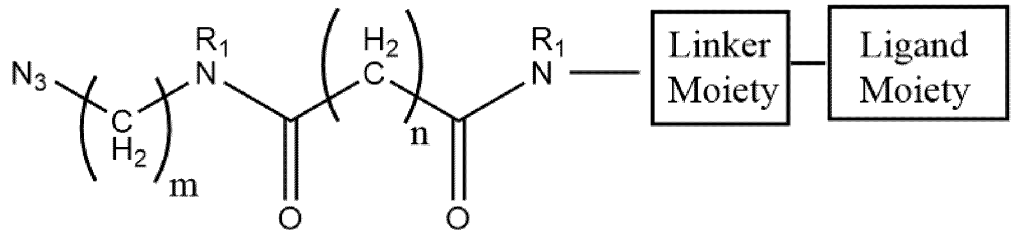



Formula (XI)

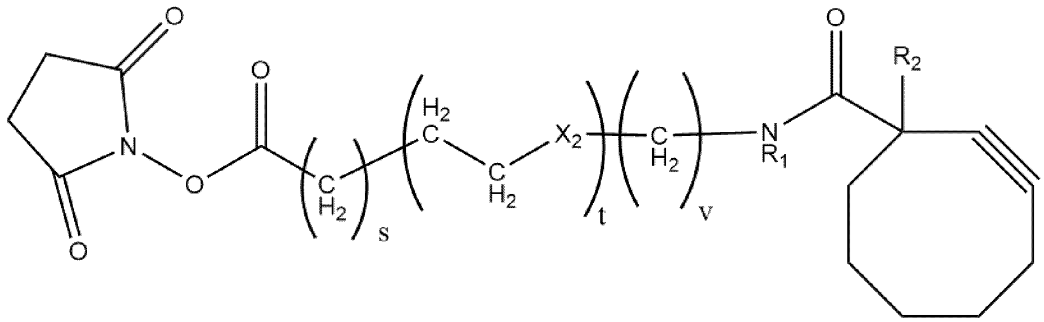


Formula (XII)

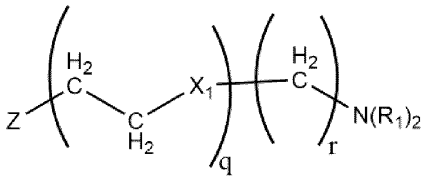
**Figure 5 cont.**




Formula (XIII)

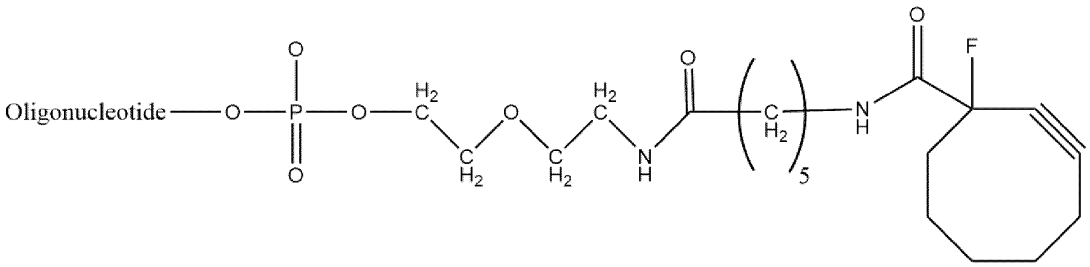



Formula (XIV)

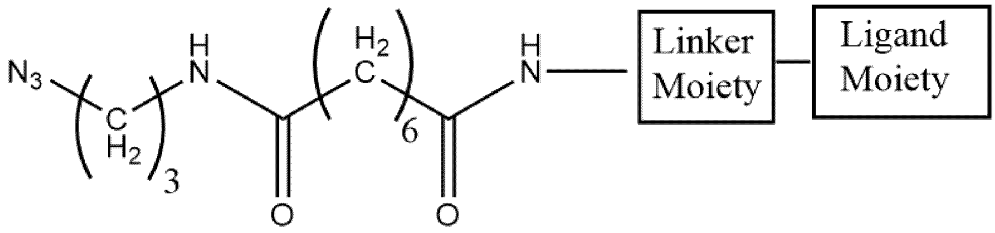



Formula (XV)

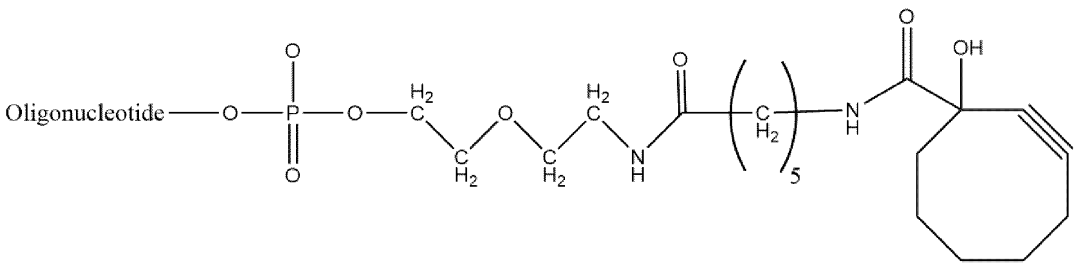
**Figure 5 cont.**




Formula (XIIa)

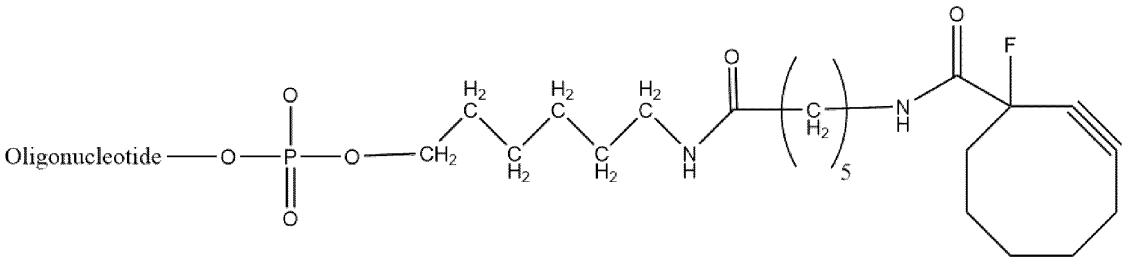



Formula (XIIIa)

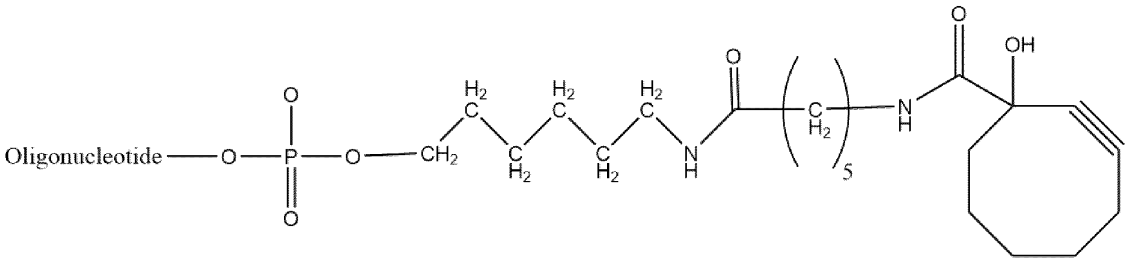



Formula (XIIb)

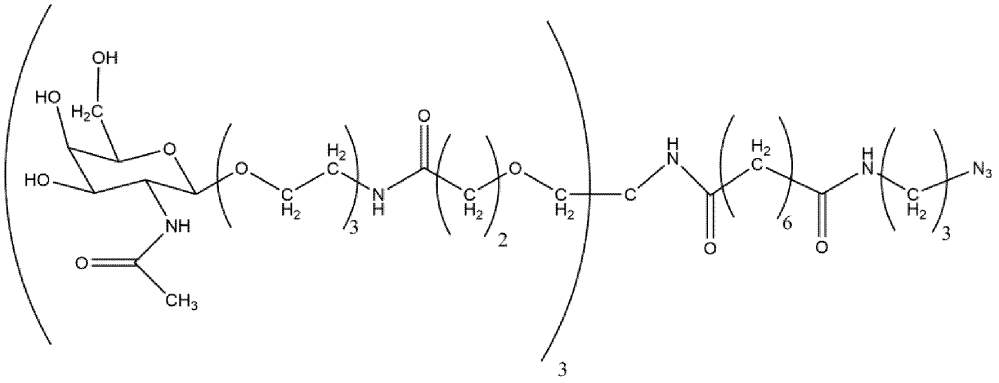
**Figure 5 cont.**




Formula (XIIc)

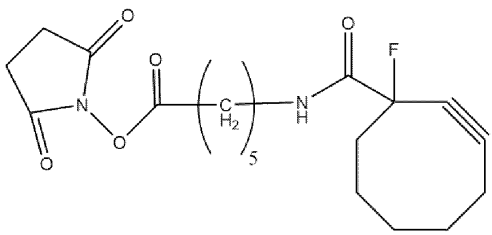



Formula (XIId)

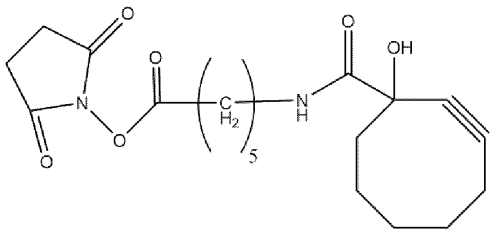



Formula (XIIIb)

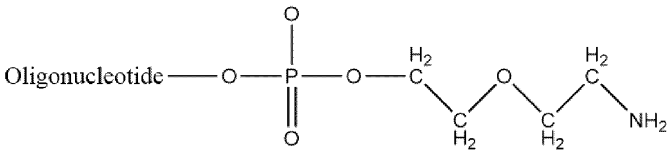
**Figure 5 cont.**



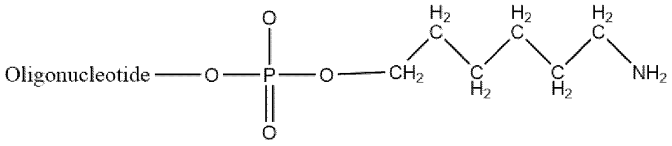
Formula (XIVa)



Formula (XIVb)

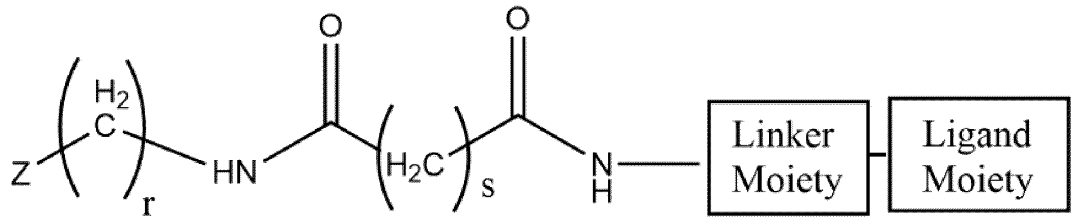


Formula (XVa)

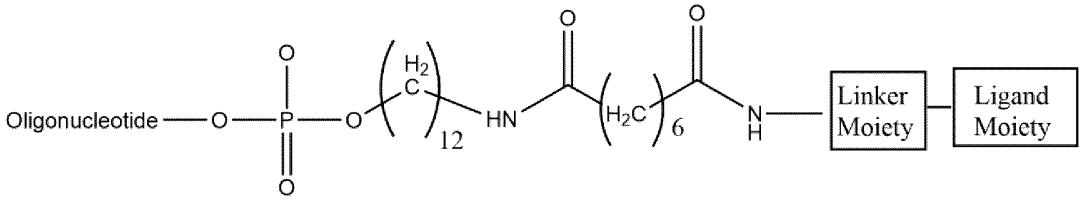


Formula (XVb)

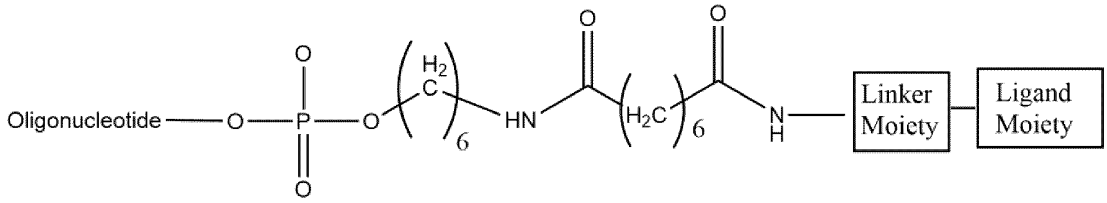
**Figure 6 (Formulae from Clauses 1- 56)**




Formula (I)

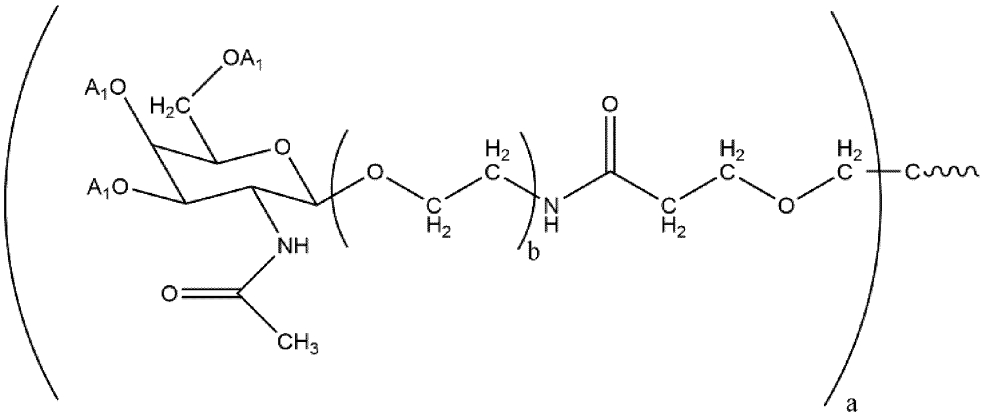



Formula (II)

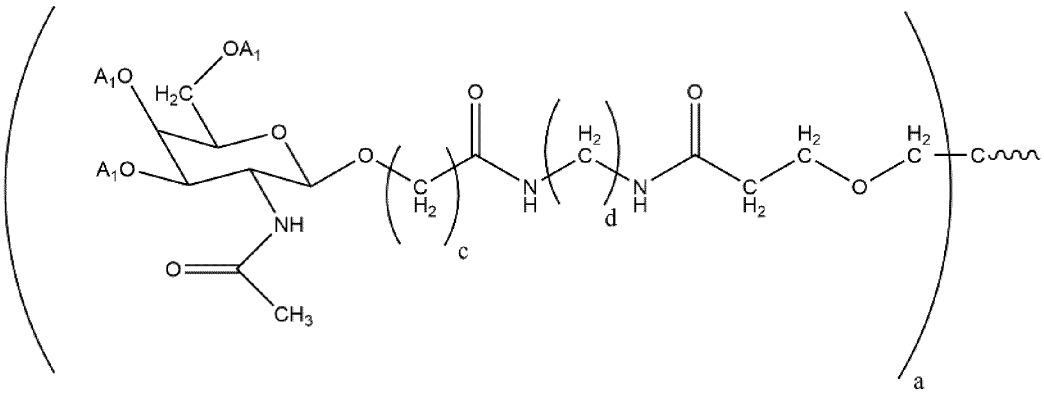



Formula (III)

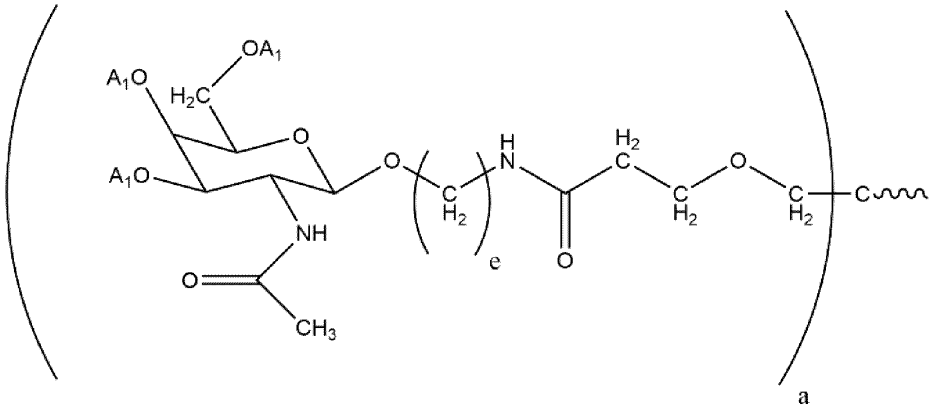
**Figure 6 cont.**



Formula (IV)

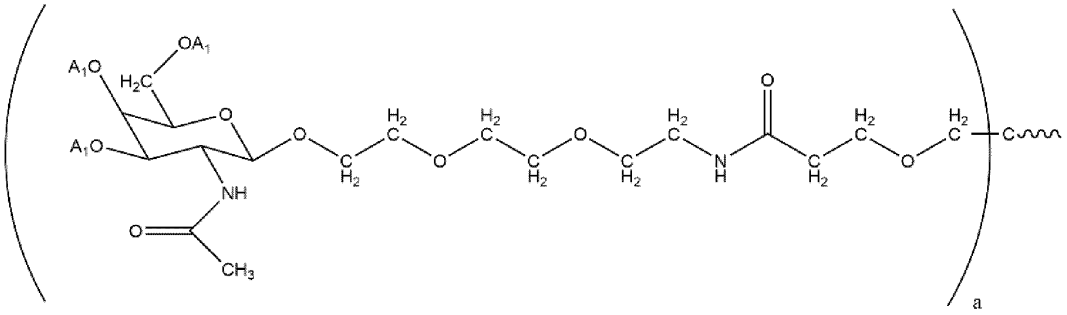


Formula (V)

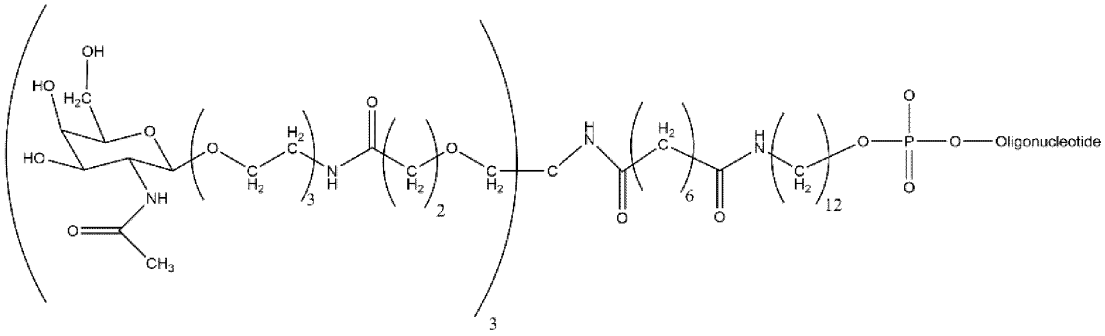


Formula (VI)

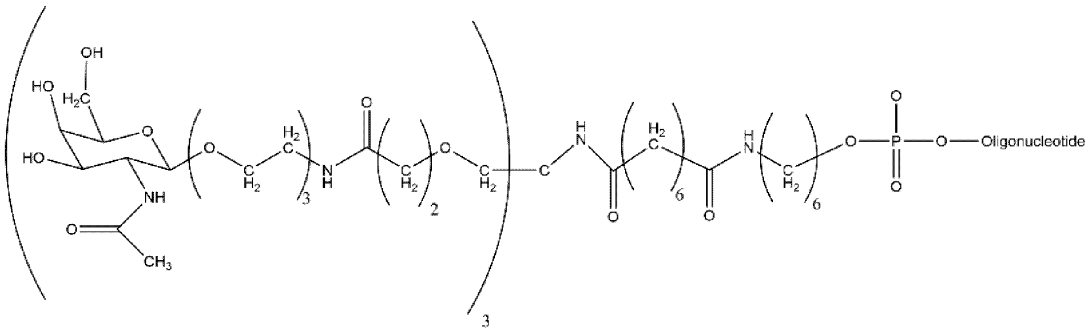
**Figure 6 cont.**



Formula (VII)

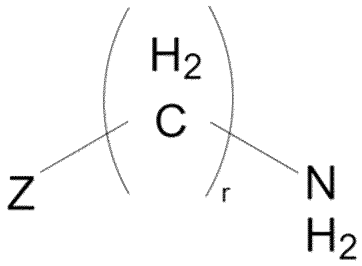


Formula (VIII)

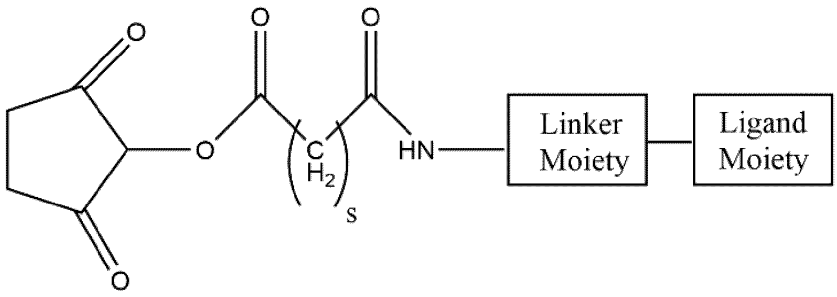


Formula (IX)

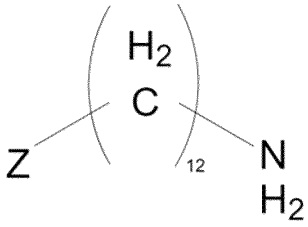
**Figure 6 cont.**



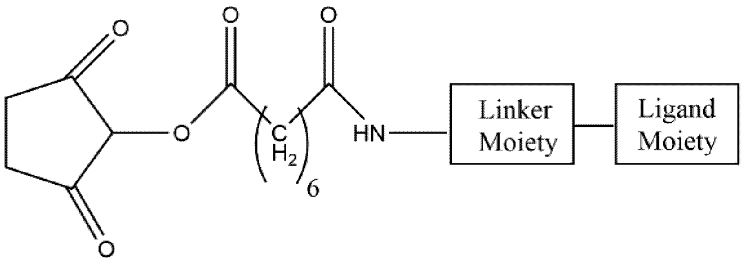

Formula (X)




Formula (XI)

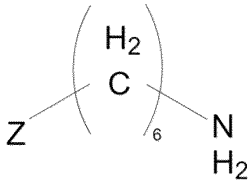



Formula (Xa)

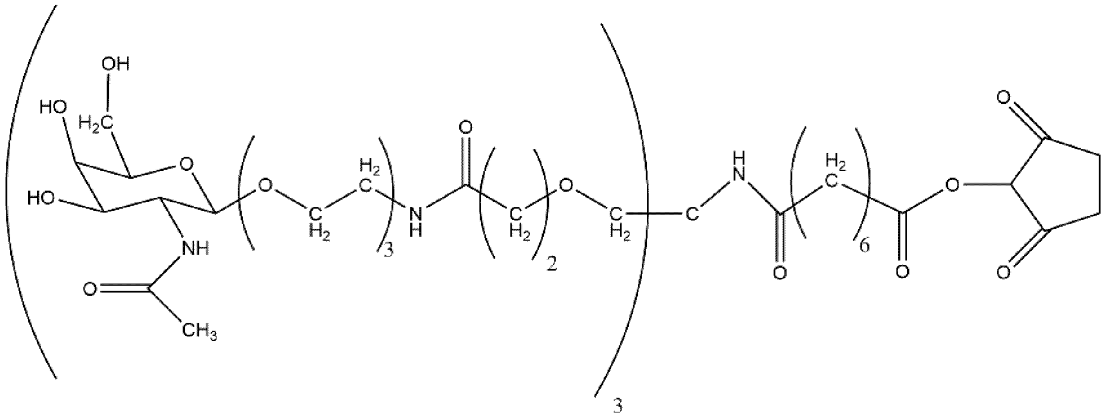



Formula (XIa)

**Figure 6 cont.**



Formula (Xb)



Formula (XIb)

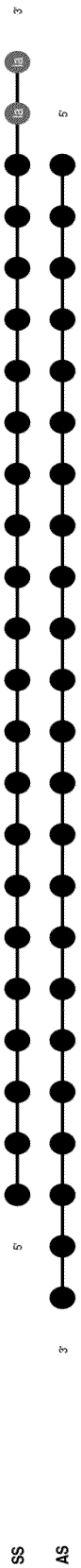



Figure 7a:

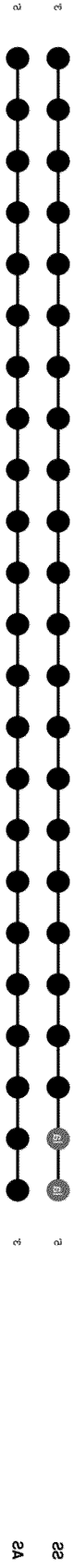



Figure 7b:

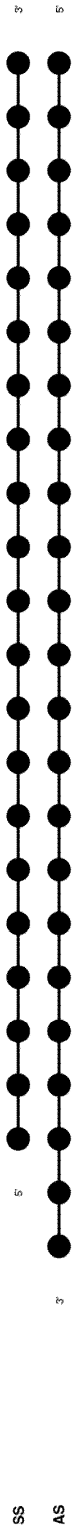



Figure 8a:

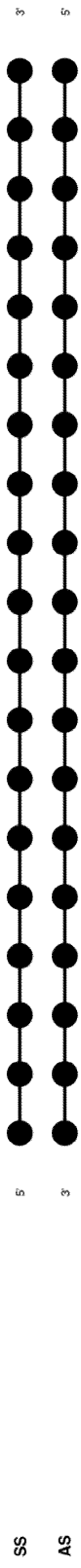



Figure 8b:

**Figure 9**

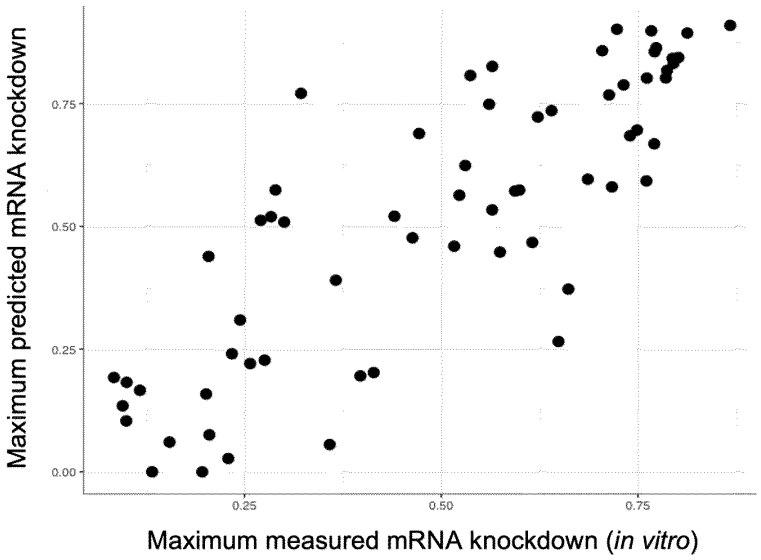



**Figure 10**

*Best Model Performance*

| Dataset | Spearman_correlation | RMSE | PrecisionAt10 | PrecisionAt20 | nSiRNAsForBest |
|---|---|---|---|---|---|
| Test set | 0.847 | 0.155 | 0.7 | 0.75 | 1 |
| Validation set (independent gene) | 0.712 | 0.288 | 0.6 | 0.60 | 11 |

**Figure 11**

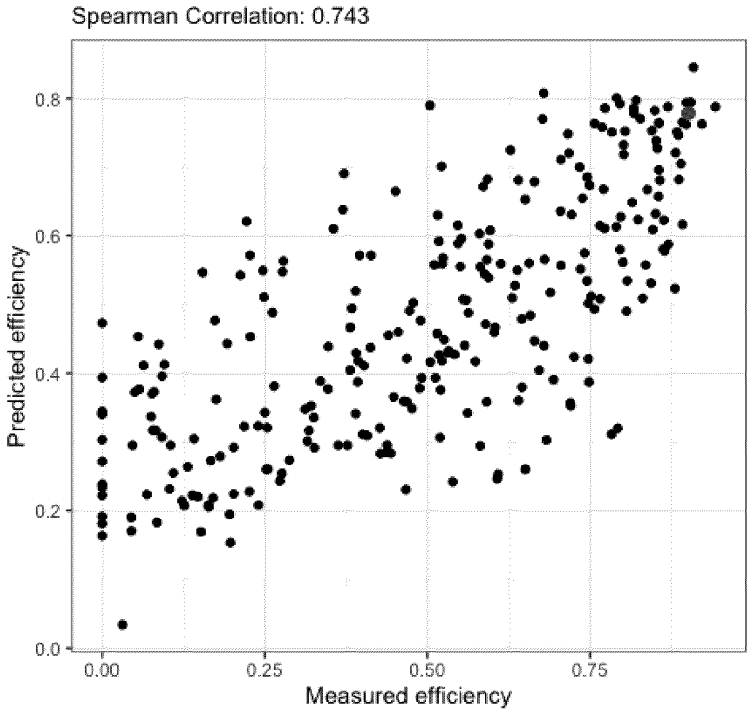



**Figure 12**

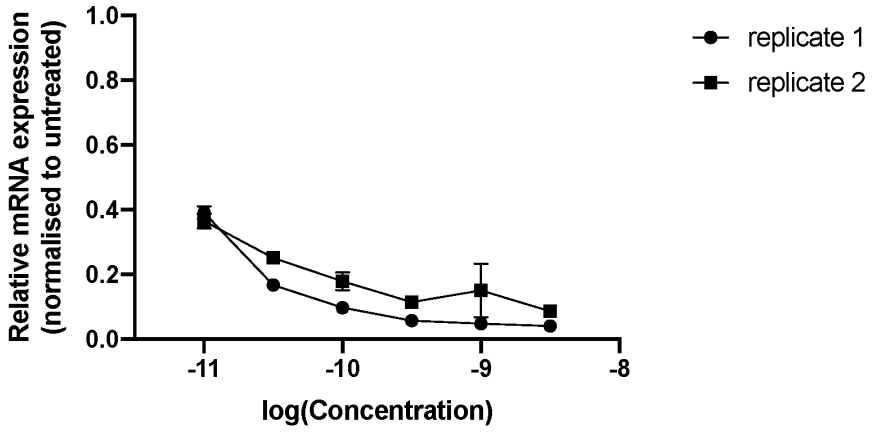


**Figure 13**

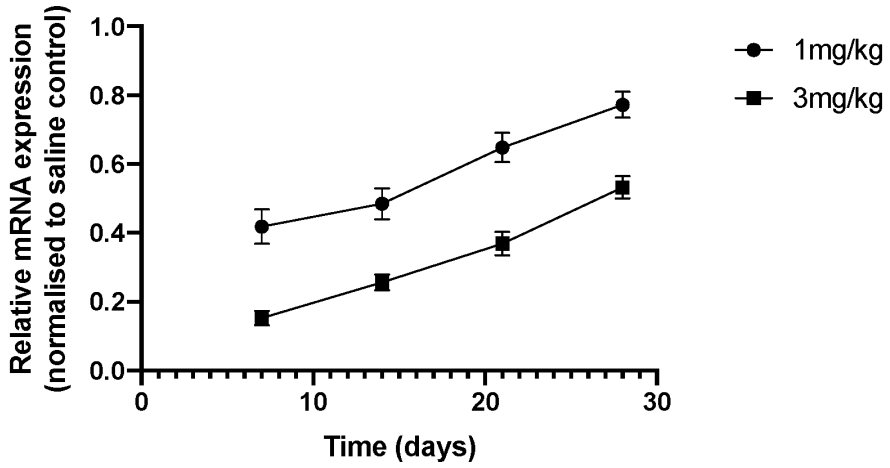



**Figure 14**

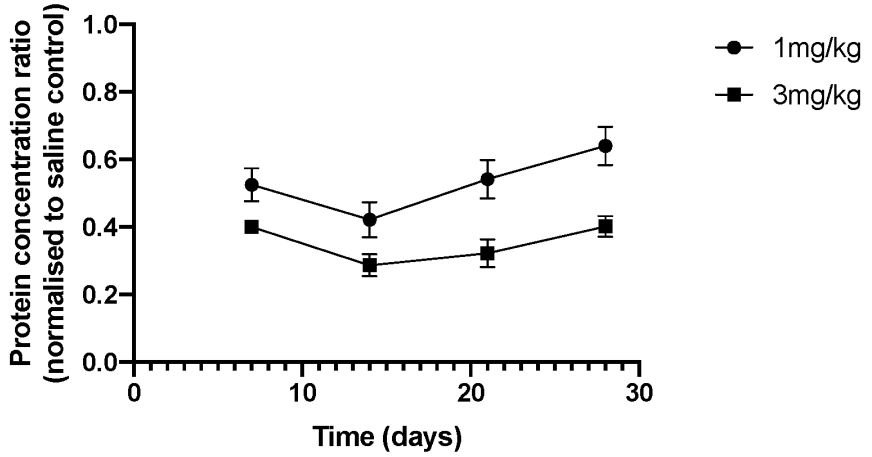


**Figure 15a**

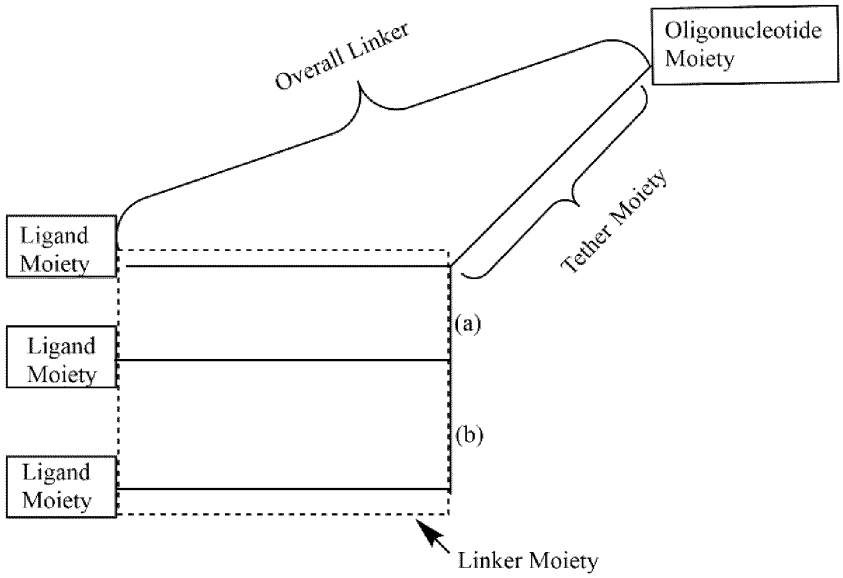
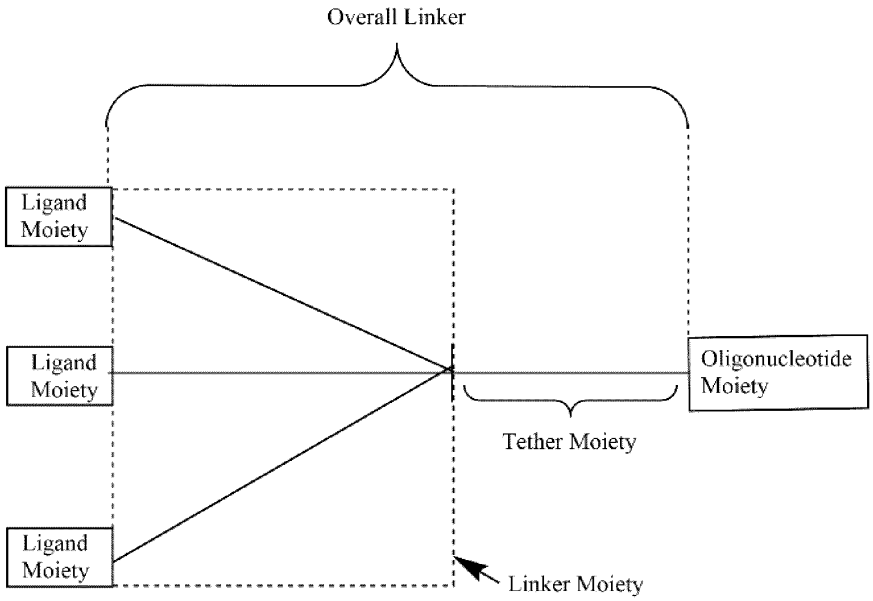



**Figure 15b**



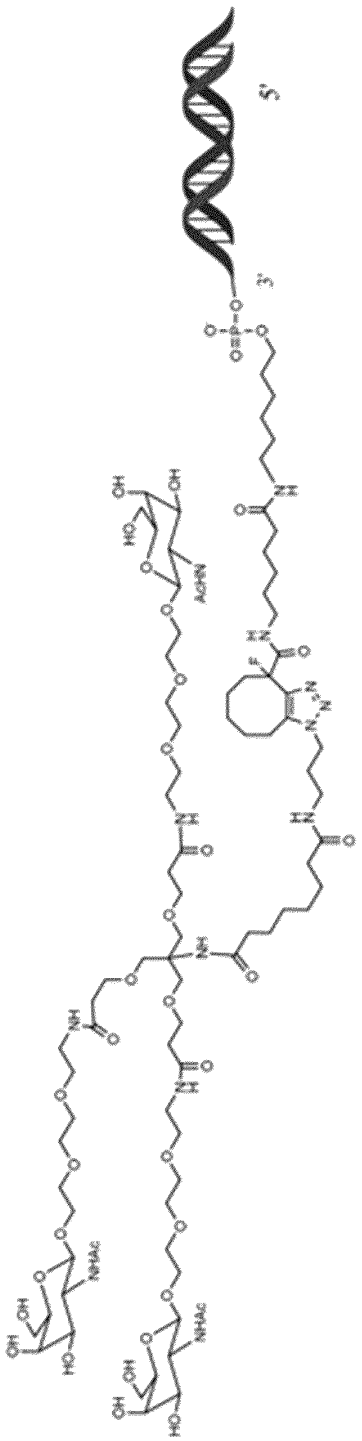



Figure 16

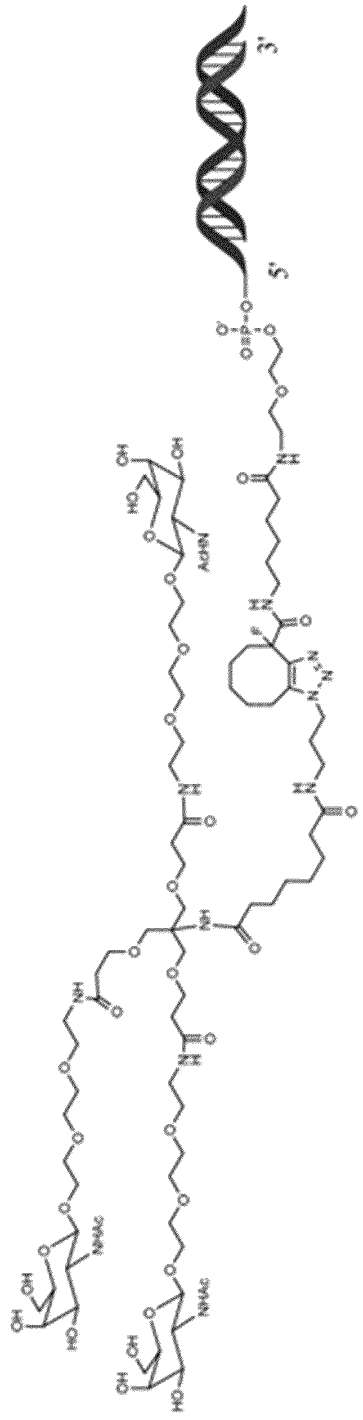



Figure 17

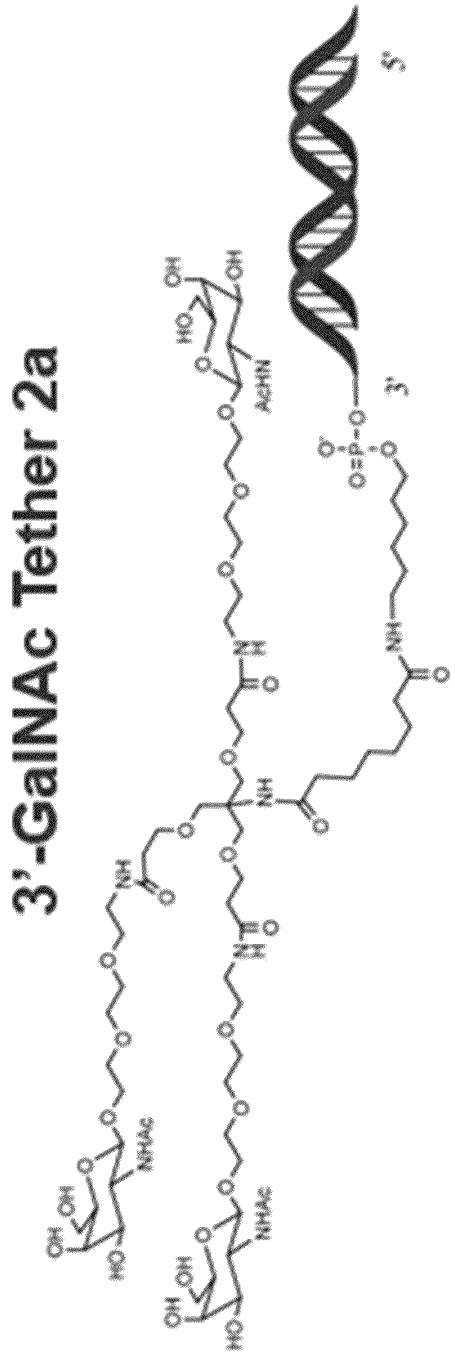



Figure 18

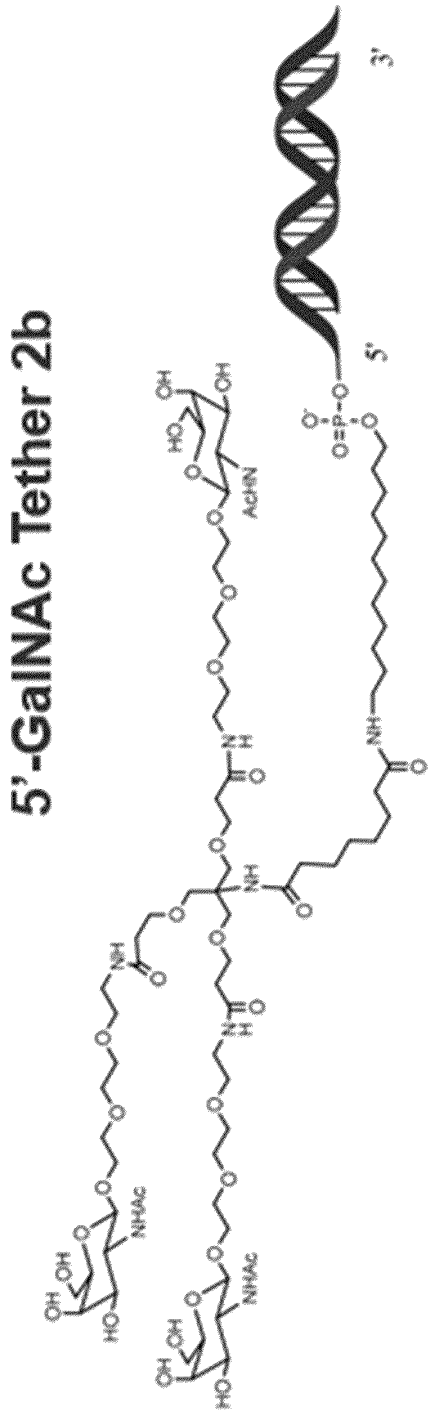



Figure 19

Figure 20

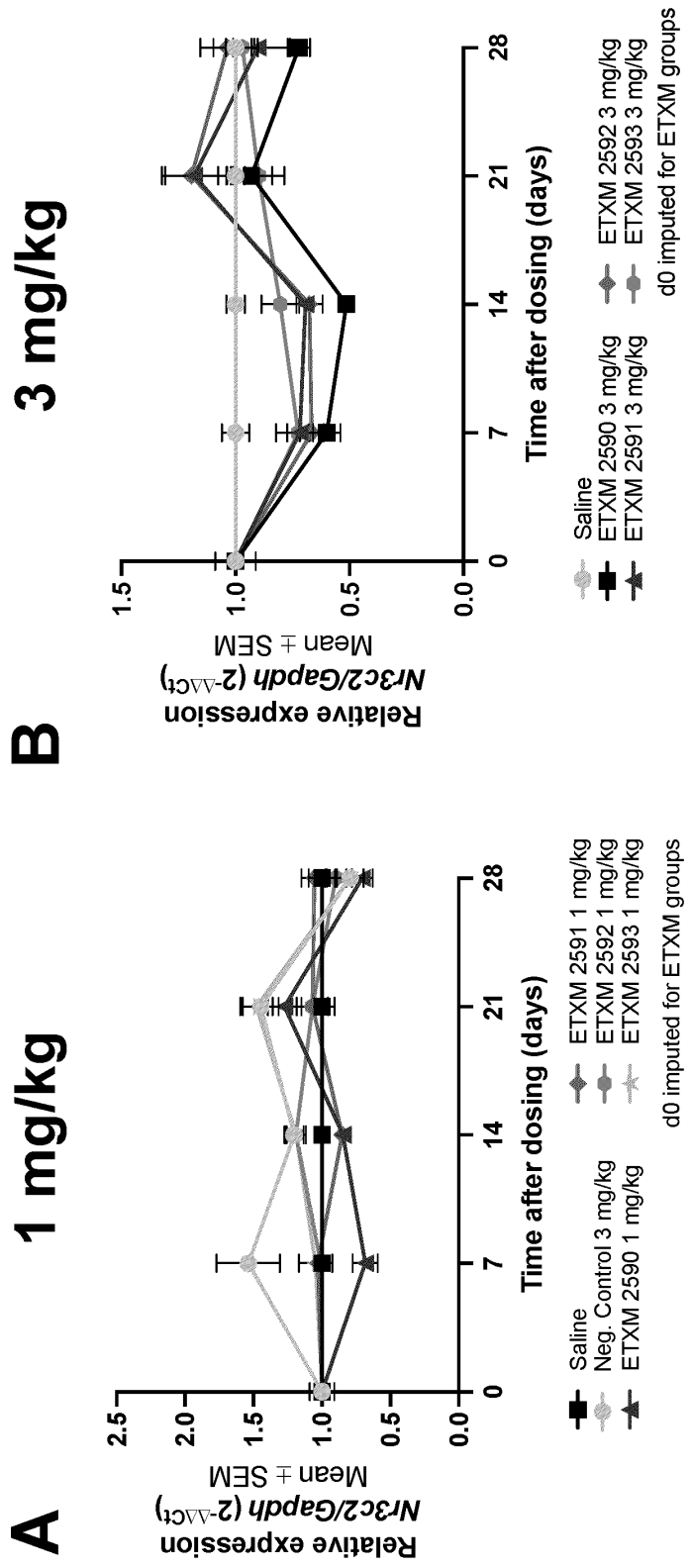

A
1 mg/kg
B
3 mg/kg
Relative expression
Nr3c2/Gapdh (2-ΔΔCt)
Mean ± SEM
Time after dosing (days)
Saline
Neg. Control 3 mg/kg
ETXM 2590 1 mg/kg
ETXM 2591 1 mg/kg
ETXM 2592 1 mg/kg
ETXM 2593 1 mg/kg
ETXM 2590 3 mg/kg
ETXM 2591 3 mg/kg
ETXM 2592 3 mg/kg
ETXM 2593 3 mg/kg
d0 imputed for ETXM groups

Figure 21

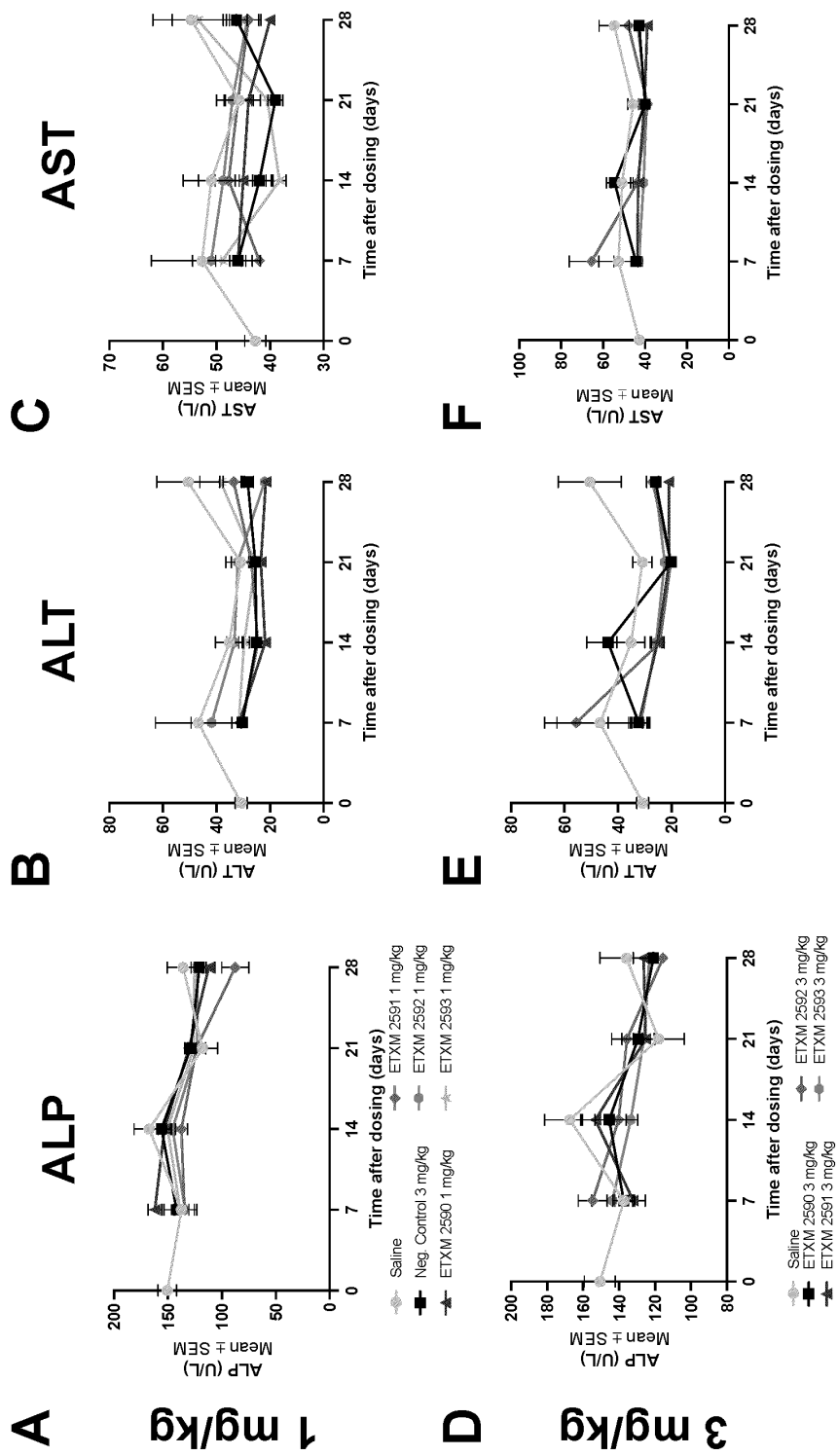

A
ALP
B
ALT
C
AST
1 mg/kg
D
E
F
3 mg/kg
ALP (U/L) Mean ± SEM
ALT (U/L) Mean ± SEM
AST (U/L) Mean ± SEM
Time after dosing (days)
Saline
Neg. Control 3 mg/kg
ETXM 2590 1 mg/kg
ETXM 2591 1 mg/kg
ETXM 2592 1 mg/kg
ETXM 2593 1 mg/kg
ETXM 2590 3 mg/kg
ETXM 2591 3 mg/kg
ETXM 2592 3 mg/kg
ETXM 2593 3 mg/kg

Figure 22

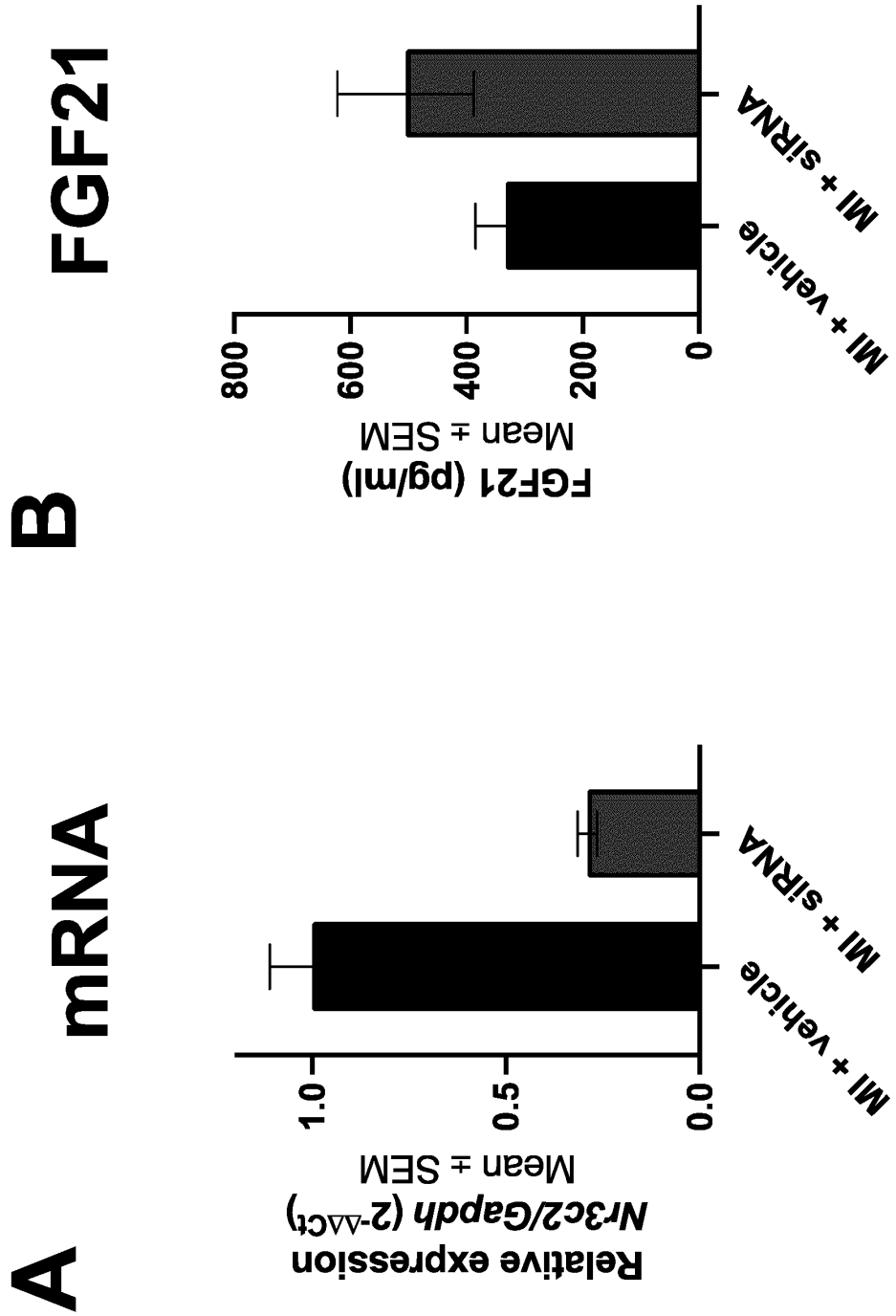

A
mRNA
Relative expression
Nr3c2/Gapdh (2-ΔΔCt)
Mean ± SEM
1.0
0.5
0.0
MI + Vehicle
MI + siRNA
B
FGF21
FGF21 (pg/ml)
Mean ± SEM
800
600
400
200
0
MI + Vehicle
MI + siRNA

Figure 23

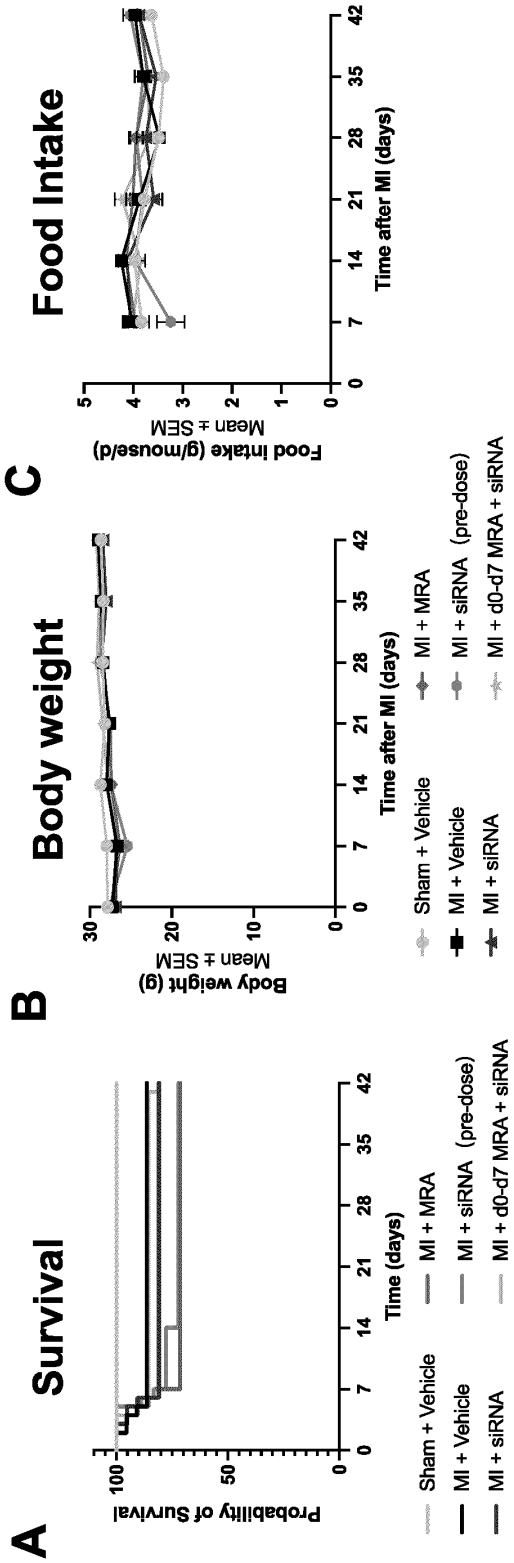

A
Survival
Probability of Survival
100
50
0
0
7
14
21
28
35
42
Time (days)
B
Body weight
Body weight (g)
Mean ± SEM
30
20
10
0
Time after MI (days)
C
Food Intake
Food intake (g/mouse/d)
Mean ± SEM
5
4
3
2
1
0
Time after MI (days)
Sham + Vehicle
MI + Vehicle
MI + siRNA
MI + MRA
MI + siRNA (pre-dose)
MI + d0-d7 MRA + siRNA

Figure 24

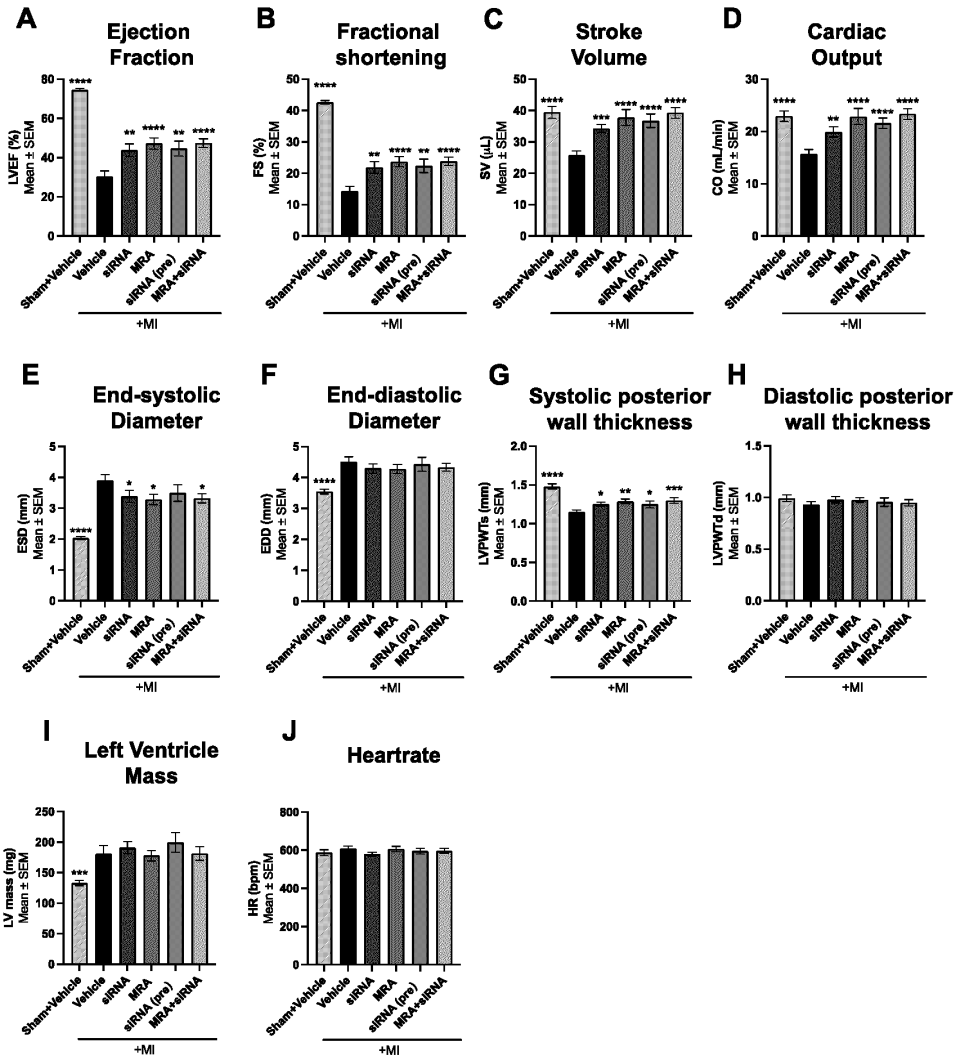

A
Ejection Fraction
LVEF (%) Mean ± SEM
B
Fractional shortening
FS (%) Mean ± SEM
C
Stroke Volume
SV (µL) Mean ± SEM
D
Cardiac Output
CO (mL/min) Mean ± SEM
E
End-systolic Diameter
ESD (mm) Mean ± SEM
F
End-diastolic Diameter
EDD (mm) Mean ± SEM
G
Systolic posterior wall thickness
LVPWTs (mm) Mean ± SEM
H
Diastolic posterior wall thickness
LVPWTd (mm) Mean ± SEM
I
Left Ventricle Mass
LV mass (mg) Mean ± SEM
J
Heartrate
HR (bpm) Mean ± SEM
Sham+Vehicle
Vehicle
siRNA
MRA
siRNA (pre)
MRA+siRNA
+MI

Figure 25

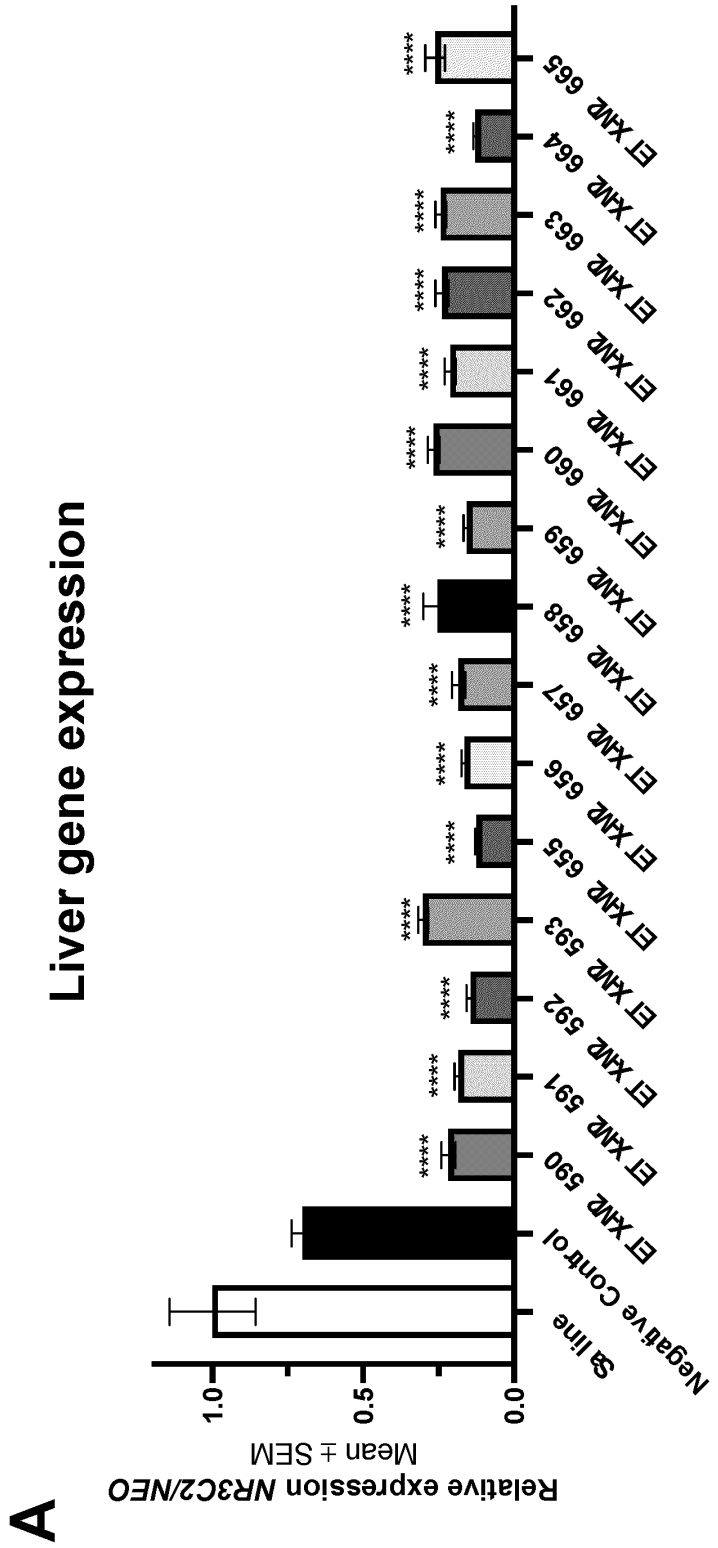

A
Liver gene expression
Relative expression NR3C2/NEO
Mean ± SEM
1.0
0.5
0.0
Saline
Negative Control
EI XMR 590
EI XMR 591
EI XMR 592
EI XMR 593
EI XMR 655
EI XMR 656
EI XMR 657
EI XMR 658
EI XMR 659
EI XMR 660
EI XMR 661
EI XMR 662
EI XMR 663
EI XMR 664
EI XMR 665
****

Figure 26

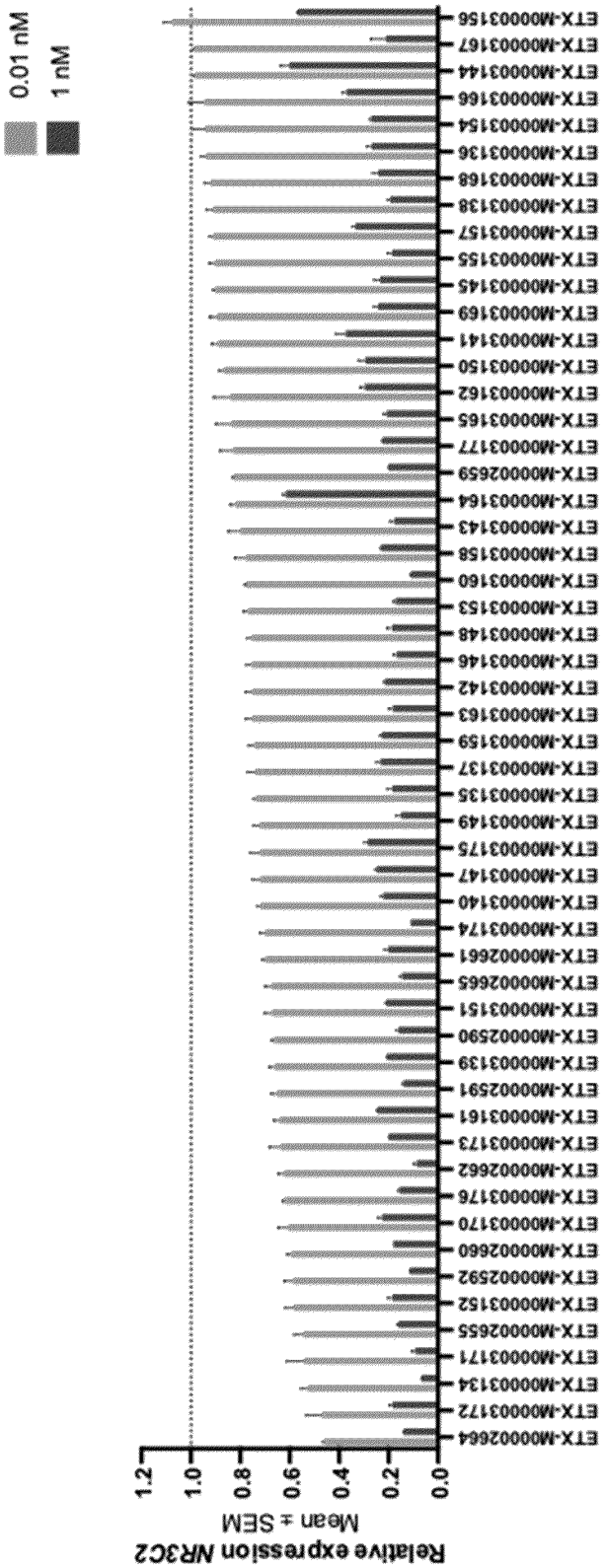

0.01 nM
1 nM
Relative expression NR3C2
Mean ± SEM
1.2
1.0
0.8
0.6
0.4
0.2
0.0
ETX-M00002664
ETX-M00003172
ETX-M00003134
ETX-M00003171
ETX-M00002655
ETX-M00003152
ETX-M00002592
ETX-M00002660
ETX-M00003170
ETX-M00003176
ETX-M00002662
ETX-M00003173
ETX-M00003161
ETX-M00002591
ETX-M00003139
ETX-M00002590
ETX-M00003151
ETX-M00002665
ETX-M00002661
ETX-M00003174
ETX-M00003140
ETX-M00003147
ETX-M00003175
ETX-M00003149
ETX-M00003135
ETX-M00003137
ETX-M00003159
ETX-M00003163
ETX-M00003142
ETX-M00003146
ETX-M00003148
ETX-M00003153
ETX-M00003160
ETX-M00003158
ETX-M00003143
ETX-M00003164
ETX-M00002659
ETX-M00003177
ETX-M00003165
ETX-M00003162
ETX-M00003150
ETX-M00003141
ETX-M00003169
ETX-M00003145
ETX-M00003155
ETX-M00003157
ETX-M00003138
ETX-M00003168
ETX-M00003136
ETX-M00003154
ETX-M00003166
ETX-M00003144
ETX-M00003167
ETX-M00003156

Figure 27

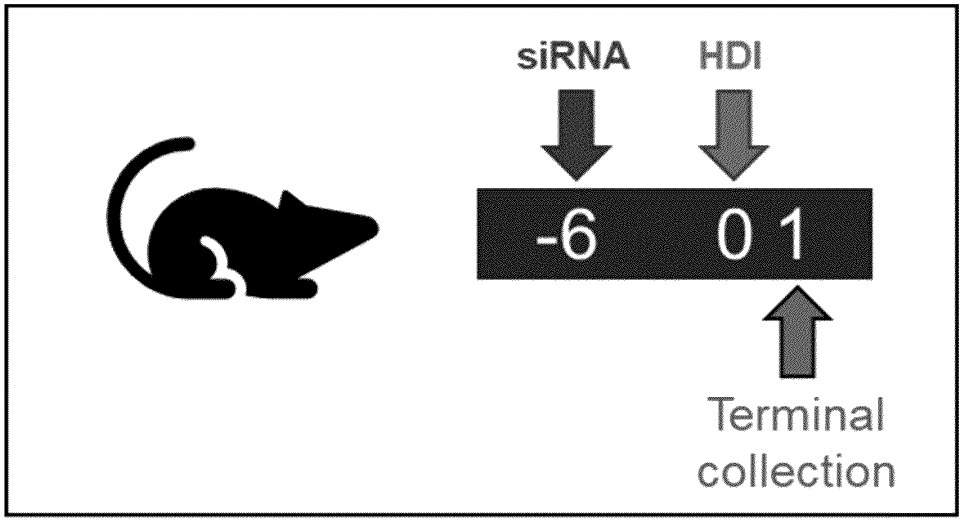


Figure 28

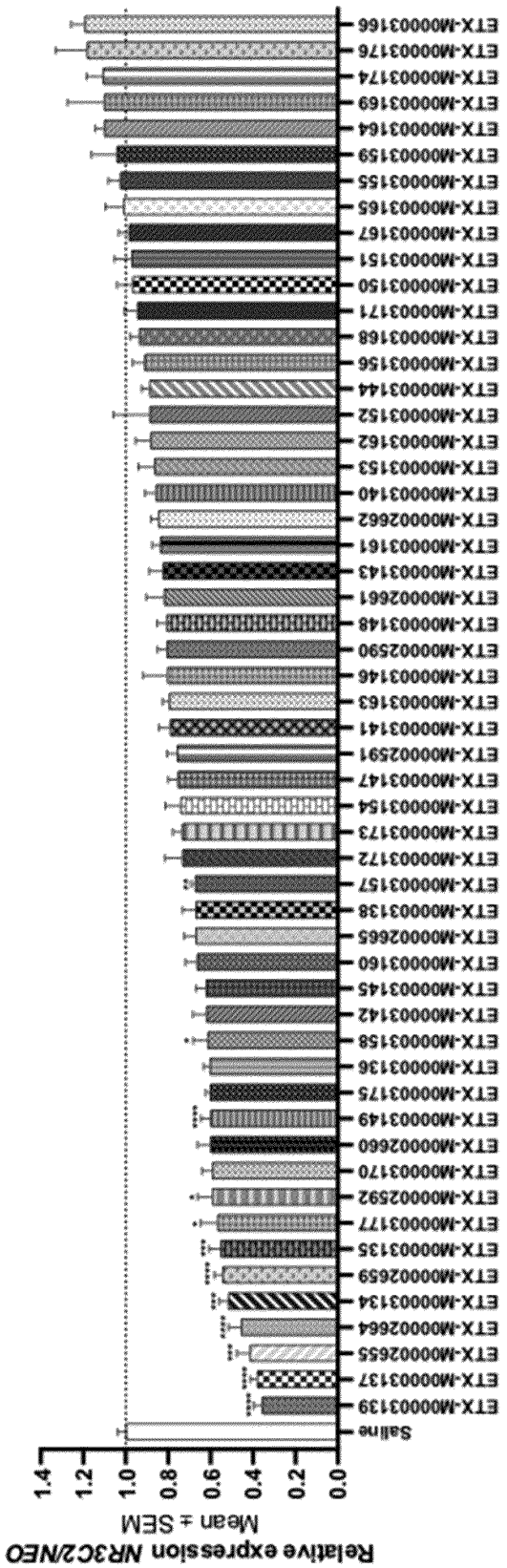

Relative expression NR3C2/NEO
Mean ± SEM
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Saline
ETX-M00003139
ETX-M00003137
ETX-M00002655
ETX-M00002664
ETX-M00003134
ETX-M00002659
ETX-M00003135
ETX-M00003177
ETX-M00002592
ETX-M00003170
ETX-M00002660
ETX-M00003149
ETX-M00003175
ETX-M00003136
ETX-M00003158
ETX-M00003142
ETX-M00003145
ETX-M00003160
ETX-M00002665
ETX-M00003138
ETX-M00003157
ETX-M00003172
ETX-M00003173
ETX-M00003154
ETX-M00003147
ETX-M00002591
ETX-M00003141
ETX-M00003163
ETX-M00003146
ETX-M00002590
ETX-M00003148
ETX-M00002661
ETX-M00003143
ETX-M00003161
ETX-M00002662
ETX-M00003140
ETX-M00003153
ETX-M00003162
ETX-M00003152
ETX-M00003144
ETX-M00003156
ETX-M00003168
ETX-M00003171
ETX-M00003150
ETX-M00003151
ETX-M00003167
ETX-M00003165
ETX-M00003155
ETX-M00003159
ETX-M00003164
ETX-M00003169
ETX-M00003174
ETX-M00003176
ETX-M00003166

Figure 29

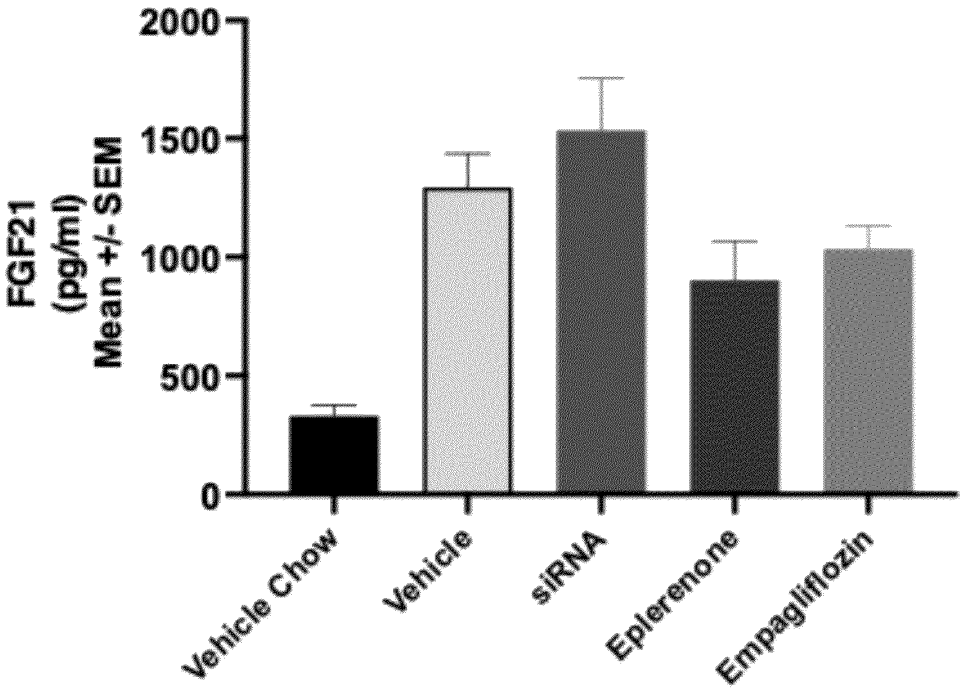

FGF21
(pg/ml)
Mean +/- SEM
2000
1500
1000
500
0
Vehicle Chow
Vehicle
siRNA
Eplerenone
Empagliflozin

Figure 30

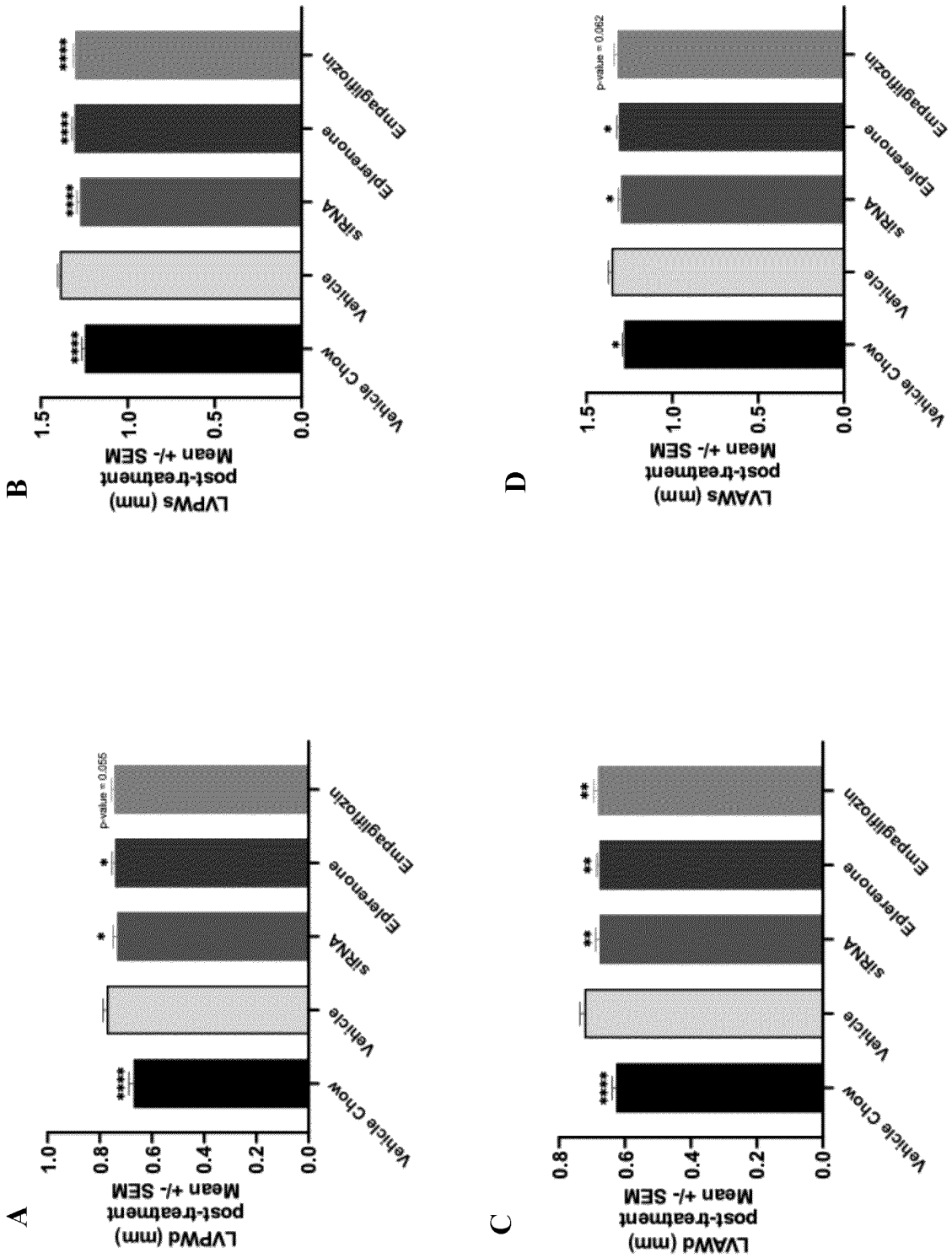

A
LVPWd (mm)
post-treatment
Mean +/- SEM
1.0
0.8
0.6
0.4
0.2
0.0
p-value = 0.055
****
*
*
Vehicle Chow
Vehicle
siRNA
Eplerenone
Empagliflozin
B
LVPWs (mm)
post-treatment
Mean +/- SEM
1.5
1.0
0.5
0.0
****
****
****
****
Vehicle Chow
Vehicle
siRNA
Eplerenone
Empagliflozin
C
LVAWd (mm)
post-treatment
Mean +/- SEM
0.8
0.6
0.4
0.2
0.0
****
**
**
**
Vehicle Chow
Vehicle
siRNA
Eplerenone
Empagliflozin
D
LVAWs (mm)
post-treatment
Mean +/- SEM
1.5
1.0
0.5
0.0
p-value = 0.062
*
*
*
Vehicle Chow
Vehicle
siRNA
Eplerenone
Empagliflozin

Figure 31

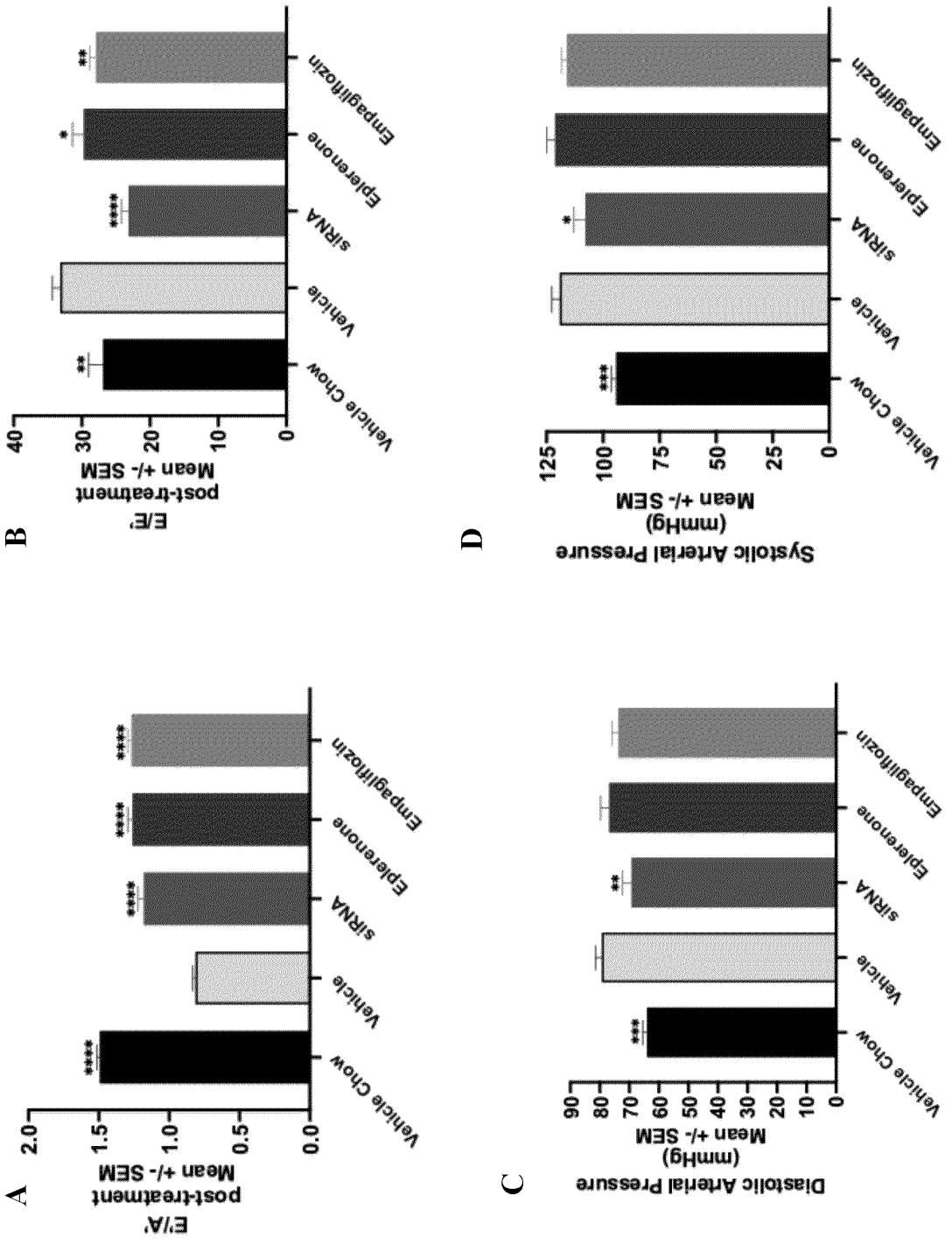

A
E'/A'
post-treatment
Mean +/- SEM
2.0
1.5
1.0
0.5
0.0
****
****
****
****
Vehicle Chow
Vehicle
siRNA
Eplerenone
Empagliflozin
B
E/E'
post-treatment
Mean +/- SEM
40
30
20
10
0
**
****
*
**
Vehicle Chow
Vehicle
siRNA
Eplerenone
Empagliflozin
C
Diastolic Arterial Pressure
(mmHg)
Mean +/- SEM
90
80
70
60
50
40
30
20
10
0
***
**
Vehicle Chow
Vehicle
siRNA
Eplerenone
Empagliflozin
D
Systolic Arterial Pressure
(mmHg)
Mean +/- SEM
125
100
75
50
25
0
***
*
Vehicle Chow
Vehicle
siRNA
Eplerenone
Empagliflozin

**Figure 31 cont.**

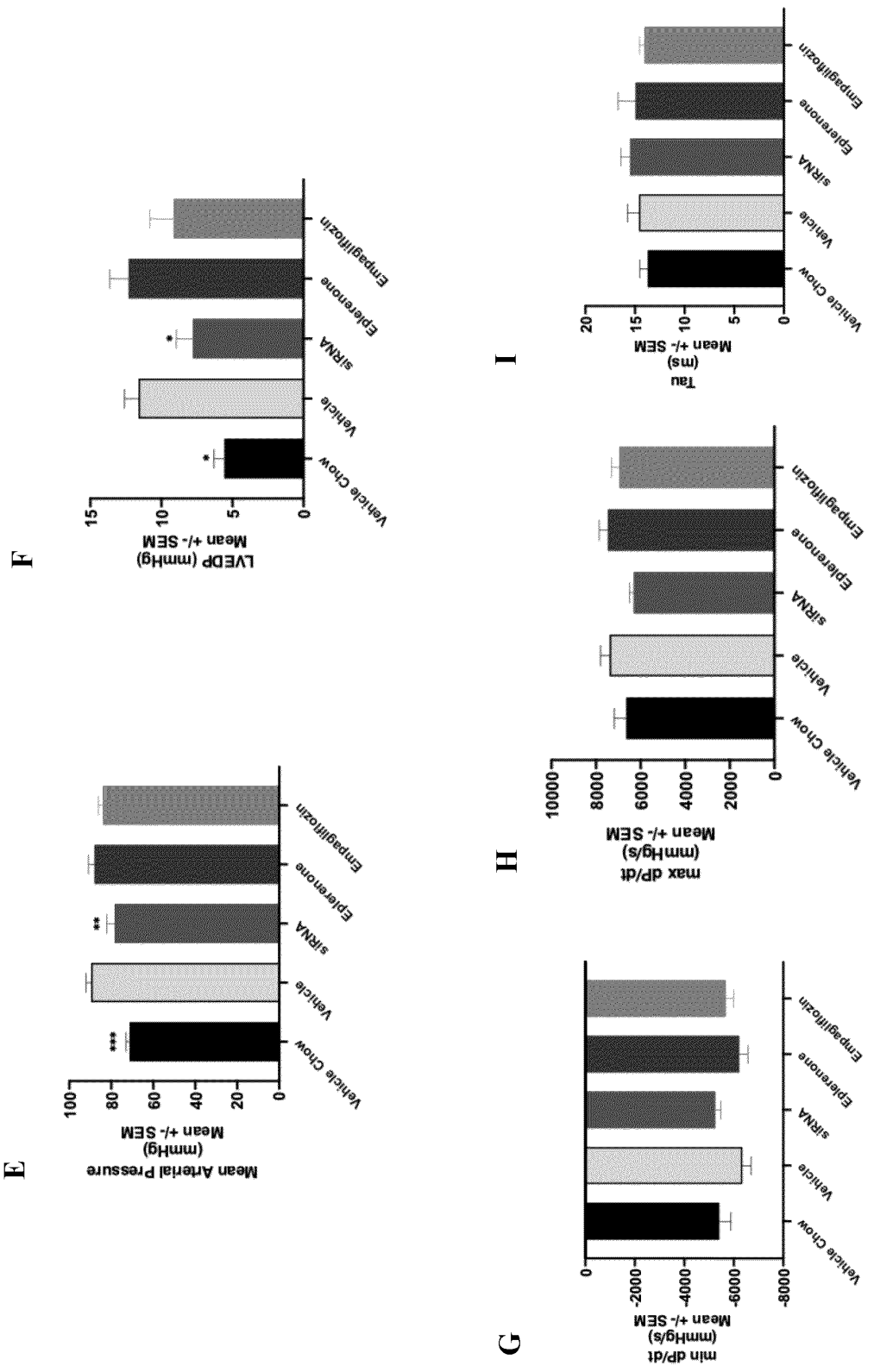
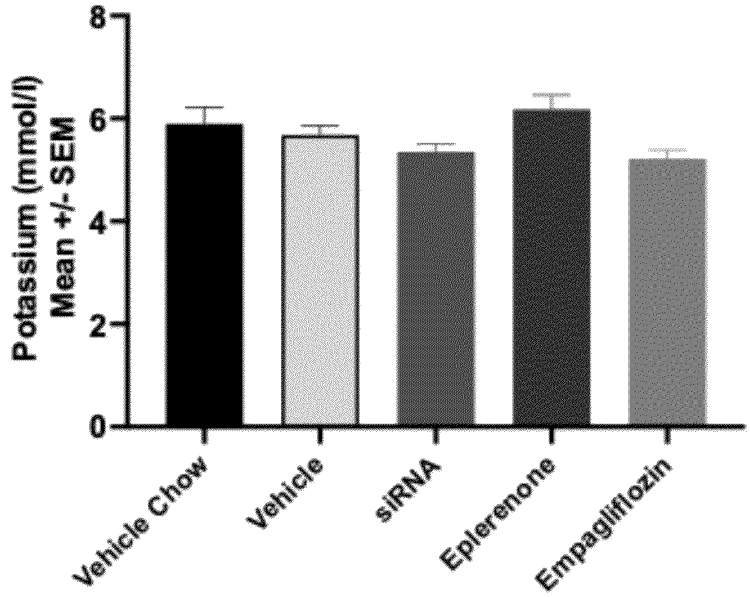


Figure 32

A


Potassium (mmol/l)
Mean +/- SEM
8
6
4
2
0
Vehicle Chow
Vehicle
siRNA
Eplerenone
Empagliflozin

B

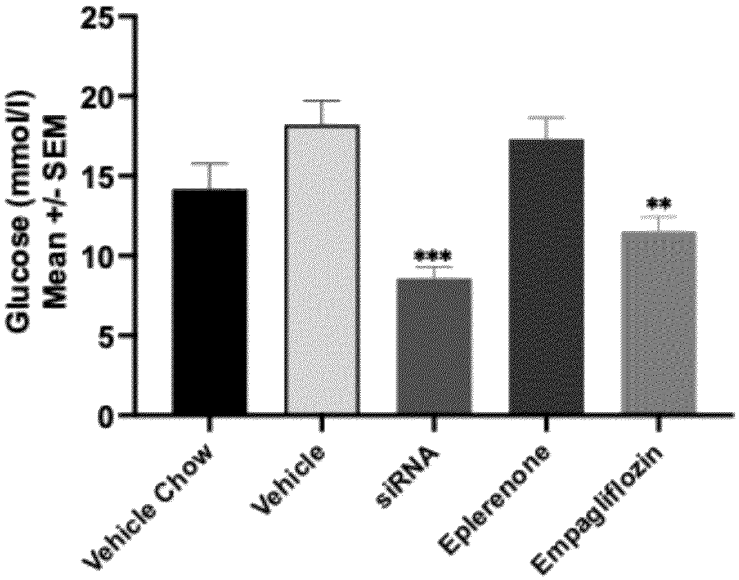
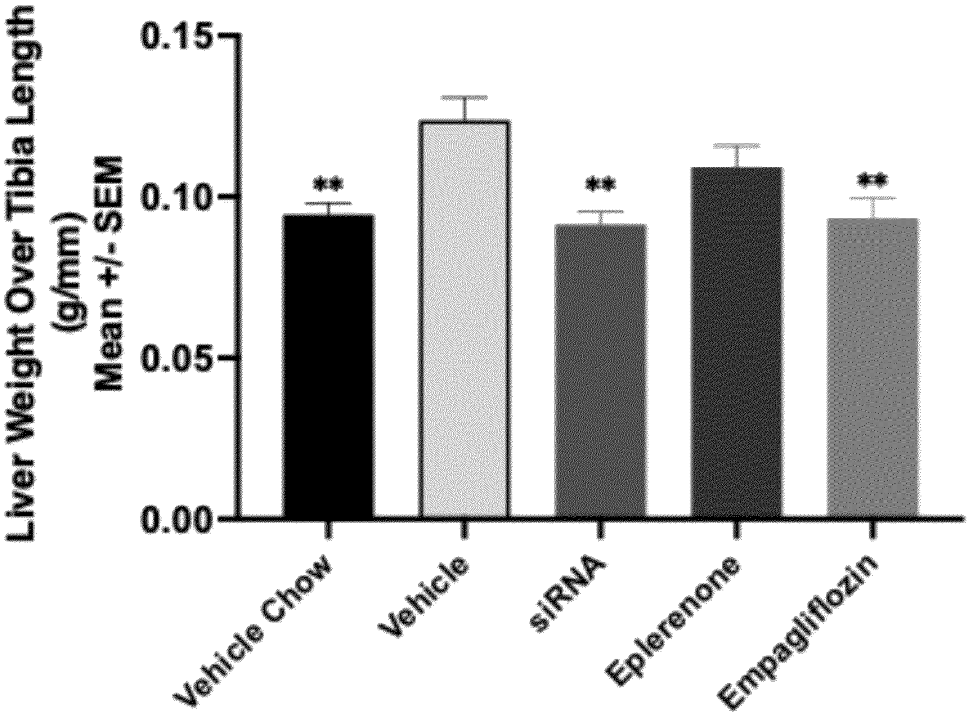

Glucose (mmol/l)
Mean +/- SEM
25
20
15
10
5
0
***
**
Vehicle Chow
Vehicle
siRNA
Eplerenone
Empagliflozin

Figure 33


Liver Weight Over Tibia Length
(g/mm)
Mean +/- SEM
0.15
0.10
0.05
0.00
**
**
**
Vehicle Chow
Vehicle
siRNA
Eplerenone
Empagliflozin