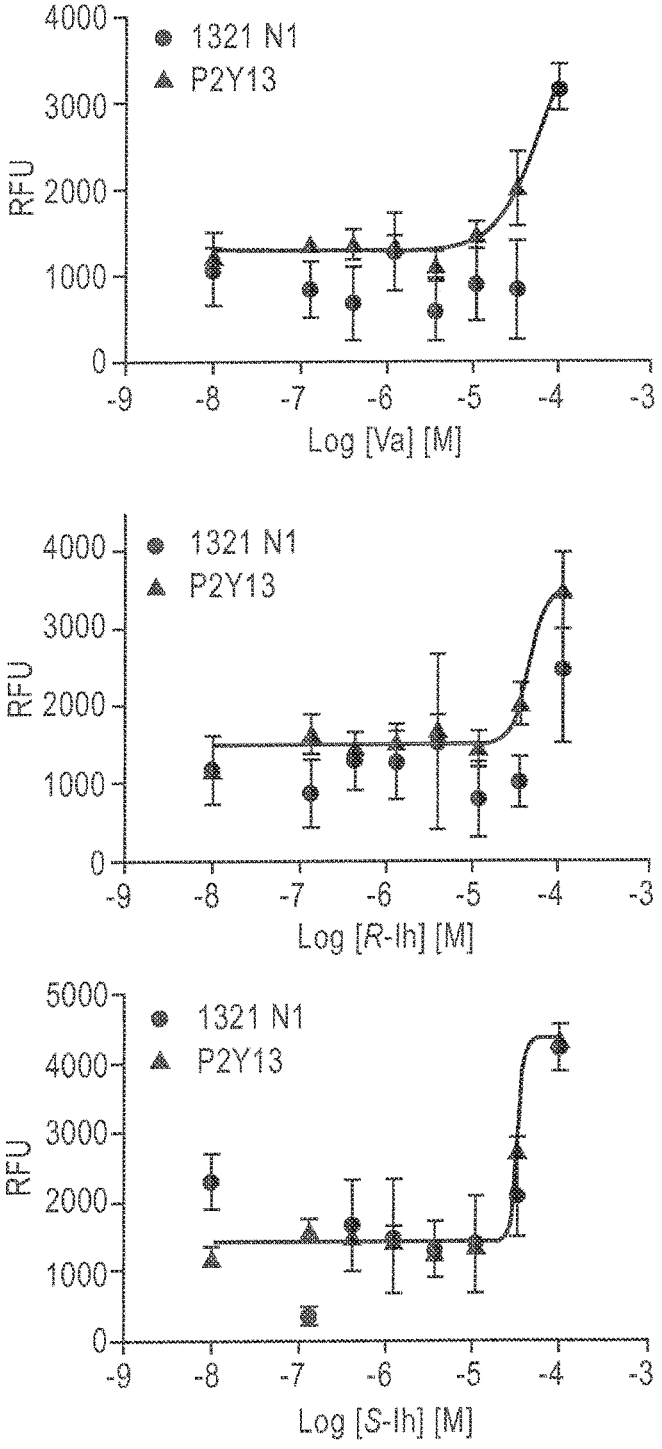

4000
3000
2000
1000
0
RFU
1321 N1
P2Y13
-9
-8
-7
-6
-5
-4
-3
Log [Va] [M]
4000
3000
2000
1000
0
RFU
1321 N1
P2Y13
-9
-8
-7
-6
-5
-4
-3
Log [R-Ih] [M]
5000
4000
3000
2000
1000
0
RFU
1321 N1
P2Y13
-9
-8
-7
-6
-5
-4
-3
Log [S-Ih] [M]

FIGURE 1

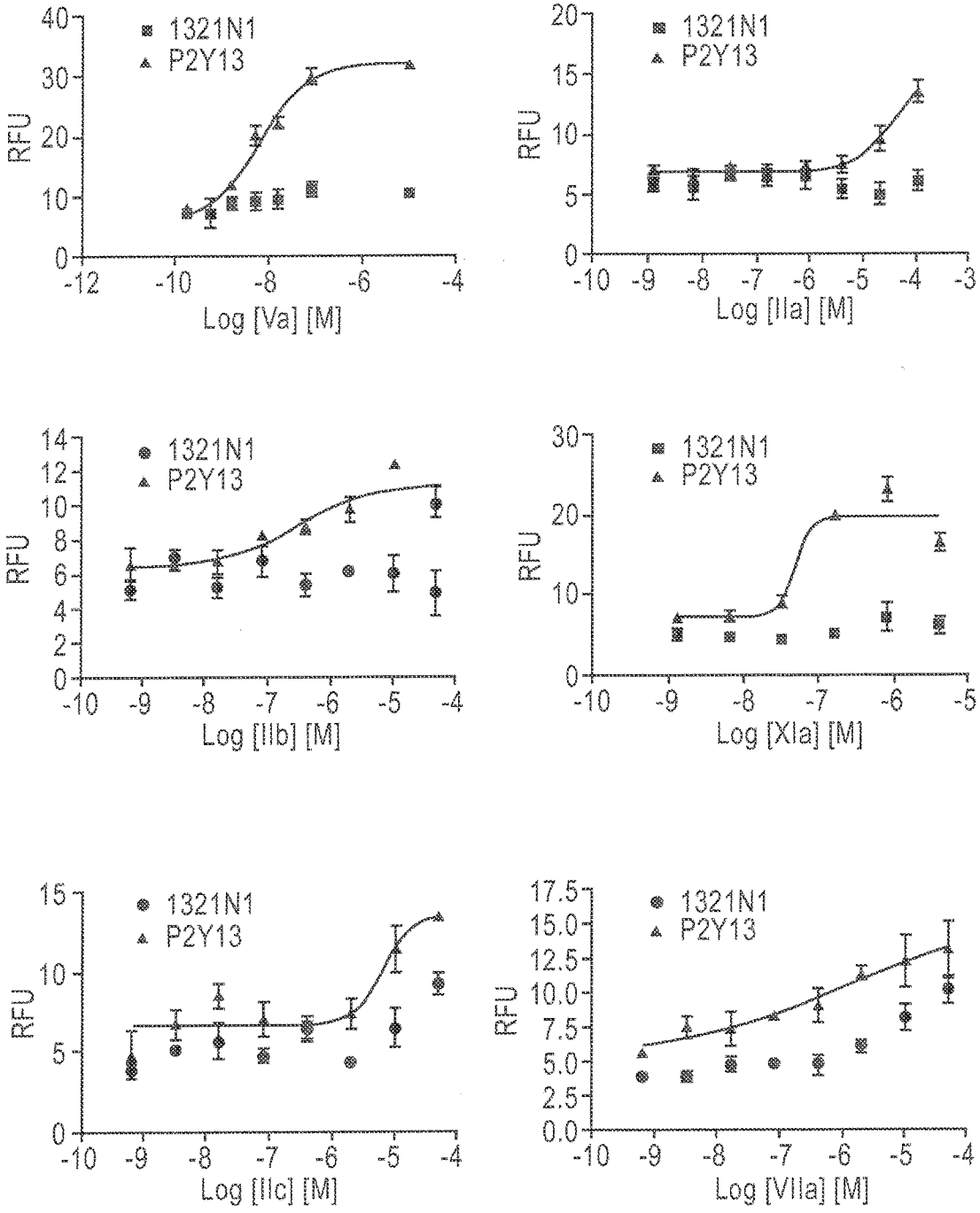

1321N1
P2Y13
RFU
Log [Va] [M]
Log [IIa] [M]
Log [IIb] [M]
Log [Xla] [M]
Log [IIc] [M]
Log [VIIa] [M]

FIGURE 2

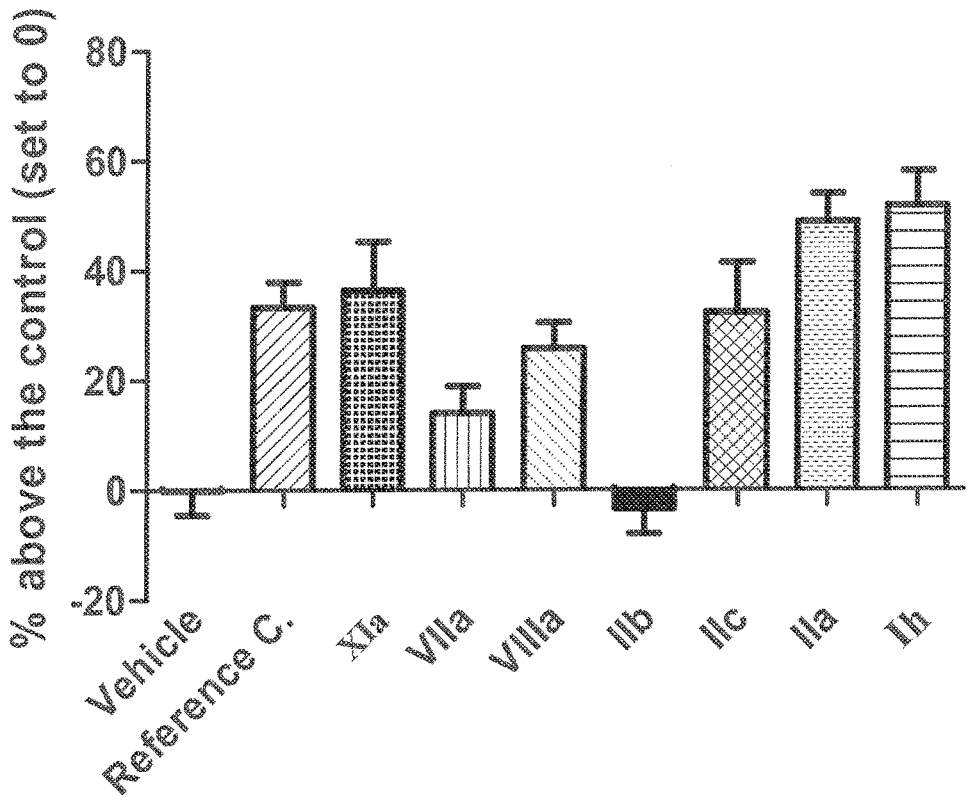
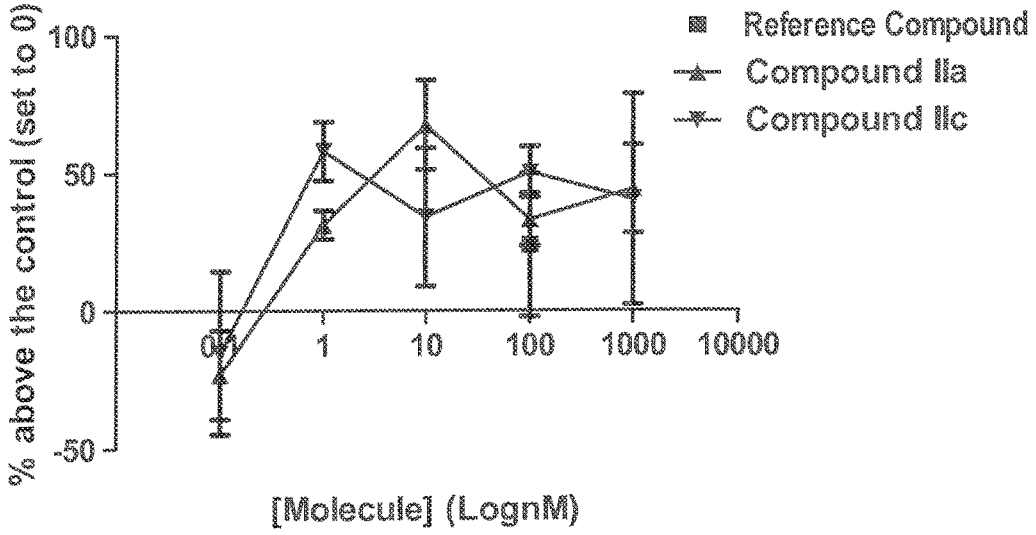

% above the control (set to 0)
80
60
40
20
0
-20
Vehicle
Reference C.
XIa
VIIa
VIIIa
IIb
IIc
IIa
Ih

FIGURE 3

A.


Reference Compound
Compound IIa
Compound IIc
% above the control (set to 0)
100
50
0
-50
0
1
10
100
1000
10000
[Molecule] (LognM)

B.

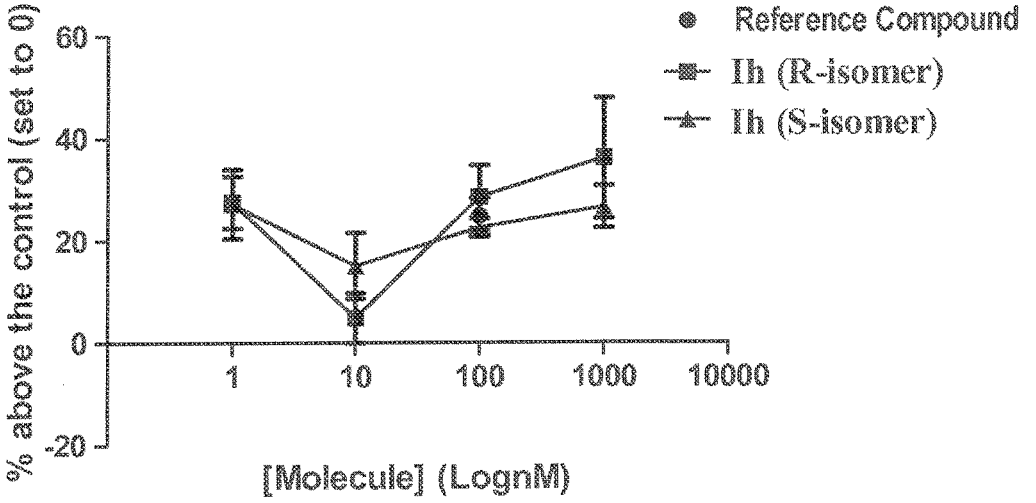

Reference Compound
Ih (R-isomer)
Ih (S-isomer)
% above the control (set to 0)
60
40
20
0
-20
1
10
100
1000
10000
[Molecule] (LognM)

FIGURE 4

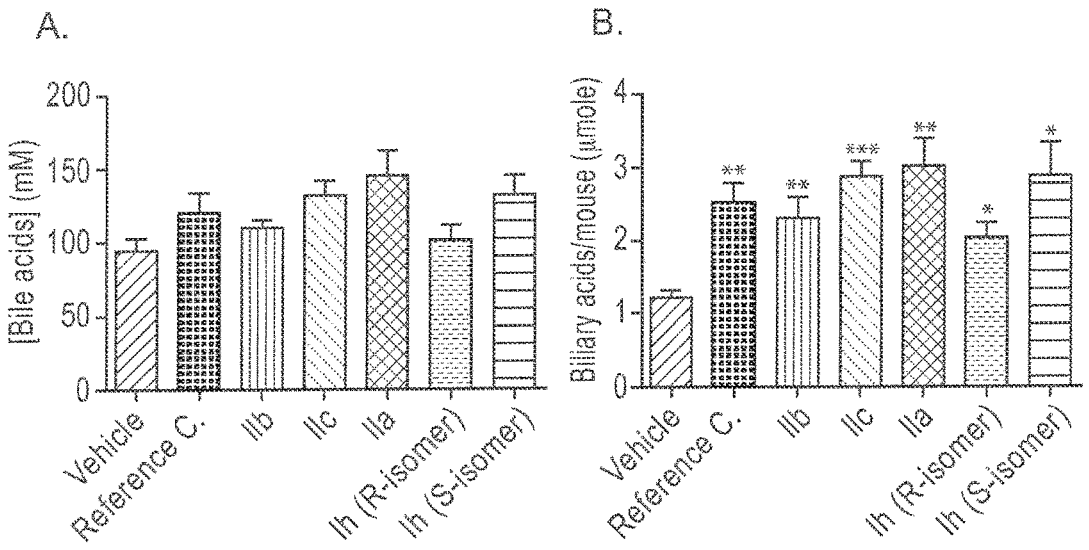

A.
[Bile acids] (mM)
200
150
100
50
0
Vehicle
Reference C.
IIb
IIc
IIa
Ih (R-isomer)
Ih (S-isomer)
B.
Biliary acids/mouse (µmole)
4
3
2
1
0
**
**
***
**
*
*
Vehicle
Reference C.
IIb
IIc
IIa
Ih (R-isomer)
Ih (S-isomer)

FIGURE 5

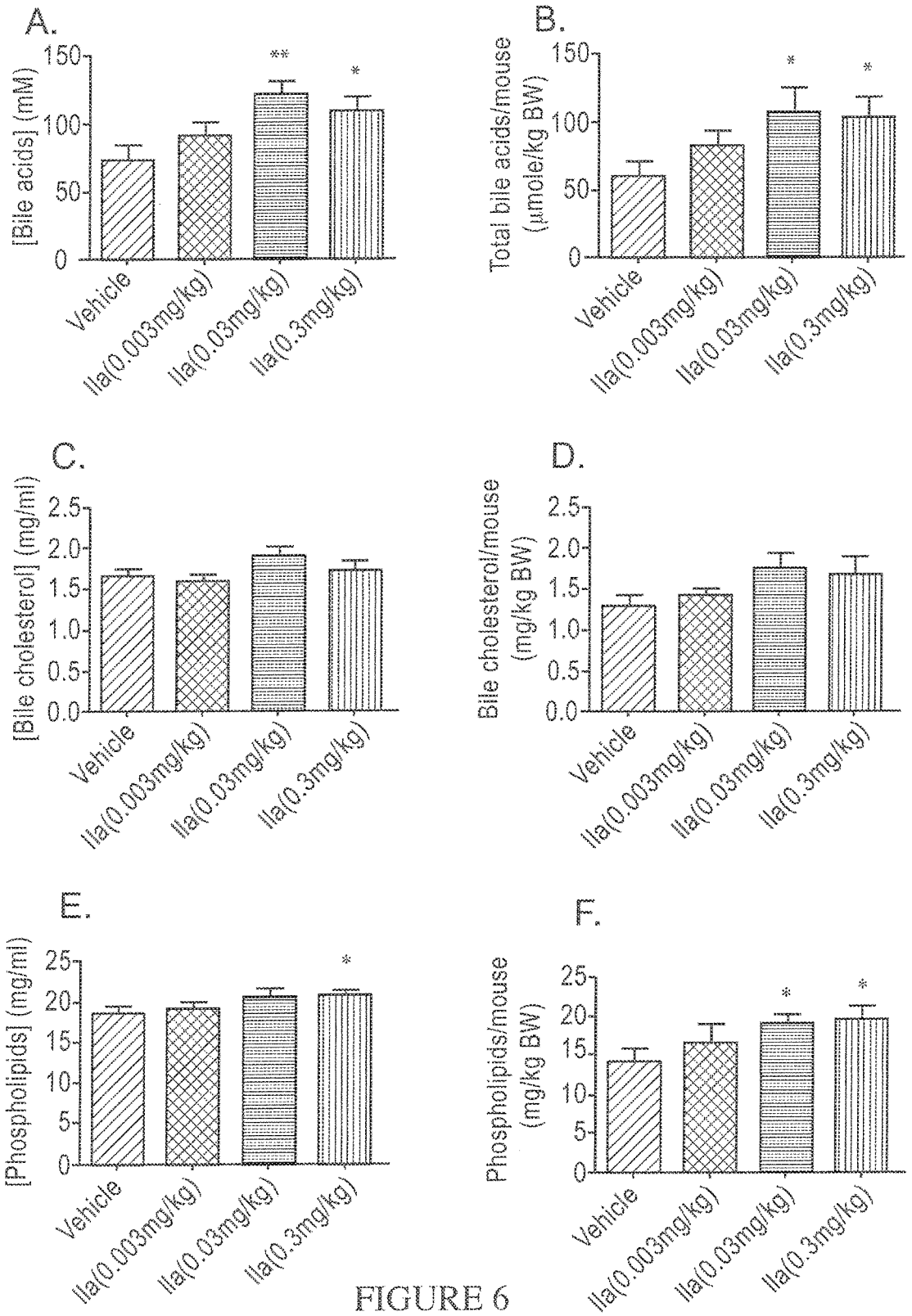

A.
[Bile acids] (mM)
150
100
50
0
**
*
Vehicle
IIa(0.003mg/kg)
IIa(0.03mg/kg)
IIa(0.3mg/kg)
B.
Total bile acids/mouse (µmole/kg BW)
150
100
50
0
*
*
Vehicle
IIa(0.003mg/kg)
IIa(0.03mg/kg)
IIa(0.3mg/kg)
C.
[Bile cholesterol] (mg/ml)
2.5
2.0
1.5
1.0
0.5
0.0
Vehicle
IIa(0.003mg/kg)
IIa(0.03mg/kg)
IIa(0.3mg/kg)
D.
Bile cholesterol/mouse (mg/kg BW)
2.5
2.0
1.5
1.0
0.5
0.0
Vehicle
IIa(0.003mg/kg)
IIa(0.03mg/kg)
IIa(0.3mg/kg)
E.
[Phospholipids] (mg/ml)
25
20
15
10
5
0
*
Vehicle
IIa(0.003mg/kg)
IIa(0.03mg/kg)
IIa(0.3mg/kg)
F.
Phospholipids/mouse (mg/kg BW)
25
20
15
10
5
0
*
*
Vehicle
IIa(0.003mg/kg)
IIa(0.03mg/kg)
IIa(0.3mg/kg)

FIGURE 6

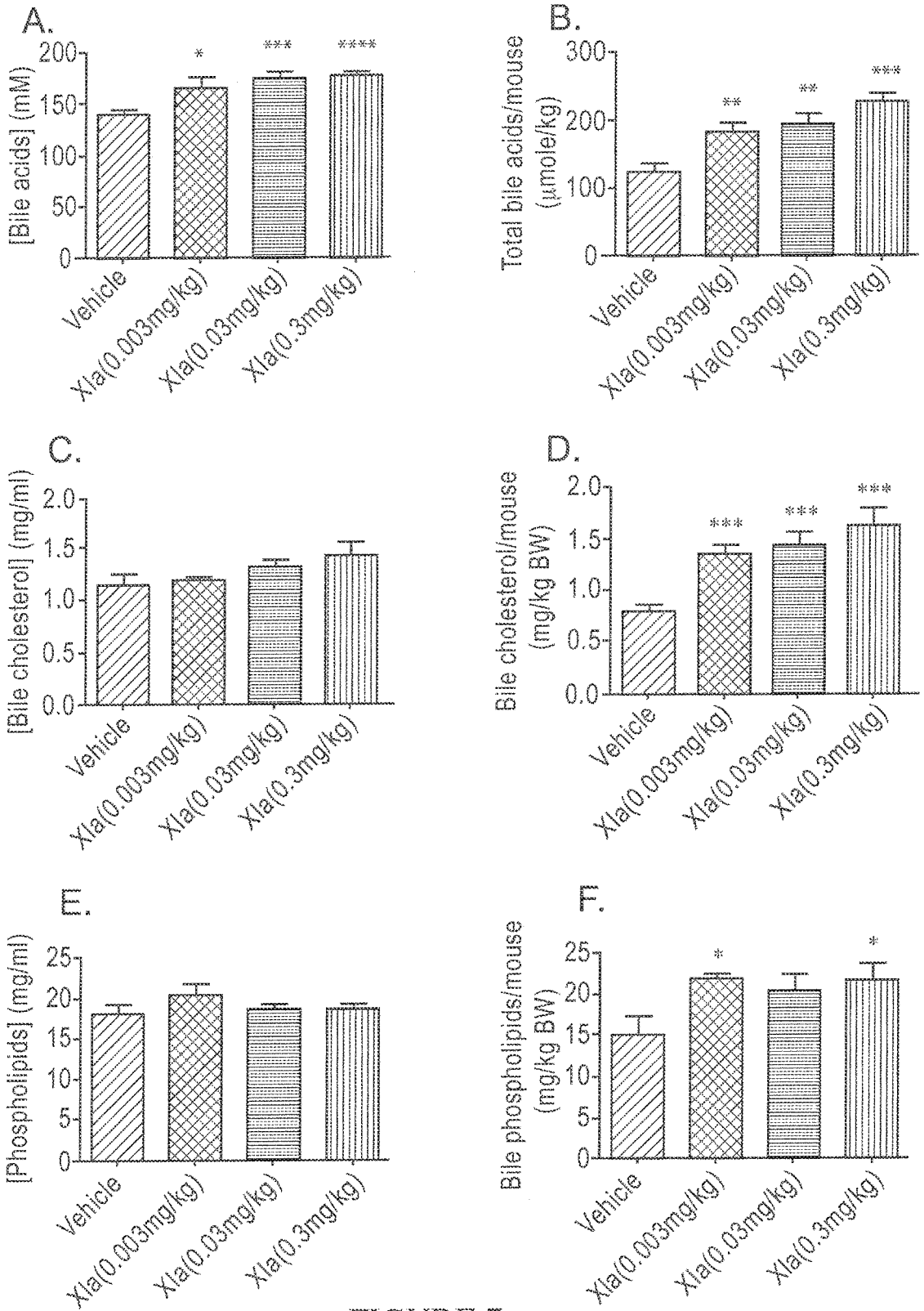

A.
[Bile acids] (mM)
200
150
100
50
0
*
***
****
Vehicle
Xla(0.003mg/kg)
Xla(0.03mg/kg)
Xla(0.3mg/kg)
B.
Total bile acids/mouse (µmole/kg)
300
200
100
0
**
**
***
Vehicle
Xla(0.003mg/kg)
Xla(0.03mg/kg)
Xla(0.3mg/kg)
C.
[Bile cholesterol] (mg/ml)
2.0
1.5
1.0
0.5
0.0
Vehicle
Xla(0.003mg/kg)
Xla(0.03mg/kg)
Xla(0.3mg/kg)
D.
Bile cholesterol/mouse (mg/kg BW)
2.0
1.5
1.0
0.5
0.0
***
***
***
Vehicle
Xla(0.003mg/kg)
Xla(0.03mg/kg)
Xla(0.3mg/kg)
E.
[Phospholipids] (mg/ml)
25
20
15
10
5
0
Vehicle
Xla(0.003mg/kg)
Xla(0.03mg/kg)
Xla(0.3mg/kg)
F.
Bile phospholipids/mouse (mg/kg BW)
25
20
15
10
5
0
*
*
Vehicle
Xla(0.003mg/kg)
Xla(0.03mg/kg)
Xla(0.3mg/kg)

FIGURE 7

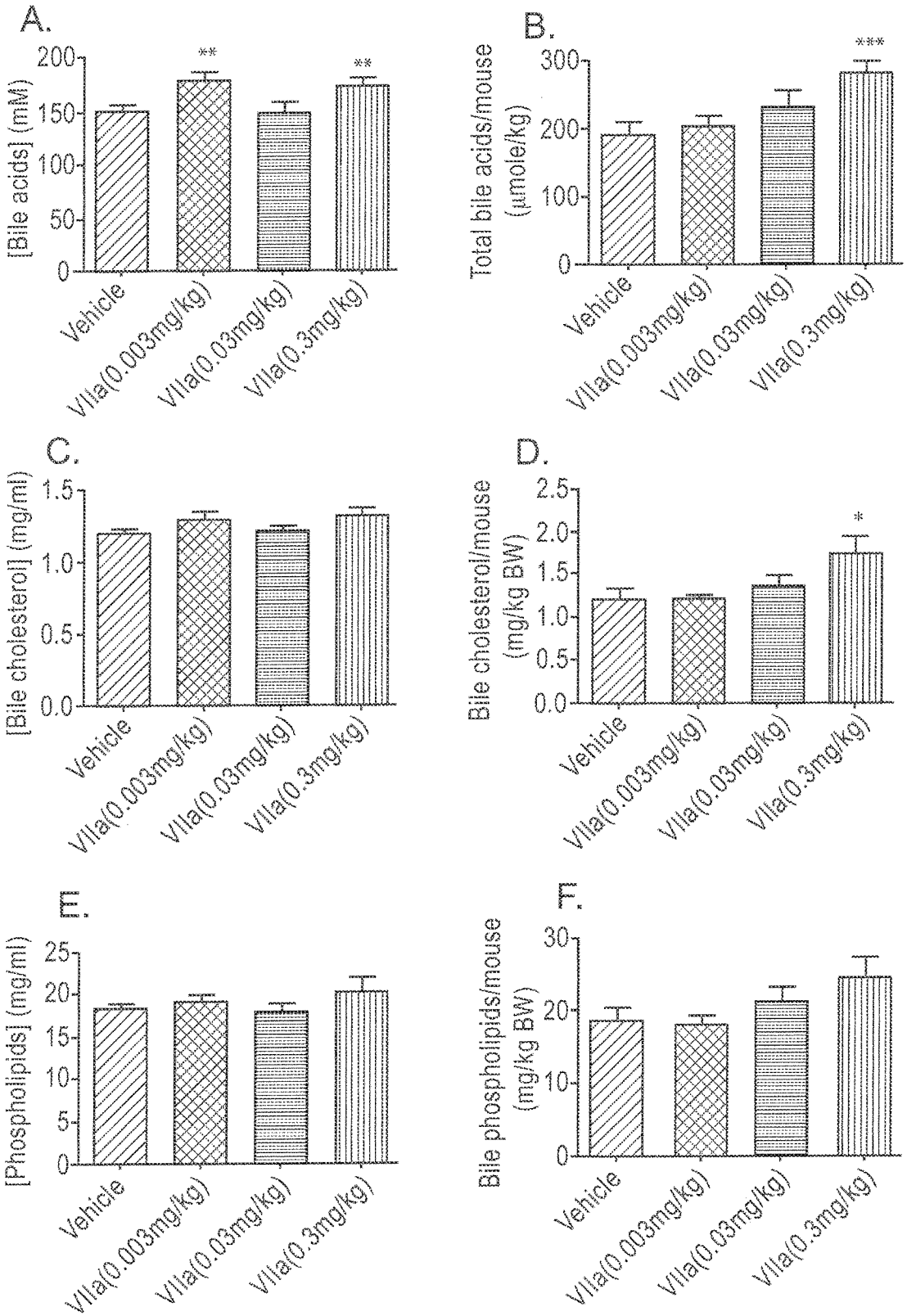

A.
[Bile acids] (mM)
200
150
100
50
0
**
**
Vehicle
VIIa(0.003mg/kg)
VIIa(0.03mg/kg)
VIIa(0.3mg/kg)
B.
Total bile acids/mouse (µmole/kg)
300
200
100
0
***
Vehicle
VIIa(0.003mg/kg)
VIIa(0.03mg/kg)
VIIa(0.3mg/kg)
C.
[Bile cholesterol] (mg/ml)
1.5
1.0
0.5
0.0
Vehicle
VIIa(0.003mg/kg)
VIIa(0.03mg/kg)
VIIa(0.3mg/kg)
D.
Bile cholesterol/mouse (mg/kg BW)
2.5
2.0
1.5
1.0
0.5
0.0
*
Vehicle
VIIa(0.003mg/kg)
VIIa(0.03mg/kg)
VIIa(0.3mg/kg)
E.
[Phospholipids] (mg/ml)
25
20
15
10
5
0
Vehicle
VIIa(0.003mg/kg)
VIIa(0.03mg/kg)
VIIa(0.3mg/kg)
F.
Bile phospholipids/mouse (mg/kg BW)
30
20
10
0
Vehicle
VIIa(0.003mg/kg)
VIIa(0.03mg/kg)
VIIa(0.3mg/kg)

FIGURE 8

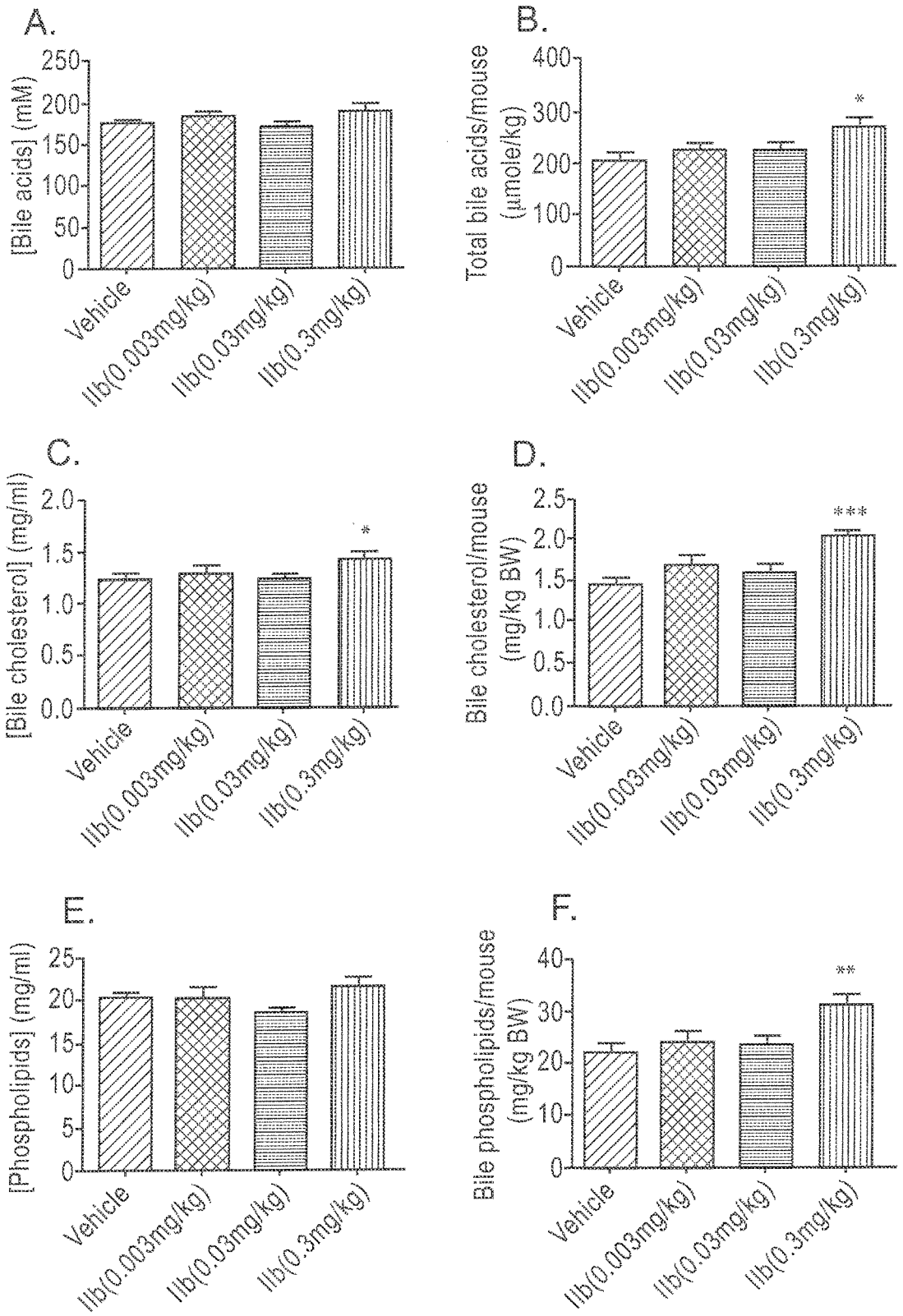

A.
[Bile acids] (mM)
250
200
150
100
50
0
Vehicle
IIb(0.003mg/kg)
IIb(0.03mg/kg)
IIb(0.3mg/kg)
B.
Total bile acids/mouse (µmole/kg)
400
300
200
100
0
*
Vehicle
IIb(0.003mg/kg)
IIb(0.03mg/kg)
IIb(0.3mg/kg)
C.
[Bile cholesterol] (mg/ml)
2.0
1.5
1.0
0.5
0.0
*
Vehicle
IIb(0.003mg/kg)
IIb(0.03mg/kg)
IIb(0.3mg/kg)
D.
Bile cholesterol/mouse (mg/kg BW)
2.5
2.0
1.5
1.0
0.5
0.0
***
Vehicle
IIb(0.003mg/kg)
IIb(0.03mg/kg)
IIb(0.3mg/kg)
E.
[Phospholipids] (mg/ml)
25
20
15
10
5
0
Vehicle
IIb(0.003mg/kg)
IIb(0.03mg/kg)
IIb(0.3mg/kg)
F.
Bile phospholipids/mouse (mg/kg BW)
40
30
20
10
0
**
Vehicle
IIb(0.003mg/kg)
IIb(0.03mg/kg)
IIb(0.3mg/kg)

FIGURE 9

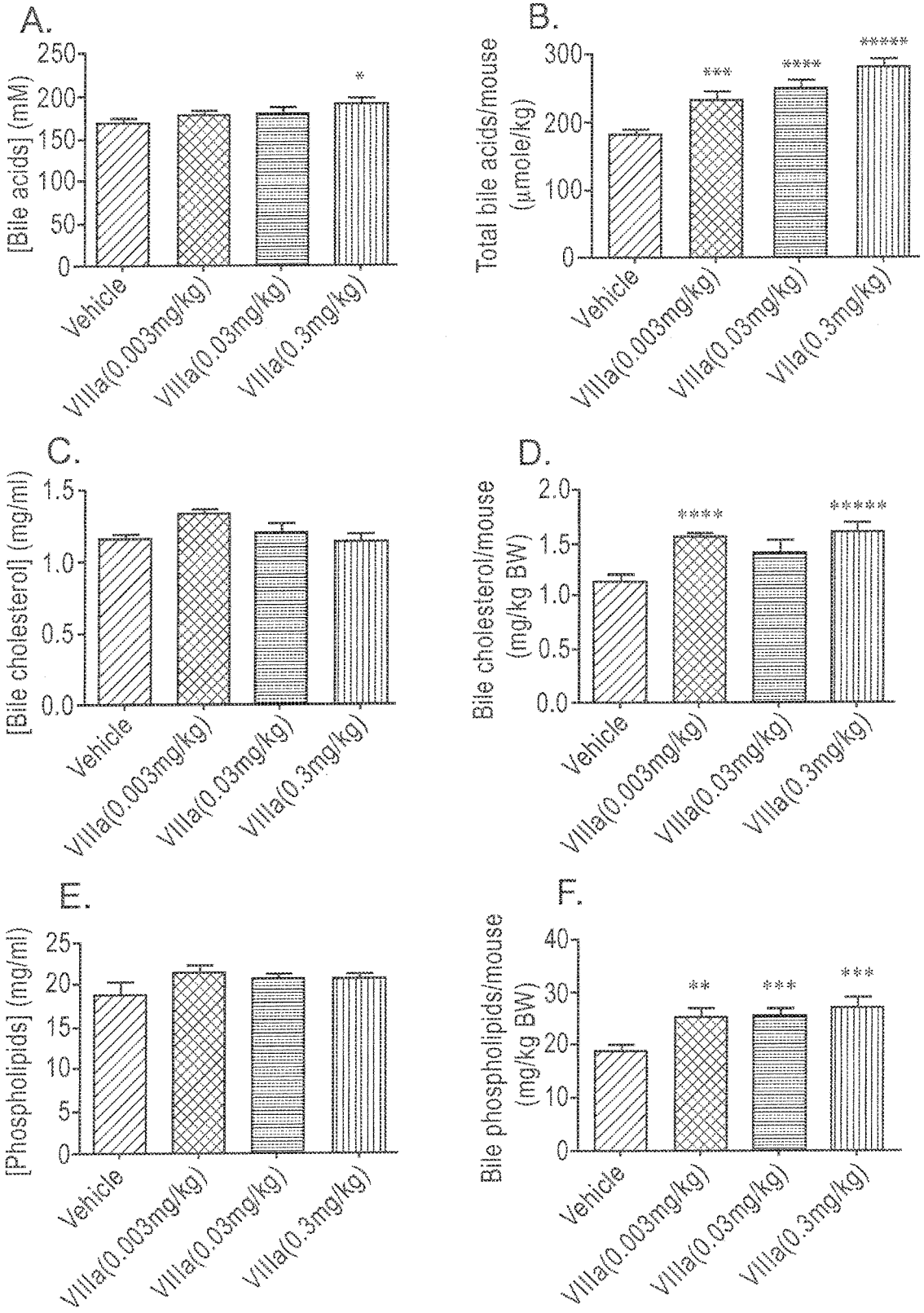

A.
[Bile acids] (mM)
250
200
150
100
50
0
*
Vehicle
VIIIa(0.003mg/kg)
VIIIa(0.03mg/kg)
VIIIa(0.3mg/kg)
B.
Total bile acids/mouse (µmole/kg)
300
200
100
0
***
****
*****
Vehicle
VIIIa(0.003mg/kg)
VIIIa(0.03mg/kg)
VIIa(0.3mg/kg)
C.
[Bile cholesterol] (mg/ml)
1.5
1.0
0.5
0.0
Vehicle
VIIIa(0.003mg/kg)
VIIIa(0.03mg/kg)
VIIIa(0.3mg/kg)
D.
Bile cholesterol/mouse (mg/kg BW)
2.0
1.5
1.0
0.5
0.0
****
*****
Vehicle
VIIIa(0.003mg/kg)
VIIIa(0.03mg/kg)
VIIIa(0.3mg/kg)
E.
[Phospholipids] (mg/ml)
25
20
15
10
5
0
Vehicle
VIIIa(0.003mg/kg)
VIIIa(0.03mg/kg)
VIIIa(0.3mg/kg)
F.
Bile phospholipids/mouse (mg/kg BW)
40
30
20
10
0
**
***
***
Vehicle
VIIIa(0.003mg/kg)
VIIIa(0.03mg/kg)
VIIIa(0.3mg/kg)

FIGURE 10

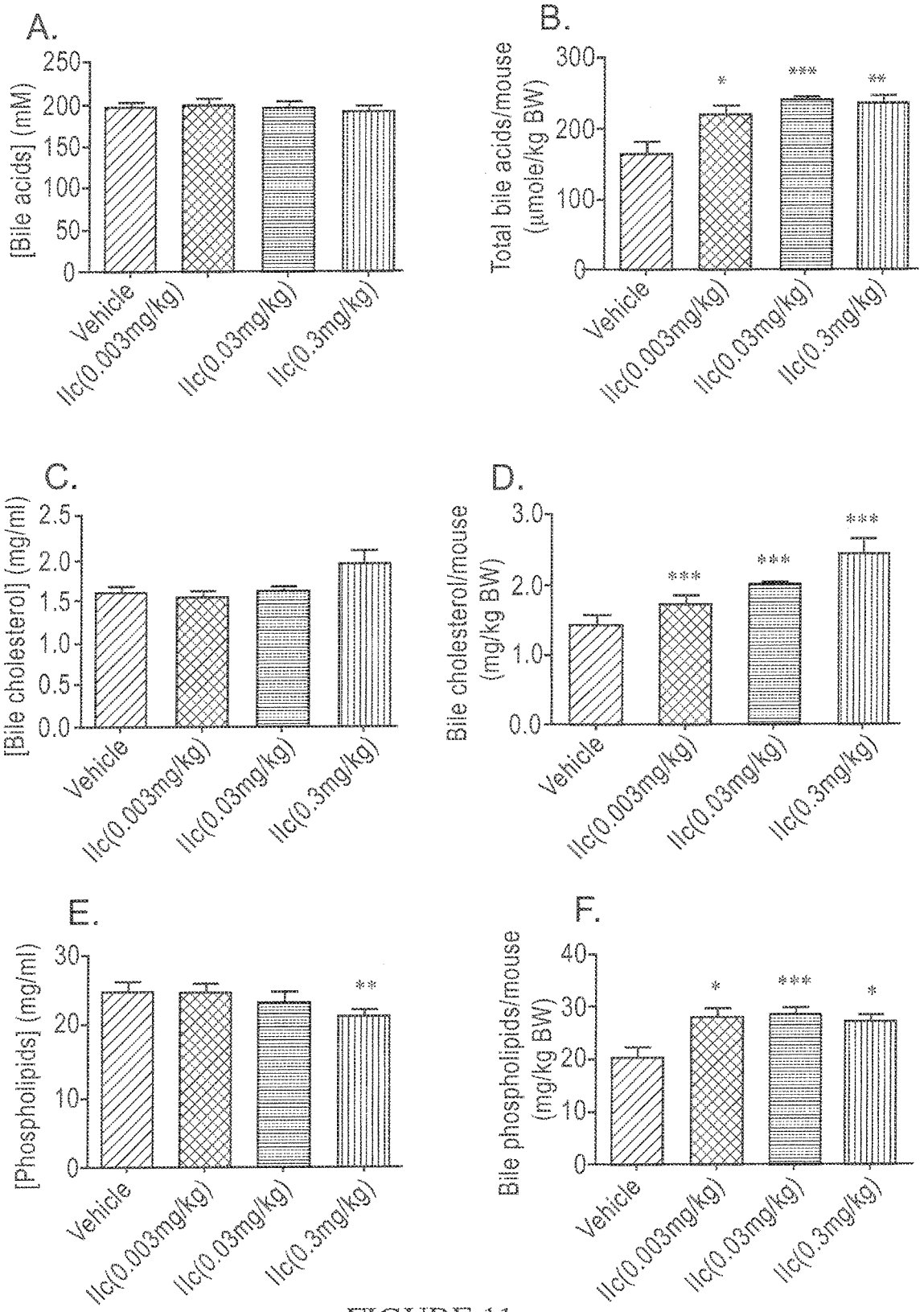

A.
[Bile acids] (mM)
250
200
150
100
50
0
Vehicle
IIc(0.003mg/kg)
IIc(0.03mg/kg)
IIc(0.3mg/kg)
B.
Total bile acids/mouse (μmole/kg BW)
300
200
100
0
*
***
**
Vehicle
IIc(0.003mg/kg)
IIc(0.03mg/kg)
IIc(0.3mg/kg)
C.
[Bile cholesterol] (mg/ml)
2.5
2.0
1.5
1.0
0.5
0.0
Vehicle
IIc(0.003mg/kg)
IIc(0.03mg/kg)
IIc(0.3mg/kg)
D.
Bile cholesterol/mouse (mg/kg BW)
3.0
2.0
1.0
0.0
***
***
***
Vehicle
IIc(0.003mg/kg)
IIc(0.03mg/kg)
IIc(0.3mg/kg)
E.
[Phospholipids] (mg/ml)
30
20
10
0
**
Vehicle
IIc(0.003mg/kg)
IIc(0.03mg/kg)
IIc(0.3mg/kg)
F.
Bile phospholipids/mouse (mg/kg BW)
40
30
20
10
0
*
***
*
Vehicle
IIc(0.003mg/kg)
IIc(0.03mg/kg)
IIc(0.3mg/kg)

FIGURE 11

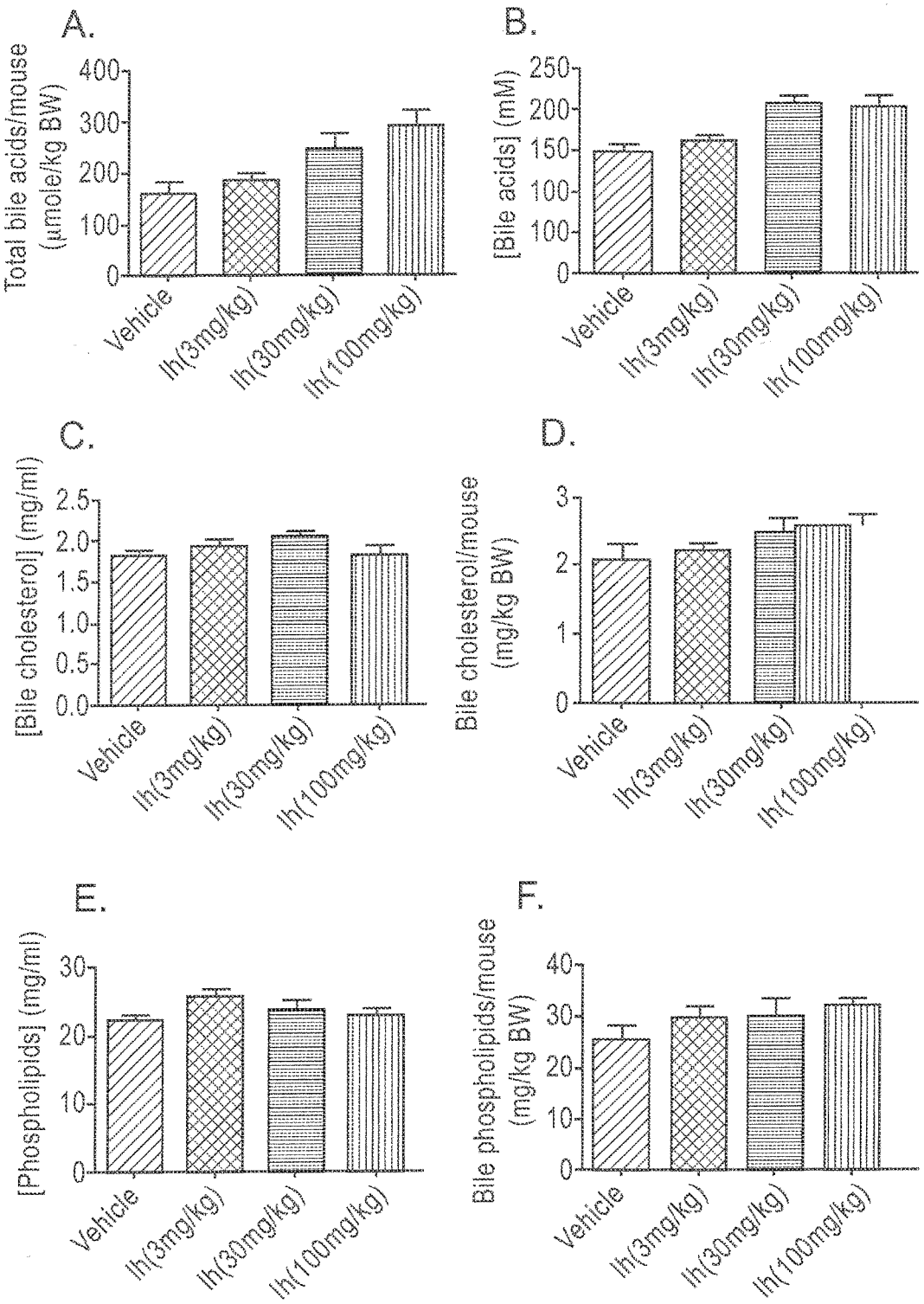

A.
Total bile acids/mouse (μmole/kg BW)
400
300
200
100
0
Vehicle
Ih(3mg/kg)
Ih(30mg/kg)
Ih(100mg/kg)
B.
[Bile acids] (mM)
250
200
150
100
0
Vehicle
Ih(3mg/kg)
Ih(30mg/kg)
Ih(100mg/kg)
C.
[Bile cholesterol] (mg/ml)
2.5
2.0
1.5
1.0
0.5
0.0
Vehicle
Ih(3mg/kg)
Ih(30mg/kg)
Ih(100mg/kg)
D.
Bile cholesterol/mouse (mg/kg BW)
3
2
1
0
Vehicle
Ih(3mg/kg)
Ih(30mg/kg)
Ih(100mg/kg)
E.
[Phospholipids] (mg/ml)
30
20
10
0
Vehicle
Ih(3mg/kg)
Ih(30mg/kg)
Ih(100mg/kg)
F.
Bile phospholipids/mouse (mg/kg BW)
40
30
20
10
0
Vehicle
Ih(3mg/kg)
Ih(30mg/kg)
Ih(100mg/kg)

FIGURE 12

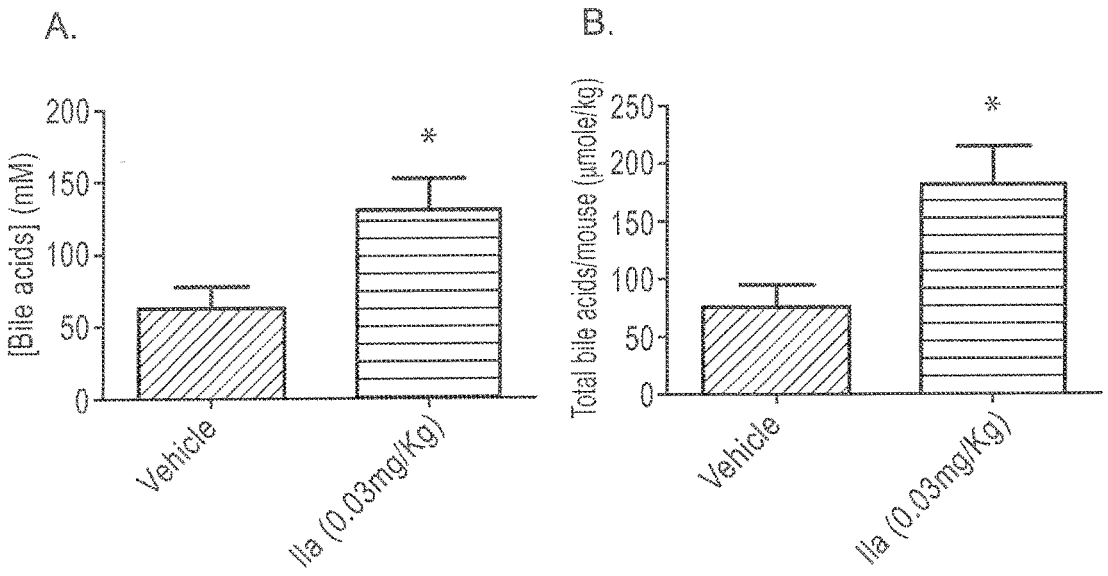

A.
[Bile acids] (mM)
200
150
100
50
0
*
Vehicle
IIa (0.03mg/Kg)
B.
Total bile acids/mouse (µmole/kg)
250
200
150
100
50
0
*
Vehicle
IIa (0.03mg/Kg)

FIGURE 13

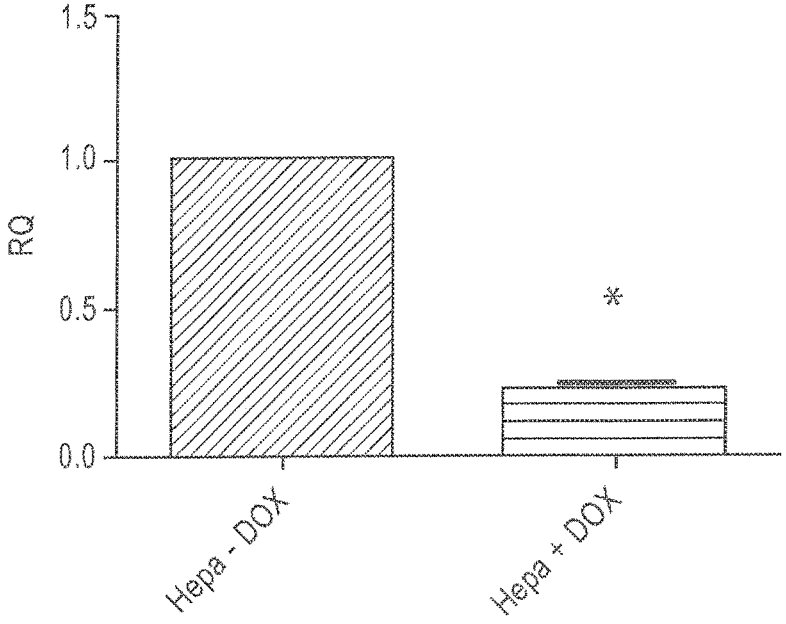


FIGURE 14

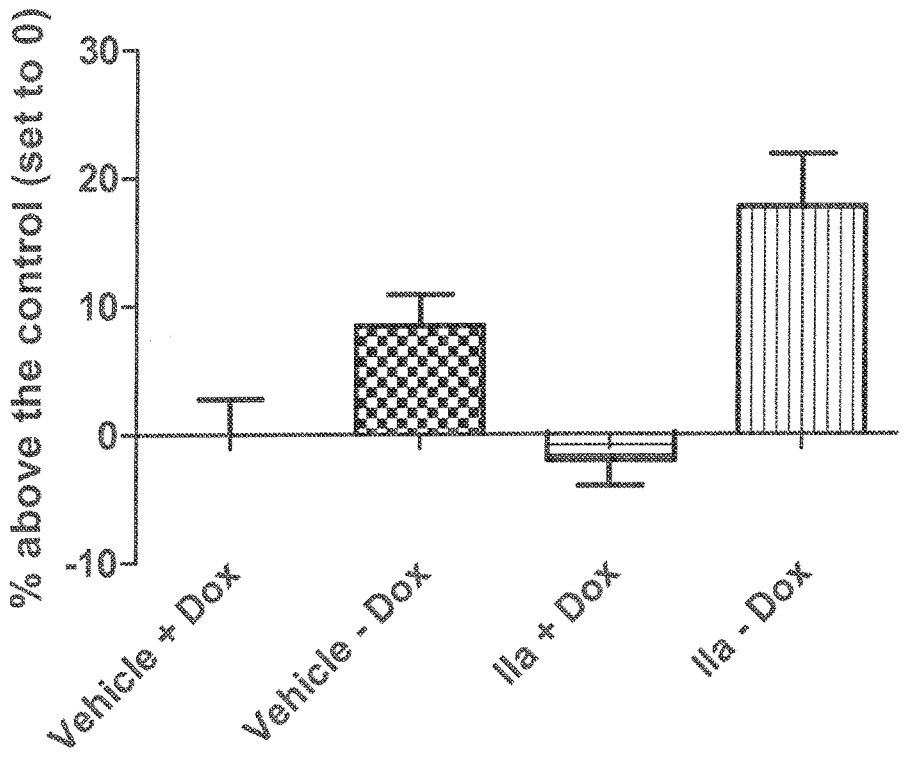

% above the control (set to 0)
30
20
10
0
-10
Vehicle + Dox
Vehicle - Dox
IIa + Dox
IIa - Dox

FIGURE 15

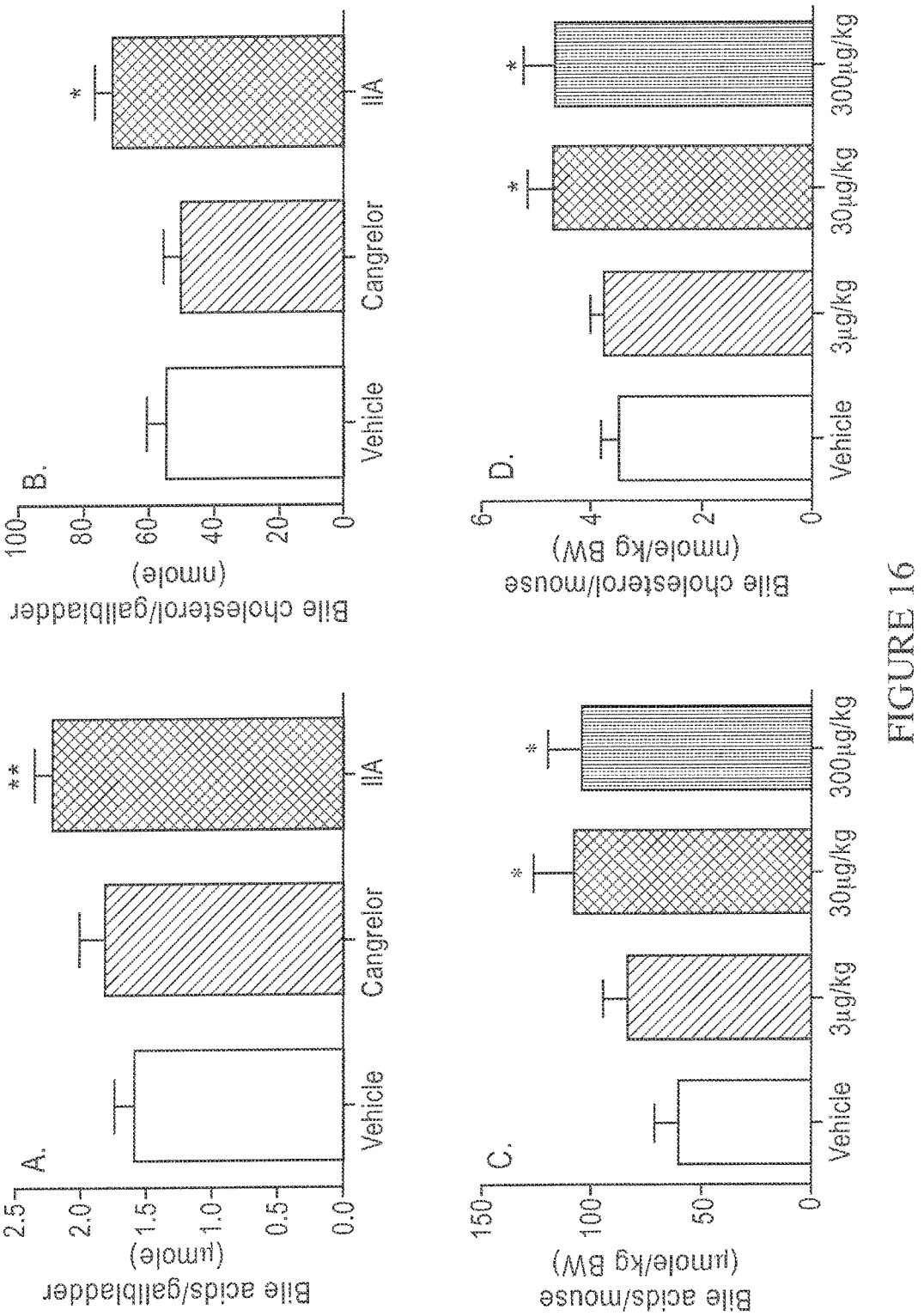

A.
Bile acids/gallbladder
(µmole)
2.5
2.0
1.5
1.0
0.5
0.0
**
Vehicle
Cangrelor
IIA
B.
Bile cholesterol/gallbladder
(nmole)
100
80
60
40
20
0
*
Vehicle
Cangrelor
IIA
C.
Bile acids/mouse
(µmole/kg BW)
150
100
50
0
*
*
Vehicle
3µg/kg
30µg/kg
300µg/kg
D.
Bile cholesterol/mouse
(nmole/kg BW)
6
4
2
0
*
*
Vehicle
3µg/kg
30µg/kg
300µg/kg

FIGURE 16

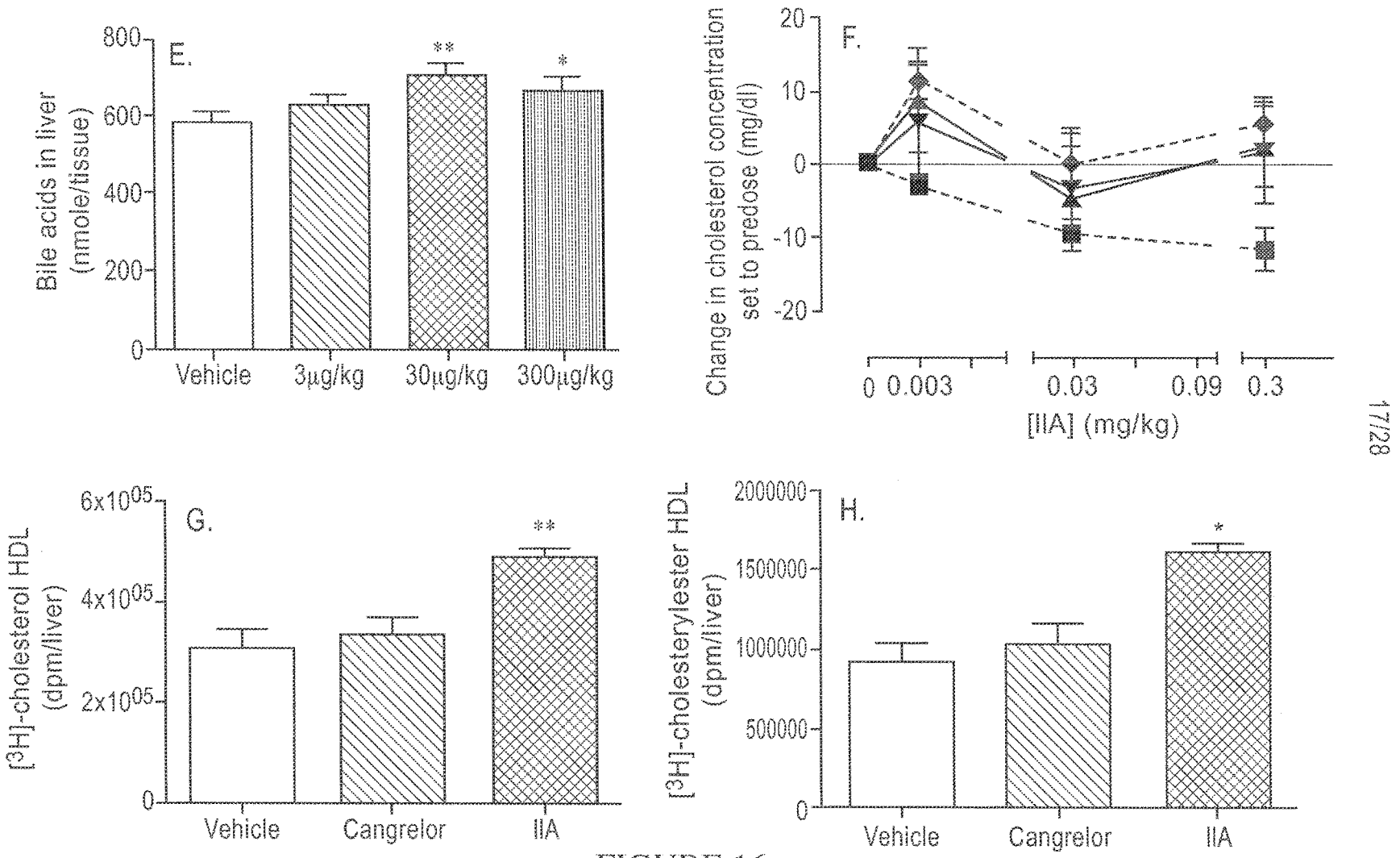

E.
Bile acids in liver (nmole/tissue)
800
600
400
200
0
**
*
Vehicle
3µg/kg
30µg/kg
300µg/kg
F.
Change in cholesterol concentration set to predose (mg/dl)
20
10
0
-10
-20
0 0.003
0.03
0.09
0.3
[IIA] (mg/kg)
G.
[3H]-cholesterol HDL (dpm/liver)
6x10^05
4x10^05
2x10^05
0
**
Vehicle
Cangrelor
IIA
H.
[3H]-cholesterylester HDL (dpm/liver)
2000000
1500000
1000000
500000
0
*
Vehicle
Cangrelor
IIA

FIGURE 16

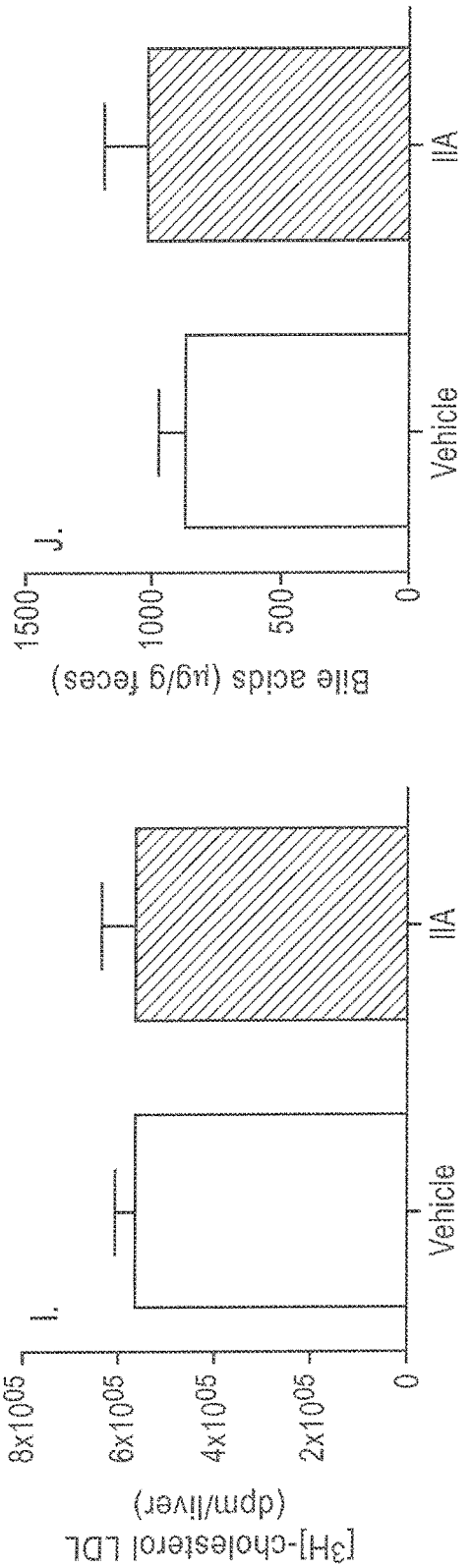

I.
[3H]-cholesterol LDL
(dpm/liver)
8x10^05
6x10^05
4x10^05
2x10^05
0
Vehicle
IIA
J.
Bile acids (µg/g feces)
1500
1000
500
0
Vehicle
IIA

FIGURE 16

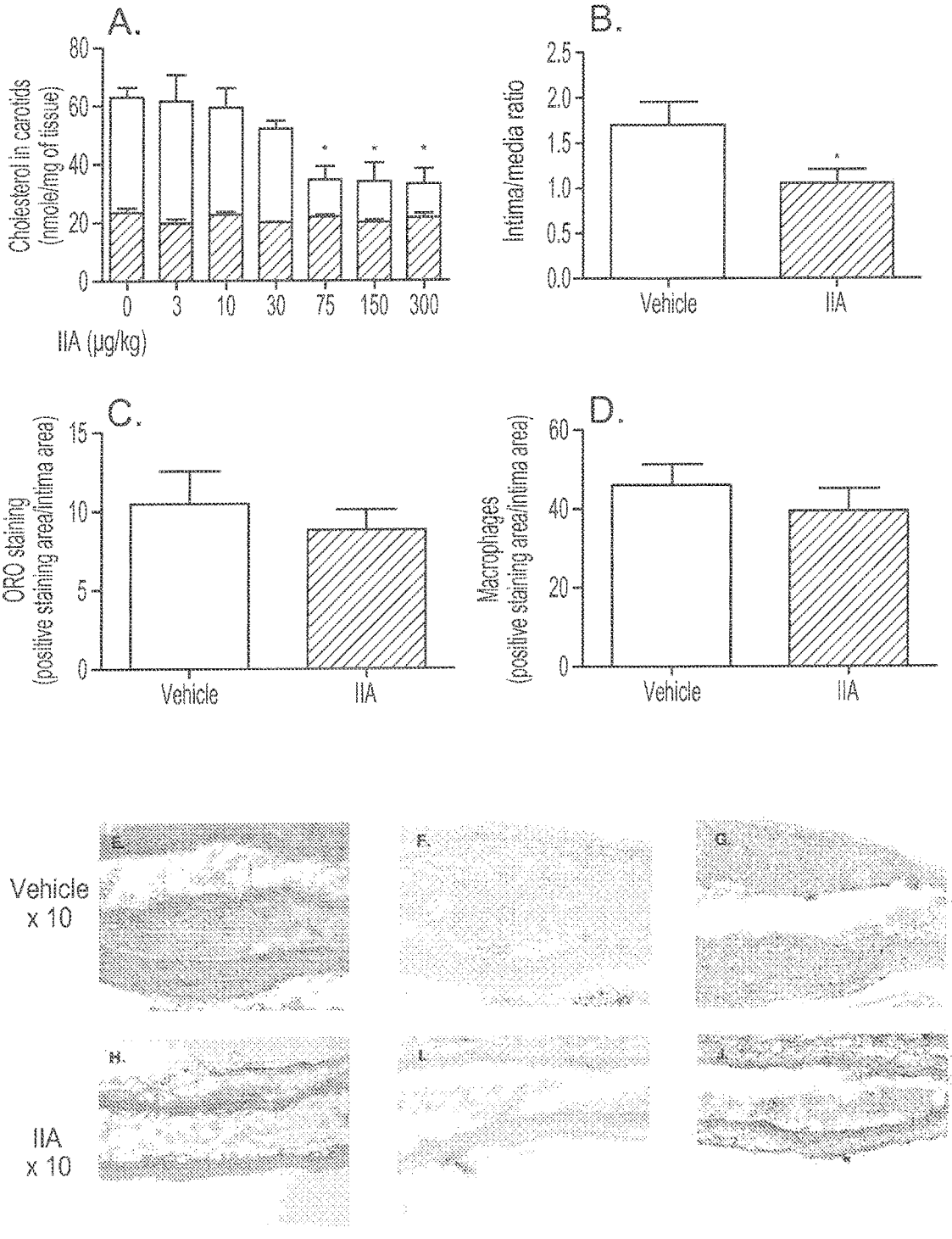

A.
Cholesterol in carotids (nmole/mg of tissue)
80
60
40
20
0
0
3
10
30
75
150
300
IIA (µg/kg)
B.
Intima/media ratio
2.5
2.0
1.5
1.0
0.5
0.0
Vehicle
IIA
C.
ORO staining (positive staining area/intima area)
15
10
5
0
Vehicle
IIA
D.
Macrophages (positive staining area/intima area)
60
40
20
0
Vehicle
IIA
Vehicle x 10
IIA x 10

FIGURE 17

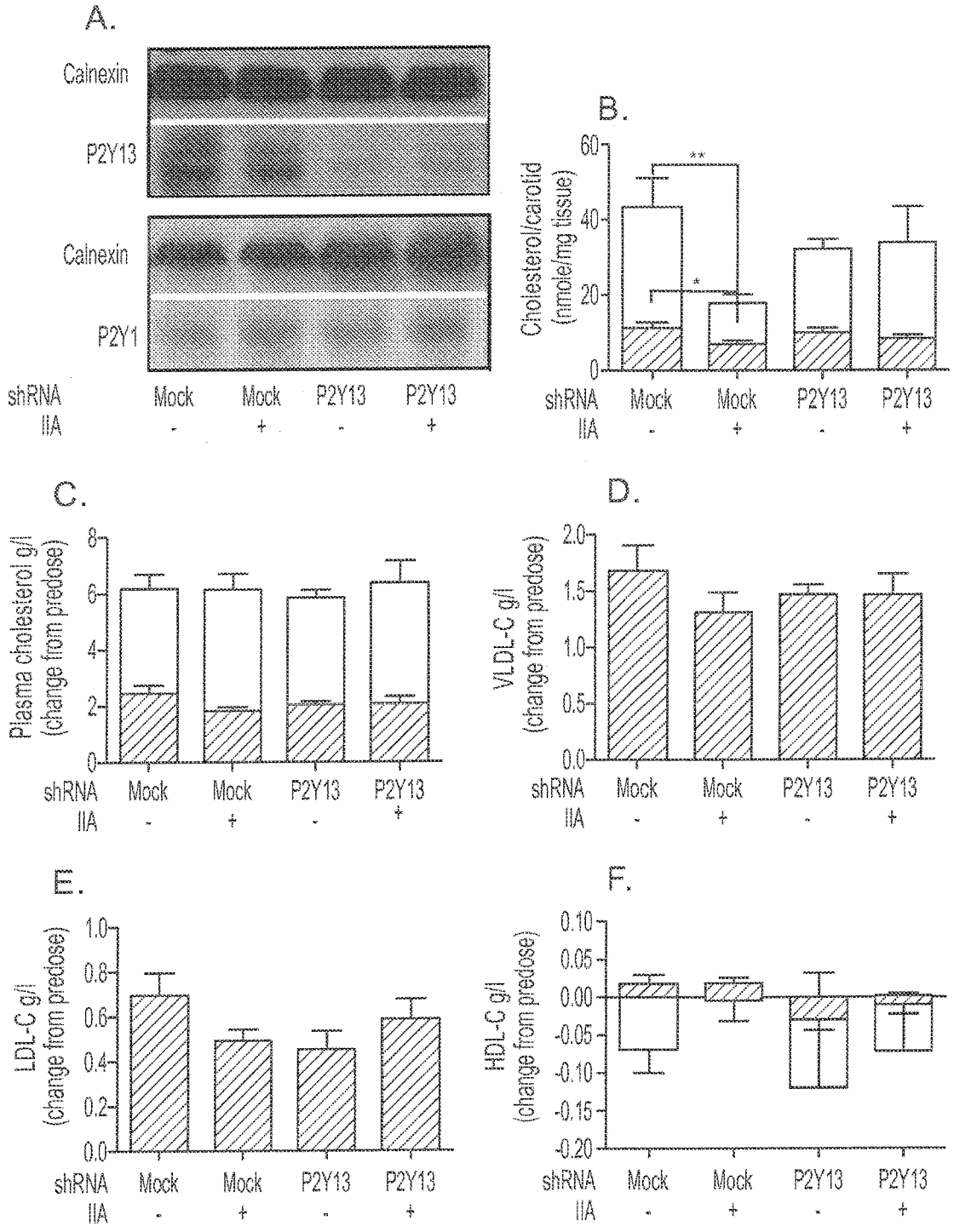

A.
Calnexin
P2Y13
Calnexin
P2Y1
shRNA Mock Mock P2Y13 P2Y13
IIA - + - +
B.
Cholesterol/carotid (nmole/mg tissue)
60
40
20
0
**
*
shRNA Mock Mock P2Y13 P2Y13
IIA - + - +
C.
Plasma cholesterol g/l (change from predose)
8
6
4
2
0
shRNA Mock Mock P2Y13 P2Y13
IIA - + - +
D.
VLDL-C g/l (change from predose)
2.0
1.5
1.0
0.5
0.0
shRNA Mock Mock P2Y13 P2Y13
IIA - + - +
E.
LDL-C g/l (change from predose)
1.0
0.8
0.6
0.4
0.2
0.0
shRNA Mock Mock P2Y13 P2Y13
IIA - + - +
F.
HDL-C g/l (change from predose)
0.10
0.05
0.00
-0.05
-0.10
-0.15
-0.20
shRNA Mock Mock P2Y13 P2Y13
IIA - + - +

FIGURE 18

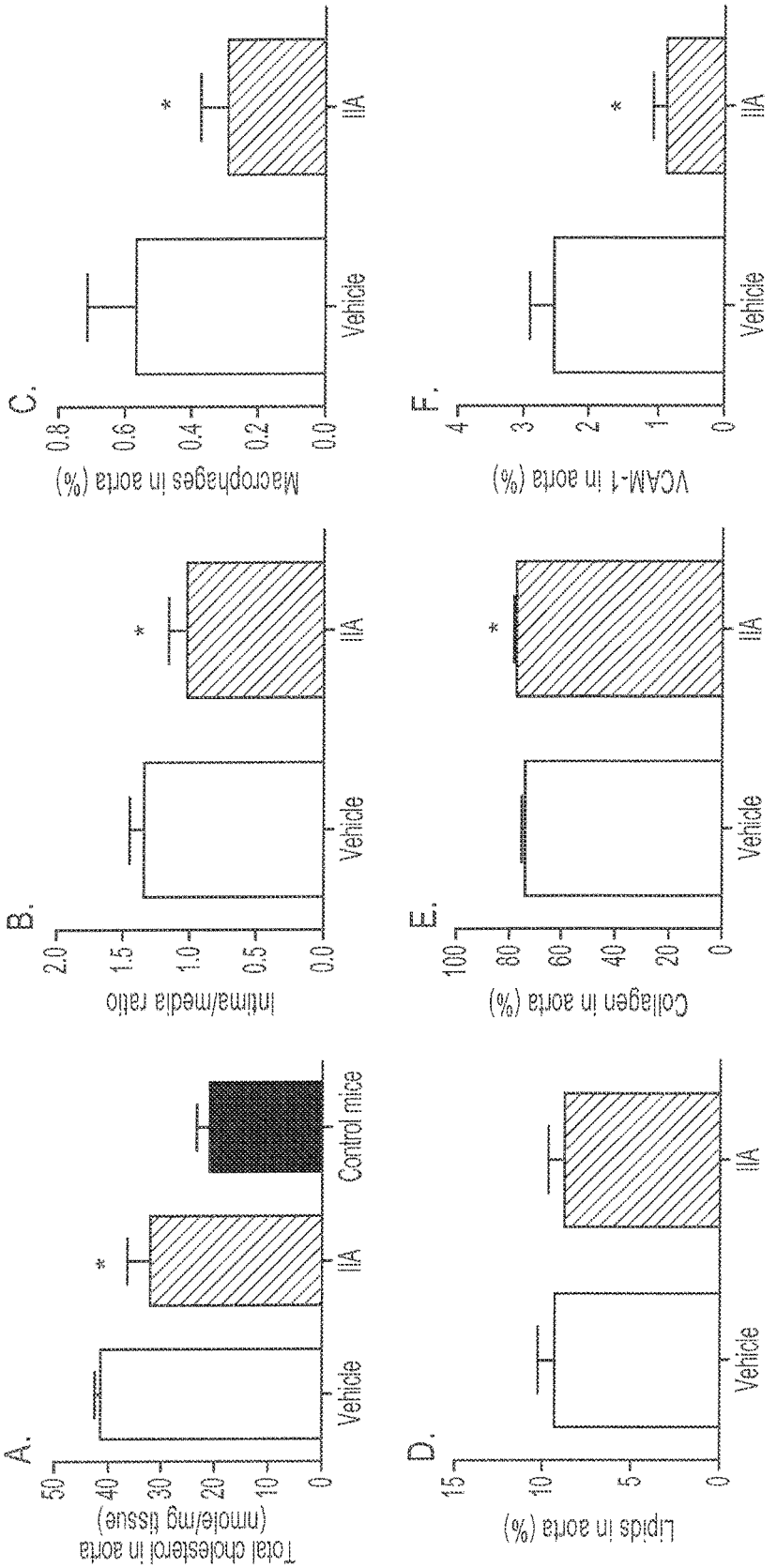

A.
Total cholesterol in aorta (nmole/mg tissue)
50
40
30
20
10
0
*
Vehicle
IIA
Control mice
B.
Intima/media ratio
2.0
1.5
1.0
0.5
0.0
*
Vehicle
IIA
C.
Macrophages in aorta (%)
0.8
0.6
0.4
0.2
0.0
*
Vehicle
IIA
D.
Lipids in aorta (%)
15
10
5
0
Vehicle
IIA
E.
Collagen in aorta (%)
100
80
60
40
20
0
*
Vehicle
IIA
F.
VCAM-1 in aorta (%)
4
3
2
1
0
*
Vehicle
IIA

FIGURE 19

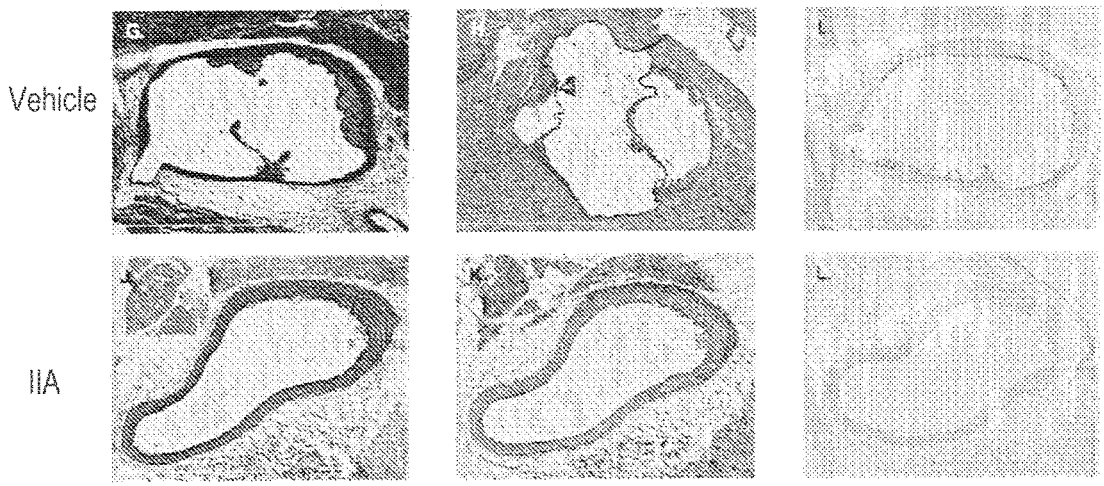


FIGURE 19

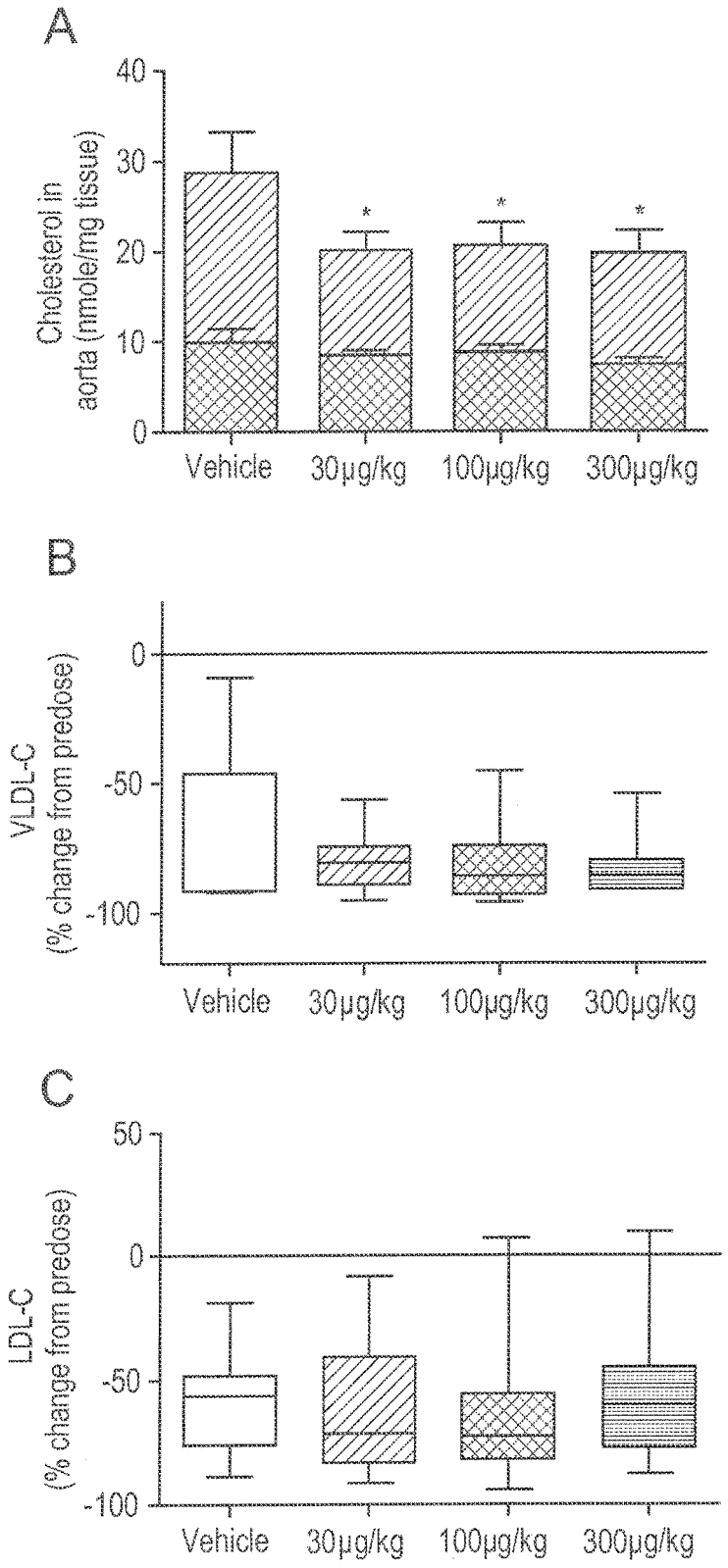

A
Cholesterol in aorta (nmole/mg tissue)
40
30
20
10
0
*
*
*
Vehicle
30μg/kg
100μg/kg
300μg/kg
B
VLDL-C (% change from predose)
0
-50
-100
Vehicle
30μg/kg
100μg/kg
300μg/kg
C
LDL-C (% change from predose)
50
0
-50
-100
Vehicle
30μg/kg
100μg/kg
300μg/kg

FIG.20

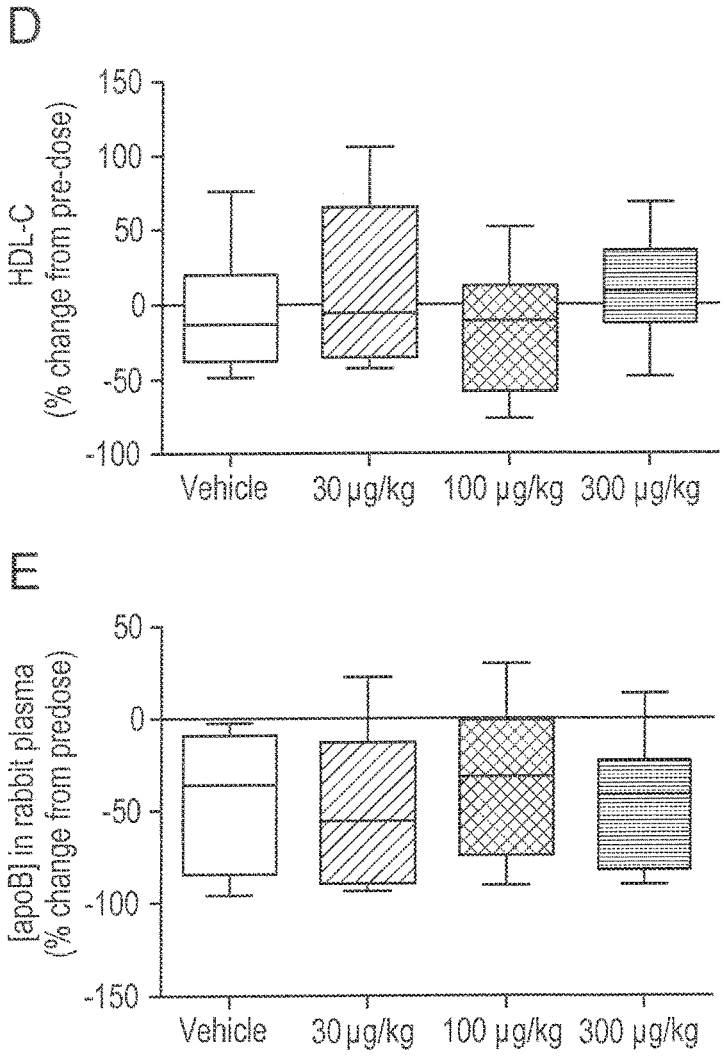

D
HDL-C
(% change from pre-dose)
150
100
50
0
-50
-100
Vehicle
30 µg/kg
100 µg/kg
300 µg/kg
m
[apoB] in rabbit plasma
(% change from predose)
50
0
-50
-100
-150
Vehicle
30 µg/kg
100 µg/kg
300 µg/kg

FIG.20

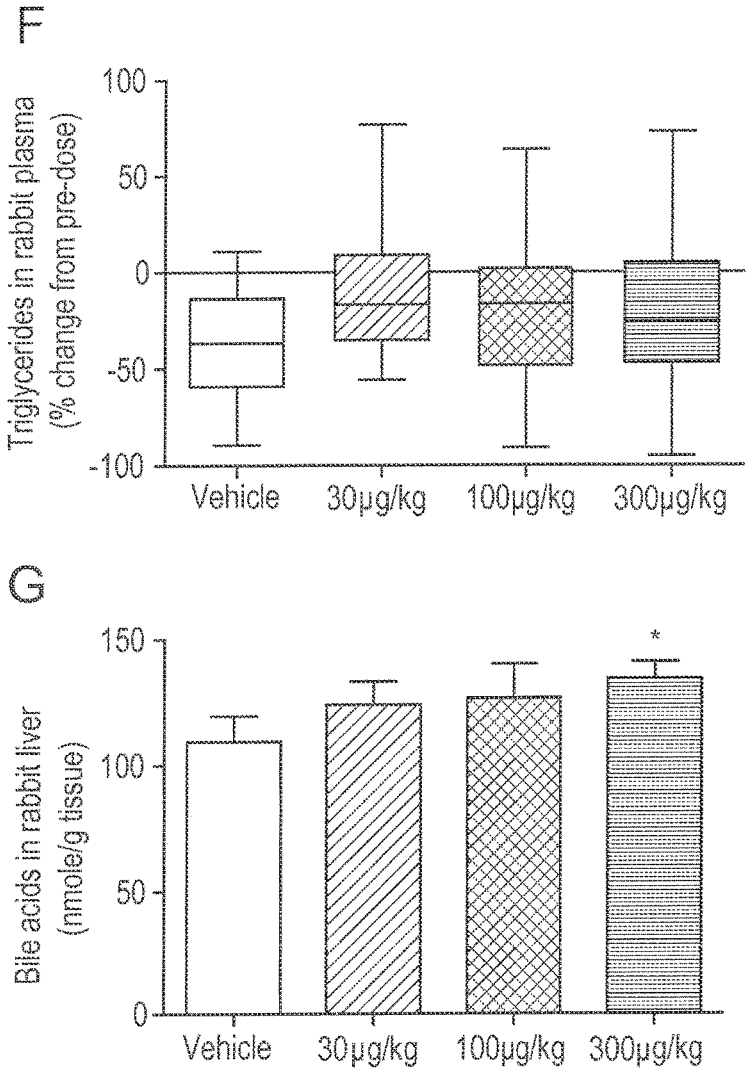

H
Triglycerides in rabbit plasma
(% change from pre-dose)
100
50
0
-50
-100
Vehicle
30µg/kg
100µg/kg
300µg/kg
G
Bile acids in rabbit liver
(nmole/g tissue)
150
100
50
0
*
Vehicle
30µg/kg
100µg/kg
300µg/kg

FIG.20

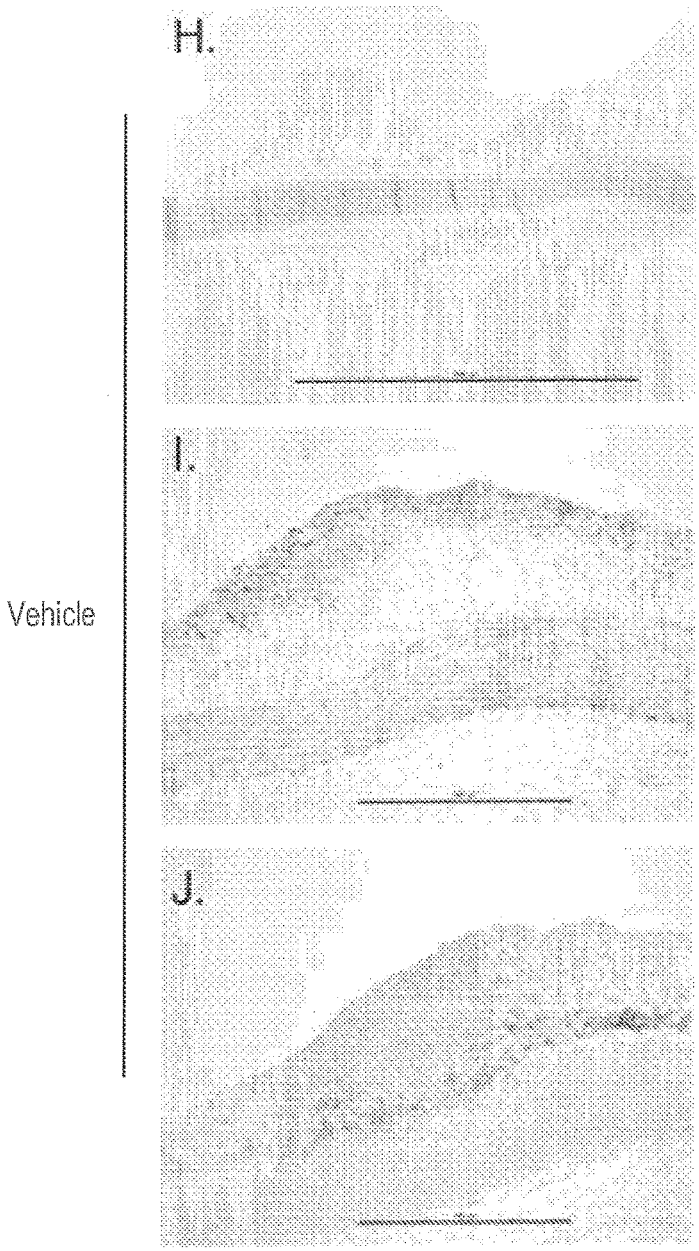


FIG.20

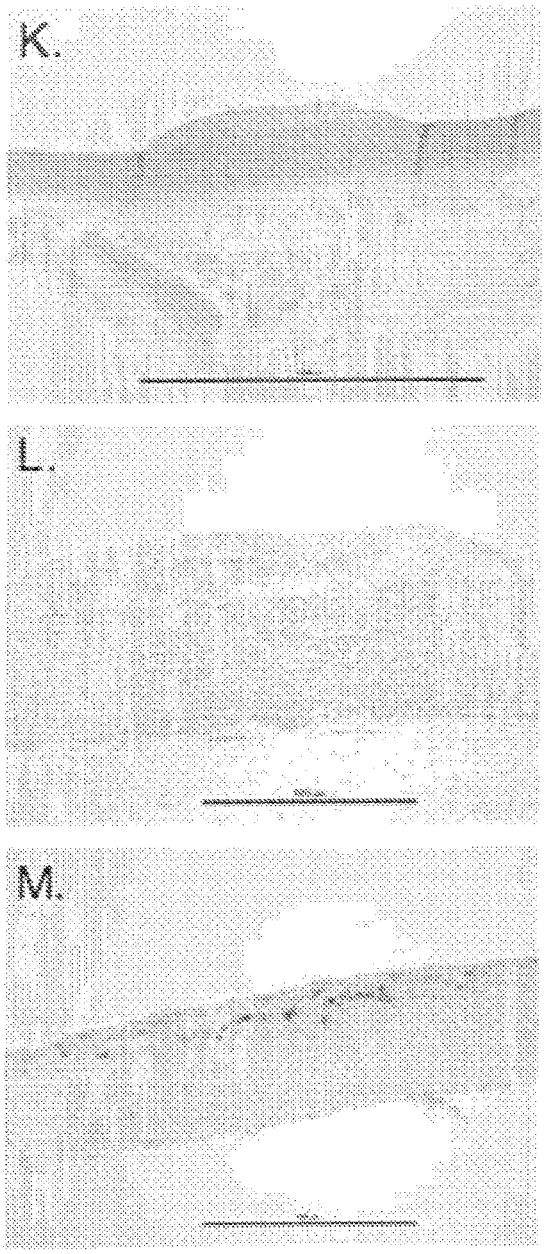


FIG.20

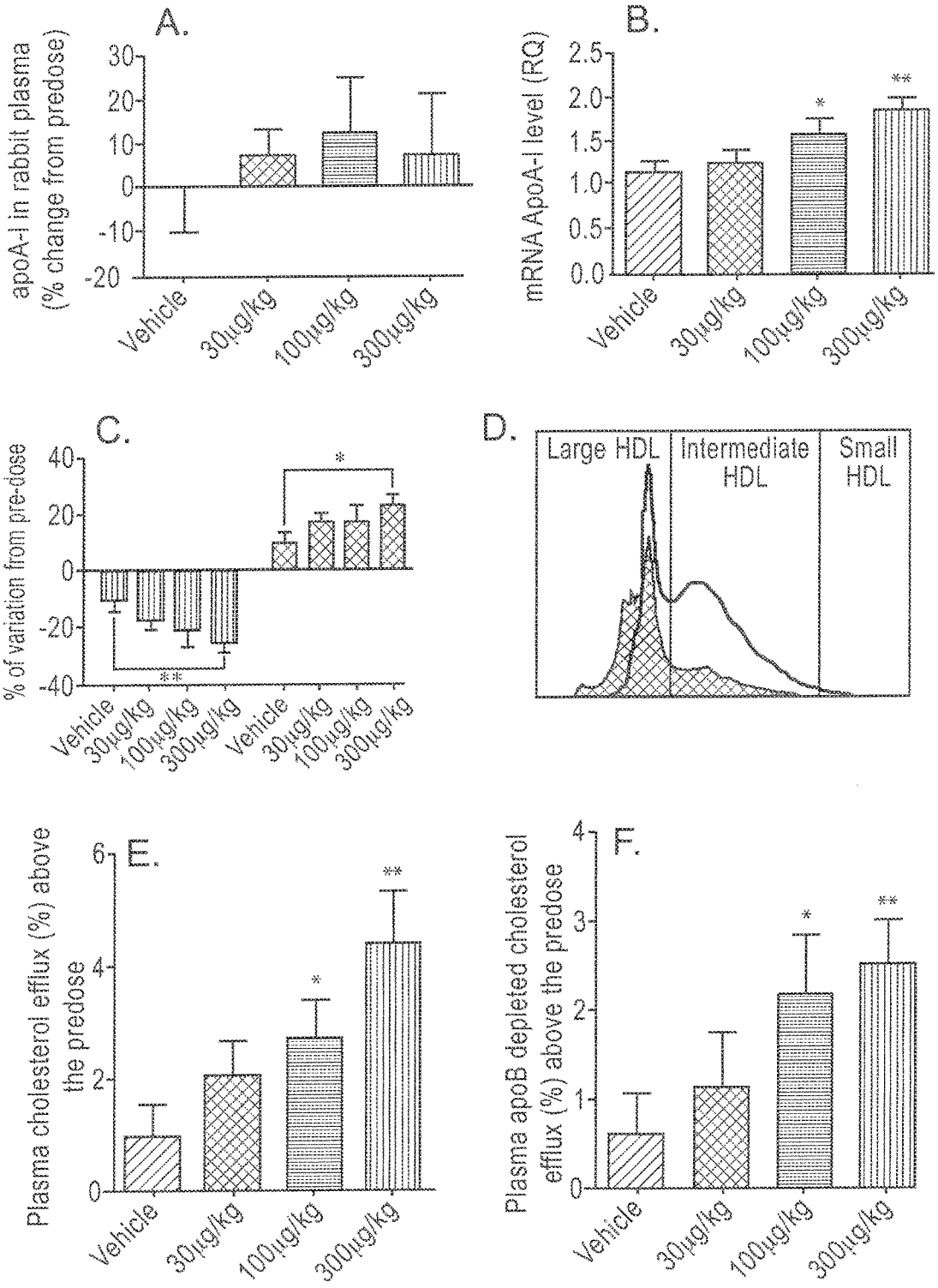

A.
apoA-I in rabbit plasma (% change from predose)
30
20
10
0
-10
-20
Vehicle
30µg/kg
100µg/kg
300µg/kg
B.
mRNA ApoA-I level (RQ)
2.5
2.0
1.5
1.0
0.5
0.0
*
**
Vehicle
30µg/kg
100µg/kg
300µg/kg
C.
% of variation from pre-dose
40
20
0
-20
-40
*
**
Vehicle
30µg/kg
100µg/kg
300µg/kg
Vehicle
30µg/kg
100µg/kg
300µg/kg
D.
Large HDL
Intermediate HDL
Small HDL
E.
Plasma cholesterol efflux (%) above the predose
6
4
2
0
*
**
Vehicle
30µg/kg
100µg/kg
300µg/kg
F.
Plasma apoB depleted cholesterol efflux (%) above the predose
4
3
2
1
0
*
**
Vehicle
30µg/kg
100µg/kg
300µg/kg

FIGURE 21