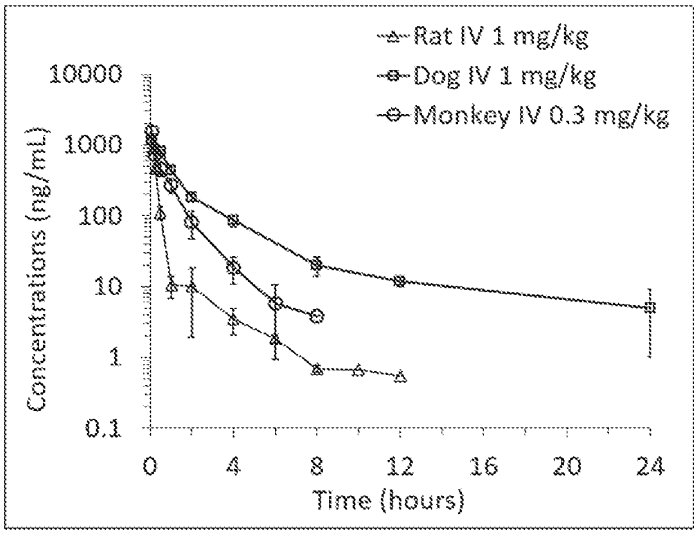

Rat IV 1 mg/kg
Dog IV 1 mg/kg
Monkey IV 0.3 mg/kg
Concentrations (ng/mL)
10000
1000
100
10
1
0.1
0
4
8
12
16
20
24
Time (hours)

FIG. 1A

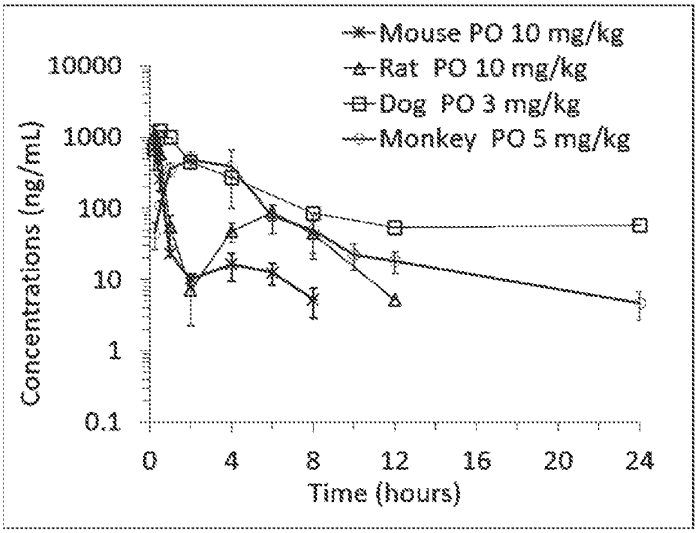

Mouse PO 10 mg/kg
Rat PO 10 mg/kg
Dog PO 3 mg/kg
Monkey PO 5 mg/kg
Concentrations (ng/mL)
10000
1000
100
10
1
0.1
0
4
8
12
16
20
24
Time (hours)

FIG. 1B

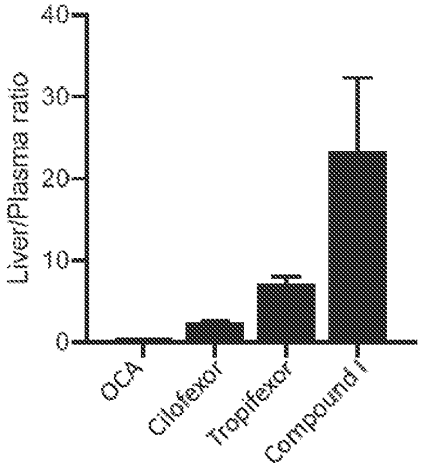

Liver/Plasma ratio
40
30
20
10
0
OCA
Cilofexor
Tropifexor
Compound I

FIG. 2A

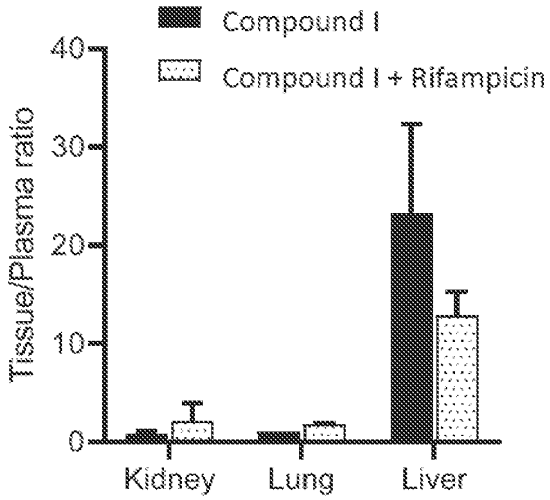

Compound I
Compound I + Rifampicin
Tissue/Plasma ratio
40
30
20
10
0
Kidney
Lung
Liver

FIG. 2B

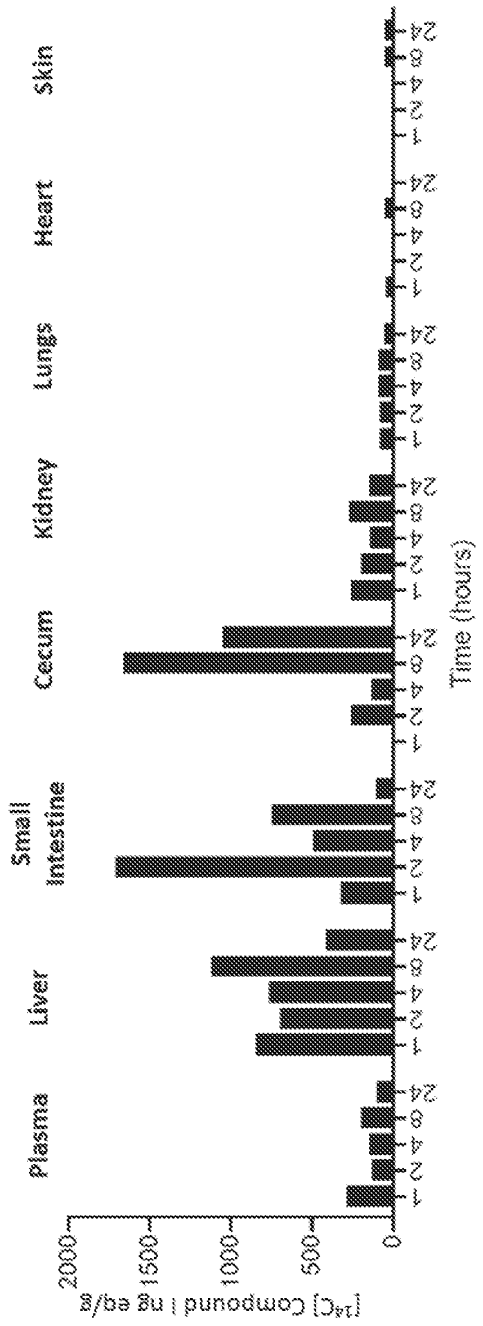

Plasma
Liver
Small Intestine
Cecum
Kidney
Lungs
Heart
Skin
[14C] Compound i ng eq/g
2000
1500
1000
500
0
Time (hours)
1
2
4
8
24

FIG. 3

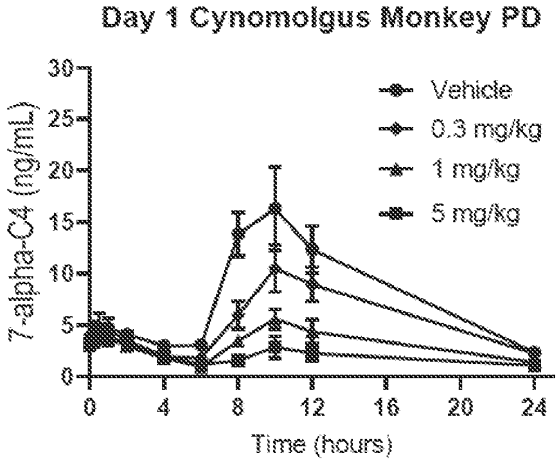


FIG. 4

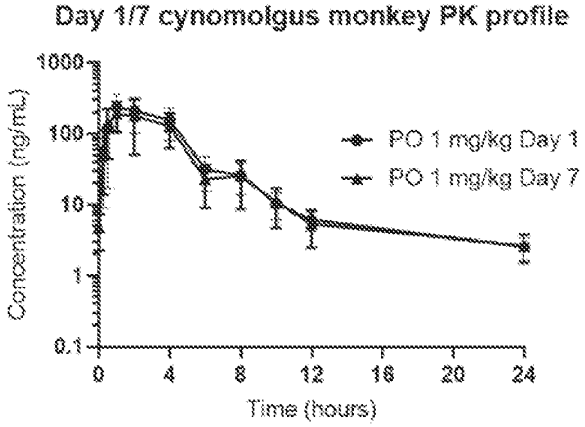


FIG. 5A

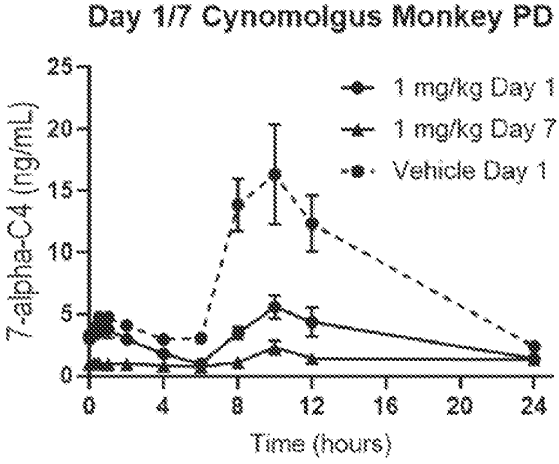


FIG. 5B

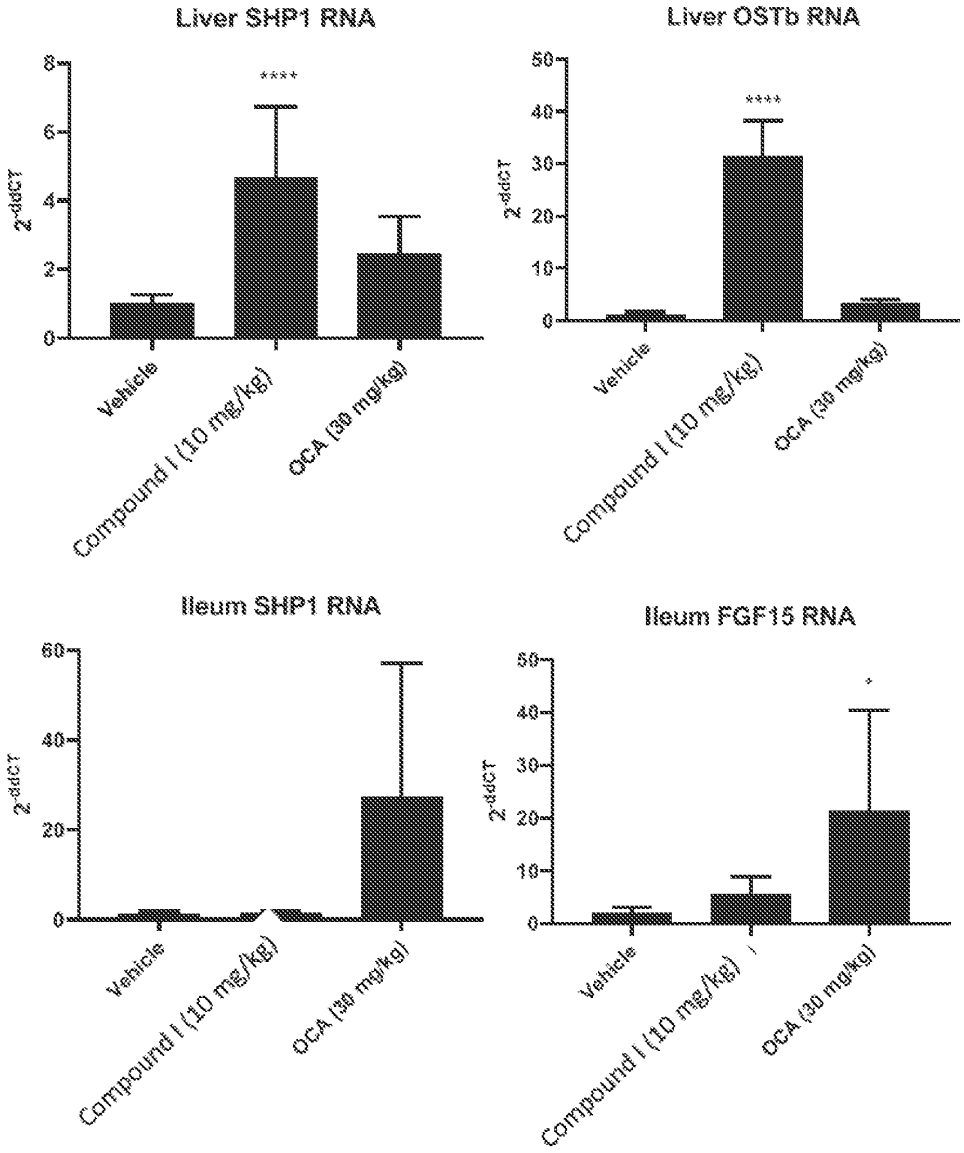

Liver SHP1 RNA
2-ddCT
****
Vehicle
Compound I (10 mg/kg)
OCA (30 mg/kg)
Liver OSTb RNA
2-ddCT
****
Vehicle
Compound I (10 mg/kg)
OCA (30 mg/kg)
Ileum SHP1 RNA
2-ddCT
Vehicle
Compound I (10 mg/kg)
OCA (30 mg/kg)
Ileum FGF15 RNA
2-ddCT
*
Vehicle
Compound I (10 mg/kg)
OCA (30 mg/kg)

FIG. 6

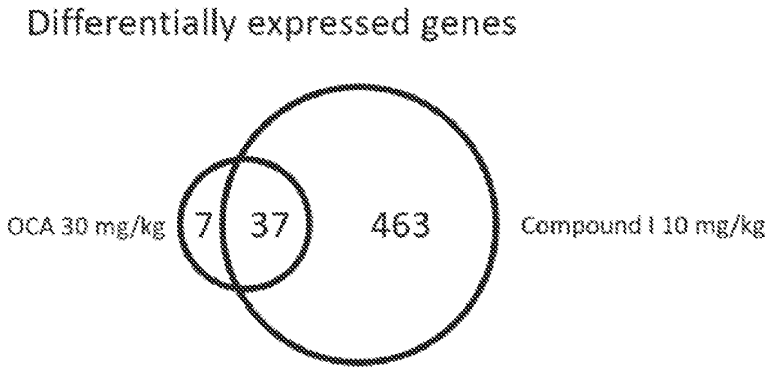

Differentially expressed genes
OCA 30 mg/kg
7
37
463
Compound I 10 mg/kg

FIG. 7A

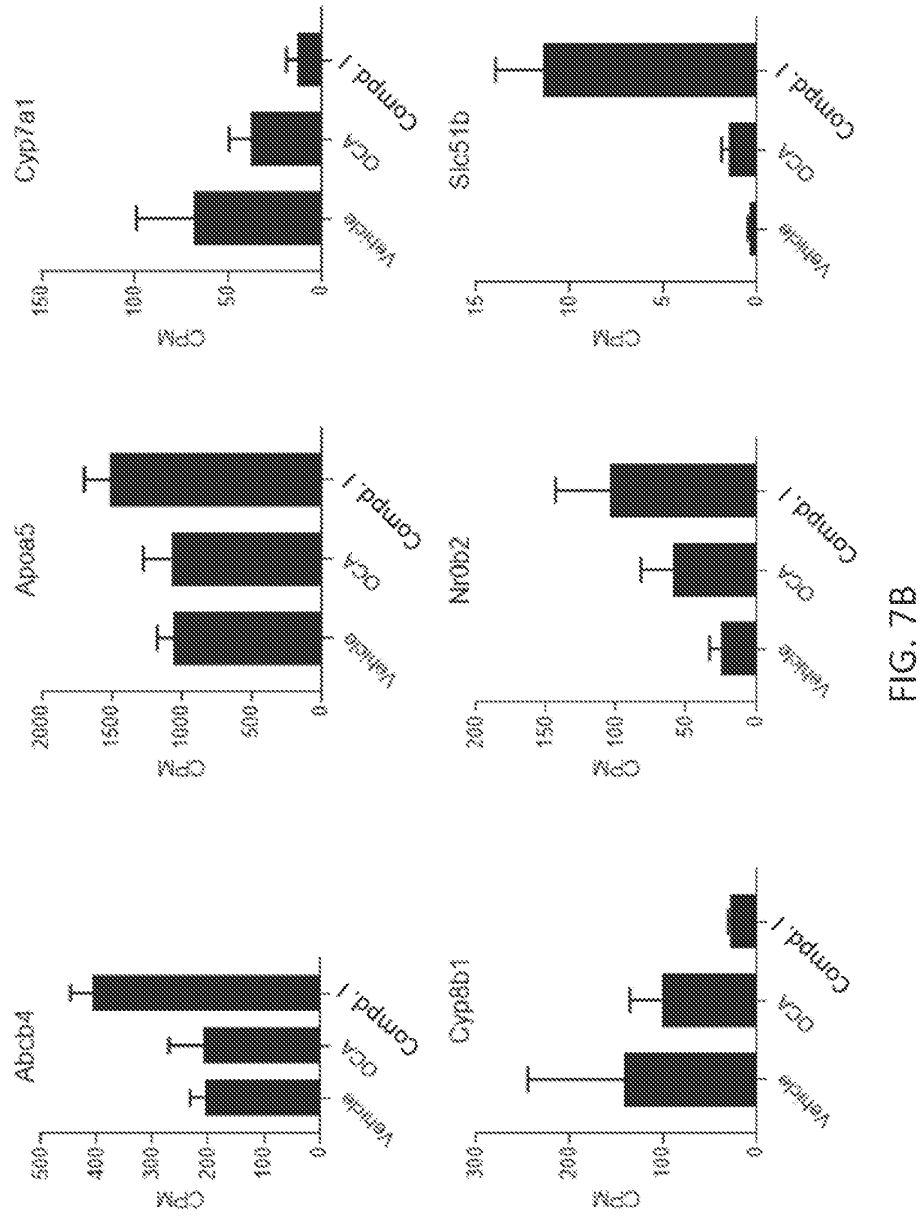

Cyp7a1
Sic51b
Apoa5
Nr0b2
Abcb4
Cyp8b1
CPM
Vehicle
OCA
Compd. I

FIG. 7B

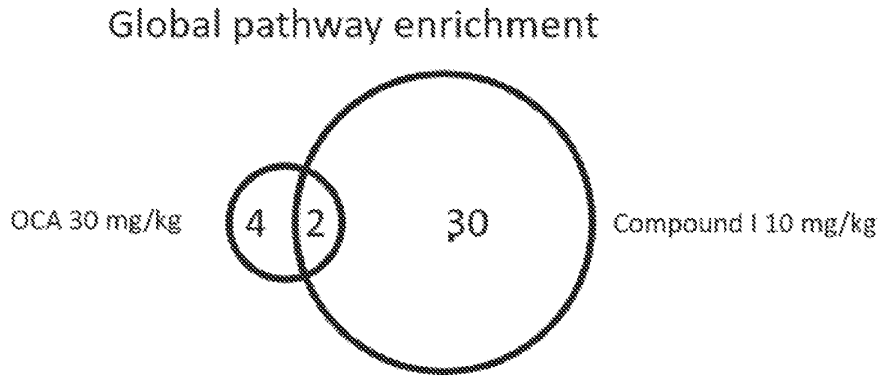

Global pathway enrichment
OCA 30 mg/kg
4
2
30
Compound I 10 mg/kg

FIG. 7C

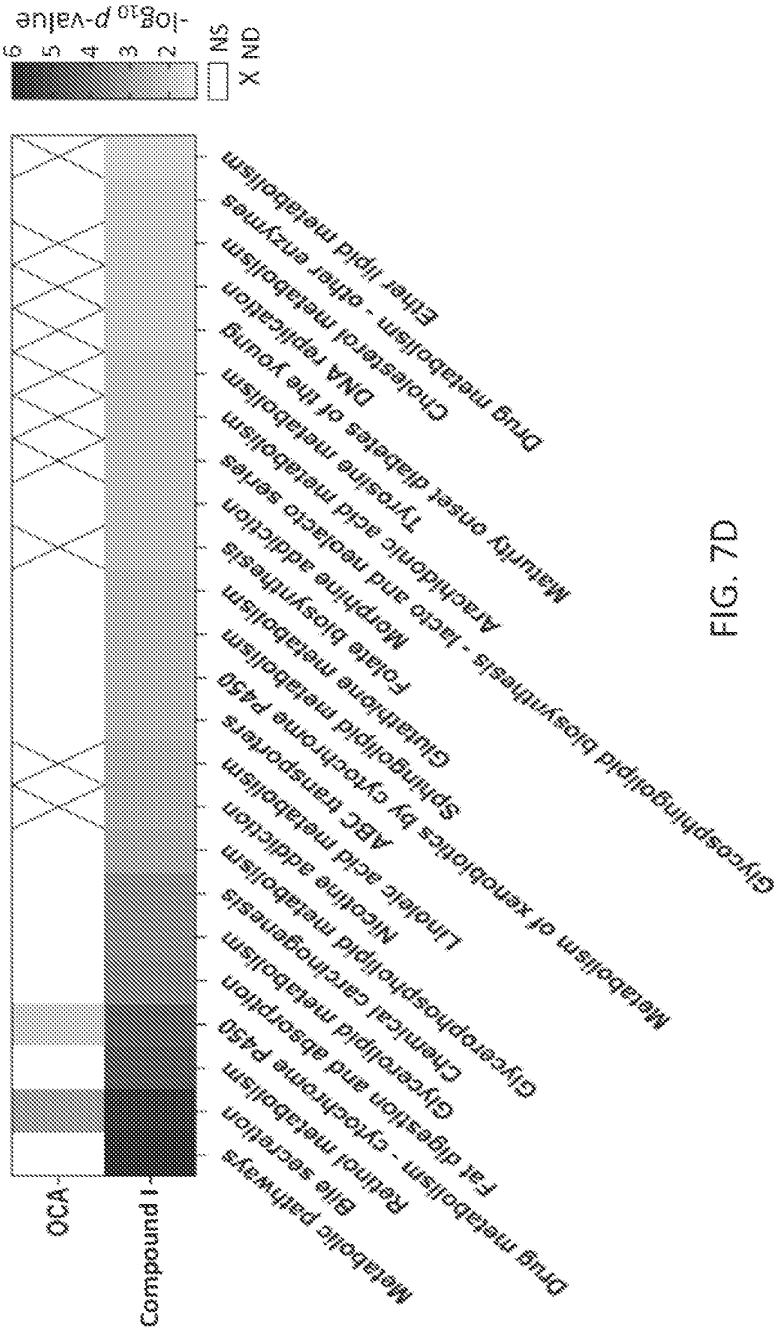

-log10 p-value
6
5
4
3
2
NS
ND
OCA
Compound I
Metabolic pathways
Bile secretion
Retinol metabolism
Fat digestion and absorption - cytochrome P450
Glycerolipid metabolism
Chemical carcinogenesis
Glycerophospholipid metabolism
Nicotine addiction
Linoleic acid metabolism
ABC transporters
Metabolism of xenobiotics by cytochrome P450
Sphingolipid metabolism
Glutathione metabolism
Folate biosynthesis
Morphine addiction
Arachidonic acid metabolism - lacto and neolacto series
Tyrosine metabolism
Maturity onset diabetes of the young
DNA replication
Cholesterol metabolism - other enzymes
Drug metabolism - other enzymes
Ether lipid metabolism
Glycosphingolipid biosynthesis - lacto and neolacto series

FIG. 7D

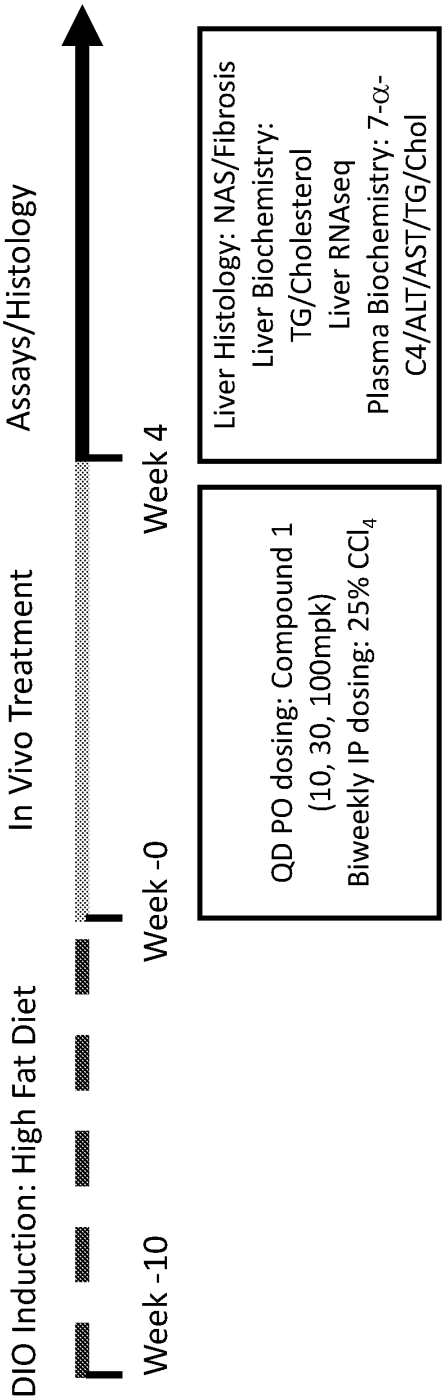

DIO Induction: High Fat Diet
In Vivo Treatment
Assays/Histology
Week -10
Week -0
Week 4
QD PO dosing: Compound 1
(10, 30, 100mpk)
Biweekly IP dosing: 25% CCl_4
Liver Histology: NAS/Fibrosis
Liver Biochemistry:
TG/Cholesterol
Liver RNAseq
Plasma Biochemistry: 7-α-
C4/ALT/AST/TG/Chol

FIG. 8

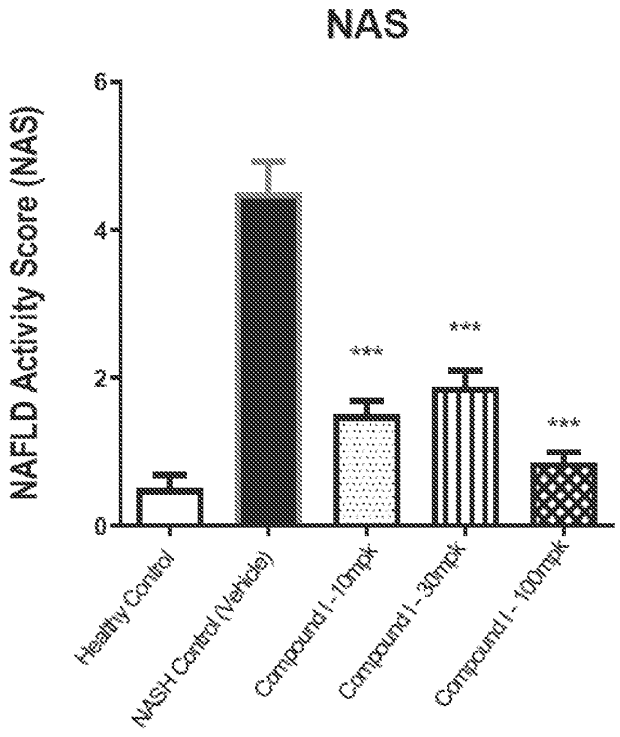

NAS
NAFLD Activity Score (NAS)
0
2
4
6
***
***
***
Healthy Control
NASH Control (Vehicle)
Compound I - 10mpk
Compound I - 30mpk
Compound I - 100mpk

FIG. 9

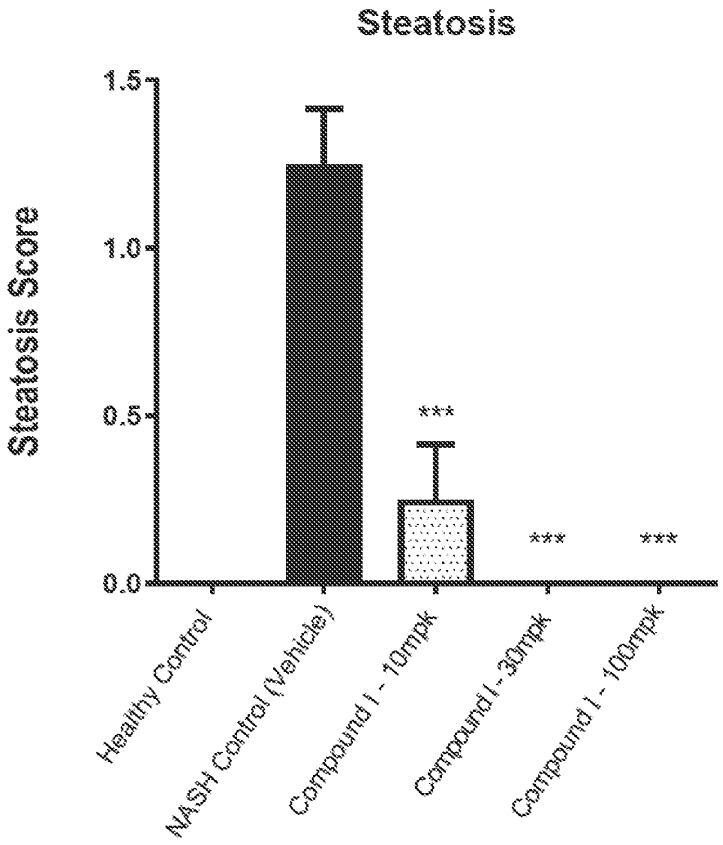

Steatosis
Steatosis Score
1.5
1.0
0.5
0.0
***
***
***
Healthy Control
NASH Control (Vehicle)
Compound I - 10mpk
Compound I - 30mpk
Compound I - 100mpk

FIG. 10A

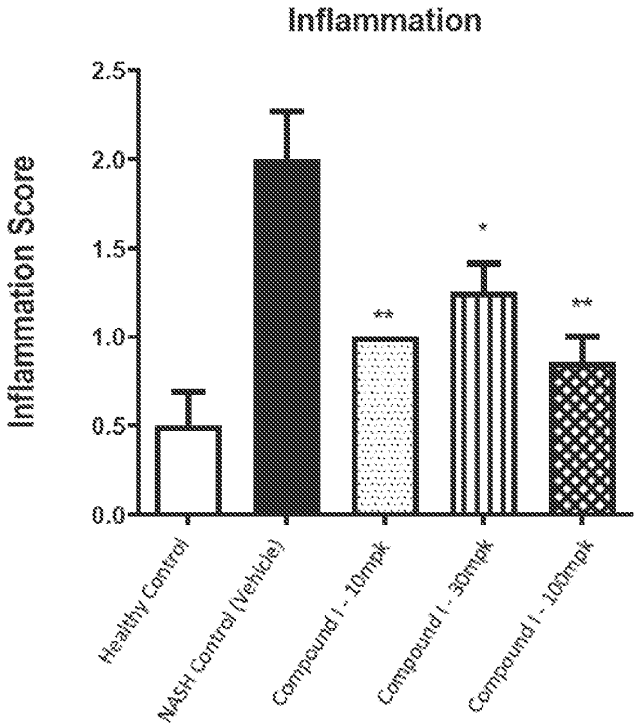

Inflammation
Inflammation Score
2.5
2.0
1.5
1.0
0.5
0.0
**
*
**
Healthy Control
NASH control (Vehicle)
Compound I - 10mpk
Compound I - 30mpk
Compound I - 10mpk

FIG. 10B

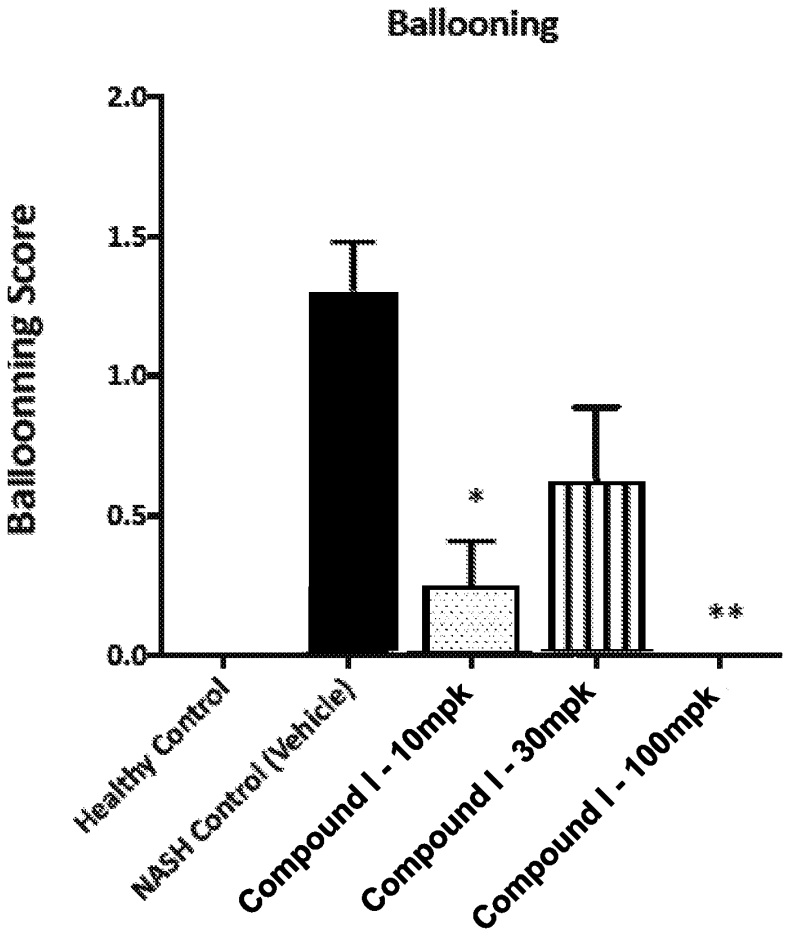

Ballooning
Ballonning Score
2.0
1.5
1.0
0.5
0.0
*
**
Healthy Control
NASH Control (Vehicle)
Compound I - 10mpk
Compound I - 30mpk
Compound I - 100mpk

FIG. 10C



FIG. 11A

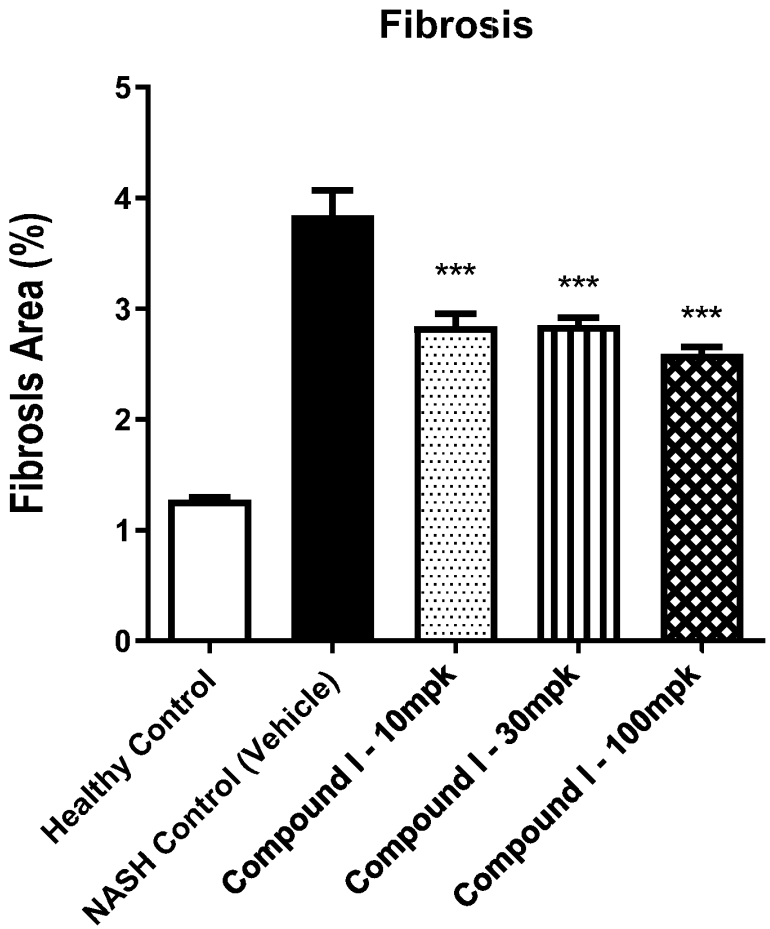

Fibrosis
Fibrosis Area (%)
5
4
3
2
1
0
***
***
***
Healthy Control
NASH Control (Vehicle)
Compound I - 10mpk
Compound I - 30mpk
Compound I - 100mpk

FIG. 11B

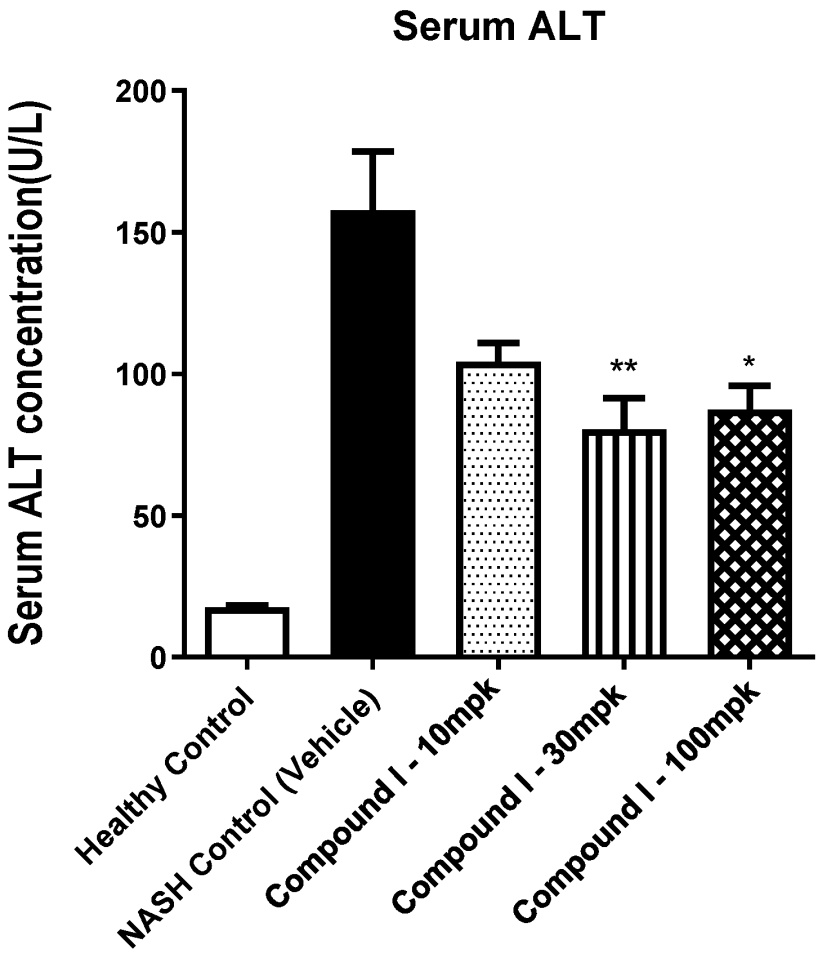

Serum ALT
Serum ALT concentration(U/L)
200
150
100
50
0
**
*
Healthy Control
NASH Control (Vehicle)
Compound I - 10mpk
Compound I - 30mpk
Compound I - 100mpk

FIG. 12A

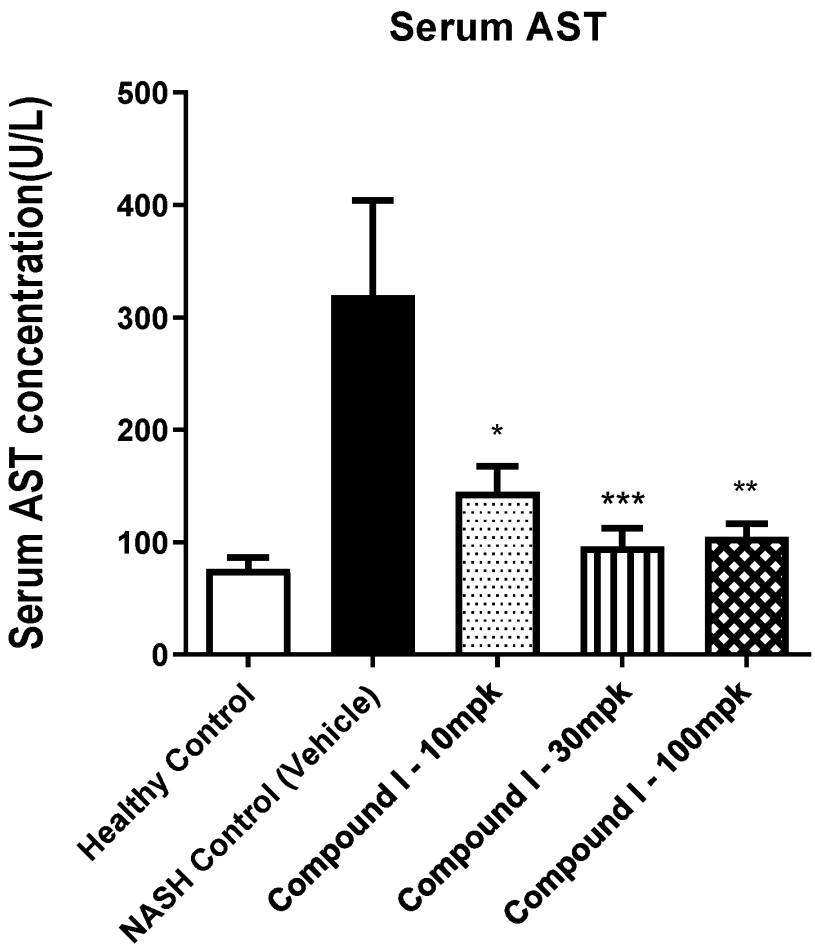

Serum AST
Serum AST concentration(U/L)
500
400
300
200
100
0
*
***
**
Healthy Control
NASH Control (Vehicle)
Compound I - 10mpk
Compound I - 30mpk
Compound I - 100mpk

FIG. 12B

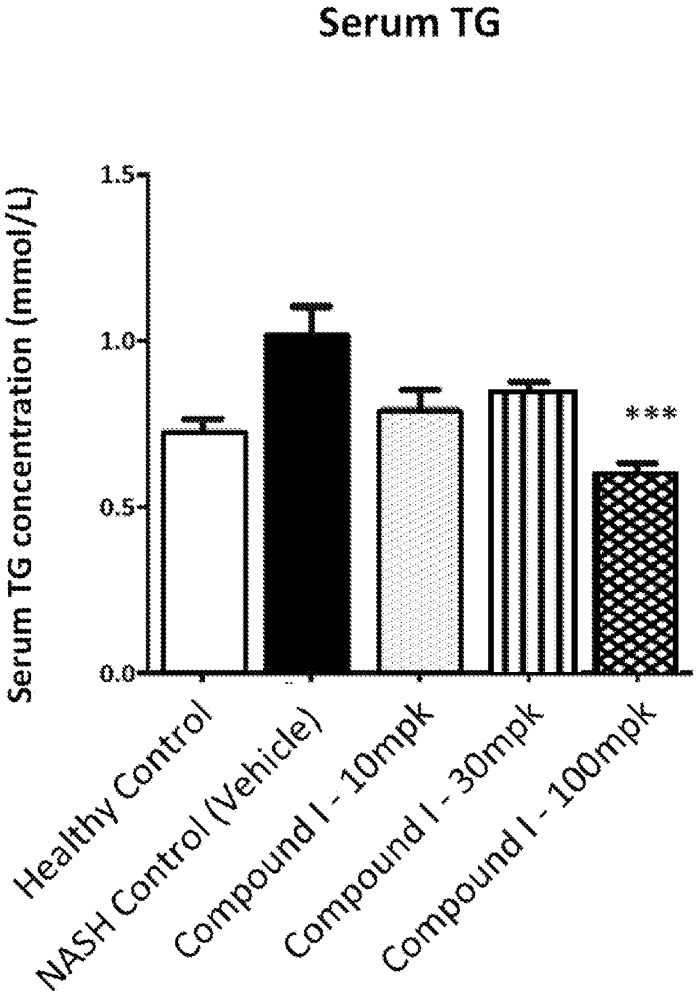

Serum TG
Serum TG concentration (mmol/L)
1.5
1.0
0.5
0.0
***
Healthy Control
NASH Control (Vehicle)
Compound I - 10mpk
Compound I - 30mpk
Compound I - 100mpk

FIG. 12C

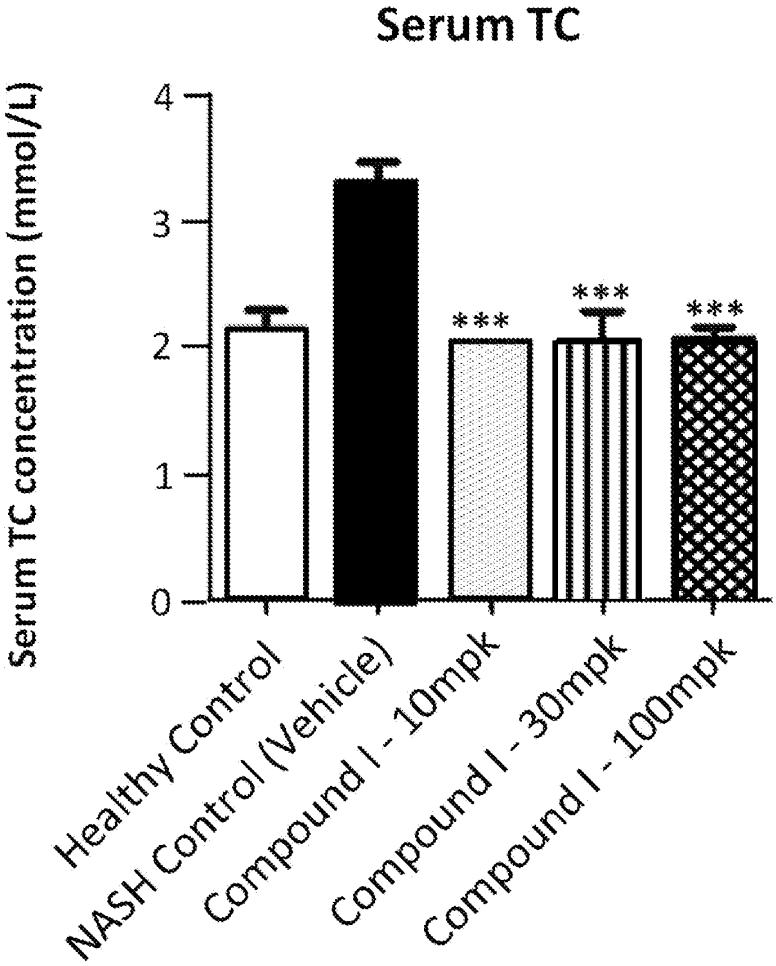

Serum TC
Serum TC concentration (mmol/L)
4
3
2
1
0
***
***
***
Healthy Control
NASH Control (Vehicle)
Compound I - 10mpk
Compound I - 30mpk
Compound I - 100mpk

FIG. 12D

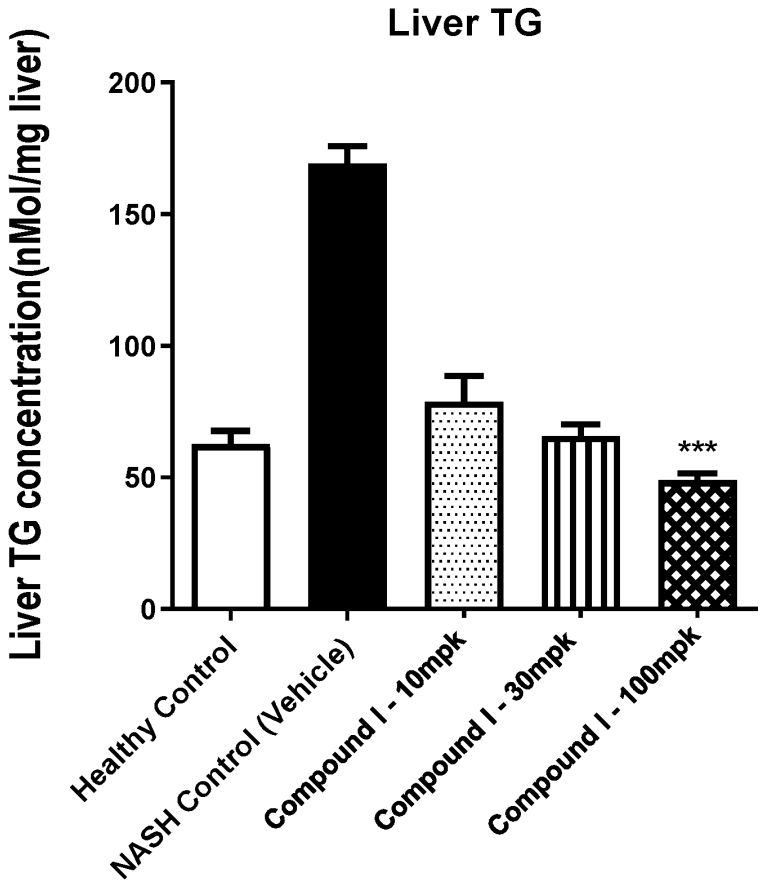

Liver TG
Liver TG concentration(nMol/mg liver)
200
150
100
50
0
***
Healthy Control
NASH Control (Vehicle)
Compound I - 10mpk
Compound I - 30mpk
Compound I - 100mpk

FIG. 13A

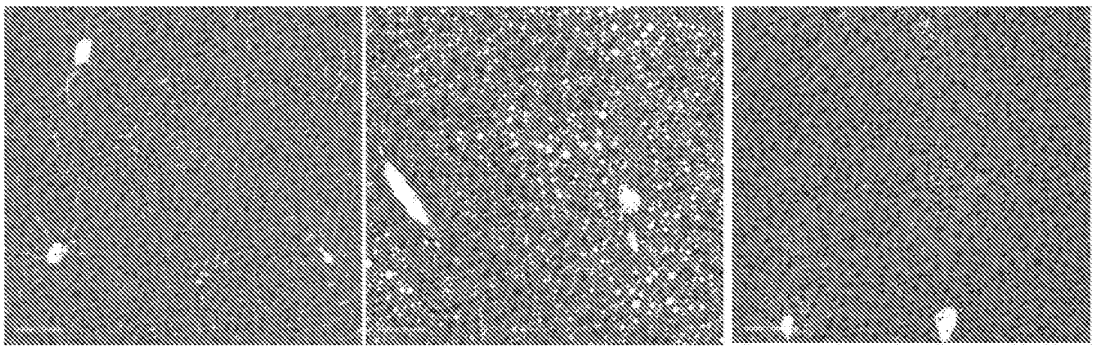


FIG. 13B

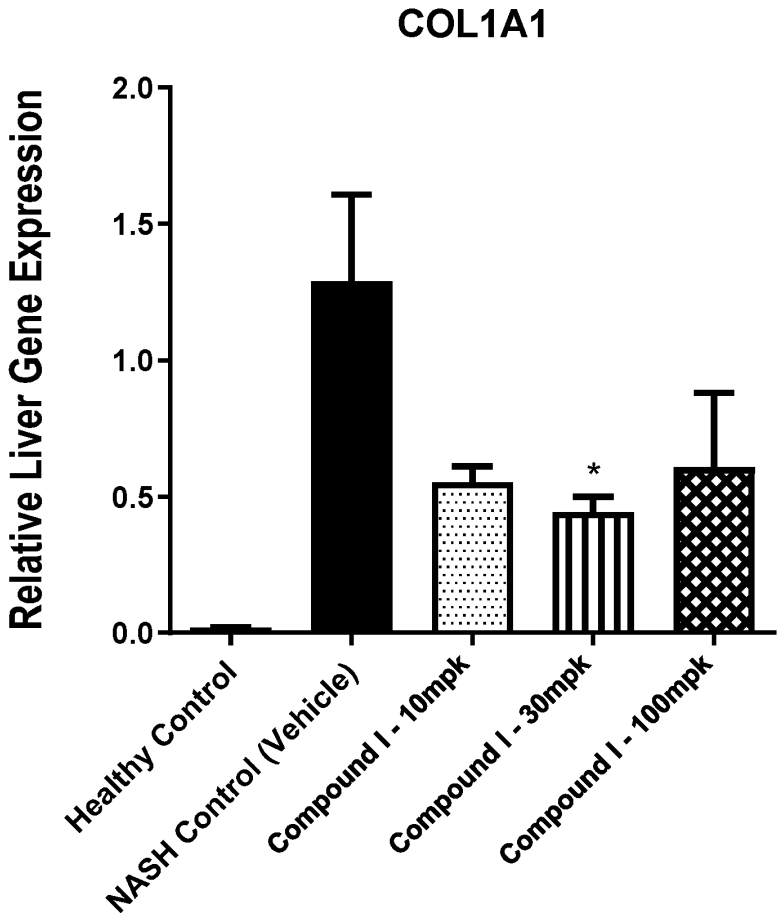

COL1A1
Relative Liver Gene Expression
2.0
1.5
1.0
0.5
0.0
*
Healthy Control
NASH Control (Vehicle)
Compound I - 10mpk
Compound I - 30mpk
Compound I - 100mpk

FIG. 14A

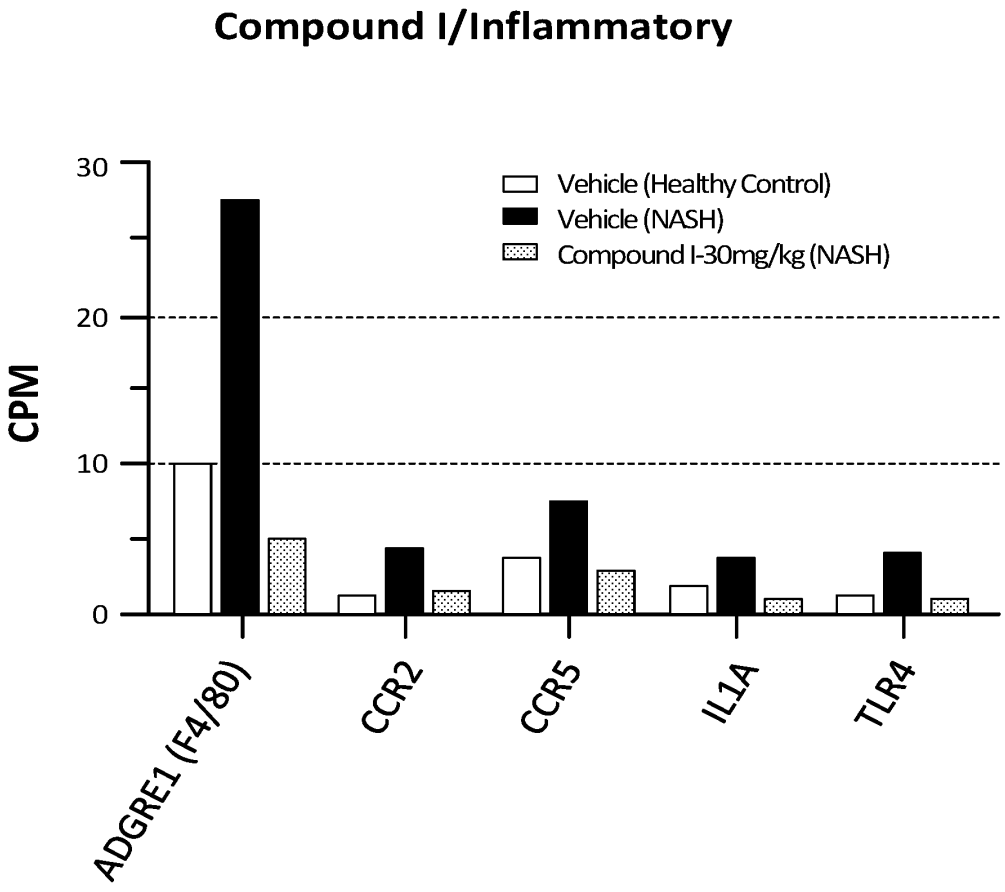

Compound I/Inflammatory
CPM
30
20
10
0
Vehicle (Healthy Control)
Vehicle (NASH)
Compound I-30mg/kg (NASH)
ADGRE1 (F4/80)
CCR2
CCR5
IL1A
TLR4

FIG. 14B

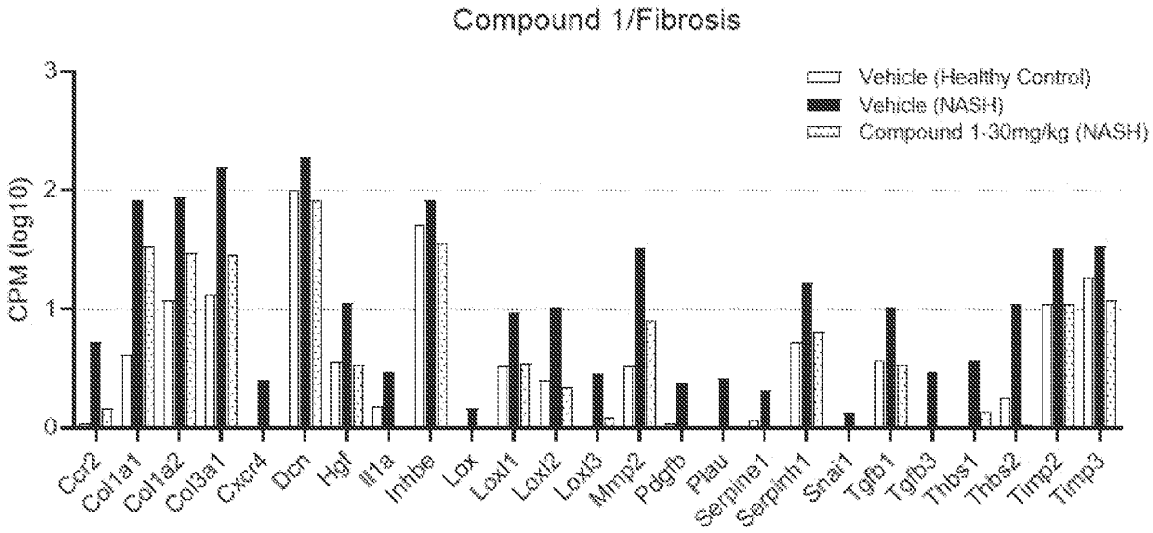

Compound 1/Fibrosis
Vehicle (Healthy Control)
Vehicle (NASH)
Compound 1-30mg/kg (NASH)
CPM (log10)
3
2
1
0
Ccr2
Col1a1
Col1a2
Col3a1
Cxcr4
Dcn
Hgf
Il1a
Inhbe
Lox
Loxl1
Loxl2
Loxl3
Mmp2
Pdgfb
Plau
Serpine1
Serpinh1
Snai1
Tgfb1
Tgfb3
Thbs1
Thbs2
Timp2
Timp3

FIG. 14C

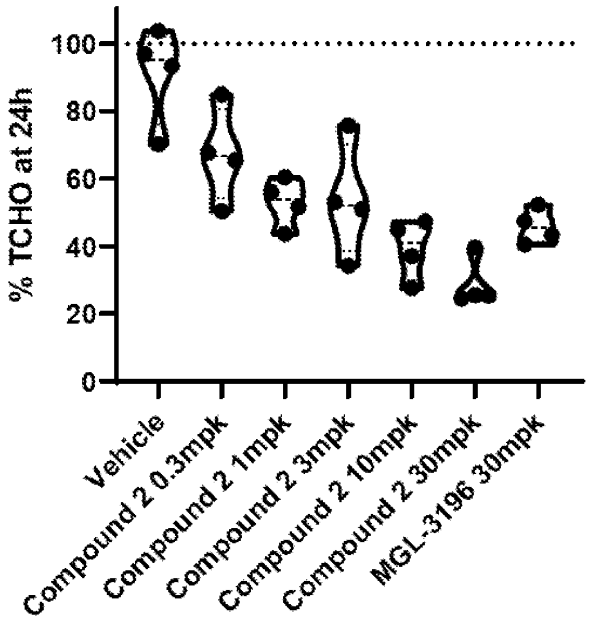


FIG. 15A

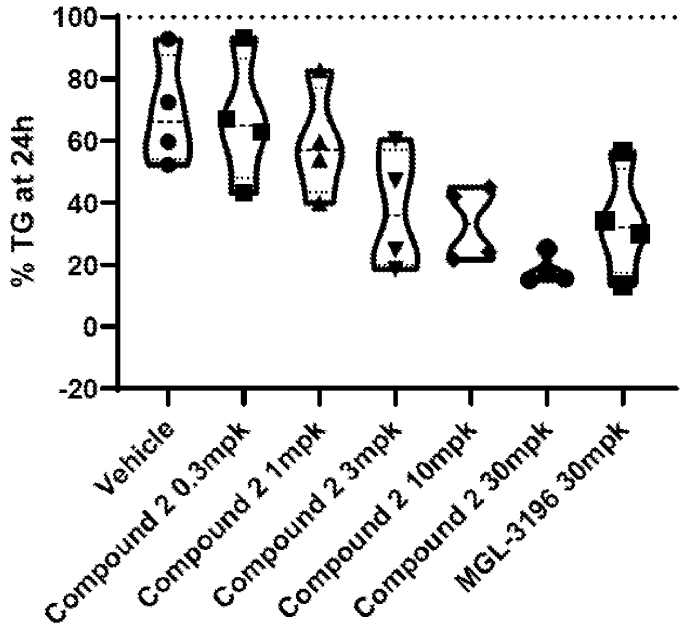


FIG. 15B

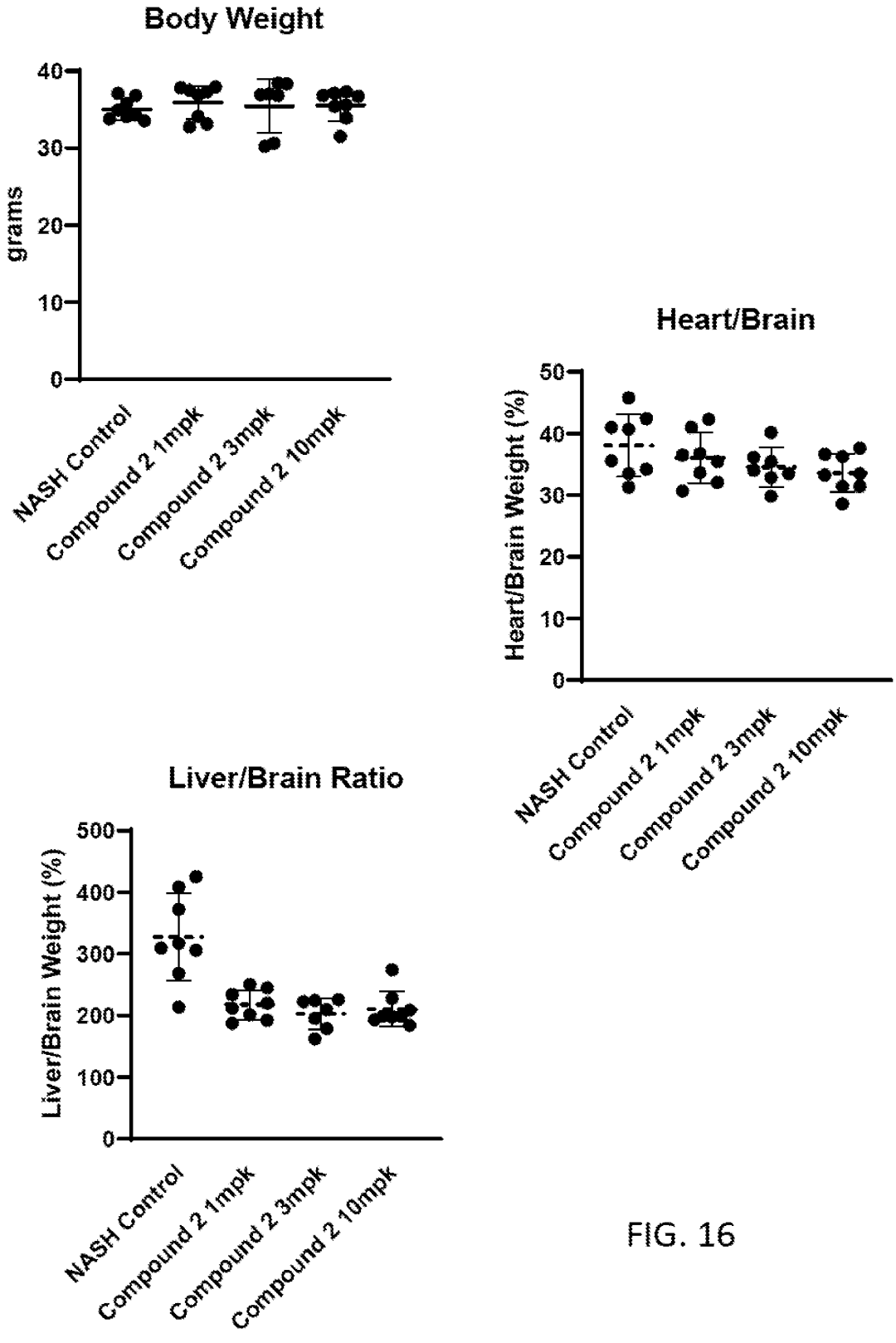

Body Weight
grams
40
30
20
10
0
NASH Control
Compound 2 1mpk
Compound 2 3mpk
Compound 2 10mpk
Heart/Brain
Heart/Brain Weight (%)
50
40
30
20
10
0
NASH Control
Compound 2 1mpk
Compound 2 3mpk
Compound 2 10mpk
Liver/Brain Ratio
Liver/Brain Weight (%)
500
400
300
200
100
0
NASH Control
Compound 2 1mpk
Compound 2 3mpk
Compound 2 10mpk

FIG. 16

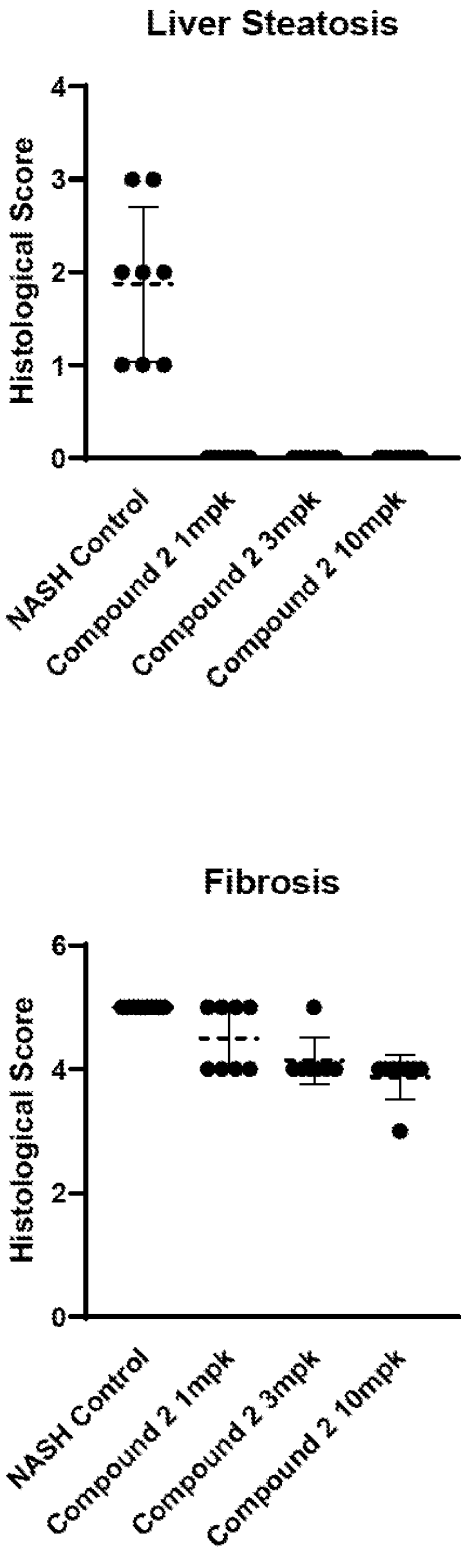

Liver Steatosis
Histological Score
0
1
2
3
4
NASH Control
Compound 2 1mpk
Compound 2 3mpk
Compound 2 10mpk
Fibrosis
Histological Score
0
2
4
6
NASH Control
Compound 2 1mpk
Compound 2 3mpk
Compound 2 10mpk
Inflammation
Histological Score
0
1
2
3
4
NASH Control
Compound 2 1mpk
Compound 2 3mpk
Compound 2 10mpk

FIG. 17

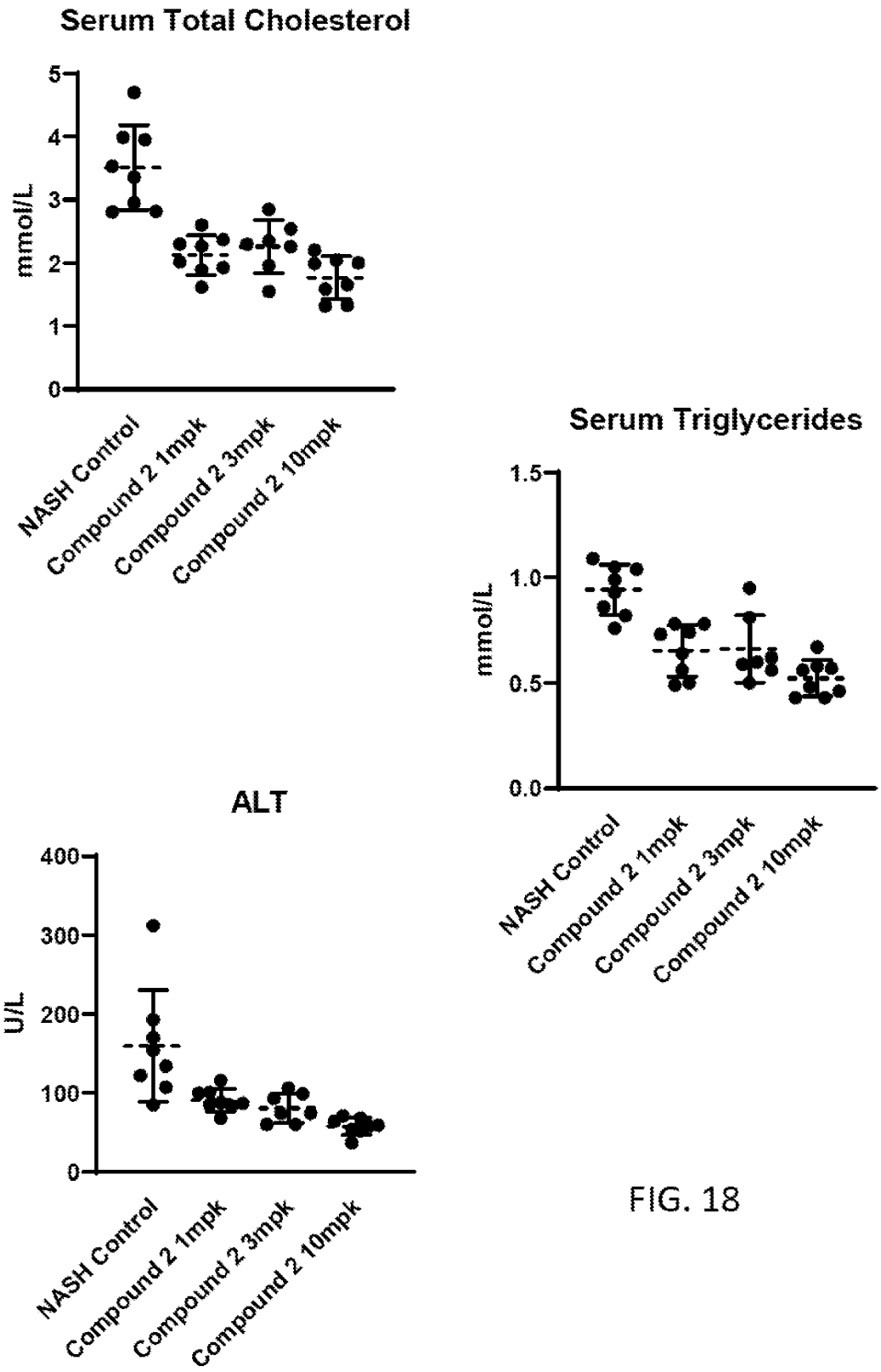

Serum Total Cholesterol
mmol/L
5
4
3
2
1
0
NASH Control
Compound 2 1mpk
Compound 2 3mpk
Compound 2 10mpk
Serum Triglycerides
mmol/L
1.5
1.0
0.5
0.0
NASH Control
Compound 2 1mpk
Compound 2 3mpk
Compound 2 10mpk
ALT
U/L
400
300
200
100
0
NASH Control
Compound 2 1mpk
Compound 2 3mpk
Compound 2 10mpk

FIG. 18

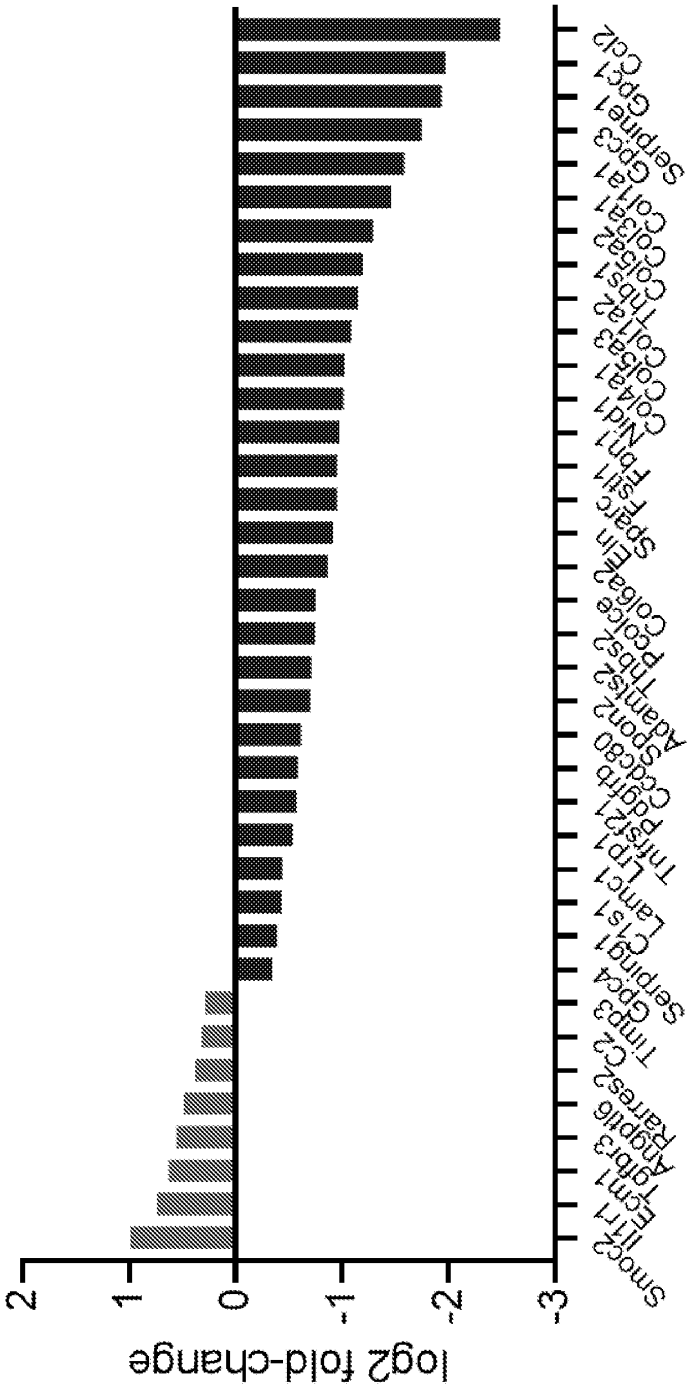
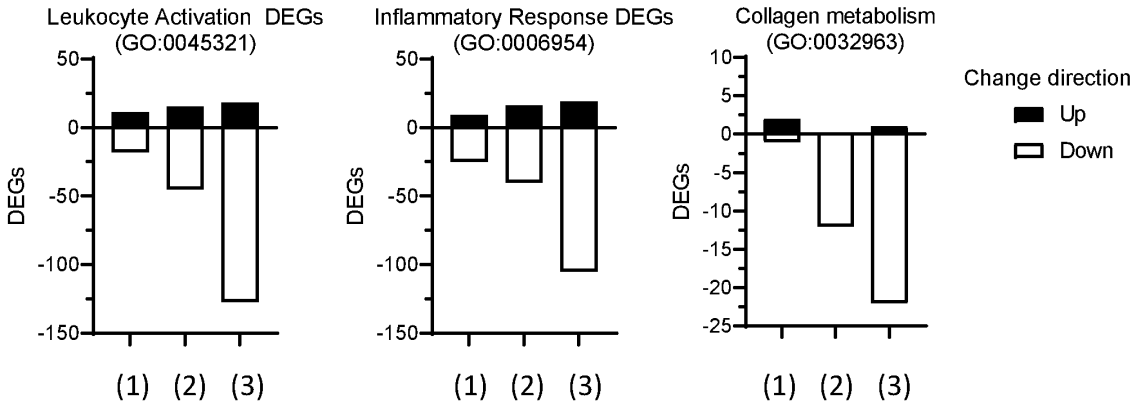

log2 fold-change
2
1
0
-1
-2
-3
Smoc2
Ifit1
Ecm1
Tgfbi3
Angptl6
Rarres2
C2
Timp3
Gpc4
Serping1
C1s1
Lamc1
Lrp1
Tnfrsf21
Pdgfrb
Ccdc80
Spon2
Adamts2
Thbs2
Pcolce
Col6a2
Efn
Sparc
Fstl1
Fbn1
Nid1
Col4a1
Col5a3
Col1a2
Thbs1
Col5a2
Col13a1
Col1a1
Gpc3
Serpine1
Gpc1
Ccl2

FIG. 19



(1) 3 mpk Compound 1
(2) 1 mpk Compound 2
(3) 3 mpk Compound 1 + 1 mpk Compound 2

FIG. 20

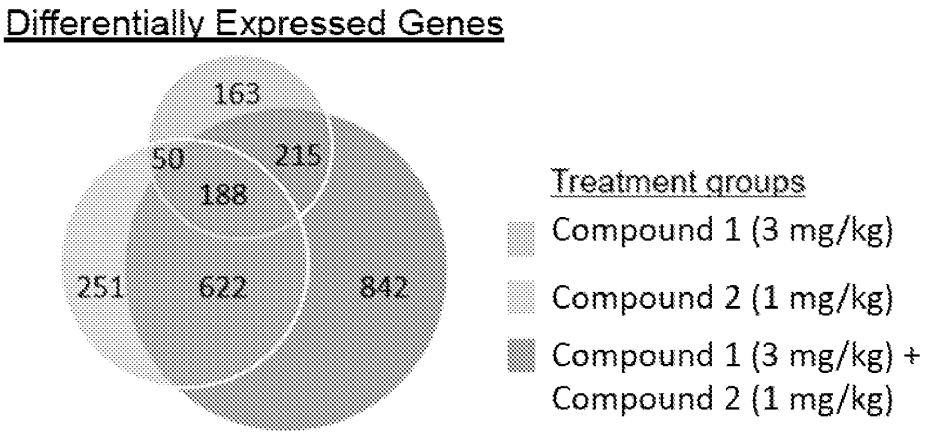

Differentially Expressed Genes
163
50
215
188
251
622
842
Treatment groups
Compound 1 (3 mg/kg)
Compound 2 (1 mg/kg)
Compound 1 (3 mg/kg) +
Compound 2 (1 mg/kg)

FIG. 21

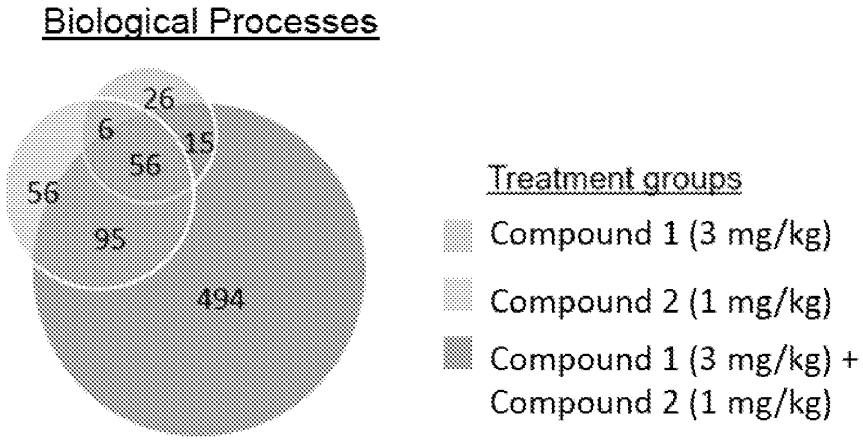

Biological Processes
26
6
15
56
56
95
494
Treatment groups
Compound 1 (3 mg/kg)
Compound 2 (1 mg/kg)
Compound 1 (3 mg/kg) +
Compound 2 (1 mg/kg)

FIG. 22

A – Healthy
B – NASH
C – Compound 1 (3 mg/kg)
D – Compound 2 (1 mg/kg)
E – Compound 1 (3 mg/kg) + Compound 2 (1 mg/kg)

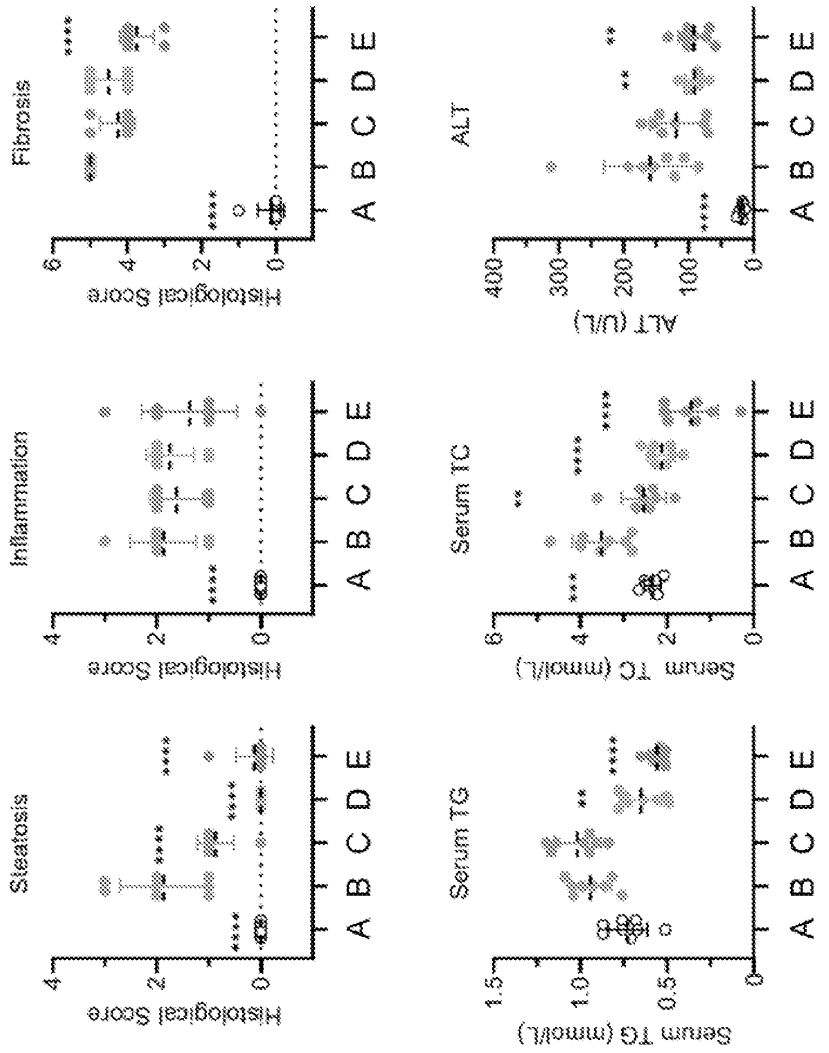


FIG. 23

A – Healthy
B – NASH
C – Compound 1 (3 mg/kg)
D – Compound 2 (1 mg/kg)
E – Compound 1 (3 mg/kg) + Compound 2 (1 mg/kg)

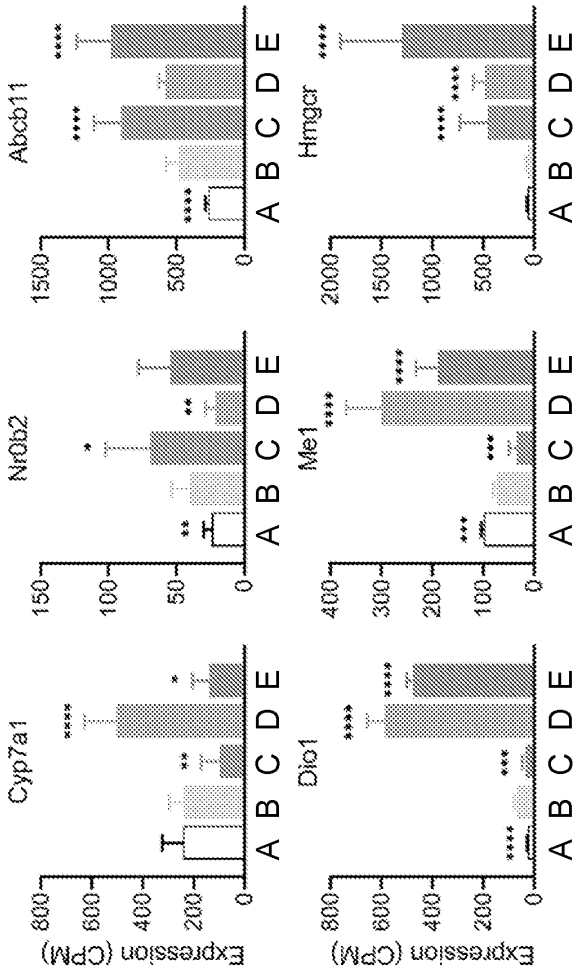


FIG. 24

A – Healthy
B – NASH
C – Compound 1 (3 mg/kg)
D – Compound 2 (1 mg/kg)
E – Compound 1 (3 mg/kg) + Compound 2 (1 mg/kg)

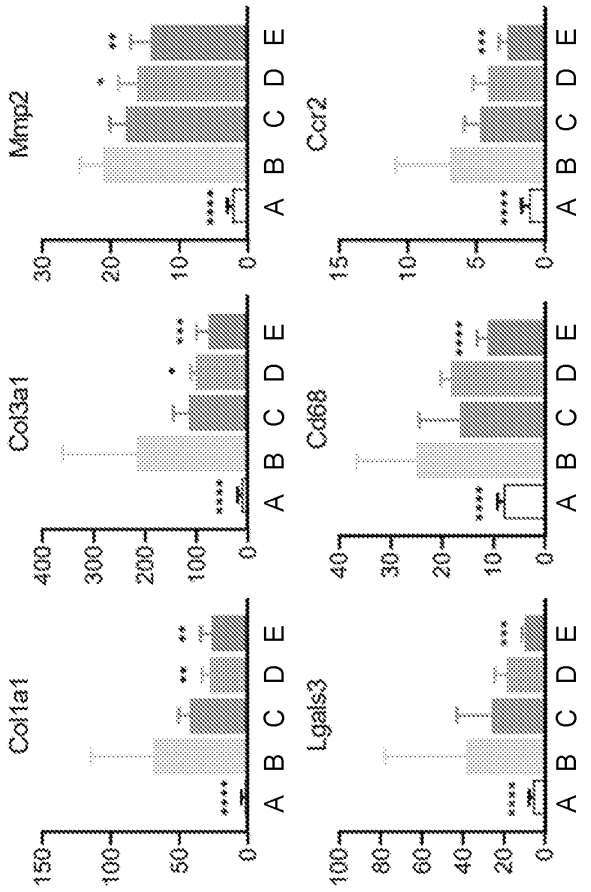


FIG. 25