Fig.1



Fig.2

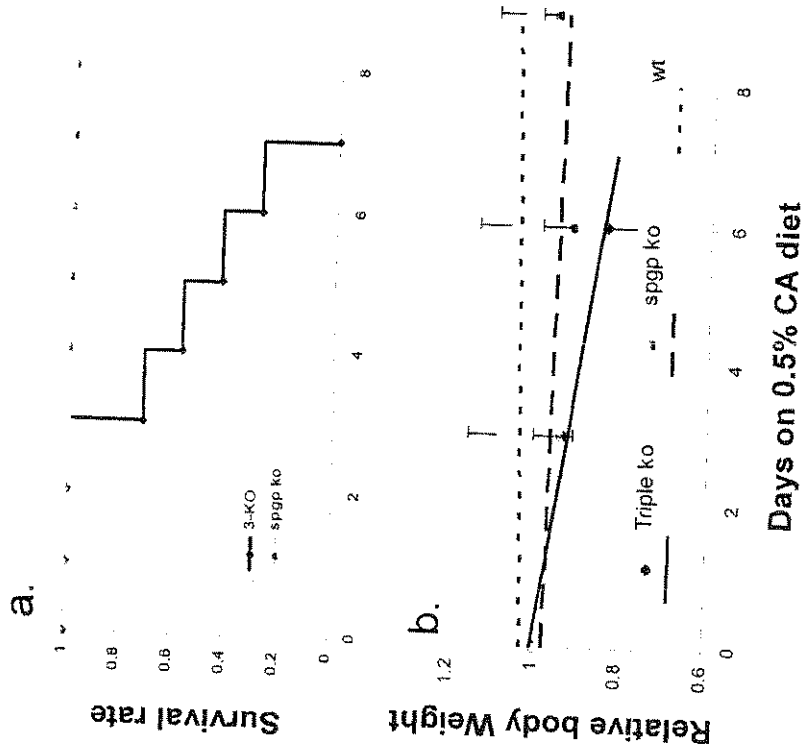

a.
Survival rate
3-KO
spgp ko
b.
Relative body Weight
Triple ko
spgp ko
wt
Days on 0.5% CA diet

Fig. 3

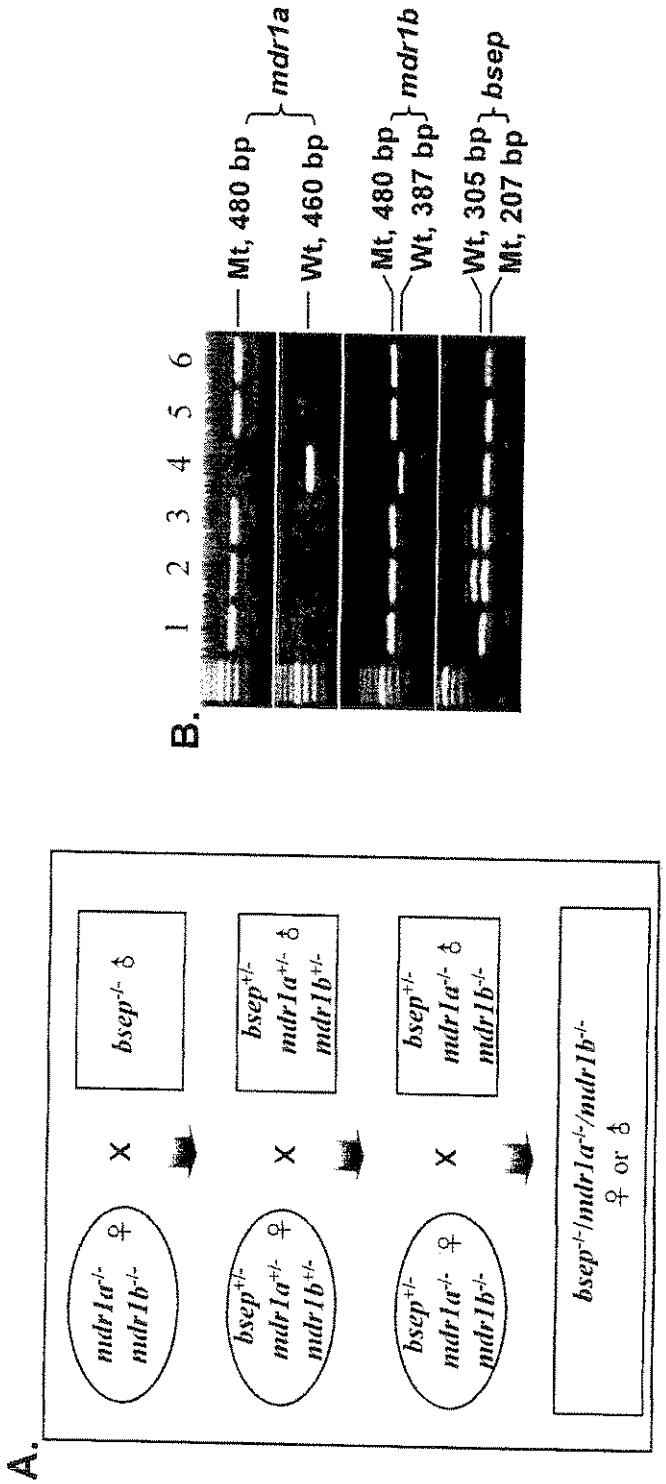
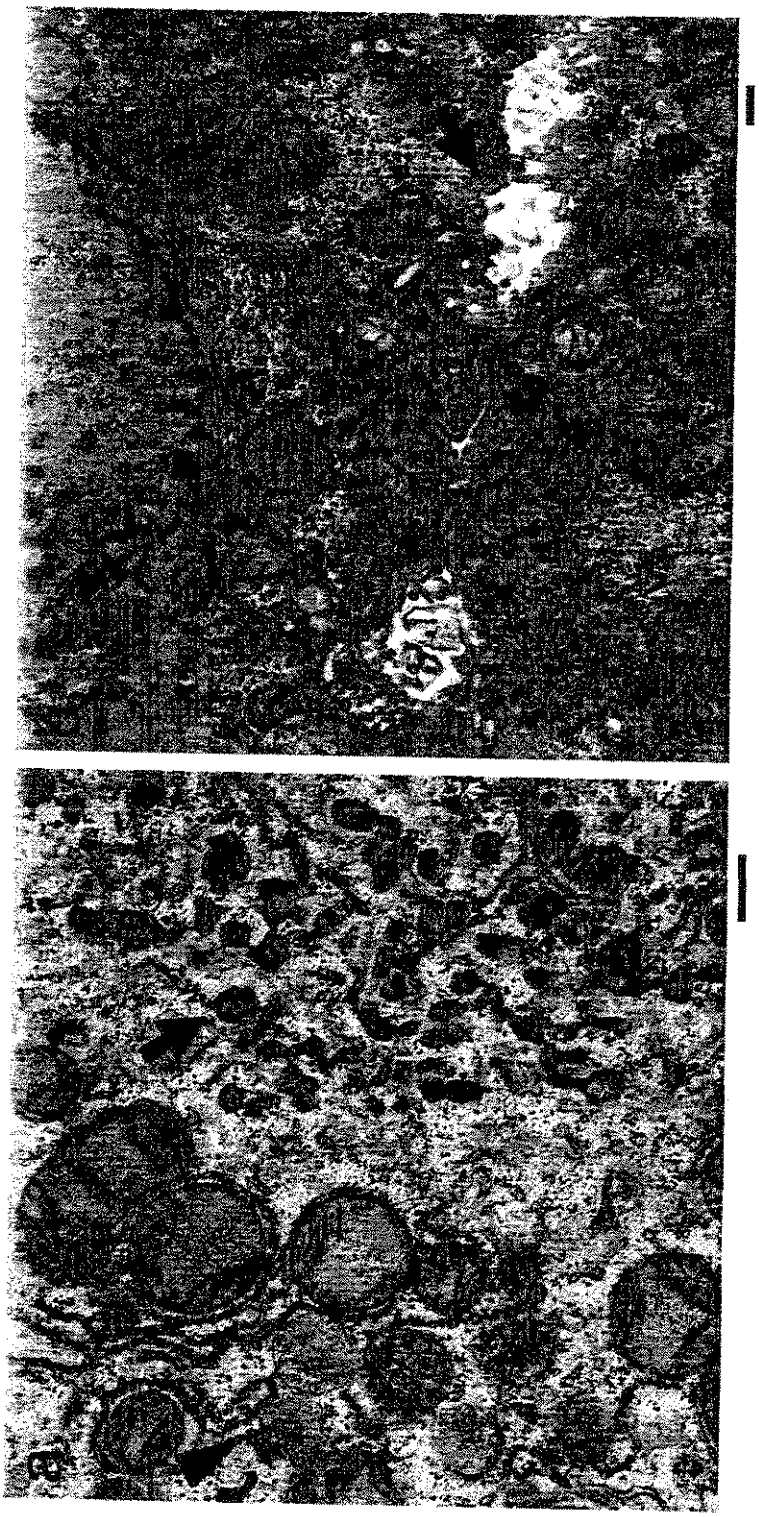

A.
mdr1a-/- mdr1b-/- ♀
bsep-/- ♂
bsep+/- mdr1a+/- mdr1b+/- ♀
bsep+/- mdr1a+/- mdr1b+/- ♂
bsep+/- mdr1a-/- mdr1b-/- ♀
bsep+/- mdr1a-/- mdr1b-/- ♂
bsep-/-/mdr1a-/-/mdr1b-/-
♀ or ♂
B.
1 2 3 4 5 6
Mt, 480 bp
Wt, 460 bp
mdr1a
Mt, 480 bp
Wt, 387 bp
mdr1b
Wt, 305 bp
Mt, 207 bp
bsep

Fig.4



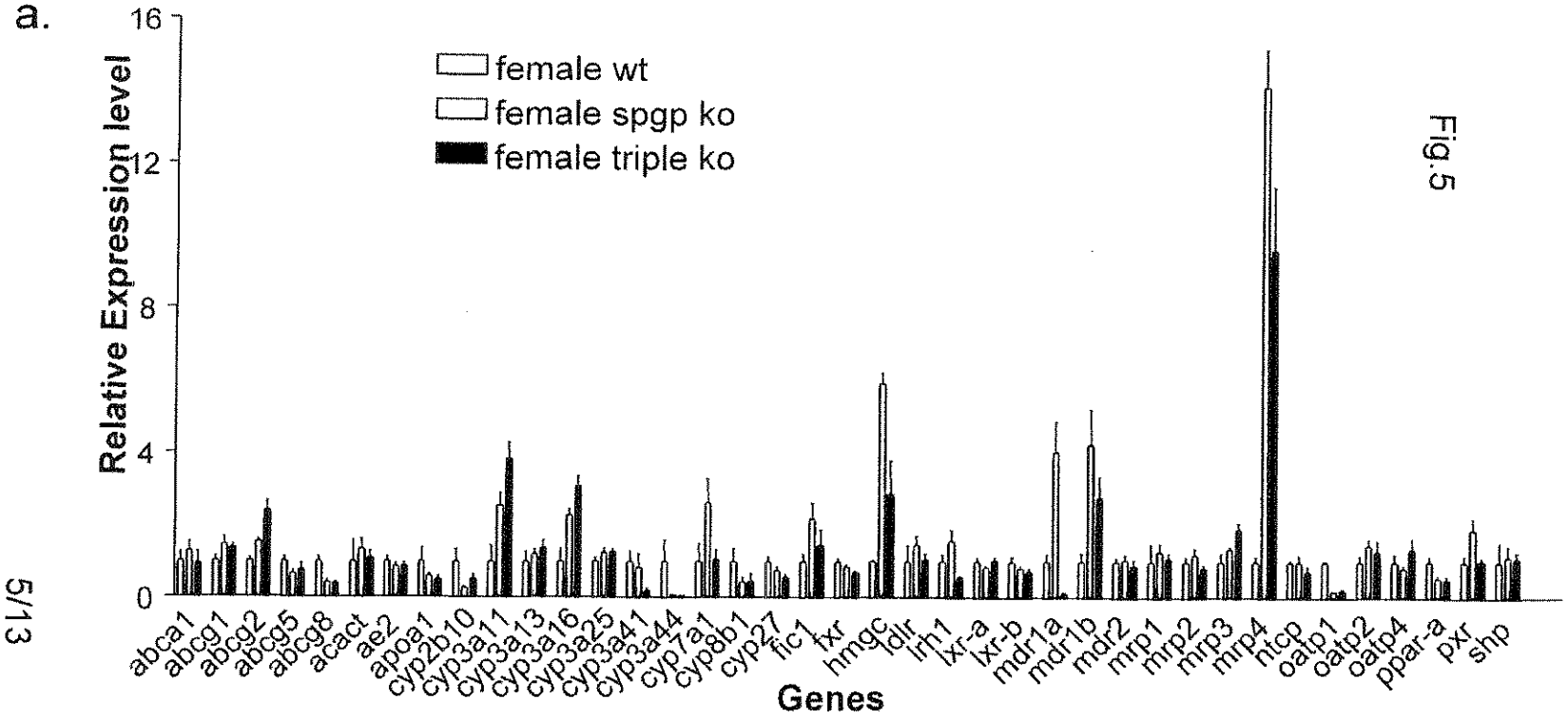


Fig.5

b. Abcb1b transcript with exon 4 deletion

```
  1 atggagtttgaagagaaccttaagggaagagcagacaagaacttctcgaagatgggcaaaaagagtaaaaaggagaagaaagaaaagaaa
    M  E  F  E  E  N  L  K  G  R  A  D  K  N  F  S  K  M  G  K  K  S  K  K  E  K  K  E  K  K
 91 cctgctgttggcgtatttgggatggtggacccaacagtactctga (SEQ. ID NO:4)
    P  A  V  G  V  F  G  M  V  D  P  T  V  L  *   (SEQ. ID NO:5)
```

c. Abcb1b transcript with exons 4, 5, 6 deletion

```
  1 atggagtttgaagagaaccttaagggaagagcagacaagaacttctcgaagatgggcaaaaagagtaaaaaggagaagaaagaaaagaaa
    M  E  F  E  E  N  L  K  G  R  A  D  K  N  F  S  K  M  G  K  K  S  K  K  E  K  K  E  K  K
 91 cctgctgttggcgtatttgggatggaattggtgacaaaattgggatgttttttcagtccataa (SEQ. ID NO:6)
    P  A  V  G  V  F  G  M  E  L  V  T  K  L  G  C  F  F  S  P  *   (SEQ. ID NO:7)
```

Fig.6

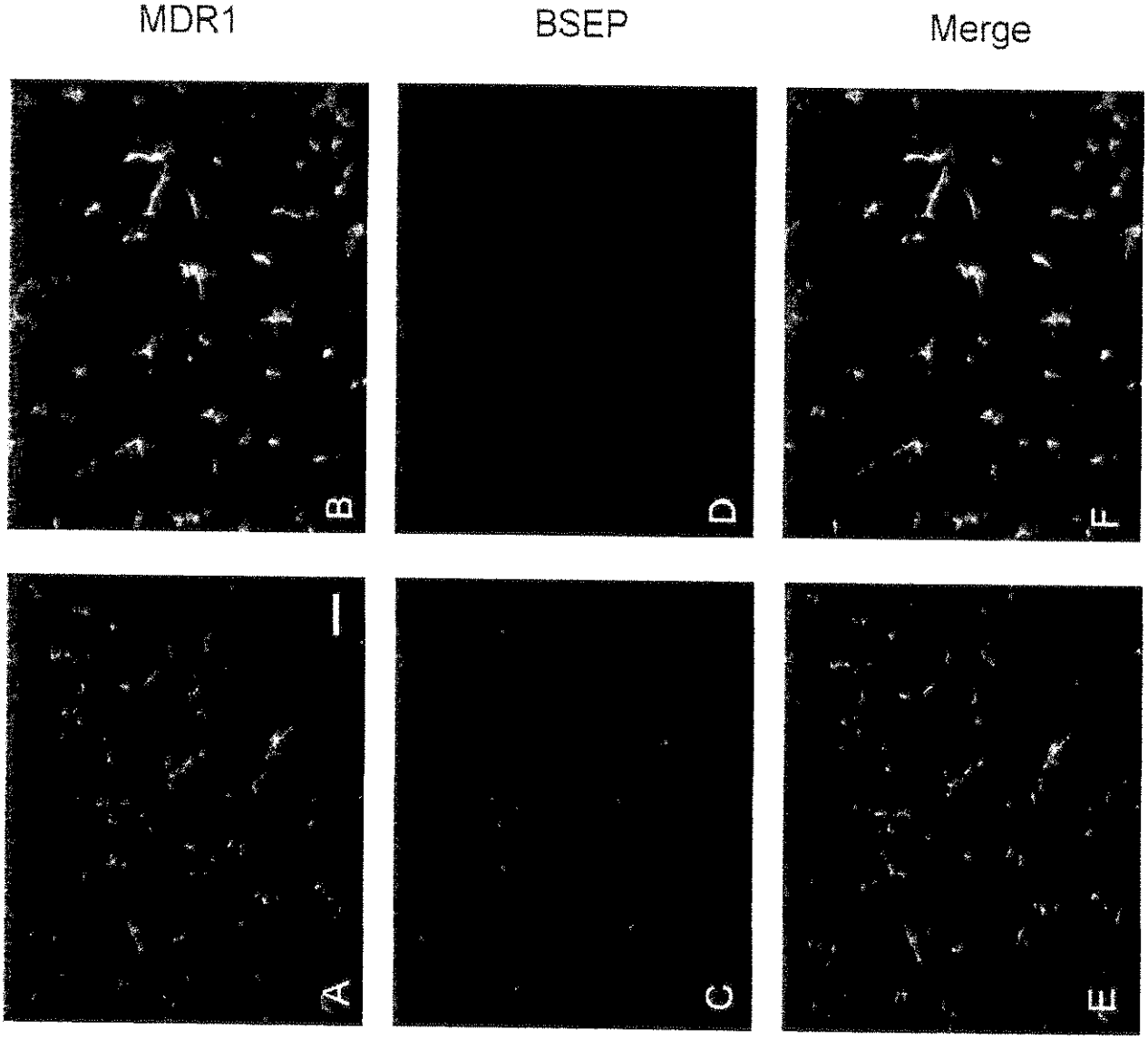


Fig. 7

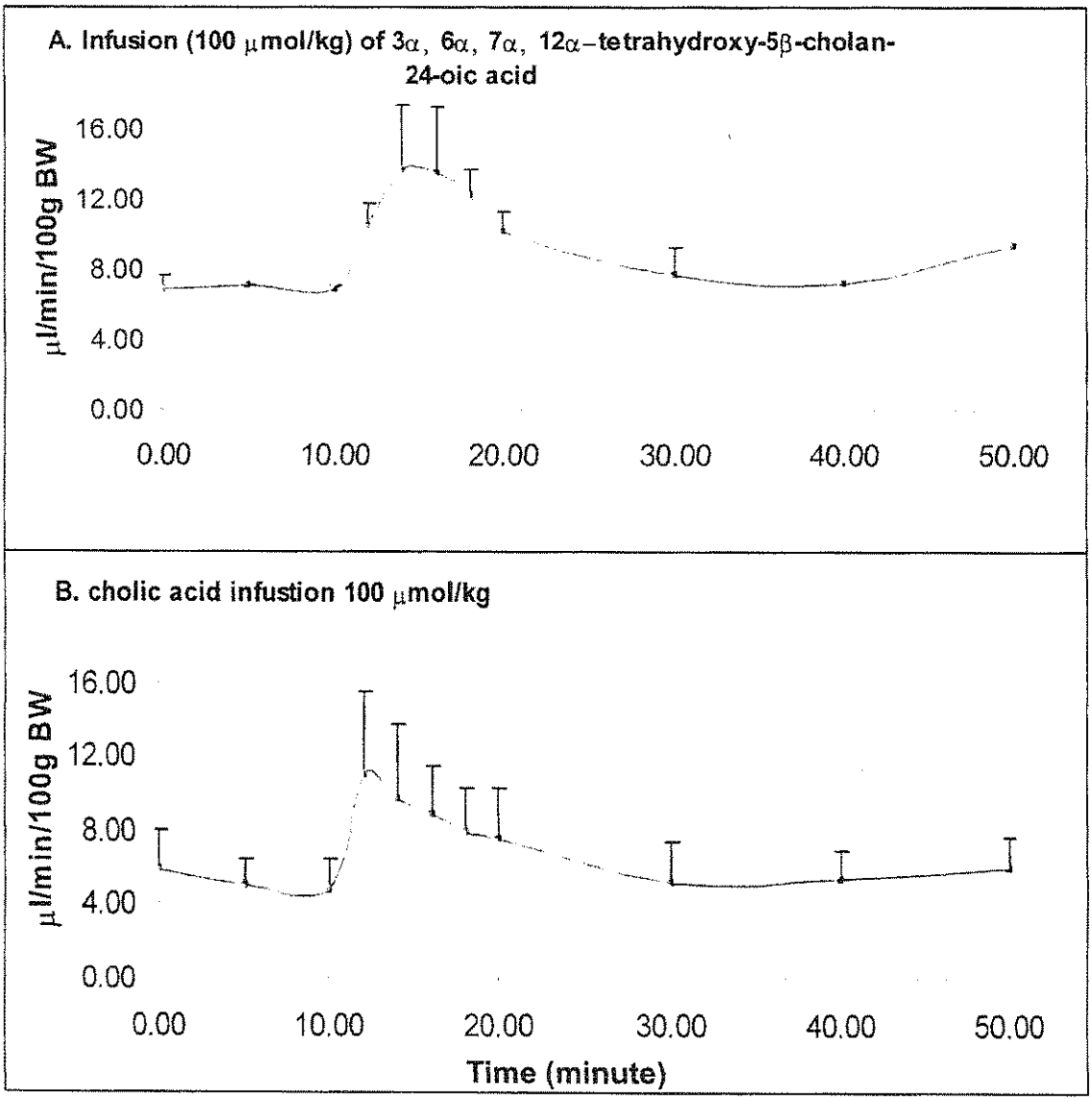

A. Infusion (100 μmol/kg) of 3α, 6α, 7α, 12α–tetrahydroxy-5β-cholan-24-oic acid
μl/min/100g BW
16.00
12.00
8.00
4.00
0.00
0.00
10.00
20.00
30.00
40.00
50.00
B. cholic acid infustion 100 μmol/kg
μl/min/100g BW
16.00
12.00
8.00
4.00
0.00
0.00
10.00
20.00
30.00
40.00
50.00
Time (minute)

Fig. 8

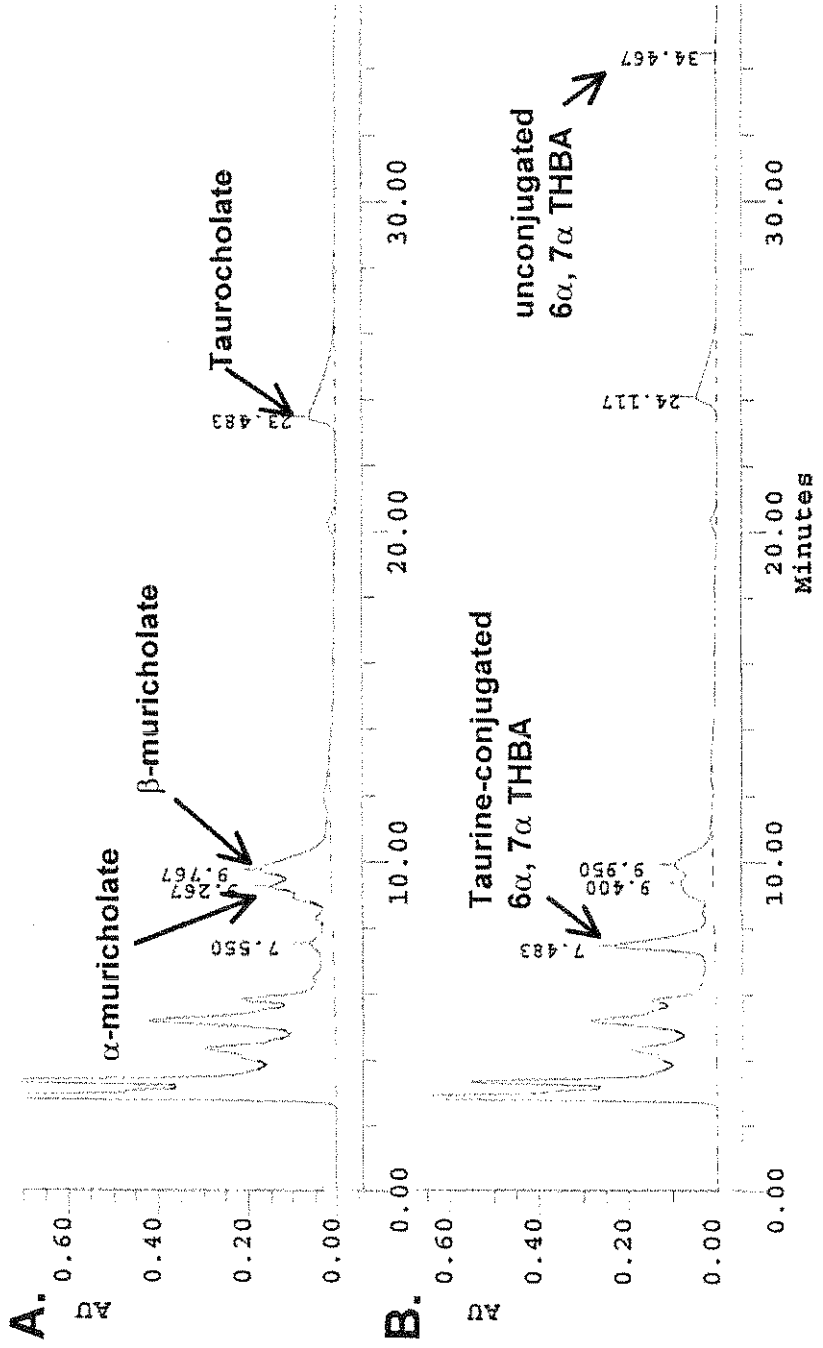
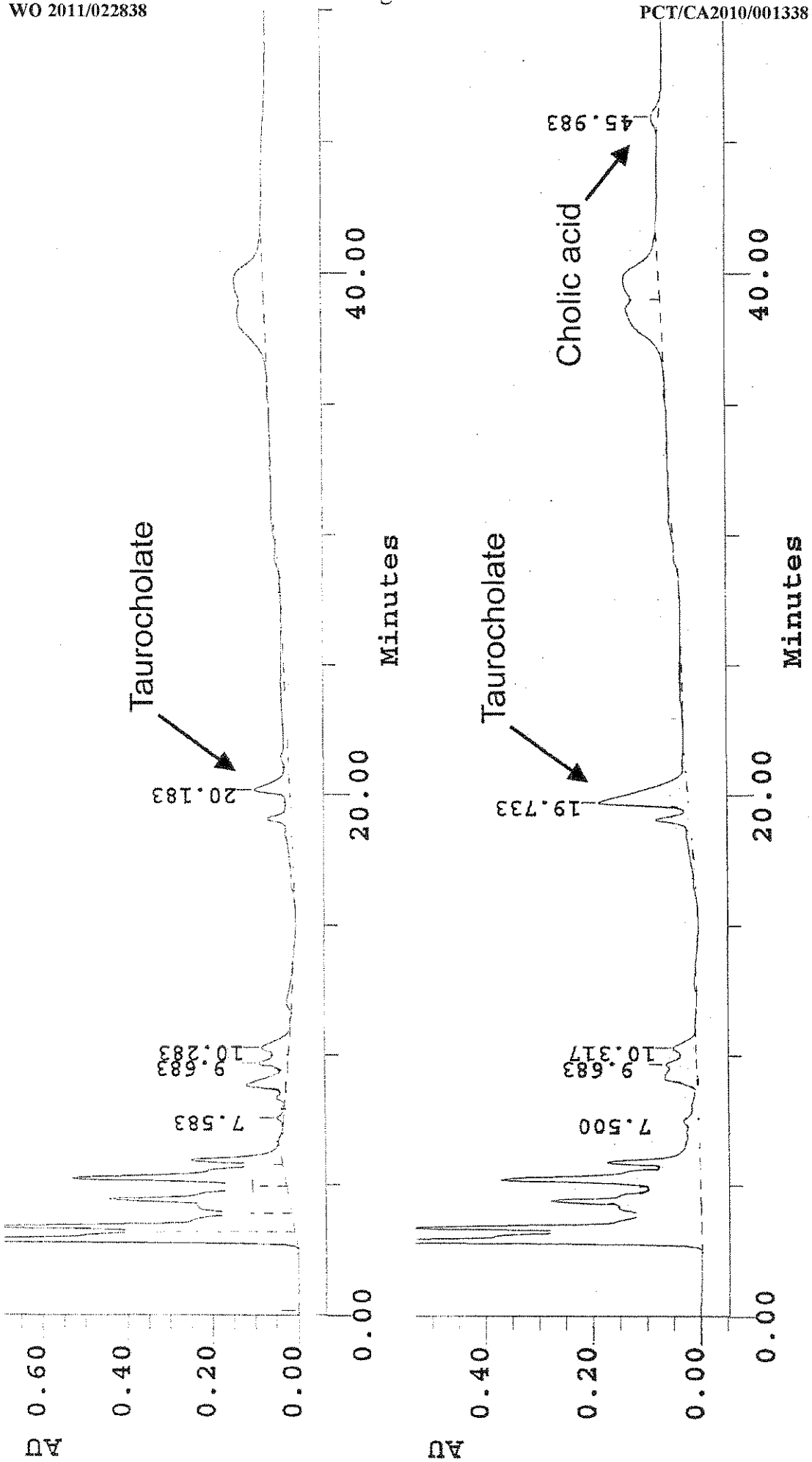

A.
B.
AU
0.60
0.40
0.20
0.00
10.00
20.00
30.00
Minutes
α-muricholate
β-muricholate
Taurocholate
7.550
9.267
9.767
23.483
Taurine-conjugated
6α, 7α THBA
unconjugated
6α, 7α THBA
7.483
9.400
9.950
24.117
34.467

Fig. 8C


Taurocholate
20.183
9.683
10.283
7.583
Minutes
0.00
20.00
40.00
AU
0.00
0.20
0.40
0.60
Taurocholate
19.733
9.683
10.317
7.500
Cholic acid
45.983
Minutes
0.00
20.00
40.00
AU
0.00
0.20
0.40

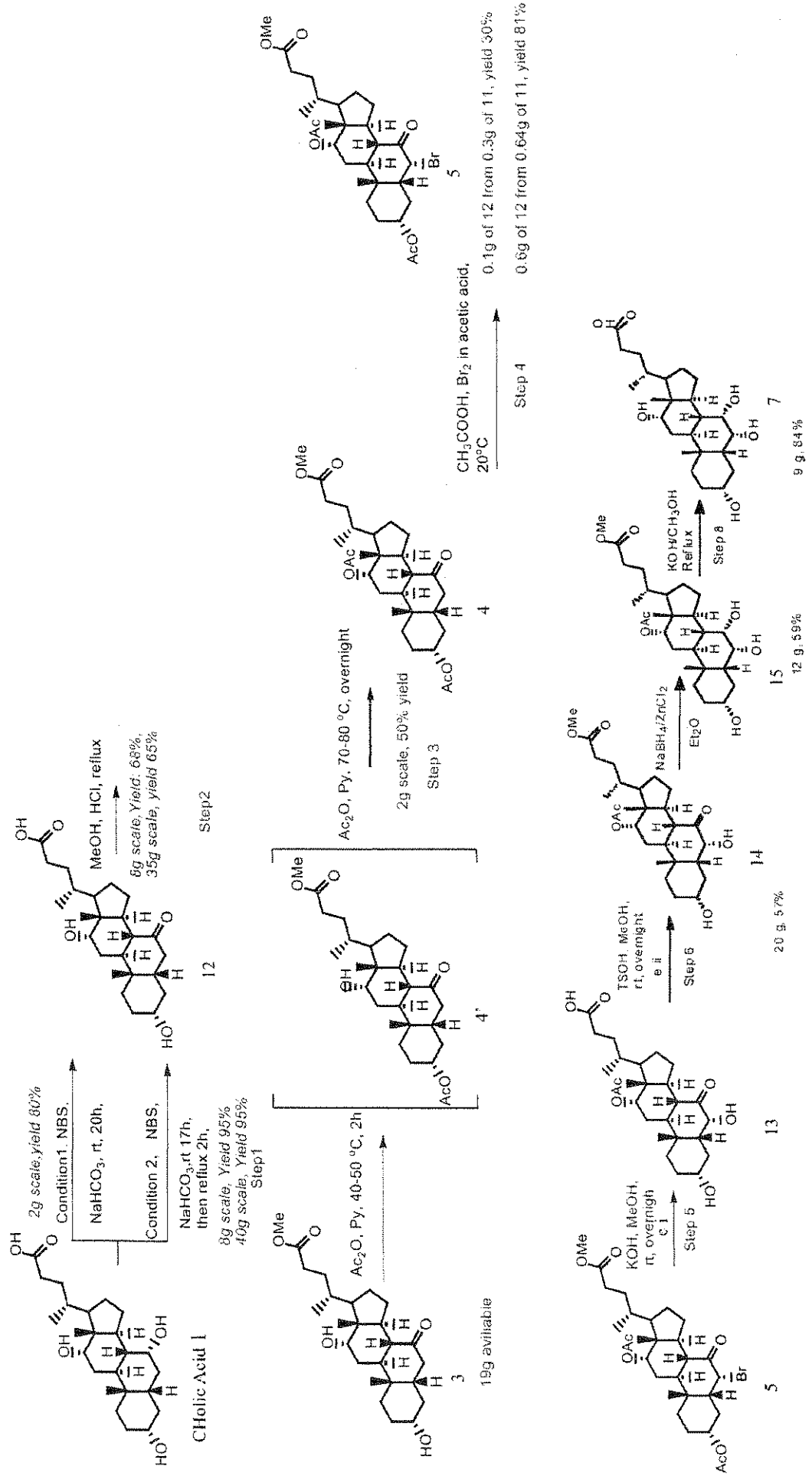

2g scale, yield 80%
Condition1 NBS,
NaHCO3, rt, 20h,
Condition 2, NBS,
NaHCO3,rt 17h,
then reflux 2h,
8g scale, Yield 95%
40g scale, Yield 95%
Step1
MeOH, HCl, reflux
6g scale, Yield: 68%,
35g scale, yield 65%
Step2
Cholic Acid 1
12
Ac2O, Py, 40-50 °C, 2h
19g avilable
3
Ac2O, Py, 70-80 °C, overnight
2g scale, 50% yield
Step 3
4
4'
CH3COOH, Br2 in acetic acid,
20°C
Step 4
0.1g of 12 from 0.3g of 11, yield 30%
0.6g of 12 from 0.64g of 11, yield 81%
5
KOH, MeOH,
rt, overnigh
c i
Step 5
TSOH, MeOH,
rt, overnight
e ii
Step 6
20 g, 57%
13
NaBH4/ZnCl2
Et2O
14
KOH/CH3OH
Reflux
Step 8
15
12 g, 59%
9 g, 84%
7

Fig. 10

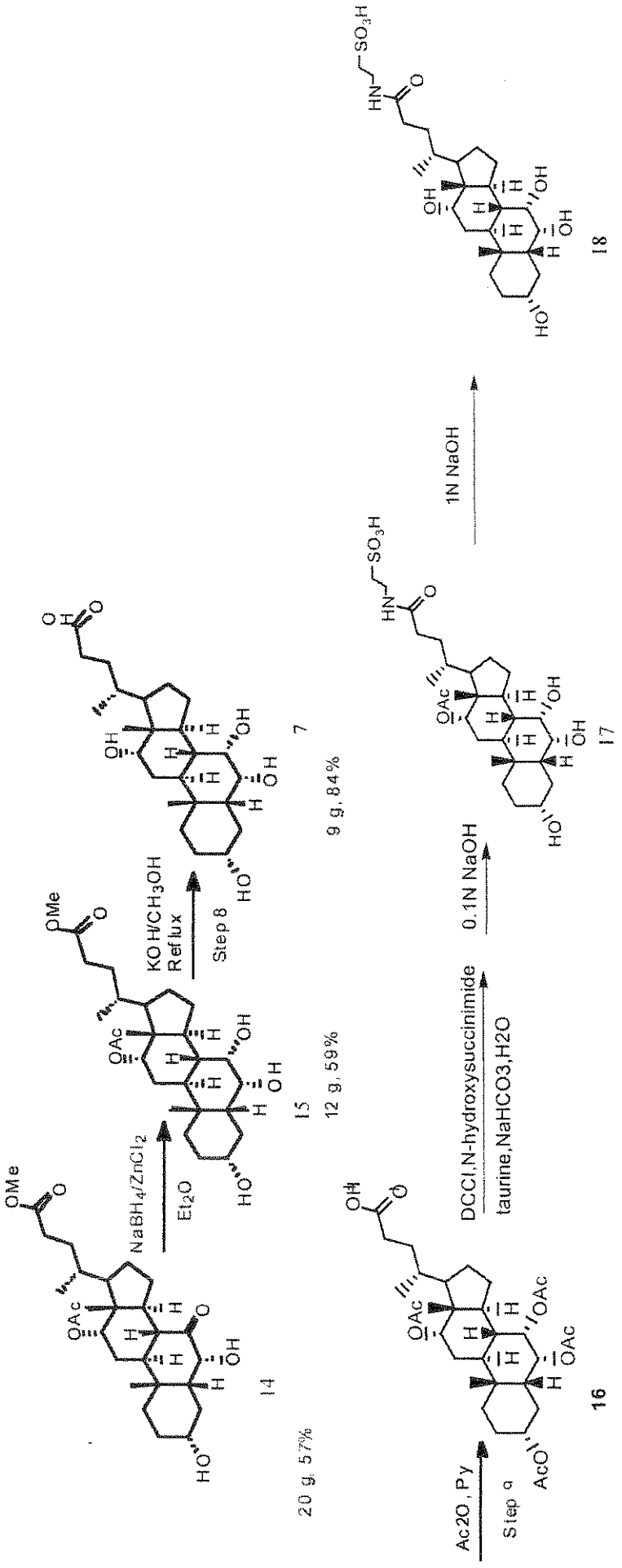

Ac2O, Py
Step a
20 g, 57%
NaBH4/ZnCl2
Et2O
KOH/CH3OH
Reflux
Step 8
9 g, 84%
12 g, 59%
DCCI,N-hydroxysuccinimide
taurine,NaHCO3,H2O
0.1N NaOH
1N NaOH

Fig. 11

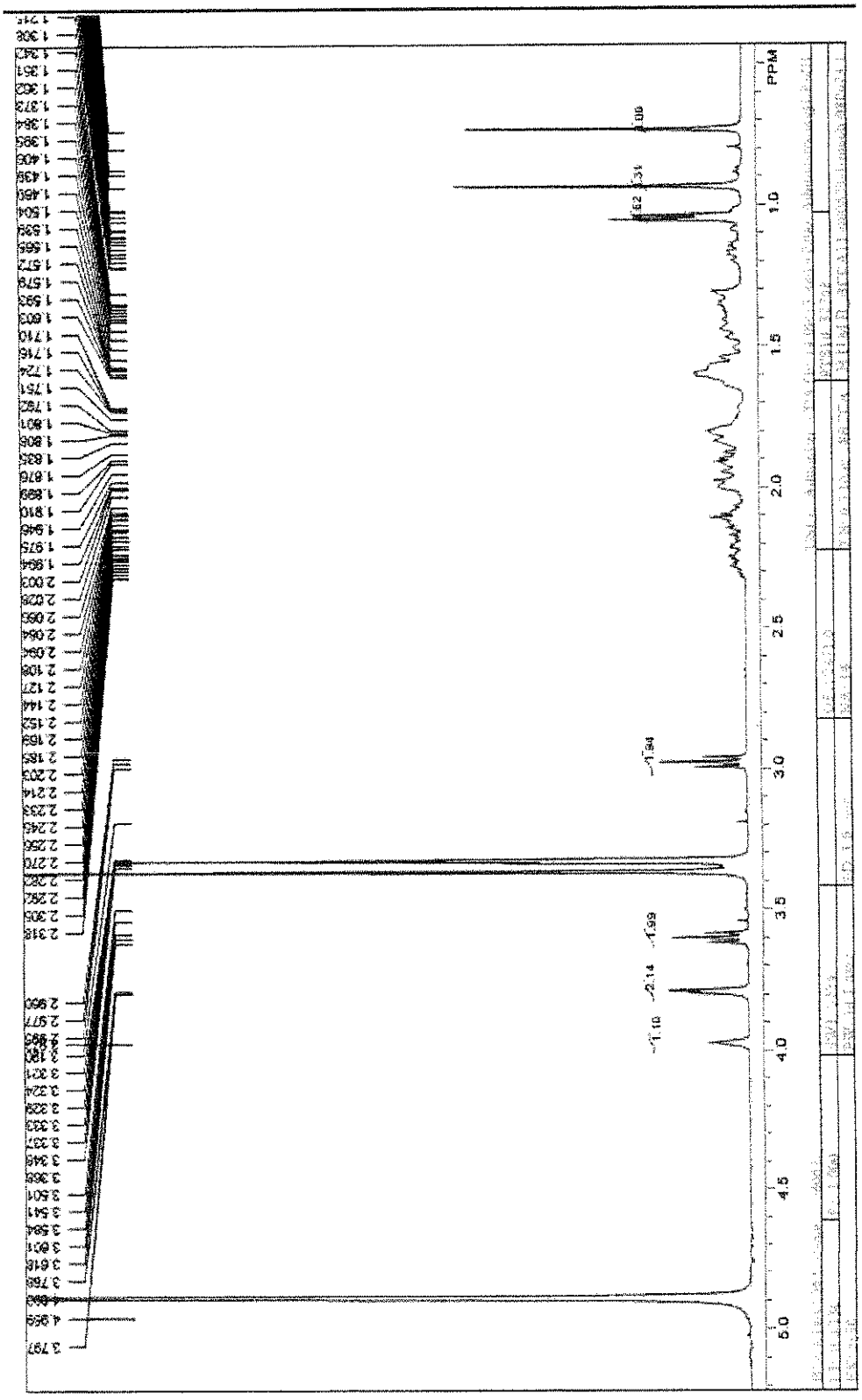
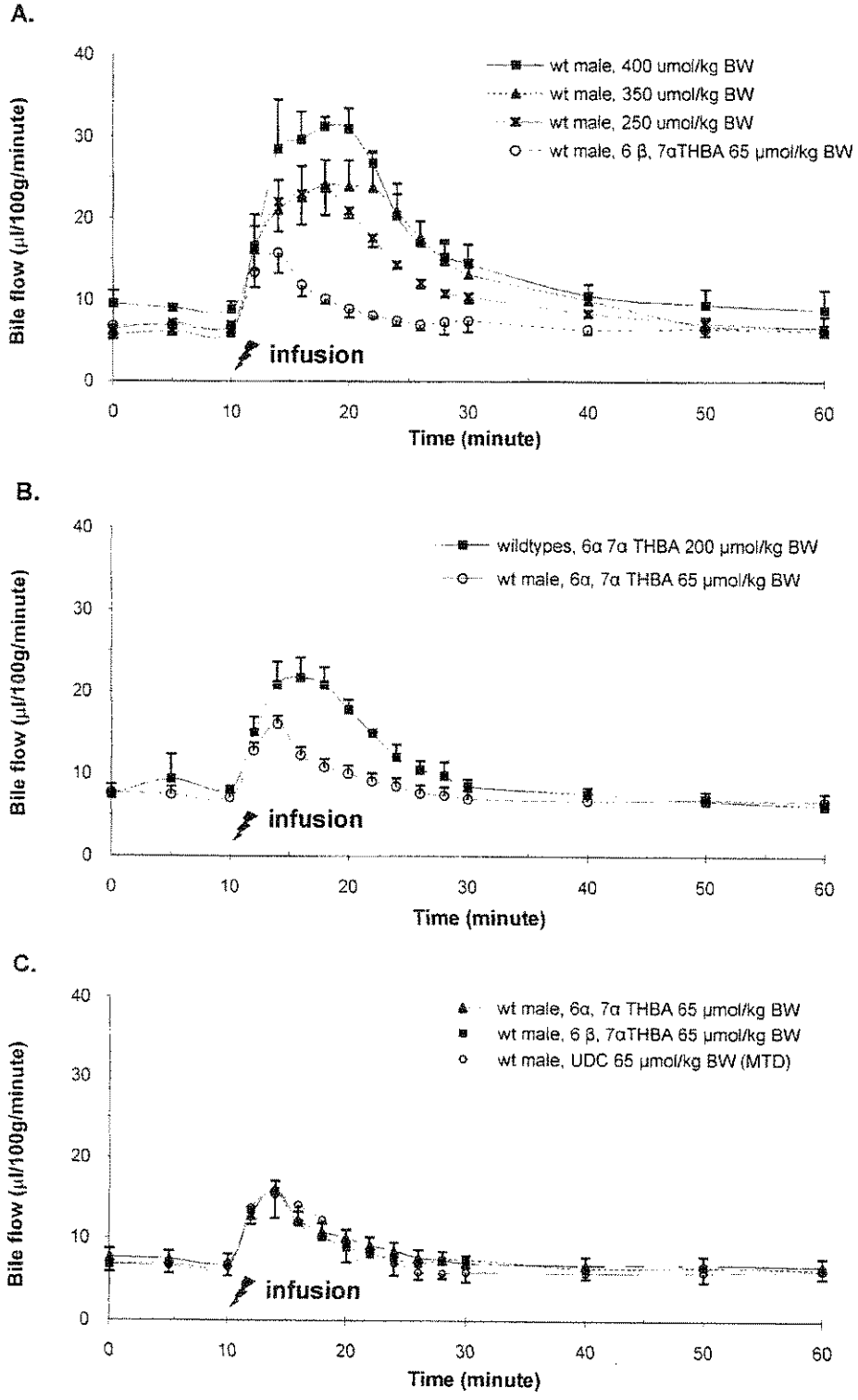


Fig. 12


A.
wt male, 400 umol/kg BW
wt male, 350 umol/kg BW
wt male, 250 umol/kg BW
wt male, 6 β, 7αTHBA 65 µmol/kg BW
Bile flow (µl/100g/minute)
infusion
Time (minute)
B.
wildtypes, 6α 7α THBA 200 µmol/kg BW
wt male, 6α, 7α THBA 65 µmol/kg BW
Bile flow (µl/100g/minute)
infusion
Time (minute)
C.
wt male, 6α, 7α THBA 65 µmol/kg BW
wt male, 6 β, 7αTHBA 65 µmol/kg BW
wt male, UDC 65 µmol/kg BW (MTD)
Bile flow (µl/100g/minute)
infusion
Time (minute)