Figures

Fig. 1a:

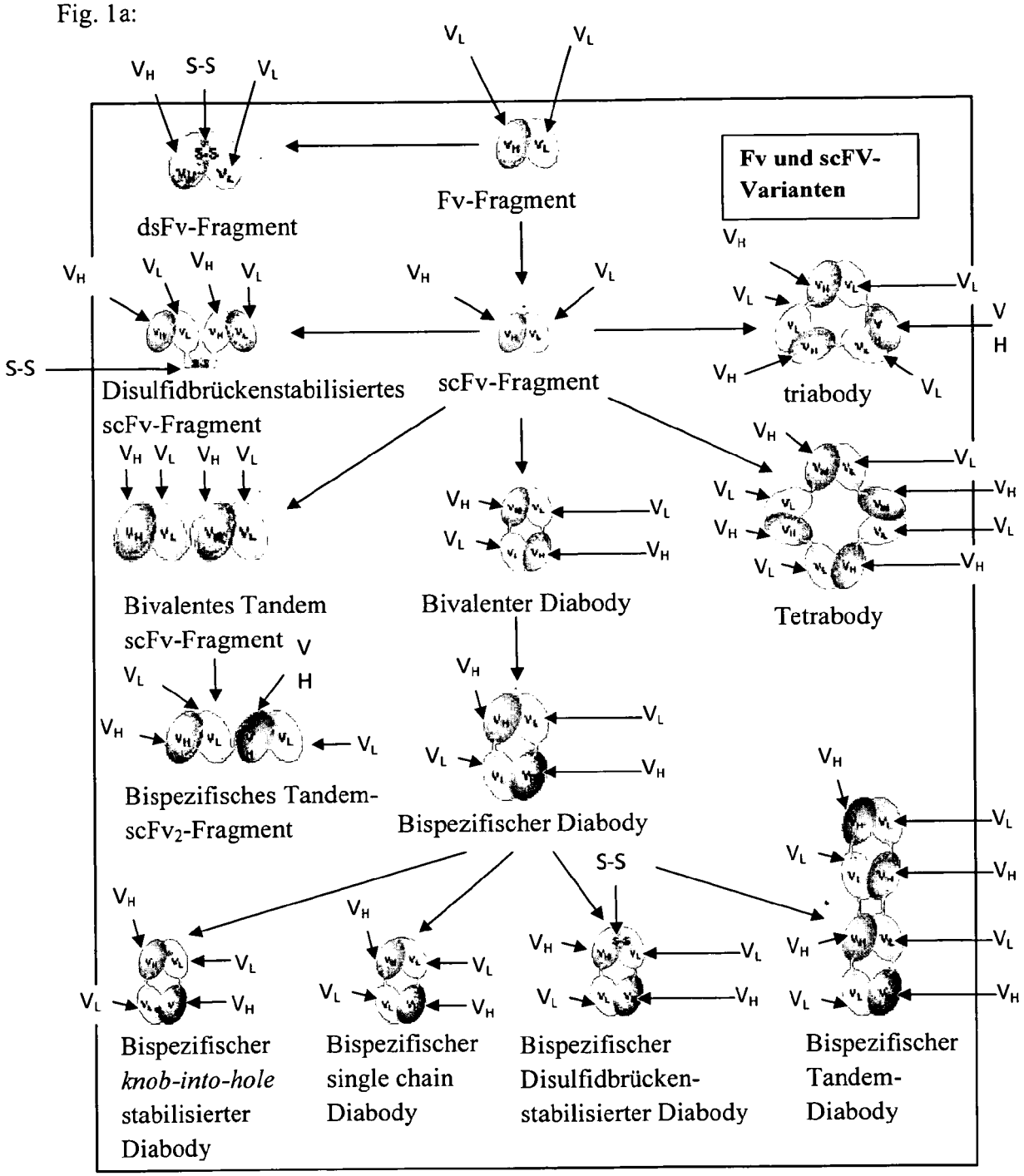


Fig. 1b:

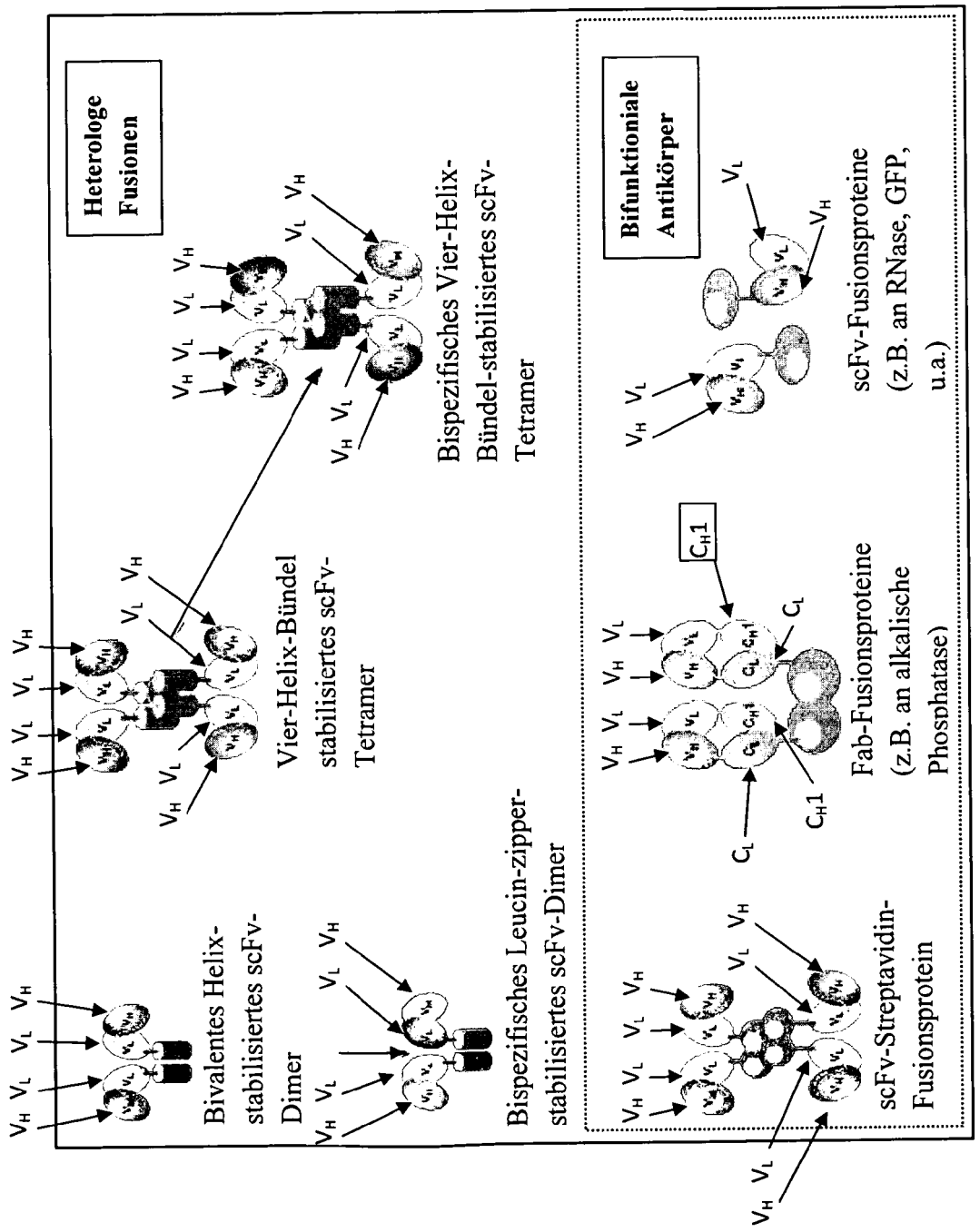

Heterologe Fusionen
Bivalentes Helix-stabilisiertes scFv-Dimer
Vier-Helix-Bündel stabilisiertes scFv-Tetramer
Bispezifisches Vier-Helix-Bündel-stabilisiertes scFv-Tetramer
Bispezifisches Leucin-zipper-stabilisiertes scFv-Dimer
Bifunktionale Antikörper
Fab-Fusionsproteine (z.B. an alkalische Phosphatase)
scFv-Fusionsproteine (z.B. an RNase, GFP, u.a.)
scFv-Streptavidin-Fusionsprotein
V_H V_L
C_H1
C_L

Fig. 1c:

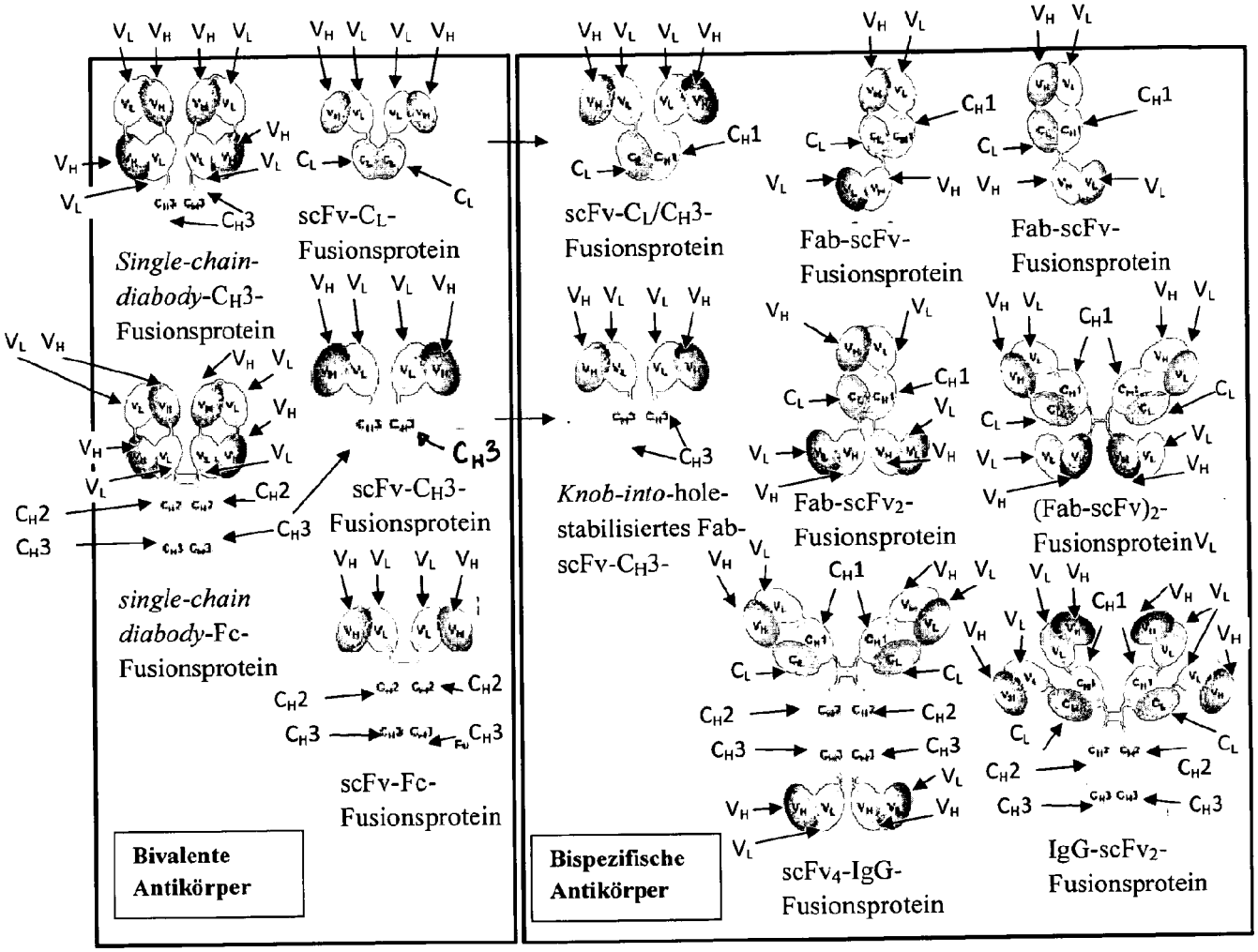

Single-chain-diabody-CH3-Fusionsprotein
scFv-CL-Fusionsprotein
scFv-CH3-Fusionsprotein
single-chain diabody-Fc-Fusionsprotein
scFv-Fc-Fusionsprotein
Bivalente Antikörper
scFv-CL/CH3-Fusionsprotein
Fab-scFv-Fusionsprotein
Fab-scFv-Fusionsprotein
Knob-into-hole-stabilisiertes Fab-scFv-CH3-
Fab-scFv2-Fusionsprotein
(Fab-scFv)2-Fusionsprotein
scFv4-IgG-Fusionsprotein
IgG-scFv2-Fusionsprotein
Bispezifische Antikörper

Fig. 2:

SEQ ID NO: 21

YRQSMNNFQGLRSFGCRFGTCTVQKLAHQIYQFTDKDKDNVAPRSKISPQGY-NH_2

SEQ ID NO: 22

YRQSMNQGSRSNGCRFGTCTFQKLAHQIYQLTDKDKDGMAPRNKISPQGY-NH_2

SEQ ID NO: 23

YRQSMNNFQGLRSFGCRFGTC

SEQ ID NO: 24

YRQSMNNFQGLRSFGCRFGTCTVQKLAHQIYQFTDKDKDNVA

SEQ ID NO: 25

PRSKISPQGY-NH2

SEQ ID NO: 26

YRQSMNNFQGLRSF

SEQ ID NO: 27

YRQSMNNFQG

SEQ ID NO: 28

YRQSMN

SEQ ID NO: 29

YRQSMNNFQGLRSFGCRFGTCTVQKLAHQIYQ

SEQ ID NO: 30

YRQSMNQGSRSNGCRFGTCTFQKLAHQIYQLTDKDKDGMA

SEQ ID NO: 31

YRQSMNQGSRSNGCRFGTCTFQKLAHQIYQL

Fig. 3 a:

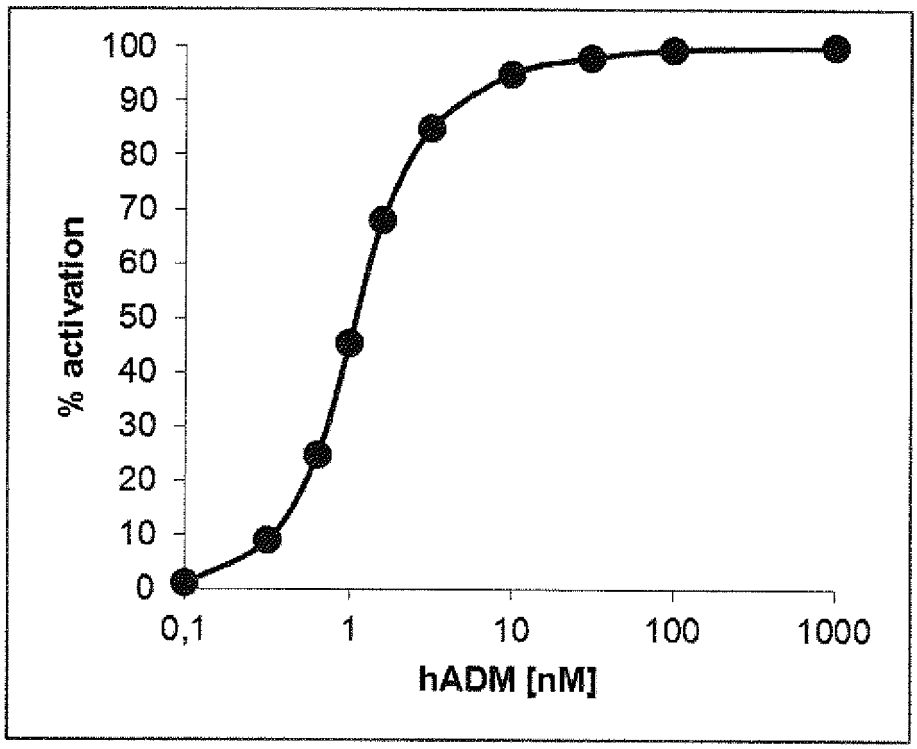


Fig. 3 b:

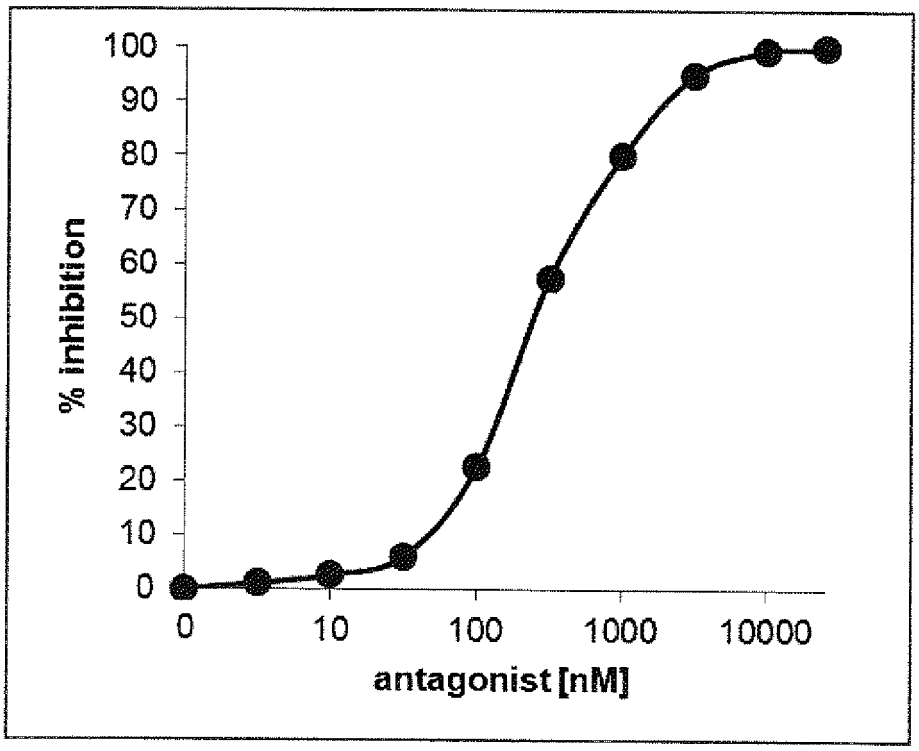

100
90
80
70
60
50
40
30
20
10
0
% inhibition
0
10
100
1000
10000
antagonist [nM]

Fig. 3 c:

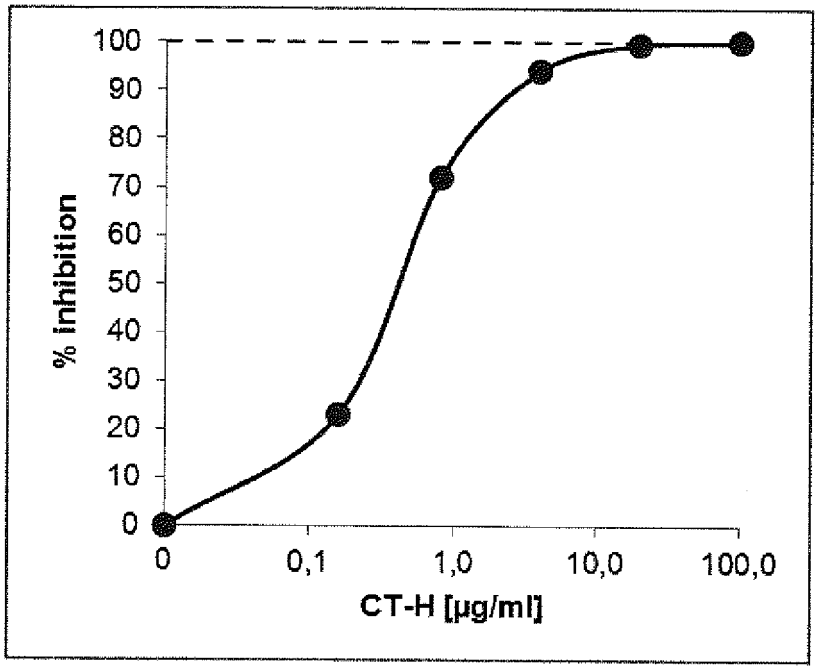

100
90
80
70
60
50
40
30
20
10
0
% inhibition
0
0,1
1,0
10,0
100,0
CT-H [µg/ml]

Fig. 3 d:

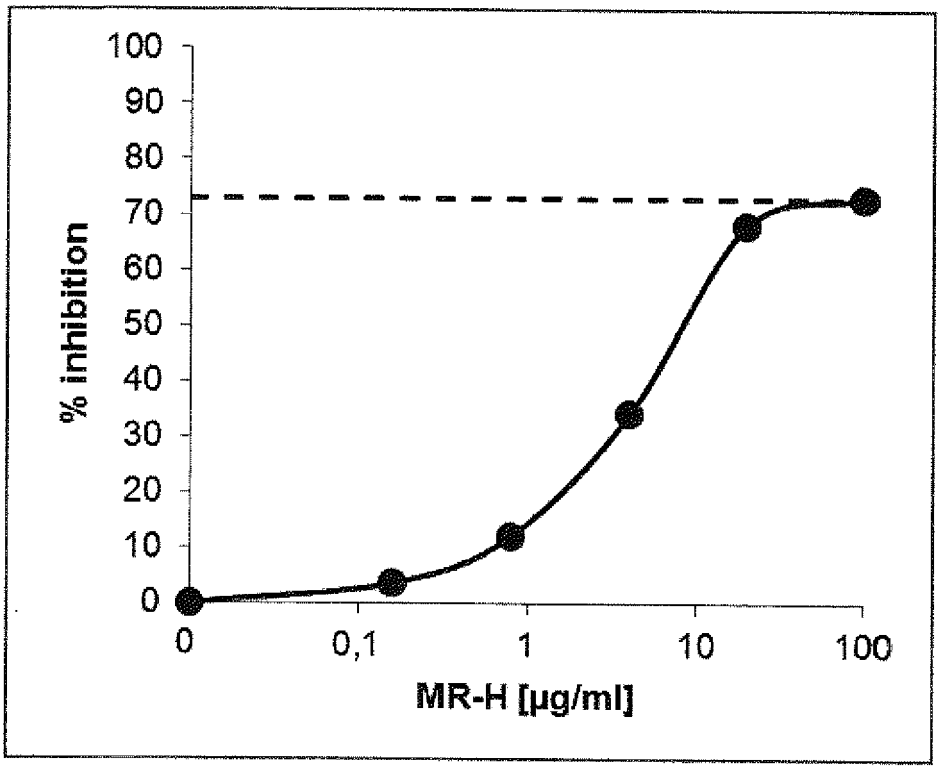

100
90
80
70
60
50
40
30
20
10
0
% inhibition
0
0,1
1
10
100
MR-H [µg/ml]

Fig. 3 e:

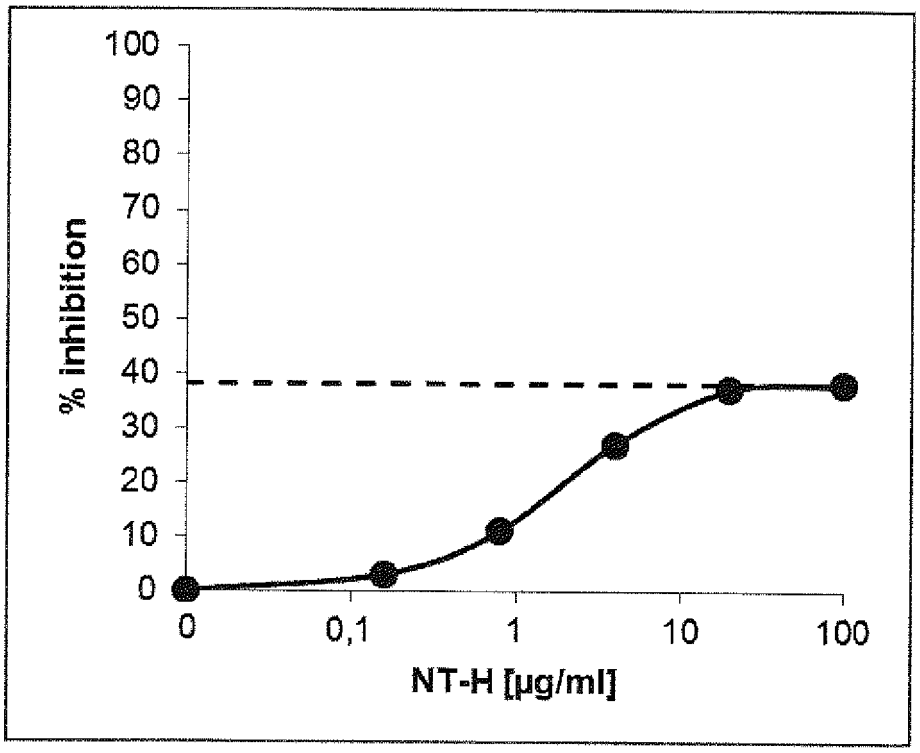

100
90
80
70
60
50
40
30
20
10
0
% inhibition
0
0,1
1
10
100
NT-H [µg/ml]

Fig. 3 f:

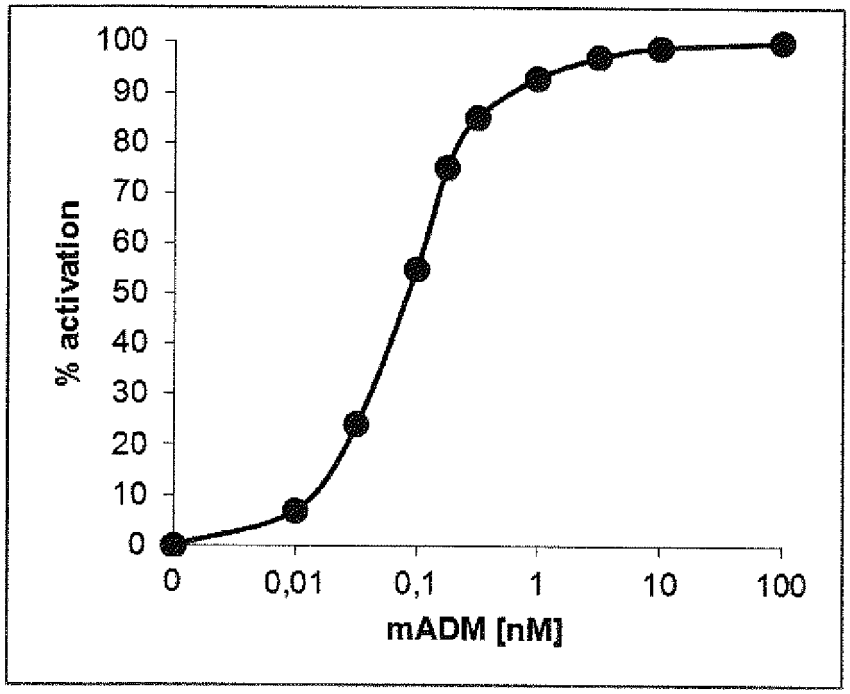

100
90
80
70
60
50
40
30
20
10
0
% activation
0
0,01
0,1
1
10
100
mADM [nM]

Fig. 3 g:

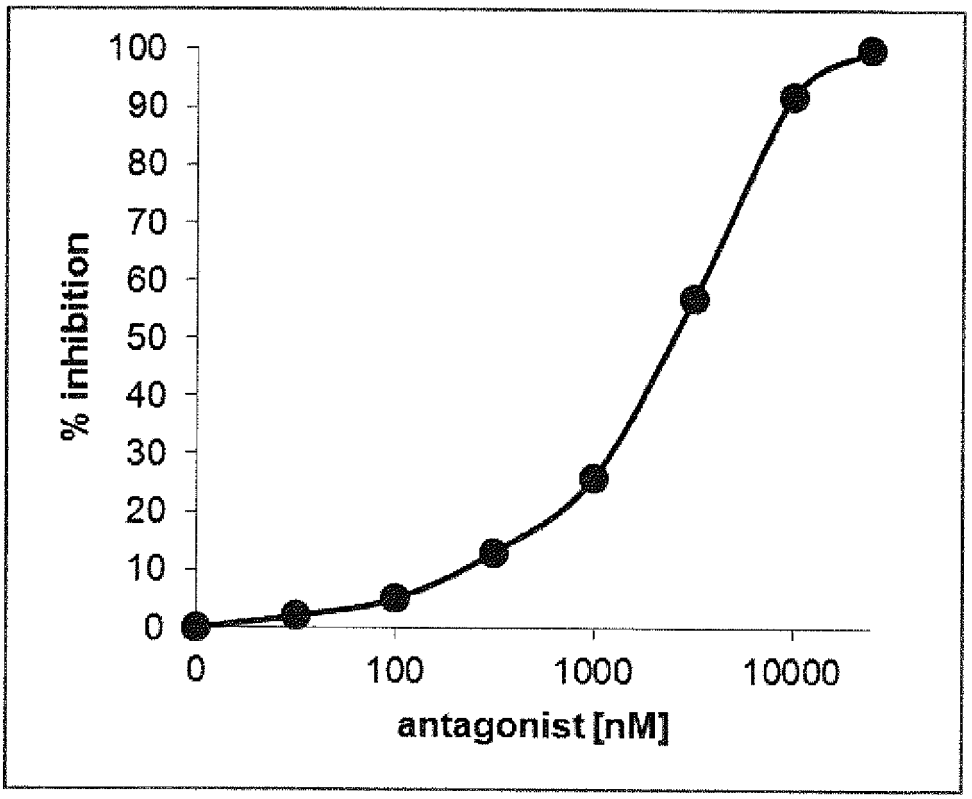

100
90
80
70
60
50
40
30
20
10
0
% inhibition
0
100
1000
10000
antagonist [nM]

Fig. 3 h:

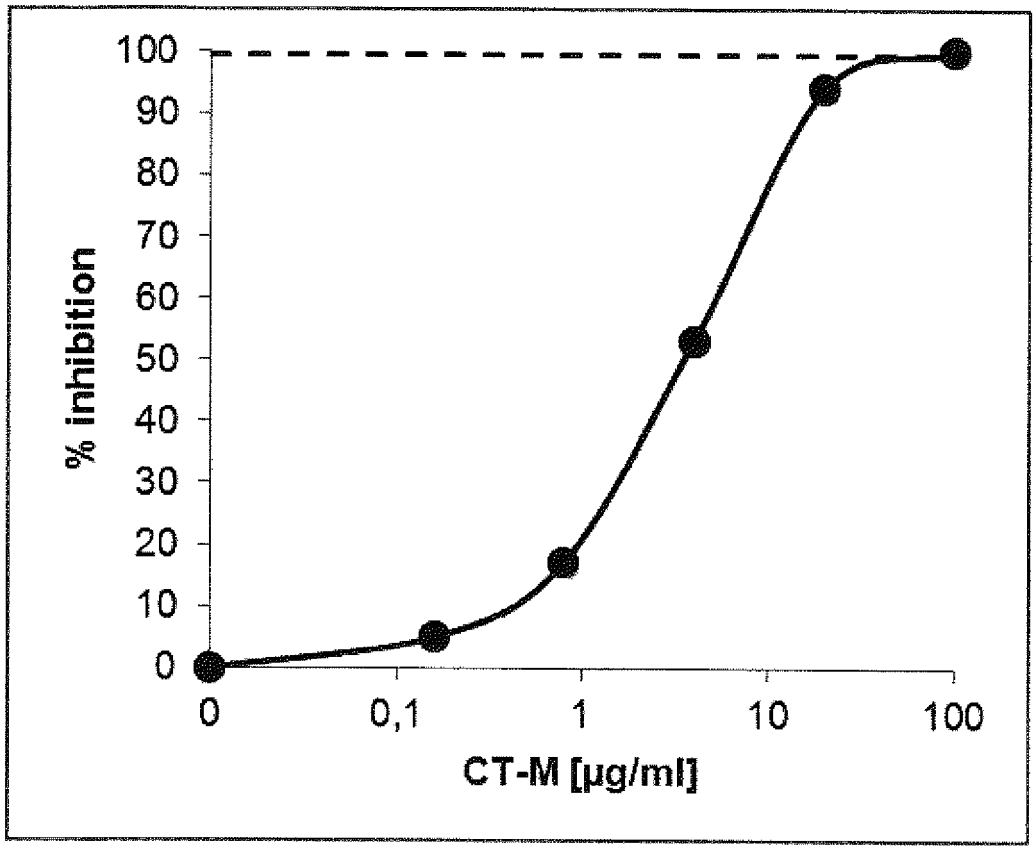

100
90
80
70
60
50
40
30
20
10
0
% inhibition
0
0,1
1
10
100
CT-M [µg/ml]

Fig. 3 i:

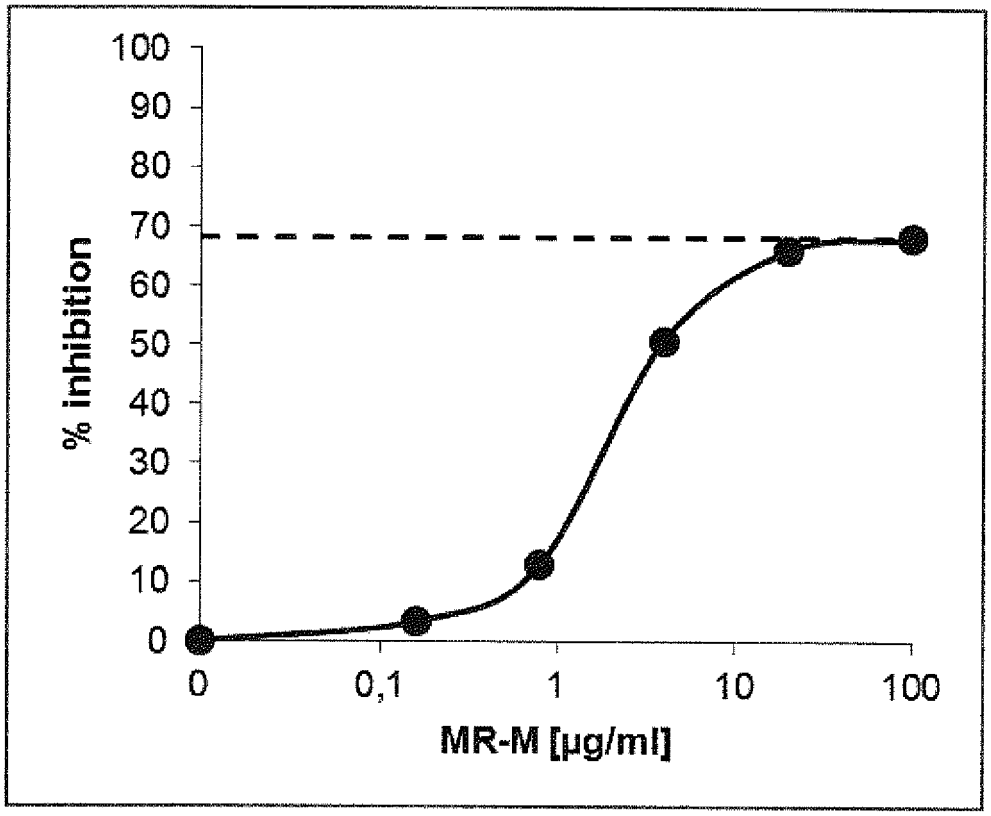

100
90
80
70
60
50
40
30
20
10
0
% inhibition
0
0,1
1
10
100
MR-M [µg/ml]

Fig. 3 j:

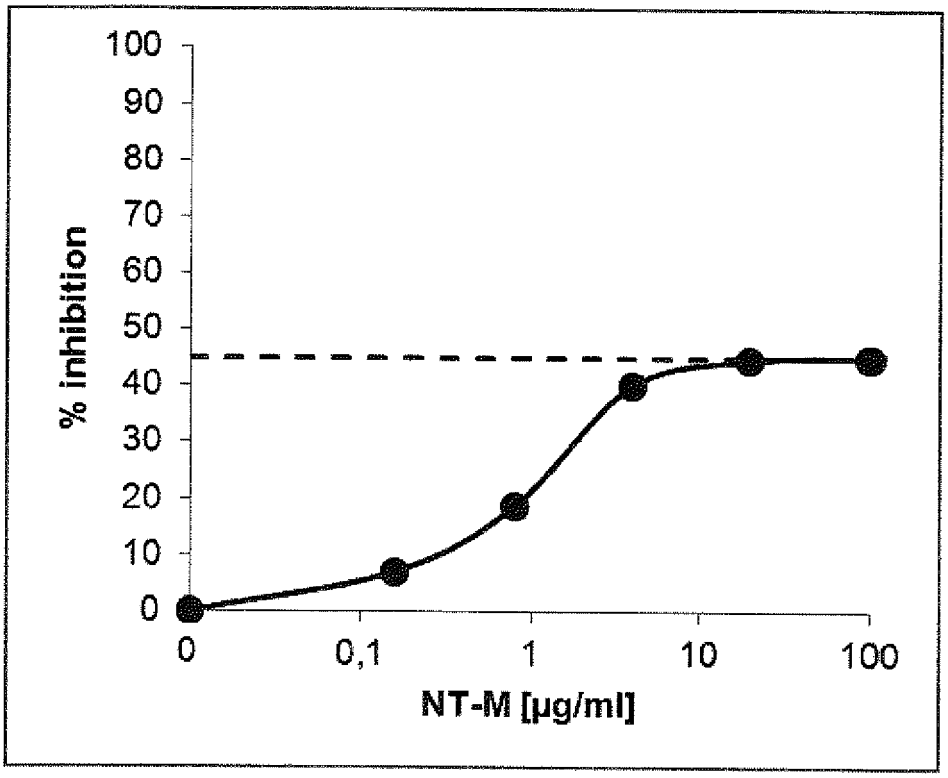

100
90
80
70
60
50
40
30
20
10
0
% inhibition
0
0,1
1
10
100
NT-M [µg/ml]

Fig. 3 k:

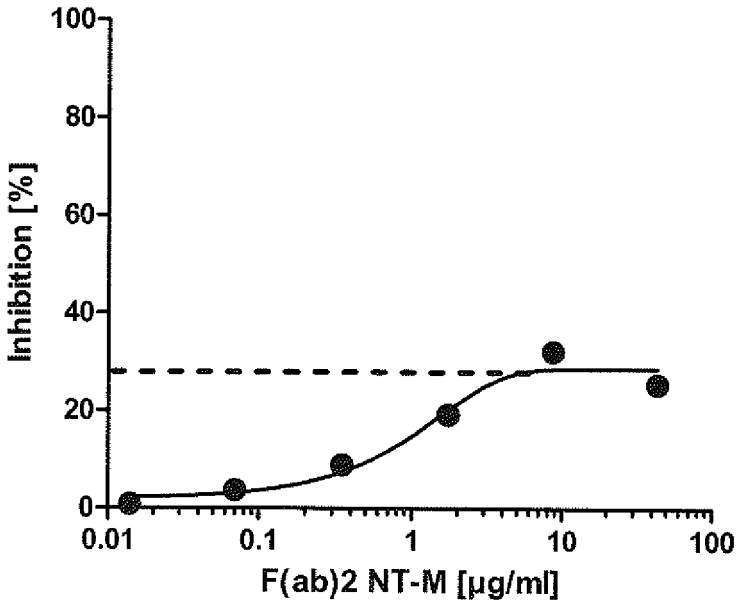

100
80
60
40
20
0
Inhibition [%]
0.01
0.1
1
10
100
F(ab)2 NT-M [µg/ml]

Fig. 3 l:

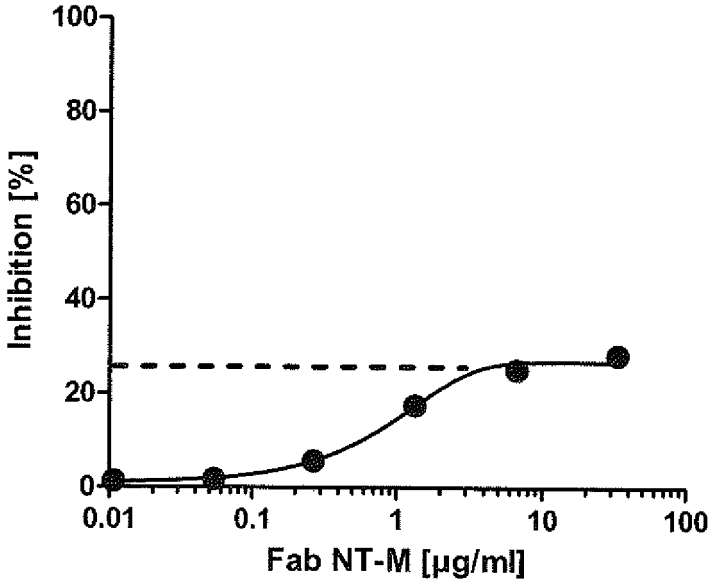

100
80
60
40
20
0
Inhibition [%]
0.01
0.1
1
10
100
Fab NT-M [µg/ml]

Fig. 4:

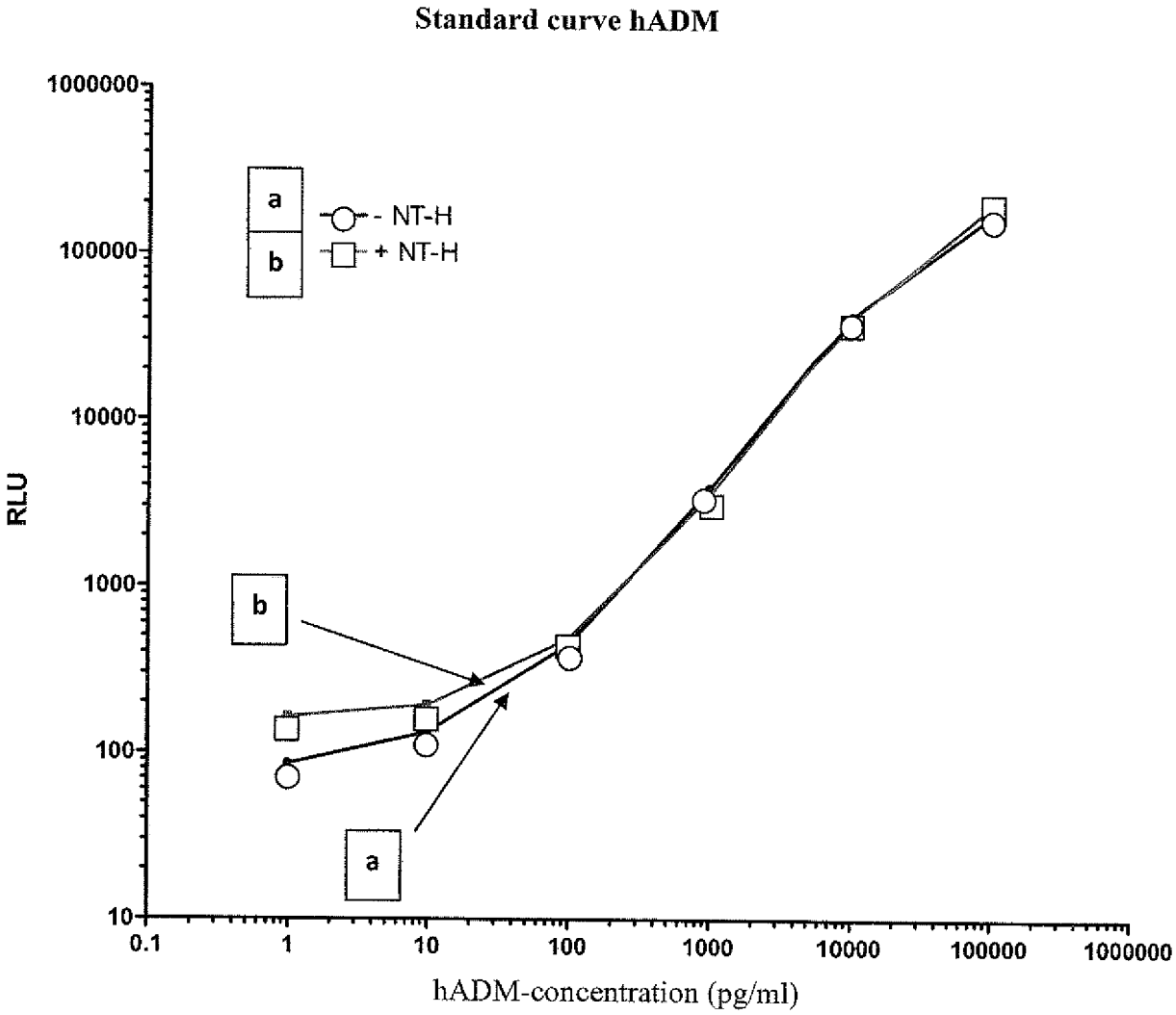

Standard curve hADM
RLU
1000000
100000
10000
1000
100
10
a
b
- NT-H
+ NT-H
b
a
0.1
1
10
100
1000
10000
100000
1000000
hADM-concentration (pg/ml)

Fig. 5:

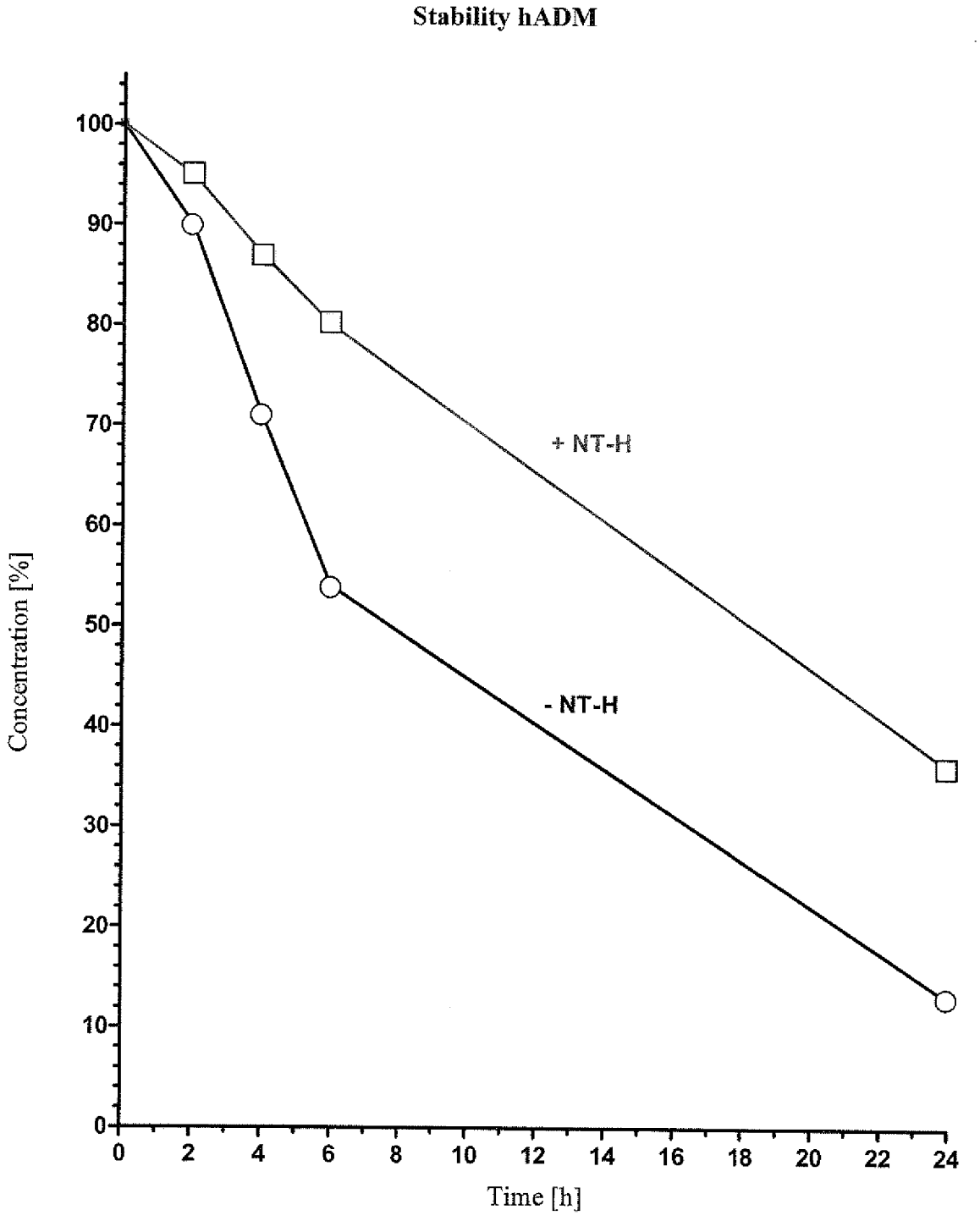

Stability hADM
Concentration [%]
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18
20
22
24
Time [h]
+ NT-H
- NT-H

Fig 6:

IGHV1-69*11:
QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGRIIPILGT
ANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARYYYYYGMDVWGQGT
TVTVSS
HB3:
QVQLQQSGAELMKPGASVKISCKATGYTFSRYWIEWVKQRPGHGLEWIGEILPGSGS
TNYNEKFKGKATITADTSSNTAYMQLSSLTSEDSAVYYCTEGYEYDGFDYWGQGTT
LTVSS

Alignment (ClustalW2): Identical amino acids are illustrated by stars; points indicate conservative changes.

```
IGHV1:

        QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGRIIPILGTANYAQKFQGR
        VTITADESTSTAYMELSSLRSEDTAVYYCARYYYYYGMDVWGQGTTVTVSS

HB3:

        QVQLQQSGAELMKPGASVKISCKATGYTFSRYWIEWVKQRPGHGLEWIGEILPGSGSTNYNEKFKGK
        ATITADTSSNTAYMQLSSLTSEDSAVYYCTEGYEYDGFDYWGQGTTLTVSS

        **** *****: ***:***:****:* *** * *.**:* **:****:*.*:*  *::** :**:*:
        .***** *:.****:**** ***:*****:. * * *:* ******:****
```

Fig. 7

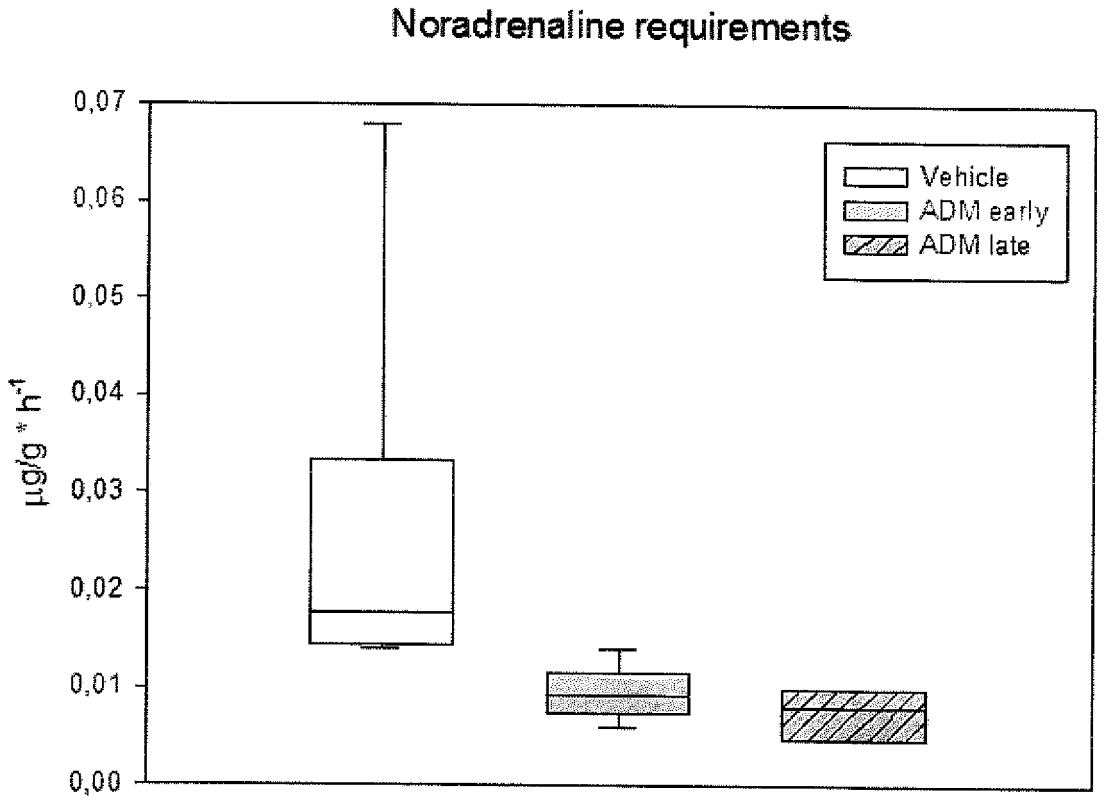

Noradrenaline requirements
0,07
0,06
0,05
0,04
0,03
0,02
0,01
0,00
µg/g * h-1
Vehicle
ADM early
ADM late

Fig. 8

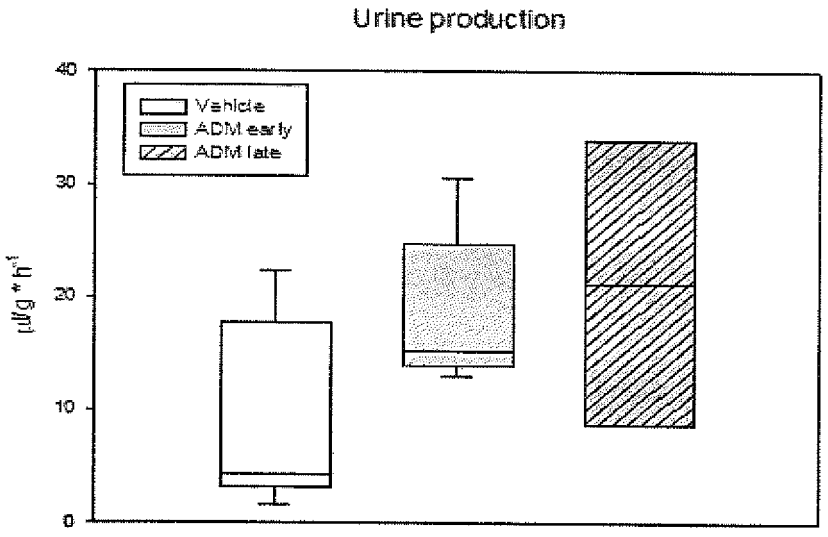

Urine production
40
30
20
10
0
µl/g * h-1
Vehicle
ADM early
ADM late

Fig. 9

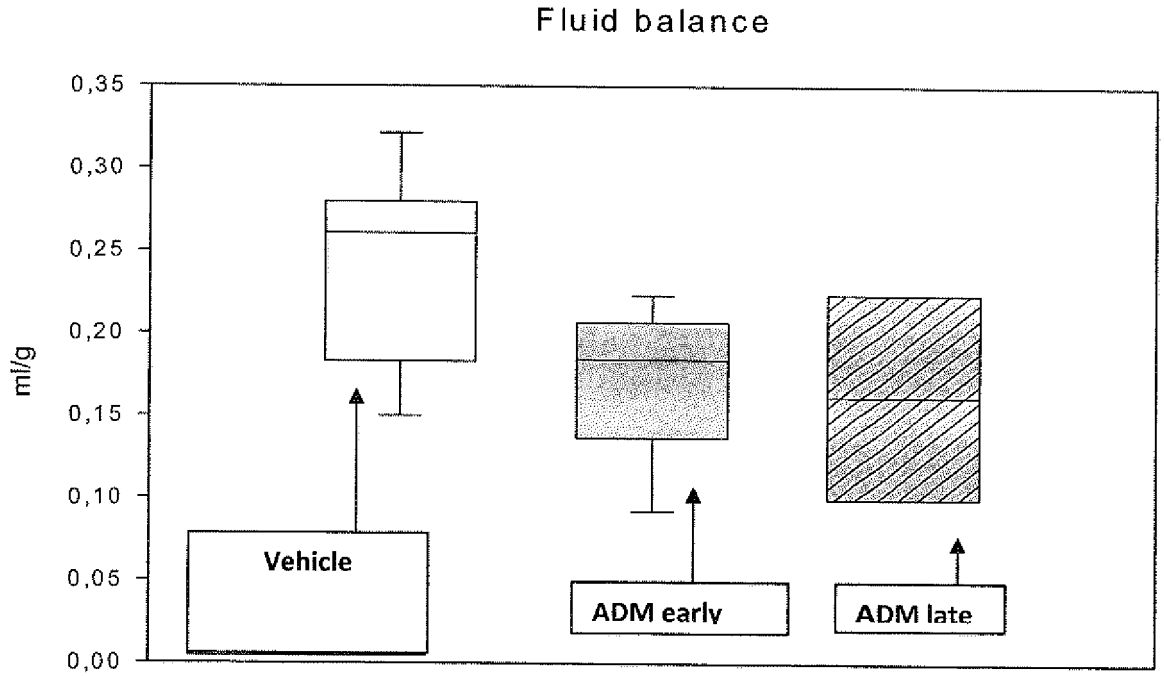

Fluid balance
0,35
0,30
0,25
0,20
0,15
0,10
0,05
0,00
ml/g
Vehicle
ADM early
ADM late

Fig. 10

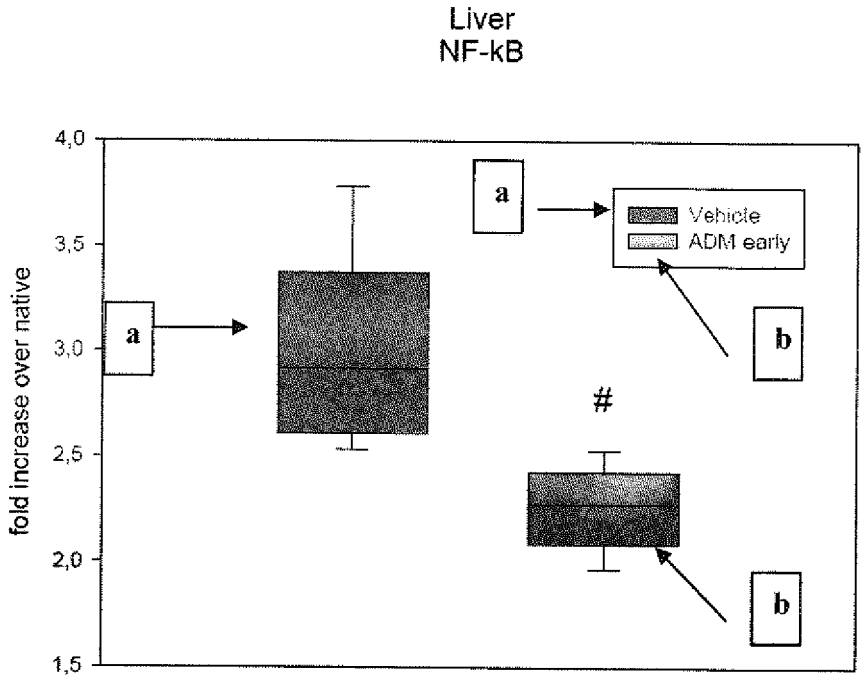

Liver
NF-kB
4,0
3,5
3,0
2,5
2,0
1,5
fold increase over native
a
a
Vehicle
ADM early
b
#
b

Fig. 11:

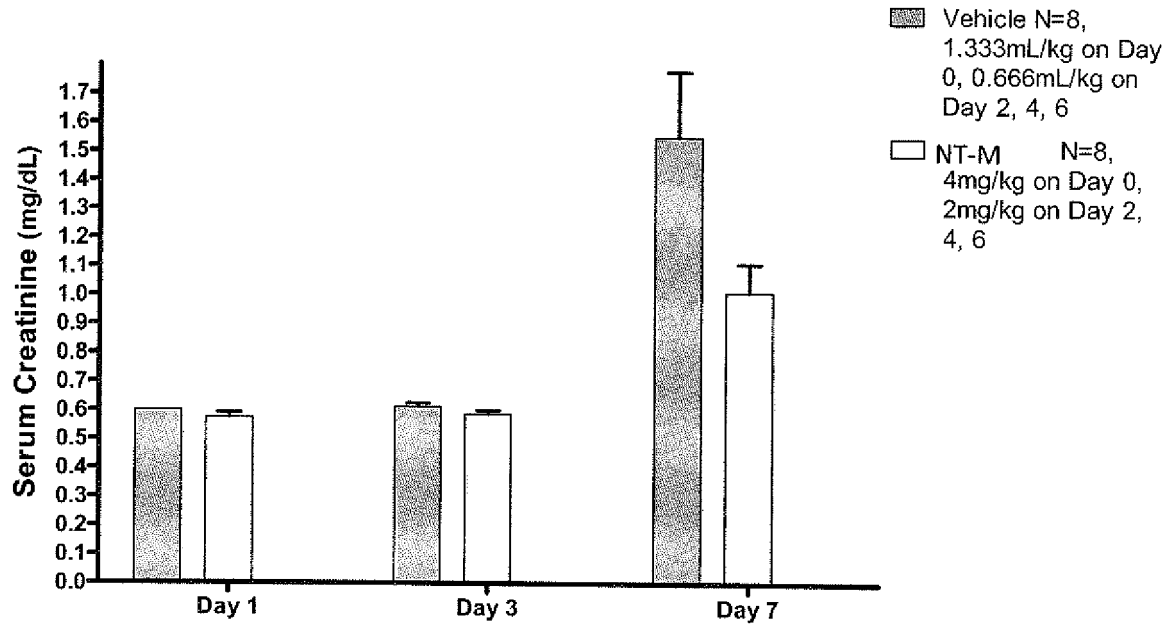


Fig. 12:

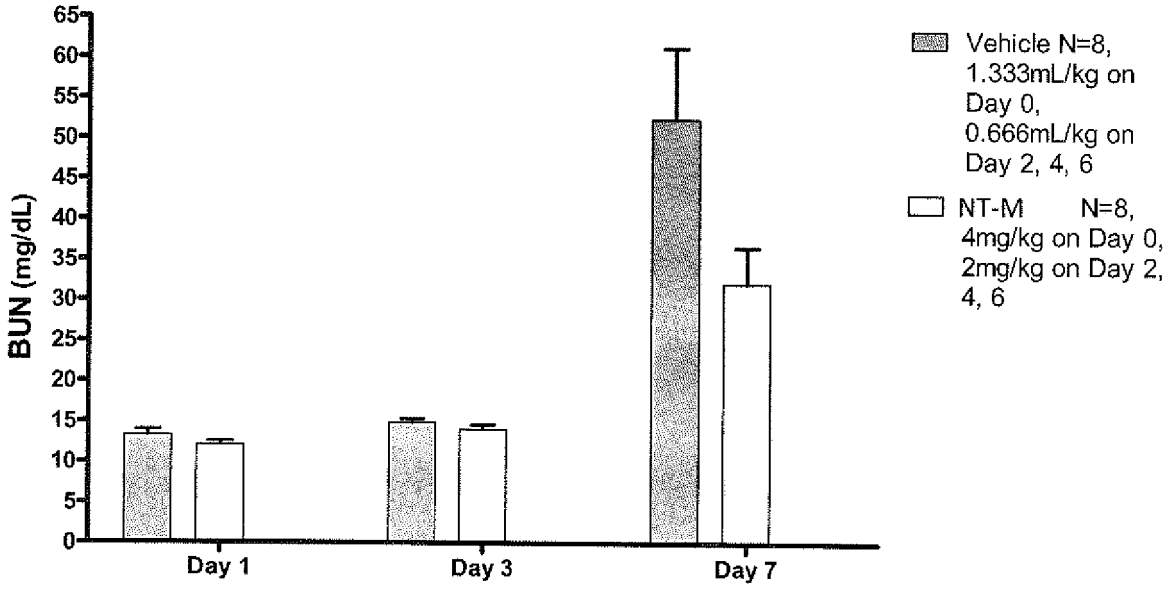


Fig. 13:

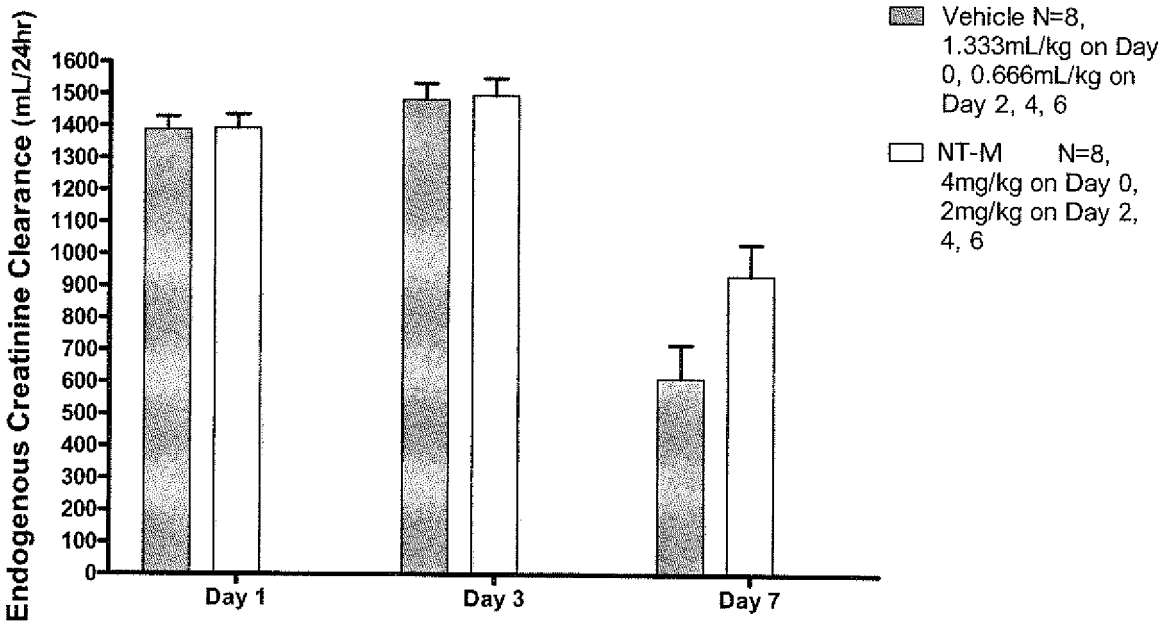

Endogenous Creatinine Clearance (mL/24hr)
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
Day 1
Day 3
Day 7
Vehicle N=8, 1.333mL/kg on Day 0, 0.666mL/kg on Day 2, 4, 6
NT-M N=8, 4mg/kg on Day 0, 2mg/kg on Day 2, 4, 6

Fig. 14:

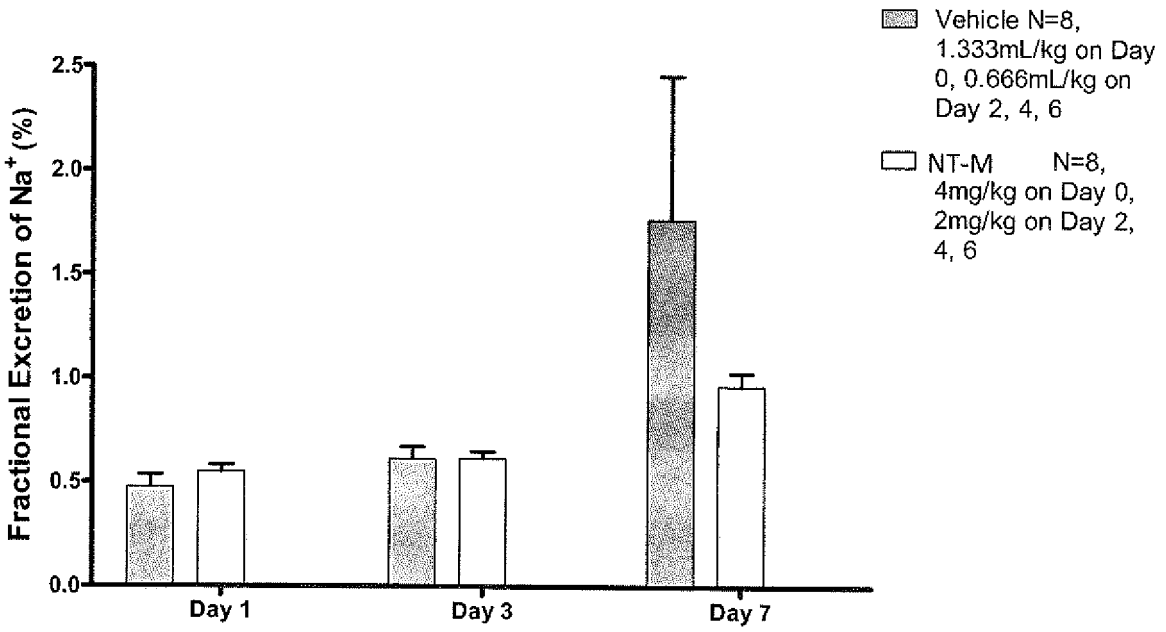

Fractional Excretion of Na+ (%)
2.5
2.0
1.5
1.0
0.5
0.0
Day 1
Day 3
Day 7
Vehicle N=8, 1.333mL/kg on Day 0, 0.666mL/kg on Day 2, 4, 6
NT-M N=8, 4mg/kg on Day 0, 2mg/kg on Day 2, 4, 6

Fig. 15:

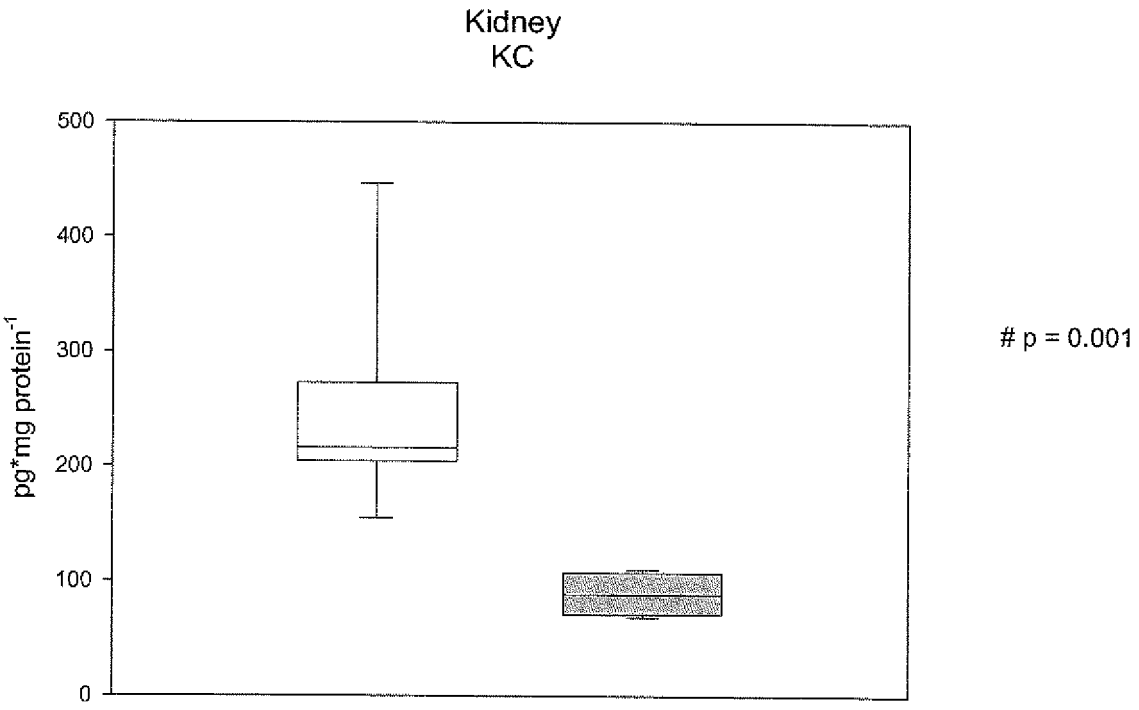


Fig. 16:

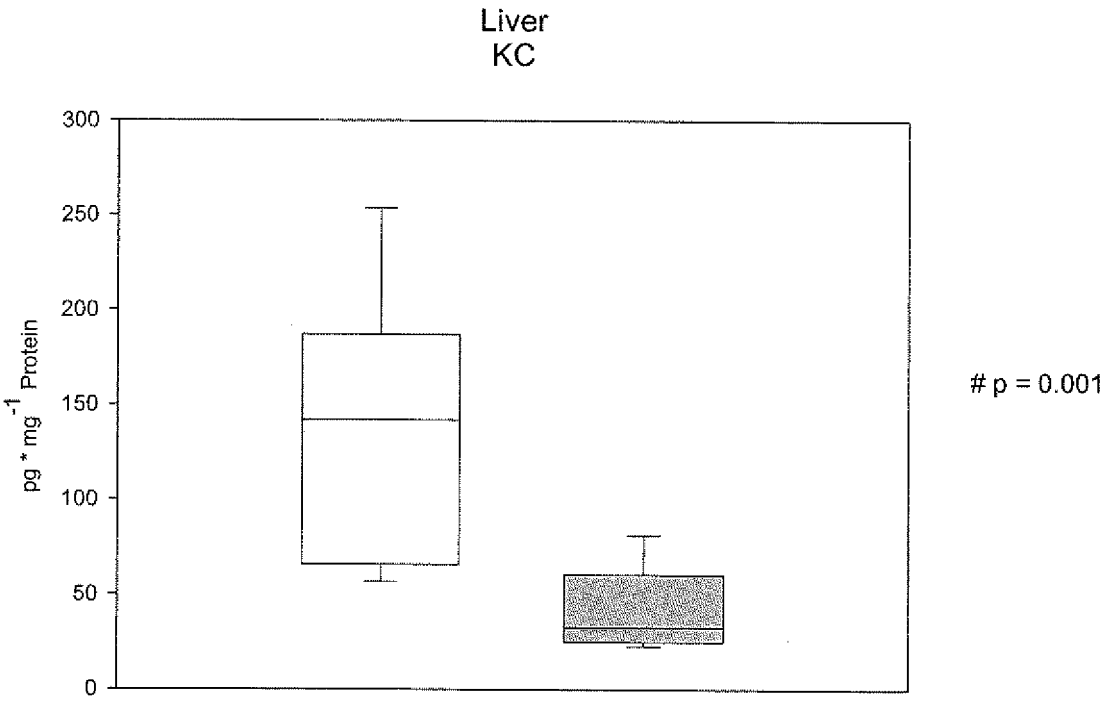


Fig. 17:

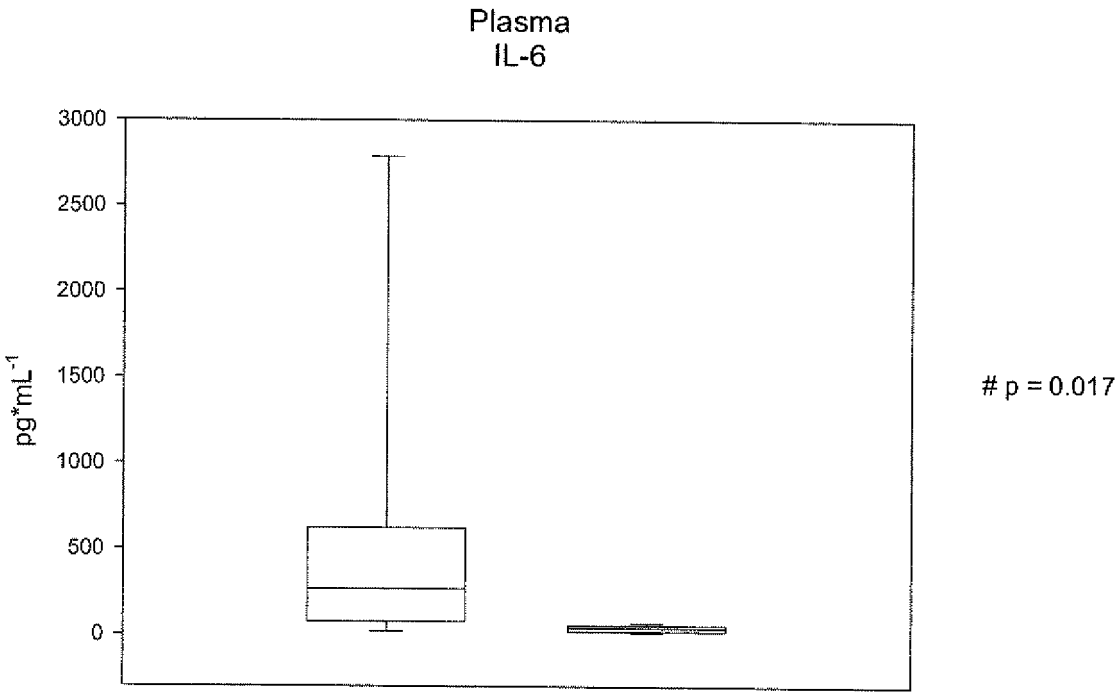


Fig. 18:

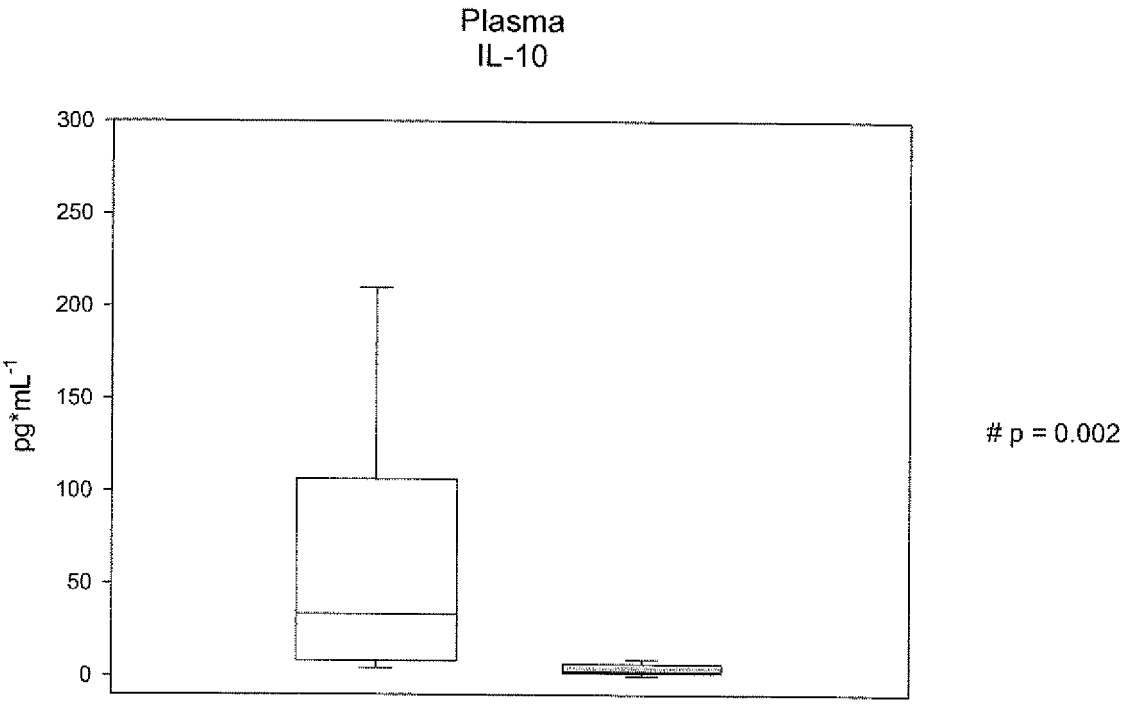


Fig. 19:

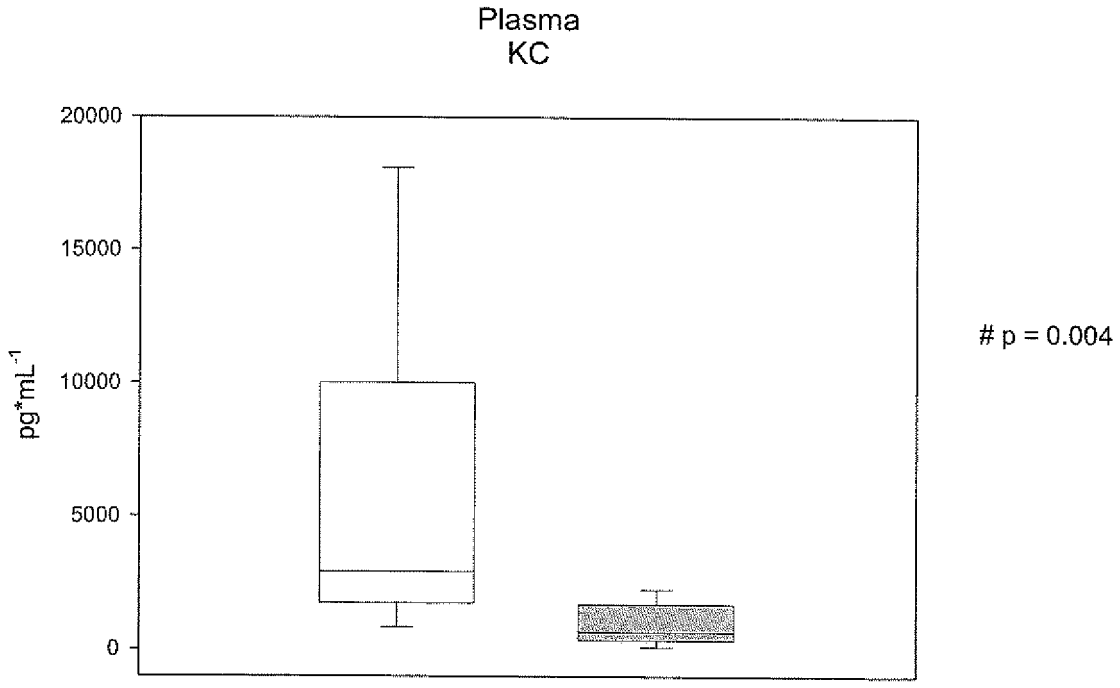

Plasma
KC
20000
15000
10000
5000
0
pg*mL-1
p = 0.004

Fig. 20:

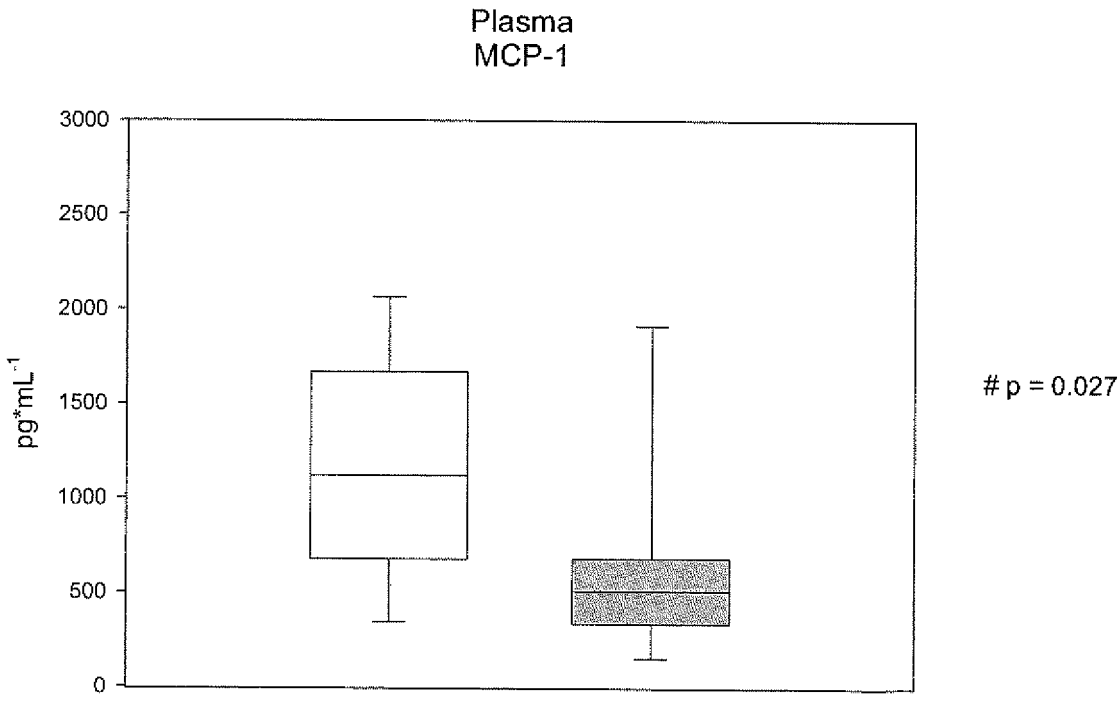

Plasma
MCP-1
3000
2500
2000
1500
1000
500
0
pg*mL-1
p = 0.027

Fig. 21:

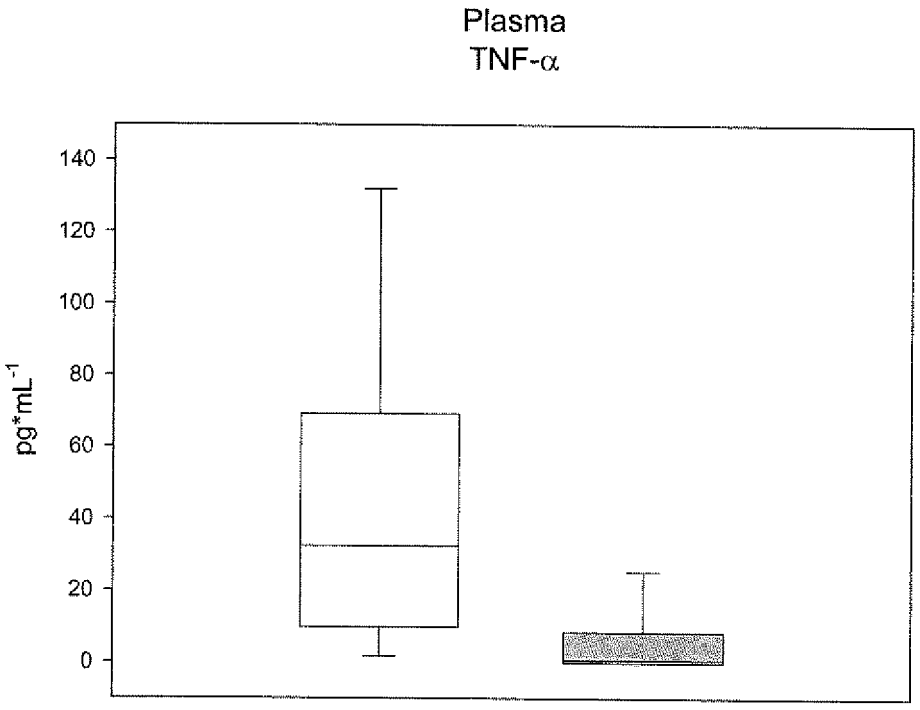


Fig. 22:

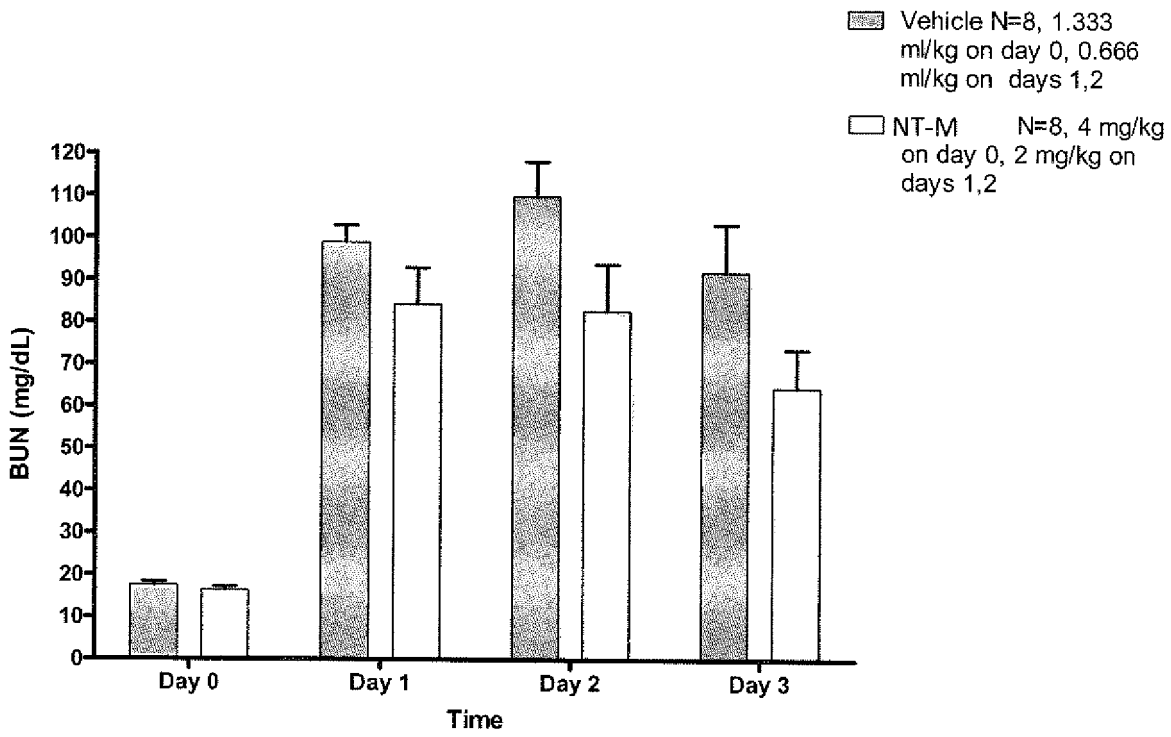

Vehicle N=8, 1.333 ml/kg on day 0, 0.666 ml/kg on days 1,2
NT-M N=8, 4 mg/kg on day 0, 2 mg/kg on days 1,2
BUN (mg/dL)
120
110
100
90
80
70
60
50
40
30
20
10
0
Day 0
Day 1
Day 2
Day 3
Time

Fig. 23:

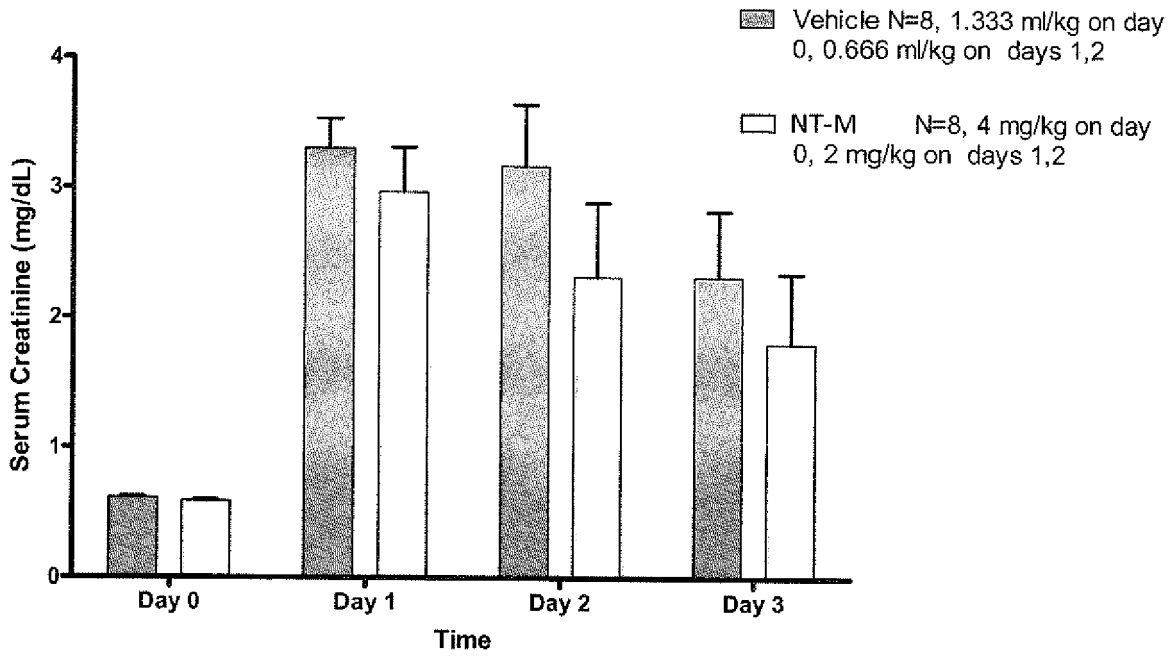
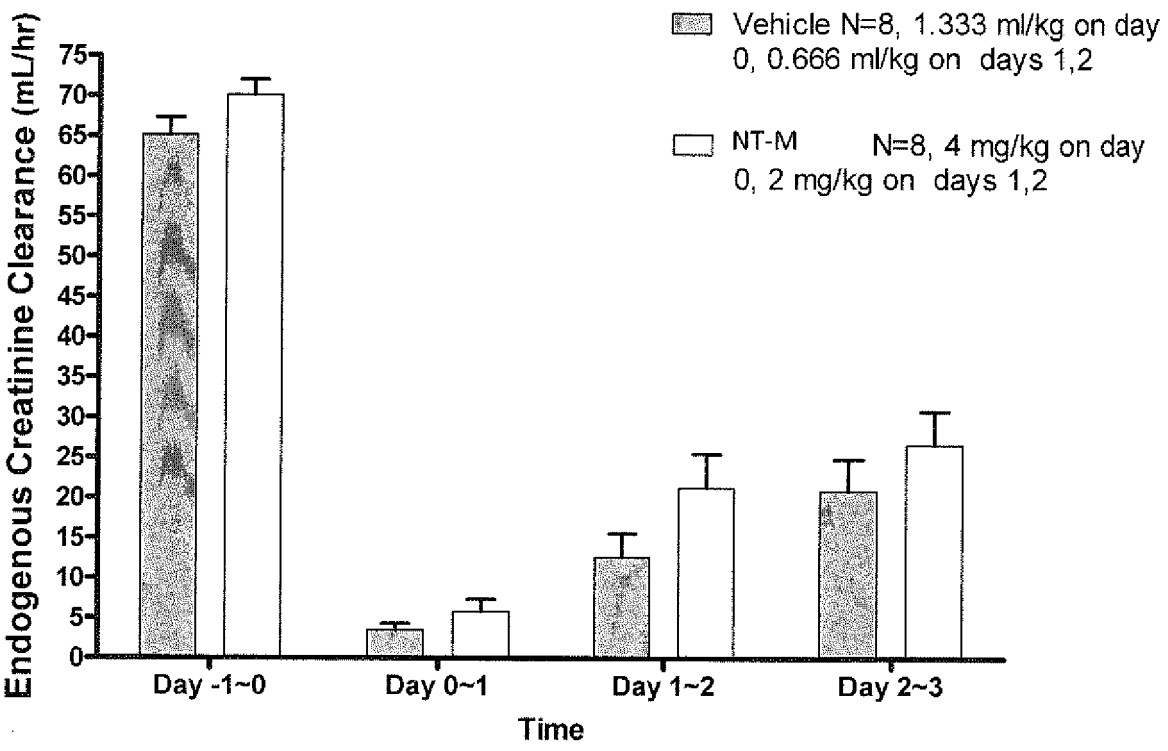

Vehicle N=8, 1.333 ml/kg on day 0, 0.666 ml/kg on days 1,2
NT-M N=8, 4 mg/kg on day 0, 2 mg/kg on days 1,2
Serum Creatinine (mg/dL)
4
3
2
1
0
Day 0
Day 1
Day 2
Day 3
Time

Fig. 24:


Vehicle N=8, 1.333 ml/kg on day 0, 0.666 ml/kg on days 1,2
NT-M N=8, 4 mg/kg on day 0, 2 mg/kg on days 1,2
Endogenous Creatinine Clearance (mL/hr)
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
Day -1~0
Day 0~1
Day 1~2
Day 2~3
Time