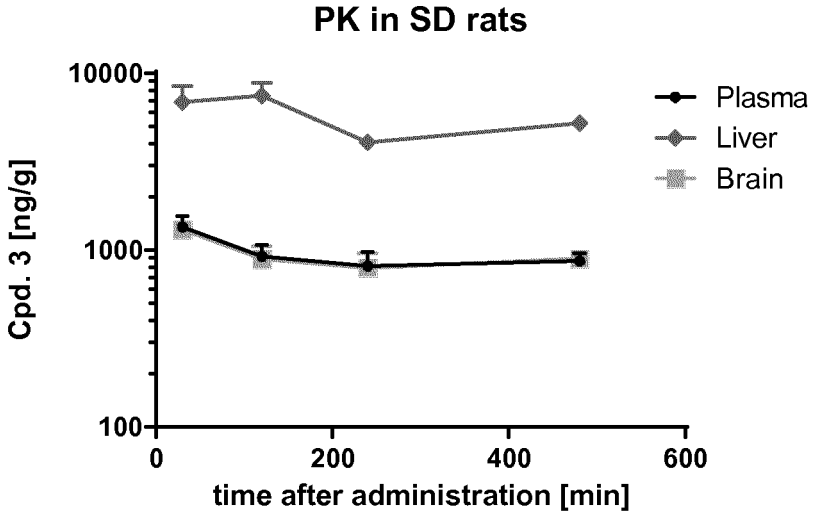
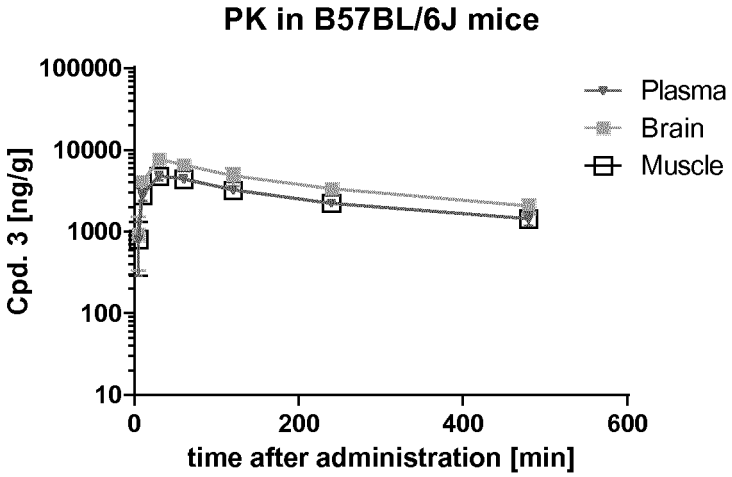

PK in SD rats
10000
1000
100
Cpd. 3 [ng/g]
0
200
400
600
time after administration [min]
Plasma
Liver
Brain

FIG. 1A


PK in B57BL/6J mice
Cpd. 3 [ng/g]
100000
10000
1000
100
10
0
200
400
600
time after administration [min]
Plasma
Brain
Muscle

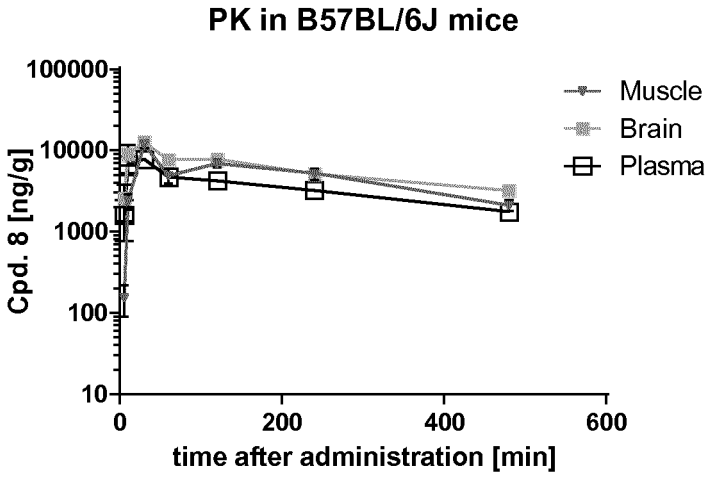

PK in B57BL/6J mice
Cpd. 8 [ng/g]
100000
10000
1000
100
10
0
200
400
600
time after administration [min]
Muscle
Brain
Plasma

FIG. 1B

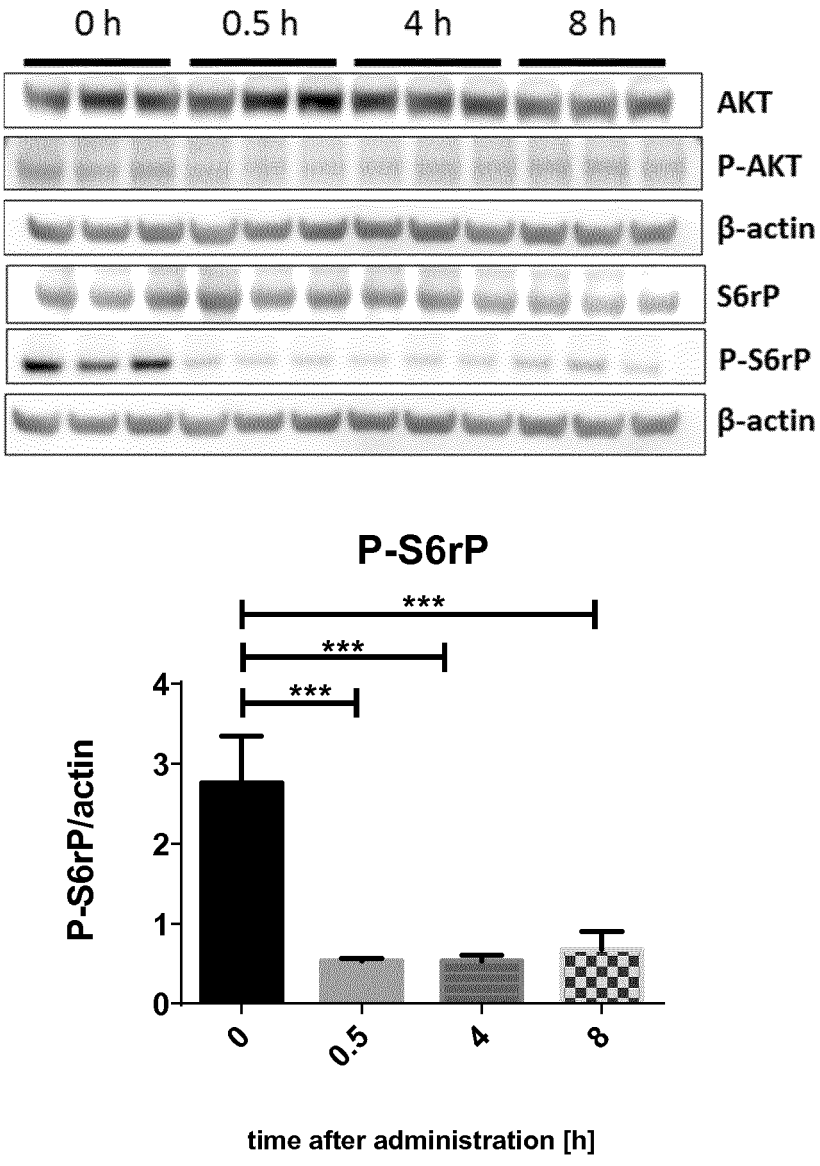

0 h
0.5 h
4 h
8 h
AKT
P-AKT
β-actin
S6rP
P-S6rP
β-actin
P-S6rP
***
***
***
P-S6rP/actin
4
3
2
1
0
0
0.5
4
8
time after administration [h]

FIG. 2A

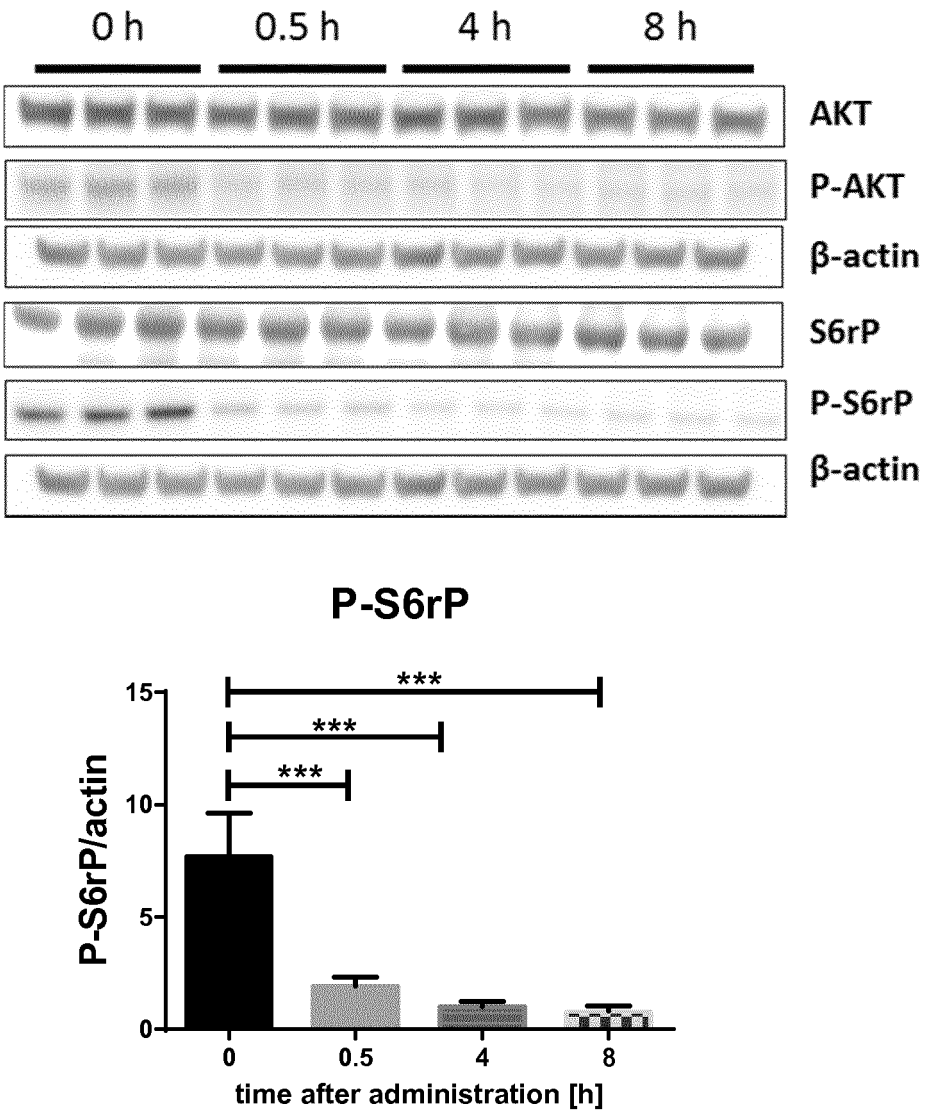

0 h
0.5 h
4 h
8 h
AKT
P-AKT
β-actin
S6rP
P-S6rP
β-actin
P-S6rP
***
***
***
15
10
5
0
P-S6rP/actin
0
0.5
4
8
time after administration [h]

FIG. 2B

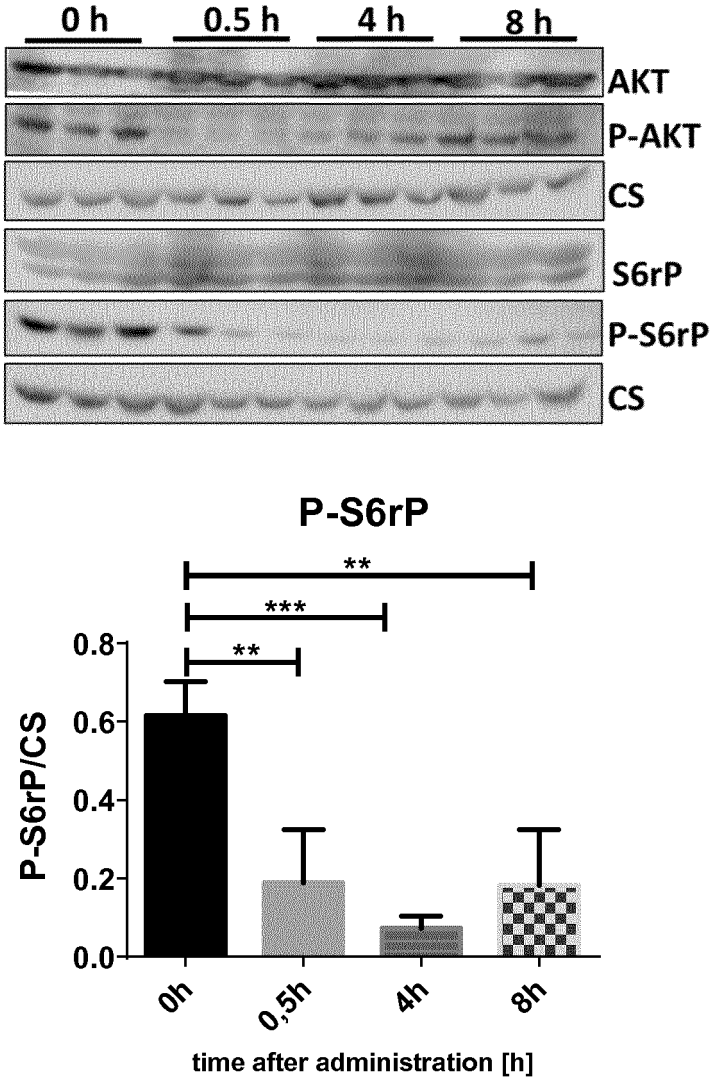

0 h
0.5 h
4 h
8 h
AKT
P-AKT
CS
S6rP
P-S6rP
CS
P-S6rP
**
***
**
P-S6rP/CS
0.8
0.6
0.4
0.2
0.0
0h
0,5h
4h
8h
time after administration [h]

FIG. 2C

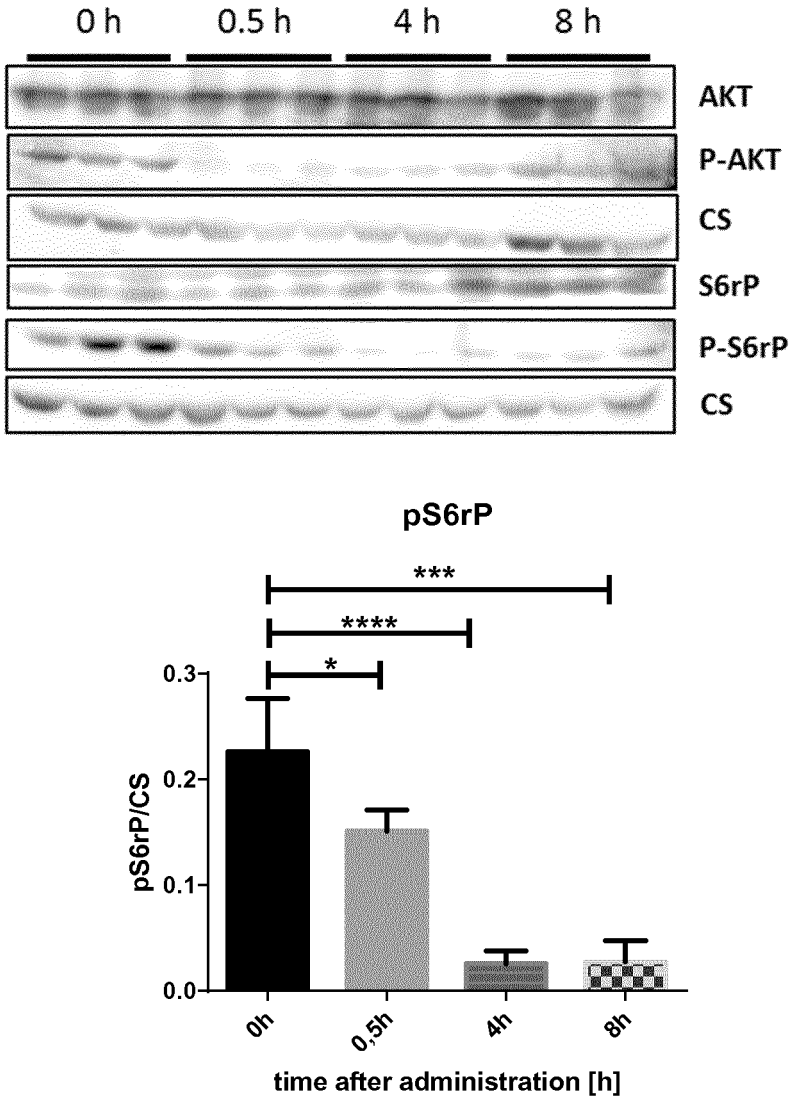

0 h
0.5 h
4 h
8 h
AKT
P-AKT
CS
S6rP
P-S6rP
CS
pS6rP
***
****
*
0.3
0.2
0.1
0.0
pS6rP/CS
0h
0,5h
4h
8h
time after administration [h]

FIG. 2D

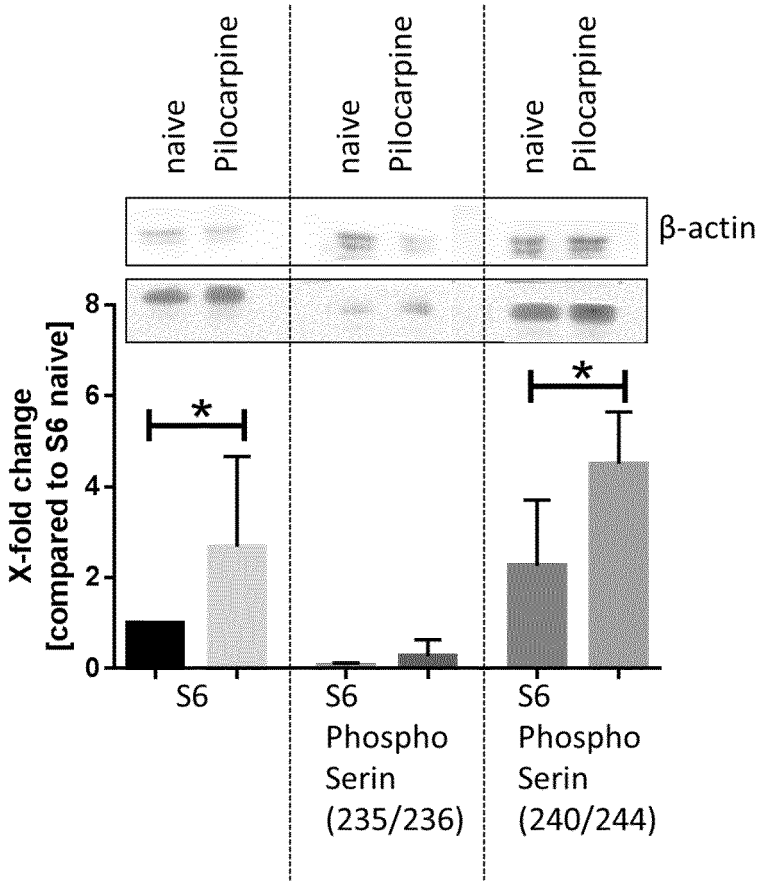

naive
Pilocarpine
naive
Pilocarpine
naive
Pilocarpine
β-actin
X-fold change
[compared to S6 naive]
8
6
4
2
0
*
*
S6
S6
Phospho
Serin
(235/236)
S6
Phospho
Serin
(240/244)

FIG. 3A

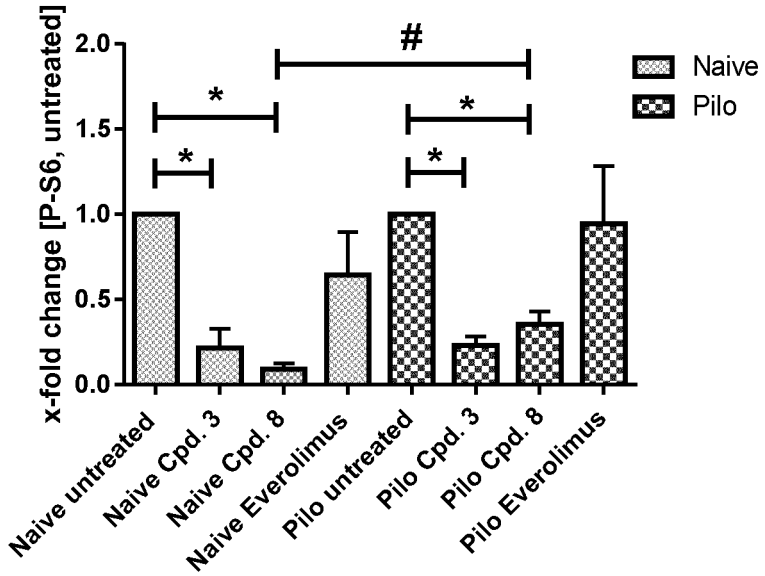

x-fold change [P-S6, untreated]
2.0
1.5
1.0
0.5
0.0
*
*
*
*
#
Naive
Pilo
Naive untreated
Naive Cpd. 3
Naive Cpd. 8
Naive Everolimus
Pilo untreated
Pilo Cpd. 3
Pilo Cpd. 8
Pilo Everolimus

FIG. 3B

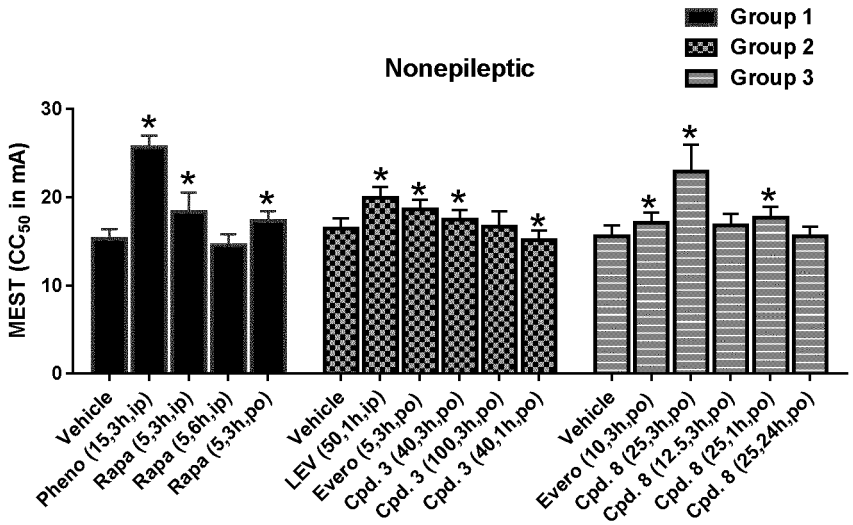

Nonepileptic
Group 1
Group 2
Group 3
MEST (CC50 in mA)
30
20
10
0
Vehicle
Pheno (15,3h,ip)
Rapa (5,3h,ip)
Rapa (5,6h,ip)
Rapa (5,3h,po)
Vehicle
LEV (50,1h,ip)
Evero (5,3h,po)
Cpd. 3 (40,3h,po)
Cpd. 3 (100,3h,po)
Cpd. 3 (40,1h,po)
Vehicle
Evero (10,3h,po)
Cpd. 8 (25,3h,po)
Cpd. 8 (12.5,3h,po)
Cpd. 8 (25,1h,po)
Cpd. 8 (25,24h,po)

FIG. 4A

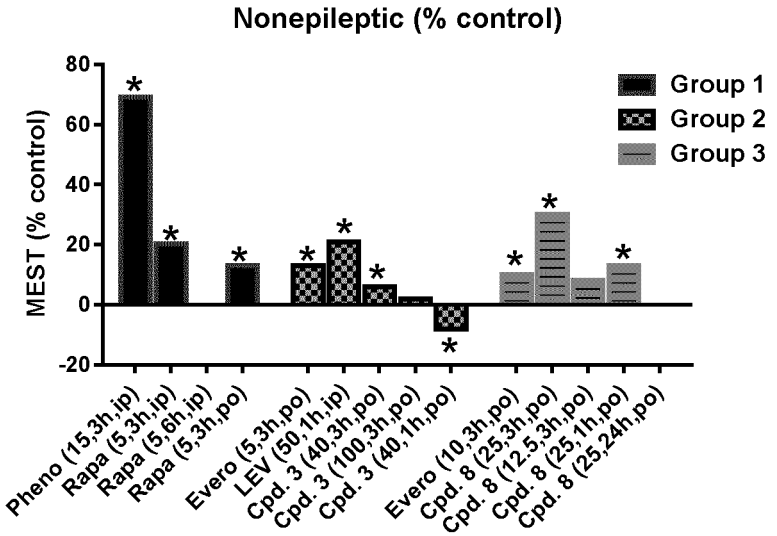

Nonepileptic (% control)
Group 1
Group 2
Group 3
MEST (% control)
80
60
40
20
0
-20
Pheno (15,3h,ip)
Rapa (5,3h,ip)
Rapa (5,6h,ip)
Rapa (5,3h,po)
Evero (5,3h,po)
LEV (50,1h,ip)
Cpd. 3 (40,3h,po)
Cpd. 3 (100,3h,po)
Cpd. 3 (40,1h,po)
Evero (10,3h,po)
Cpd. 8 (25,3h,po)
Cpd. 8 (12.5,3h,po)
Cpd. 8 (25,1h,po)
Cpd. 8 (25,24h,po)

FIG. 4B

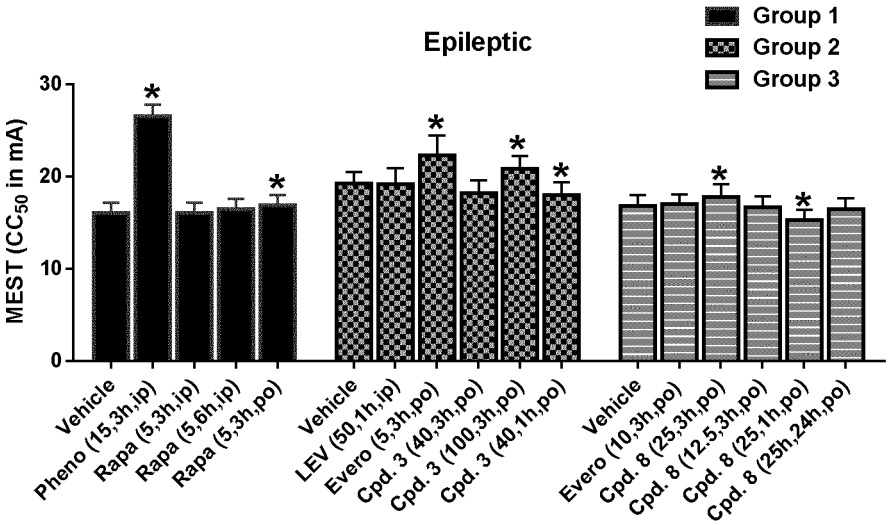

Epileptic
Group 1
Group 2
Group 3
MEST (CC50 in mA)
30
20
10
0
Vehicle
Pheno (15,3h,ip)
Rapa (5,3h,ip)
Rapa (5,6h,ip)
Rapa (5,3h,po)
Vehicle
LEV (50,1h,ip)
Evero (5,3h,po)
Cpd. 3 (40,3h,po)
Cpd. 3 (100,3h,po)
Cpd. 3 (40,1h,po)
Vehicle
Evero (10,3h,po)
Cpd. 8 (25,3h,po)
Cpd. 8 (12.5,3h,po)
Cpd. 8 (25,1h,po)
Cpd. 8 (25h,24h,po)

FIG. 4C

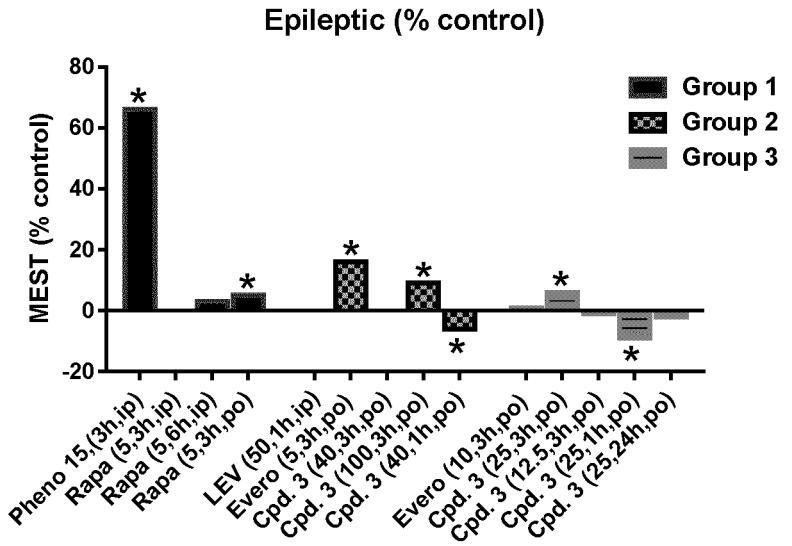

Epileptic (% control)
Group 1
Group 2
Group 3
MEST (% control)
80
60
40
20
0
-20
Pheno 15,(3h,ip)
Rapa (5,3h,ip)
Rapa (5,6h,ip)
Rapa (5,3h,po)
LEV (50,1h,ip)
Evero (5,3h,po)
Cpd. 3 (40,3h,po)
Cpd. 3 (100,3h,po)
Cpd. 3 (40,1h,po)
Evero (10,3h,po)
Cpd. 3 (25,3h,po)
Cpd. 3 (12.5,3h,po)
Cpd. 3 (25,1h,po)
Cpd. 3 (25,24h,po)

FIG. 4D

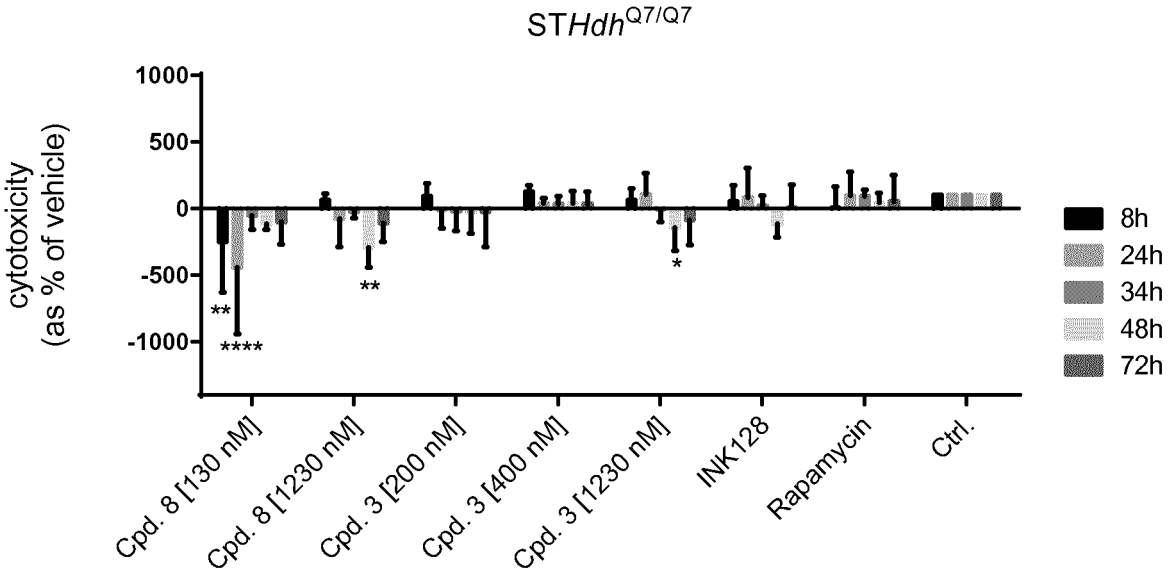

STHdh^Q7/Q7
cytotoxicity (as % of vehicle)
1000
500
0
-500
-1000
**
****
**
*
8h
24h
34h
48h
72h
Cpd. 8 [130 nM]
Cpd. 8 [1230 nM]
Cpd. 3 [200 nM]
Cpd. 3 [400 nM]
Cpd. 3 [1230 nM]
INK128
Rapamycin
Ctrl.

FIG. 5A

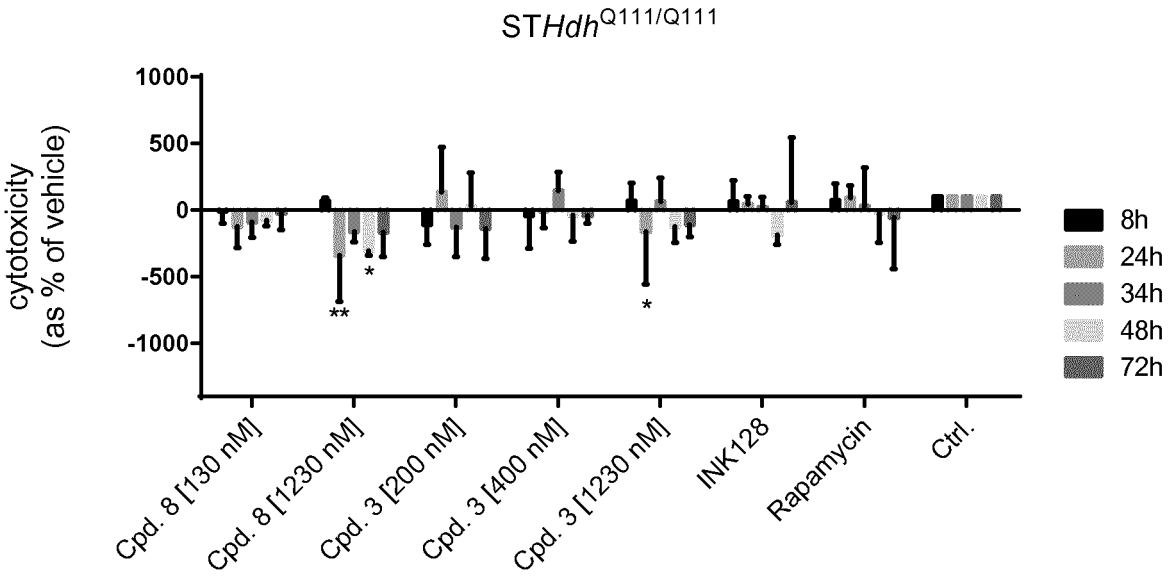

STHdh^Q111/Q111
cytotoxicity (as % of vehicle)
1000
500
0
-500
-1000
**
*
*
8h
24h
34h
48h
72h
Cpd. 8 [130 nM]
Cpd. 8 [1230 nM]
Cpd. 3 [200 nM]
Cpd. 3 [400 nM]
Cpd. 3 [1230 nM]
INK128
Rapamycin
Ctrl.

FIG. 5B

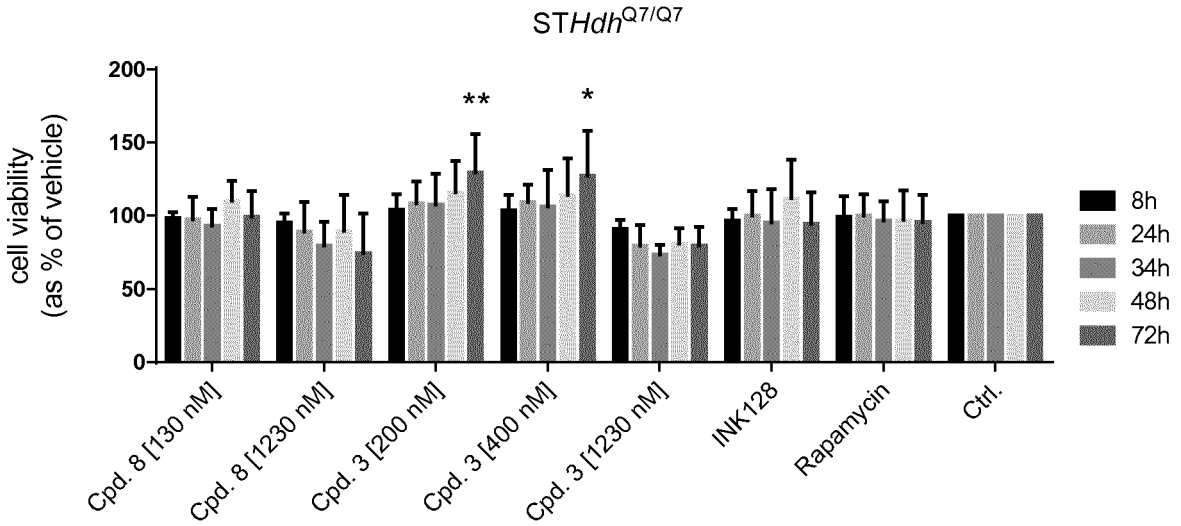

STHdhQ7/Q7
cell viability
(as % of vehicle)
200
150
100
50
0
**
*
8h
24h
34h
48h
72h
Cpd. 8 [130 nM]
Cpd. 8 [1230 nM]
Cpd. 3 [200 nM]
Cpd. 3 [400 nM]
Cpd. 3 [1230 nM]
INK128
Rapamycin
Ctrl.

FIG. 5C

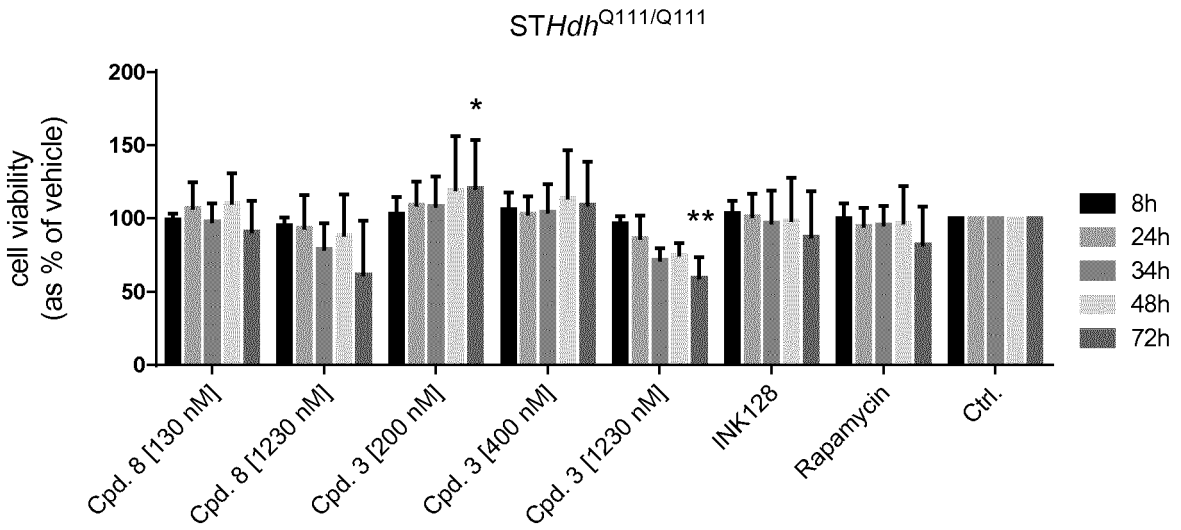

STHdhQ111/Q111
cell viability
(as % of vehicle)
200
150
100
50
0
*
**
8h
24h
34h
48h
72h
Cpd. 8 [130 nM]
Cpd. 8 [1230 nM]
Cpd. 3 [200 nM]
Cpd. 3 [400 nM]
Cpd. 3 [1230 nM]
INK128
Rapamycin
Ctrl.

FIG. 5D

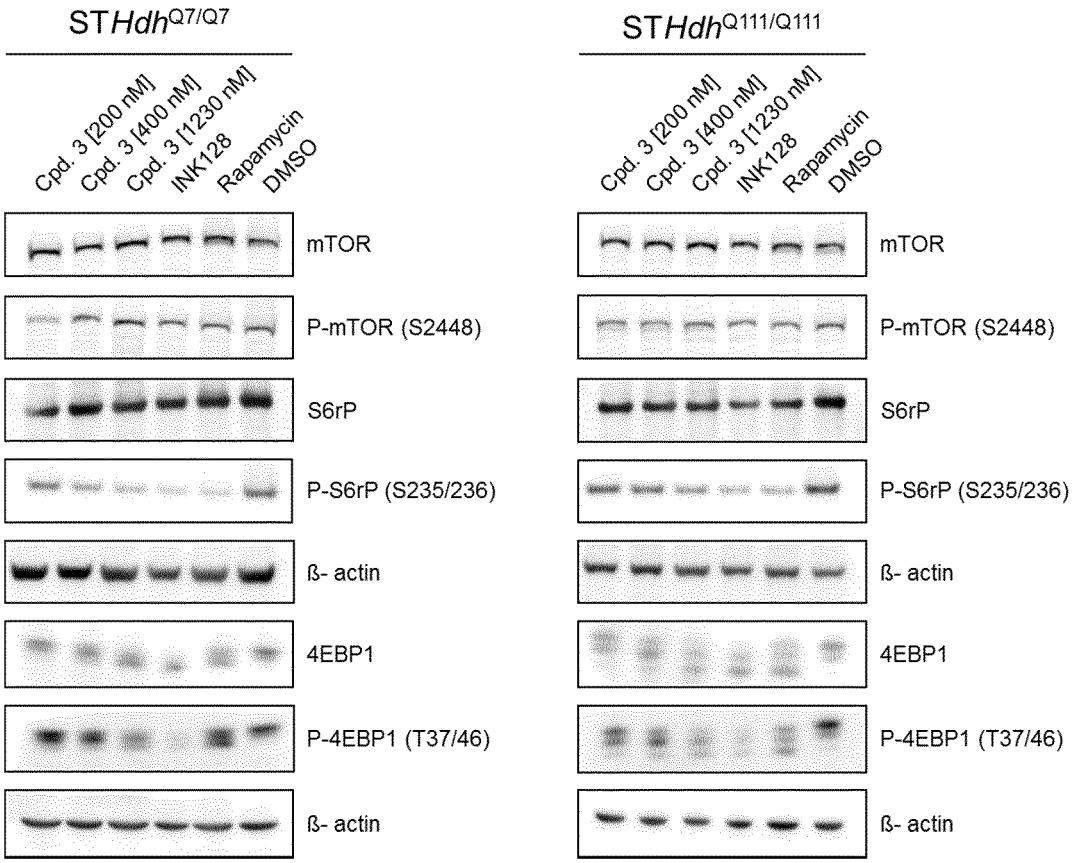

STHdhQ7/Q7
Cpd. 3 [200 nM]
Cpd. 3 [400 nM]
Cpd. 3 [1230 nM]
INK128
Rapamycin
DMSO
mTOR
P-mTOR (S2448)
S6rP
P-S6rP (S235/236)
ß- actin
4EBP1
P-4EBP1 (T37/46)
ß- actin
STHdhQ111/Q111
Cpd. 3 [200 nM]
Cpd. 3 [400 nM]
Cpd. 3 [1230 nM]
INK128
Rapamycin
DMSO
mTOR
P-mTOR (S2448)
S6rP
P-S6rP (S235/236)
ß- actin
4EBP1
P-4EBP1 (T37/46)
ß- actin

FIG. 6A

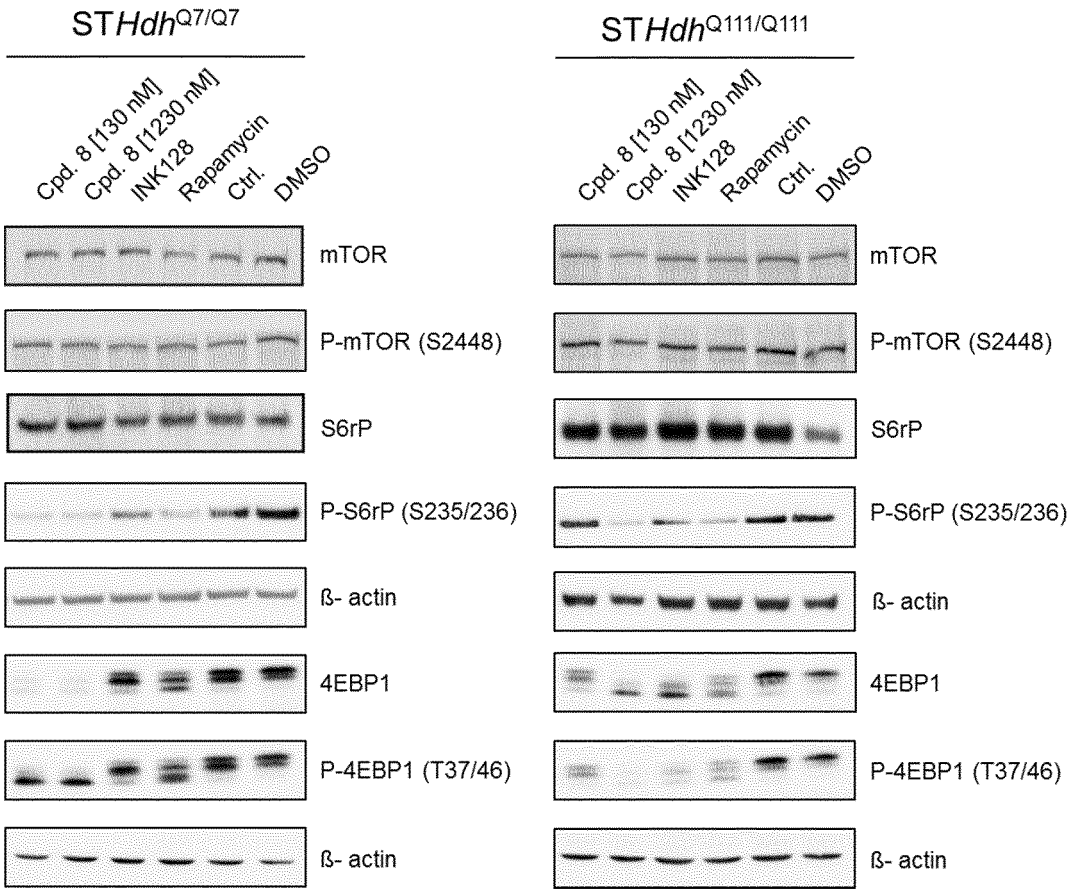
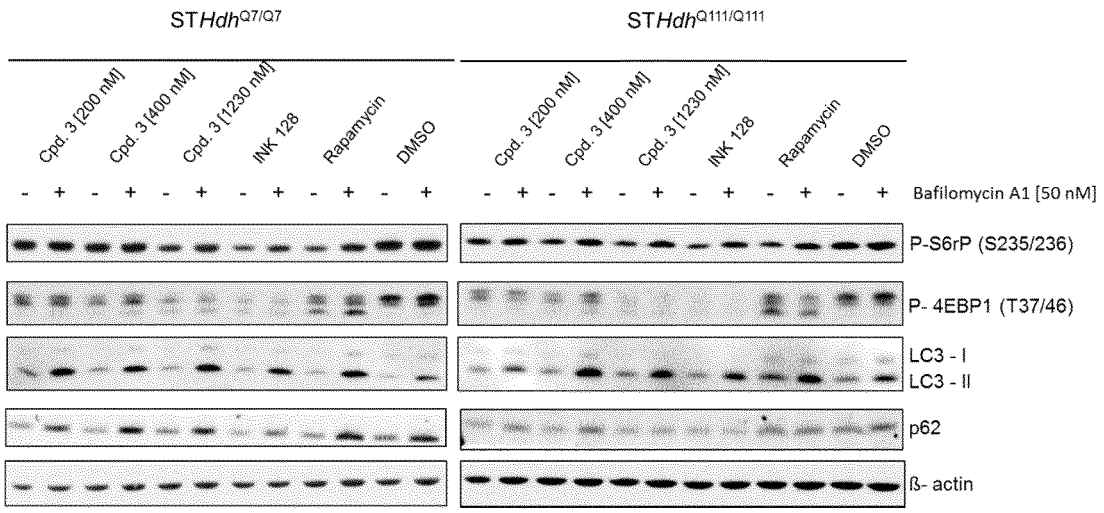

STHdhQ7/Q7
STHdhQ111/Q111
Cpd. 8 [130 nM]
Cpd. 8 [1230 nM]
INK128
Rapamycin
Ctrl.
DMSO
mTOR
P-mTOR (S2448)
S6rP
P-S6rP (S235/236)
ß- actin
4EBP1
P-4EBP1 (T37/46)
ß- actin

FIG. 6B


STHdhQ7/Q7
STHdhQ111/Q111
Cpd. 3 [200 nM]
Cpd. 3 [400 nM]
Cpd. 3 [1230 nM]
INK 128
Rapamycin
DMSO
Bafilomycin A1 [50 nM]
P-S6rP (S235/236)
P- 4EBP1 (T37/46)
LC3 - I
LC3 - II
p62
ß- actin

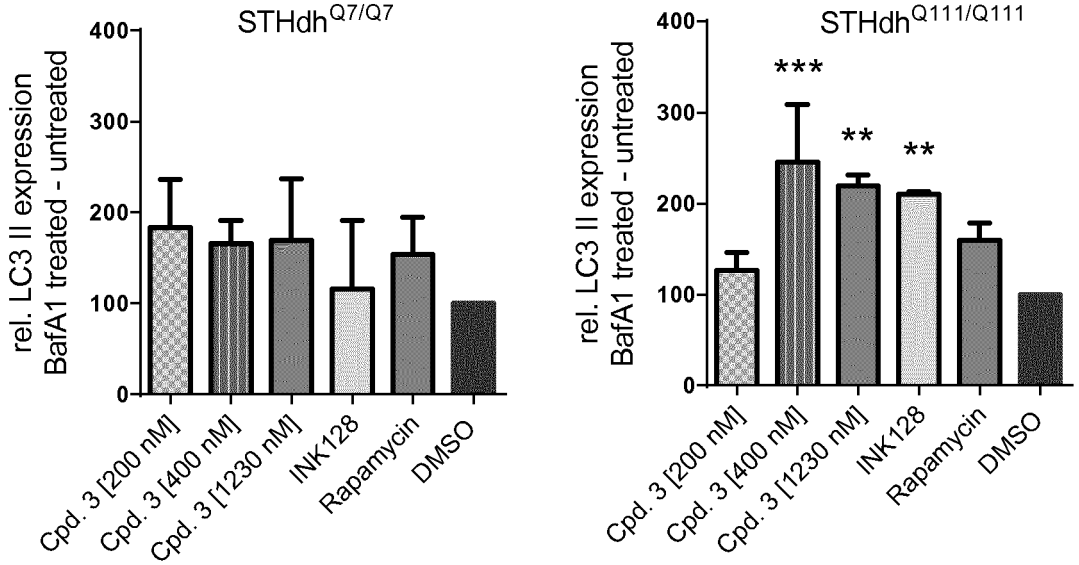

STHdhQ7/Q7
STHdhQ111/Q111
rel. LC3 II expression
BafA1 treated - untreated
400
300
200
100
0
***
**
**
Cpd. 3 [200 nM]
Cpd. 3 [400 nM]
Cpd. 3 [1230 nM]
INK128
Rapamycin
DMSO

FIG. 6C

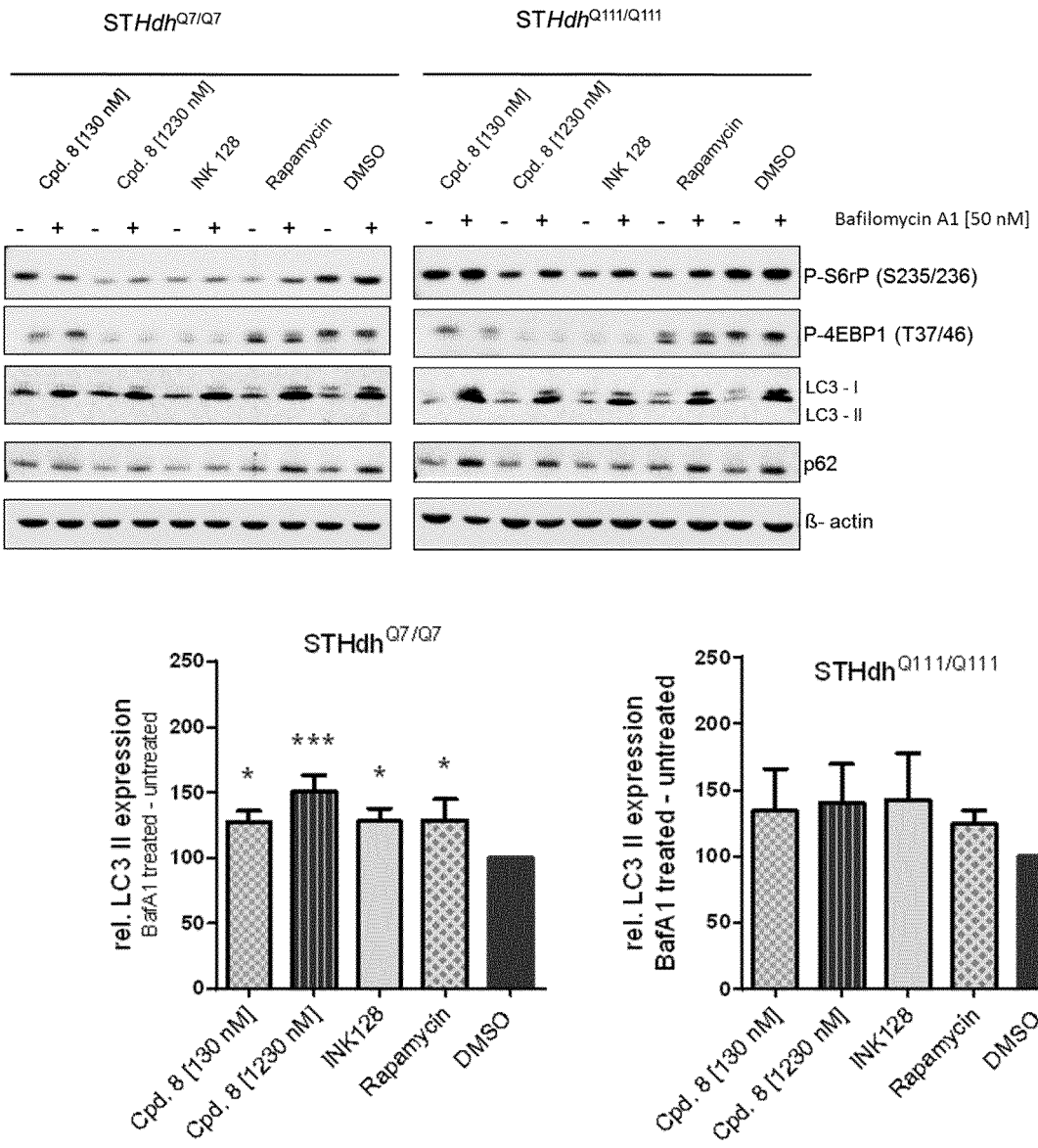

STHdhQ7/Q7
STHdhQ111/Q111
Cpd. 8 [130 nM]
Cpd. 8 [1230 nM]
INK 128
Rapamycin
DMSO
Bafilomycin A1 [50 nM]
P-S6rP (S235/236)
P-4EBP1 (T37/46)
LC3 - I
LC3 - II
p62
ß- actin
rel. LC3 II expression
BafA1 treated - untreated
250
200
150
100
50
0
*
***
*
*
INK128

FIG. 6D

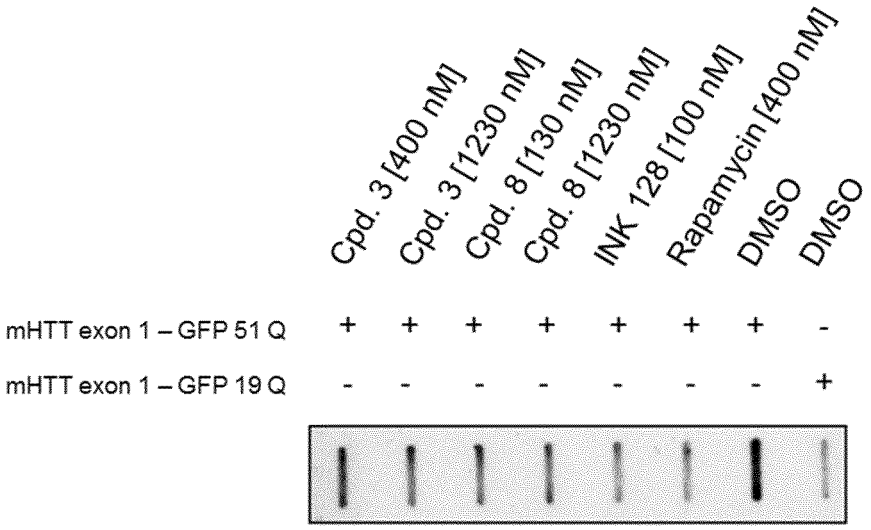

Cpd. 3 [400 nM]
Cpd. 3 [1230 nM]
Cpd. 8 [130 nM]
Cpd. 8 [1230 nM]
INK 128 [100 nM]
Rapamycin [400 nM]
DMSO
DMSO
mHTT exon 1 – GFP 51 Q + + + + + + + -
mHTT exon 1 – GFP 19 Q - - - - - - - +

FIG. 7A

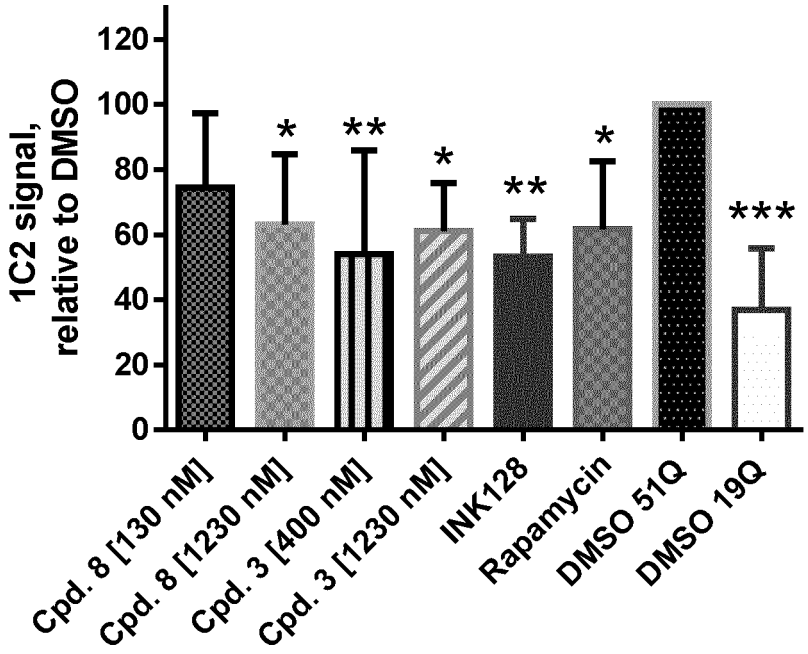

1C2 signal, relative to DMSO
120
100
80
60
40
20
0
*
**
*
**
*
***
Cpd. 8 [130 nM]
Cpd. 8 [1230 nM]
Cpd. 3 [400 nM]
Cpd. 3 [1230 nM]
INK128
Rapamycin
DMSO 51Q
DMSO 19Q

FIG. 7B

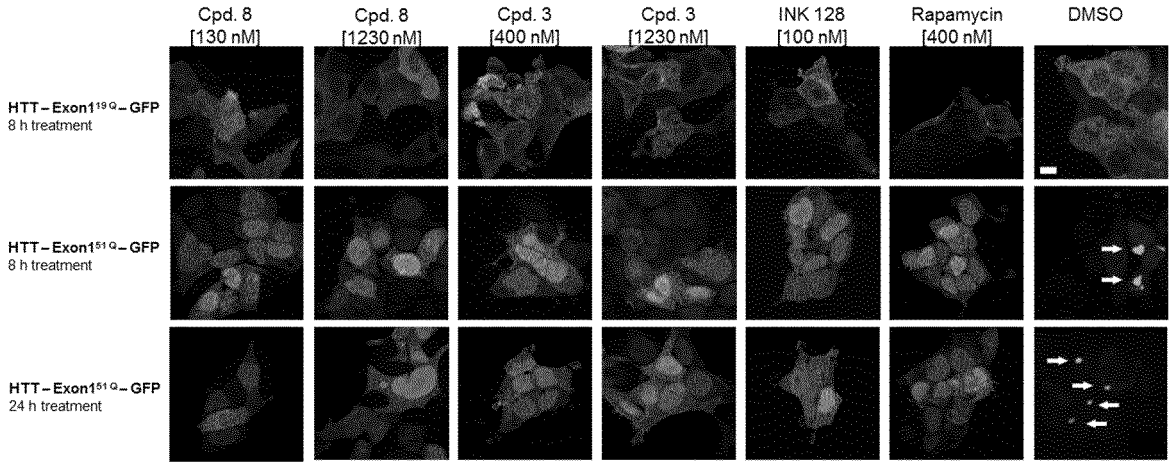

Cpd. 8 [130 nM]
Cpd. 8 [1230 nM]
Cpd. 3 [400 nM]
Cpd. 3 [1230 nM]
INK 128 [100 nM]
Rapamycin [400 nM]
DMSO
HTT – Exon1 19Q – GFP 8 h treatment
HTT – Exon1 51Q – GFP 8 h treatment
HTT – Exon1 51Q – GFP 24 h treatment

FIG. 7C

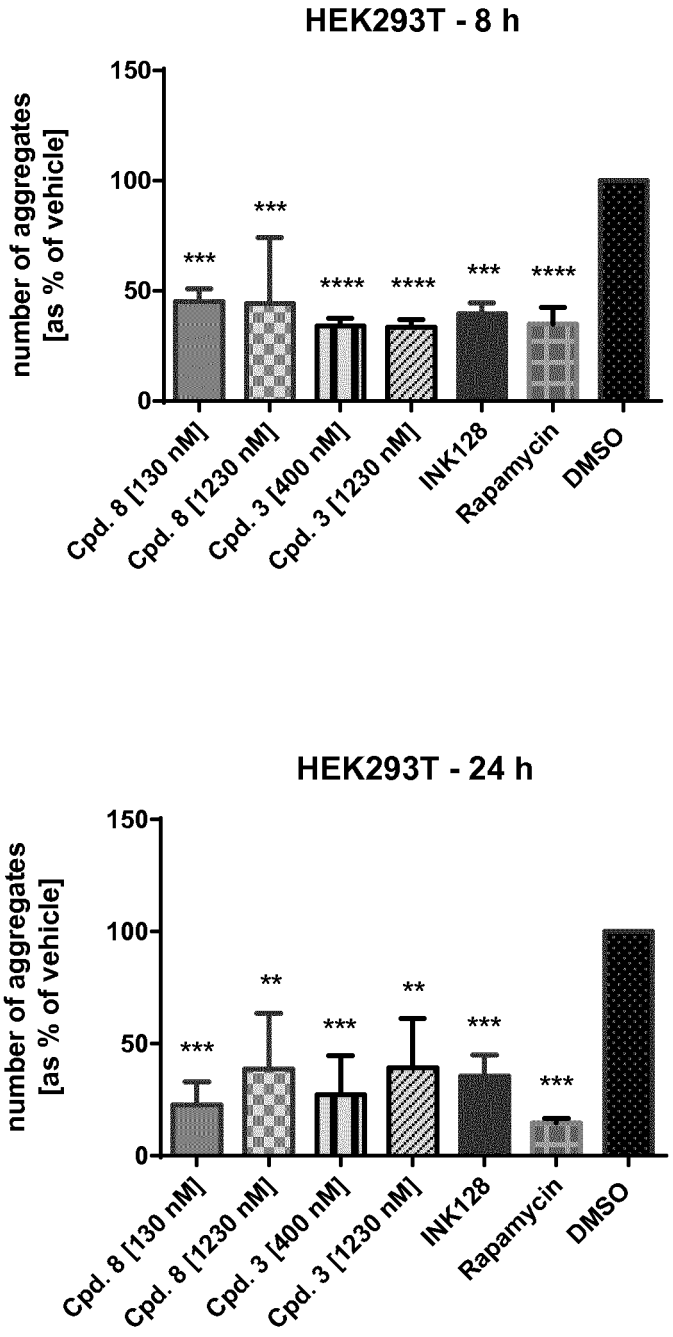

HEK293T - 8 h
number of aggregates [as % of vehicle]
150
100
50
0
***
***
****
****
***
****
Cpd. 8 [130 nM]
Cpd. 8 [1230 nM]
Cpd. 3 [400 nM]
Cpd. 3 [1230 nM]
INK128
Rapamycin
DMSO
HEK293T - 24 h
number of aggregates [as % of vehicle]
150
100
50
0
***
**
***
**
***
***
Cpd. 8 [130 nM]
Cpd. 8 [1230 nM]
Cpd. 3 [400 nM]
Cpd. 3 [1230 nM]
INK128
Rapamycin
DMSO

FIG. 7D

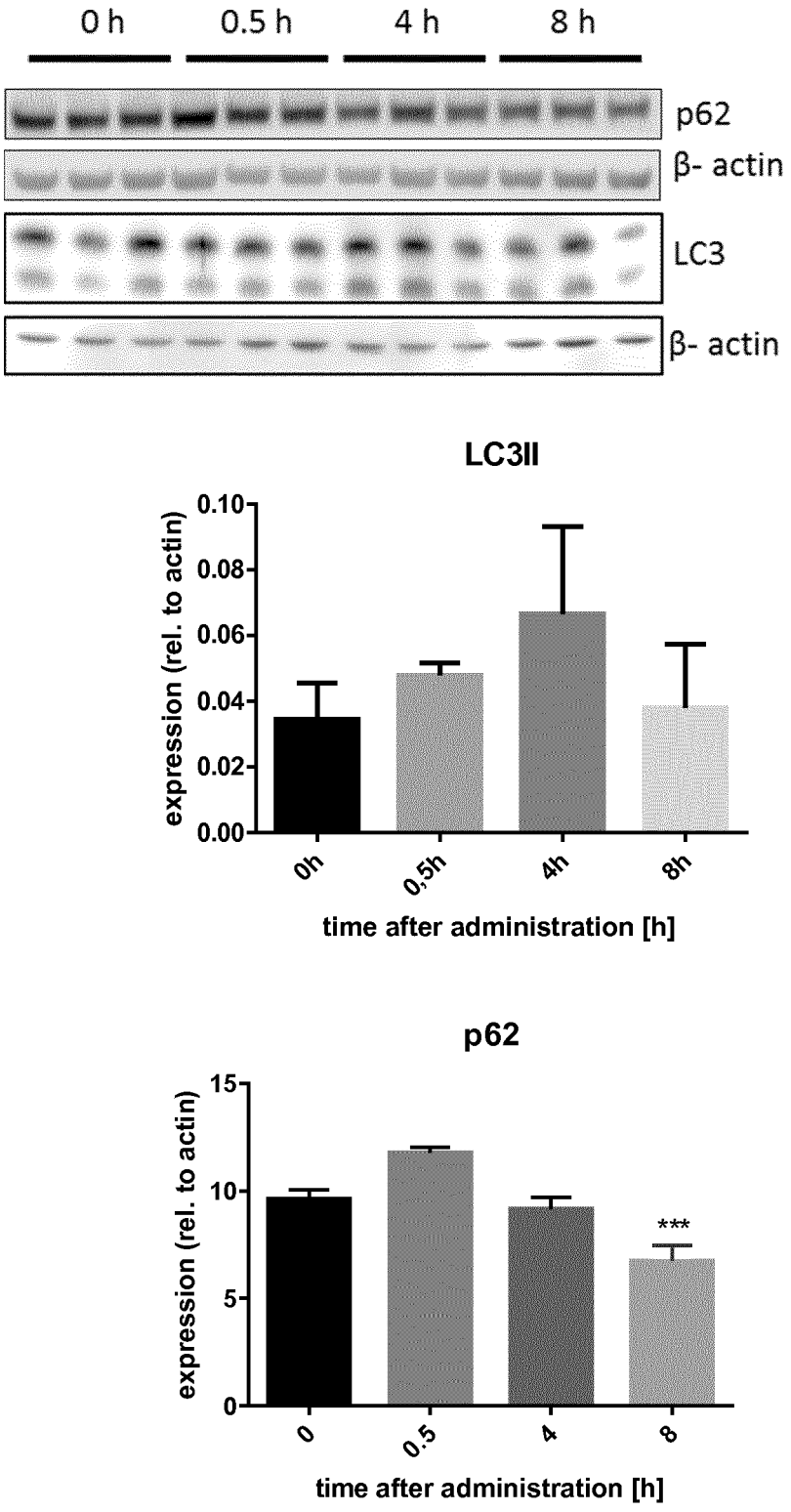

0 h
0.5 h
4 h
8 h
p62
β- actin
LC3
β- actin
LC3II
expression (rel. to actin)
0.10
0.08
0.06
0.04
0.02
0.00
0h
0,5h
4h
8h
time after administration [h]
p62
expression (rel. to actin)
15
10
5
0
***
0
0.5
4
8
time after administration [h]

FIG. 8A

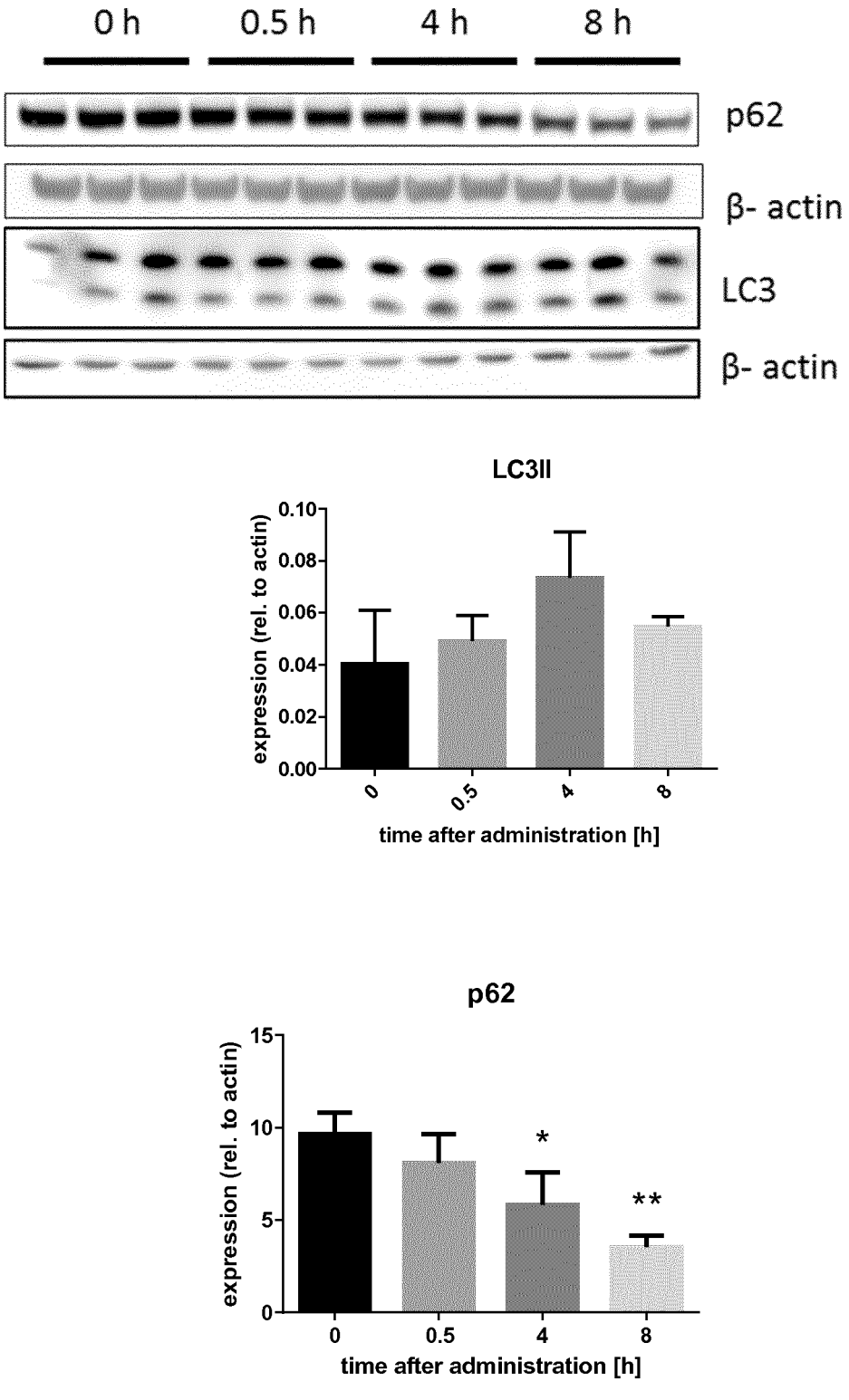

0 h
0.5 h
4 h
8 h
p62
β- actin
LC3
β- actin
LC3II
expression (rel. to actin)
0.10
0.08
0.06
0.04
0.02
0.00
0
0.5
4
8
time after administration [h]
p62
expression (rel. to actin)
15
10
5
0
*
**
0
0.5
4
8
time after administration [h]

FIG. 8B

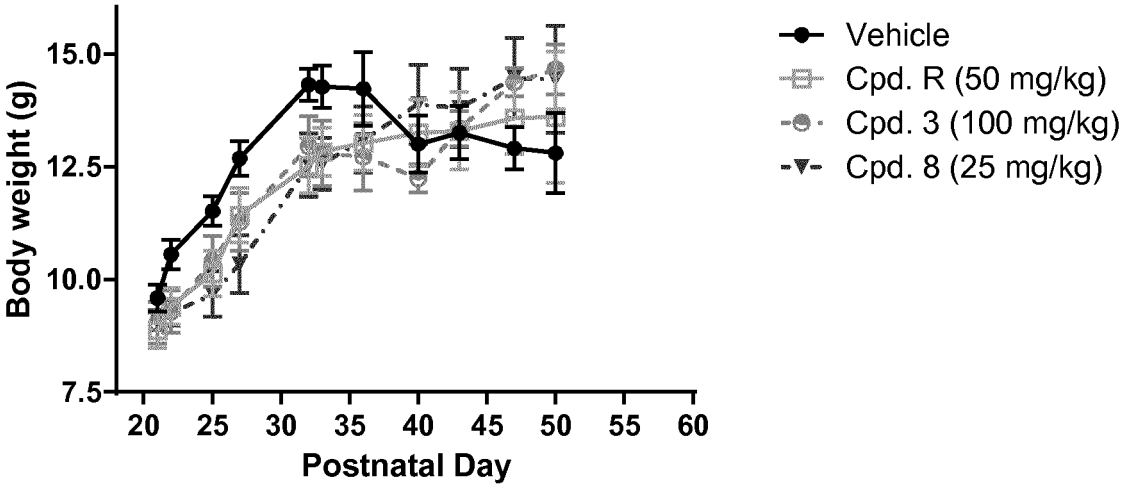

Body weight (g)
15.0
12.5
10.0
7.5
20
25
30
35
40
45
50
55
60
Postnatal Day
Vehicle
Cpd. R (50 mg/kg)
Cpd. 3 (100 mg/kg)
Cpd. 8 (25 mg/kg)

FIG. 9A

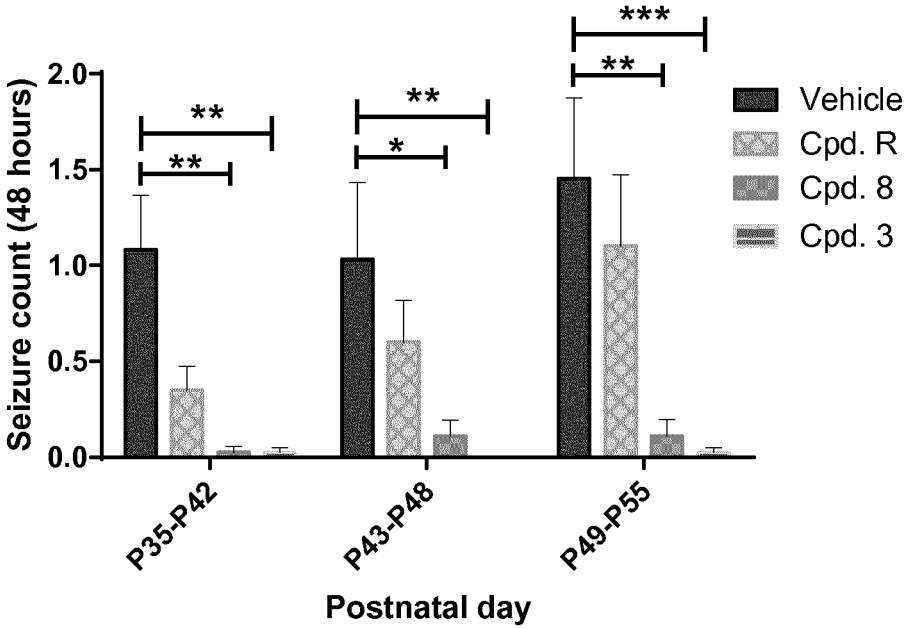
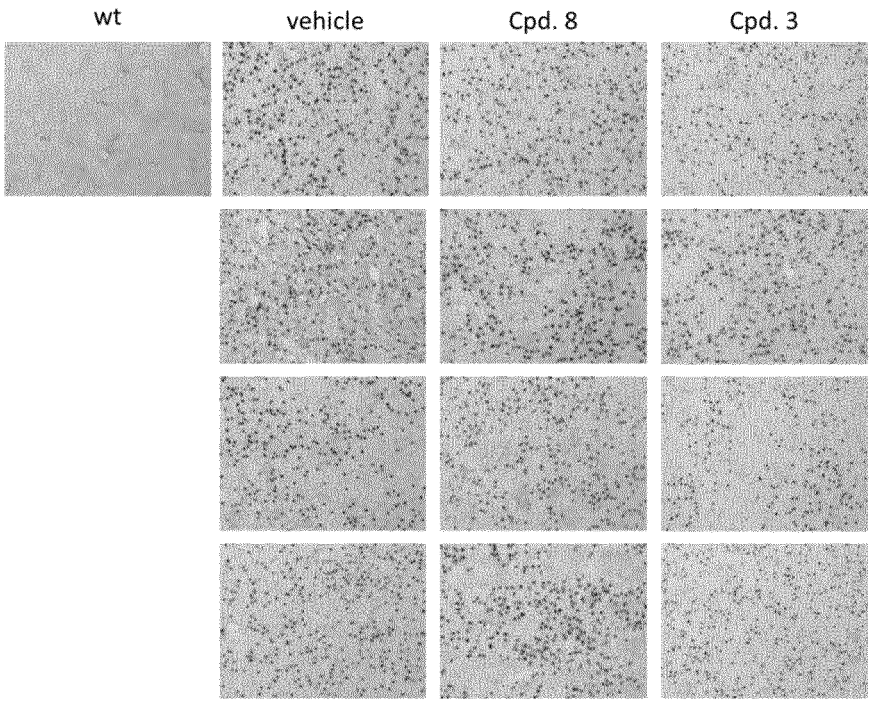

Seizure count (48 hours)
2.0
1.5
1.0
0.5
0.0
**
**
**
*
***
**
P35-P42
P43-P48
P49-P55
Postnatal day
Vehicle
Cpd. R
Cpd. 8
Cpd. 3

FIG. 9B


wt
vehicle
Cpd. 8
Cpd. 3

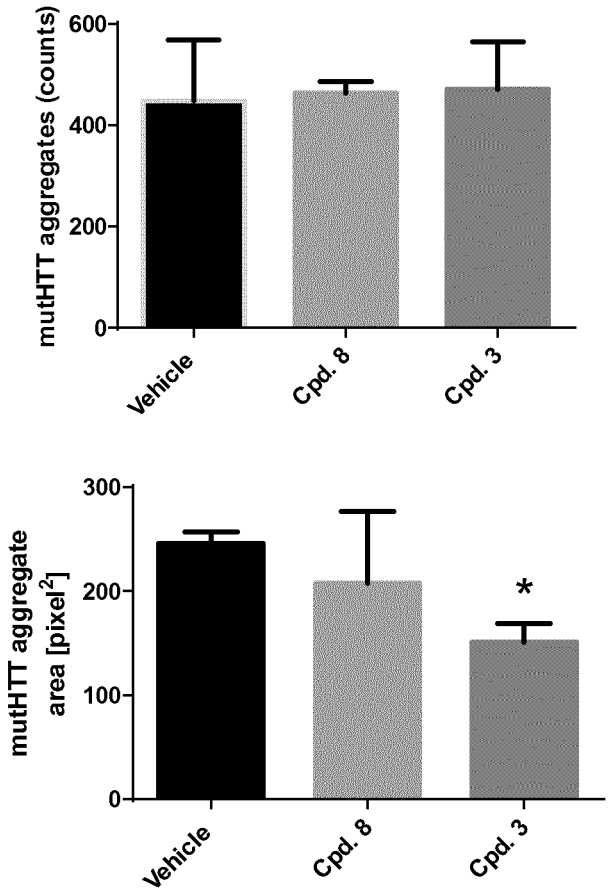

mutHTT aggregates (counts)
600
400
200
0
Vehicle
Cpd. 8
Cpd. 3
mutHTT aggregate area [pixel²]
300
200
100
0
*
Vehicle
Cpd. 8
Cpd. 3

FIG. 10