Figure 1

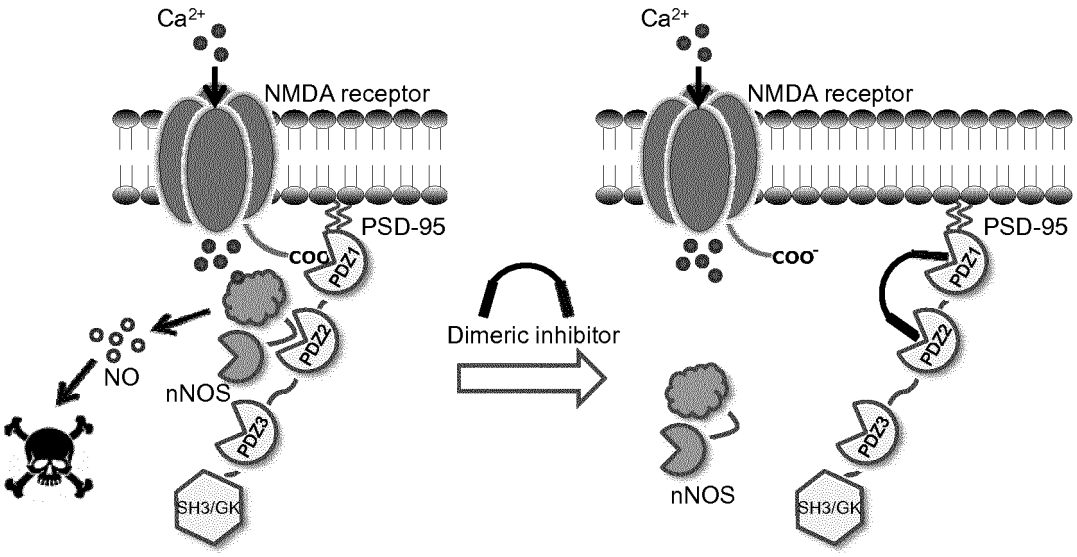
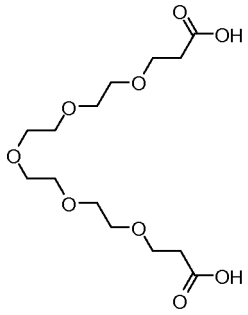
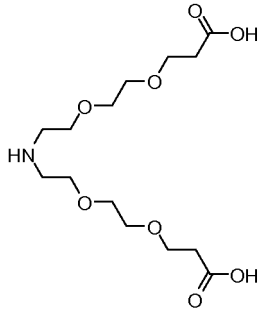

Ca2+
NMDA receptor
PSD-95
COO-
PDZ1
PDZ2
PDZ3
SH3/GK
NO
nNOS
Dimeric inhibitor
Ca2+
NMDA receptor
PSD-95
COO-
PDZ1
PDZ2
PDZ3
SH3/GK
nNOS

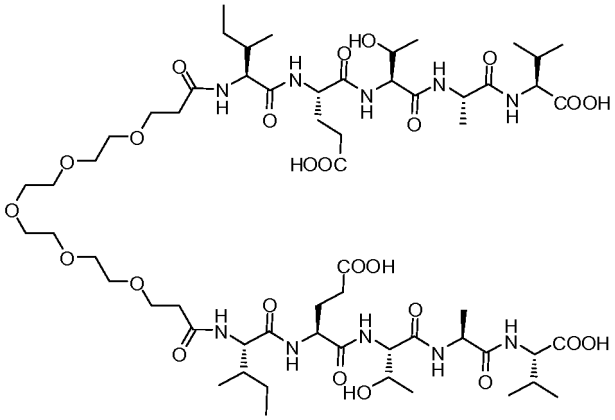
Figure 2



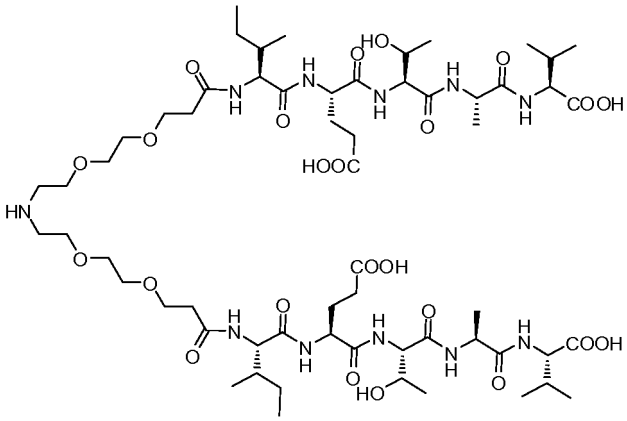
PEG4-diacid linker



***N*PEG4-diacid linker**

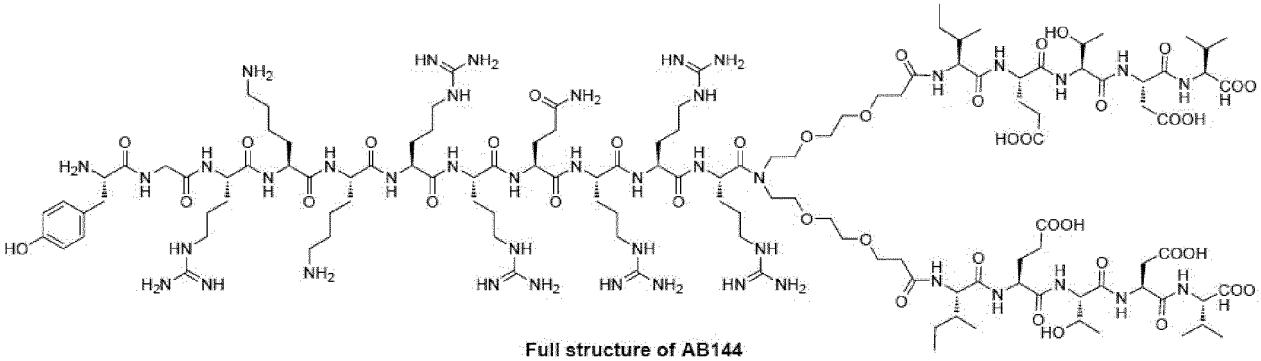


AB125
PEG4(IETAV)$_2$

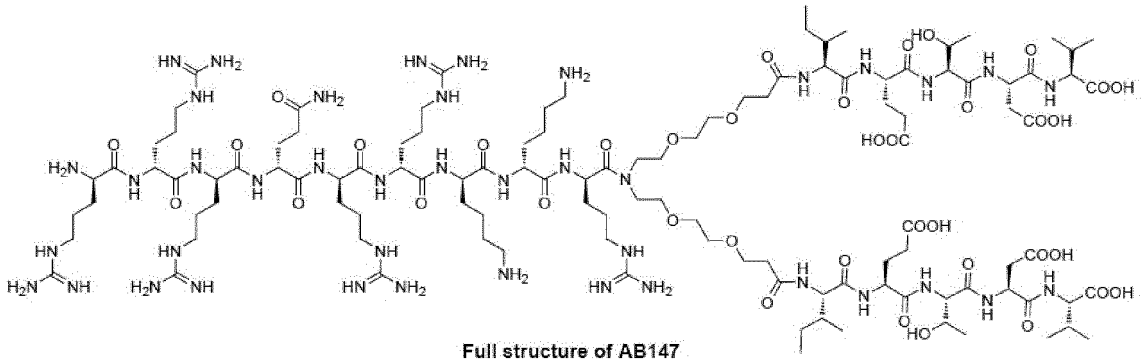


AB141
*N*PEG4(IETAV)$_2$

Figure 3



Full structure of AB144
Tat-*N*PEG4(IETDV)$_2$

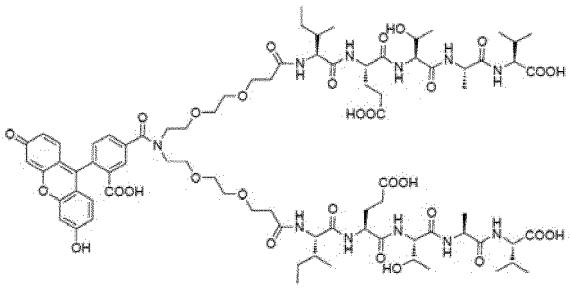


Full structure of AB147
Retroinverso-D-Tat-*N*PEG4(IETDV)$_2$

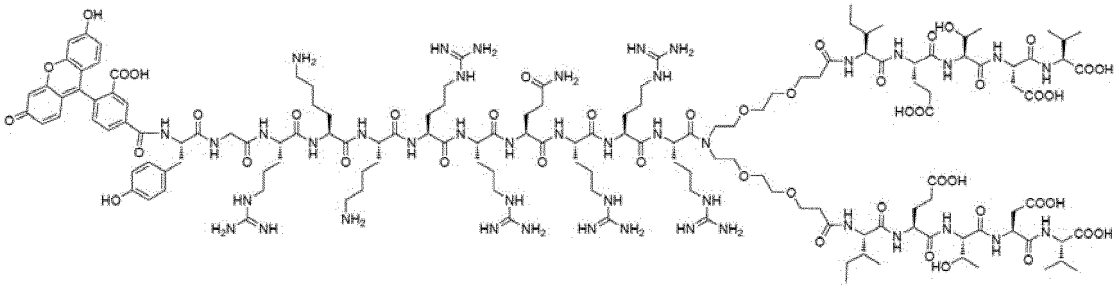


Alternative structural representation of **AB144** and **AB147**

Figure 4

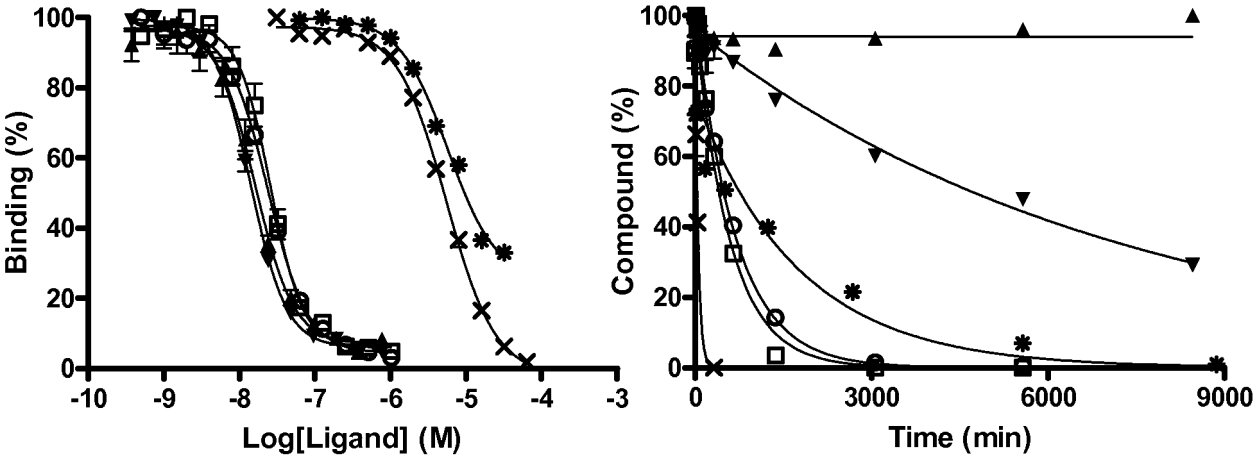


Structure of AB143
5-FAM-*N*PEG4(IETAV)2



Structure of AB145
5-FAM-Tat-*N*PEG4(IETDV)2

Figure 5



	K_i ± SEM (nM)	$T_{1/2}$ ± SEM (min)
▼ AB144	4.6 ± 0.3	4900 ± 100
▲ AB147	5.1 ± 0.4	>8000
○ AB125	9.5 ± 0.3	450 ± 20
□ AB141	9.3 ± 1	410 ± 20
× IETDV	1800 ± 200	37 ± 6
✱ Tat-NR2B9c	4600 ± 300	1100 ± 300

Figure 6

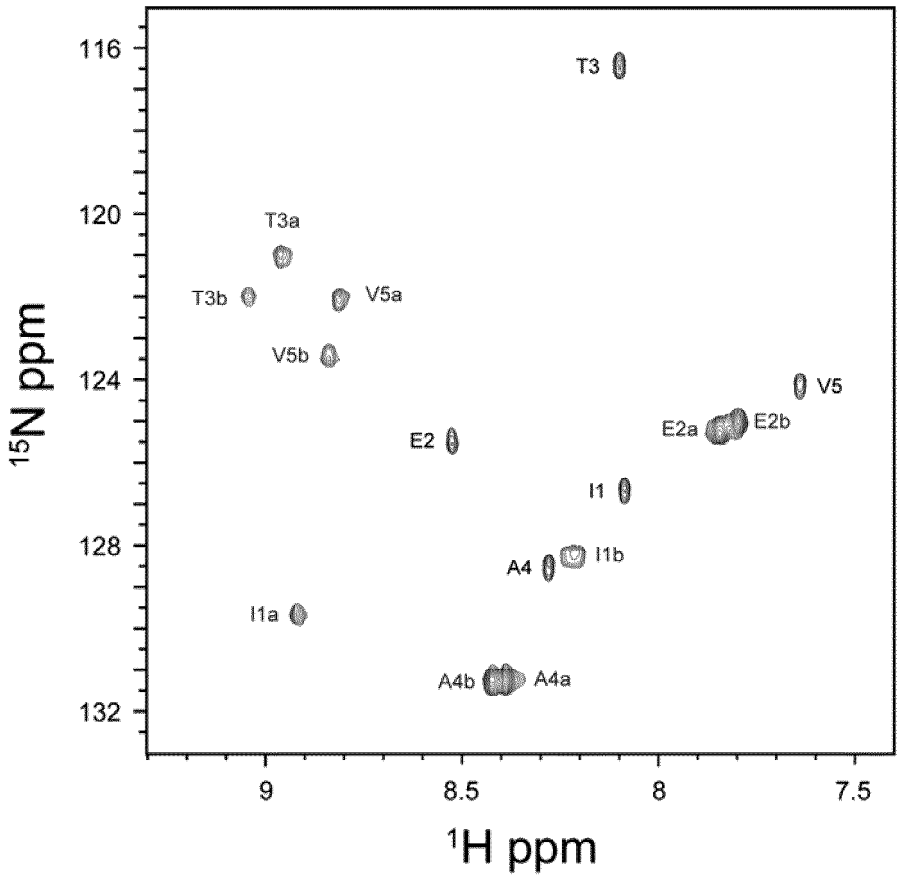

116
120
124
128
132
^{15}N ppm
9
8.5
8
7.5
^{1}H ppm
T3
T3a
T3b
V5a
V5b
V5
E2a
E2b
E2
I1
A4
I1b
I1a
A4b
A4a

Figure 7

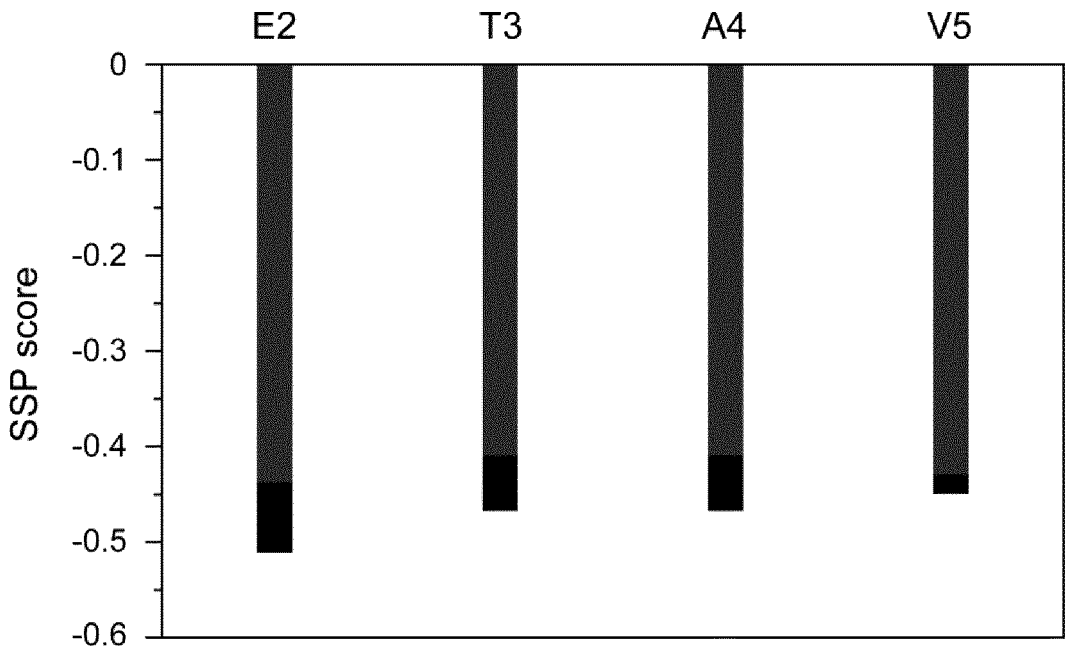


Figure 8

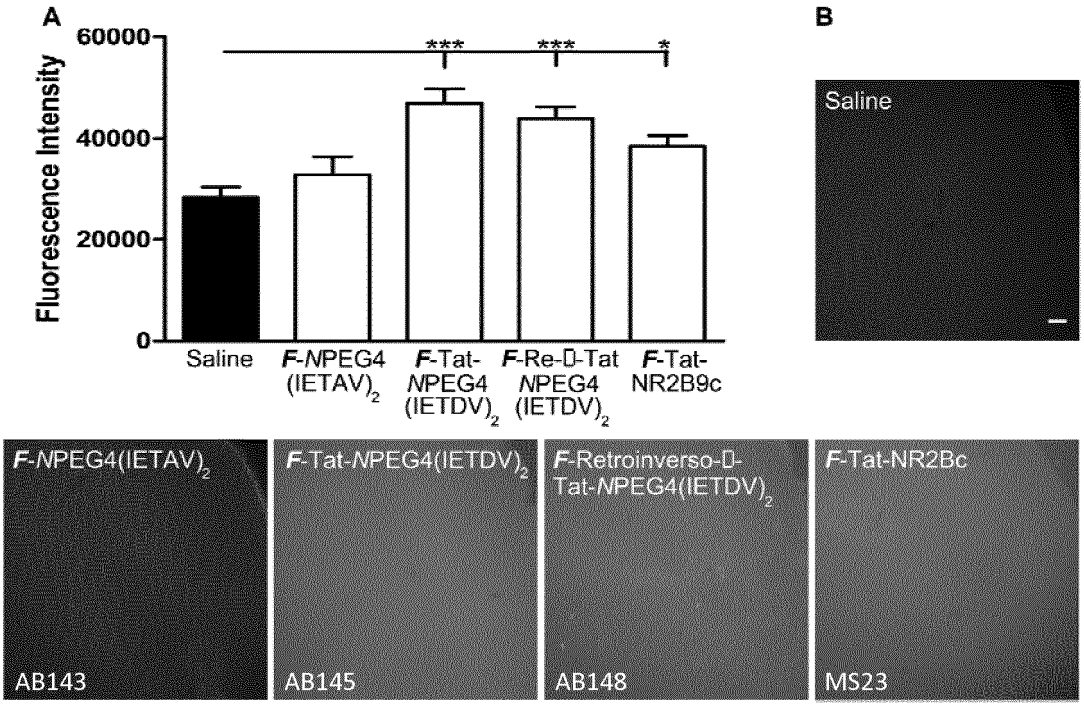

A
B
Fluorescence Intensity
60000
40000
20000
0
***
***
*
Saline
F-NPEG4 (IETAV)2
F-Tat-NPEG4 (IETDV)2
F-Re-D-Tat NPEG4 (IETDV)2
F-Tat-NR2B9c
Saline
F-NPEG4(IETAV)2
AB143
F-Tat-NPEG4(IETDV)2
AB145
F-Retroinverso-D-Tat-NPEG4(IETDV)2
AB148
F-Tat-NR2Bc
MS23

Figure 9

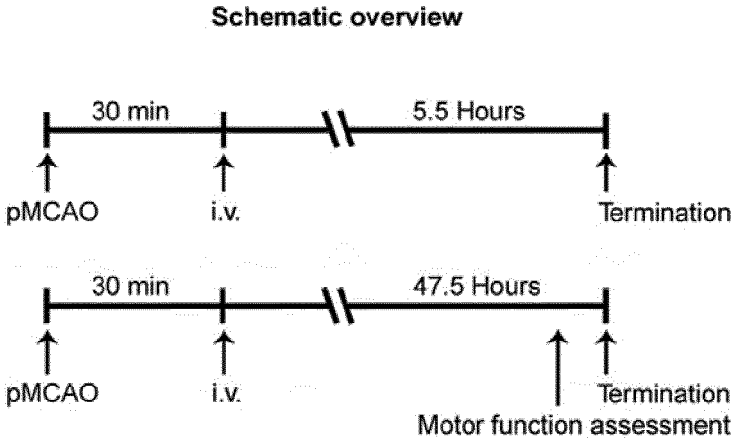

Schematic overview
30 min
5.5 Hours
pMCAO
i.v.
Termination
30 min
47.5 Hours
pMCAO
i.v.
Termination
Motor function assessment

Figure 10

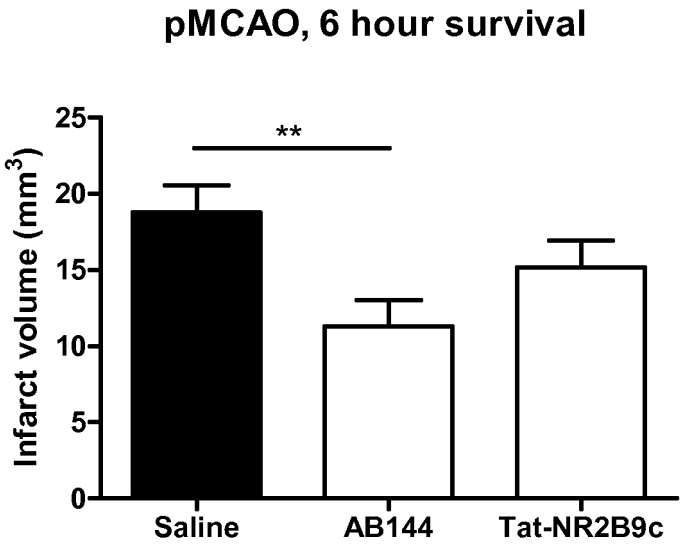

pMCAO, 6 hour survival
Infarct volume (mm3)
25
20
15
10
5
0
**
Saline
AB144
Tat-NR2B9c

Figure 11

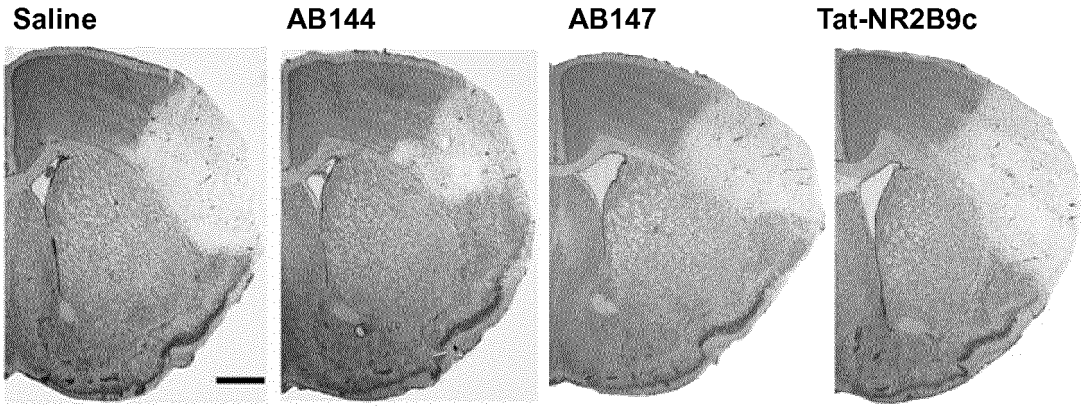


Figure 12

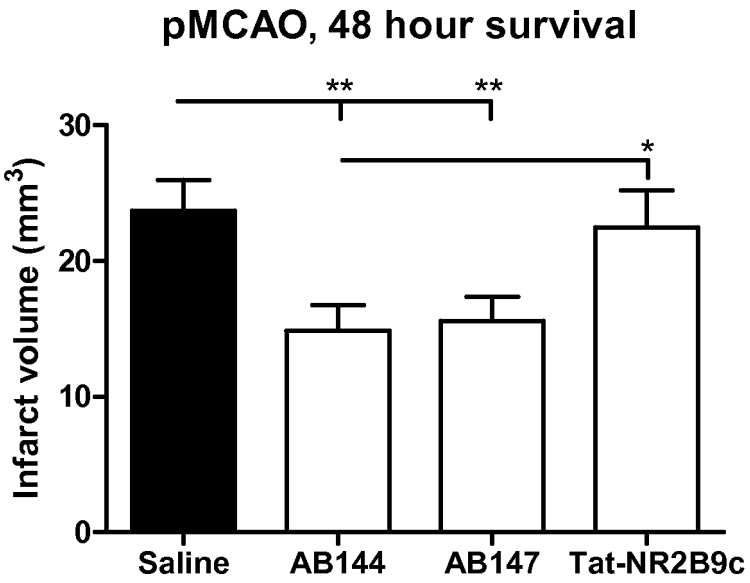

pMCAO, 48 hour survival
**
**
*
30
20
10
0
Infarct volume (mm3)
Saline
AB144
AB147
Tat-NR2B9c

Figure 13

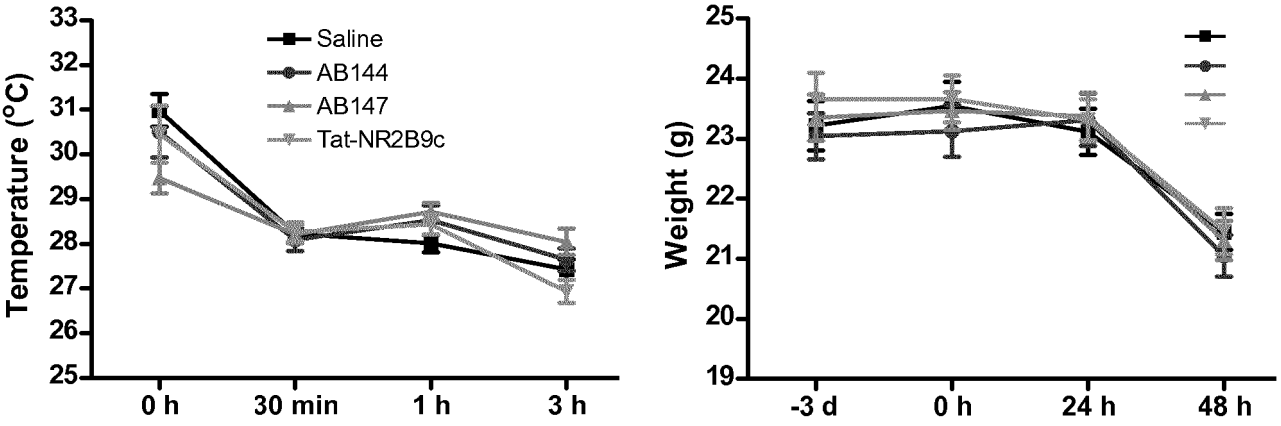

Temperature (°C)
33
32
31
30
29
28
27
26
25
Saline
AB144
AB147
Tat-NR2B9c
0 h
30 min
1 h
3 h
Weight (g)
25
24
23
22
21
20
19
-3 d
0 h
24 h
48 h

Figure 14

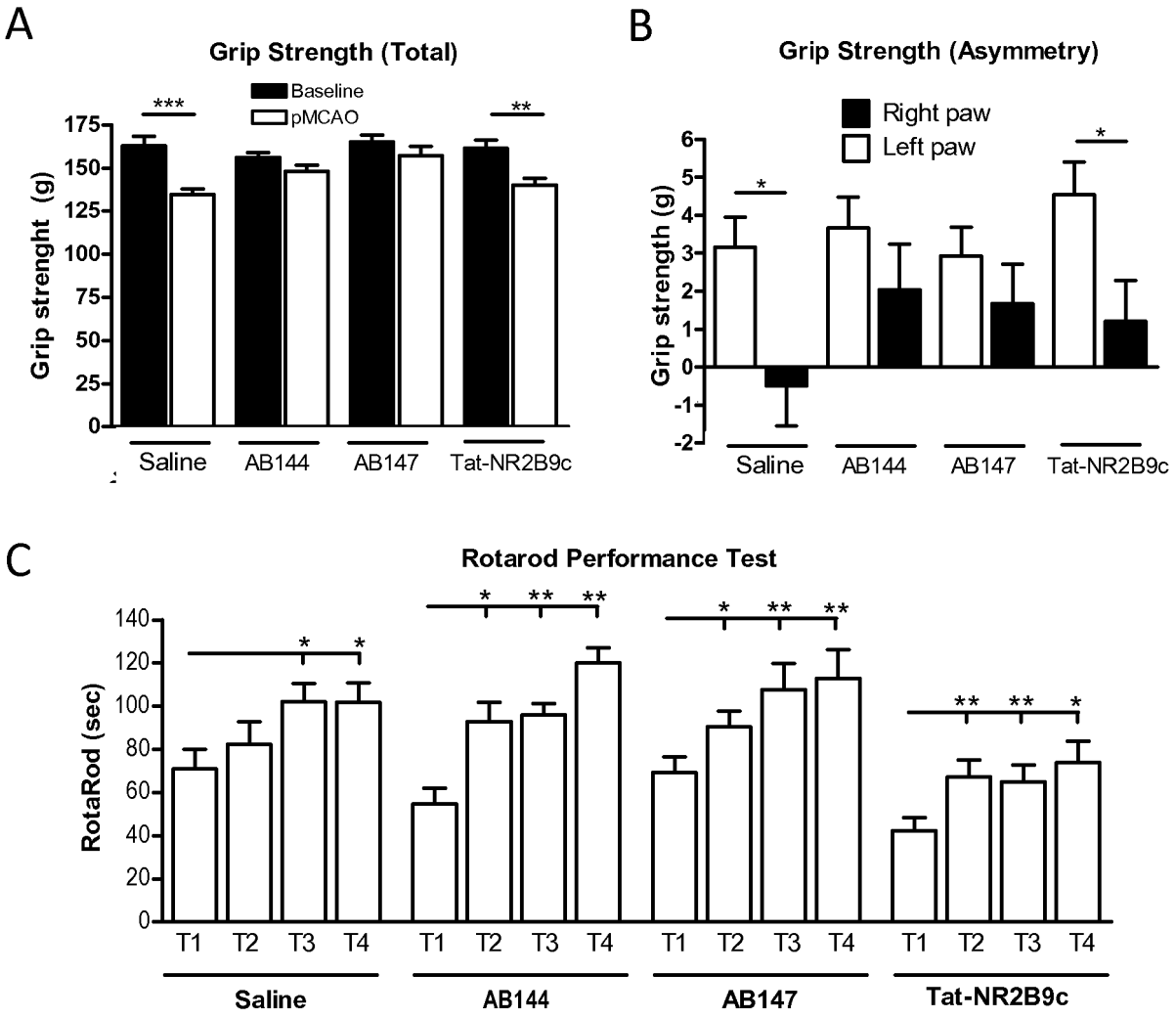

A
Grip Strength (Total)
Baseline
pMCAO
Grip strenght (g)
175
150
125
100
75
50
25
0
***
**
Saline
AB144
AB147
Tat-NR2B9c
B
Grip Strength (Asymmetry)
Right paw
Left paw
Grip strength (g)
6
5
4
3
2
1
0
-1
-2
*
*
Saline
AB144
AB147
Tat-NR2B9c
C
Rotarod Performance Test
RotaRod (sec)
140
120
100
80
60
40
20
0
T1
T2
T3
T4
Saline
AB144
AB147
Tat-NR2B9c

Figure 15

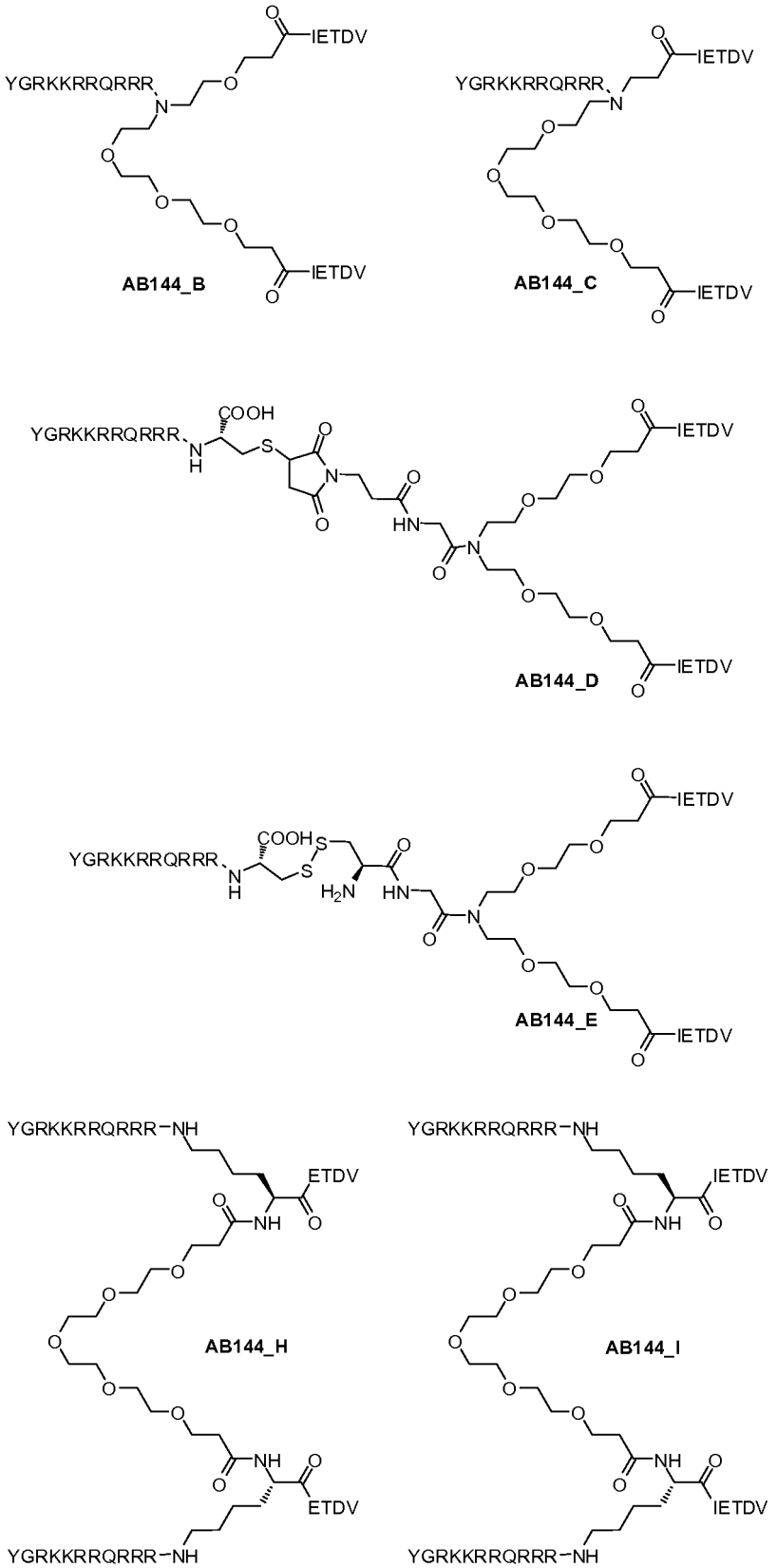

YGRKKRRQRRR
IETDV
AB144_B
AB144_C
COOH
AB144_D
AB144_E
ETDV
AB144_H
AB144_I

Figure 16

Scheme 1

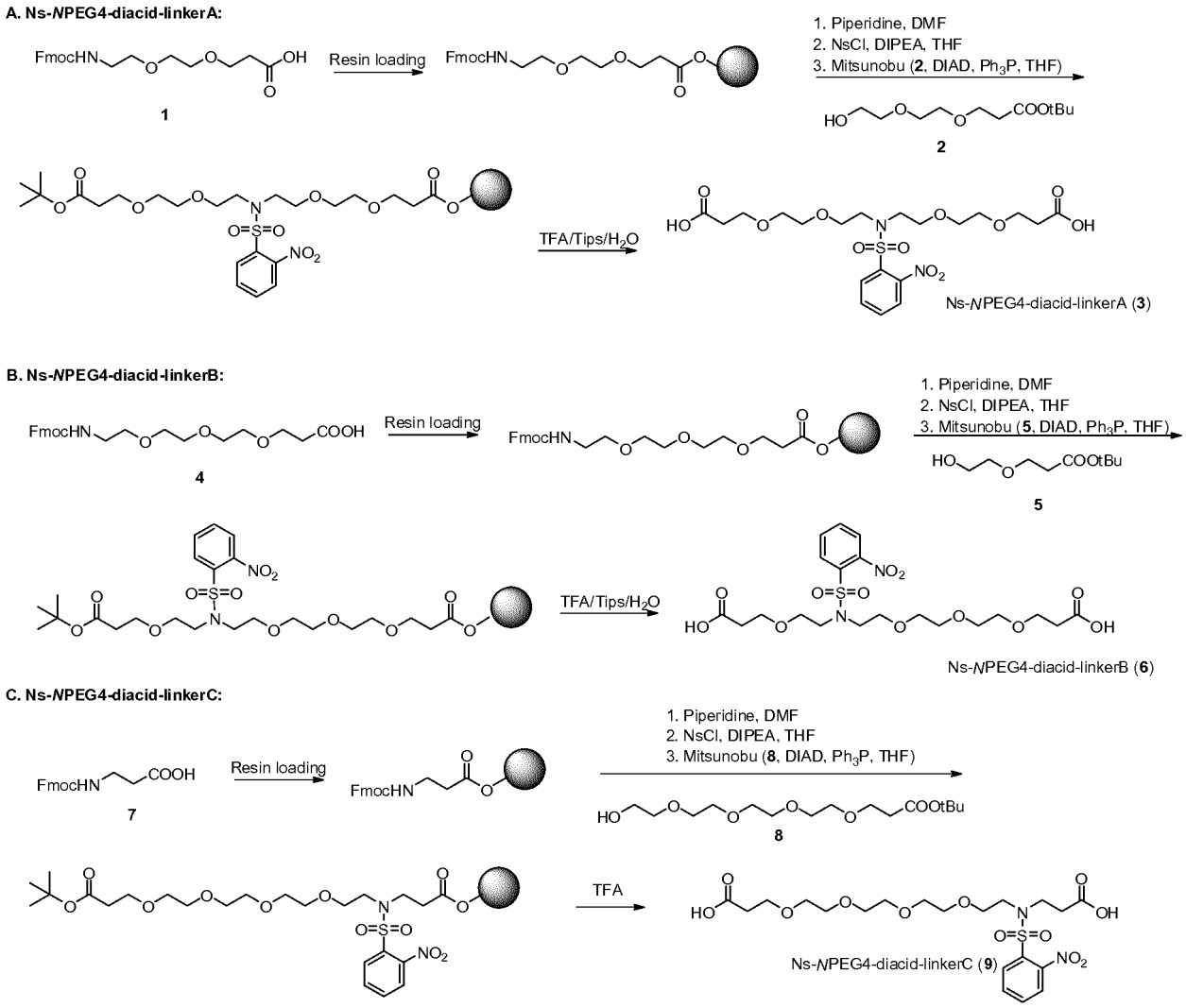


Figure 17

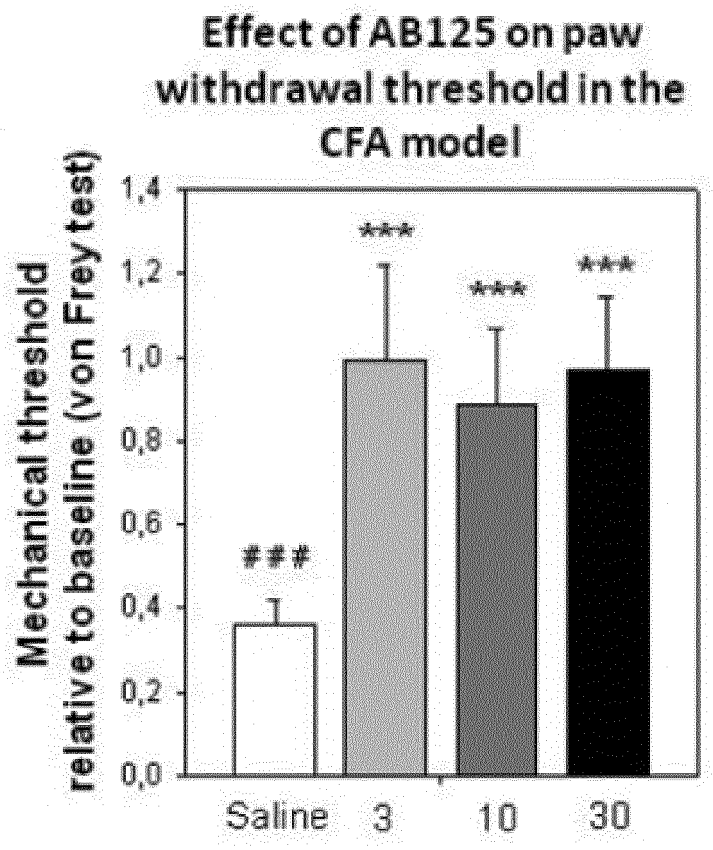

Effect of AB125 on paw withdrawal threshold in the CFA model
Mechanical threshold relative to baseline (von Frey test)
1,4
1,2
1,0
0,8
0,6
0,4
0,2
0,0
###
***
***
***
Saline
3
10
30

Figure 18

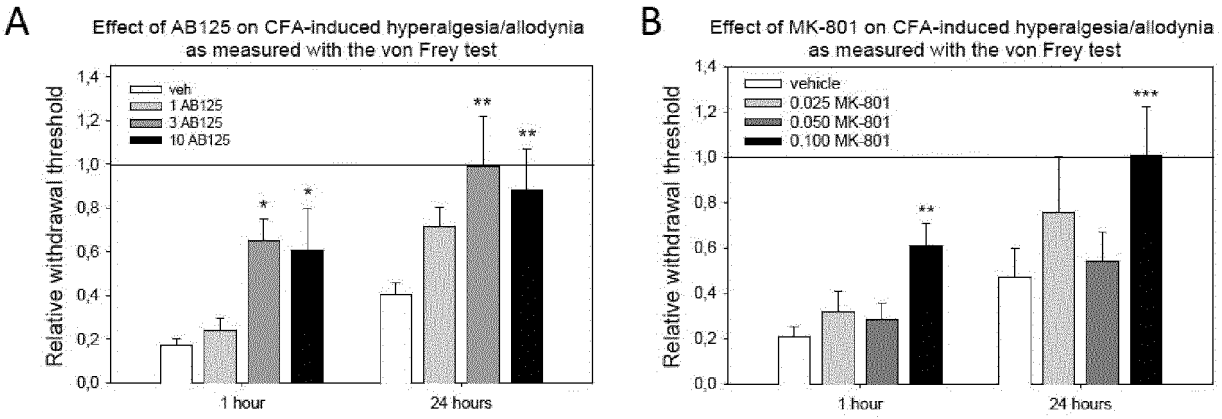

A
Effect of AB125 on CFA-induced hyperalgesia/allodynia as measured with the von Frey test
Relative withdrawal threshold
1,4
1,2
1,0
0,8
0,6
0,4
0,2
0,0
veh
1 AB125
3 AB125
10 AB125
*
*
**
**
1 hour
24 hours
B
Effect of MK-801 on CFA-induced hyperalgesia/allodynia as measured with the von Frey test
Relative withdrawal threshold
vehicle
0.025 MK-801
0.050 MK-801
0.100 MK-801
**
***
1 hour
24 hours

Figure 19

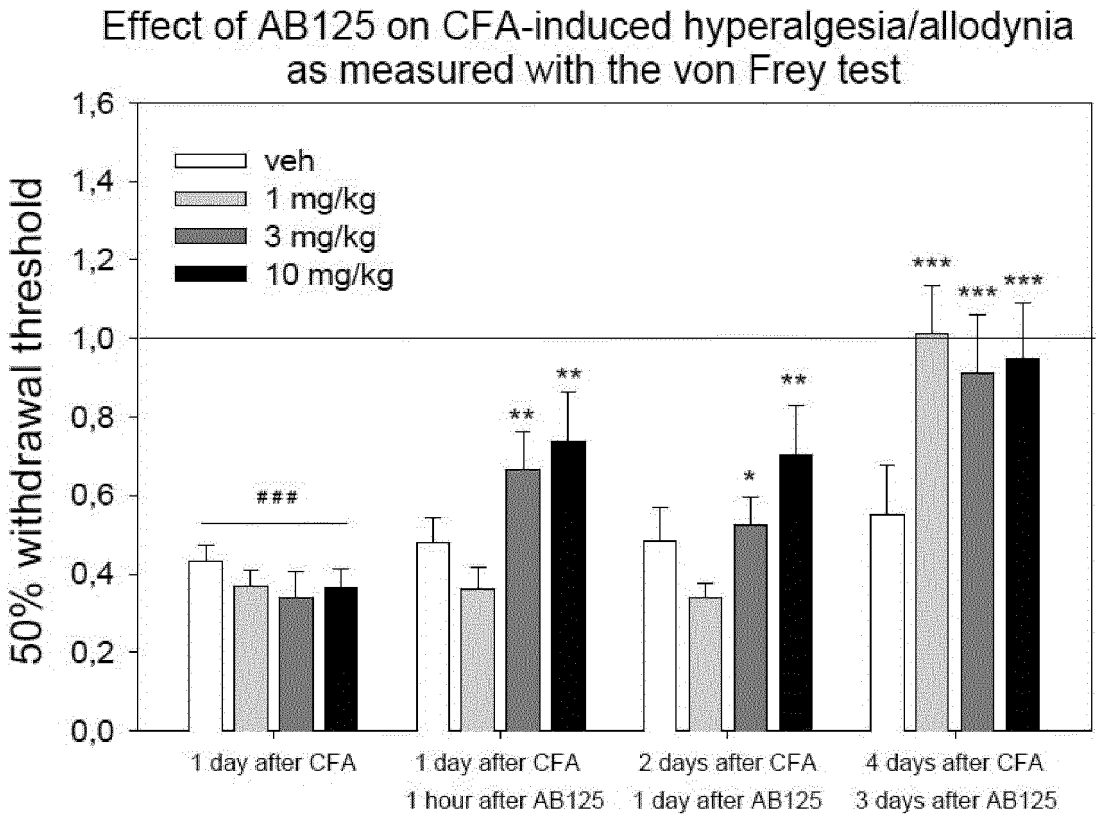

Effect of AB125 on CFA-induced hyperalgesia/allodynia as measured with the von Frey test
50% withdrawal threshold
1,6
1,4
1,2
1,0
0,8
0,6
0,4
0,2
0,0
veh
1 mg/kg
3 mg/kg
10 mg/kg
###
**
**
*
**
***
***
***
1 day after CFA
1 day after CFA
1 hour after AB125
2 days after CFA
1 day after AB125
4 days after CFA
3 days after AB125

Figure 20

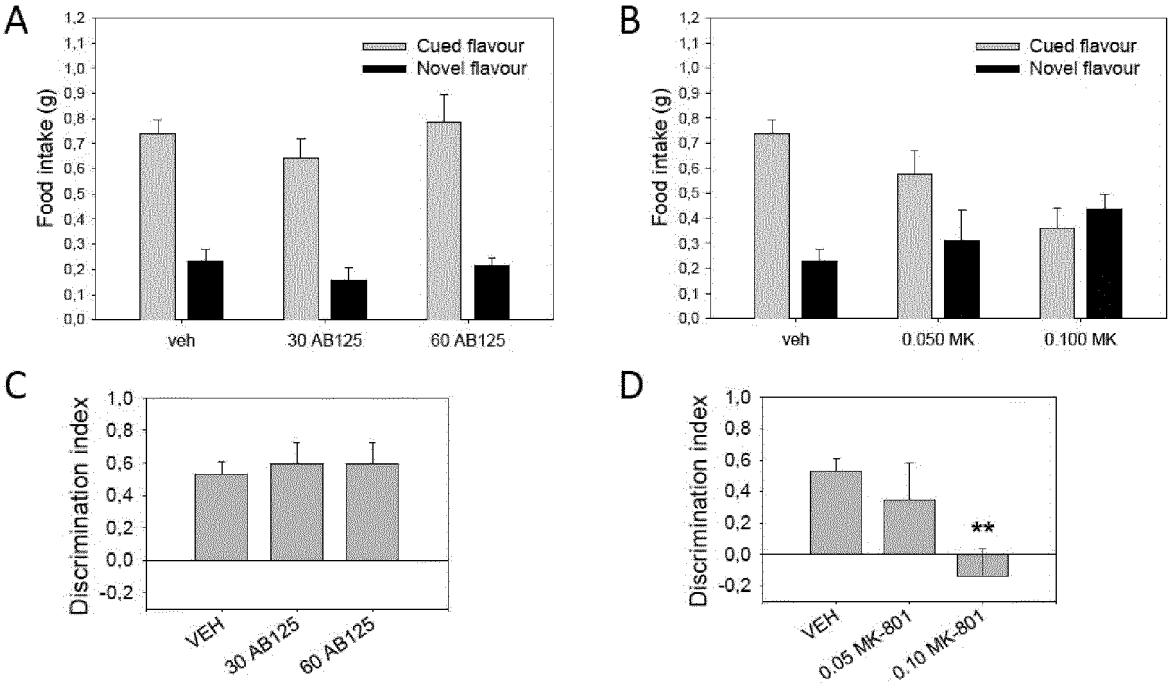

A
Food intake (g)
Cued flavour
Novel flavour
veh
30 AB125
60 AB125
B
Food intake (g)
Cued flavour
Novel flavour
veh
0.050 MK
0.100 MK
C
Discrimination index
VEH
30 AB125
60 AB125
D
Discrimination index
**
VEH
0.05 MK-801
0.10 MK-801

Figure 21

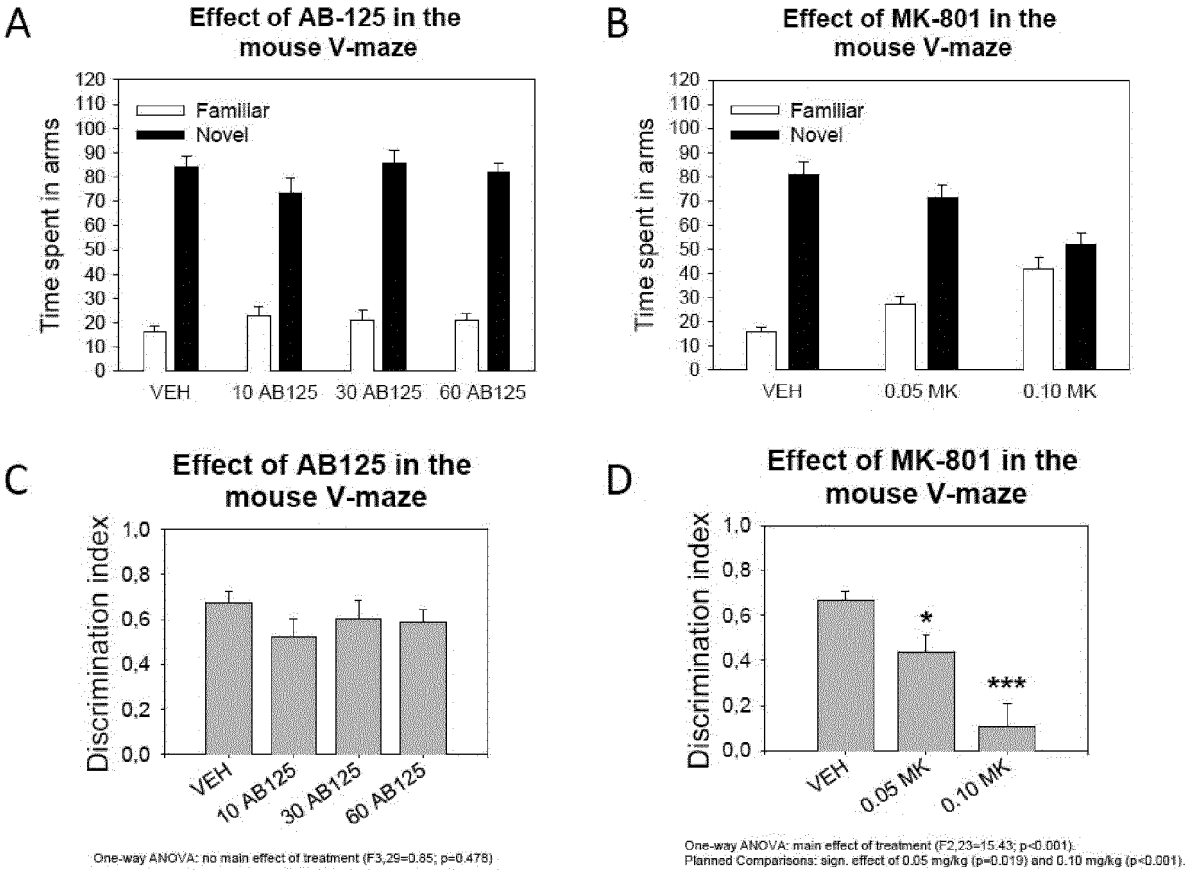

A
Effect of AB-125 in the mouse V-maze
Time spent in arms
Familiar
Novel
VEH
10 AB125
30 AB125
60 AB125
B
Effect of MK-801 in the mouse V-maze
Time spent in arms
Familiar
Novel
VEH
0.05 MK
0.10 MK
C
Effect of AB125 in the mouse V-maze
Discrimination index
VEH
10 AB125
30 AB125
60 AB125
One-way ANOVA: no main effect of treatment (F3,29=0.85; p=0.478)
D
Effect of MK-801 in the mouse V-maze
Discrimination index
*
***
VEH
0.05 MK
0.10 MK
One-way ANOVA: main effect of treatment (F2,23=15.43; p<0.001).
Planned Comparisons: sign. effect of 0.05 mg/kg (p=0.019) and 0.10 mg/kg (p<0.001).

Figure 22

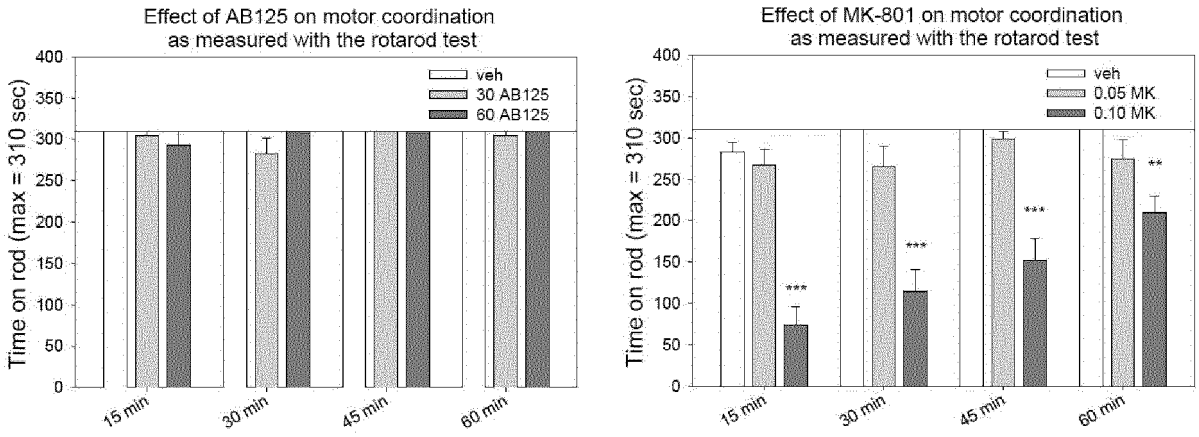
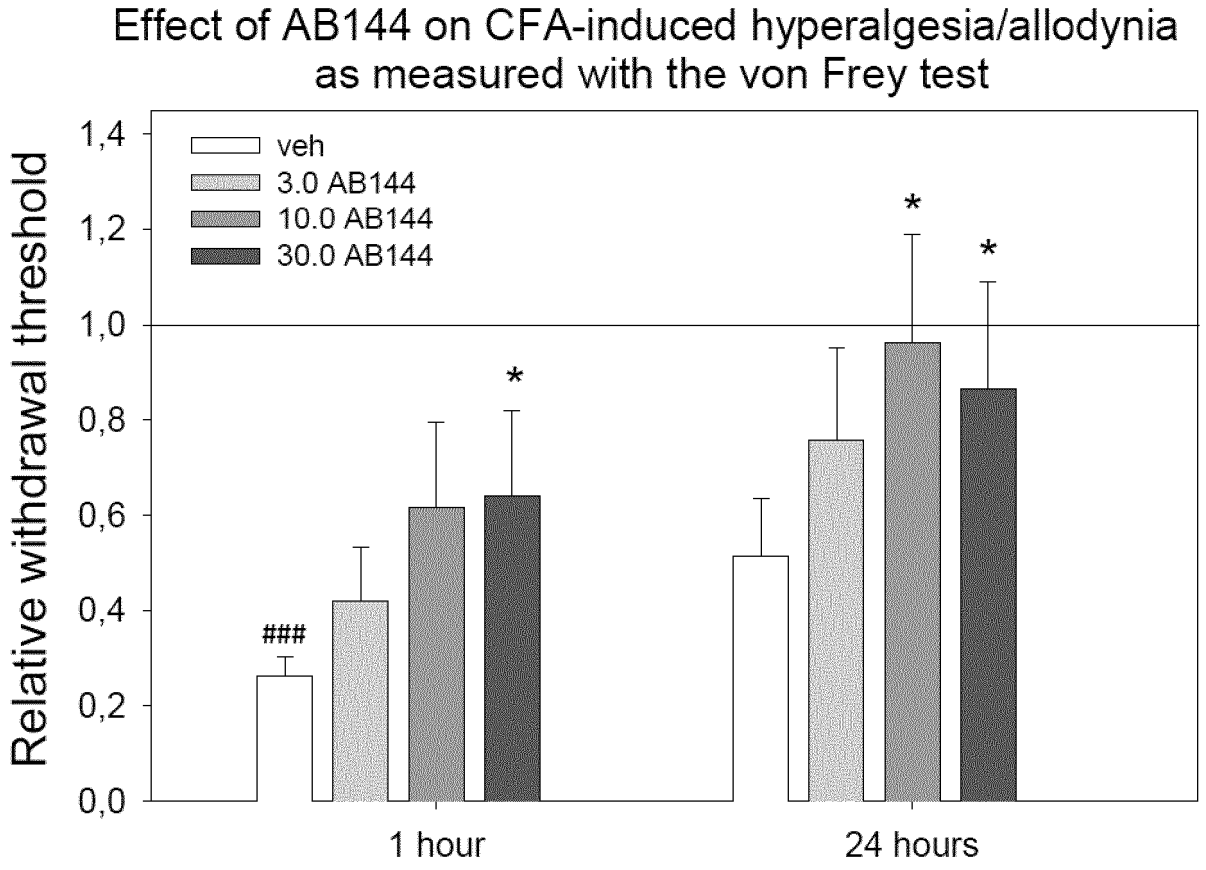

Effect of AB125 on motor coordination
as measured with the rotarod test
Time on rod (max = 310 sec)
400
350
300
250
200
150
100
50
0
veh
30 AB125
60 AB125
15 min
30 min
45 min
60 min
Effect of MK-801 on motor coordination
as measured with the rotarod test
Time on rod (max = 310 sec)
veh
0.05 MK
0.10 MK
***
***
***
**
15 min
30 min
45 min
60 min

Figure 23


Effect of AB144 on CFA-induced hyperalgesia/allodynia as measured with the von Frey test
Relative withdrawal threshold
1,4
1,2
1,0
0,8
0,6
0,4
0,2
0,0
veh
3.0 AB144
10.0 AB144
30.0 AB144
###
*
*
*
1 hour
24 hours