FIG. 1

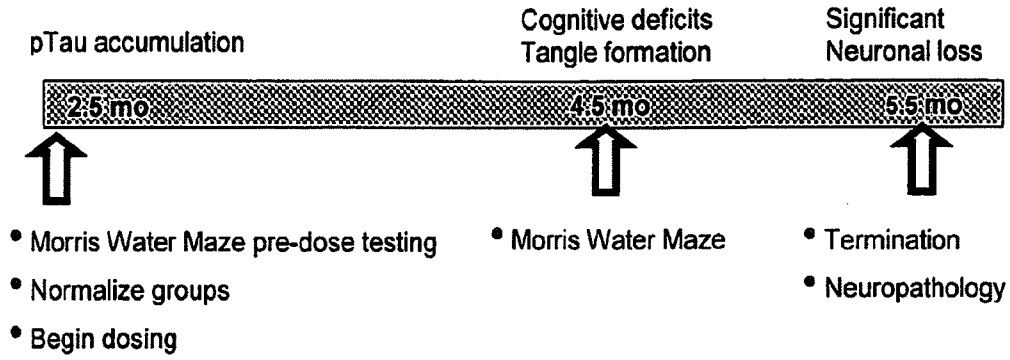

pTau accumulation
Cognitive deficits
Tangle formation
Significant
Neuronal loss
2.5 mo
4.5 mo
5.5 mo
• Morris Water Maze pre-dose testing
• Normalize groups
• Begin dosing
• Morris Water Maze
• Termination
• Neuropathology

FIG. 2

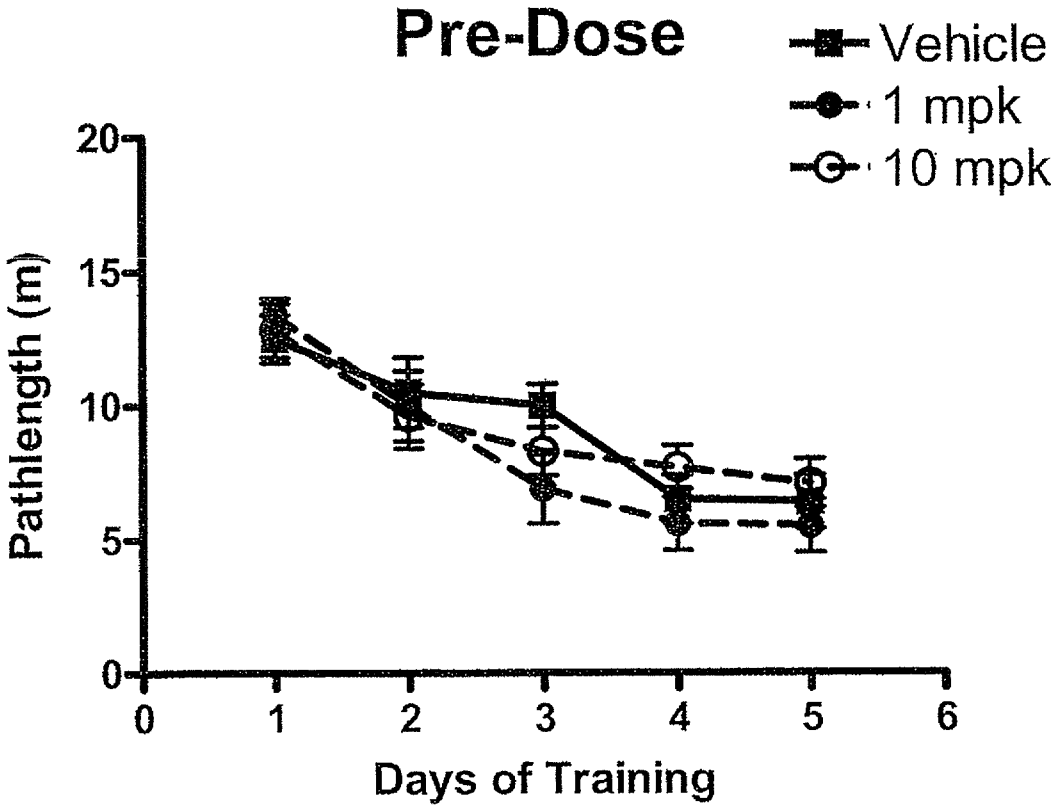

Pre-Dose
Vehicle
1 mpk
10 mpk
Pathlength (m)
20
15
10
5
0
0
1
2
3
4
5
6
Days of Training

FIG. 3

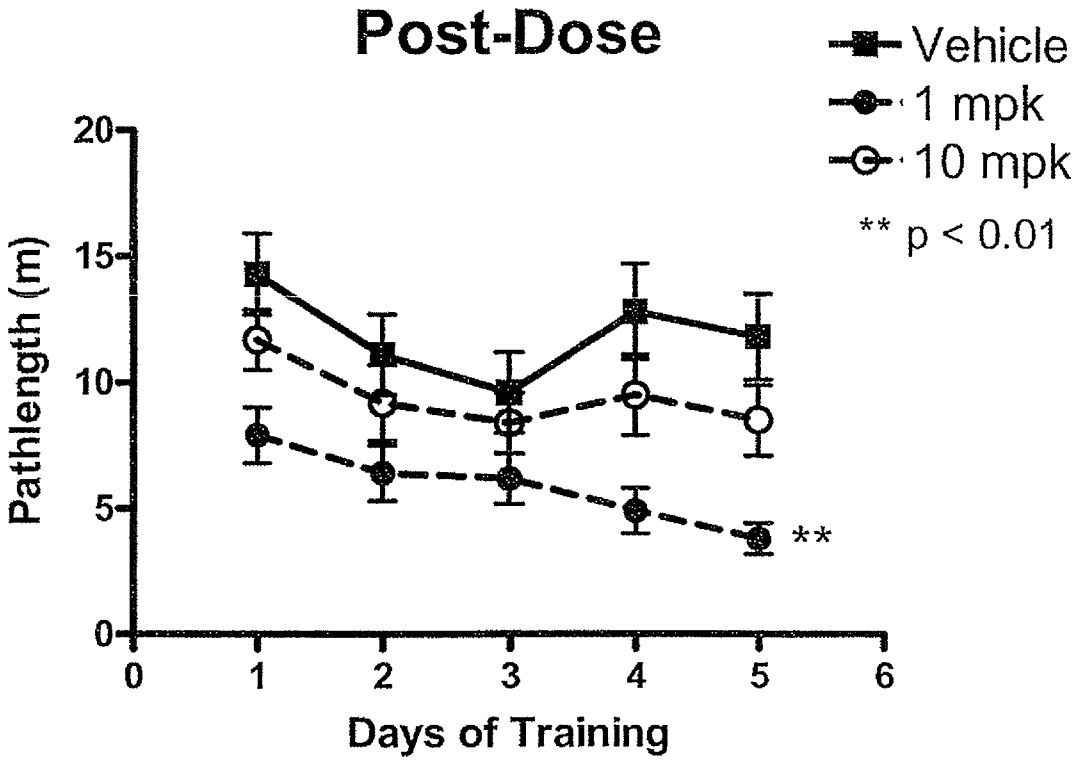

Post-Dose
Vehicle
1 mpk
10 mpk
** p < 0.01
Pathlength (m)
20
15
10
5
0
0
1
2
3
4
5
6
**
Days of Training

FIG. 4

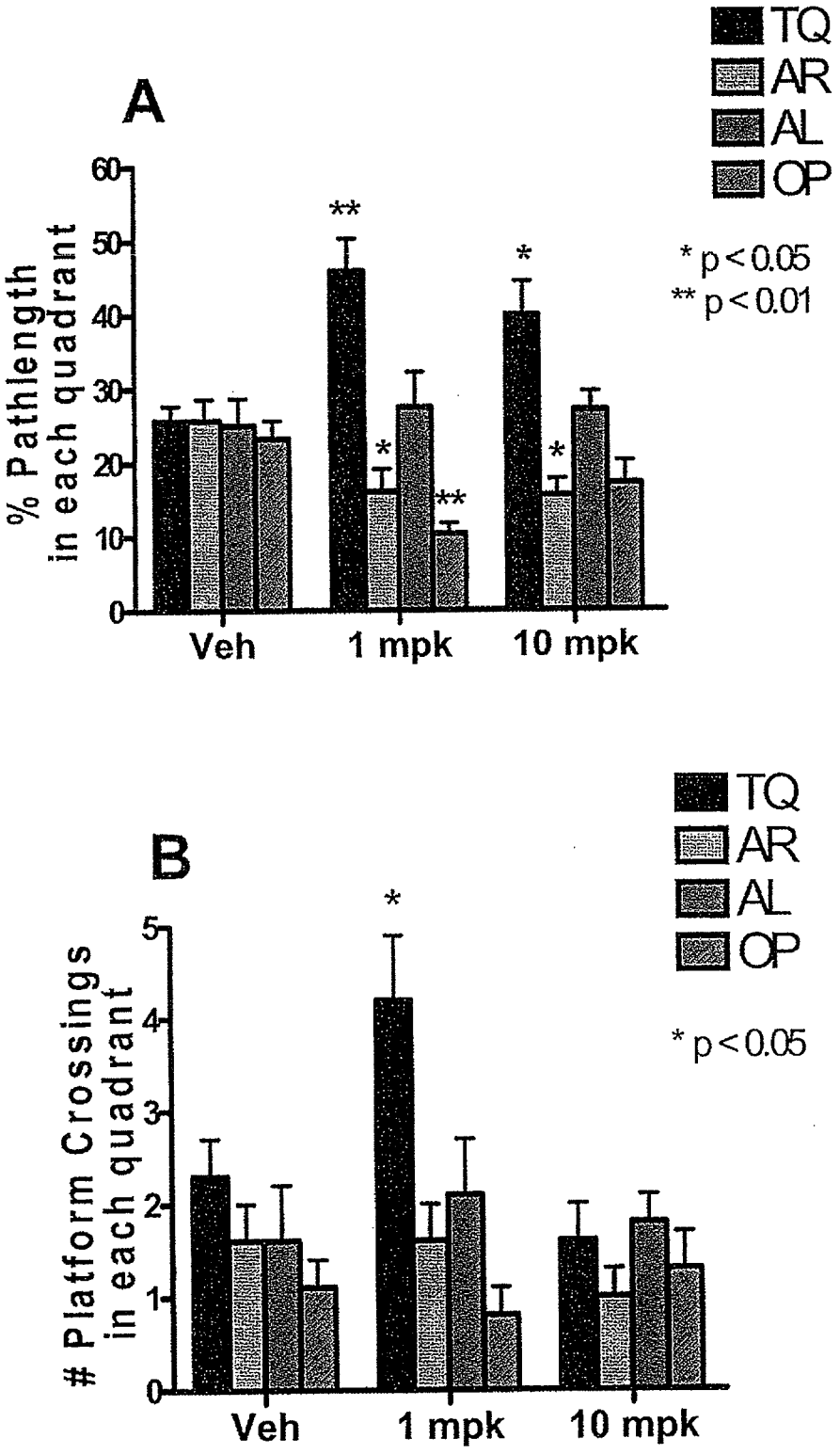

A
% Pathlength in each quadrant
60
50
40
30
20
10
0
**
*
*
*
**
Veh
1 mpk
10 mpk
TQ
AR
AL
OP
* p < 0.05
** p < 0.01
B
Platform Crossings in each quadrant
5
4
3
2
1
0
*
Veh
1 mpk
10 mpk
TQ
AR
AL
OP
* p < 0.05

FIG. 5

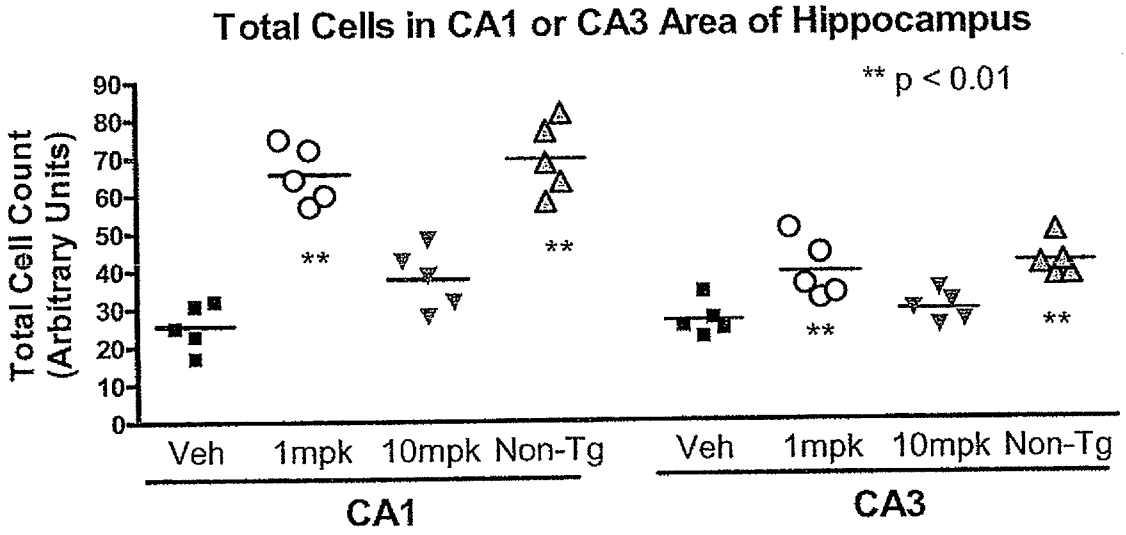

Total Cells in CA1 or CA3 Area of Hippocampus
** p < 0.01
Total Cell Count (Arbitrary Units)
90
80
70
60
50
40
30
20
10
0
**
**
**
**
Veh
1mpk
10mpk
Non-Tg
Veh
1mpk
10mpk
Non-Tg
CA1
CA3

FIG. 6

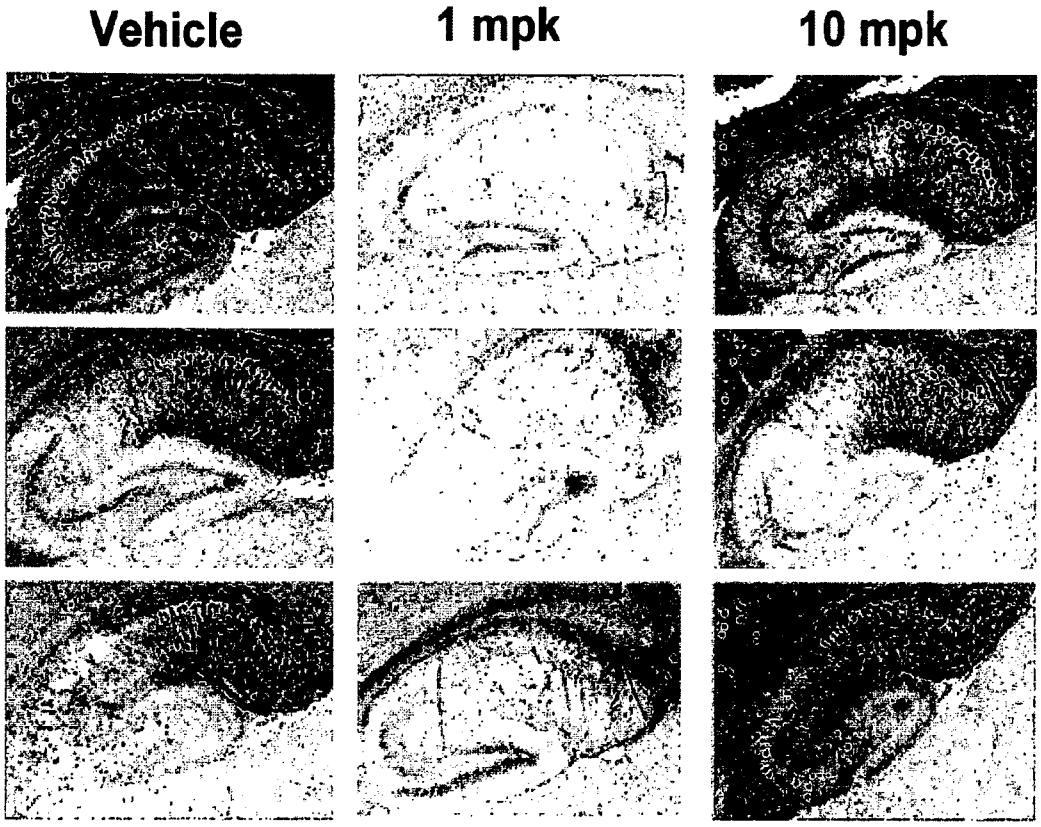


FIG. 7A

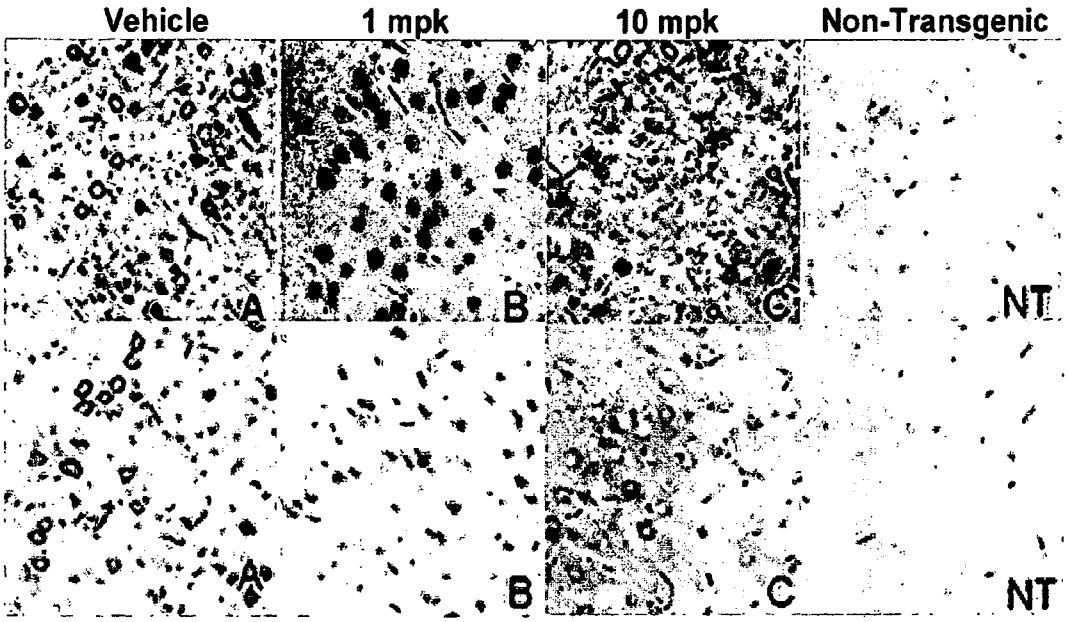

Vehicle
1 mpk
10 mpk
Non-Transgenic
A
B
C
NT
A
B
C
NT

FIG. 7B

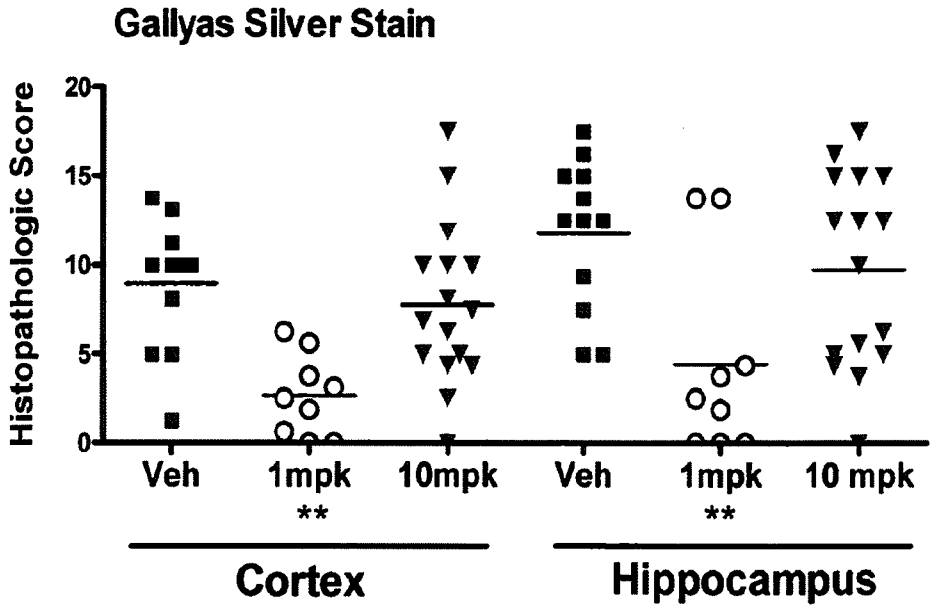

Gallyas Silver Stain
Histopathologic Score
20
15
10
5
0
Veh
1mpk
10mpk
Veh
1mpk
10 mpk
**
**
Cortex
Hippocampus

FIG. 8A

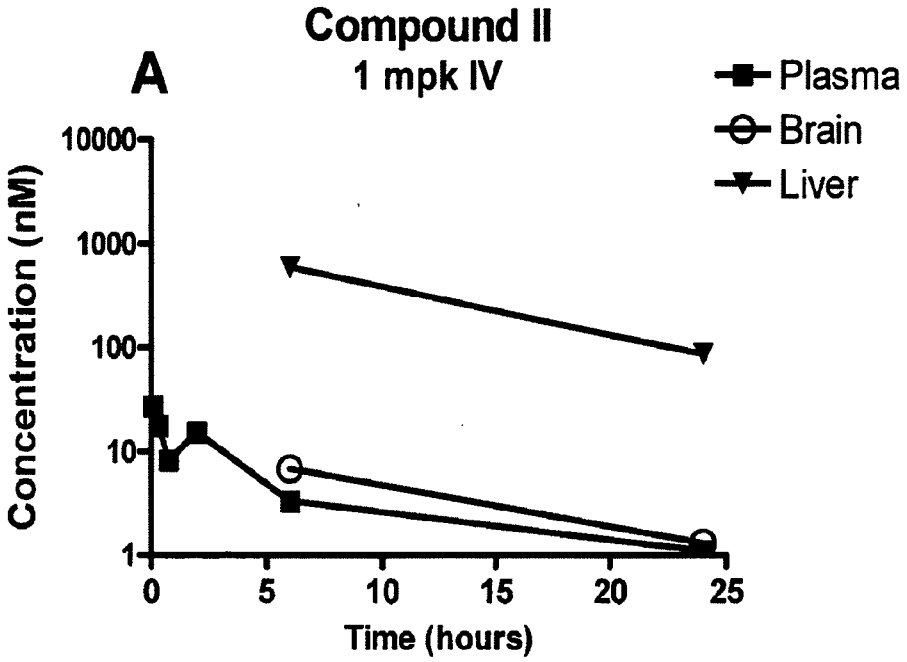

Compound II
1 mpk IV
A
Plasma
Brain
Liver
Concentration (nM)
10000
1000
100
10
1
0
5
10
15
20
25
Time (hours)

FIG. 8B

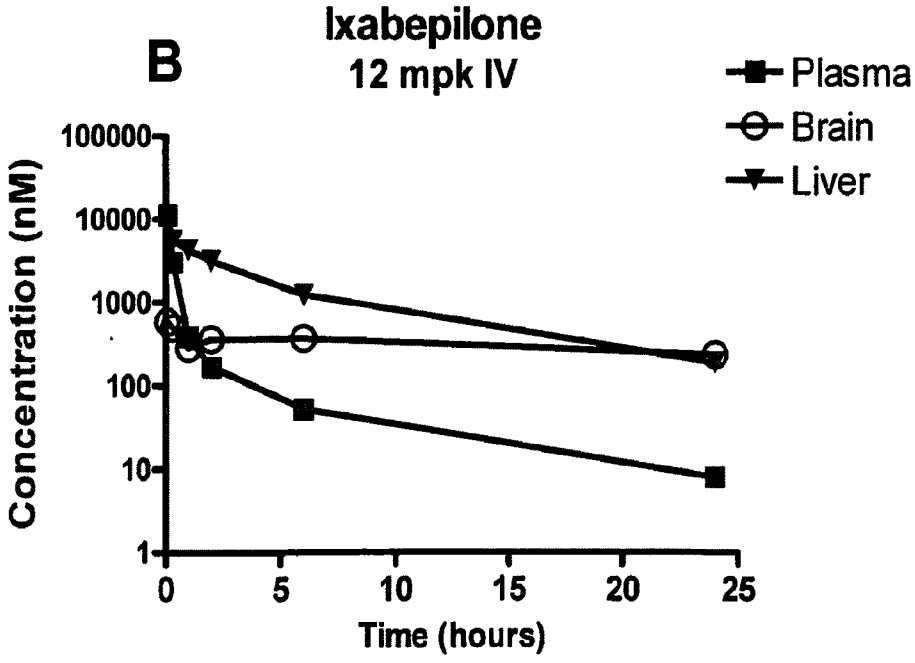

Ixabepilone
12 mpk IV
B
Plasma
Brain
Liver
Concentration (nM)
100000
10000
1000
100
10
1
0
5
10
15
20
25
Time (hours)

FIG. 8C

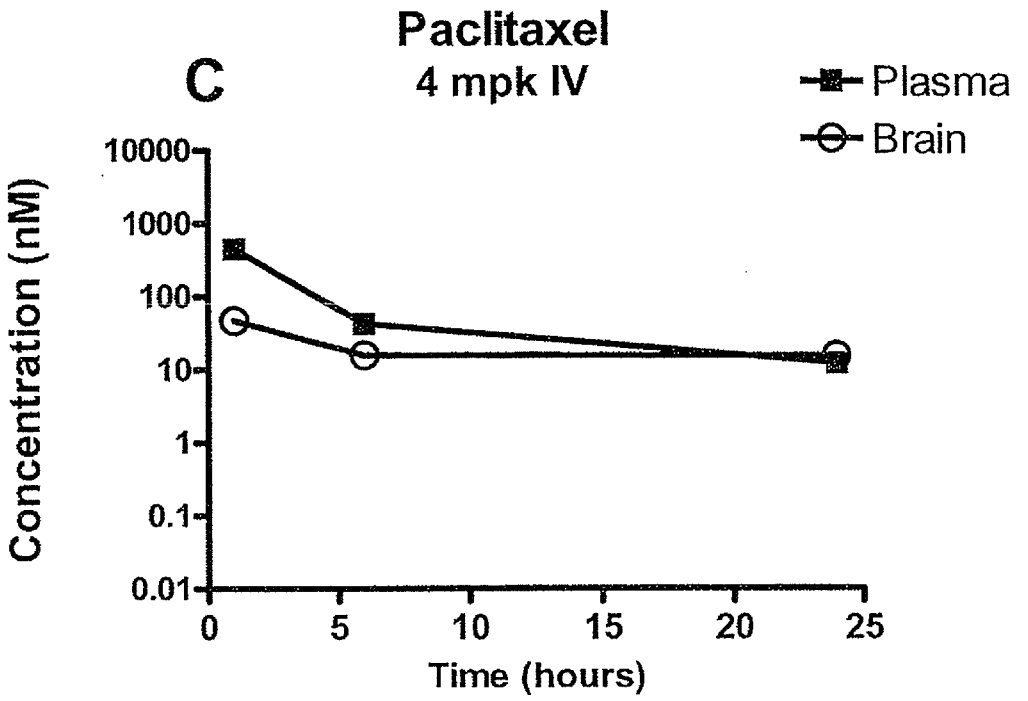

Paclitaxel
4 mpk IV
C
Plasma
Brain
Concentration (nM)
10000
1000
100
10
1
0.1
0.01
0
5
10
15
20
25
Time (hours)

FIG. 8D

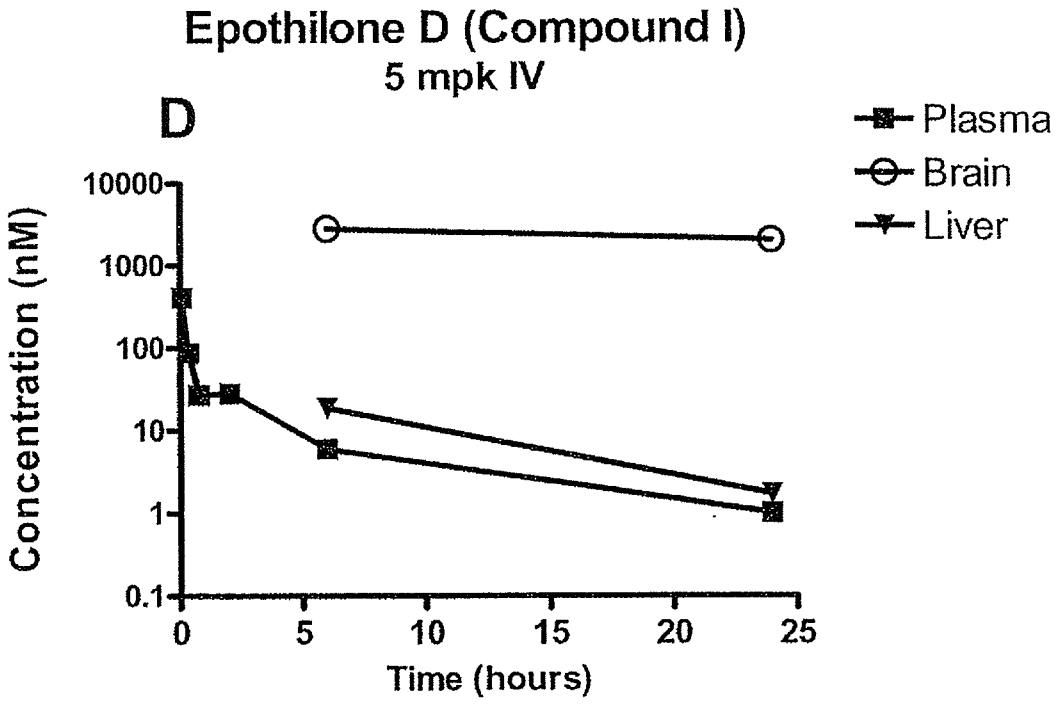

Epothilone D (Compound I)
5 mpk IV
D
Plasma
Brain
Liver
Concentration (nM)
10000
1000
100
10
1
0.1
0
5
10
15
20
25
Time (hours)

FIG. 9

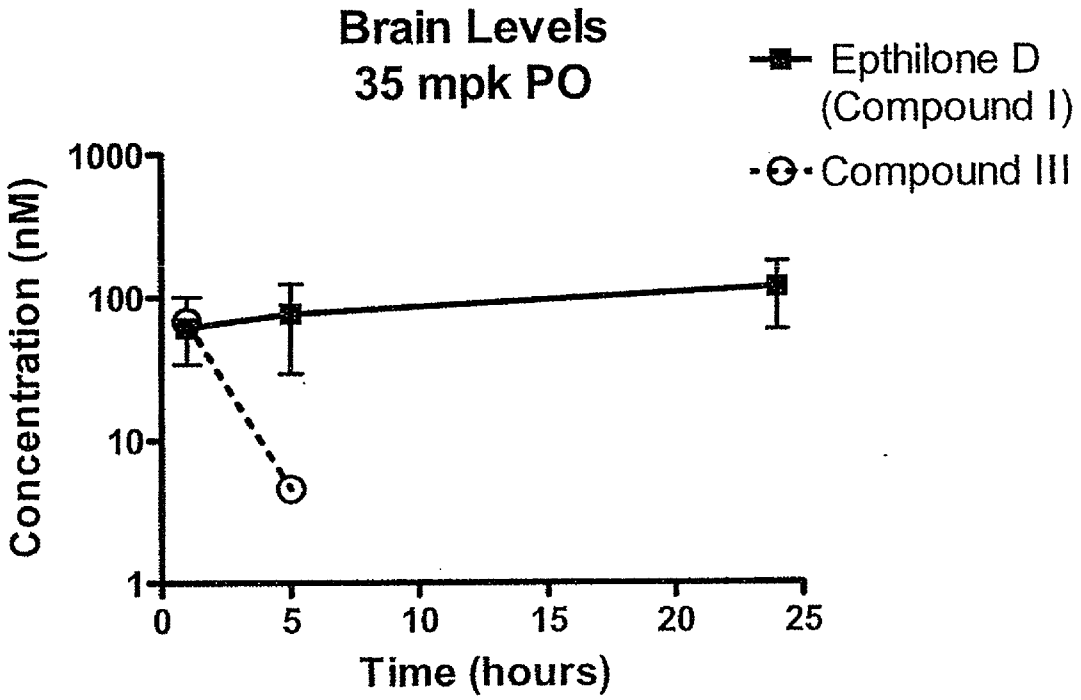
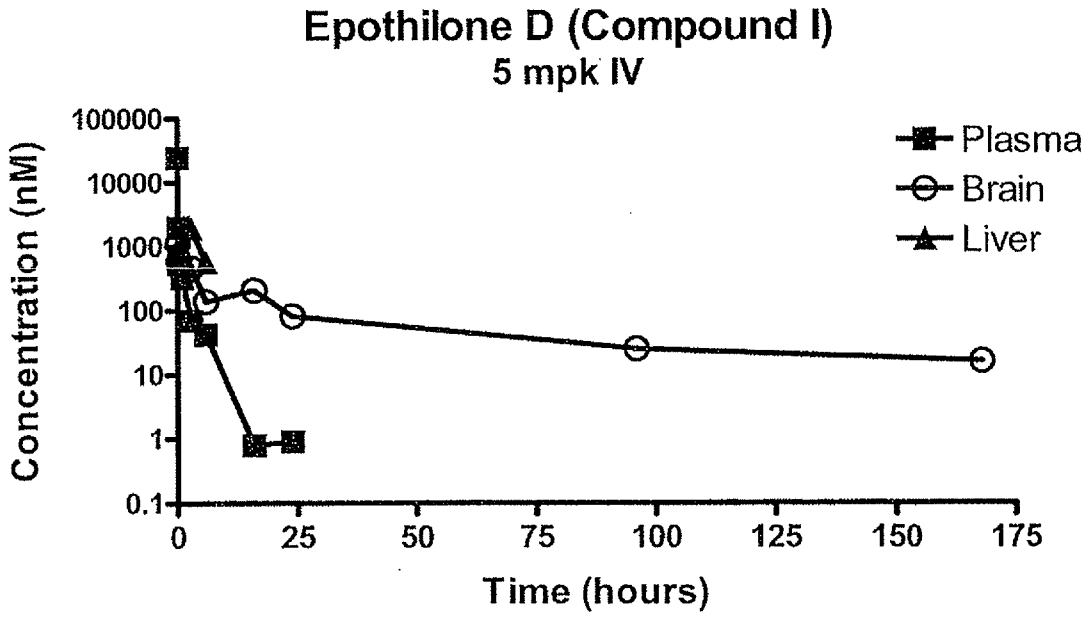

Brain Levels
35 mpk PO
Epthilone D
(Compound I)
Compound III
Concentration (nM)
1000
100
10
1
0
5
10
15
20
25
Time (hours)

FIG. 10


Epothilone D (Compound I)
5 mpk IV
Concentration (nM)
100000
10000
1000
100
10
1
0.1
0
25
50
75
100
125
150
175
Time (hours)
Plasma
Brain
Liver