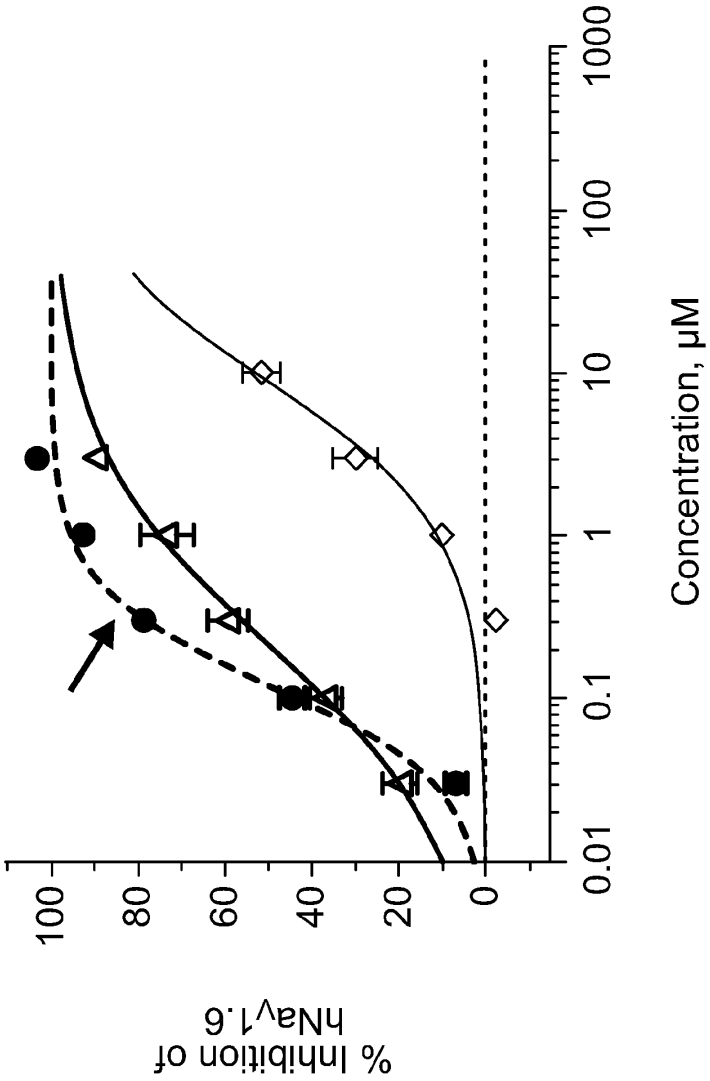

% Inhibition of
hNaV1.6
100
80
60
40
20
0
0.01
0.1
1
10
100
1000
Concentration, μM

FIG. 1A

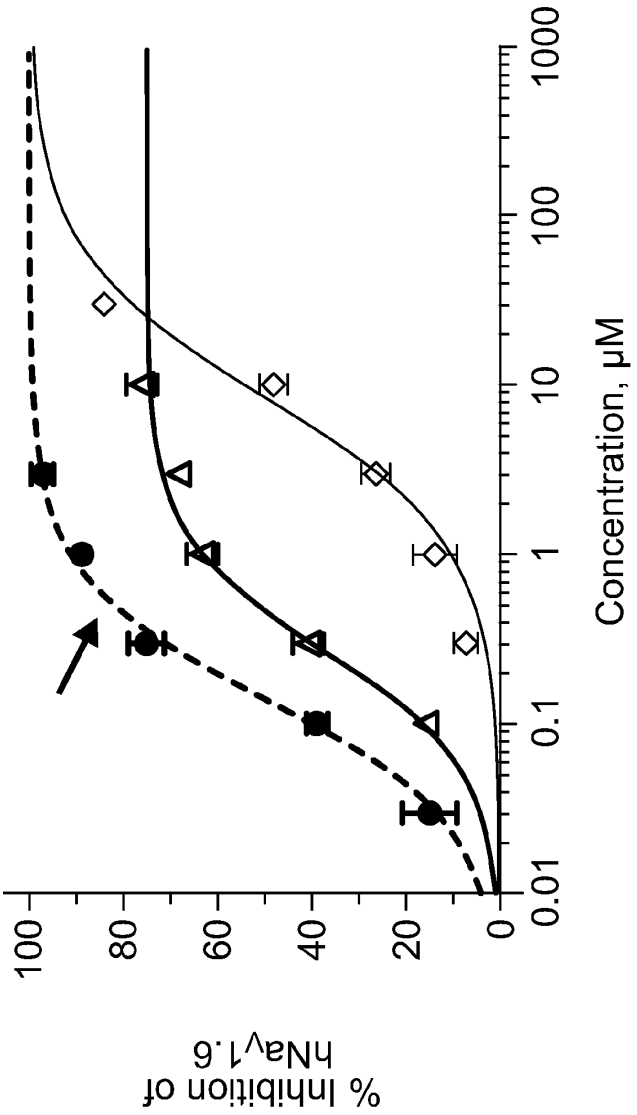

% Inhibition of
hNaV1.6
100
80
60
40
20
0
0.01
0.1
1
10
100
1000
Concentration, μM

FIG. 1B

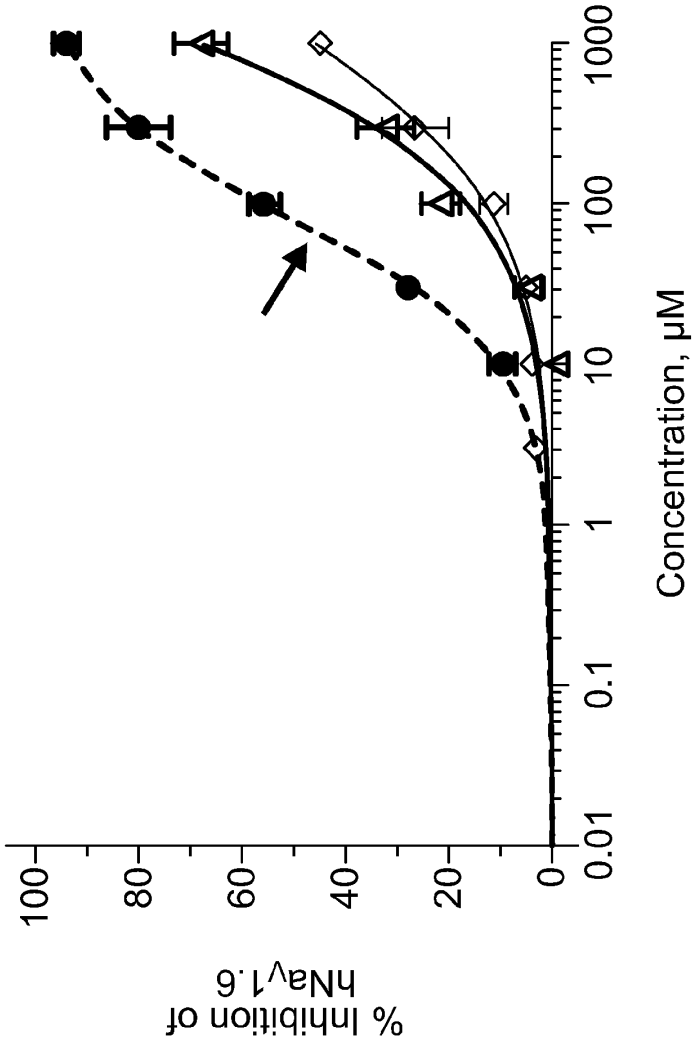

% Inhibition of
hNaV1.6
100
80
60
40
20
0
0.01
0.1
1
10
100
1000
Concentration, μM

FIG. 1C

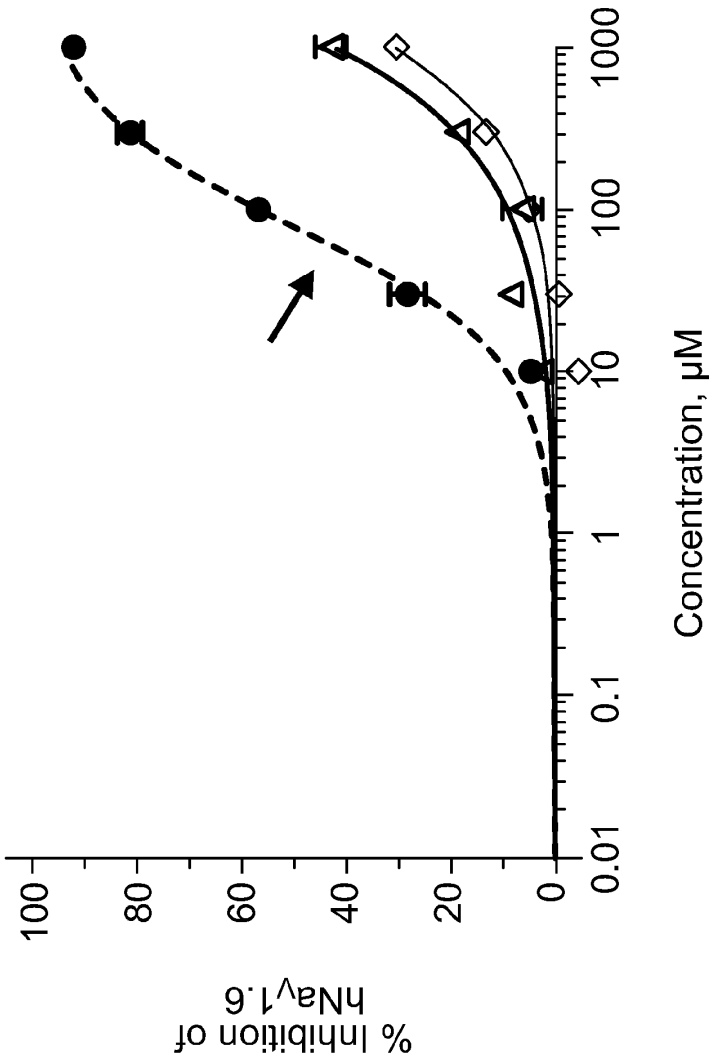

% Inhibition of
hNaV1.6
100
80
60
40
20
0
0.01
0.1
1
10
100
1000
Concentration, μM

FIG. 1D

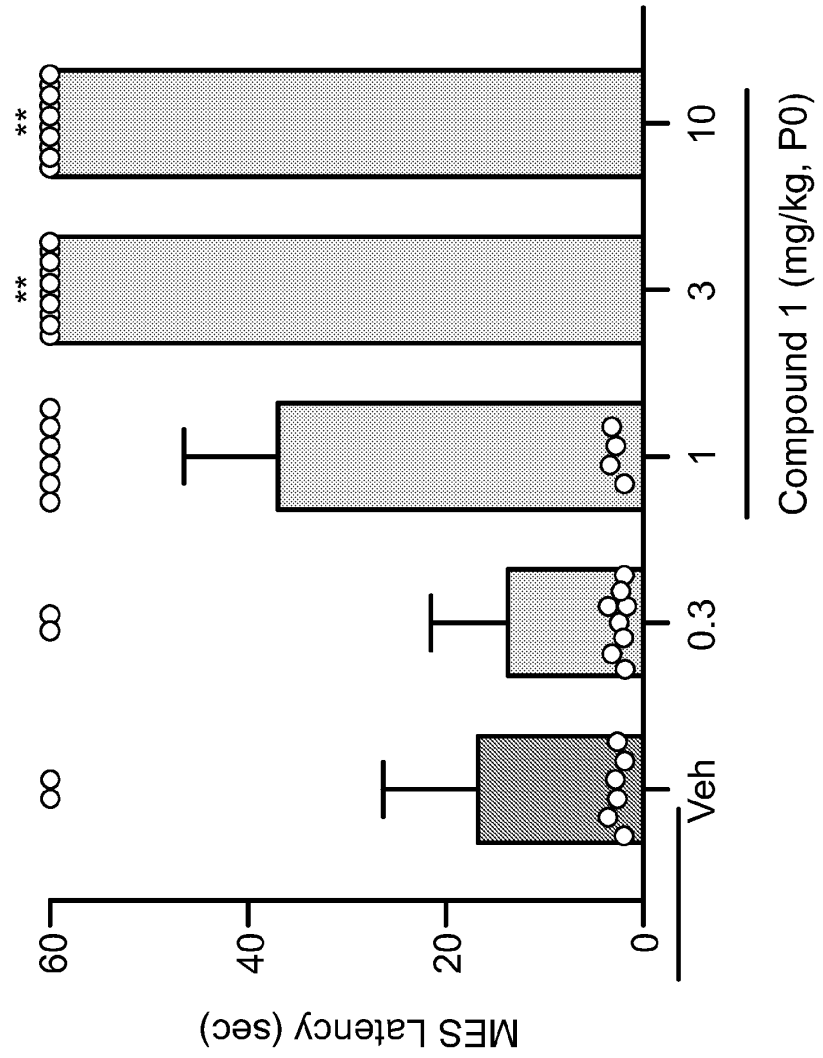


FIG. 2

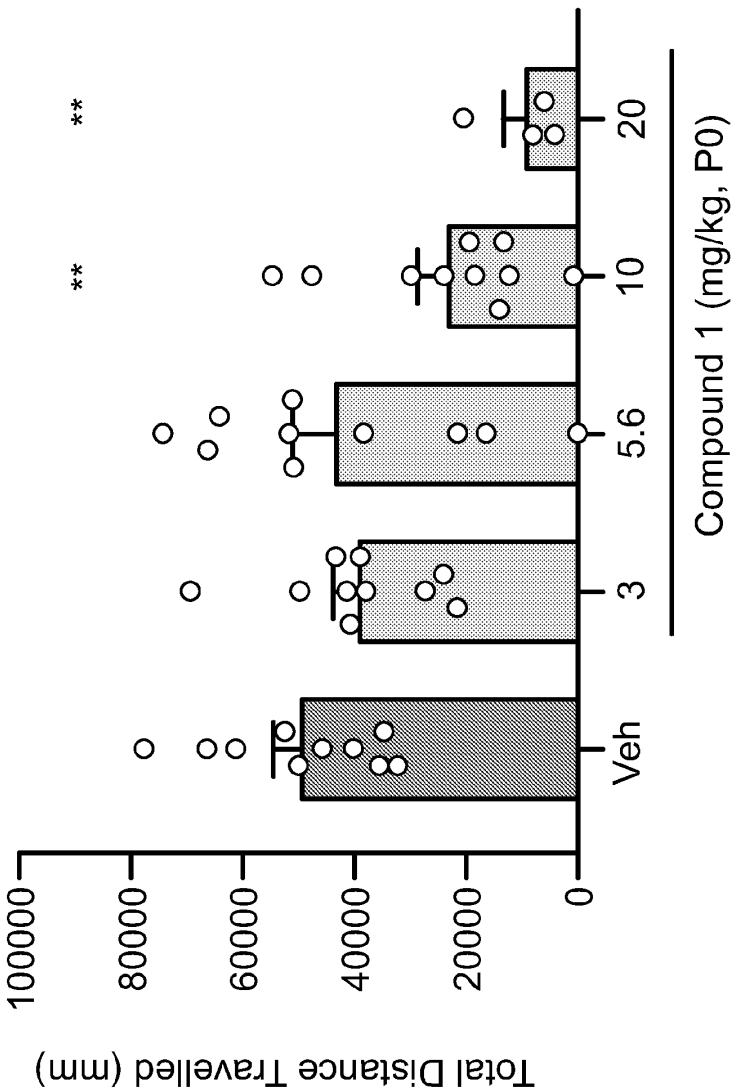

Total Distance Travelled (mm)
100000
80000
60000
40000
20000
0
**
**
Veh
3
5.6
10
20
Compound 1 (mg/kg, P0)

FIG. 3

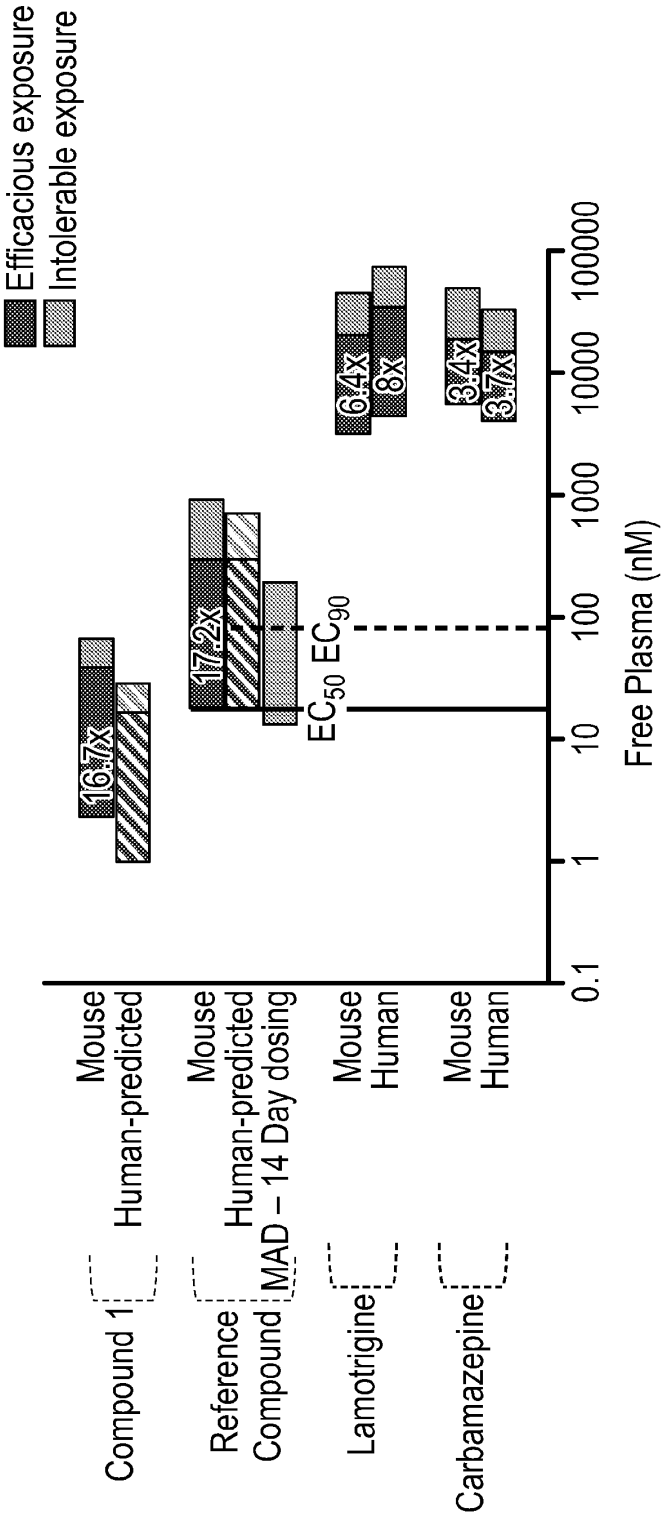

Efficacious exposure
Intolerable exposure
16.7x
17.2x
6.4x
8x
3.4x
3.7x
EC50 EC90
0.1
1
10
100
1000
10000
100000
Free Plasma (nM)
Mouse
Human-predicted
Mouse
Human-predicted
MAD – 14 Day dosing
Mouse
Human
Mouse
Human
Compound 1
Reference Compound
Lamotrigine
Carbamazepine

FIG. 4

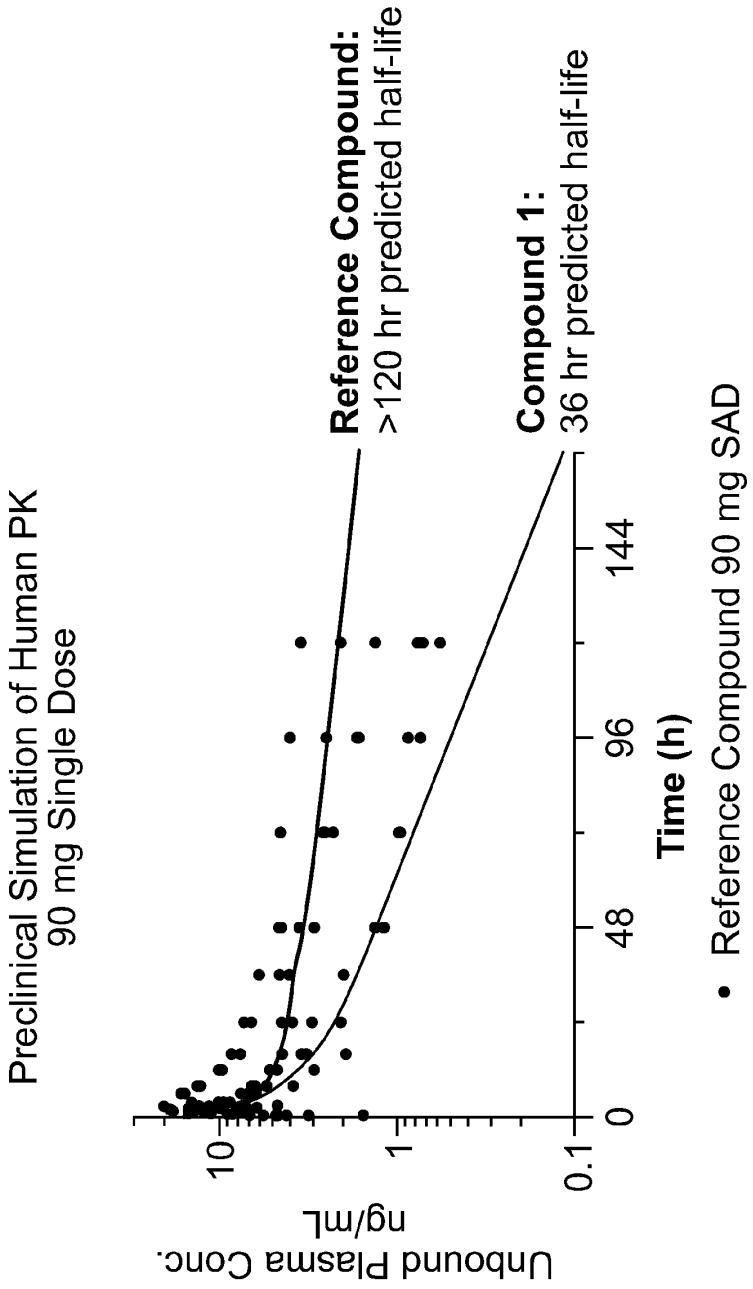

Preclinical Simulation of Human PK
90 mg Single Dose
Unbound Plasma Conc.
ng/mL
10
1
0.1
0
48
96
144
Time (h)
Reference Compound:
>120 hr predicted half-life
Compound 1:
36 hr predicted half-life
• Reference Compound 90 mg SAD

FIG. 5

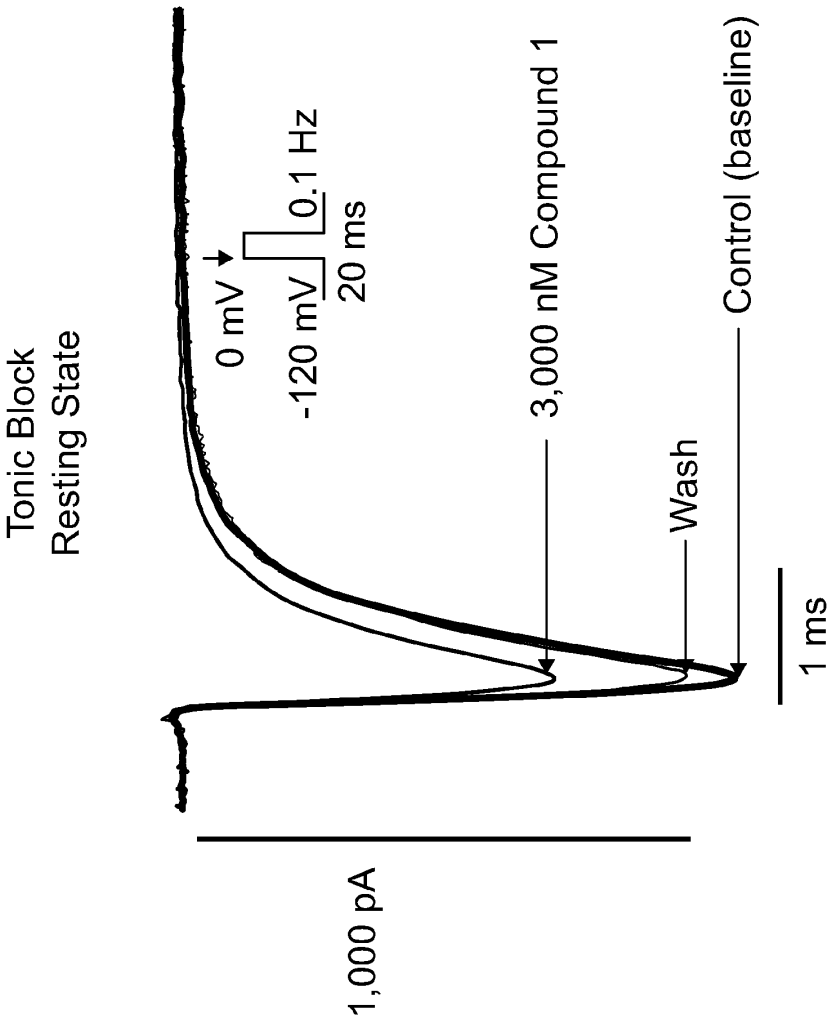

Tonic Block
Resting State
0 mV
-120 mV
0.1 Hz
20 ms
3,000 nM Compound 1
Wash
Control (baseline)
1,000 pA
1 ms

FIG. 6A

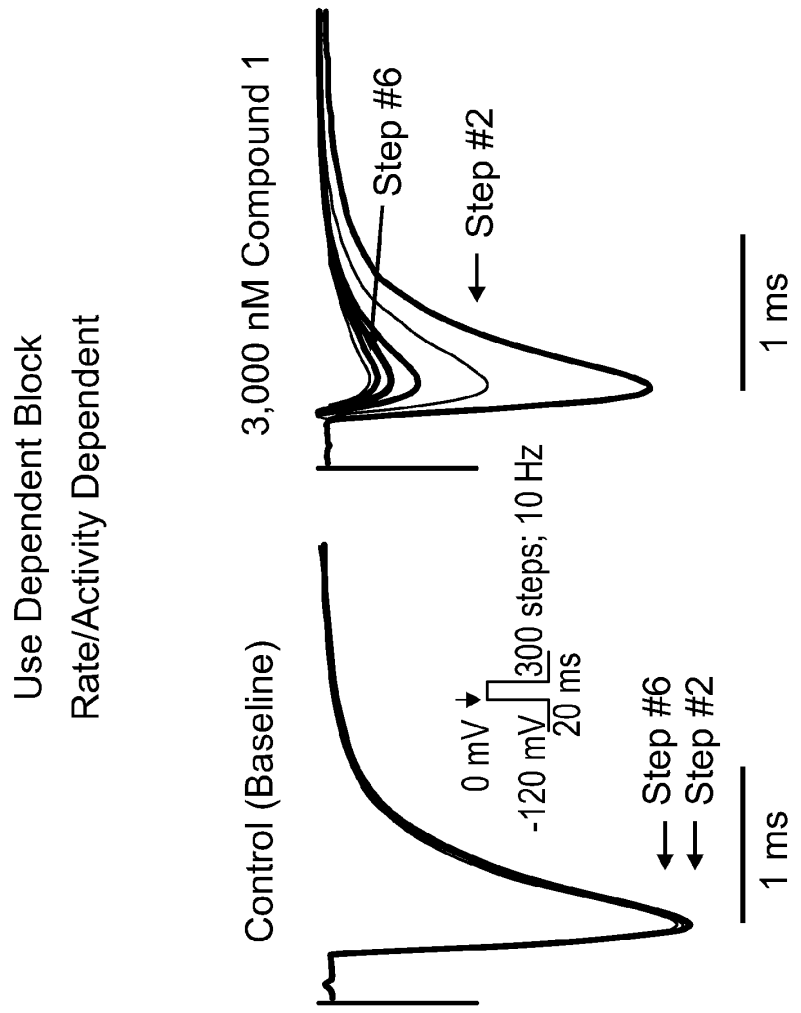

Use Dependent Block
Rate/Activity Dependent
Control (Baseline)
3,000 nM Compound 1
Step #6
Step #2
0 mV
-120 mV
20 ms
300 steps; 10 Hz
Step #6
Step #2
1 ms
1 ms

FIG. 6B

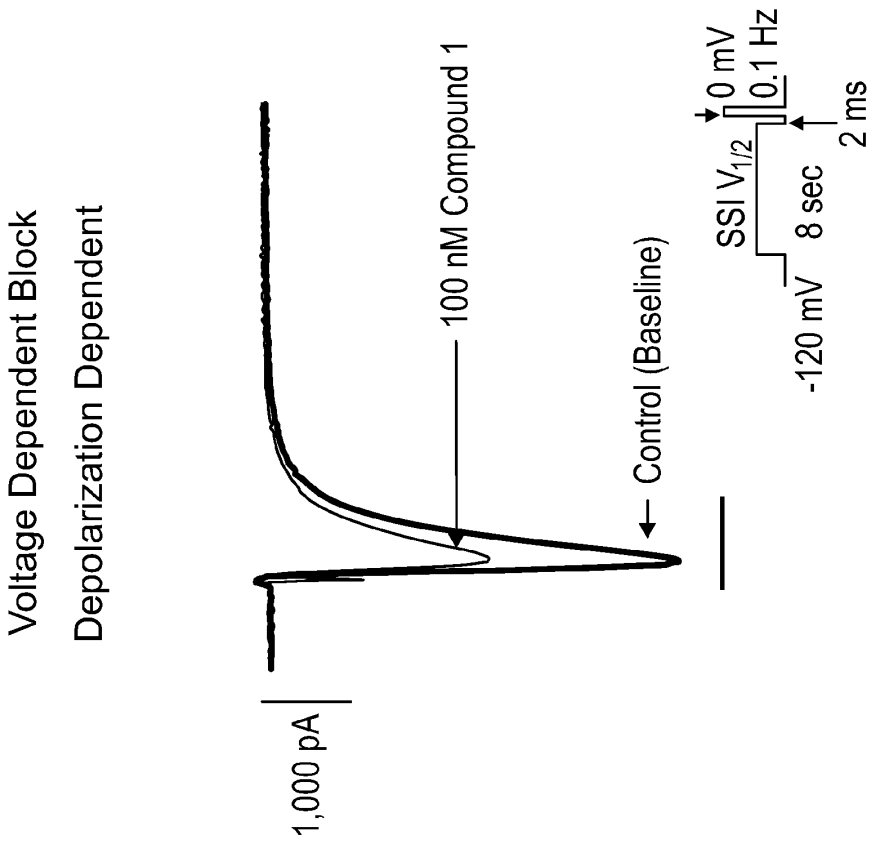

Voltage Dependent Block
Depolarization Dependent
1,000 pA
100 nM Compound 1
Control (Baseline)
SSI $V_{1/2}$
0 mV
0.1 Hz
-120 mV
8 sec
2 ms

FIG. 6C

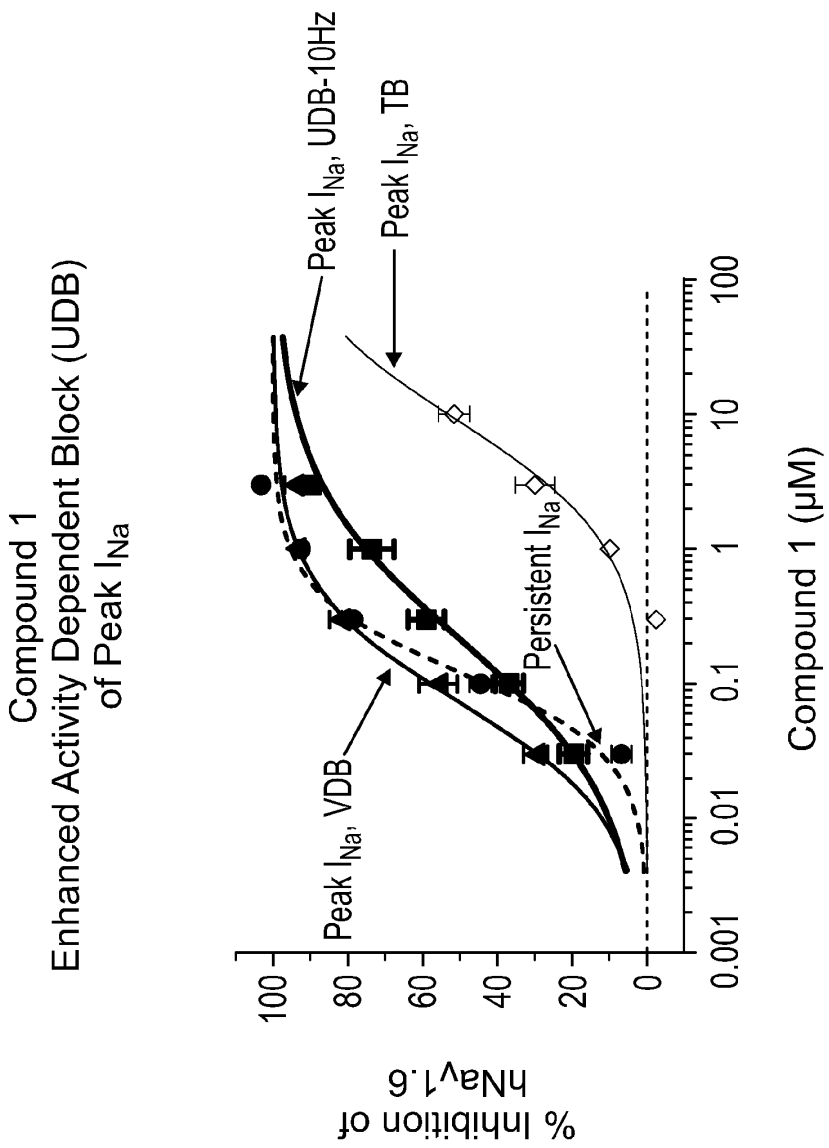

Compound 1
Enhanced Activity Dependent Block (UDB)
of Peak I_{Na}
% Inhibition of
hNav1.6
100
80
60
40
20
0
0.001
0.01
0.1
1
10
100
Compound 1 (μM)
Peak I_{Na}, UDB-10Hz
Peak I_{Na}, TB
Persistent I_{Na}
Peak I_{Na}, VDB

FIG. 7A

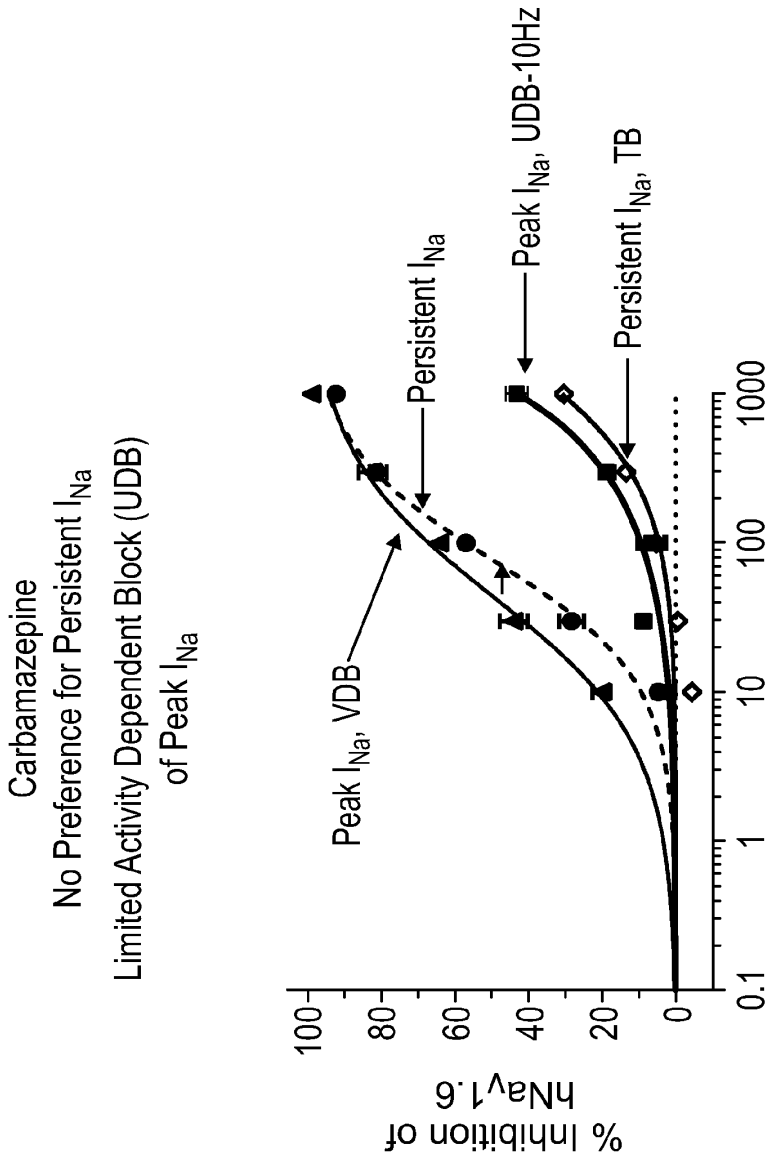

Carbamazepine
No Preference for Persistent I_{Na}
Limited Activity Dependent Block (UDB)
of Peak I_{Na}
% Inhibition of
hNaV1.6
100
80
60
40
20
0
0.1
1
10
100
1000
Carbamazepine (μM)
Peak I_{Na}, VDB
Persistent I_{Na}
Peak I_{Na}, UDB-10Hz
Persistent I_{Na}, TB

FIG. 7B

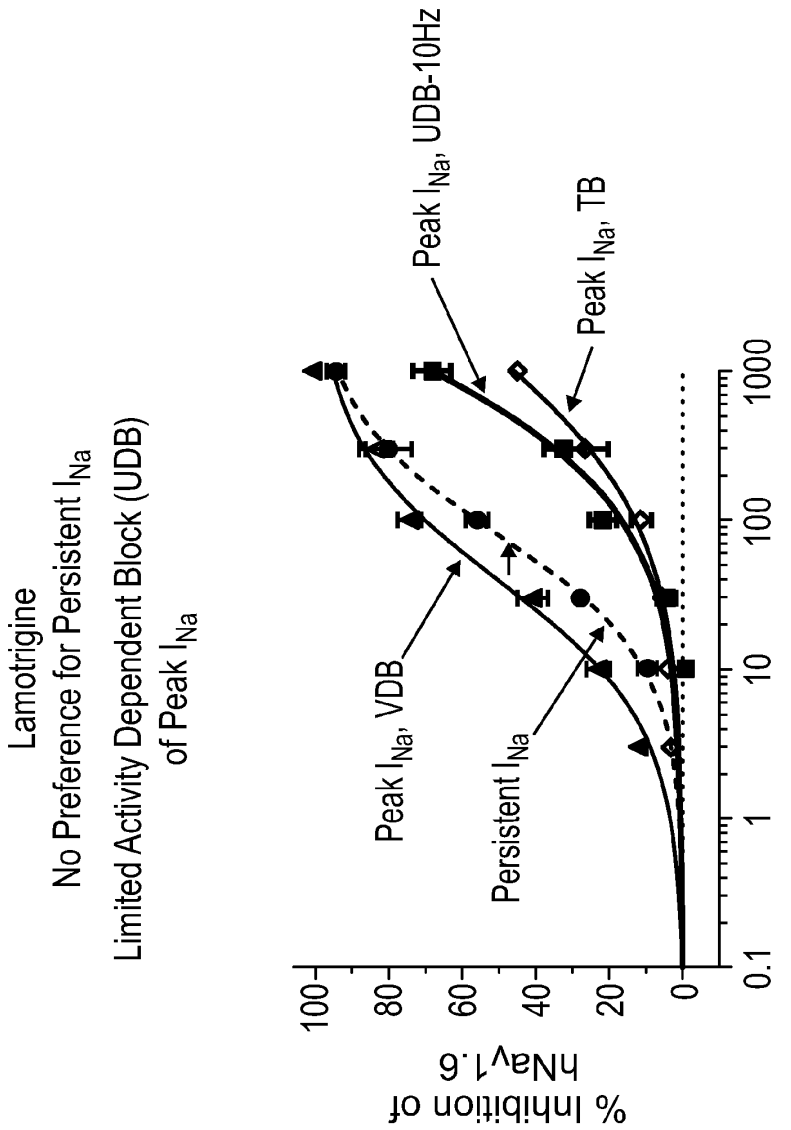

Lamotrigine
No Preference for Persistent I_{Na}
Limited Activity Dependent Block (UDB)
of Peak I_{Na}
% Inhibition of
hNav1.6
100
80
60
40
20
0
0.1
1
10
100
1000
Lamotrigine (μM)
Peak I_{Na}, VDB
Persistent I_{Na}
Peak I_{Na}, UDB-10Hz
Peak I_{Na}, TB

FIG. 7C

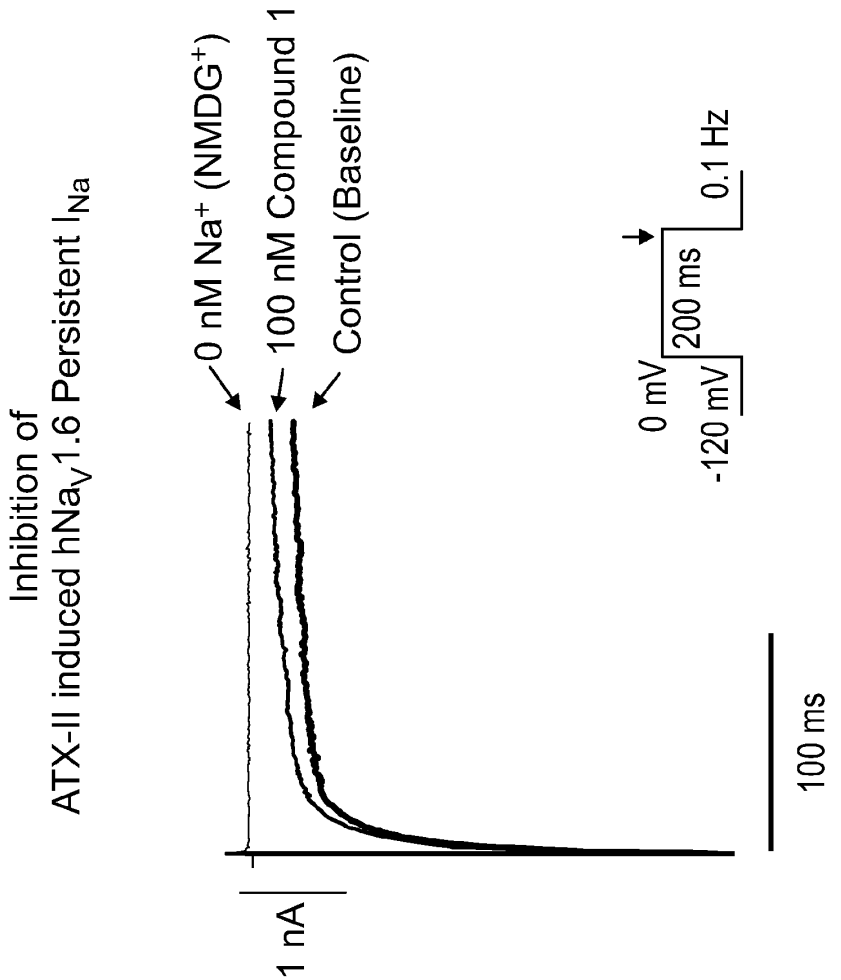

Inhibition of
ATX-II induced hNa$_V$1.6 Persistent I_{Na}
0 nM Na^+ (NMDG$^+$)
100 nM Compound 1
Control (Baseline)
0 mV
200 ms
0.1 Hz
-120 mV
1 nA
100 ms

FIG. 8A

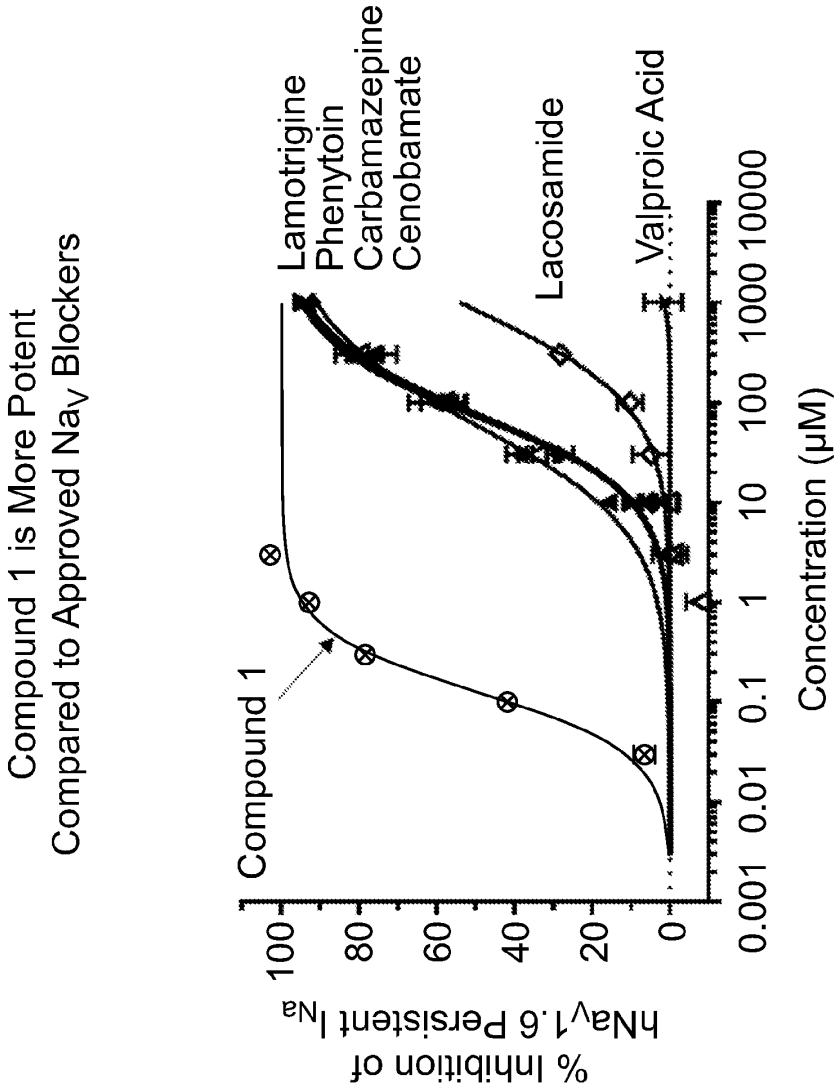

Compound 1 is More Potent
Compared to Approved Na_V Blockers
Compound 1
Lamotrigine
Phenytoin
Carbamazepine
Cenobamate
Lacosamide
Valproic Acid
% Inhibition of
hNaV1.6 Persistent I_{Na}
100
80
60
40
20
0
0.001 0.01 0.1 1 10 100 1000 10000
Concentration (μM)

FIG. 8B

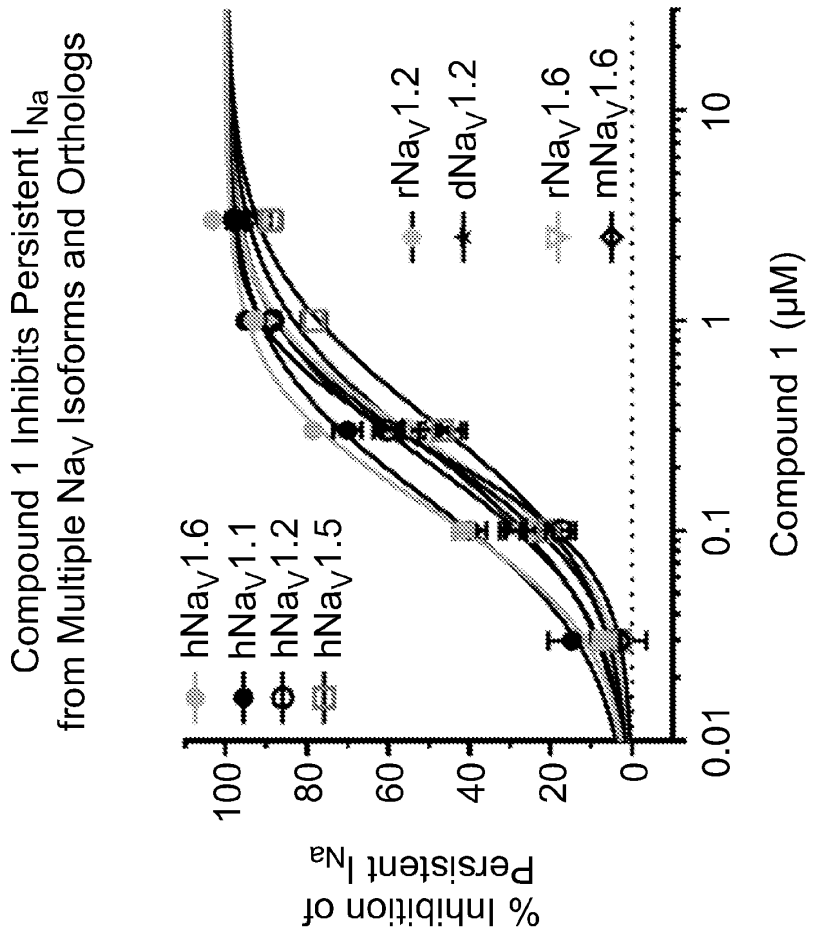

Compound 1 Inhibits Persistent I_{Na}
from Multiple Na_V Isoforms and Orthologs
% Inhibition of
Persistent I_{Na}
100
80
60
40
20
0
0.01
0.1
1
10
Compound 1 (μM)
hNaV1.6
hNaV1.1
hNaV1.2
hNaV1.5
rNaV1.2
dNaV1.2
rNaV1.6
mNaV1.6

FIG. 8C

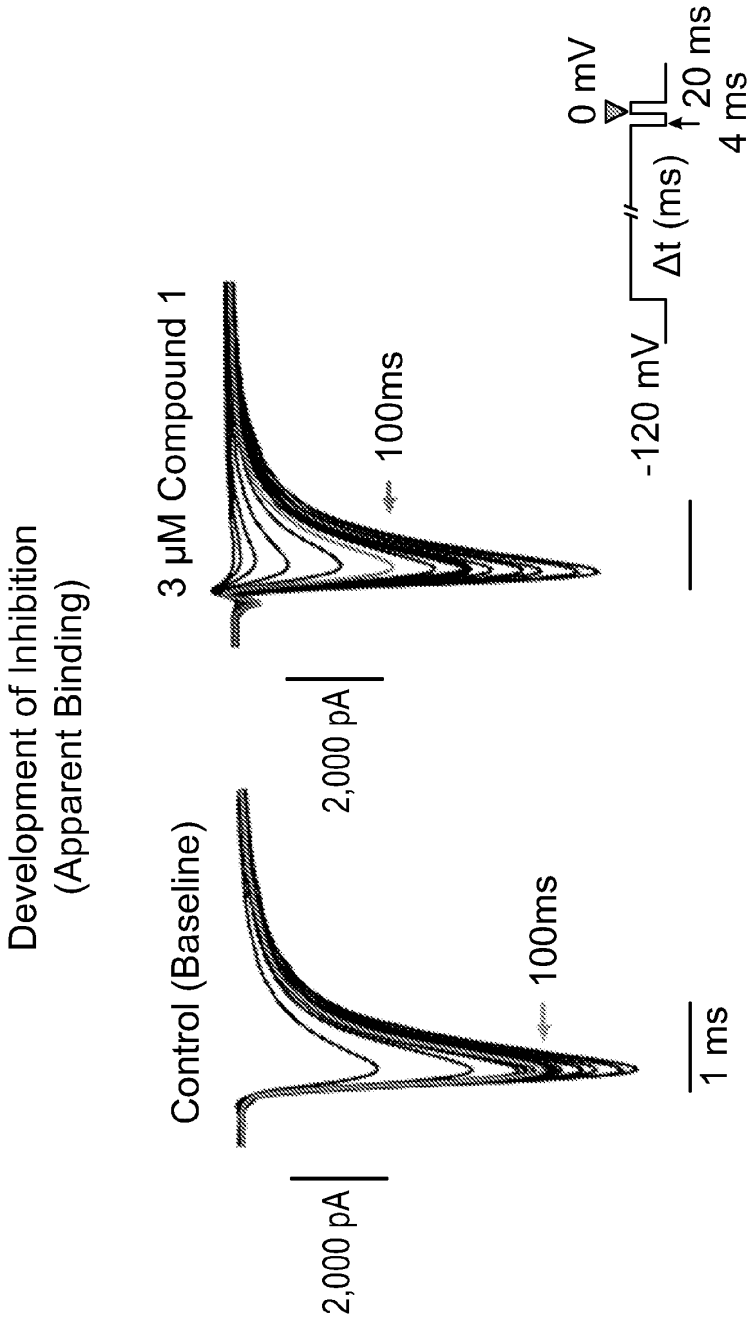

Development of Inhibition
(Apparent Binding)
Control (Baseline)
3 μM Compound 1
100ms
100ms
2,000 pA
2,000 pA
1 ms
-120 mV
Δt (ms)
0 mV
20 ms
4 ms

FIG. 9A

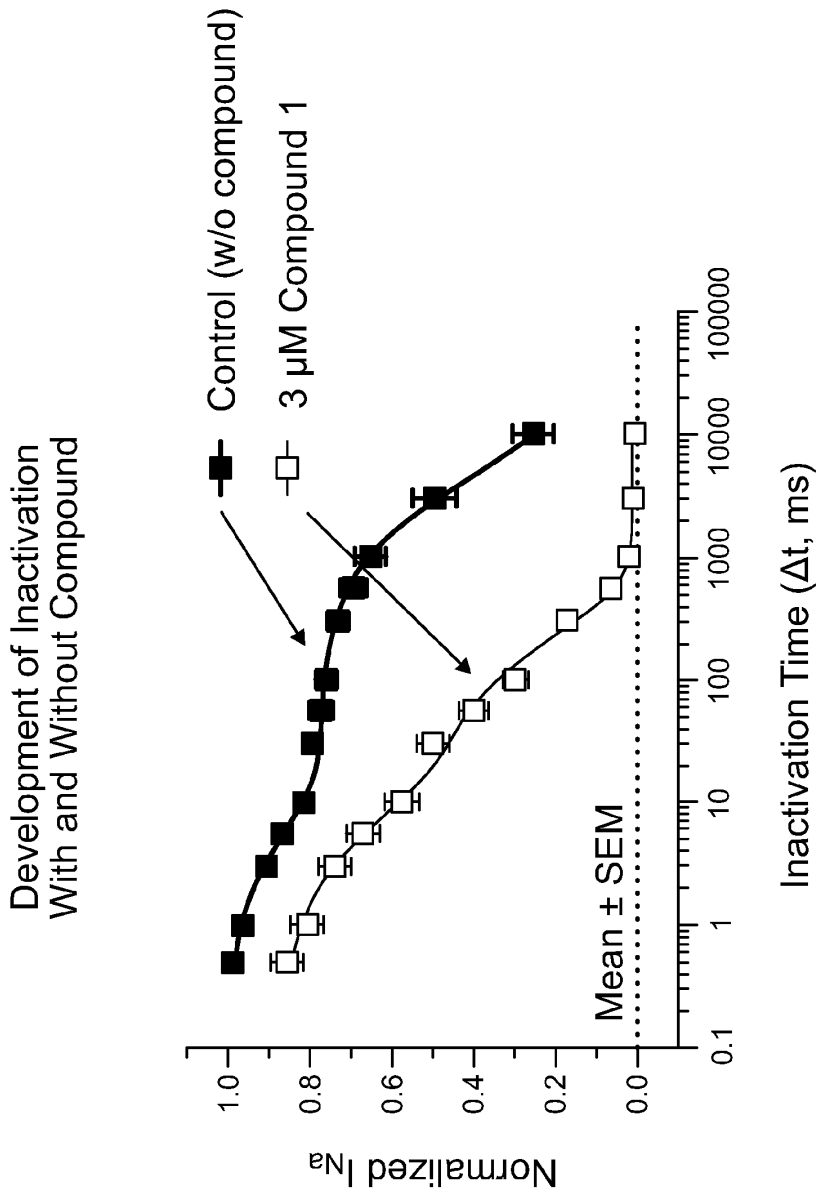

Development of Inactivation
With and Without Compound
Control (w/o compound)
3 µM Compound 1
Mean ± SEM
Normalized I_{Na}
1.0
0.8
0.6
0.4
0.2
0.0
0.1
1
10
100
1000
10000
100000
Inactivation Time (Δt, ms)

FIG. 9B

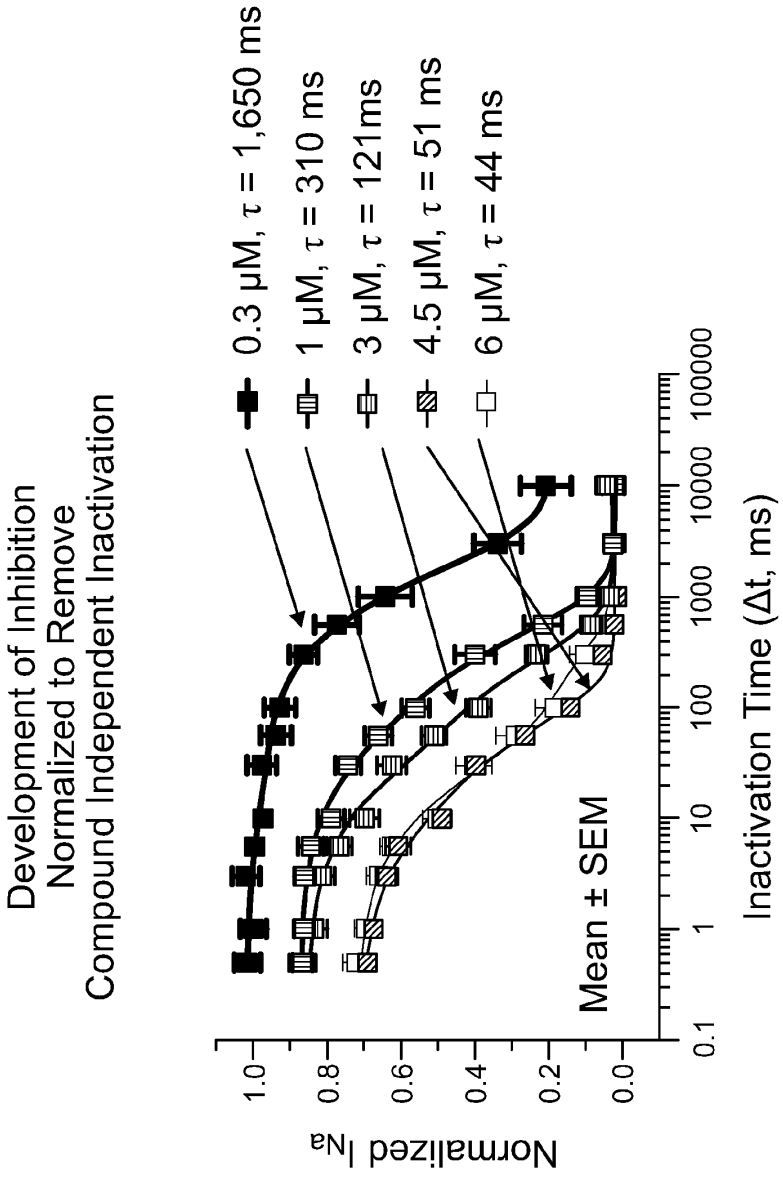

Development of Inhibition
Normalized to Remove
Compound Independent Inactivation
0.3 µM, τ = 1,650 ms
1 µM, τ = 310 ms
3 µM, τ = 121ms
4.5 µM, τ = 51 ms
6 µM, τ = 44 ms
Mean ± SEM
Normalized I_Na
1.0
0.8
0.6
0.4
0.2
0.0
0.1
1
10
100
1000
10000
100000
Inactivation Time (Δt, ms)

FIG. 9C

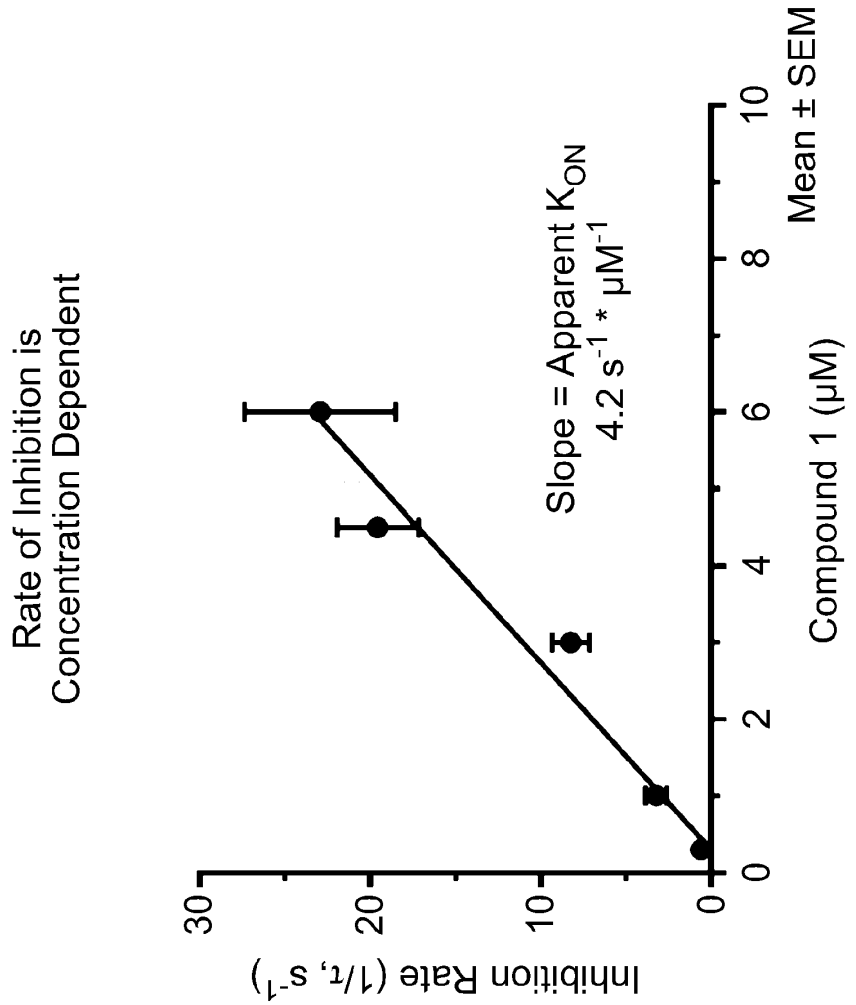

Rate of Inhibition is
Concentration Dependent
Slope = Apparent K_{ON}
4.2 s^{-1} * μM^{-1}
Inhibition Rate ($1/\tau$, s^{-1})
Compound 1 (μM)
Mean ± SEM
0
10
20
30
0
2
4
6
8
10

FIG. 9D

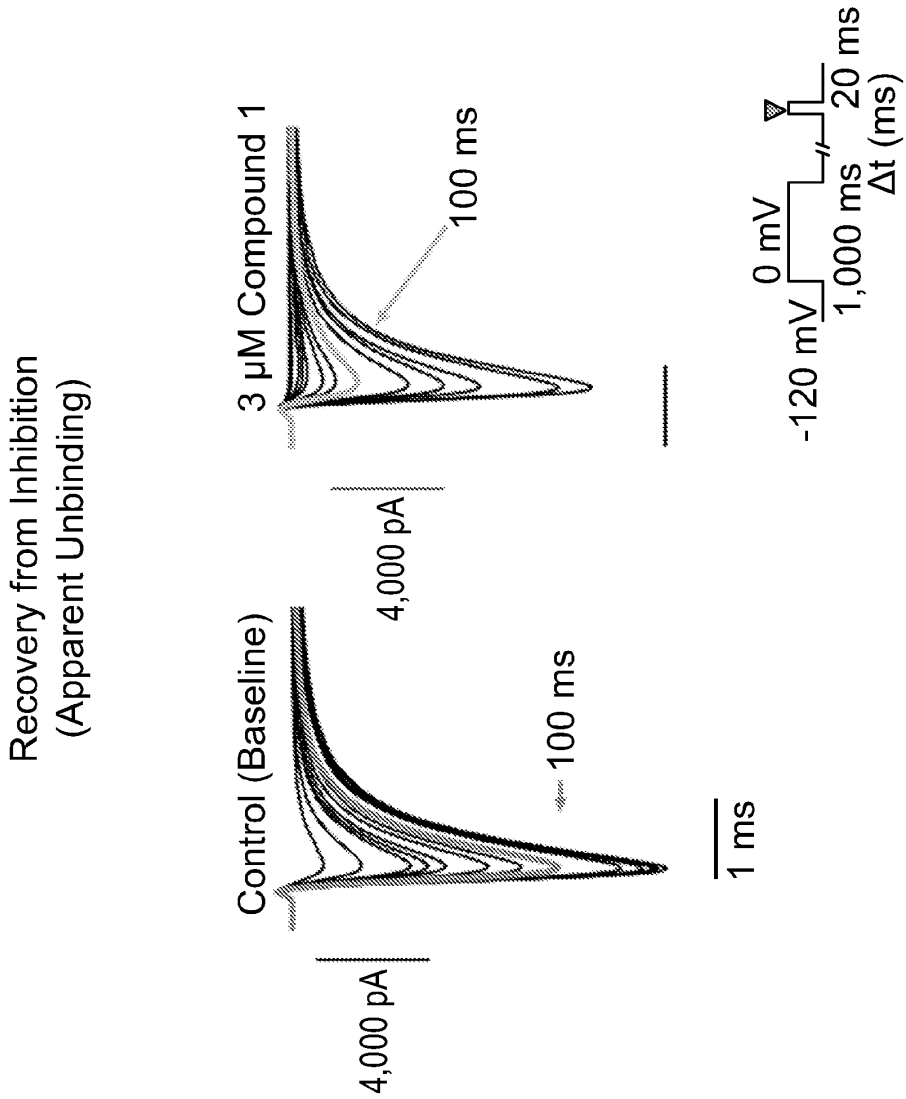

Recovery from Inhibition
(Apparent Unbinding)
Control (Baseline)
3 µM Compound 1
4,000 pA
100 ms
1 ms
0 mV
-120 mV
1,000 ms
20 ms
Δt (ms)

FIG. 9E

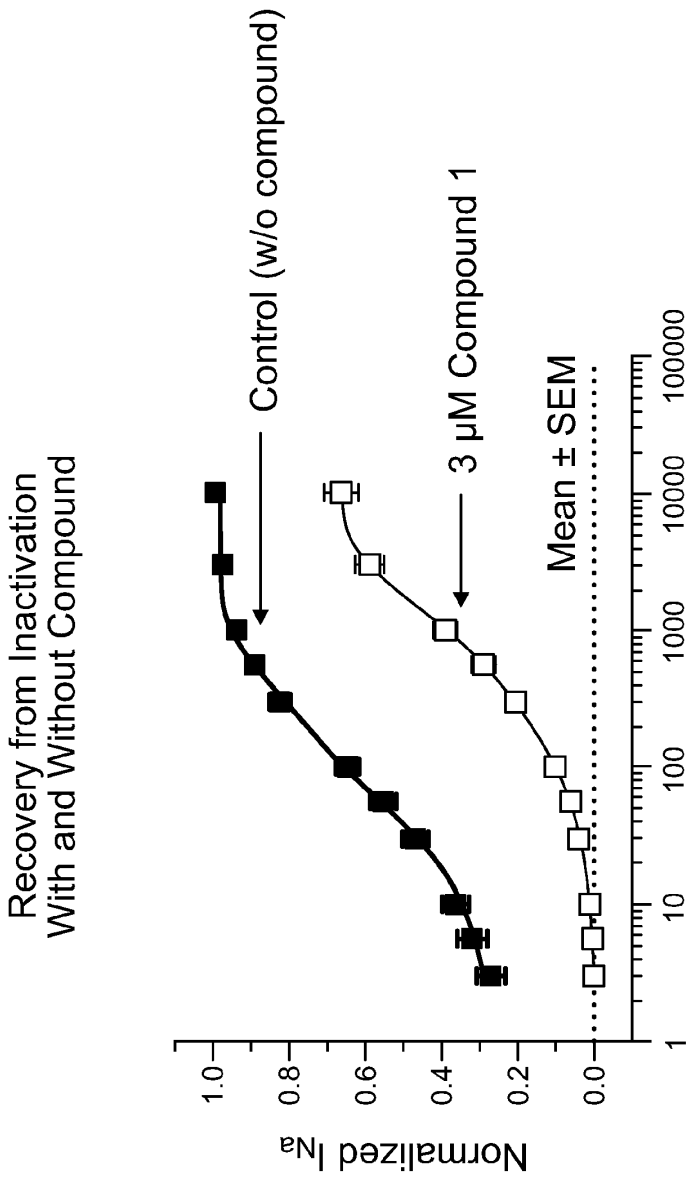

Recovery from Inactivation
With and Without Compound
Control (w/o compound)
3 μM Compound 1
Mean ± SEM
Normalized I_{Na}
1.0
0.8
0.6
0.4
0.2
0.0
1
10
100
1000
10000
100000
Recovery Time (Δt, msec)

FIG. 9F

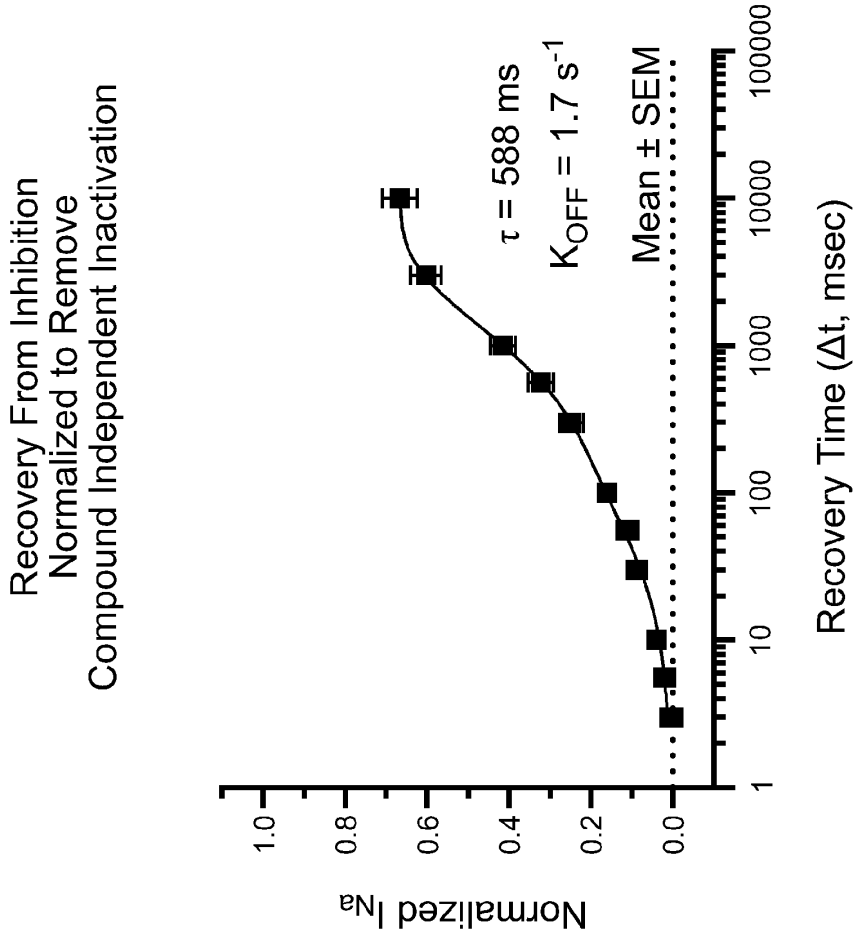

Recovery From Inhibition
Normalized to Remove
Compound Independent Inactivation
Normalized I_{Na}
1.0
0.8
0.6
0.4
0.2
0.0
τ = 588 ms
K_{OFF} = 1.7 s^{-1}
Mean ± SEM
1
10
100
1000
10000
100000
Recovery Time (Δt, msec)

FIG. 9G

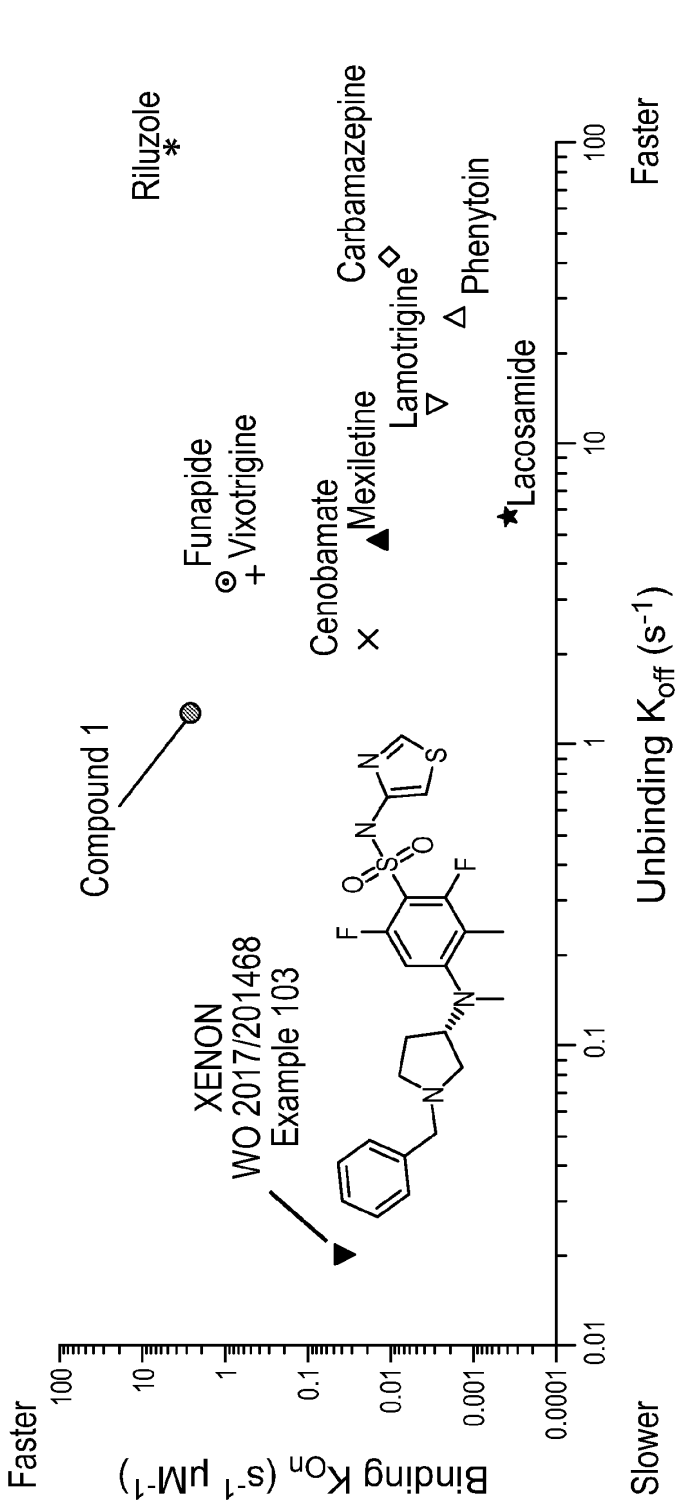

Compound 1
Fast ON
Moderate OFF
Riluzole
Carbamazepine
Phenytoin
Lamotrigine
Lacosamide
Mexiletine
Cenobamate
Vixotrigine
Funapide
Compound 1
XENON
WO 2017/201468
Example 103
Faster
Slower
Binding K_{On} (s^{-1} μM^{-1})
Unbinding K_{off} (s^{-1})
100
10
1
0.1
0.01
0.001
0.0001
0.01
0.1
1
10
100
Faster

FIG. 9H

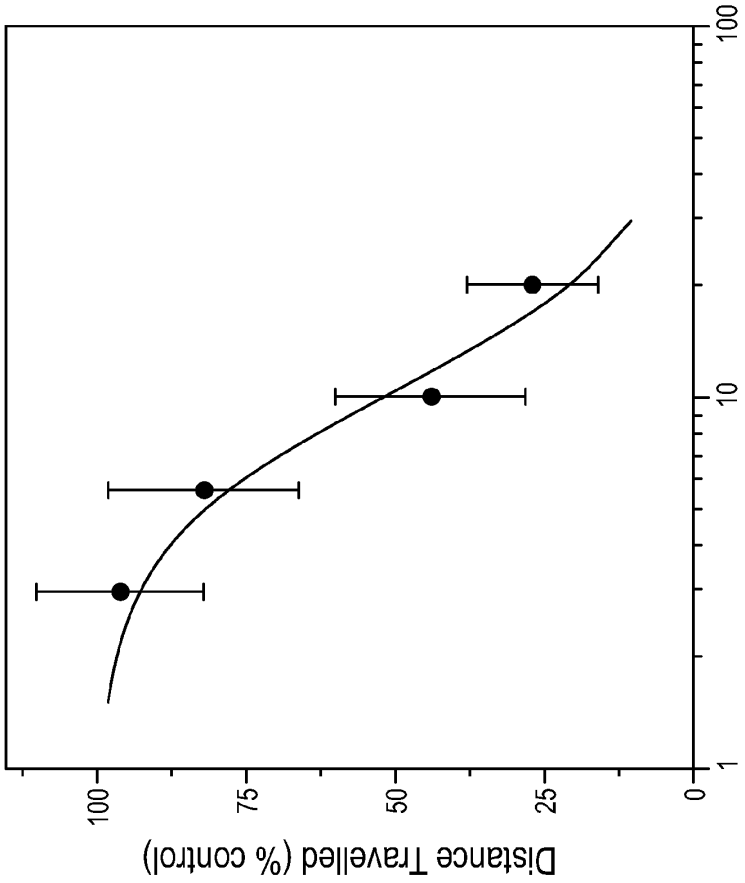

Distance Travelled (% control)
0
25
50
75
100
1
10
100
Compound 1 (mg/kg)

FIG. 10A

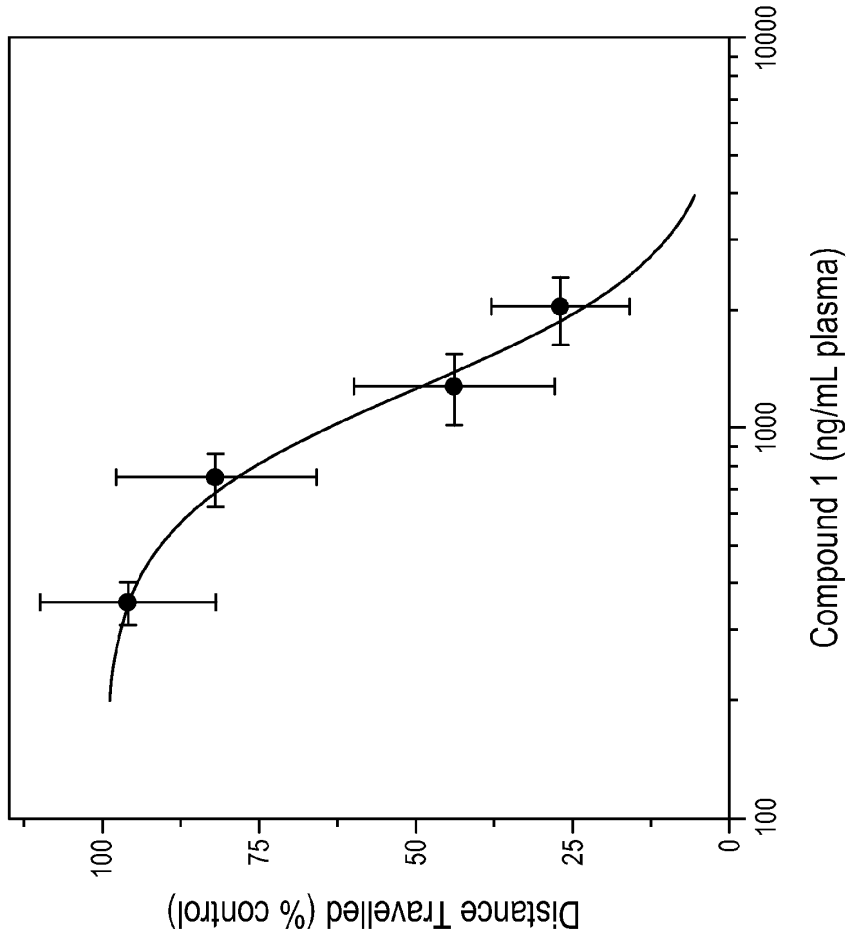

Distance Travelled (% control)
0
25
50
75
100
100
1000
10000
Compound 1 (ng/mL plasma)

FIG. 10B

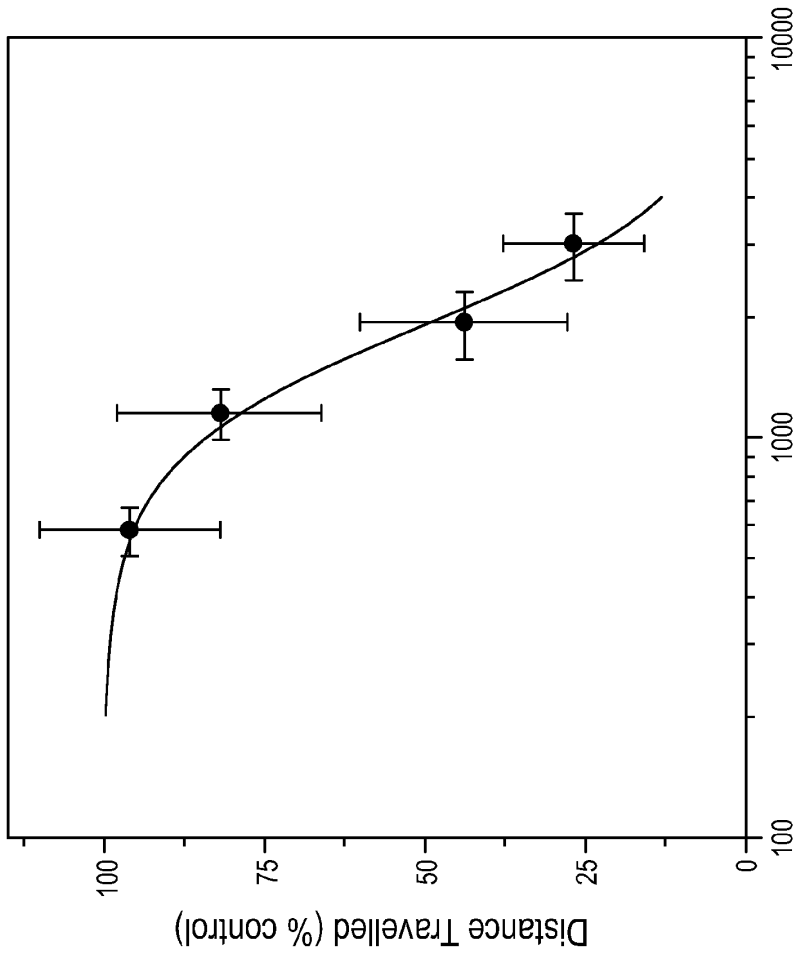

Distance Travelled (% control)
0
25
50
75
100
100
1000
10000
Compound 1 (ng/g plasma)

FIG. 10C

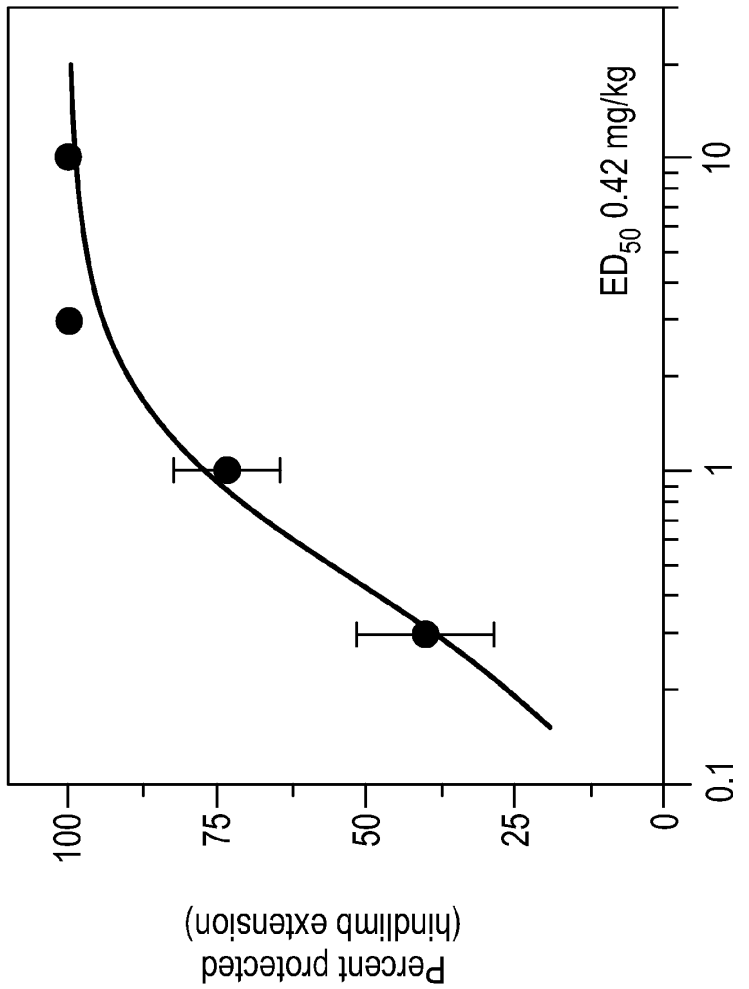

Percent protected
(hindlimb extension)
100
75
50
25
0
0.1
1
10
Compound 1 (mg/kg)
ED_{50} 0.42 mg/kg

FIG. 11A

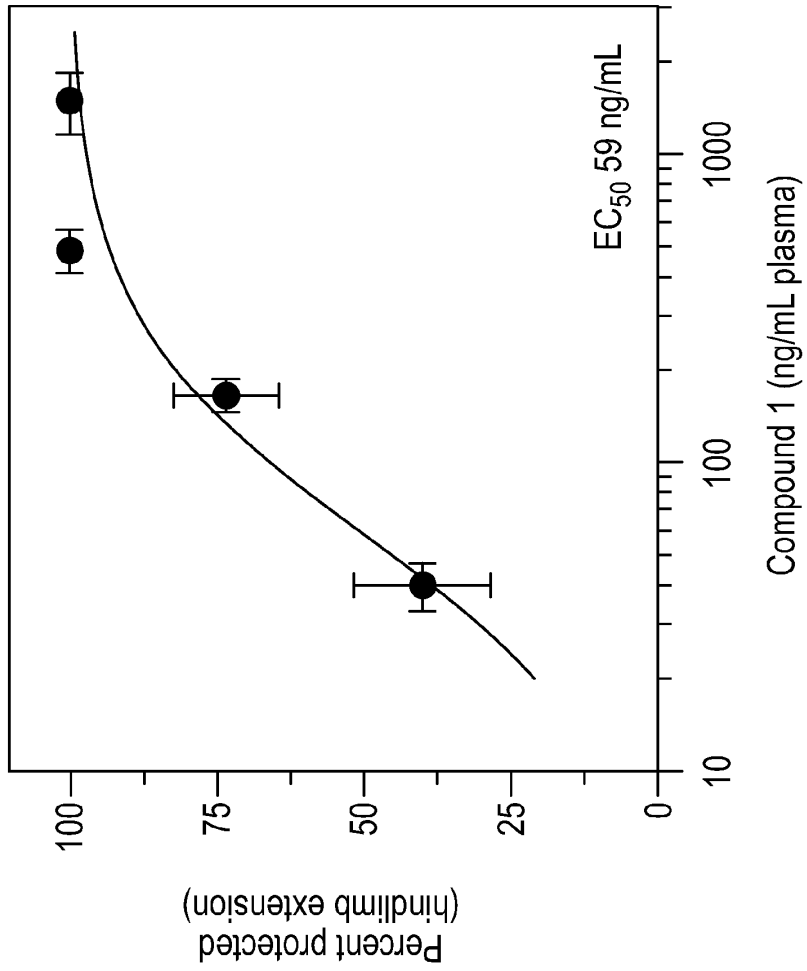

Percent protected
(hindlimb extension)
100
75
50
25
0
10
100
1000
Compound 1 (ng/mL plasma)
EC50 59 ng/mL

FIG. 11B

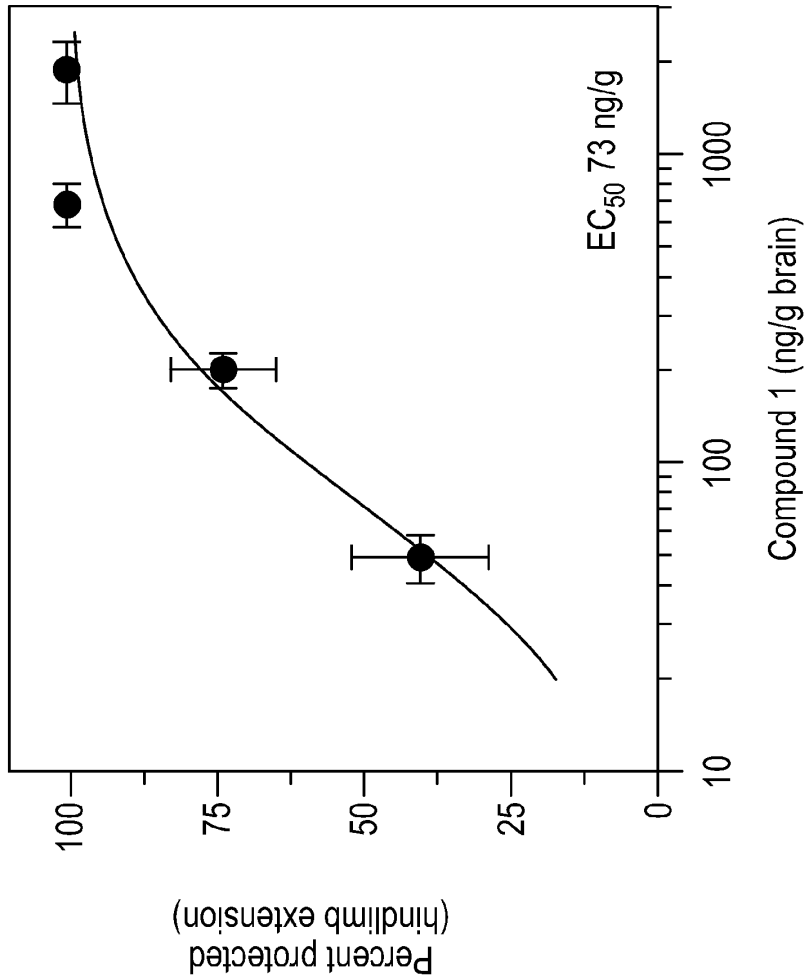

Percent protected
(hindlimb extension)
100
75
50
25
0
10
100
1000
Compound 1 (ng/g brain)
EC50 73 ng/g

FIG. 11C

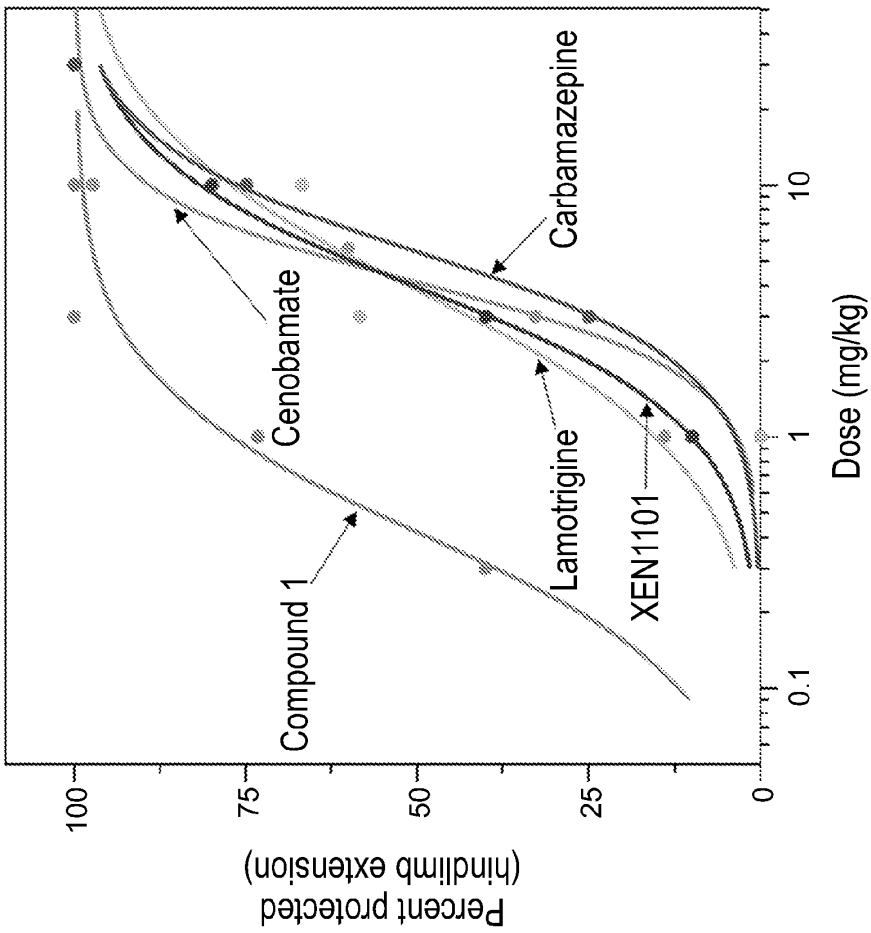

Percent protected
(hindlimb extension)
100
75
50
25
0
0.1
1
10
Dose (mg/kg)
Compound 1
Cenobamate
Lamotrigine
XEN1101
Carbamazepine

FIG. 11D

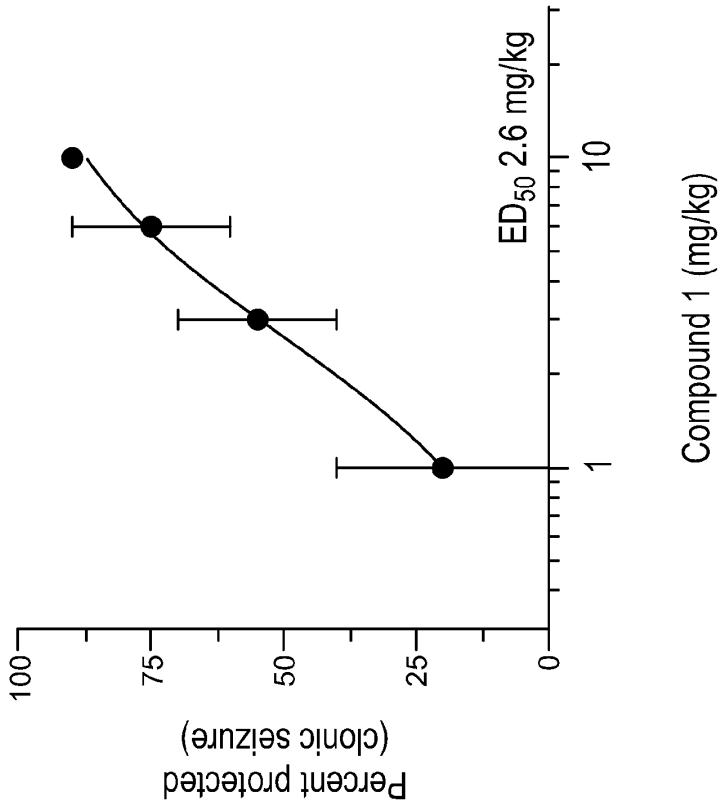

Percent protected
(clonic seizure)
100
75
50
25
0
1
10
Compound 1 (mg/kg)
ED50 2.6 mg/kg

FIG. 12A

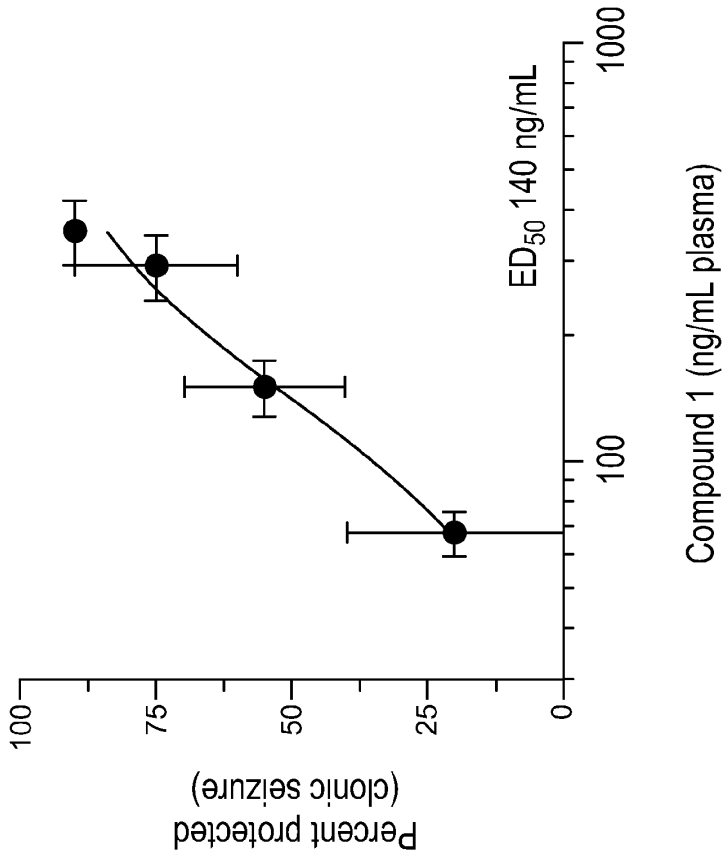

Percent protected
(clonic seizure)
100
75
50
25
0
100
1000
ED50 140 ng/mL
Compound 1 (ng/mL plasma)

FIG. 12B

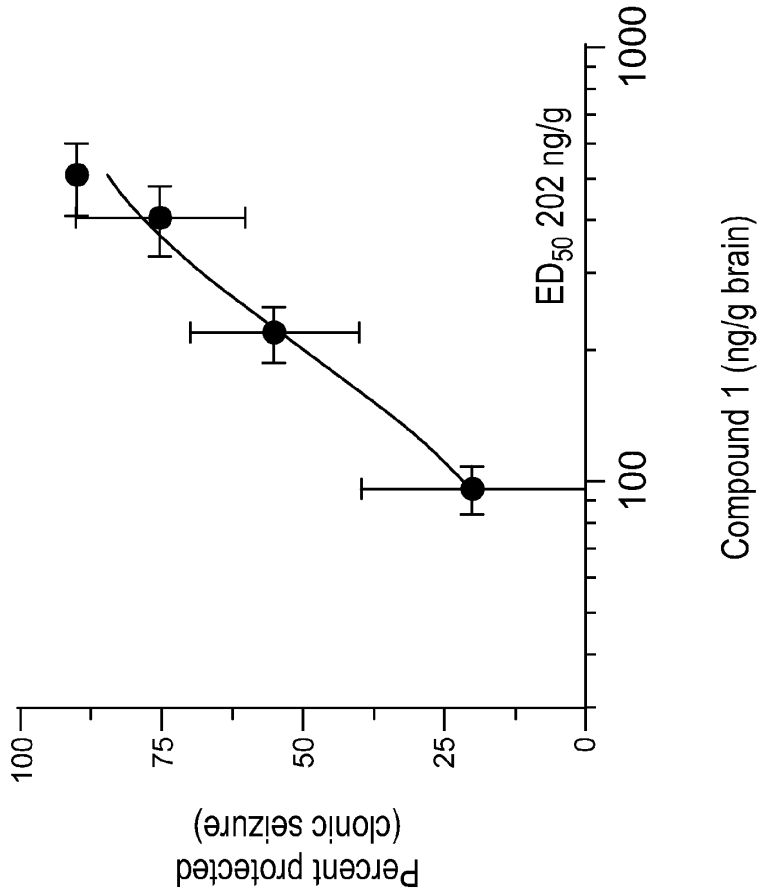

Percent protected
(clonic seizure)
100
75
50
25
0
100
1000
Compound 1 (ng/g brain)
ED50 202 ng/g

FIG. 12C

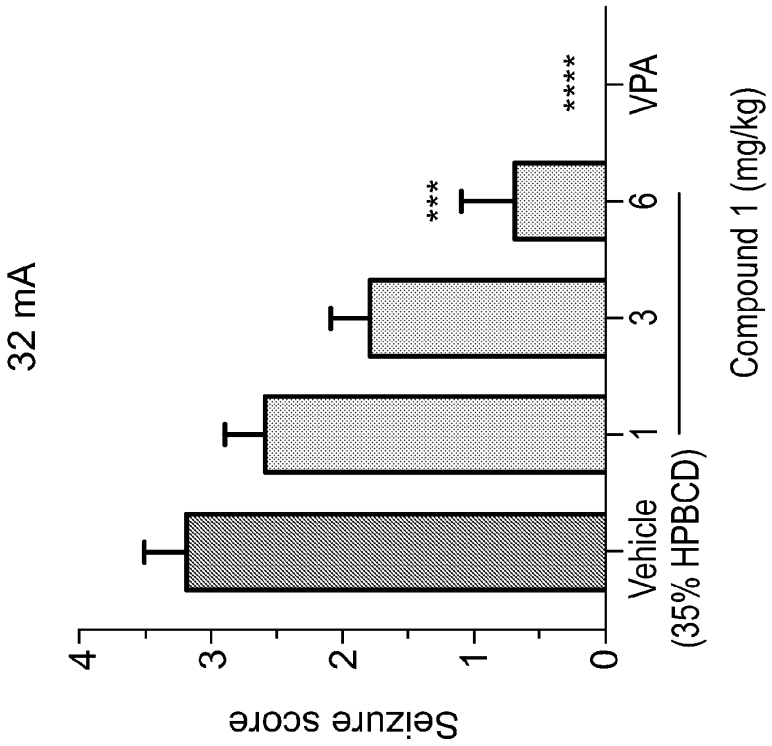

32 mA
Seizure score
0
1
2
3
4
Vehicle
(35% HPBCD)
1
3
6
VPA
Compound 1 (mg/kg)
***
****

FIG. 13A

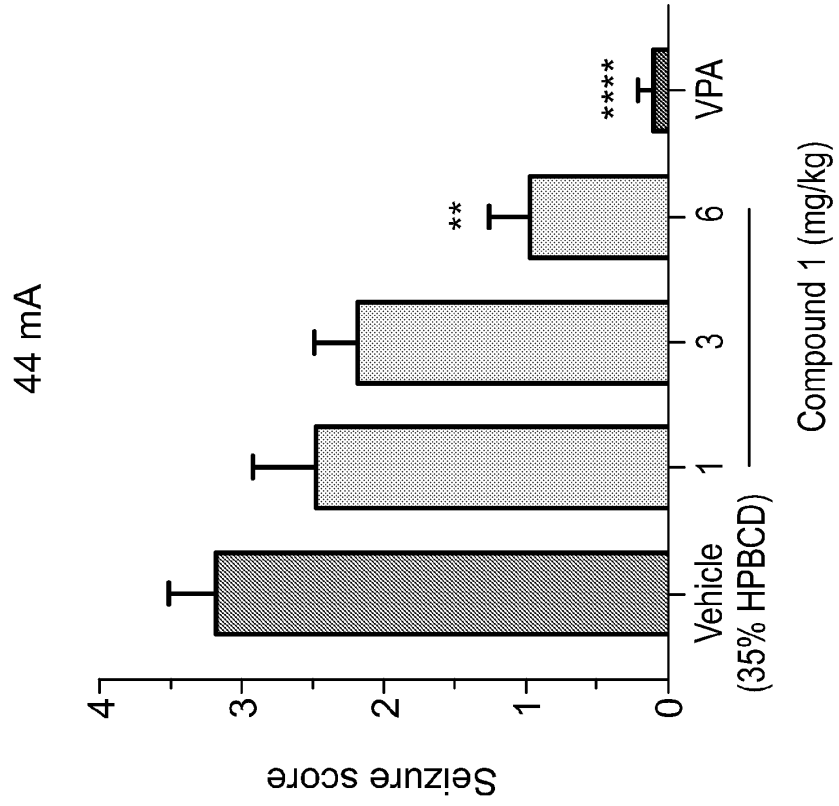

44 mA
Seizure score
0
1
2
3
4
Vehicle
(35% HPBCD)
1
3
6
VPA
Compound 1 (mg/kg)
**
****

FIG. 13B

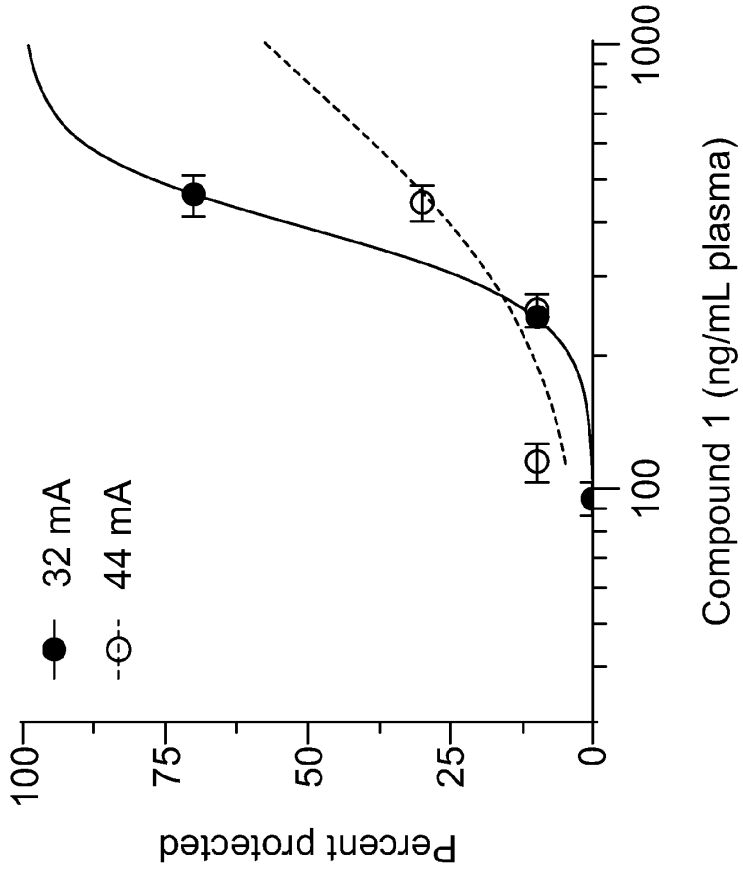

Percent protected
100
75
50
25
0
32 mA
44 mA
100
1000
Compound 1 (ng/mL plasma)

FIG. 13C

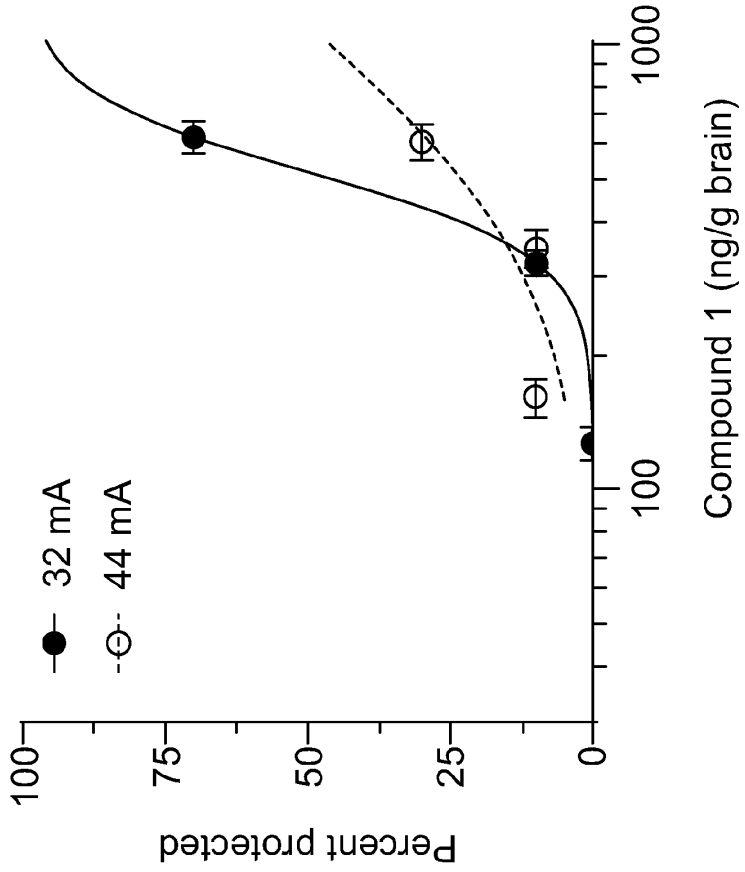

Percent protected
100
75
50
25
0
32 mA
44 mA
100
1000
Compound 1 (ng/g brain)

FIG. 13D

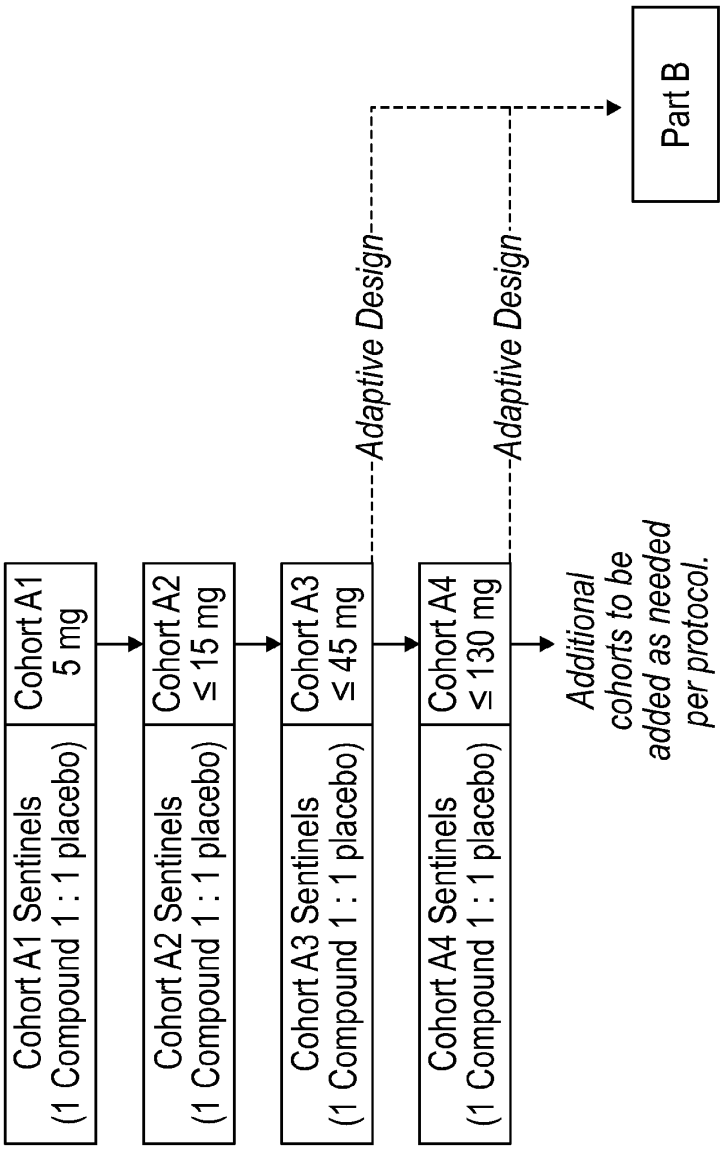

Cohort A1 Sentinels (1 Compound 1 : 1 placebo)
Cohort A1 5 mg
Cohort A2 Sentinels (1 Compound 1 : 1 placebo)
Cohort A2 ≤ 15 mg
Cohort A3 Sentinels (1 Compound 1 : 1 placebo)
Cohort A3 ≤ 45 mg
Cohort A4 Sentinels (1 Compound 1 : 1 placebo)
Cohort A4 ≤ 130 mg
Adaptive Design
Adaptive Design
Part B
Additional cohorts to be added as needed per protocol.
Fasted
N=8 Per Cohort
Active (6) : Placebo (2)

FIG. 14A

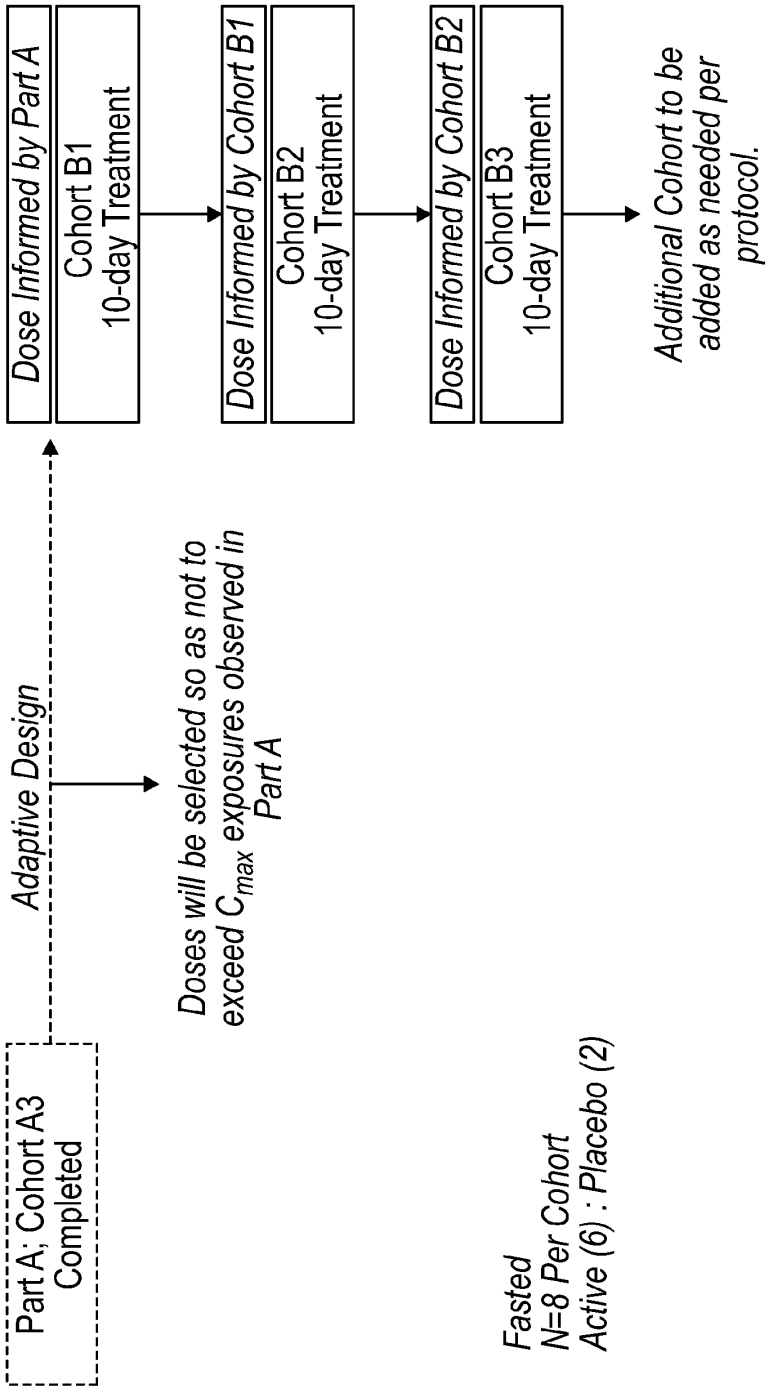

Part A; Cohort A3 Completed
Adaptive Design
Doses will be selected so as not to exceed C_{max} exposures observed in Part A
Fasted
N=8 Per Cohort
Active (6) : Placebo (2)
Dose Informed by Part A
Cohort B1
10-day Treatment
Dose Informed by Cohort B1
Cohort B2
10-day Treatment
Dose Informed by Cohort B2
Cohort B3
10-day Treatment
Additional Cohort to be added as needed per protocol.

FIG. 14B

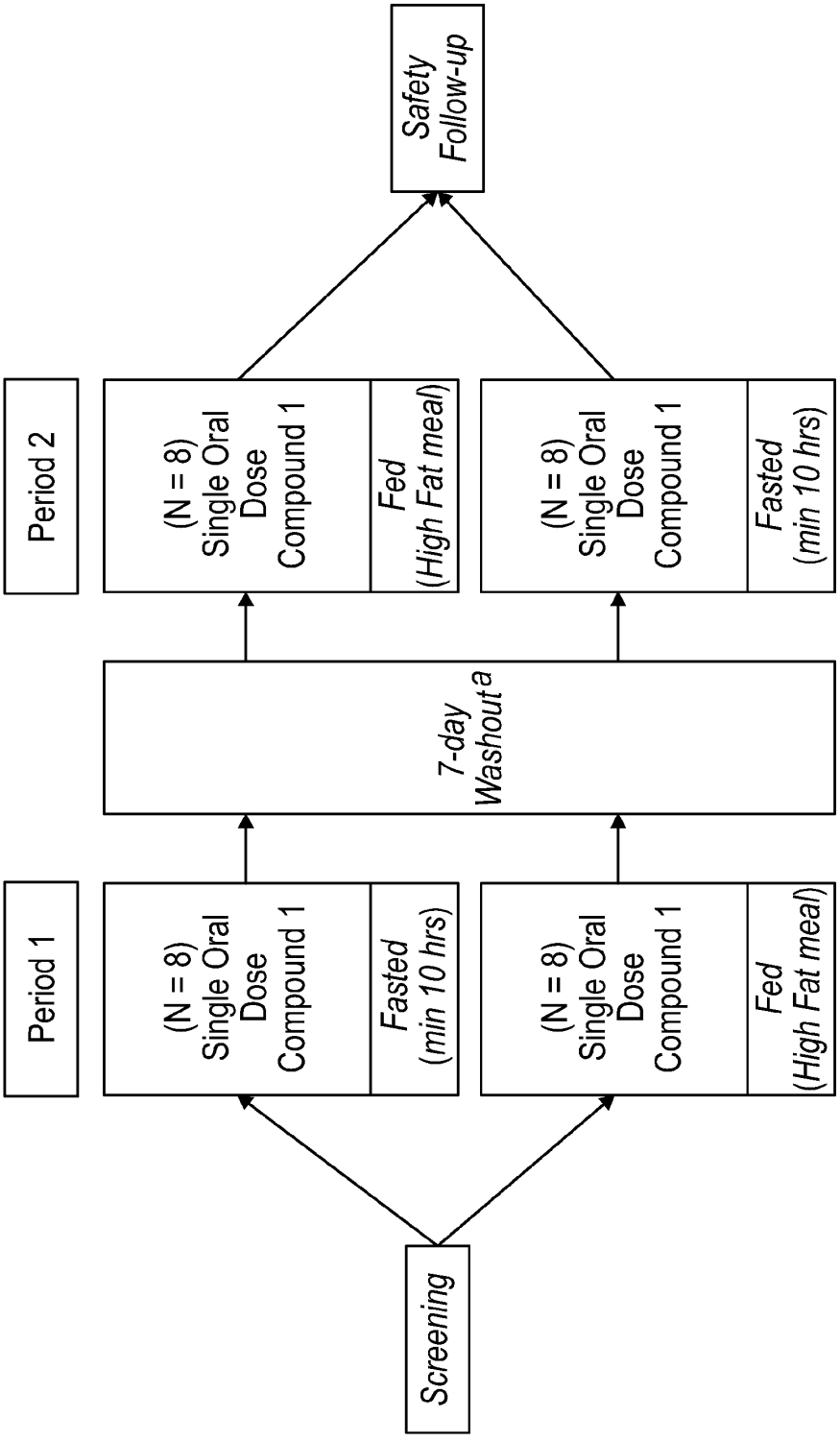

Screening
Period 1
(N = 8) Single Oral Dose Compound 1
Fasted (min 10 hrs)
(N = 8) Single Oral Dose Compound 1
Fed (High Fat meal)
7-day Washout[a]
Period 2
(N = 8) Single Oral Dose Compound 1
Fed (High Fat meal)
(N = 8) Single Oral Dose Compound 1
Fasted (min 10 hrs)
Safety Follow-up

FIG. 14C

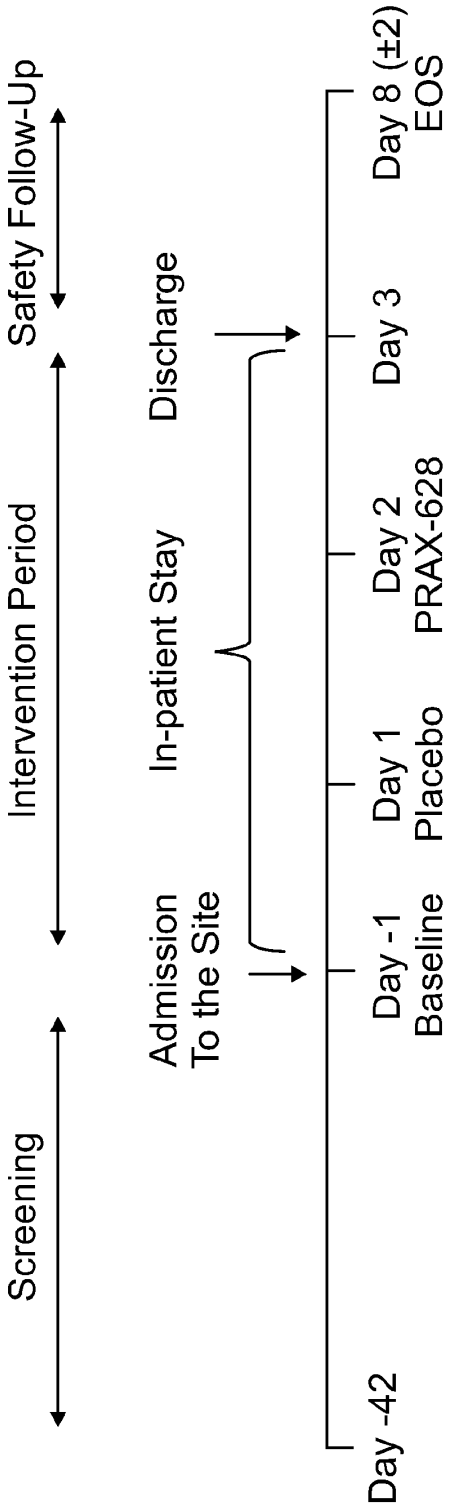

Safety Follow-Up
Intervention Period
Screening
Discharge
In-patient Stay
Admission
To the Site
Day -42
Day -1
Baseline
Day 1
Placebo
Day 2
PRAX-628
Day 3
Day 8 (±2)
EOS
EOS=end of study

FIG. 15