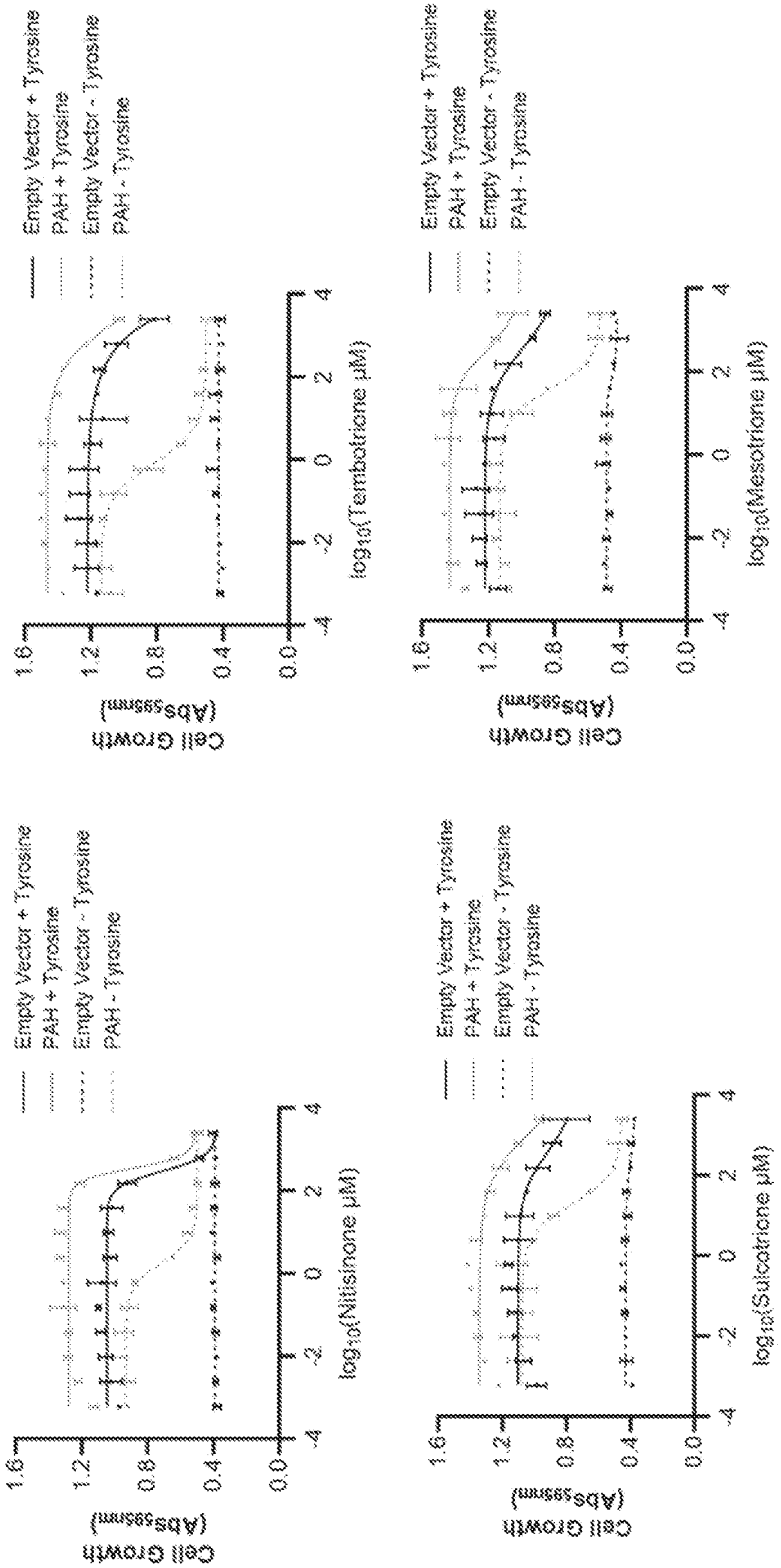
FIG. 1


Empty Vector + Tyrosine
PAH + Tyrosine
Empty Vector - Tyrosine
PAH - Tyrosine
Cell Growth
(Abs595nm)
1.6
1.2
0.8
0.4
0.0
-4
-2
0
2
4
log10(Nitisinone µM)
log10(Tembotrione µM)
log10(Mesotrione µM)
log10(Sulcotrione µM)

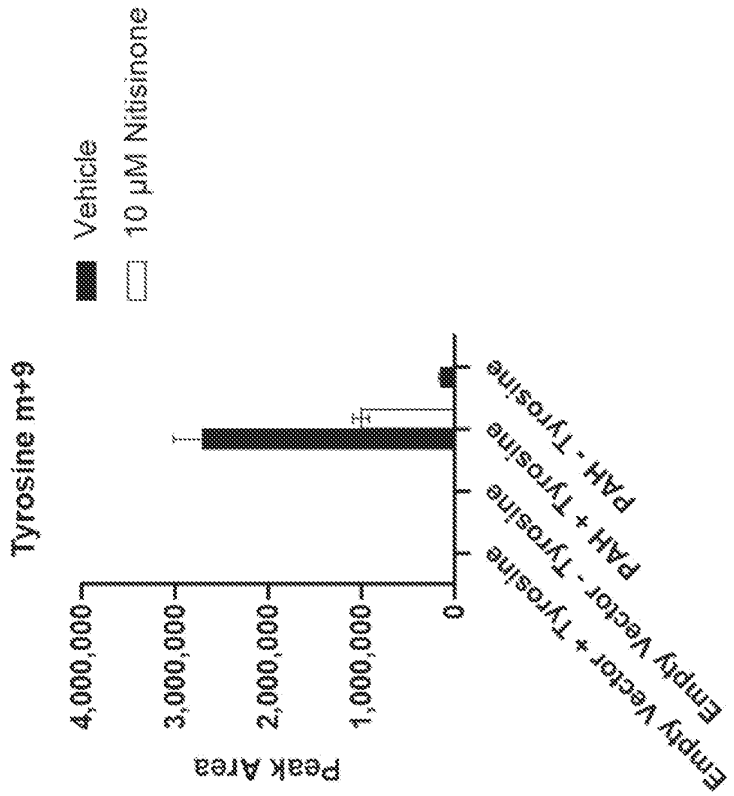

Tyrosine m+9
Vehicle
10 µM Nitisinone
Peak Area
4,000,000
3,000,000
2,000,000
1,000,000
0
Empty Vector + Tyrosine
Empty Vector - Tyrosine
PAH + Tyrosine
PAH - Tyrosine

FIG. 2

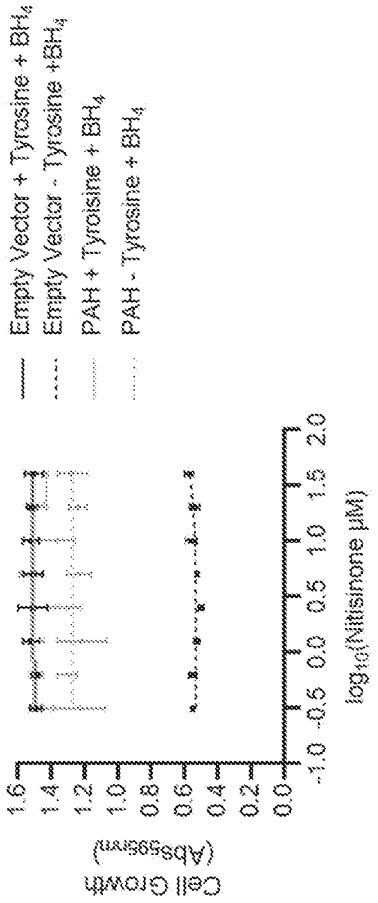

Empty Vector + Tyrosine + BH4
Empty Vector - Tyrosine +BH4
PAH + Tyroisine + BH4
PAH - Tyrosine + BH4
Cell Growth
(Abs595nm)
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-1.0 -0.5 0.0 0.5 1.0 1.5 2.0
log10(Nitisinone µM)

FIG. 3

FIG. 4

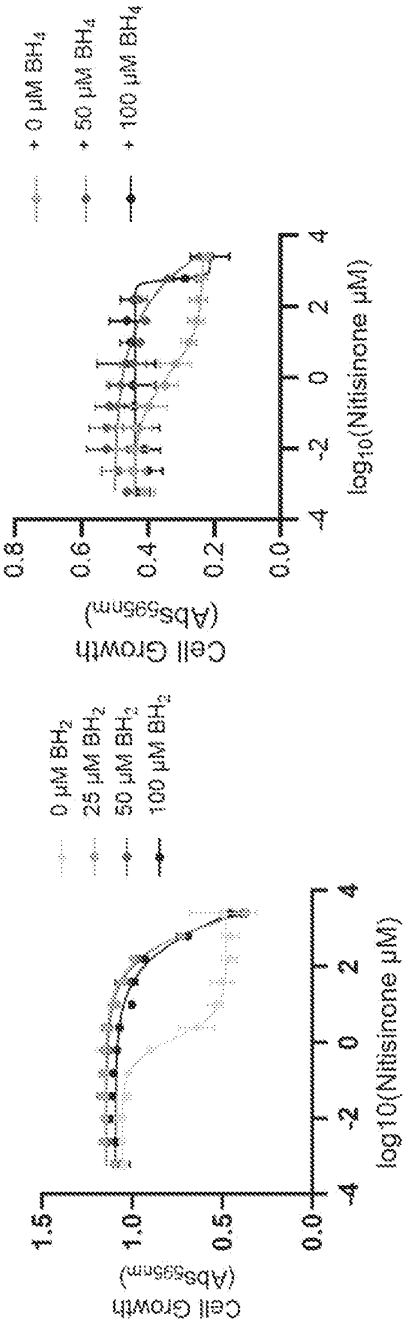
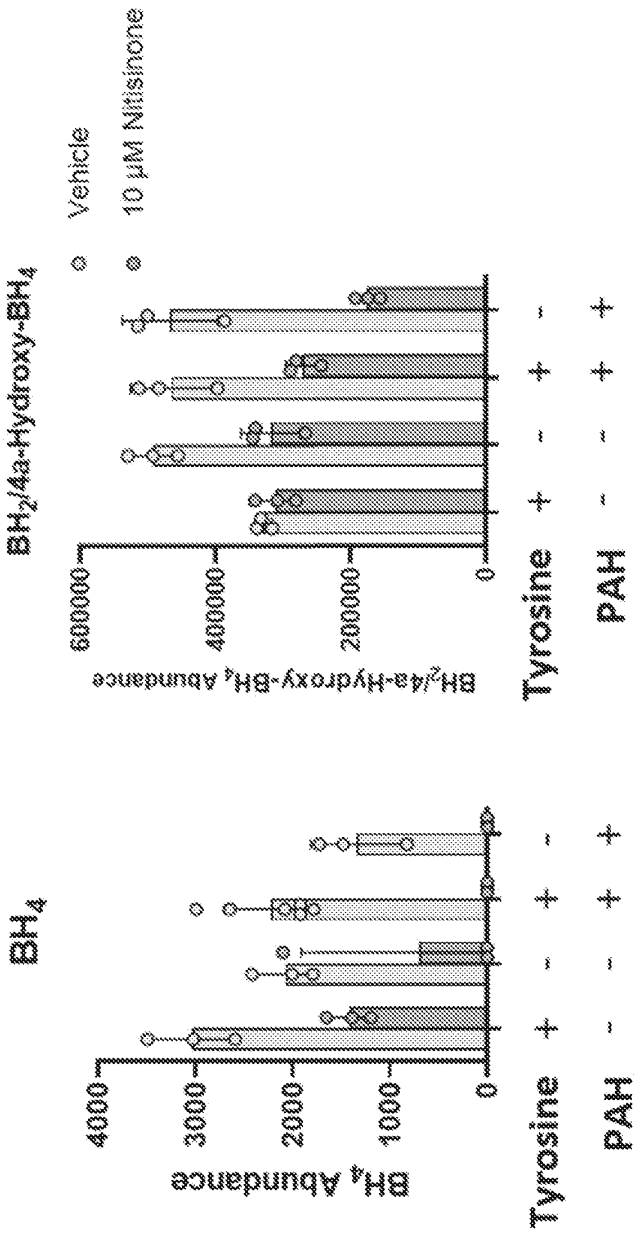

+ 0 μM BH_4
+ 50 μM BH_4
+ 100 μM BH_4
Cell Growth (Abs_{595nm})
0.8
0.6
0.4
0.2
0.0
-4
-2
0
2
4
log_{10}(Nitisinone μM)
0 μM BH_2
25 μM BH_2
50 μM BH_2
100 μM BH_2
Cell Growth (Abs_{595nm})
1.5
1.0
0.5
0.0
-4
-2
0
2
4
log10(Nitisinone μM)

FIG. 5


BH4
BH4 Abundance
4000
3000
2000
1000
0
Tyrosine + - + -
PAH - - + +
BH2/4a-Hydroxy-BH4
Vehicle
10 µM Nitisinone
BH2/4a-Hydroxy-BH4 Abundance
600000
400000
200000
0
Tyrosine + - + -
PAH - - + +

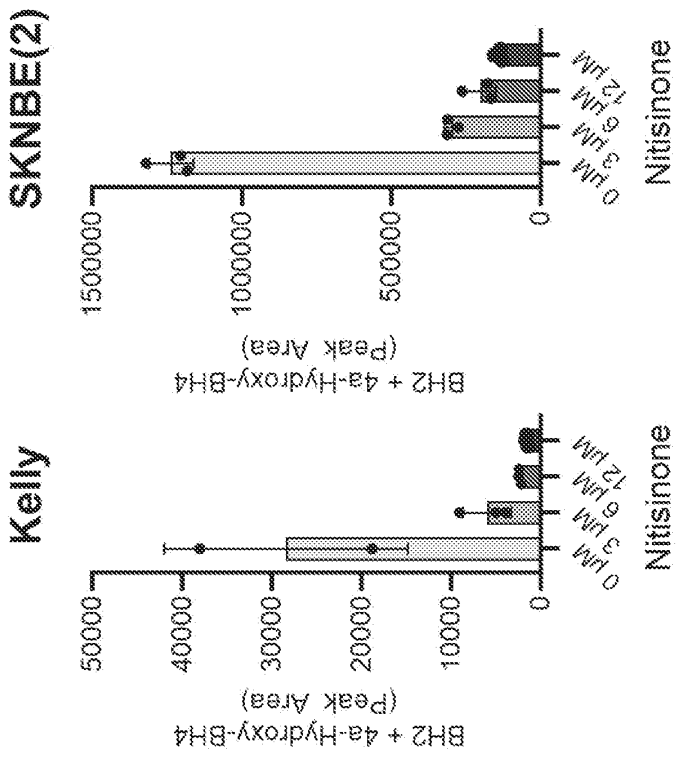

SKNBE(2)
Kelly
BH2 + 4a-Hydroxy-BH4
(Peak Area)
1500000
1000000
500000
0
50000
40000
30000
20000
10000
0 µM
3 µM
6 µM
12 µM
Nitisinone

FIG. 6

FIG. 7

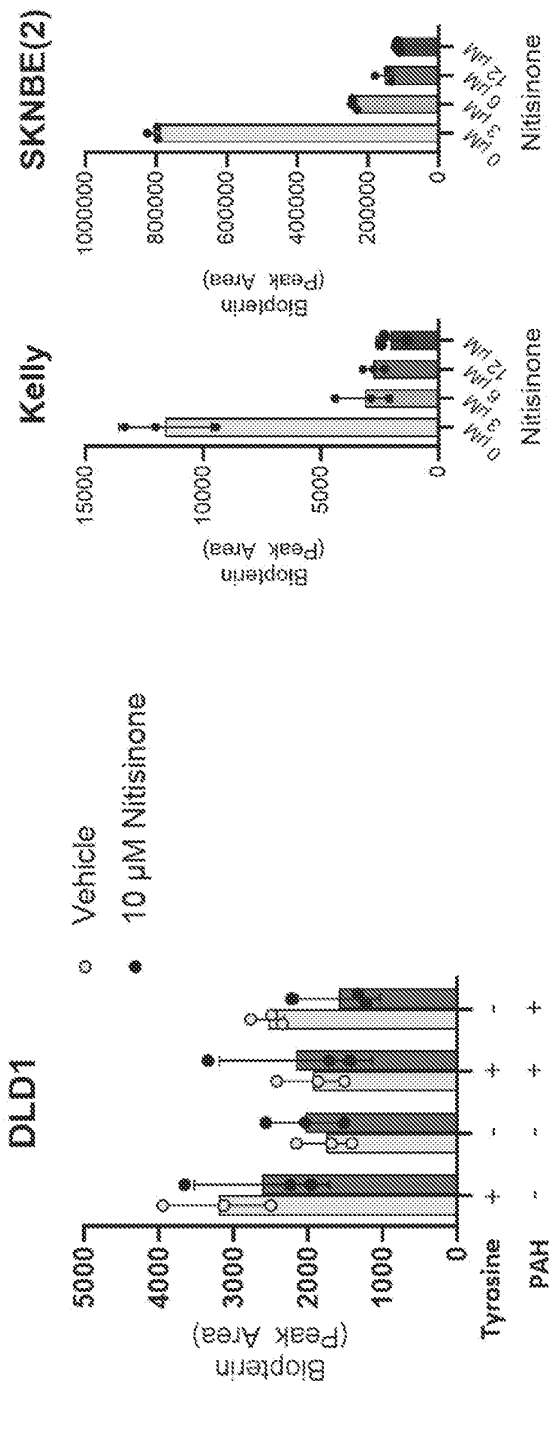

DLD1
Kelly
SKNBE(2)
Vehicle
10 μM Nitisinone
Biopterin (Peak Area)
Tyrosine
PAH
Nitisinone
0 μM
3 μM
6 μM
12 μM

FIG. 8

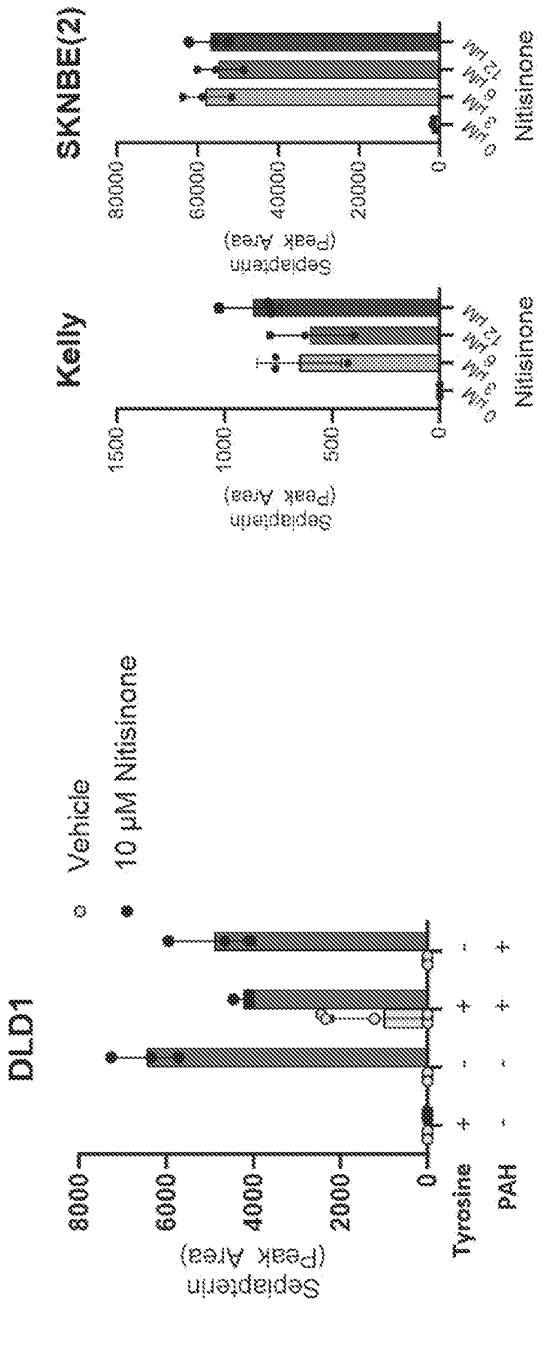

DLD1
Vehicle
10 μM Nitisinone
Sepiapterin (Peak Area)
8000
6000
4000
2000
0
Tyrosine
PAH
+
-
Kelly
SKNBE(2)
1500
1000
500
80000
60000
40000
20000
Nitisinone
0
3 μM
6 μM
12 μM

FIG. 9

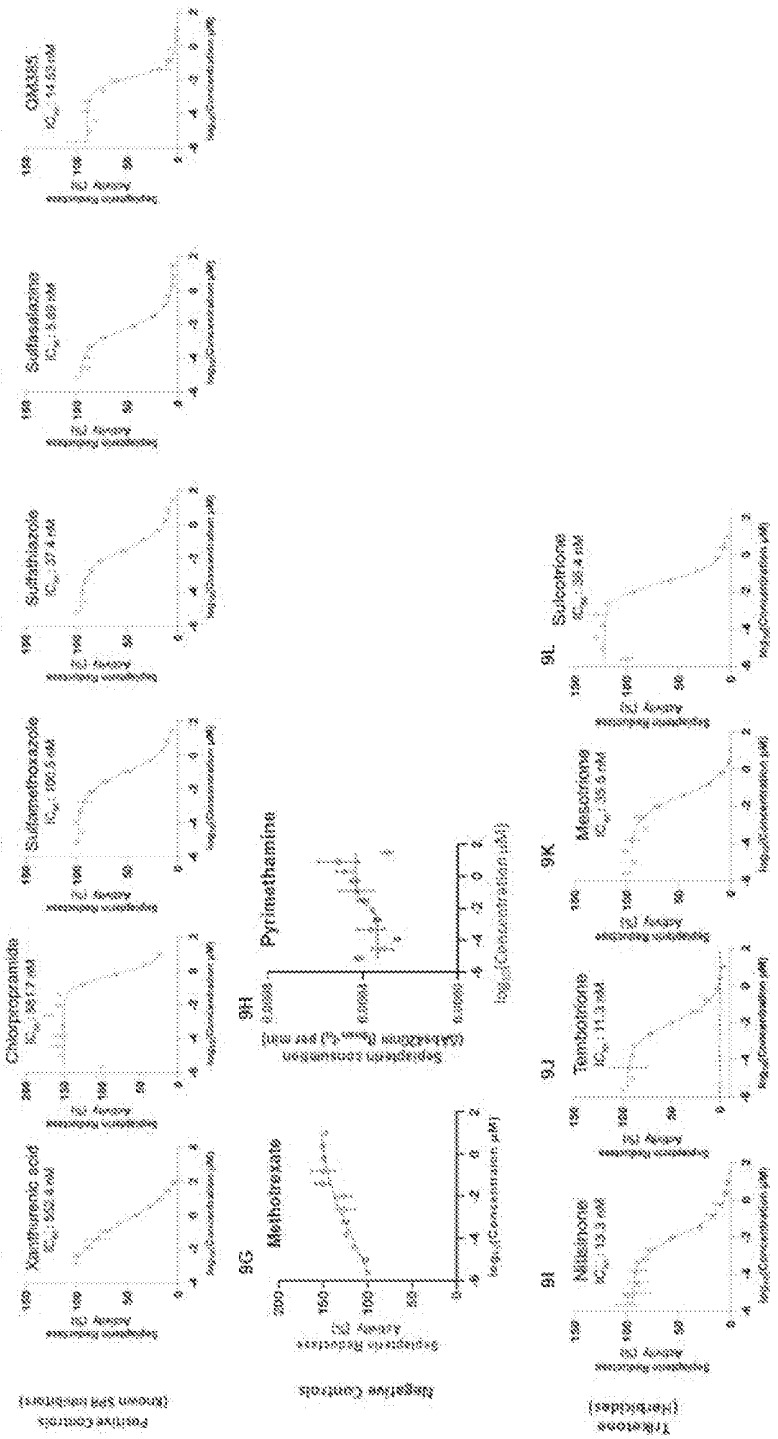
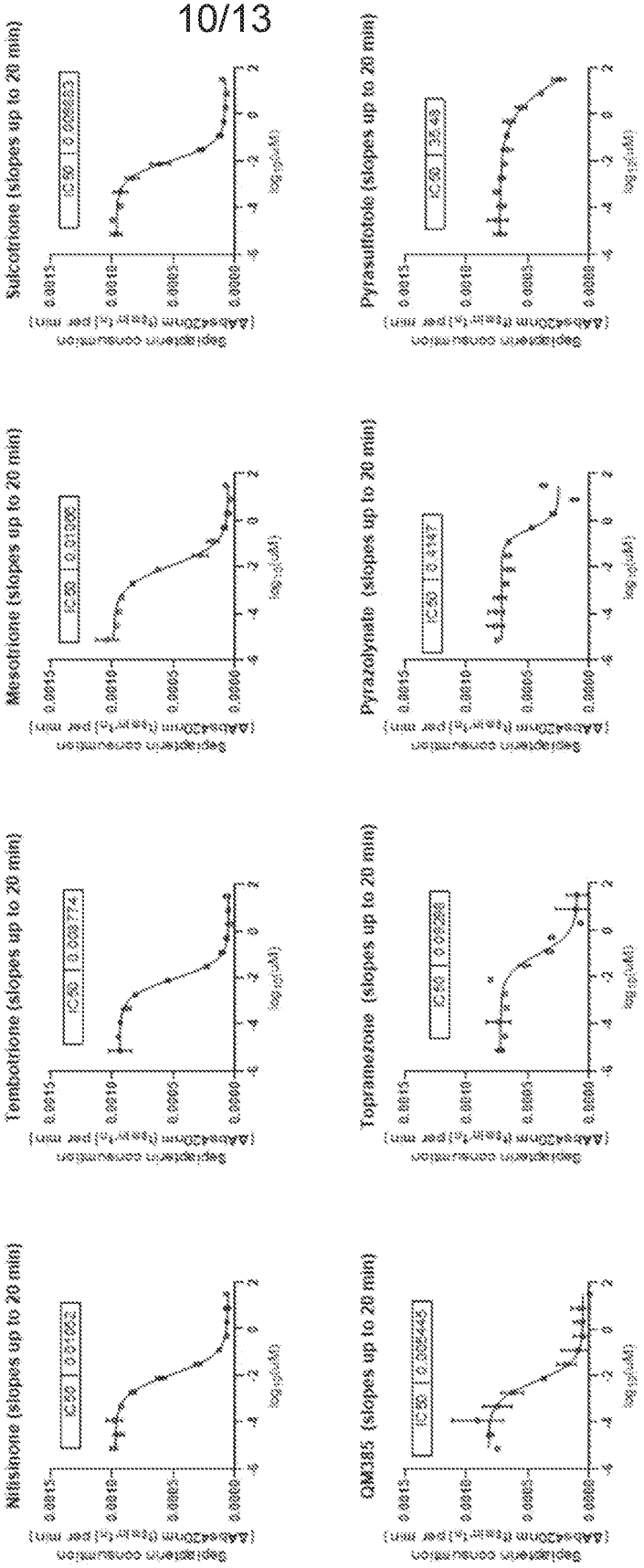

9A
Xanthurenic acid
9B
Chlorpropamide
9C
Sulfamethoxazole
9D
Sulfathiazole
9E
Sulfasalazine
9F
QM385
9G
Methotrexate
9H
Pyrimethamine
9I
Nitisinone
9J
Tembotrione
9K
Mesotrione
9L
Sulcotrione
Positive Controls
(Known SPR Inhibitors)
Negative Controls
Triketone
(Herbicides)

FIG. 10

Mouse SPR
IC50s are in µM



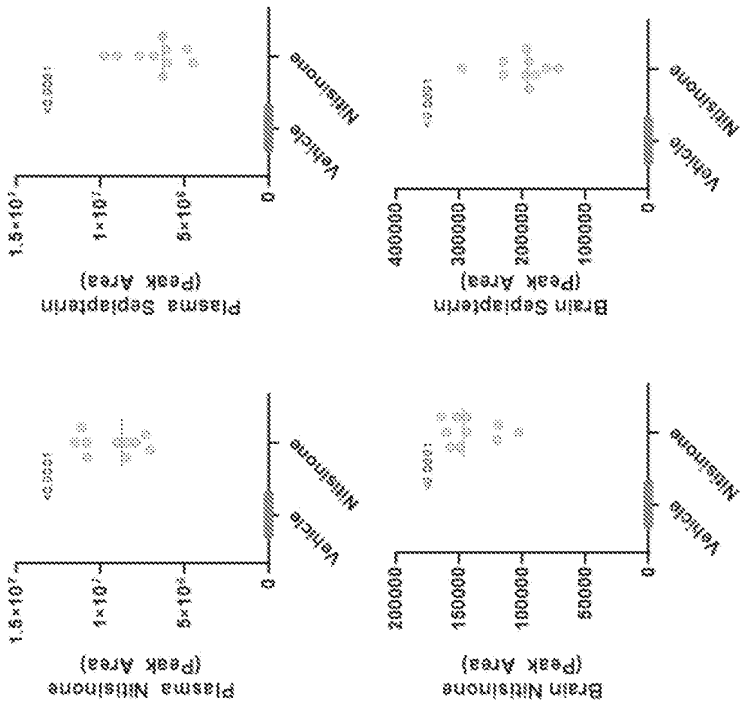

Plasma Nitisinone
(Peak Area)
Brain Nitisinone
(Peak Area)
Plasma Seplapterin
(Peak Area)
Brain Seplapterin
(Peak Area)
Vehicle
Nitisinone

FIG. 11

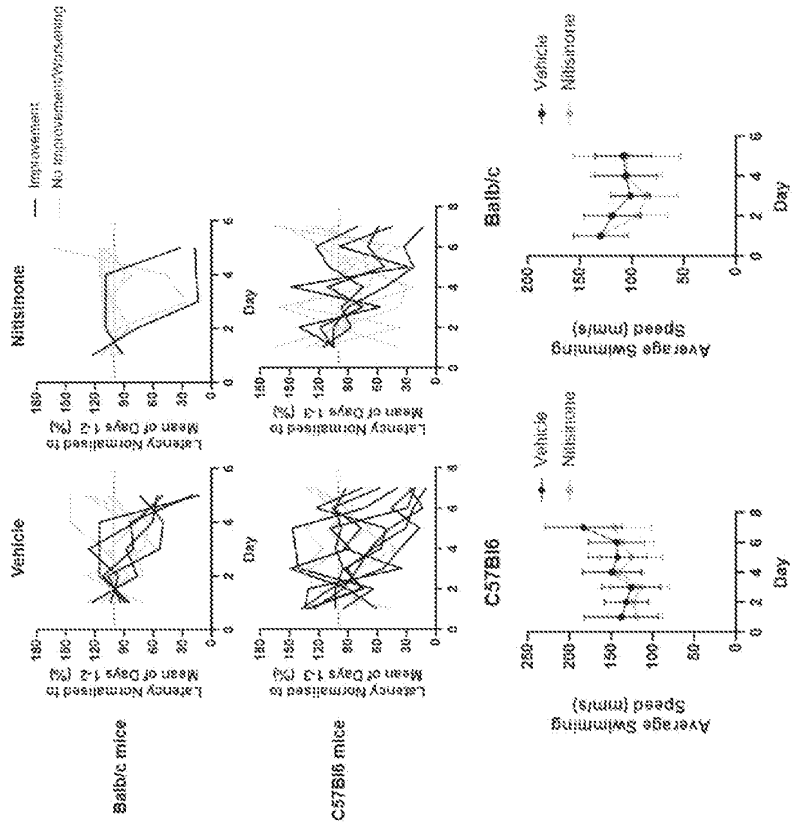
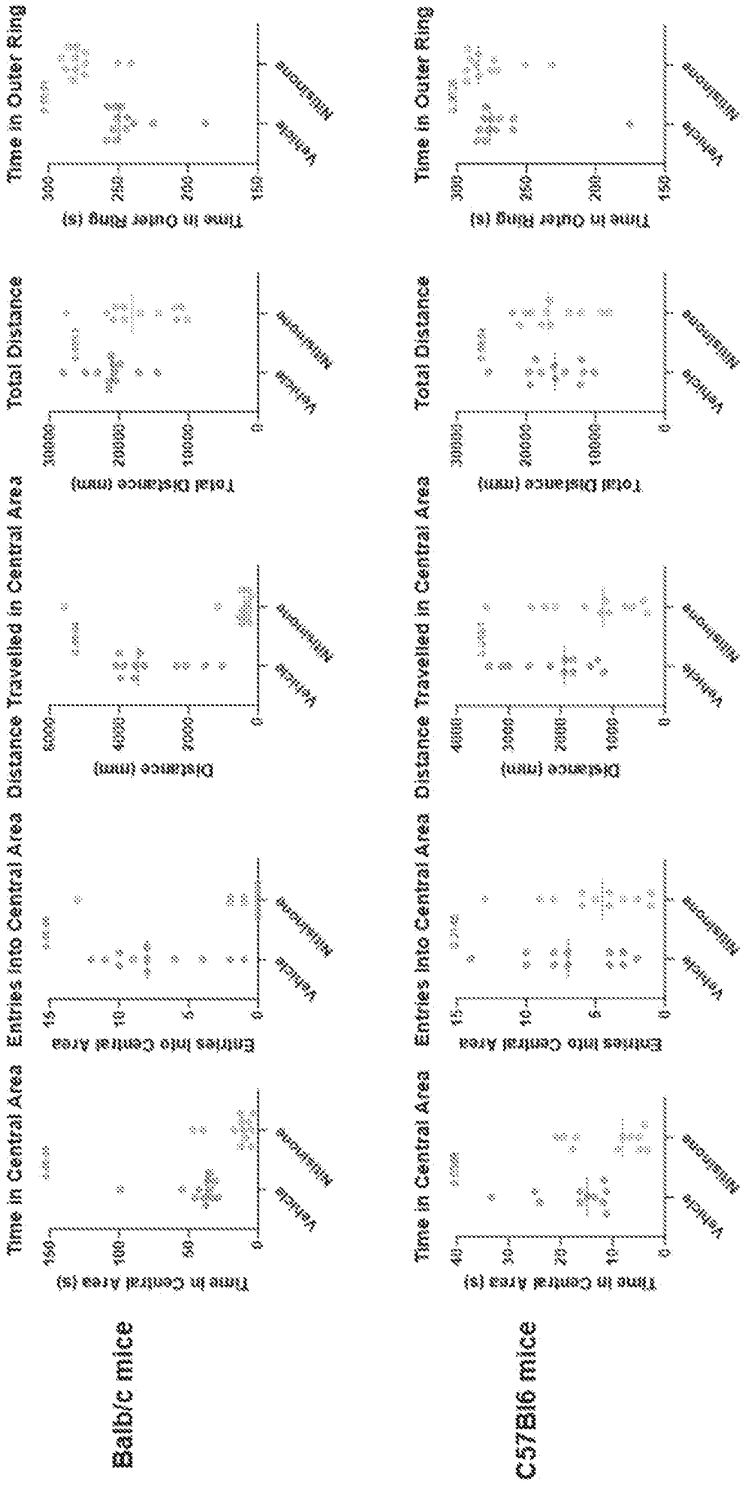

Improvement
No improvement/worsening
Vehicle
Nitisinone
Balb/c mice
C57Bl6 mice
Latency Normalized to Mean of Days 1-2 (%)
Latency Normalized to Mean of Days 1-3 (%)
Day
C57Bl6
Balb/c
Vehicle
Nitisinone
Average Swimming Speed (mm/s)
Day

FIG. 12

FIG. 13


Balb/c mice
C57Bl6 mice
Time in Central Area
Entries into Central Area
Distance Travelled in Central Area
Total Distance
Time in Outer Ring
Time in Central Area (s)
Entries into Central Area
Distance (mm)
Total Distance (mm)
Time in Outer Ring (s)
Vehicle
Risperidone