FIG. 1

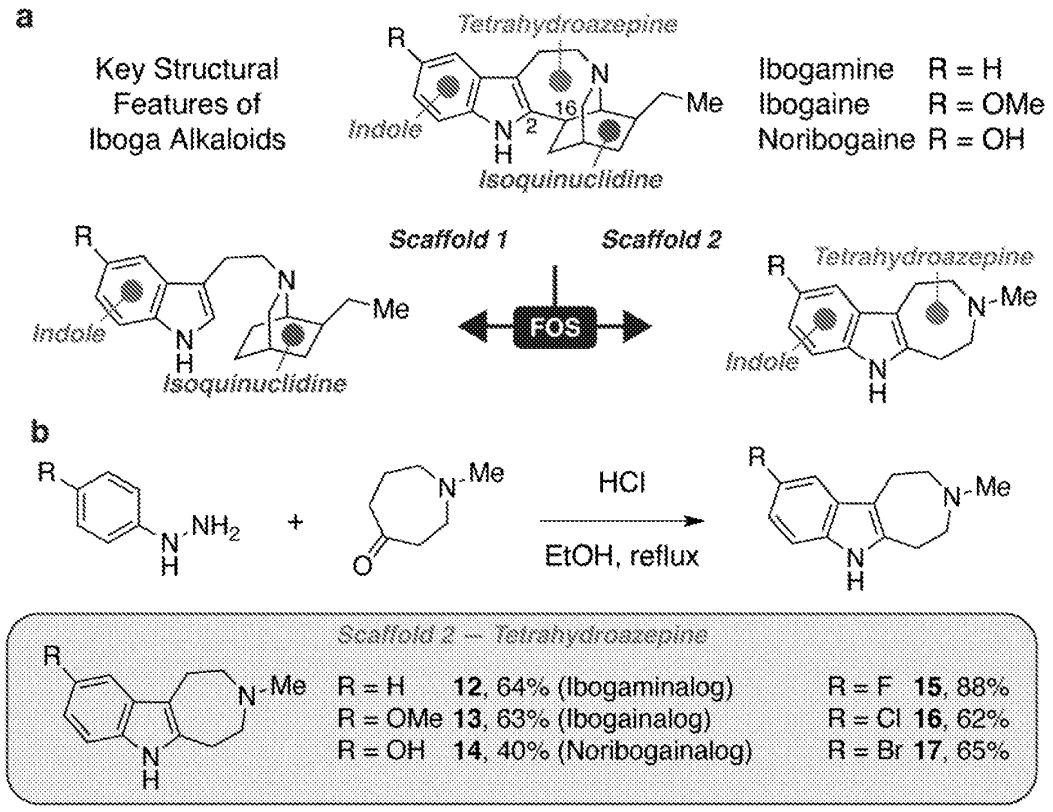

a
Key Structural Features of Iboga Alkaloids
Tetrahydroazepine
Indole
Isoquinuclidine
Ibogamine R = H
Ibogaine R = OMe
Noribogaine R = OH
Scaffold 1
Scaffold 2
FOS
b
HCl
EtOH, reflux
Scaffold 2 — Tetrahydroazepine
R = H 12, 64% (Ibogaminalog)
R = OMe 13, 63% (Ibogainalog)
R = OH 14, 40% (Noribogainalog)
R = F 15, 88%
R = Cl 16, 62%
R = Br 17, 65%

FIG. 2

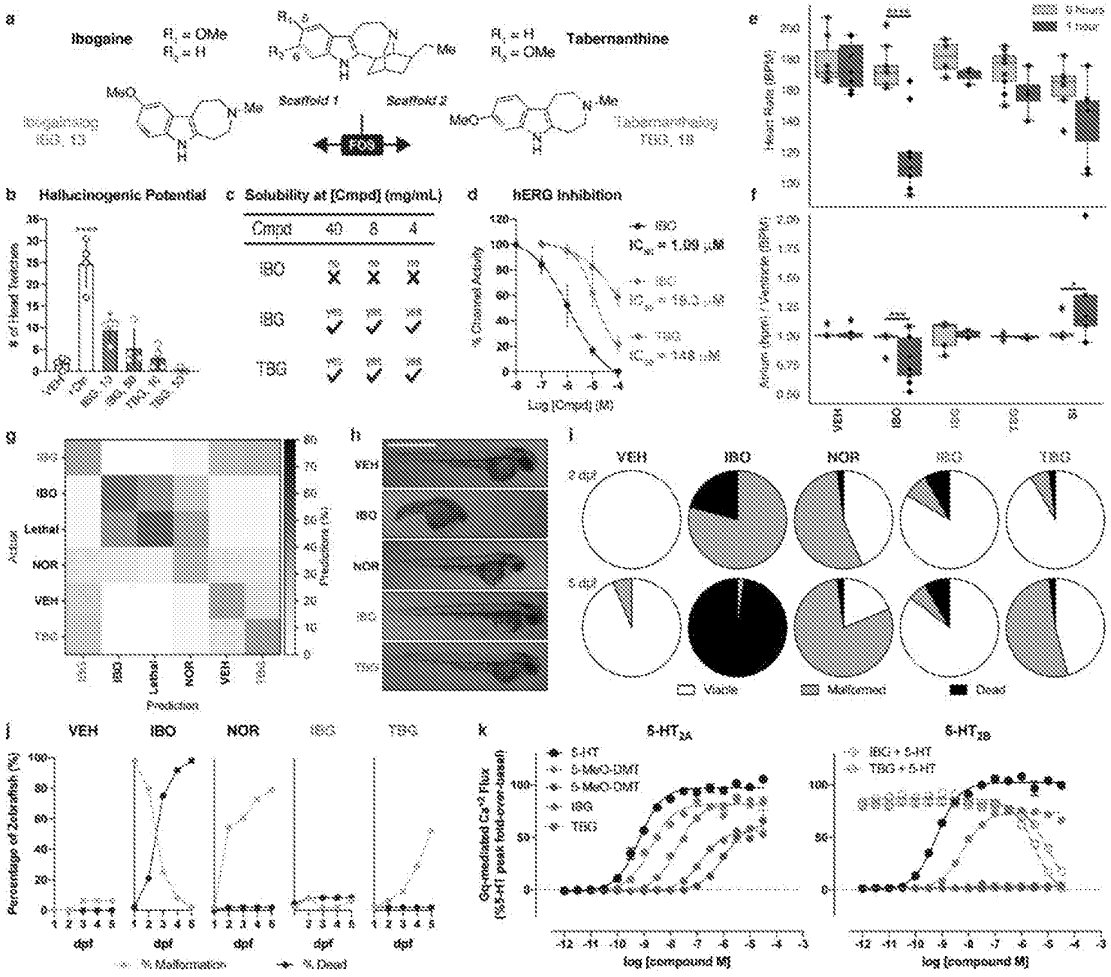

a
Ibogaine
Tabernanthine
Scaffold 1
Scaffold 2
IBG, 13
TBG, 18
b Hallucinogenic Potential
c Solubility at [Cmpd] (mg/mL)
Cmpd 40 8 4
IBO
IBG
TBG
d hERG Inhibition
IBO
IBG
TBG
Log [Cmpd] (M)
e
f
Atrium (Bpm) / Ventricle (BPM)
g
Actual
Prediction
Lethal
NOR
VEH
h
i
VEH
IBO
NOR
IBG
TBG
2 dpf
5 dpf
Viable
Malformed
Dead
j
Percentage of Zebrafish (%)
dpf
% Malformation
% Dead
k
5-HT2A
5-HT2B
5-HT
5-MeO-DMT
5-MeO-DMT
IBG
TBG
IBG + 5-HT
TBG + 5-HT
log [compound M]

FIG. 3

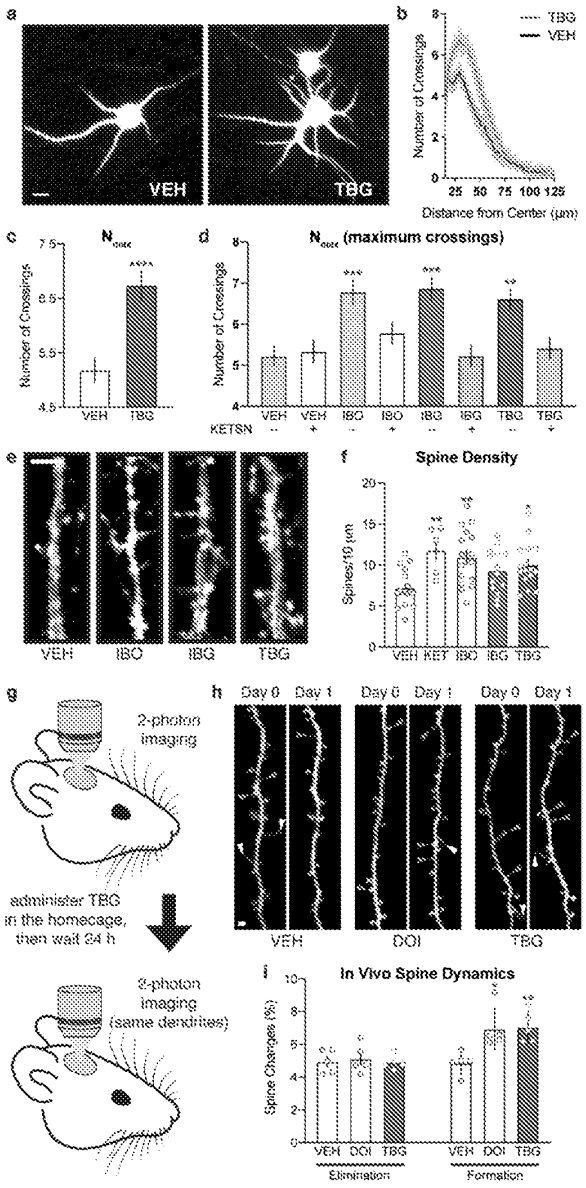

a
VEH
TBG
b
TBG
VEH
Number of Crossings
Distance from Center (μm)
c
Number of Crossings
VEH
TBG
d
Number of Crossings (maximum crossings)
KETSN
e
VEH
IBO
IBG
TBG
f
Spine Density
Spines/10 μm
VEH KET IBO IBG TBG
g
2-photon imaging
administer TBG in the homecage, then wait 24 h
2-photon imaging (same dendrites)
h
Day 0 Day 1
VEH
DOI
TBG
i
In Vivo Spine Dynamics
Spine Changes (%)
VEH DOI TBG
Elimination
Formation

FIG. 4

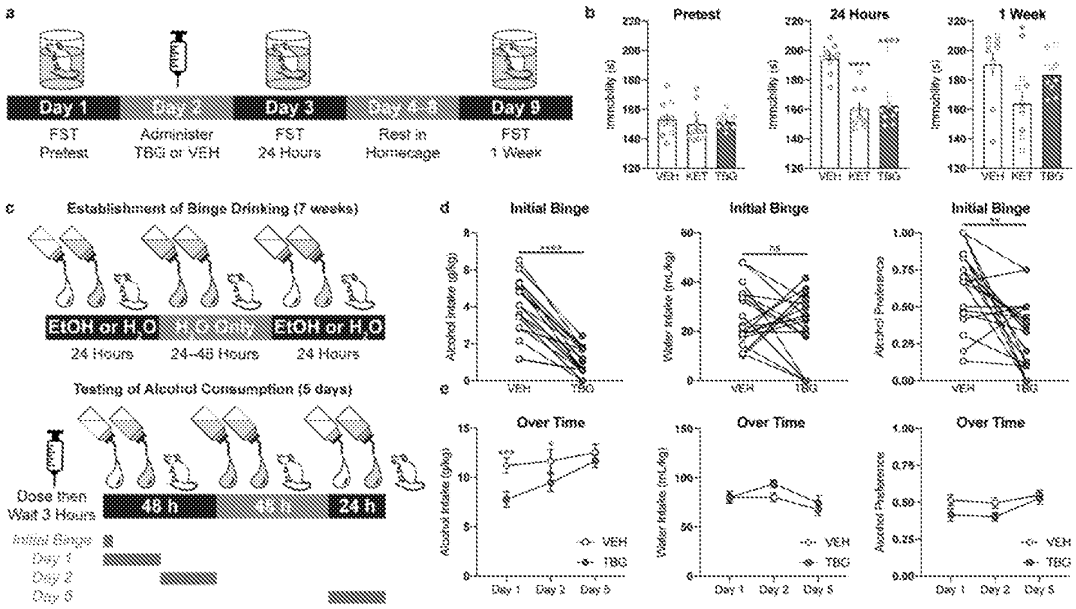

a
Day 1
Day 3
Day 9
FST
Pretest
Administer
TBG or VEH
FST
24 Hours
Rest in
Homecage
FST
1 Week
b
Pretest
24 Hours
1 Week
Immobility (s)
VEH
KET
TBG
c
Establishment of Binge Drinking (7 weeks)
EtOH or H2O
H2O Only
EtOH or H2O
24 Hours
24–48 Hours
24 Hours
Testing of Alcohol Consumption (5 days)
Dose then
Wait 3 Hours
48 h
24 h
Initial Binge
Day 1
Day 2
Day 5
d
Initial Binge
Alcohol Intake (g/kg)
Water Intake (mL/kg)
Alcohol Preference
e
Over Time
Day 1
Day 2
Day 5
VEH
TBG

FIG. 5

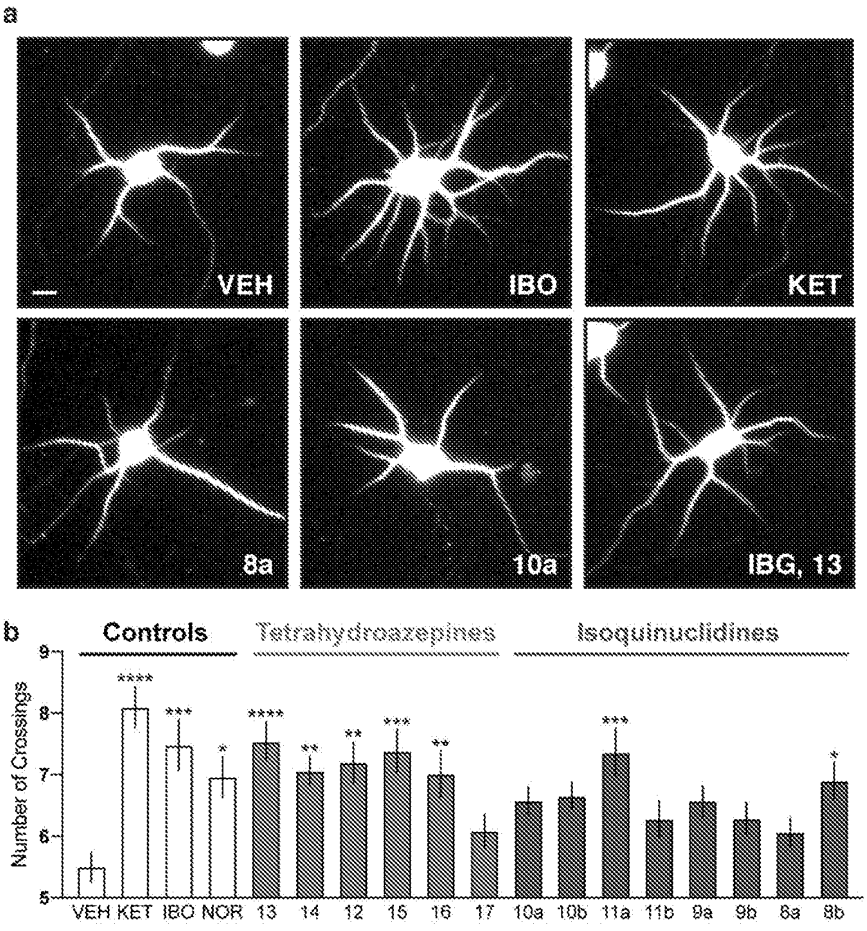

a
VEH
IBO
KET
8a
10a
IBG, 13
b
Controls
Tetrahydroazepines
Isoquinuclidines
Number of Crossings
9
8
7
6
5
****
***
*
****
**
**
***
**
***
*
VEH KET IBO NOR 13 14 12 15 16 17 10a 10b 11a 11b 9a 9b 8a 8b

FIG. 6

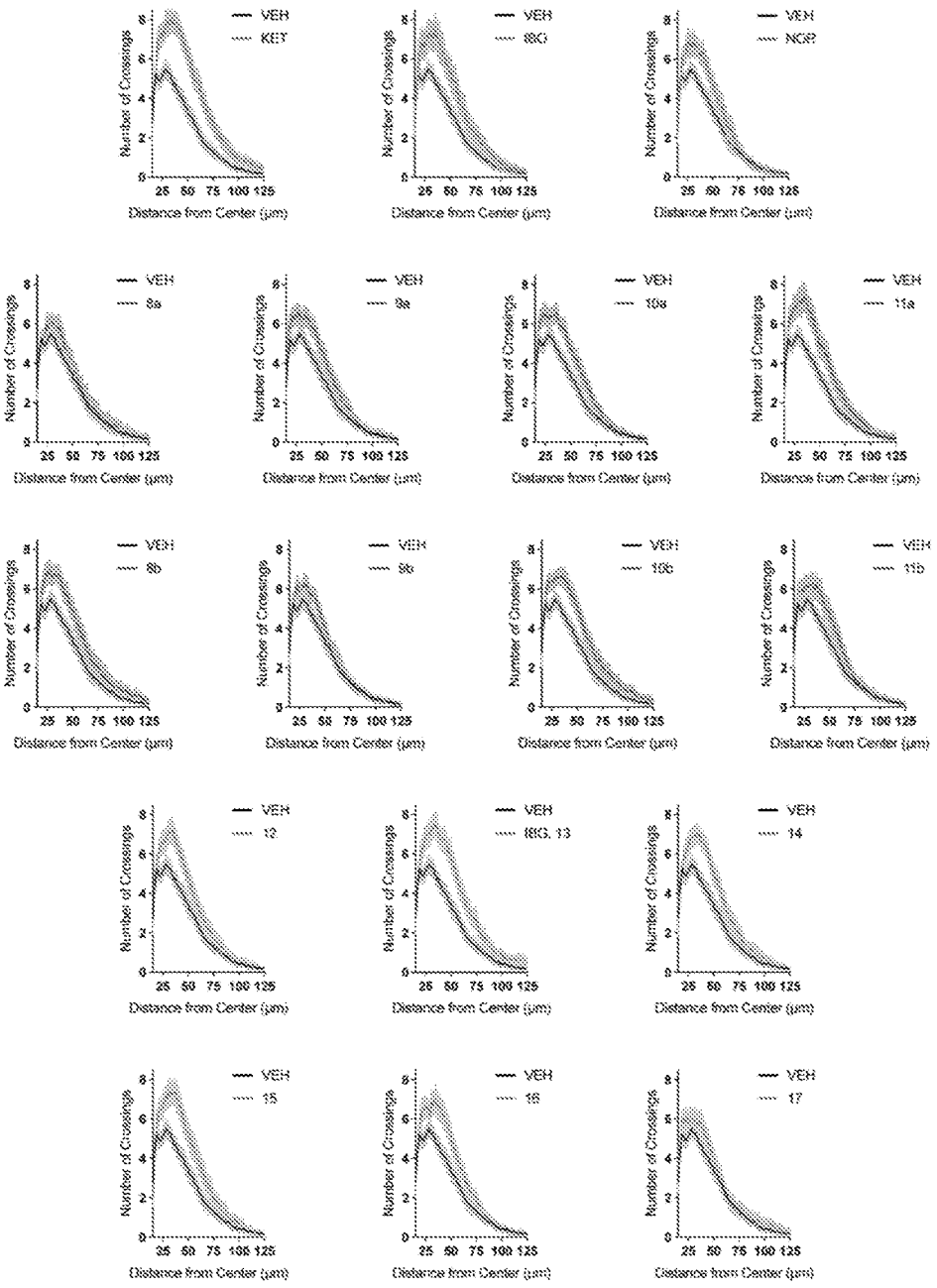

VEH
KET
IBG
NCP
8a
9a
10a
11a
8b
9b
10b
11b
12
IBG, 13
14
15
16
17
Number of Crossings
Distance from Center (μm)
0
2
4
6
8
25
50
75
100
125

FIG. 7

Vehicle Conditions	Concentration	Soluble?
Saline + 10% EtOH + 10% DMSO	40 mg/ml	NO ✗
Saline + 10% EtOH	8 mg/ml	NO ✗
Saline + 10% DMSO	8 mg/ml	NO ✗
Saline + 10% EtOH + 10% DMSO	8 mg/ml	NO ✗
Saline + 10% EtOH + 10% Kolliphor	8 mg/ml	NO ✗
Saline + 10% EtOH + 20% Kolliphor	8 mg/ml	NO ✗
Saline + 10% EtOH + 25% Kolliphor	8 mg/ml	NO ✗
Saline + 10% EtOH + 30% Kolliphor	8 mg/ml	NO ✗
Saline + 10% EtOH + 40% Kolliphor	8 mg/ml	NO ✗
Saline + 10% DMSO + 10% Kolliphor	8 mg/ml	NO ✗
Saline + 10% DMSO + 25% Kolliphor	8 mg/ml	NO ✗
Saline + 10% DMSO + 15% Glycerol	8 mg/ml	NO ✗
Saline + 10 mM ATP	8 mg/ml	NO ✗
Saline + 10% DMSO	4 mg/ml	NO ✗
Saline + 10% DMSO + 25% Kolliphor	4 mg/ml	NO ✗
Saline + 10% DMSO	1 mg/ml	YES ●

FIG. 8

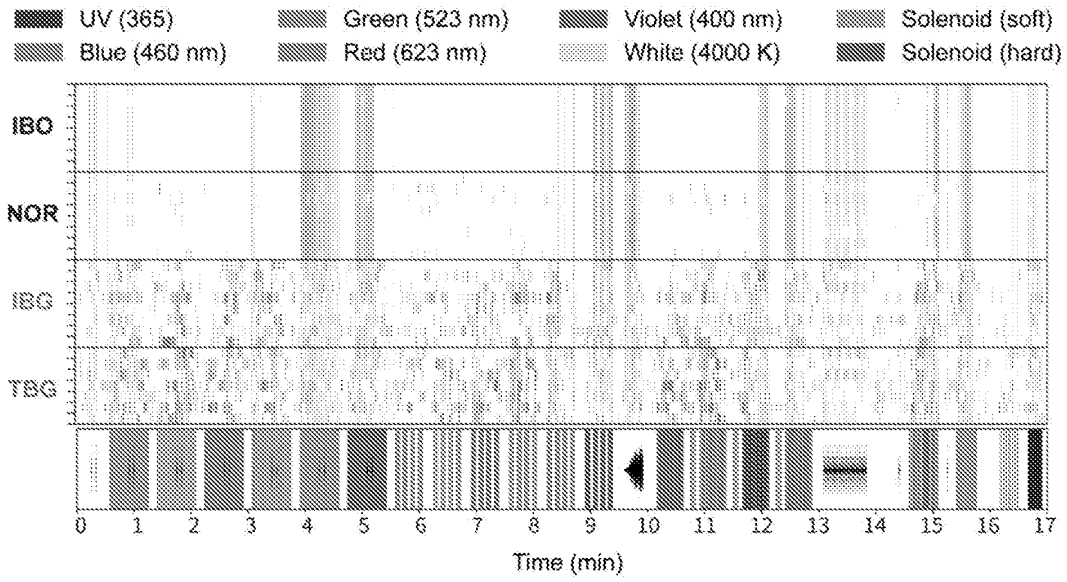

UV (365)
Blue (460 nm)
Green (523 nm)
Red (623 nm)
Violet (400 nm)
White (4000 K)
Solenoid (soft)
Solenoid (hard)
IBO
NOR
IBG
TBG
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Time (min)

FIG. 9

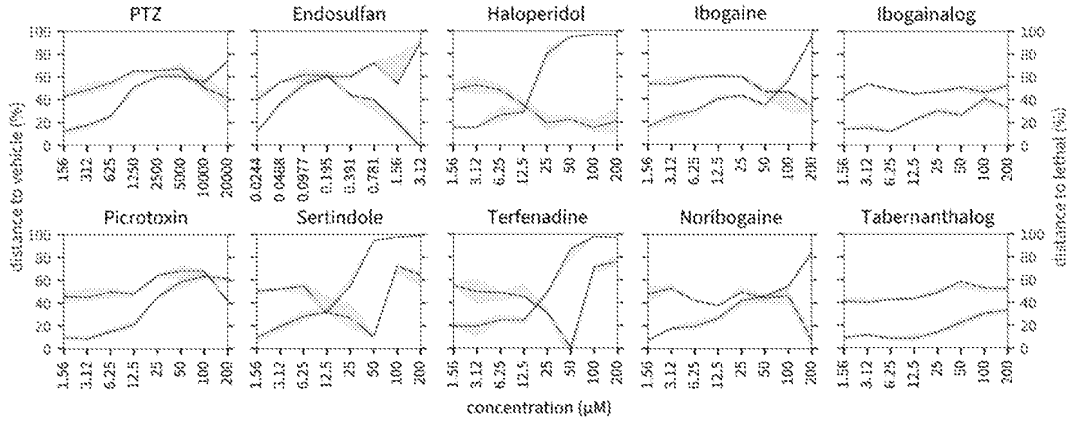

PTZ
Endosulfan
Haloperidol
Ibogaine
Ibogainalog
Picrotoxin
Sertindole
Terfenadine
Noribogaine
Tabernanthalog
distance to vehicle (%)
distance to lethal (%)
concentration (μM)

FIG. 10

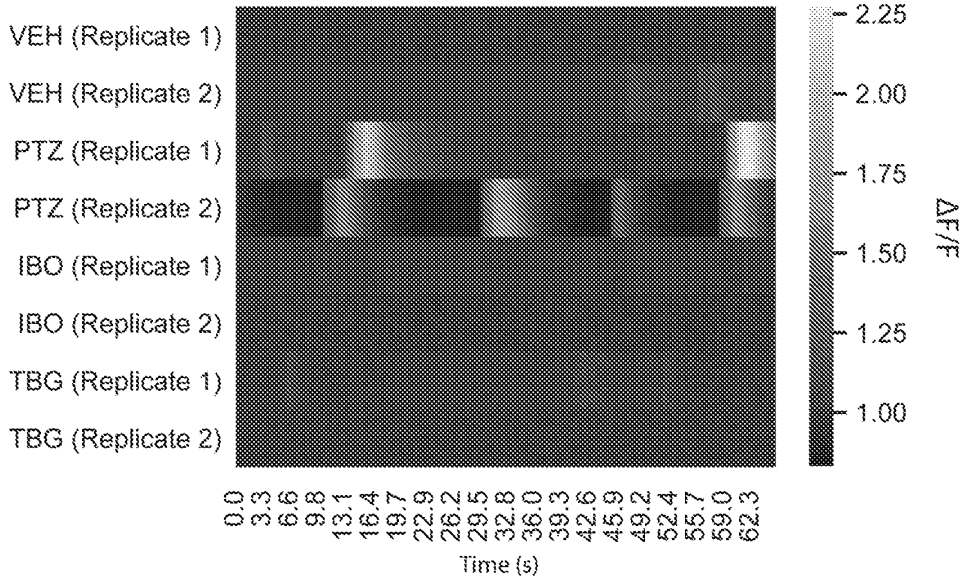

VEH (Replicate 1)
VEH (Replicate 2)
PTZ (Replicate 1)
PTZ (Replicate 2)
IBO (Replicate 1)
IBO (Replicate 2)
TBG (Replicate 1)
TBG (Replicate 2)
2.25
2.00
1.75
1.50
1.25
1.00
ΔF/F
0.0
3.3
6.6
9.8
13.1
16.4
19.7
22.9
26.2
29.5
32.8
36.0
39.3
42.6
45.9
49.2
52.4
55.7
59.0
62.3
Time (s)

FIG. 11

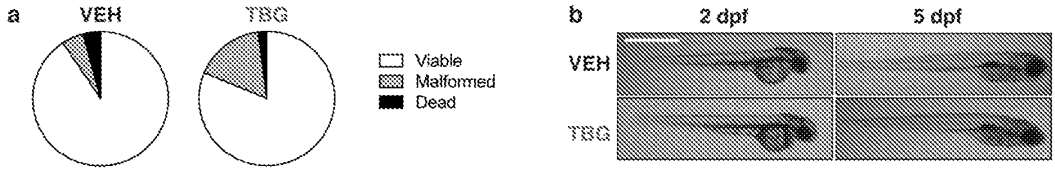


FIG. 12

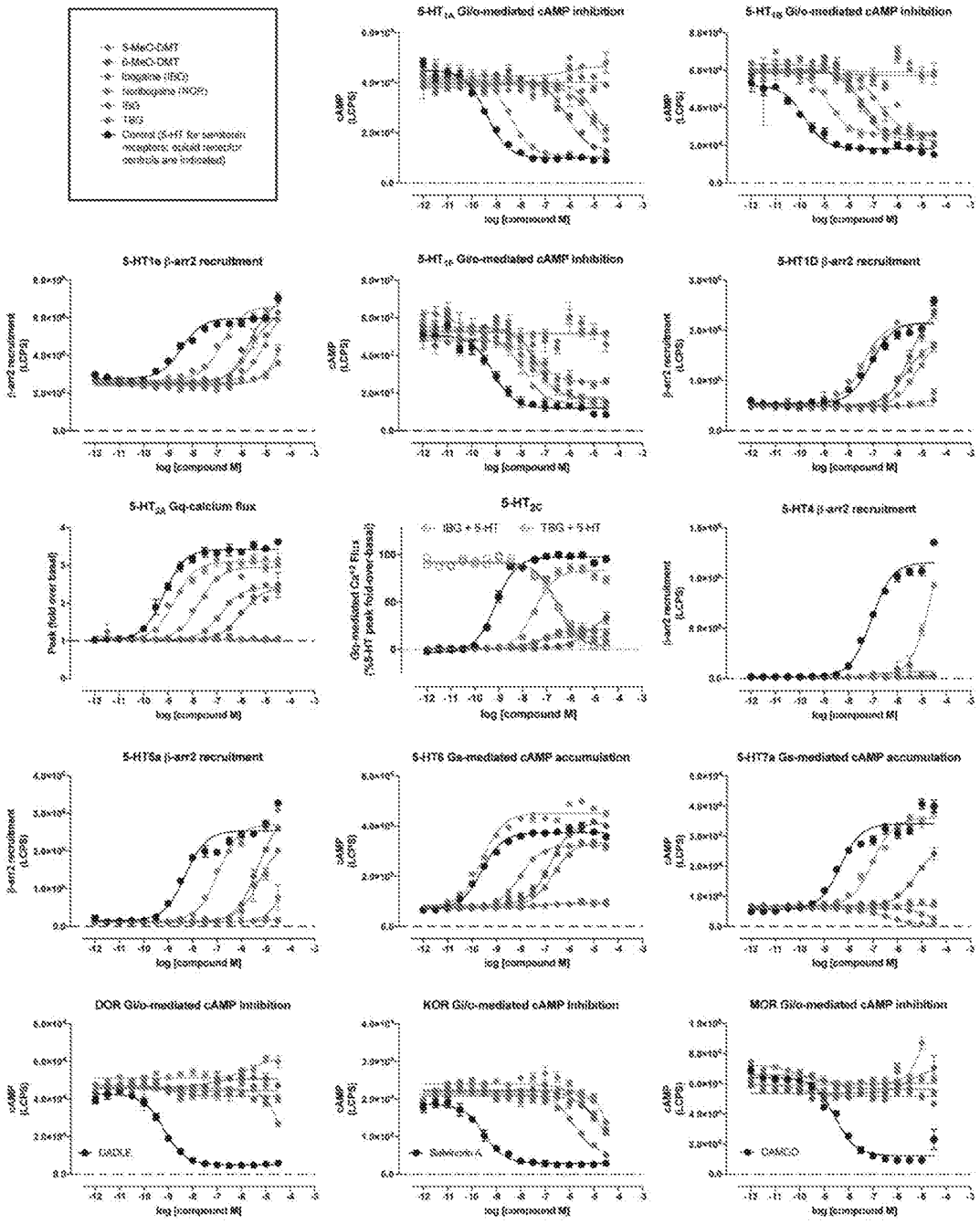

5-MeO-DMT
5-MeO-DMT
ibogaine (IBG)
noribogaine (NOR)
IBG
TBG
Control (5-HT for serotonin receptors; docked reference controls are indicated)
5-HT1A Gi/o-mediated cAMP inhibition
5-HT1B Gi/o-mediated cAMP inhibition
5-HT1e β-arr2 recruitment
5-HT1E Gi/o-mediated cAMP inhibition
5-HT1D β-arr2 recruitment
5-HT2A Gq-calcium flux
5-HT2C
IBG + 5-HT
TBG + 5-HT
5-HT4 β-arr2 recruitment
5-HT5a β-arr2 recruitment
5-HT6 Gs-mediated cAMP accumulation
5-HT7a Gs-mediated cAMP accumulation
DOR Gi/o-mediated cAMP inhibition
KOR Gi/o-mediated cAMP inhibition
MOR Gi/o-mediated cAMP inhibition
cAMP (LCPS)
β-arr2 recruitment (LCPS)
Peak (fold over basal)
Gq-mediated Ca2+ flux (%5-HT peak fold-over-basal)
log [compound M]

FIG. 13

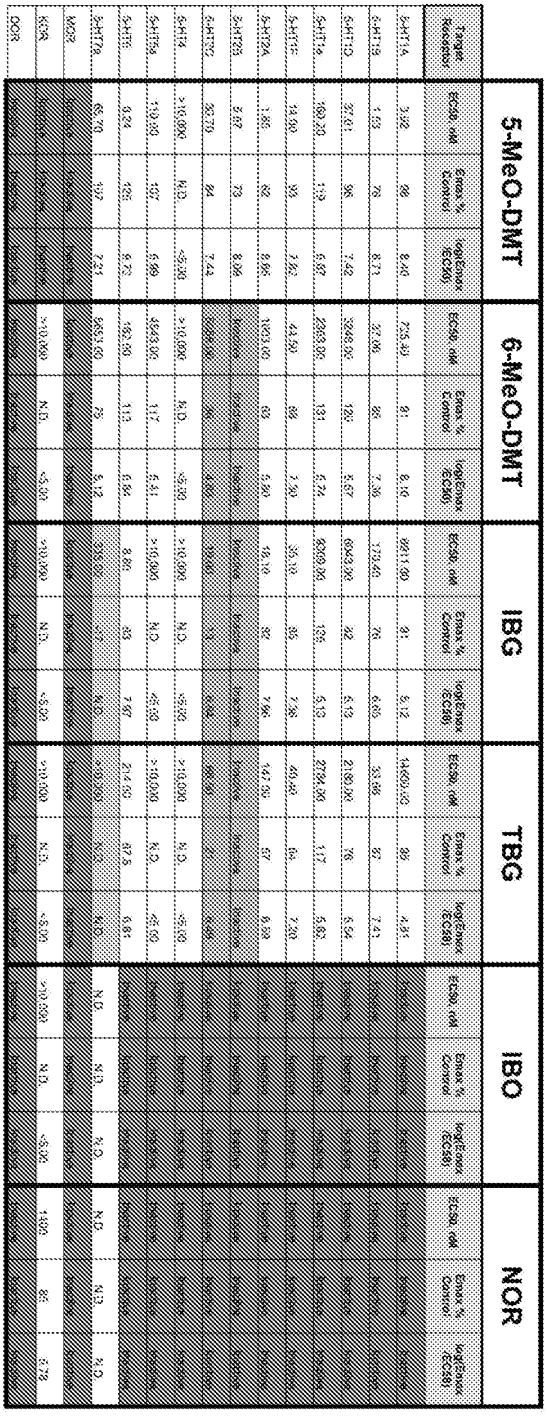

5-MeO-DMT
6-MeO-DMT
IBG
TBG
IBO
NOR
Target Receptor
EC50, nM
Emax % Control
log(Emax/EC50)
5-HT1A
5-HT1D
5-HT1E
5-HT2A
5-HT2B
5-HT6
5-HT7a
M2R
KOR
DOR

FIG. 14

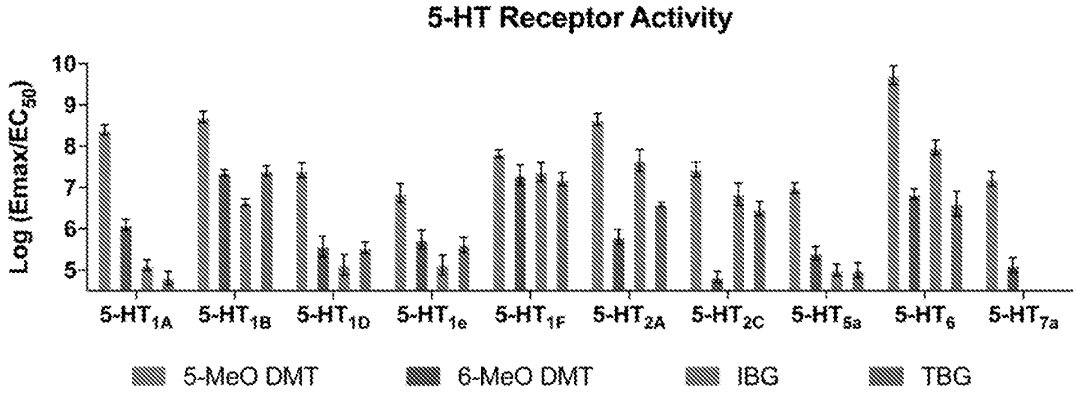

5-HT Receptor Activity
Log (Emax/EC50)
10
9
8
7
6
5
5-HT1A
5-HT1B
5-HT1D
5-HT1e
5-HT1F
5-HT2A
5-HT2C
5-HT5a
5-HT6
5-HT7a
5-MeO DMT
6-MeO DMT
IBG
TBG

FIG. 15

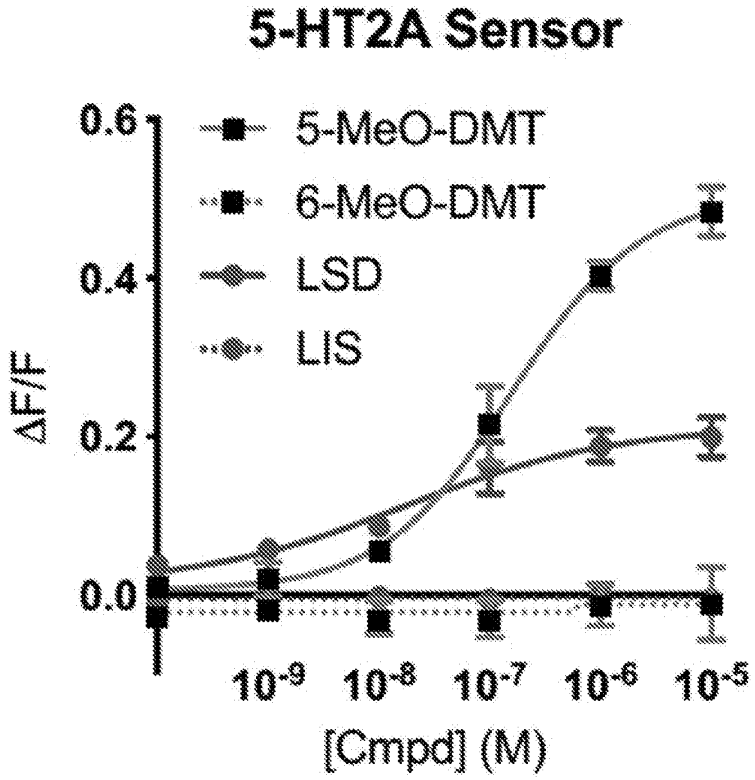

5-HT2A Sensor
0.6
0.4
0.2
0.0
ΔF/F
5-MeO-DMT
6-MeO-DMT
LSD
LIS
10-9
10-8
10-7
10-6
10-5
[Cmpd] (M)

FIG. 16

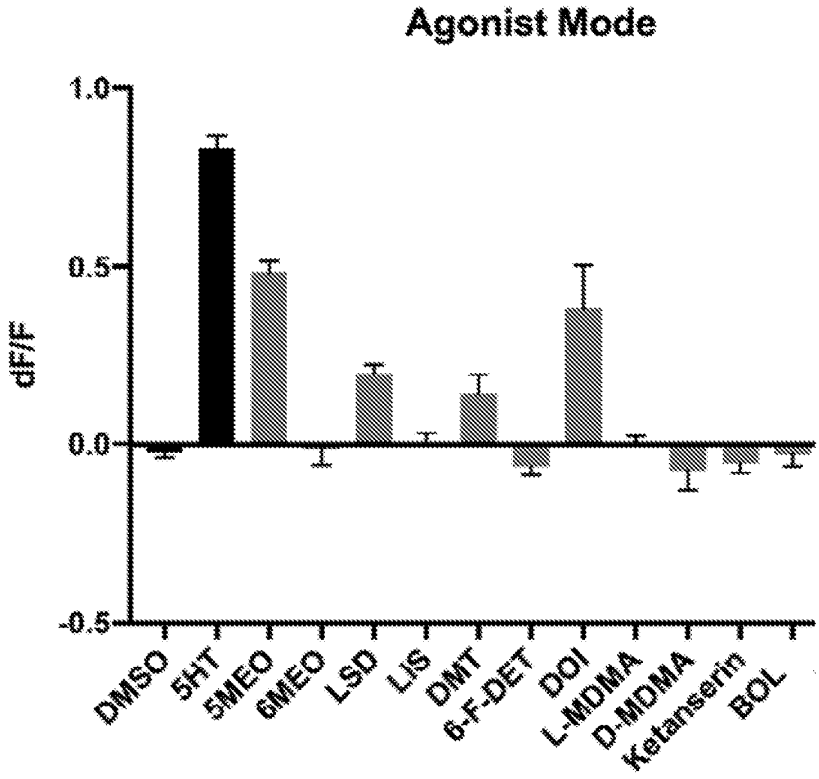

Agonist Mode
dF/F
1.0
0.5
0.0
-0.5
DMSO
5HT
5MEO
6MEO
LSD
LJS
DMT
6-F-DET
DOI
L-MDMA
D-MDMA
Ketanserin
BOL

FIG. 17

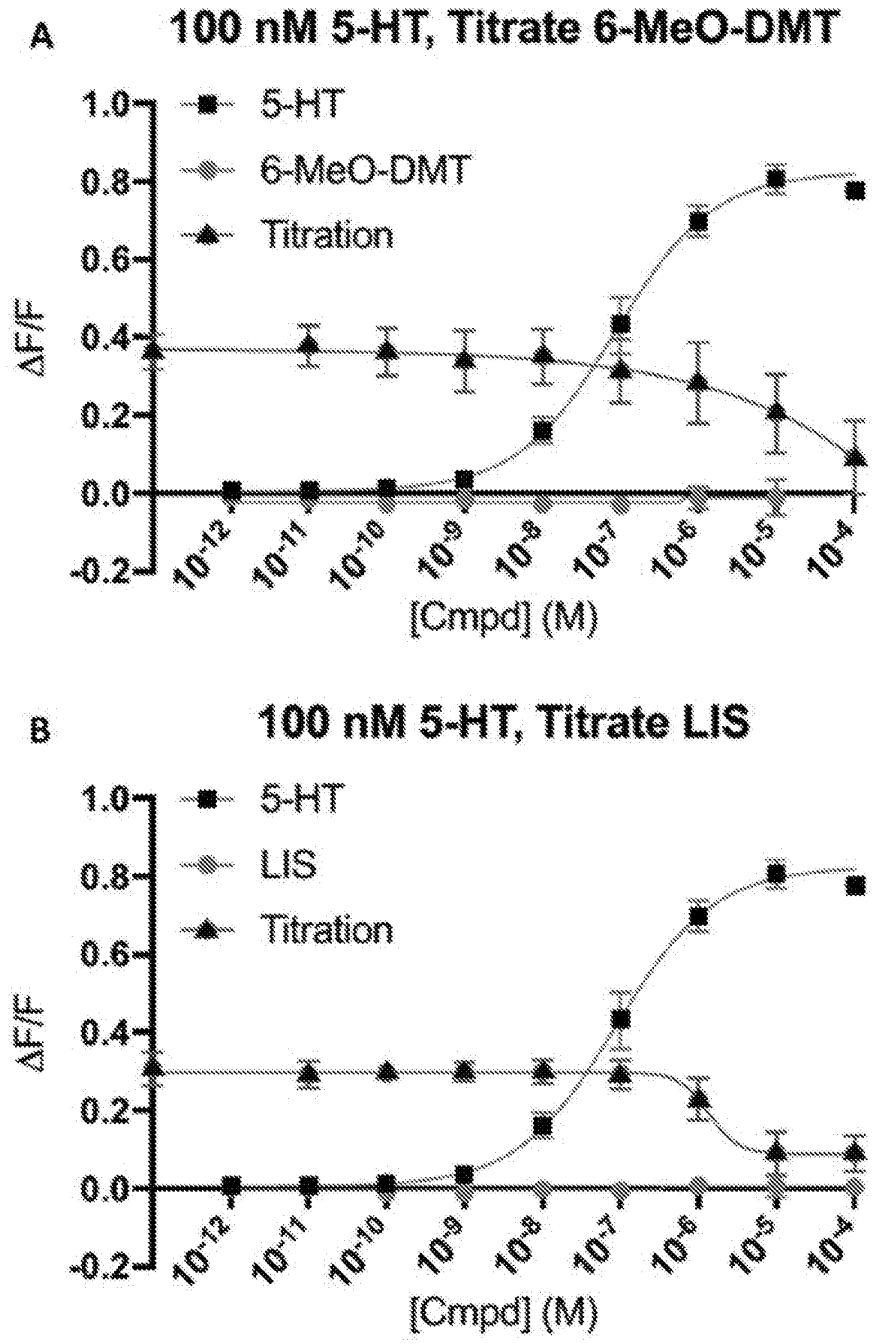
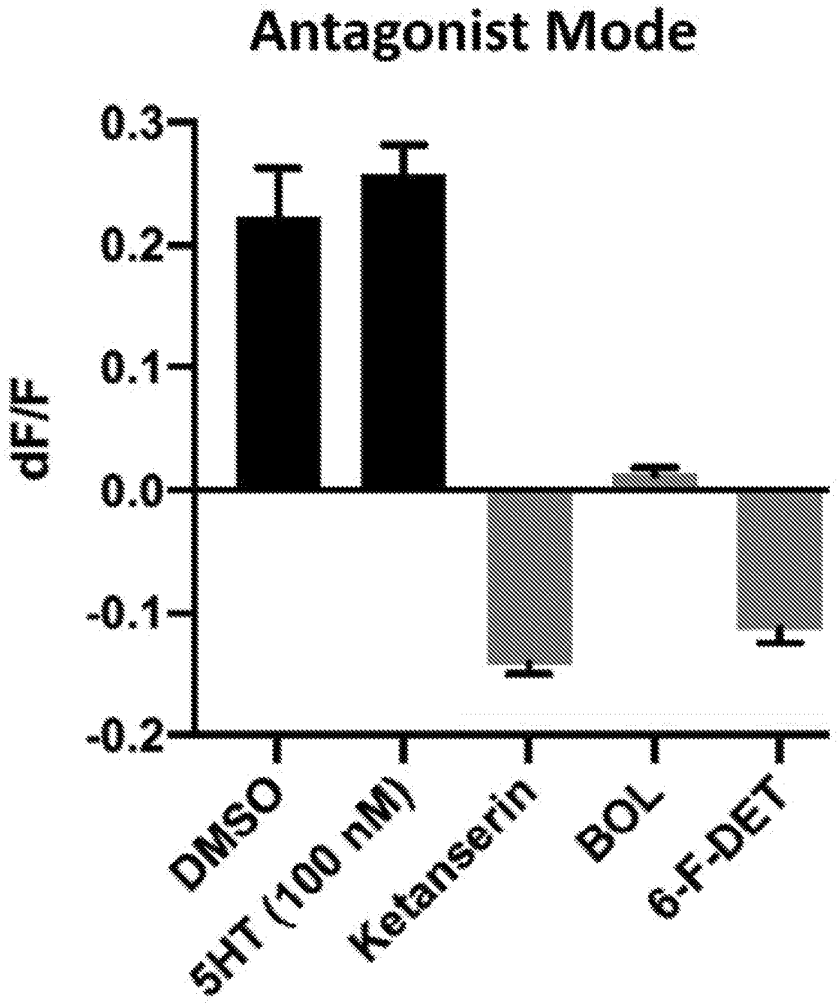

A
100 nM 5-HT, Titrate 6-MeO-DMT
5-HT
6-MeO-DMT
Titration
ΔF/F
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
10-12
10-11
10-10
10-9
10-8
10-7
10-6
10-5
10-4
[Cmpd] (M)
B
100 nM 5-HT, Titrate LIS
5-HT
LIS
Titration
ΔF/F
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
10-12
10-11
10-10
10-9
10-8
10-7
10-6
10-5
10-4
[Cmpd] (M)

FIG. 18


Antagonist Mode
dF/F
0.3
0.2
0.1
0.0
-0.1
-0.2
DMSO
5HT (100 nM)
Ketanserin
BOL
6-F-DET