Figure 1

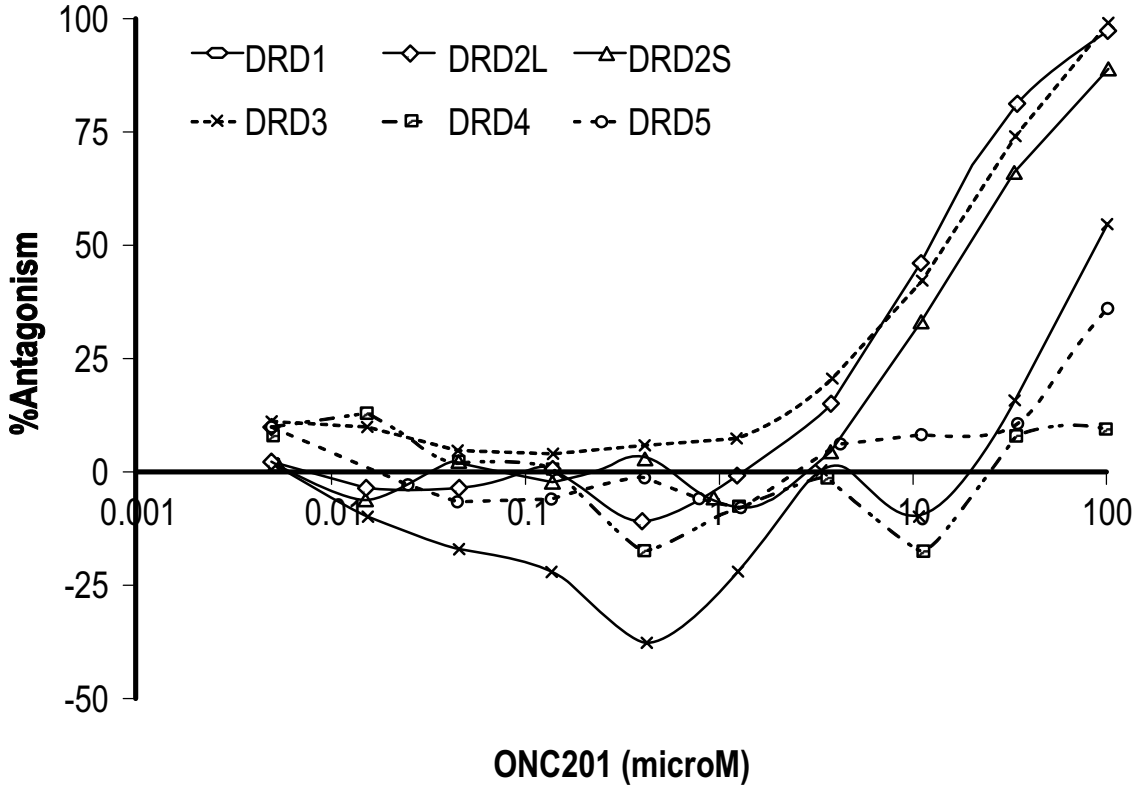
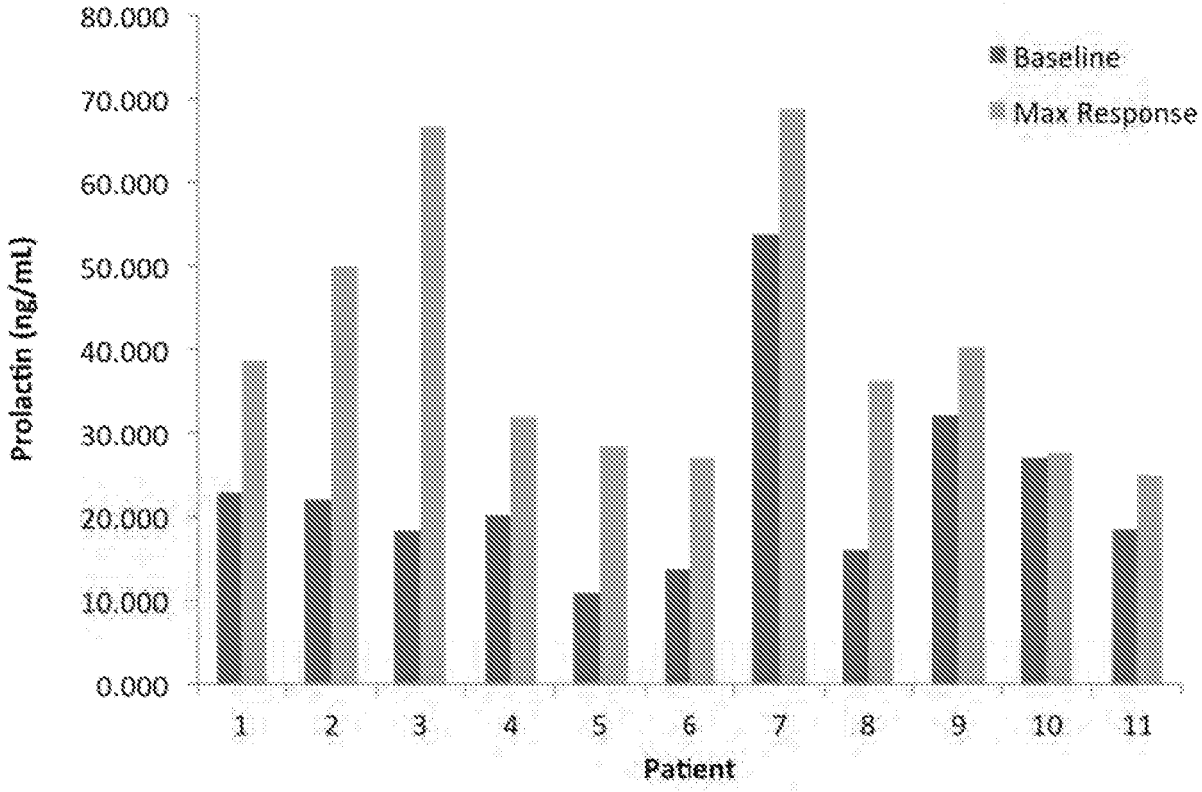

100
75
50
25
0
-25
-50
%Antagonism
DRD1
DRD2L
DRD2S
DRD3
DRD4
DRD5
0.001
0.01
0.1
1
10
100
ONC201 (microM)

Figure 2


80.000
70.000
60.000
50.000
40.000
30.000
20.000
10.000
0.000
Prolactin (ng/mL)
Baseline
Max Response
1
2
3
4
5
6
7
8
9
10
11
Patient

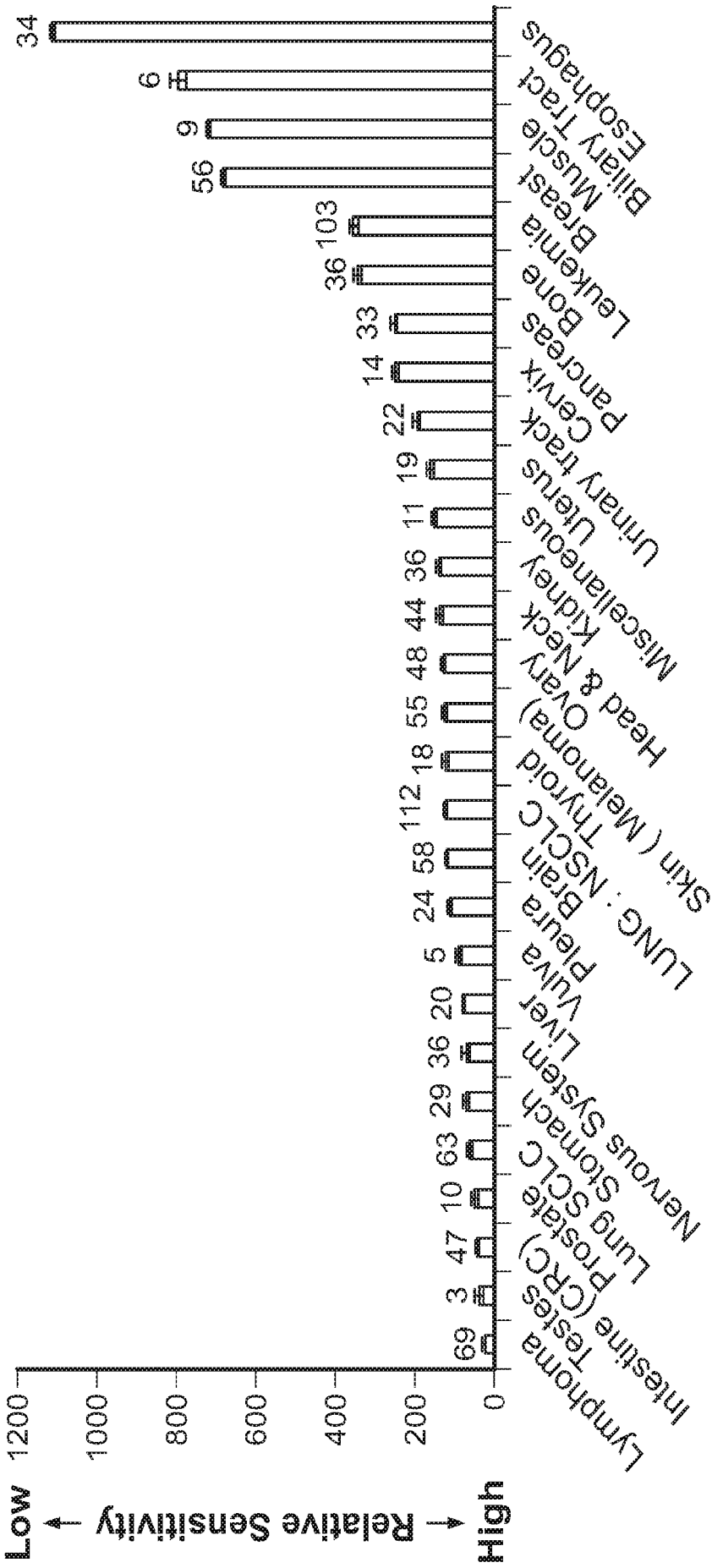

Low
Relative Sensitivity
High
1200
1000
800
600
400
200
0
69
3
47
10
63
29
36
20
5
24
58
112
18
55
48
44
36
11
19
22
14
33
36
103
56
9
6
34
Lymphoma
Testes
Intestine (CRC)
Prostate
Lung SCLC
Stomach
Nervous System
Liver
Vulva
Pleura
Brain
LUNG : NSCLC
Thyroid
Skin (Melanoma)
Ovary
Head & Neck
Kidney
Miscellaneous
Uterus
Urinary track
Cervix
Pancreas
Bone
Leukemia
Breast
Muscle
Biliary Tract
Esophagus

Figure 3

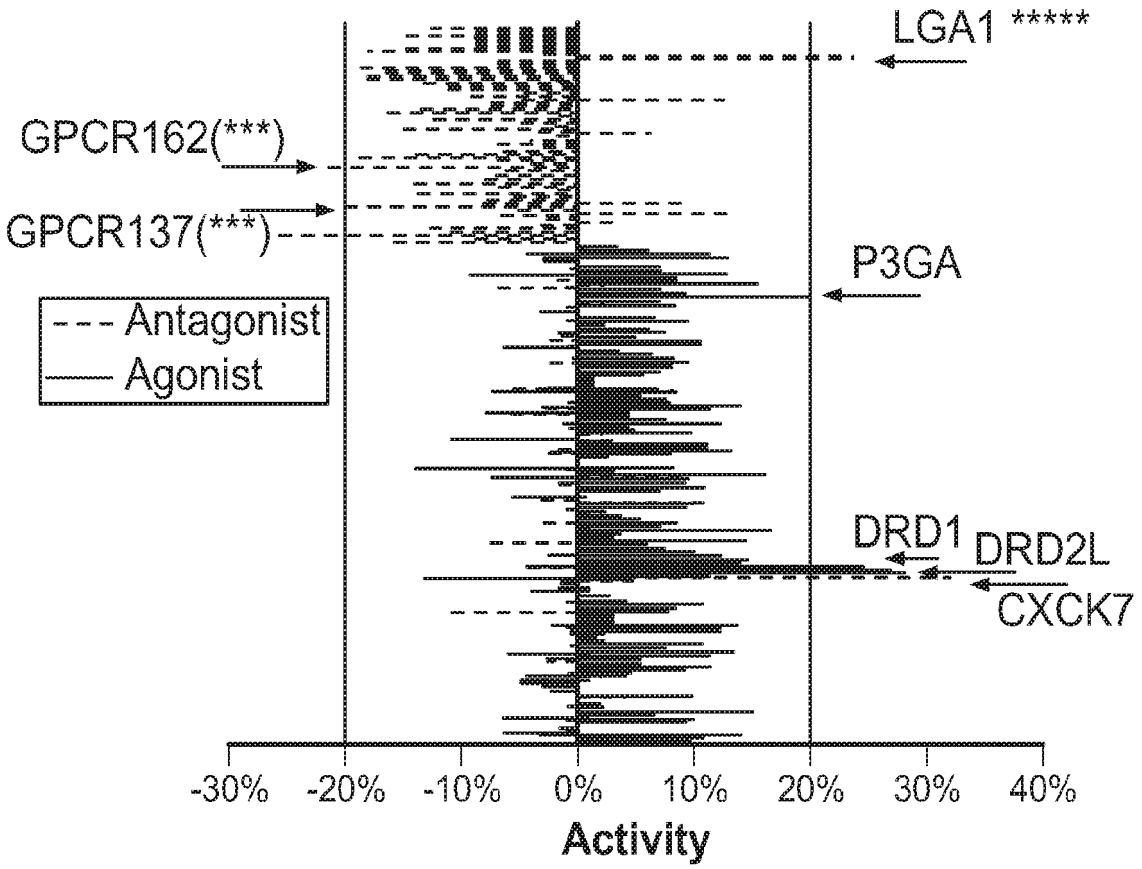


Figure 4A

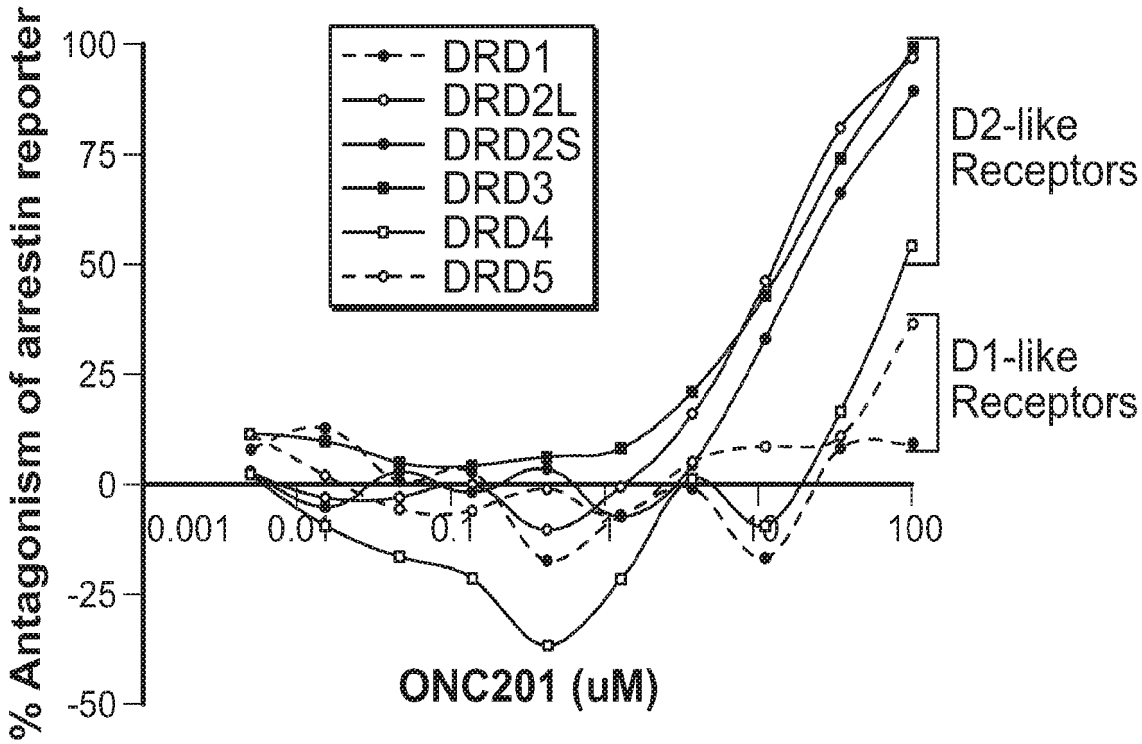


Figure 4B

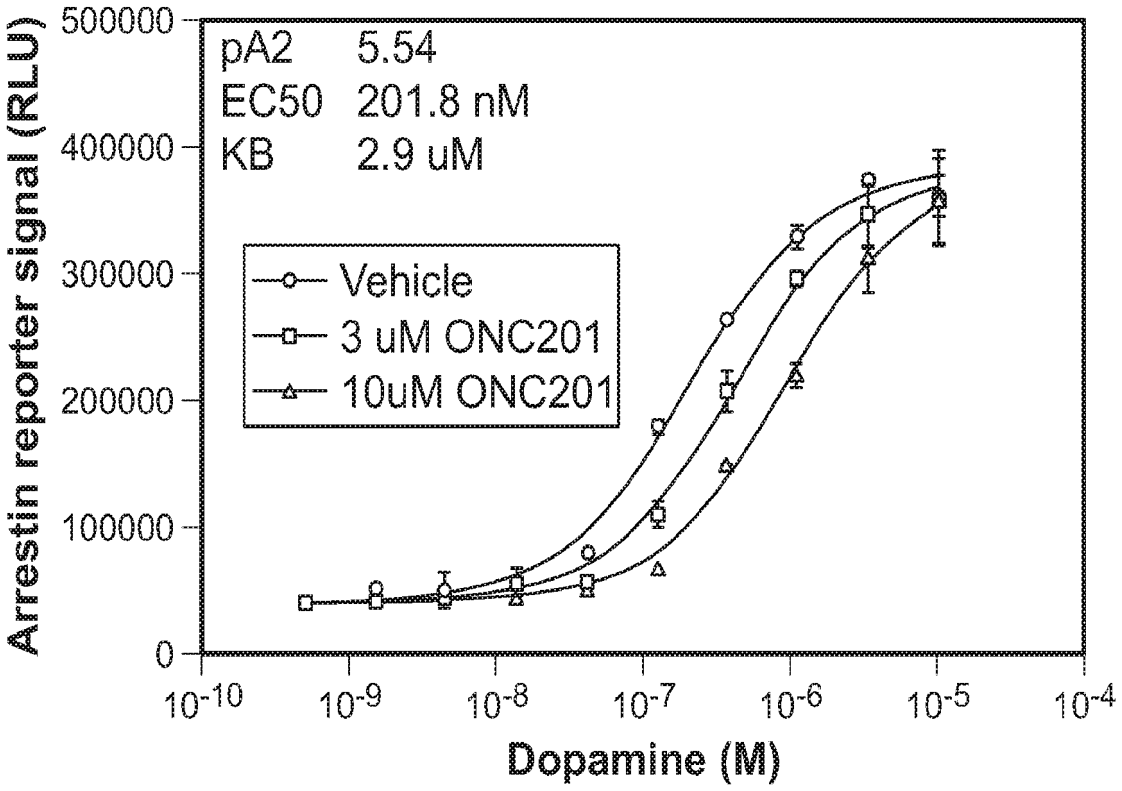


Figure 4C

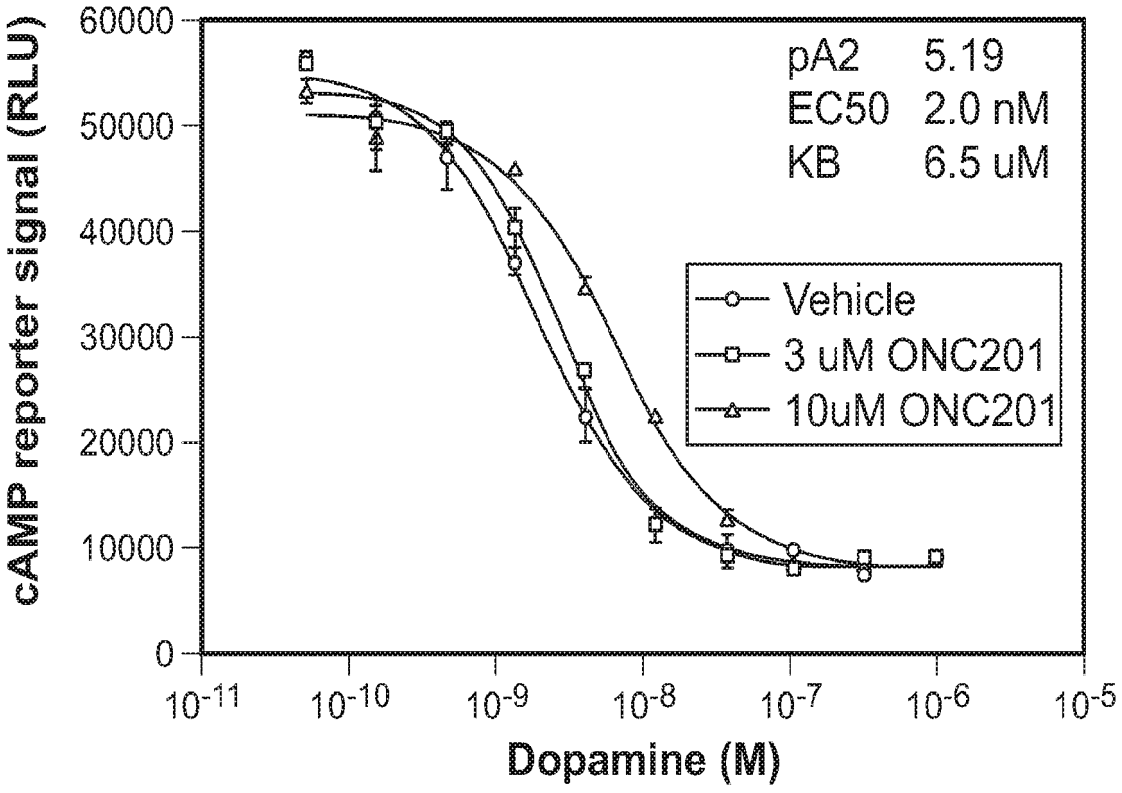


Figure 4D

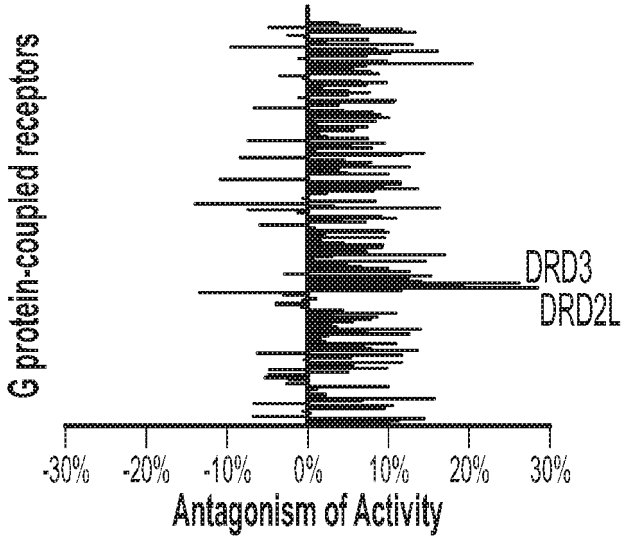


Figure 5A

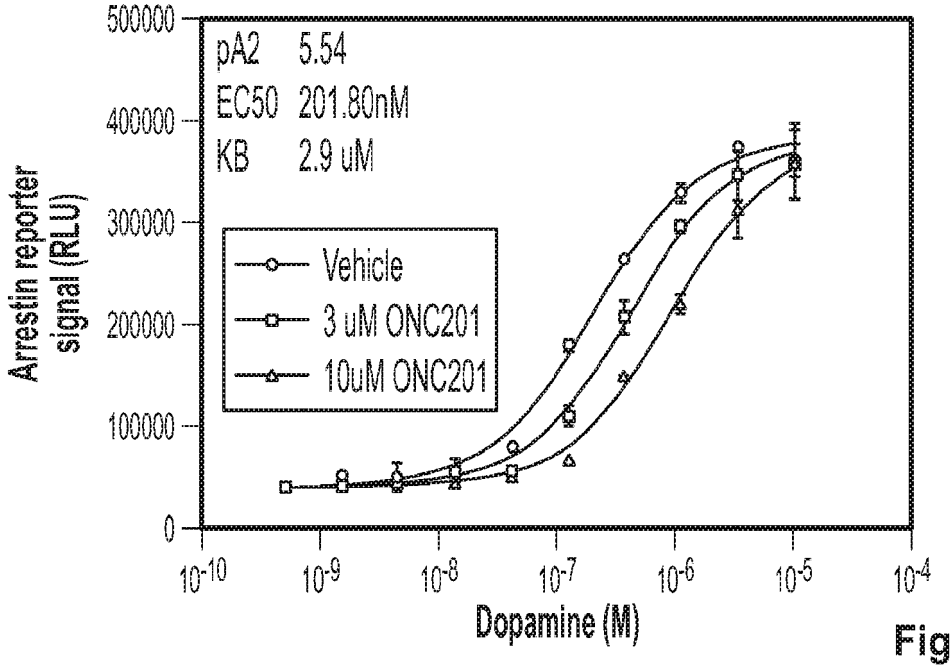


Figure 5B

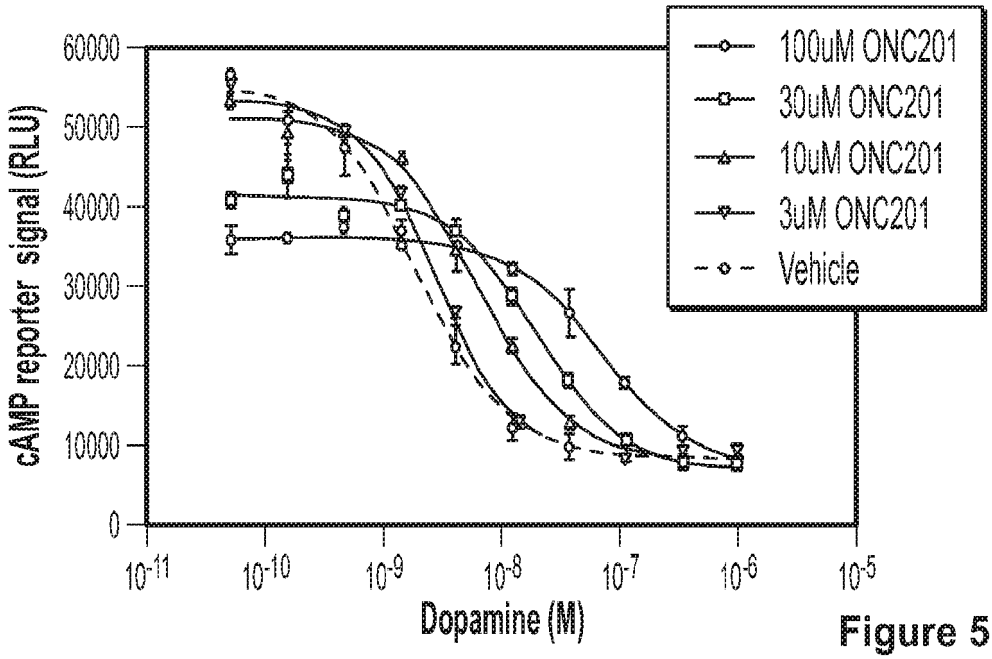


Figure 5C

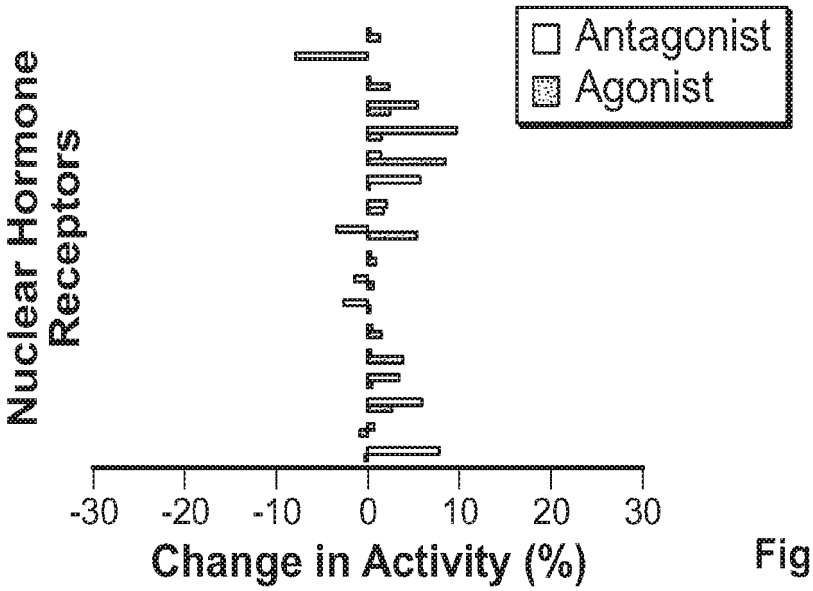


Figure 5D

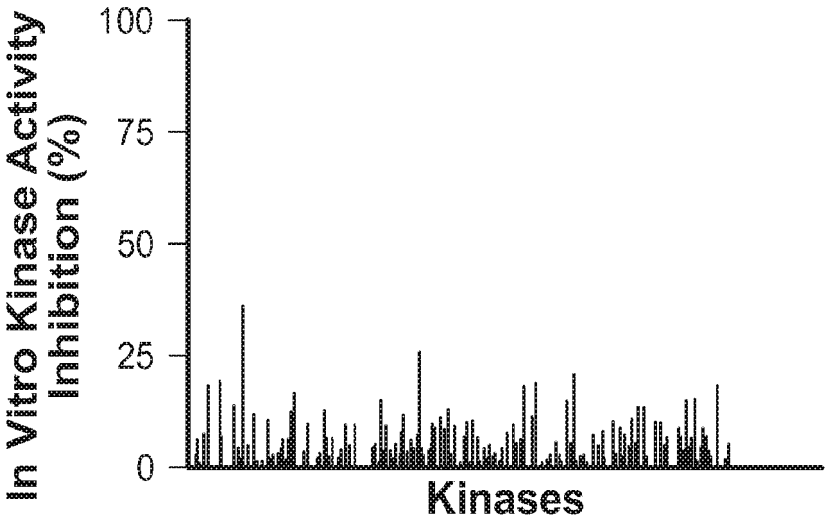


Figure 5E

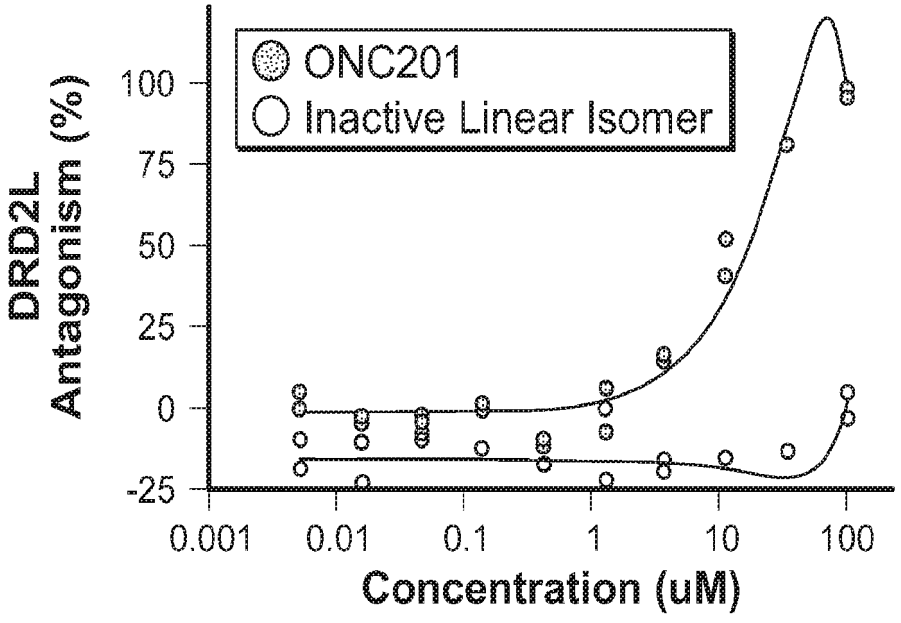
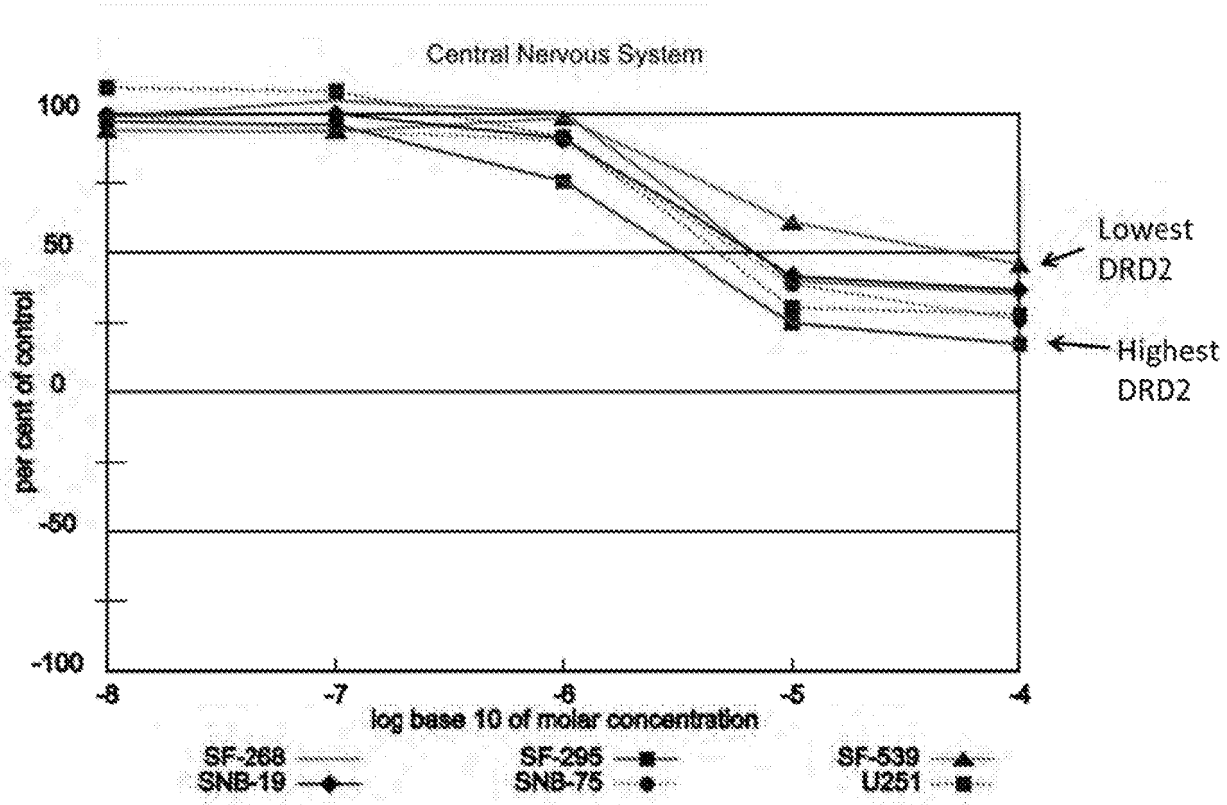


Figure 5F

Figure 6

A


Central Nervous System
100
50
0
-50
-100
per cent of control
-8
-7
-6
-5
-4
log base 10 of molar concentration
Lowest DRD2
Highest DRD2
SF-268
SNB-19
SF-295
SNB-75
SF-539
U251

B

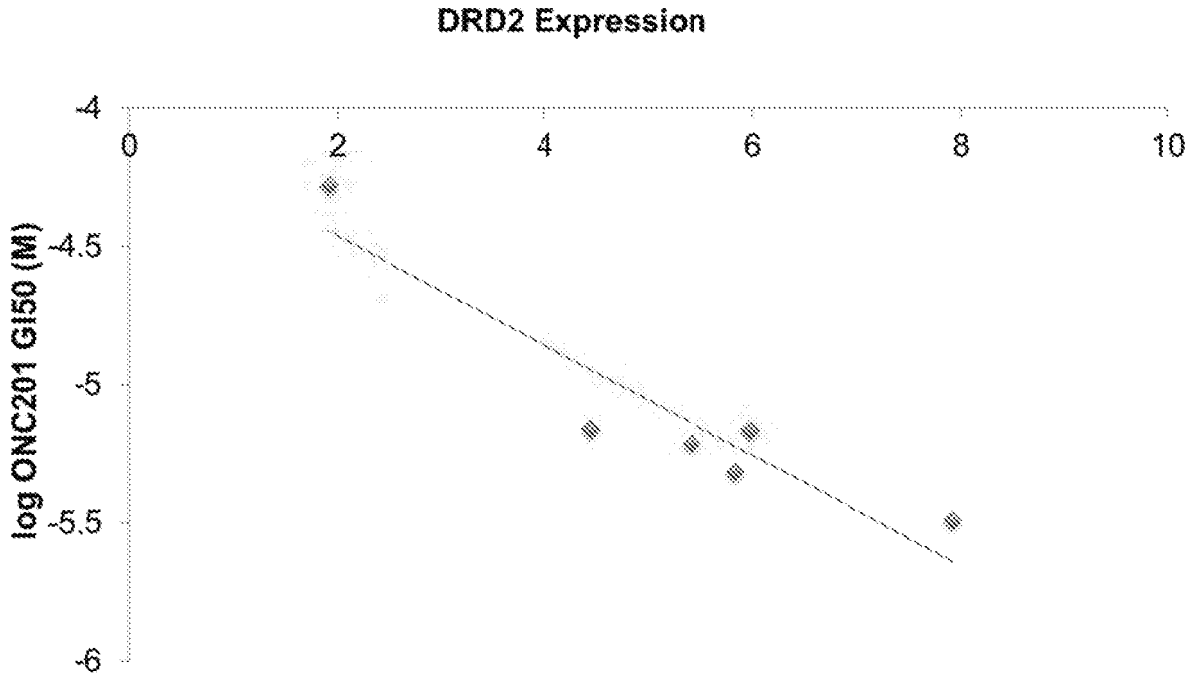
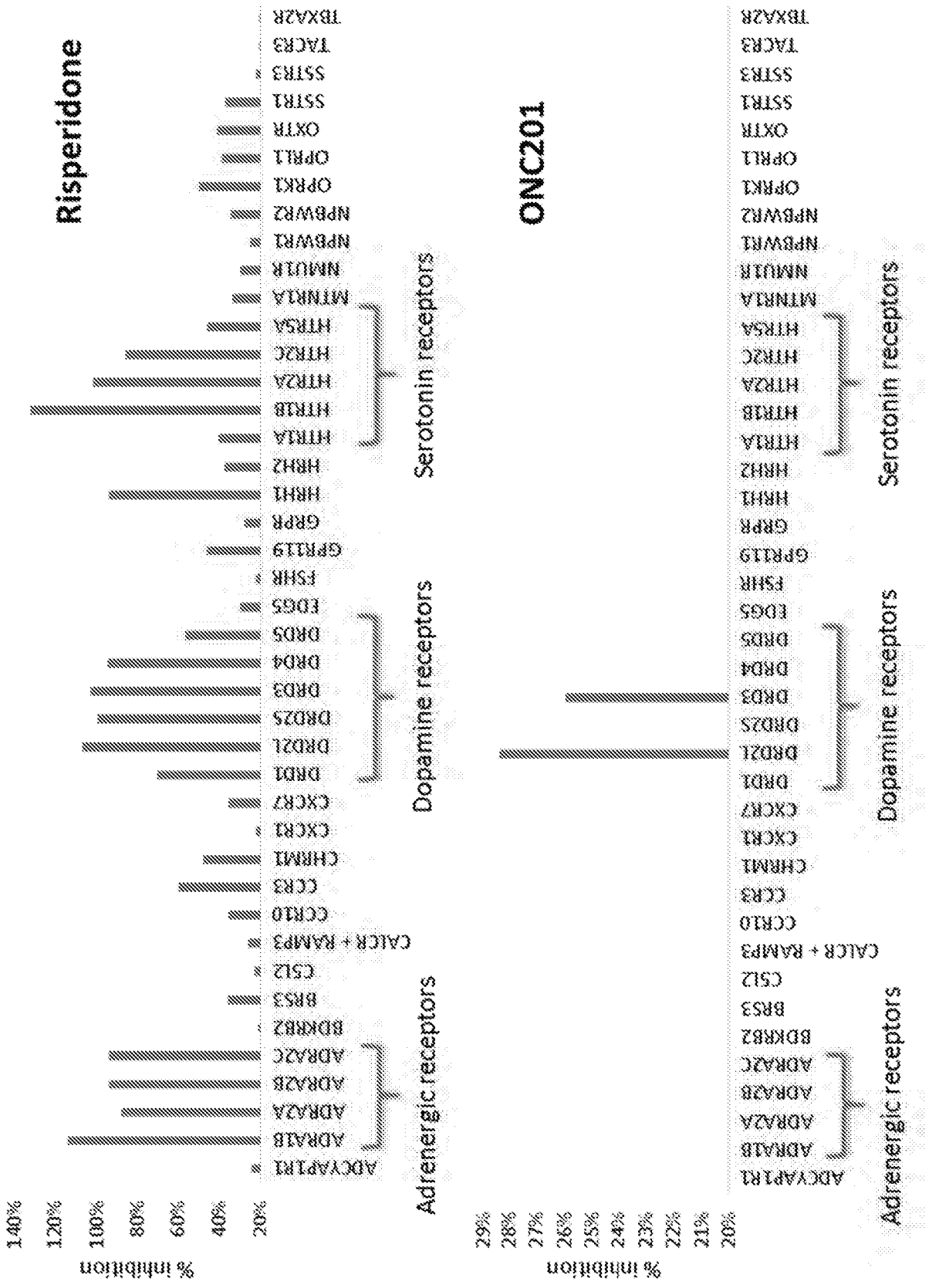

DRD2 Expression
-4
-4.5
-5
-5.5
-6
log ONC201 GI50 (M)
0
2
4
6
8
10

Figure 7


Risperidone
% inhibition
140%
120%
100%
80%
60%
40%
20%
ADCYAP1R1
ADRA1B
ADRA2A
ADRA2B
ADRA2C
BDKRB2
BRS3
C5L2
CALCR + RAMP3
CCR10
CCR3
CHRM1
CXCR1
CXCR7
DRD1
DRD2L
DRD2S
DRD3
DRD4
DRD5
EDG5
FSHR
GPR119
GRPR
HRH1
HRH2
HTR1A
HTR1B
HTR2A
HTR2C
HTR5A
MTNR1A
NMUR
NPBWR1
NPBWR2
OPRK1
OPRL1
OXTR
SSTR1
SSTR3
TACR3
TBXA2R
Adrenergic receptors
Dopamine receptors
Serotonin receptors
ONC201
% inhibition
29%
28%
27%
26%
25%
24%
23%
22%
21%
20%
ADCYAP1R1
ADRA1B
ADRA2A
ADRA2B
ADRA2C
BDKRB2
BRS3
C5L2
CALCR + RAMP3
CCR10
CCR3
CHRM1
CXCR1
CXCR7
DRD1
DRD2L
DRD2S
DRD3
DRD4
DRD5
EDG5
FSHR
GPR119
GRPR
HRH1
HRH2
HTR1A
HTR1B
HTR2A
HTR2C
HTR5A
MTNR1A
NMUR
NPBWR1
NPBWR2
OPRK1
OPRL1
OXTR
SSTR1
SSTR3
TACR3
TBXA2R
Adrenergic receptors
Dopamine receptors
Serotonin receptors

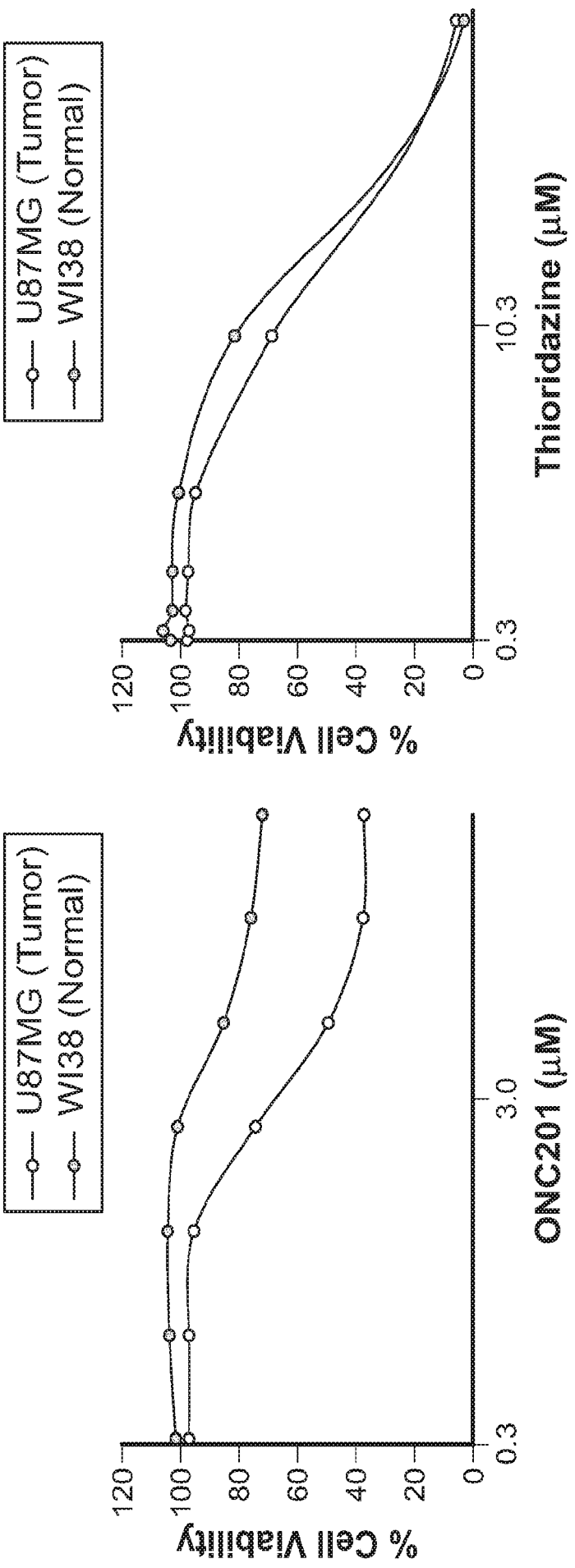

U87MG (Tumor)
WI38 (Normal)
% Cell Viability
120
100
80
60
40
20
0
0.3
3.0
ONC201 (µM)
U87MG (Tumor)
WI38 (Normal)
% Cell Viability
120
100
80
60
40
20
0
0.3
10.3
Thioridazine (µM)

Figure 8

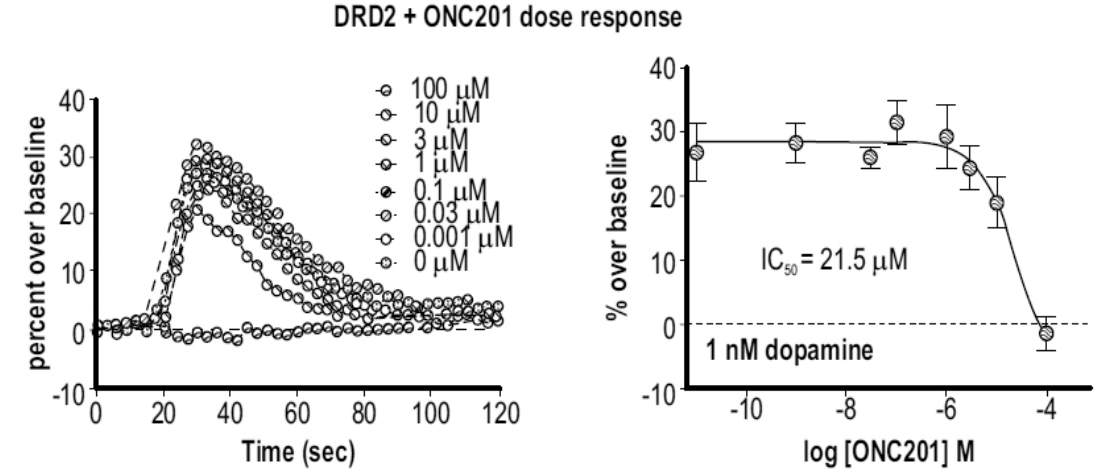


Figure 9A

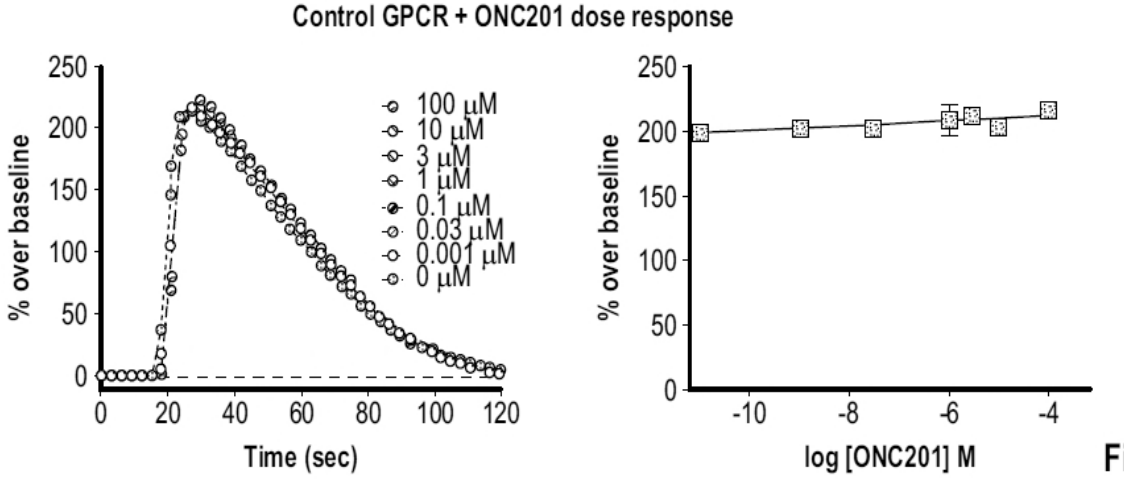


Figure 9B

Figure 10

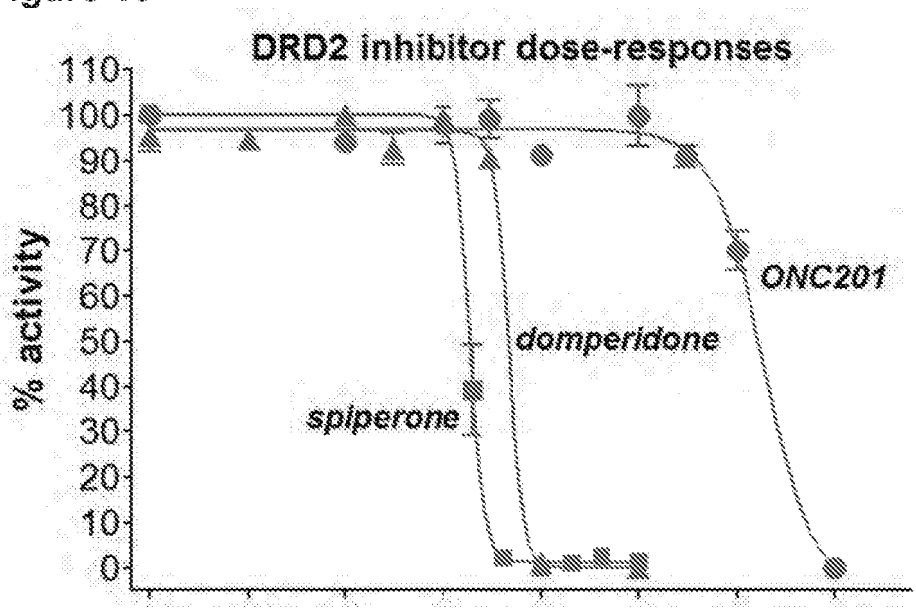
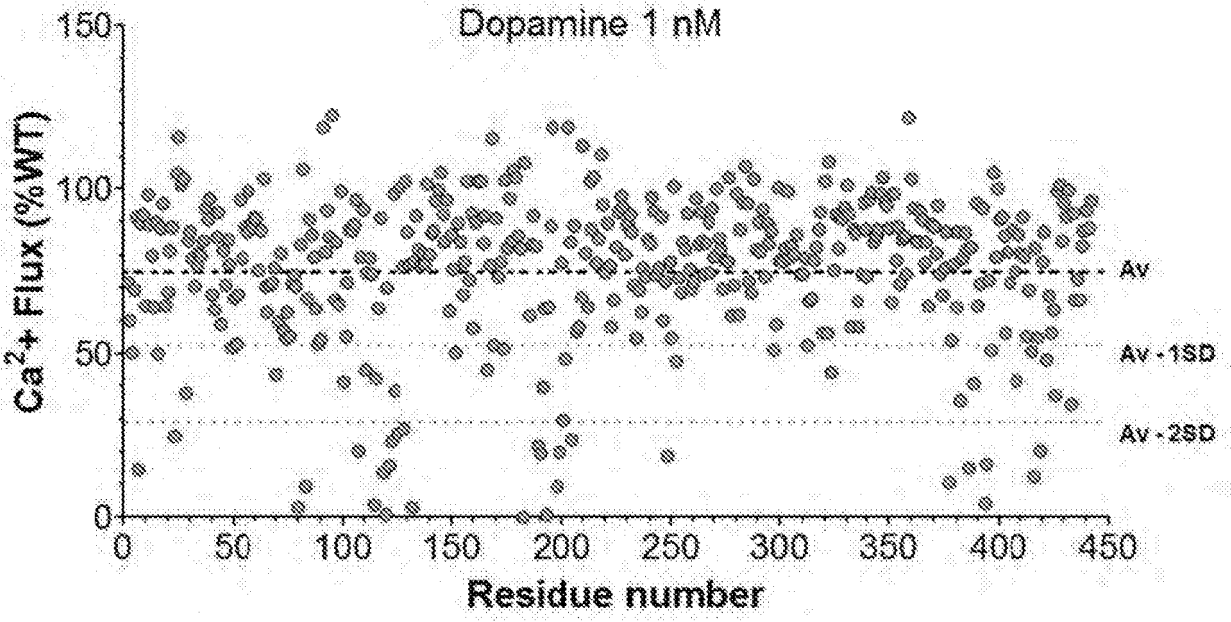


Figure 11

A


Dopamine 1 nM
Ca2+ Flux (%WT)
150
100
50
0
0
50
100
150
200
250
300
350
400
450
Residue number
Av
Av - 1SD
Av - 2SD

B

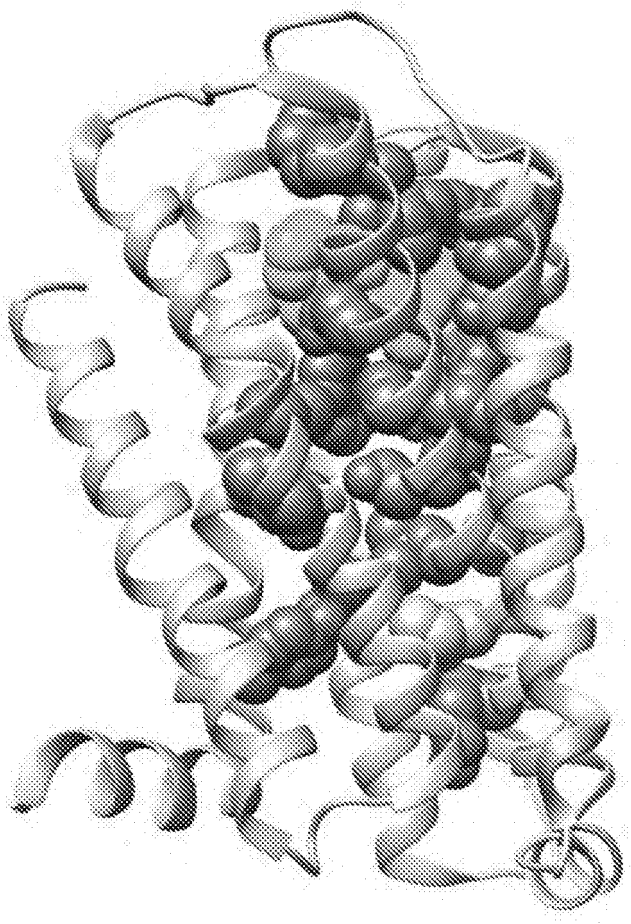
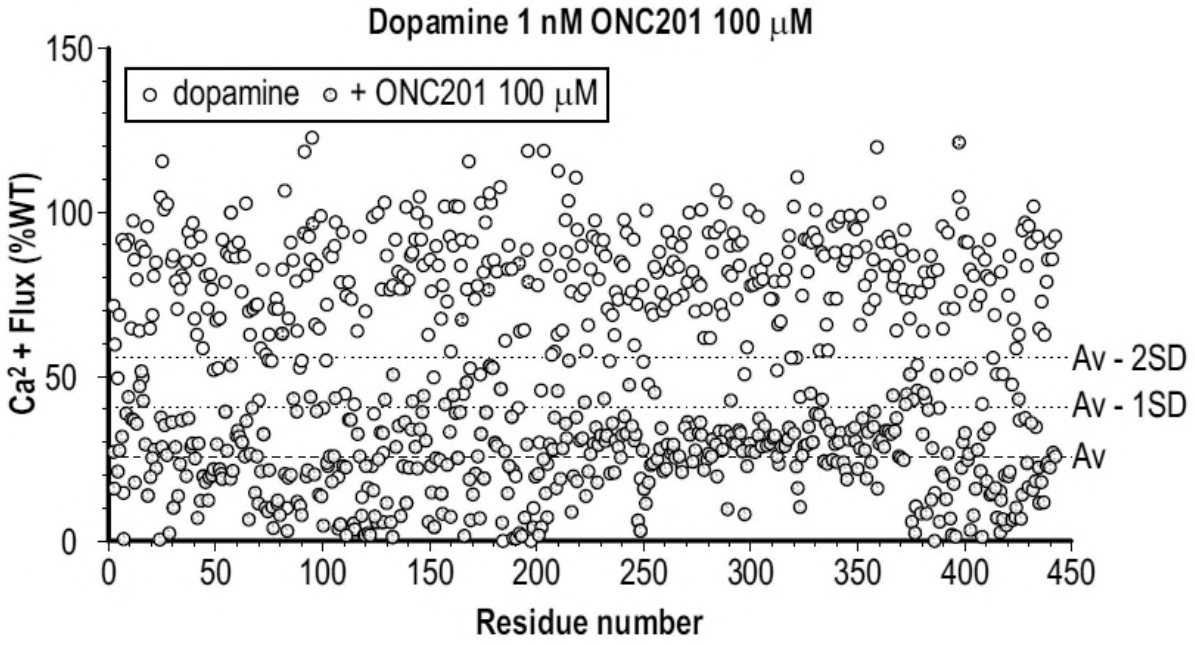
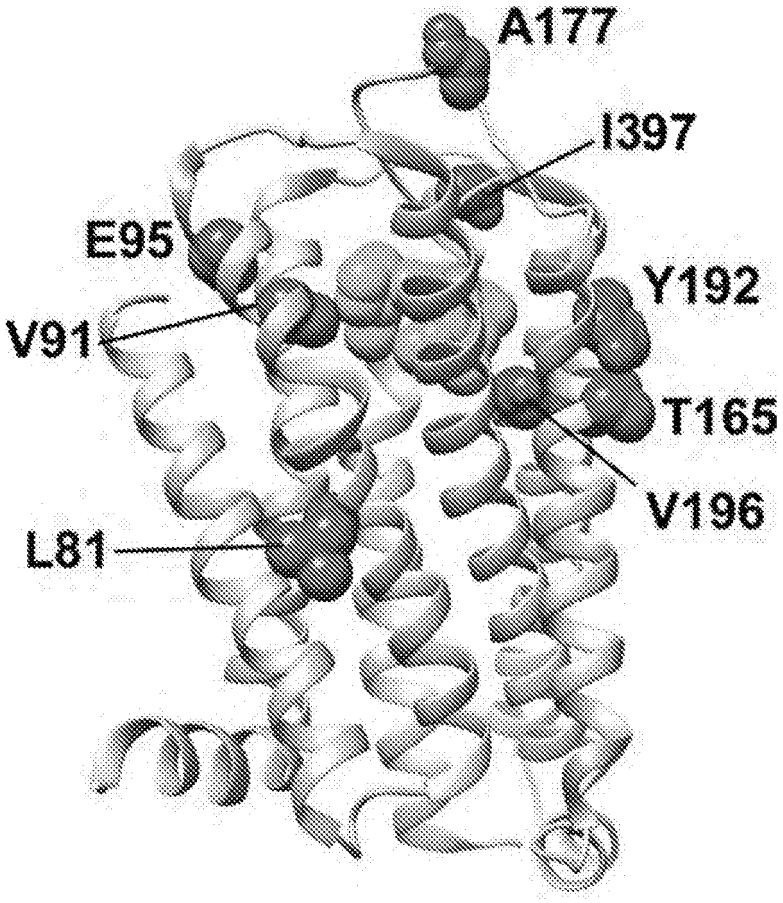


Figure 12

A


Dopamine 1 nM ONC201 100 μM
dopamine
+ ONC201 100 μM
Ca2 + Flux (%WT)
150
100
50
0
0
50
100
150
200
250
300
350
400
450
Residue number
Av - 2SD
Av - 1SD
Av

B


A177
I397
E95
Y192
V91
T165
V196
L81

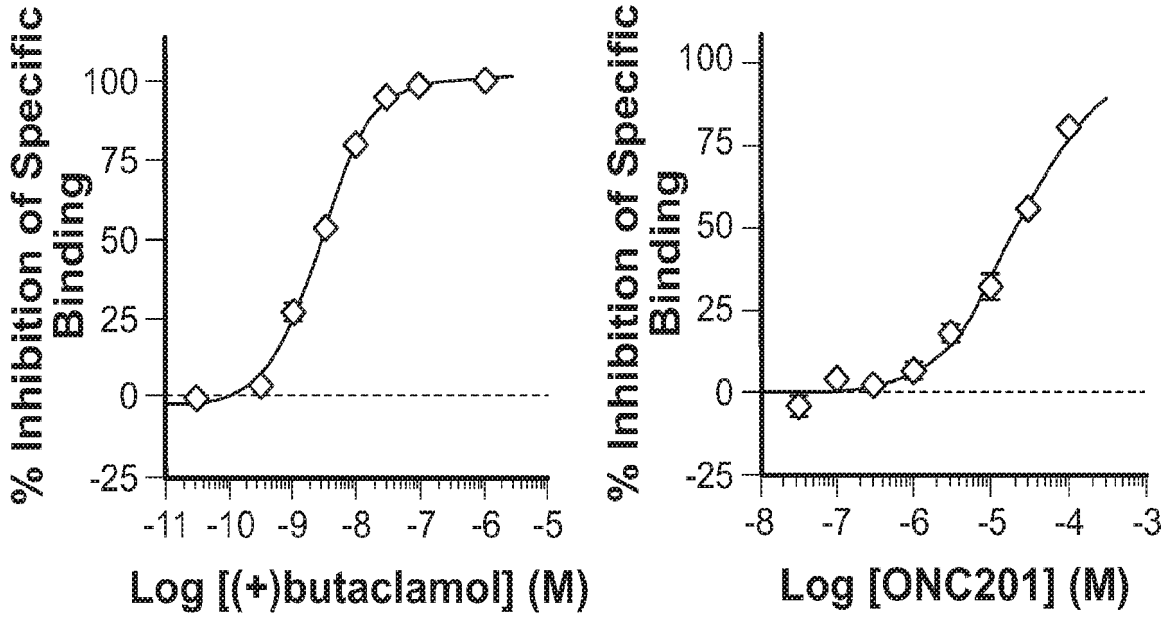


Figure 13

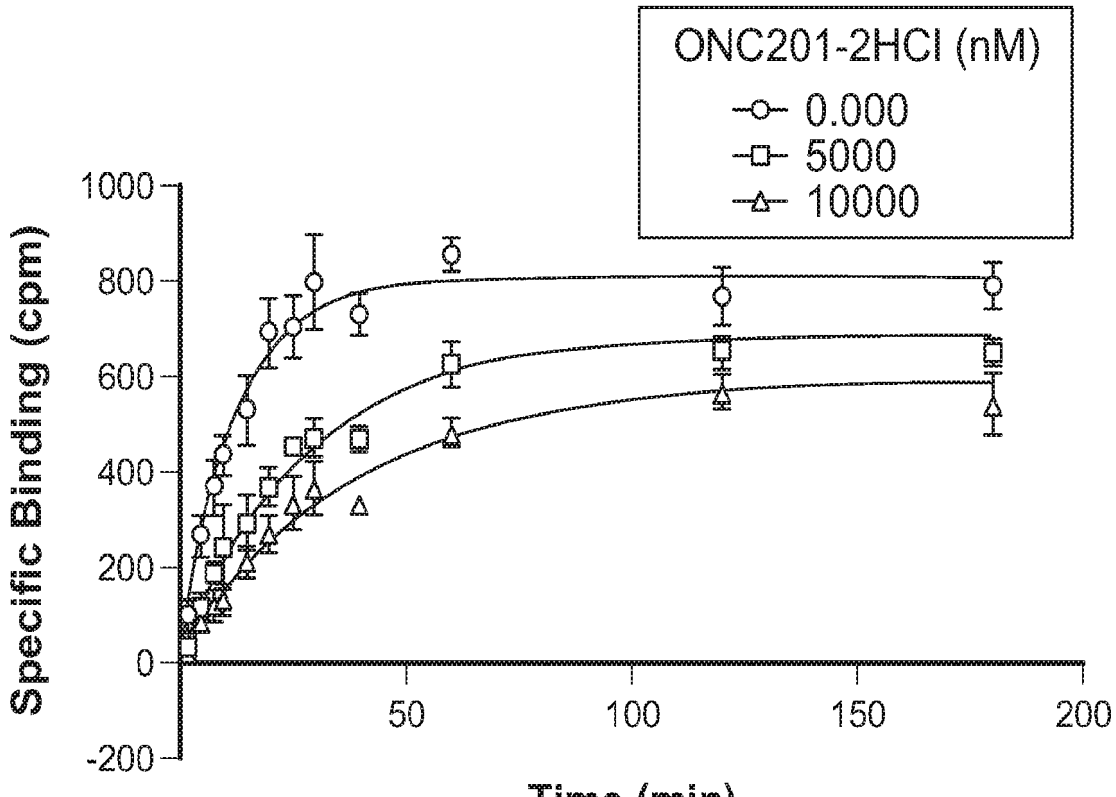


Figure 14

] Figure 15

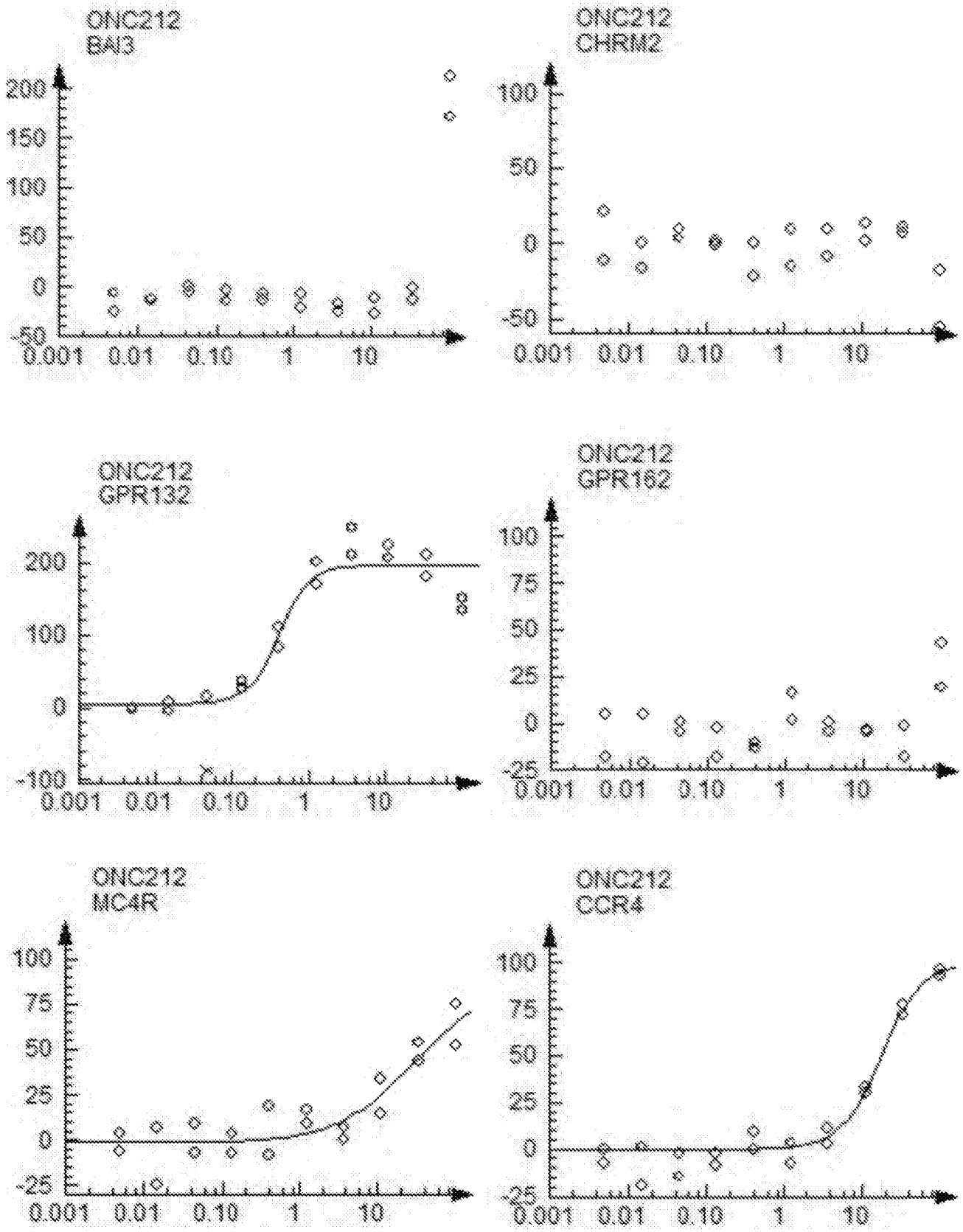
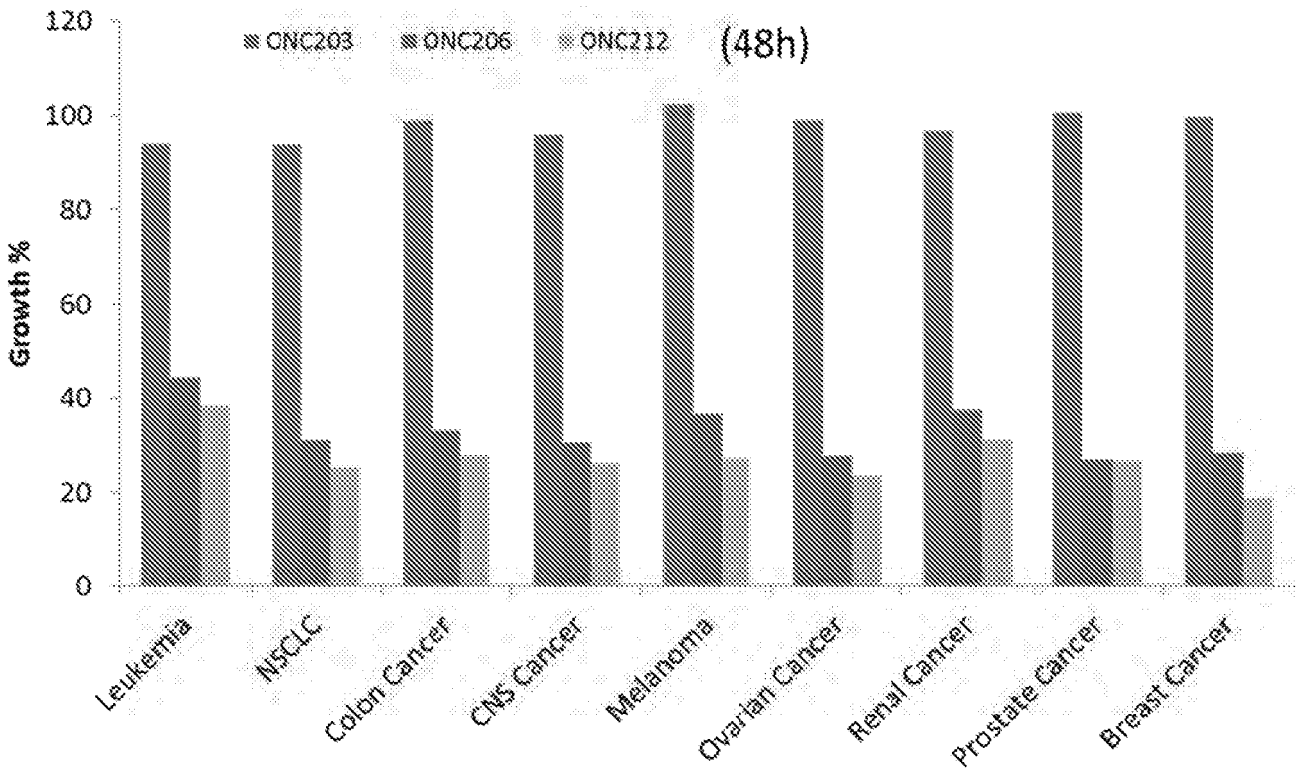

ONC212
BAI3
200
150
100
50
0
-50
0.001
0.01
0.10
1
10
ONC212
CHRM2
100
50
0
-50
0.001
0.01
0.10
1
10
ONC212
GPR132
200
100
0
-100
0.001
0.01
0.10
1
10
ONC212
GPR182
100
75
50
25
0
-25
0.001
0.01
0.10
1
10
ONC212
MC4R
100
75
50
25
0
-25
0.001
0.01
0.10
1
10
ONC212
CCR4
100
75
50
25
0
-25
0.001
0.01
0.10
1
10

Figure 16


120
100
80
60
40
20
0
Growth %
ONC203
ONC206
ONC212
(48h)
Leukemia
NSCLC
Colon Cancer
CNS Cancer
Melanoma
Ovarian Cancer
Renal Cancer
Prostate Cancer
Breast Cancer

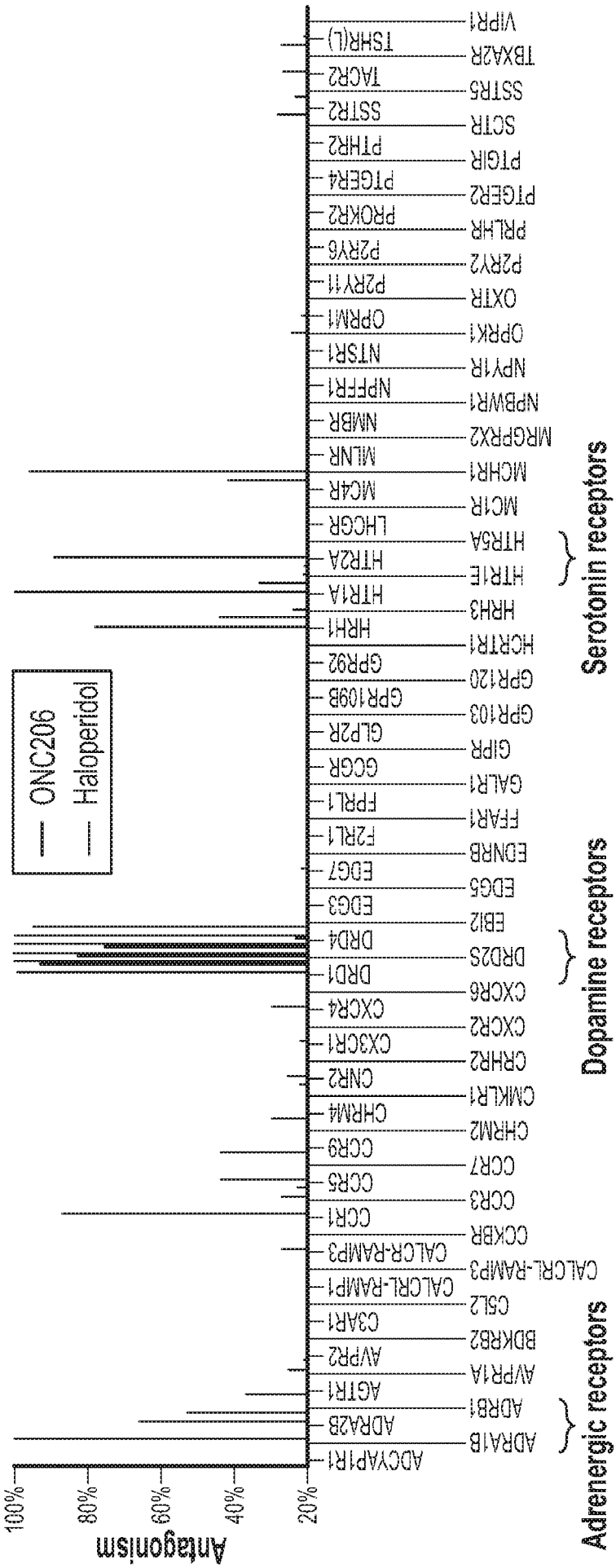

ONC206
Haloperidol
Antagonism
100%
80%
60%
40%
20%
ADCYAP1R1
ADRA1B
ADRA2B
ADRB1
AGTR1
AVPR1A
AVPR2
BDKRB2
C3AR1
C5L2
CALCRL-RAMP1
CALCRL-RAMP3
CALCR-RAMP3
CCKBR
CCR1
CCR3
CCR5
CCR7
CCR9
CHRM2
CHRM4
CNR2
CNMLR1
CRHR2
CX3CR1
CXCR2
CXCR4
CXCR6
DRD1
DRD2S
DRD4
EBI2
EDG5
EDG7
EDNRB
F2RL1
FFAR1
FPRL1
GALR1
GCGR
GIPR
GLP2R
GPR109B
GPR103
GPR120
GPR92
HCRTR1
HRH1
HRH3
HTR1A
HTR1E
HTR2A
HTR5A
LHCGR
MC1R
MC4R
MCHR1
MLNR
MRGPRX2
NMBR
NPBWR1
NPFFR1
NPY1R
NTSR1
OPRK1
OPRM1
OXTR
P2RY11
P2RY2
P2RY6
PRLHR
PROKR2
PTGER2
PTGER4
PTGIR
PTHR2
SCTR
SSTR2
SSTR5
TACR2
TBXA2R
TSHR(L)
VIPR1
Adrenergic receptors
Dopamine receptors
Serotonin receptors

Figure 17

Figure 18

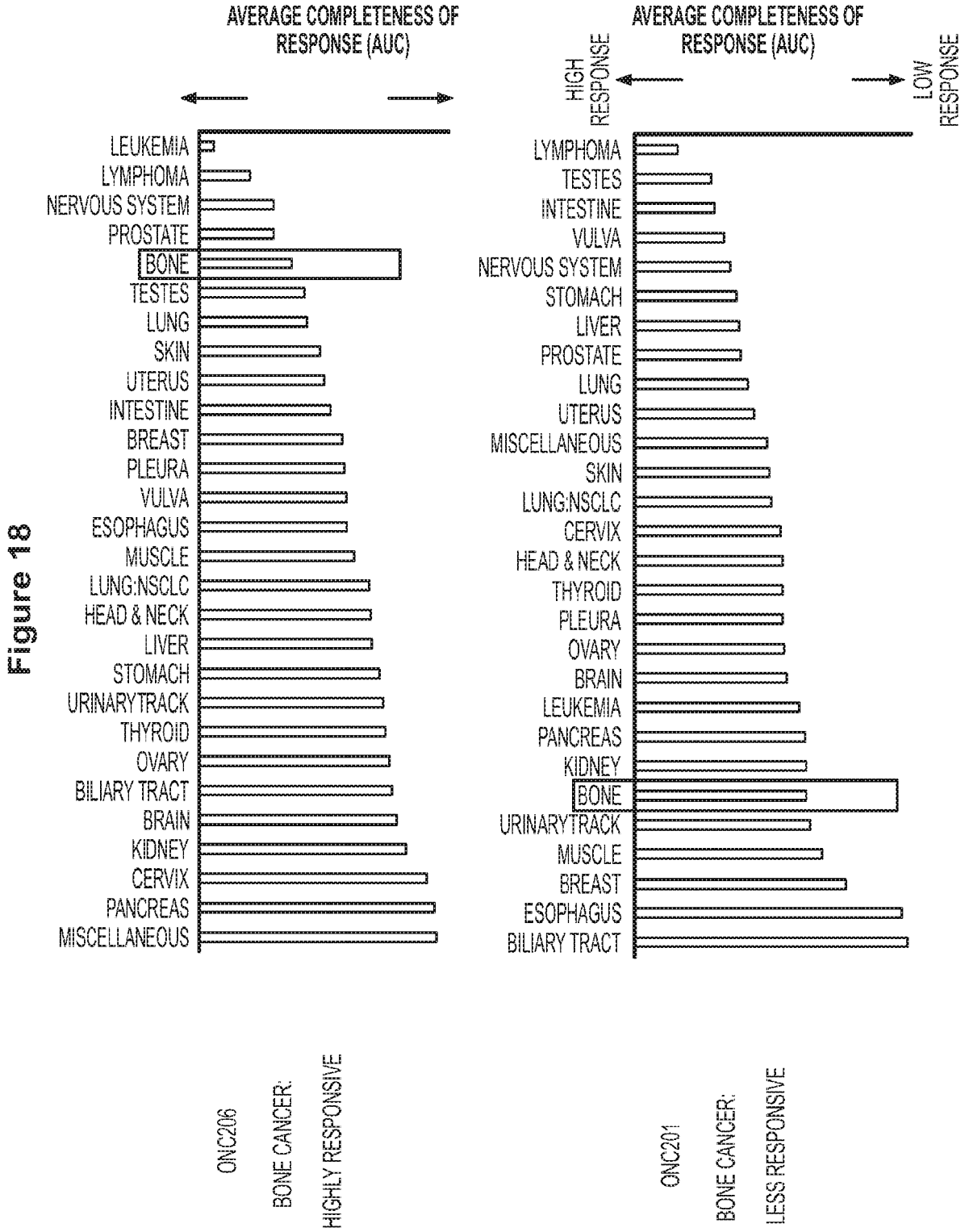
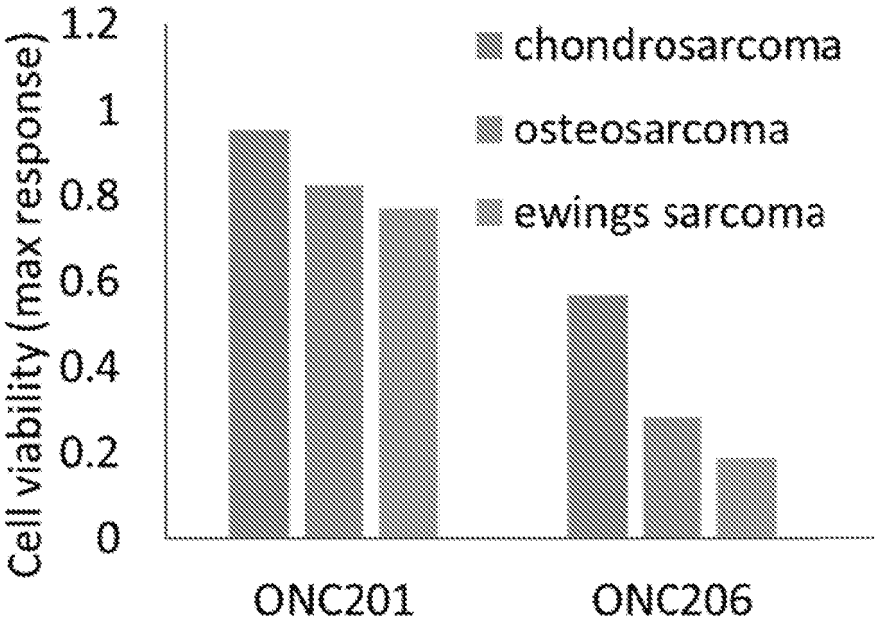
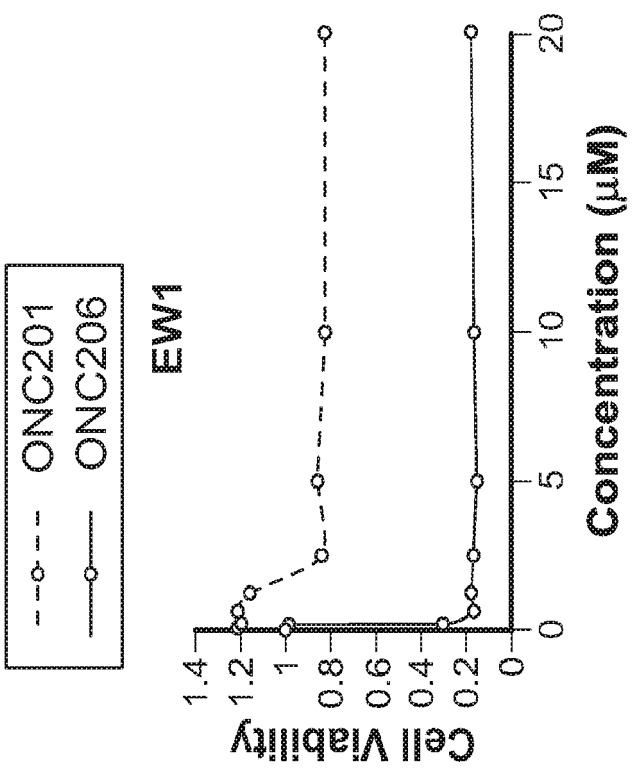

AVERAGE COMPLETENESS OF RESPONSE (AUC)
LEUKEMIA
LYMPHOMA
NERVOUS SYSTEM
PROSTATE
BONE
TESTES
LUNG
SKIN
UTERUS
INTESTINE
BREAST
PLEURA
VULVA
ESOPHAGUS
MUSCLE
LUNG:NSCLC
HEAD & NECK
LIVER
STOMACH
URINARYTRACK
THYROID
OVARY
BILIARY TRACT
BRAIN
KIDNEY
CERVIX
PANCREAS
MISCELLANEOUS
ONC206
BONE CANCER:
HIGHLY RESPONSIVE
AVERAGE COMPLETENESS OF RESPONSE (AUC)
HIGH RESPONSE
LOW RESPONSE
LYMPHOMA
TESTES
INTESTINE
VULVA
NERVOUS SYSTEM
STOMACH
LIVER
PROSTATE
LUNG
UTERUS
MISCELLANEOUS
SKIN
LUNG:NSCLC
CERVIX
HEAD & NECK
THYROID
PLEURA
OVARY
BRAIN
LEUKEMIA
PANCREAS
KIDNEY
BONE
URINARYTRACK
MUSCLE
BREAST
ESOPHAGUS
BILIARY TRACT
ONC201
BONE CANCER:
LESS RESPONSIVE

Figure 19


Cell viability (max response)
1.2
1
0.8
0.6
0.4
0.2
0
chondrosarcoma
osteosarcoma
ewings sarcoma
ONC201
ONC206


ONC201
ONC206
EW1
Cell Viability
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
5
10
15
20
Concentration (μM)

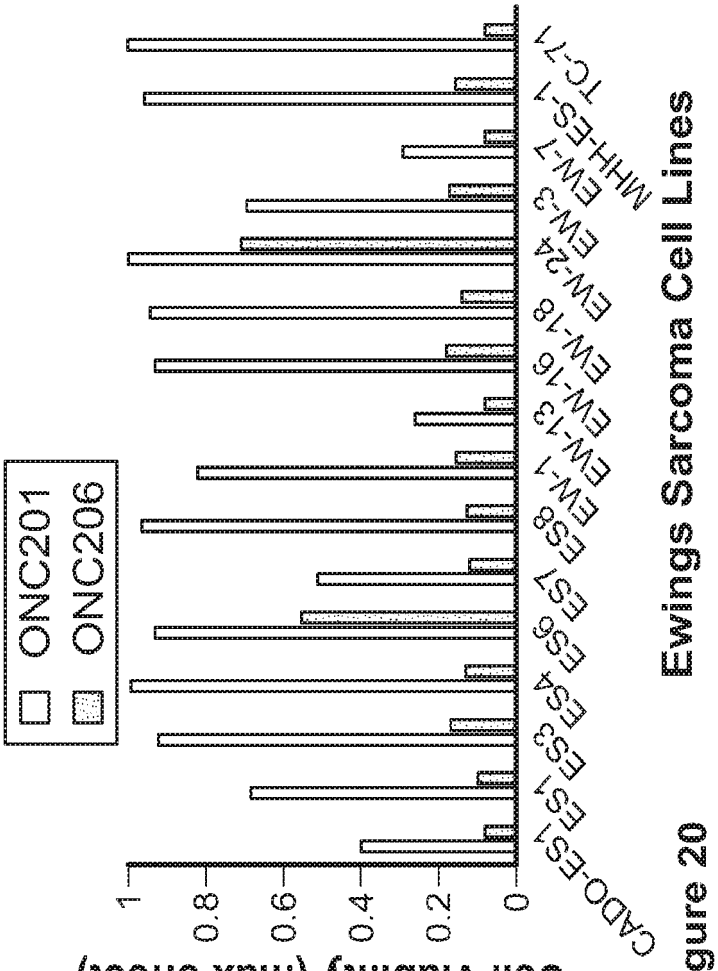

ONC201
ONC206
Cell Viability (max effect)
1
0.8
0.6
0.4
0.2
0
CADO-ES1
ES-1
ES-3
ES-4
ES-6
ES-7
ES-8
EW-1
EW-13
EW-16
EW-18
EW-24
EW-3
EW-7
MHH-ES-1
TC-71
Ewings Sarcoma Cell Lines

Figure 20

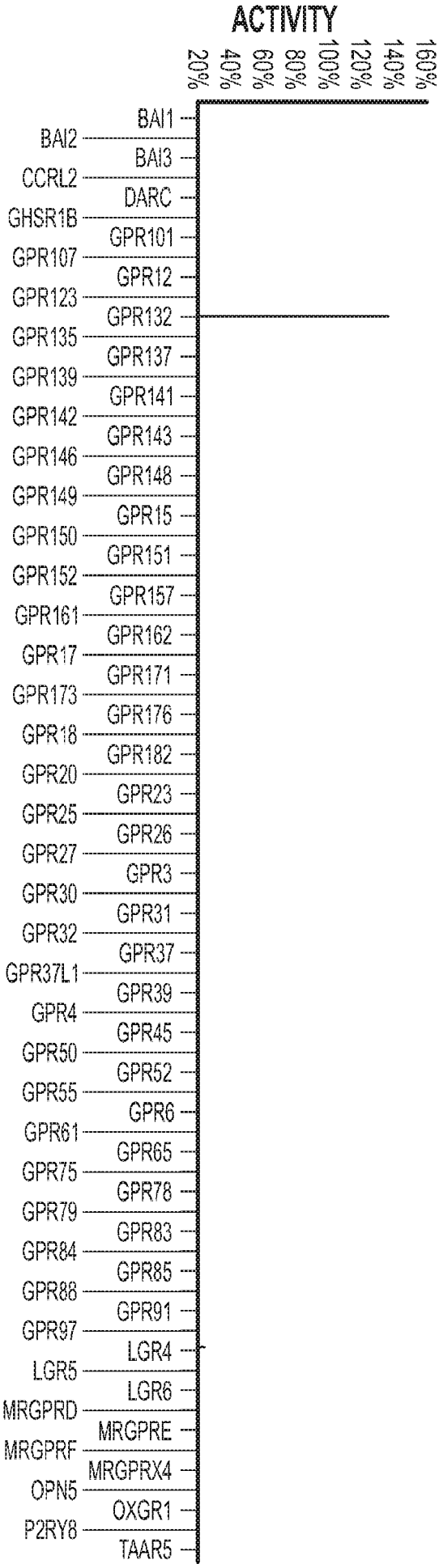

ACTIVITY
20%
40%
60%
80%
100%
120%
140%
160%
BAI1
BAI2
BAI3
CCRL2
DARC
GHSR1B
GPR101
GPR107
GPR12
GPR123
GPR132
GPR135
GPR137
GPR139
GPR141
GPR142
GPR143
GPR146
GPR148
GPR149
GPR15
GPR150
GPR151
GPR152
GPR157
GPR161
GPR162
GPR17
GPR171
GPR173
GPR176
GPR18
GPR182
GPR20
GPR23
GPR25
GPR26
GPR27
GPR3
GPR30
GPR31
GPR32
GPR37
GPR37L1
GPR39
GPR4
GPR45
GPR50
GPR52
GPR55
GPR6
GPR61
GPR65
GPR75
GPR78
GPR79
GPR83
GPR84
GPR85
GPR88
GPR91
GPR97
LGR4
LGR5
LGR6
MRGPRD
MRGPRE
MRGPRF
MRGPRX4
OPN5
OXGR1
P2RY8
TAAR5

Figure 21

Figure 22

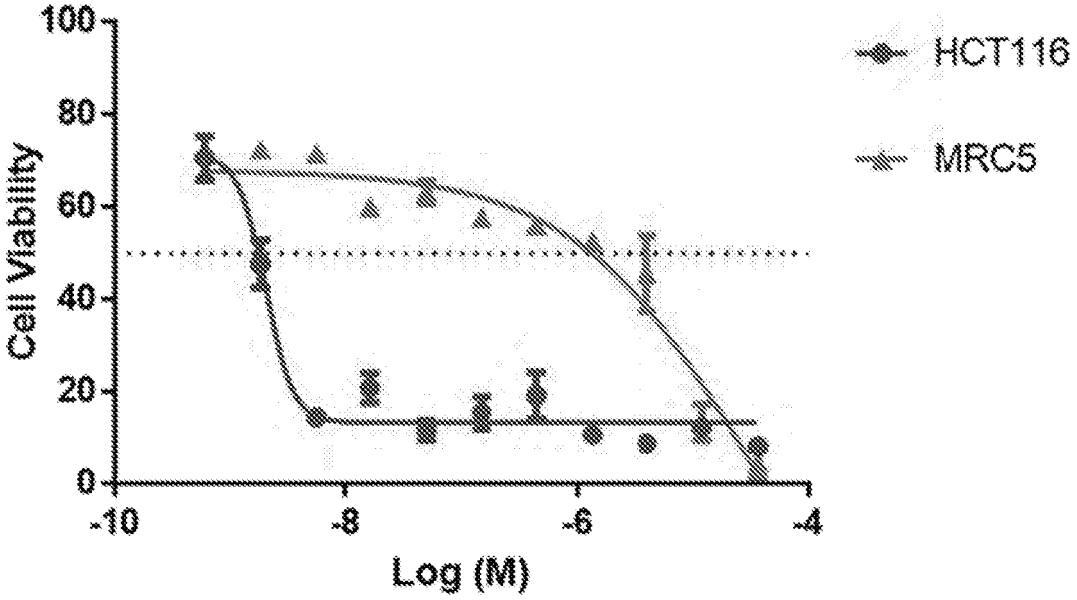
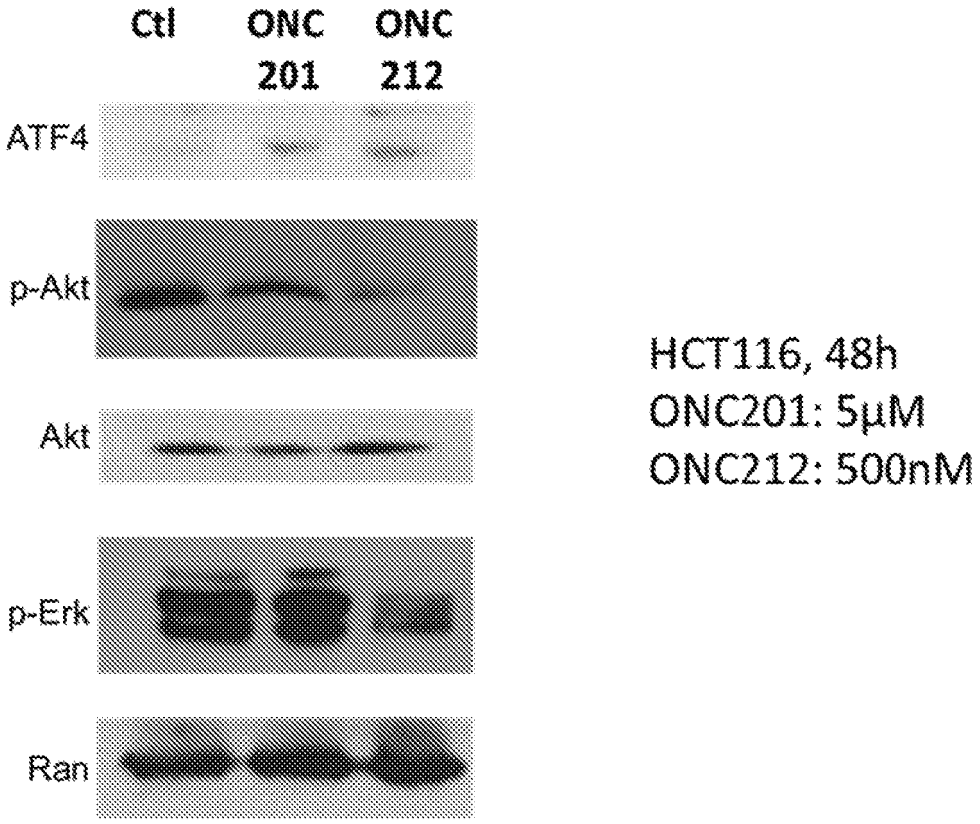
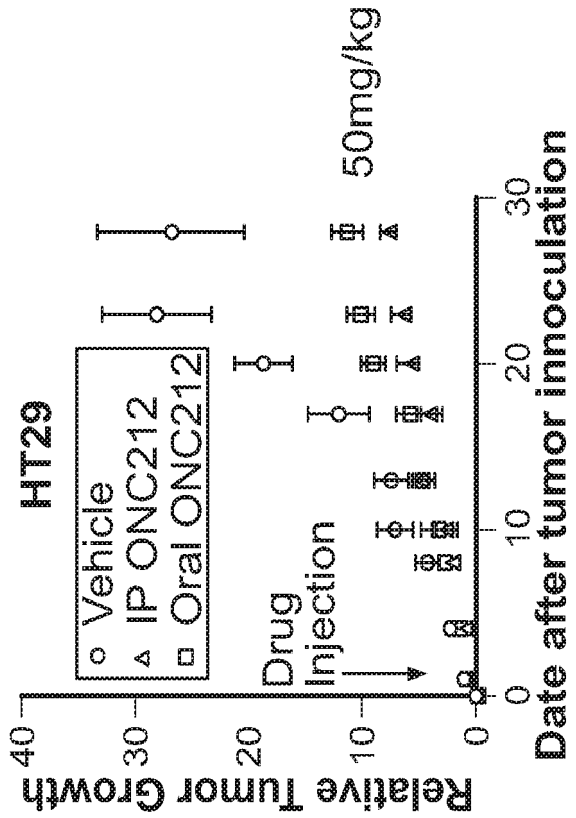


Figure 23




HT29
Vehicle
IP ONC212
Oral ONC212
50mg/kg
Drug Injection
Relative Tumor Growth
Date after tumor innoculation
0
10
20
30
40

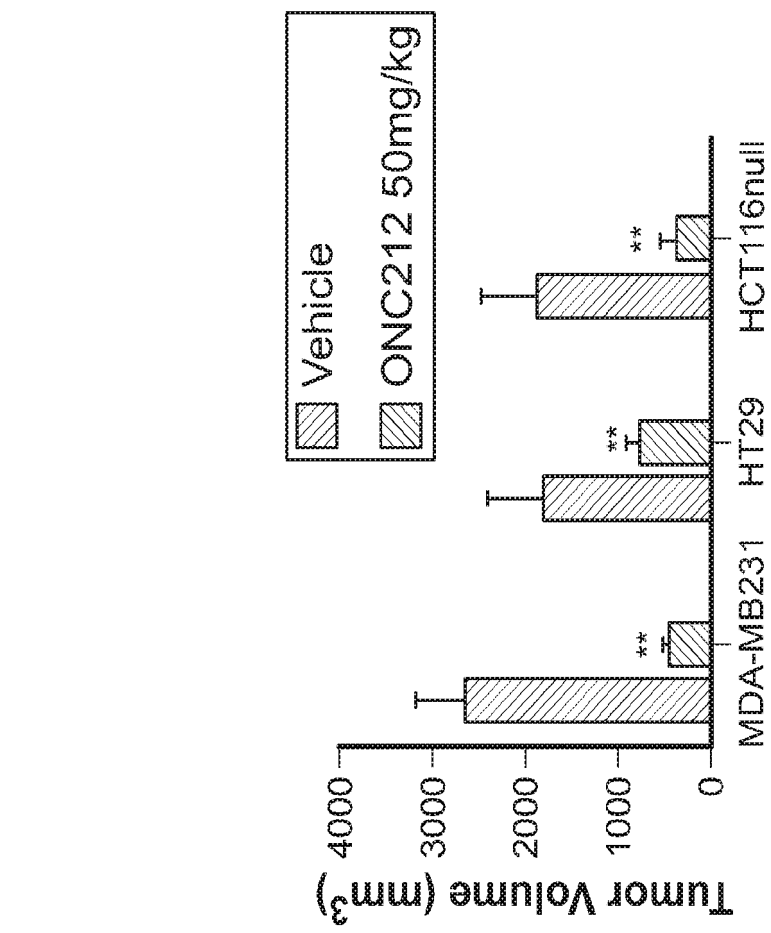
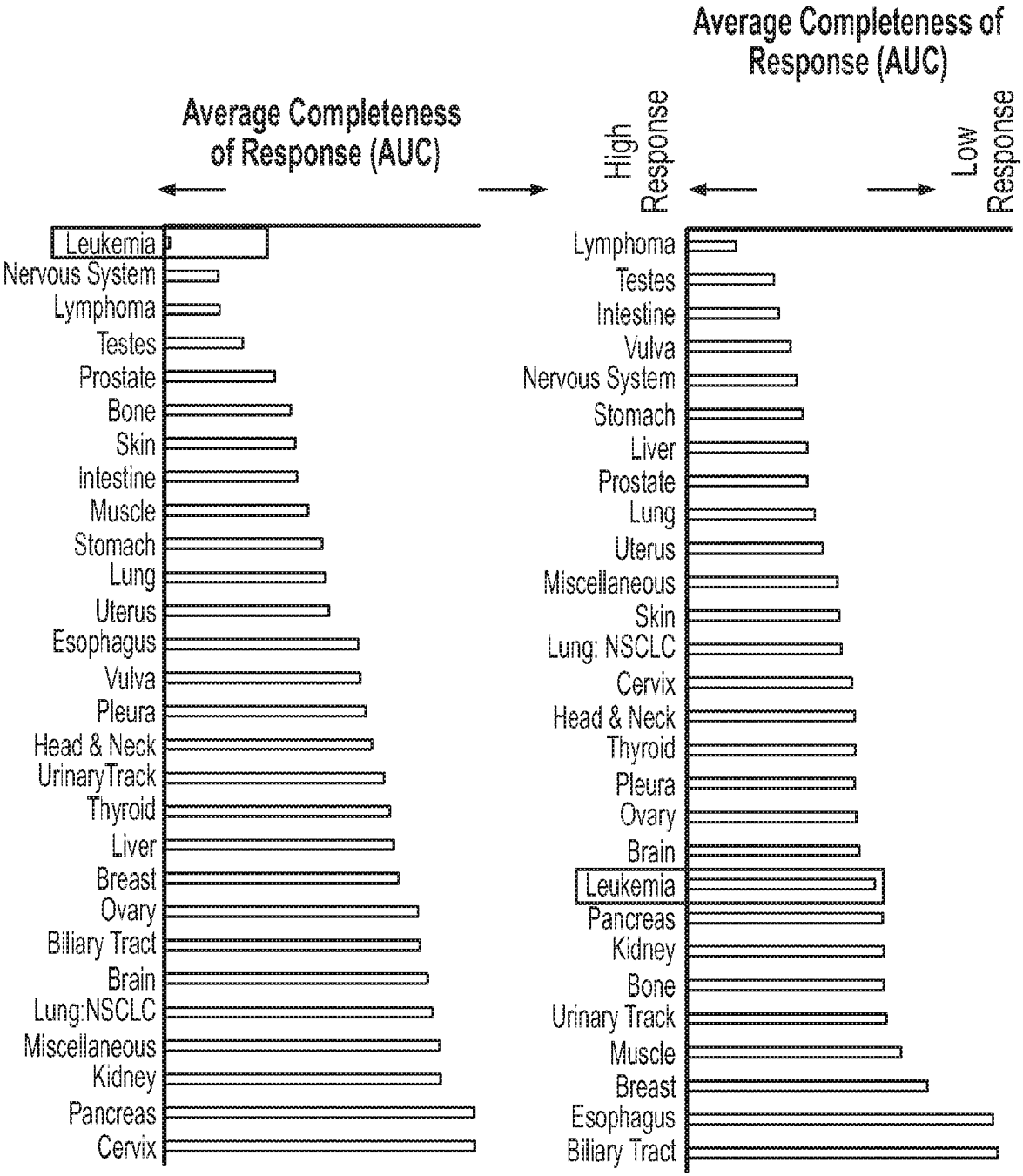

Vehicle
ONC212 50mg/kg
Tumor Volume (mm3)
0
1000
2000
3000
4000
**
**
**
MDA-MB231
HT29
HCT116null

Figure 24

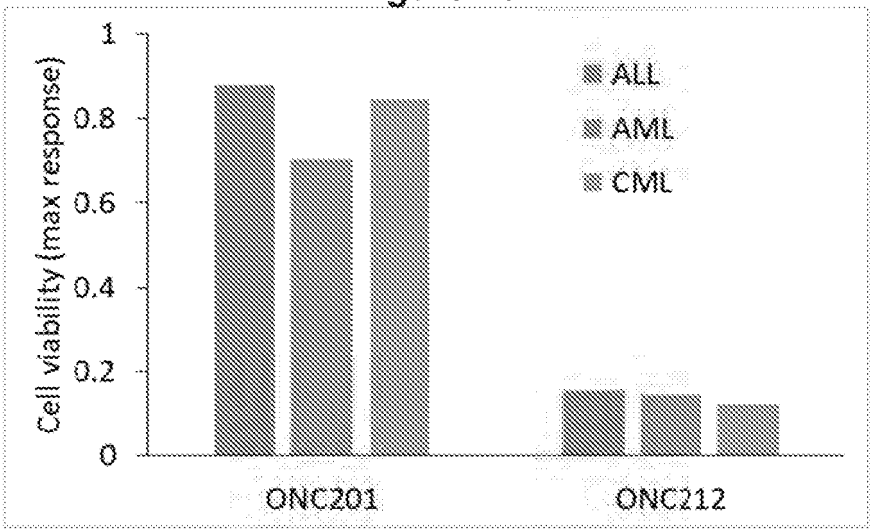


ONC212
Leukemia:
Highly Responsive

ONC201
Leukemia:
Less Responsive

Figure 25

Figure 26


Cell viability (max response)
1
0.8
0.6
0.4
0.2
0
ALL
AML
CML
ONC201
ONC212

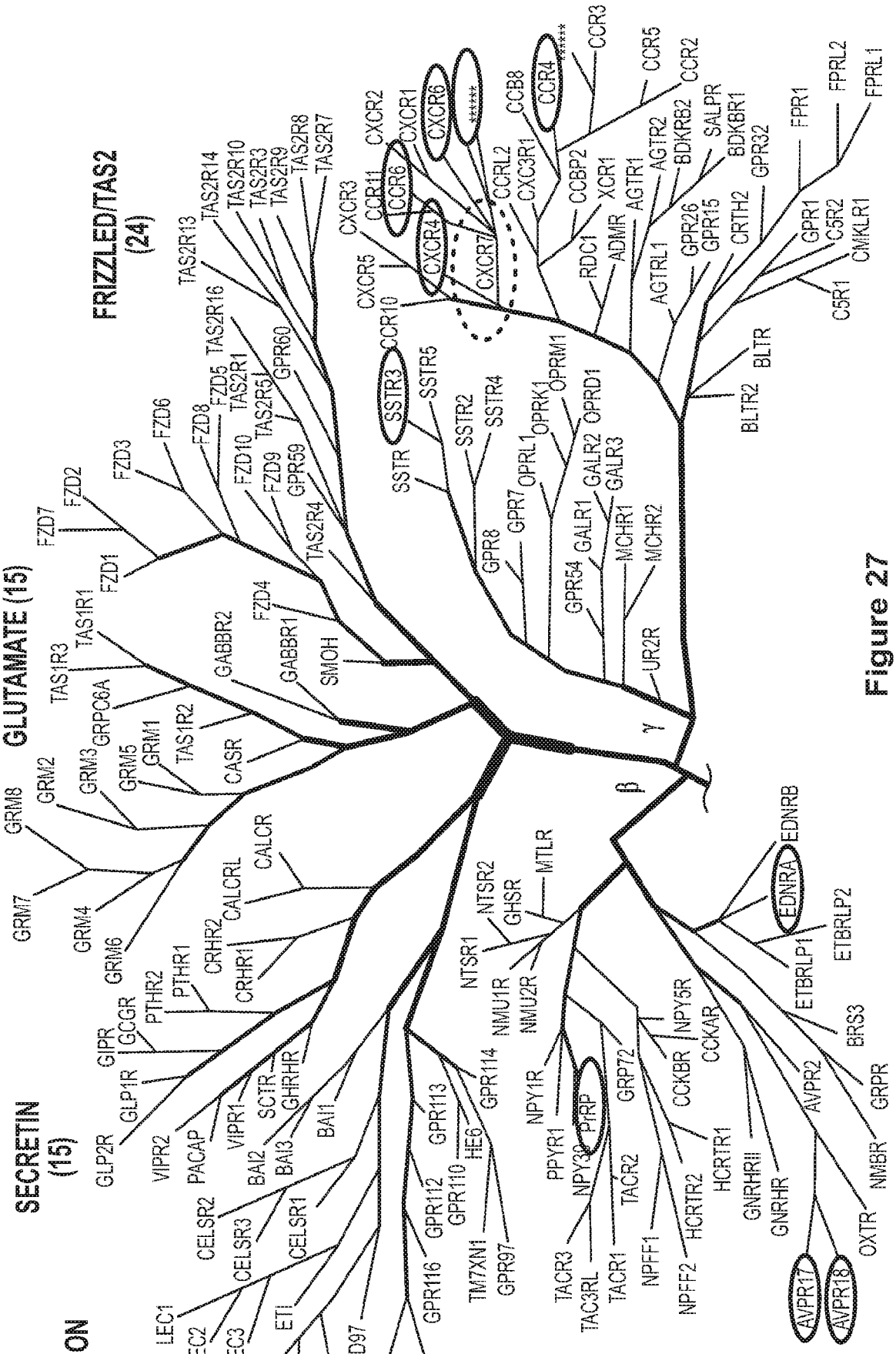

ADHESION (24)
SECRETIN (15)
GLUTAMATE (15)
FRIZZLED/TAS2 (24)
α
β
γ
LEC1
LEC2
LEC3
EMR2
EMR3
ETL
EMR1
CD97
GPR111
GPR115
GPR116
CELSR2
CELSR3
CELSR1
GPR112
GPR110
TM7XN1
GPR97
HE6
GPR113
GPR114
BAI2
BAI3
BAI1
VIPR1
PACAP
VIPR2
SCTR
GHRHR
GLP2R
GLP1R
GIPR
GCGR
PTHR2
PTHR1
CRHR2
CRHR1
CALCRL
CALCR
GRM7
GRM8
GRM4
GRM6
GRM2
GRM3
GRM5
GRM1
GRPC6A
TAS1R3
TAS1R1
TAS1R2
CASR
GABBR2
GABBR1
SMOH
FZD4
FZD7
FZD2
FZD1
FZD3
FZD6
FZD8
FZD5
FZD10
FZD9
TAS2R4
GPR59
TAS2R1
TAS2R3
TAS2R16
GPR60
TAS2R13
TAS2R14
TAS2R10
TAS2R3
TAS2R9
TAS2R8
TAS2R7
CXCR3
CXCR5
CCR10
CCR11
CXCR2
CCR6
CXCR1
CXCR6
CXCR4
CXCR7
CCRL2
CCB8
CXC3R1
CCR4
CCR3
CCR5
CCR2
CCBP2
XCR1
RDC1
ADMR
AGTR1
AGTR2
AGTRL1
BDKRB2
SALPR
GPR26
GPR15
BDKBR1
CRTH2
GPR32
BLTR2
BLTR
FPR1
GPR1
C5R2
FPRL2
C5R1
CMKLR1
FPRL1
SSTR
SSTR3
SSTR5
SSTR2
SSTR4
OPRK1
OPRM1
OPRL1
OPRD1
GPR8
GPR7
GPR54
GALR1
GALR2
GALR3
MCHR1
MCHR2
UR2R
NTSR1
NTSR2
GHSR
MTLR
NMU1R
NMU2R
PPYR1
NPY1R
NPY2R
PYRP
TACR3
TAC3RL
TACR1
TACR2
GRP72
NPFF1
NPFF2
HCRTR2
HCRTR1
CCKBR
NPY5R
CCKAR
GNRHRII
GNRHR
EDNRA
EDNRB
ETBRLP1
ETBRLP2
BRS3
AVPR17
AVPR18
AVPR2
GRPR
OXTR
NMBR

Figure 27

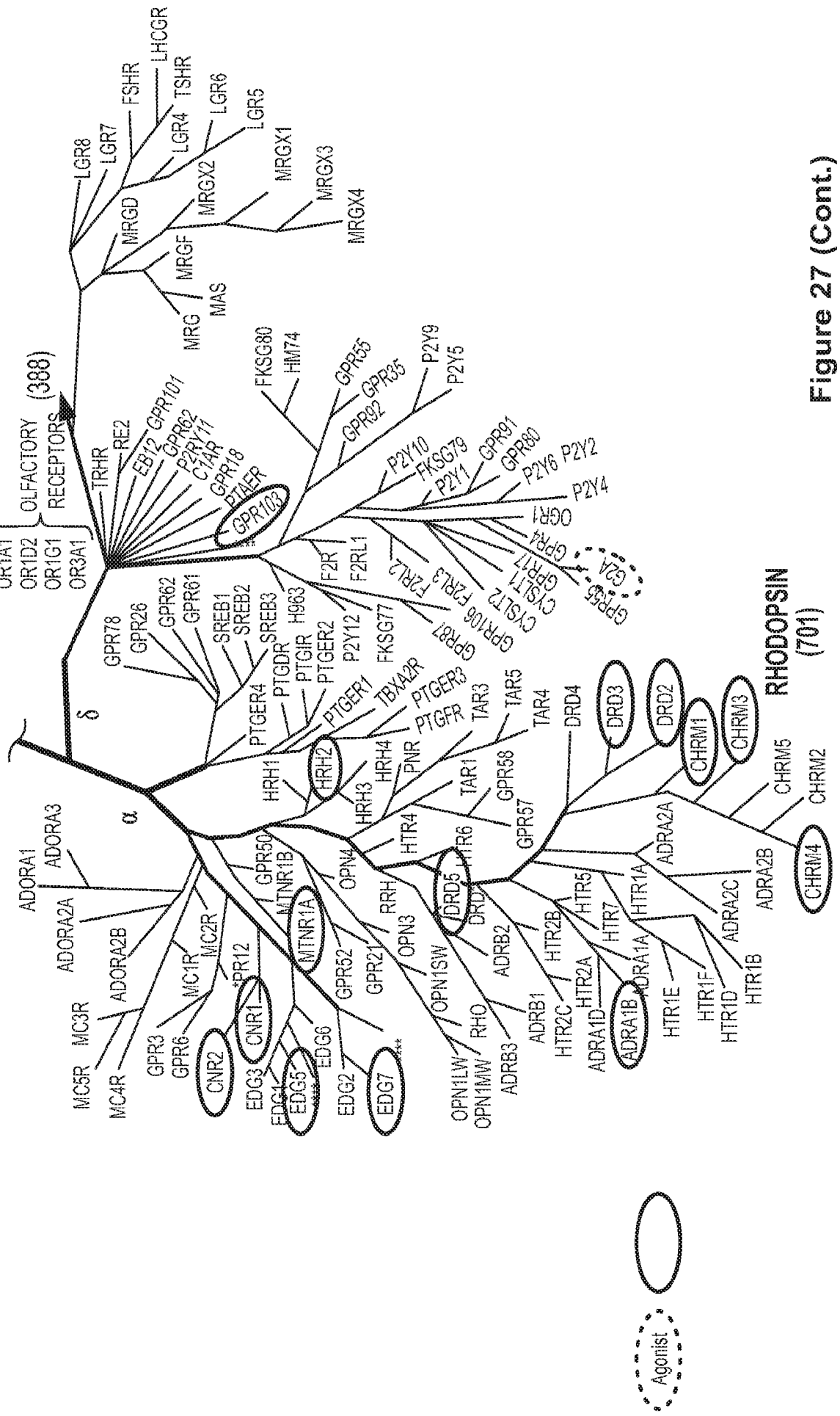
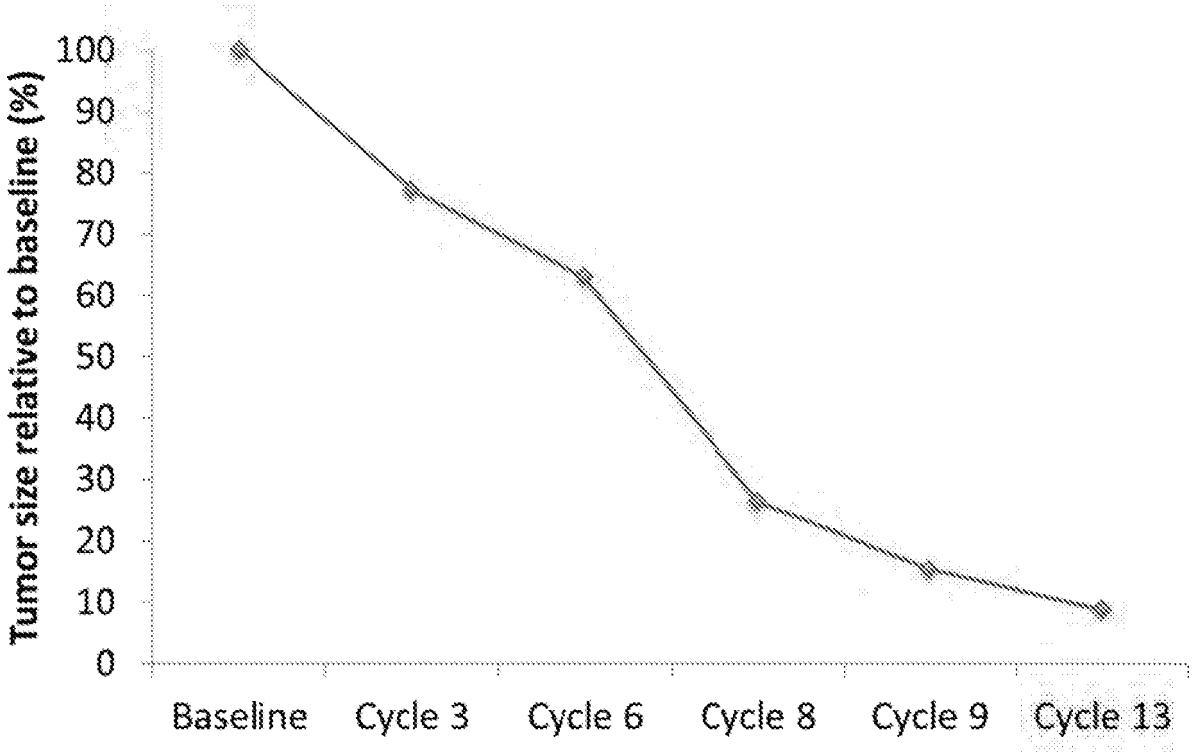


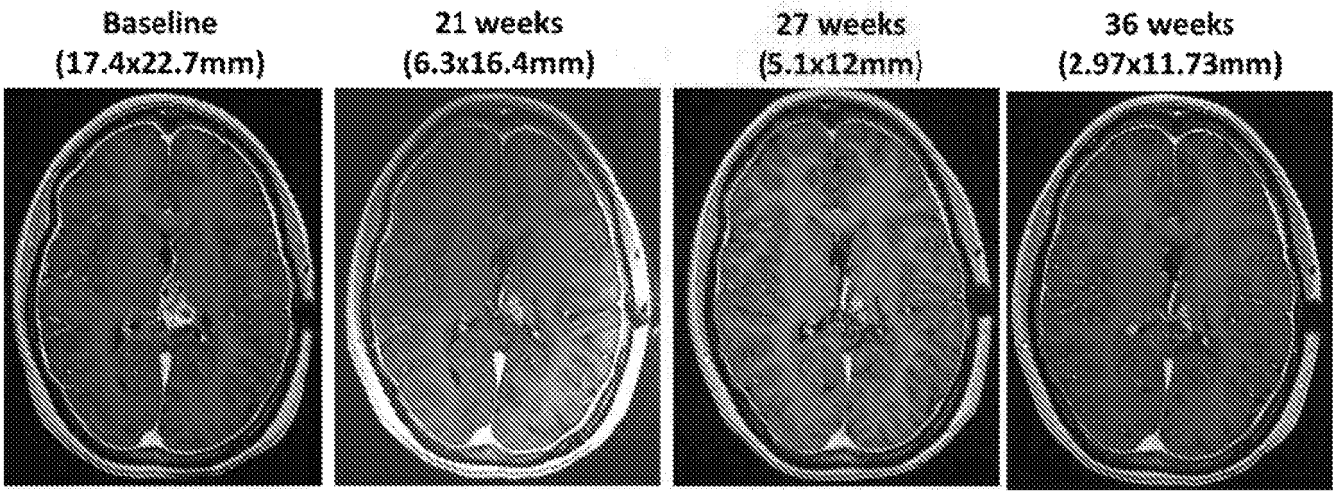
Figure 27 (Cont.)

Figure 28

A


Tumor size relative to baseline (%)
100
90
80
70
60
50
40
30
20
10
0
Baseline
Cycle 3
Cycle 6
Cycle 8
Cycle 9
Cycle 13

B


Baseline
(17.4x22.7mm)
21 weeks
(6.3x16.4mm)
27 weeks
(5.1x12mm)
36 weeks
(2.97x11.73mm)

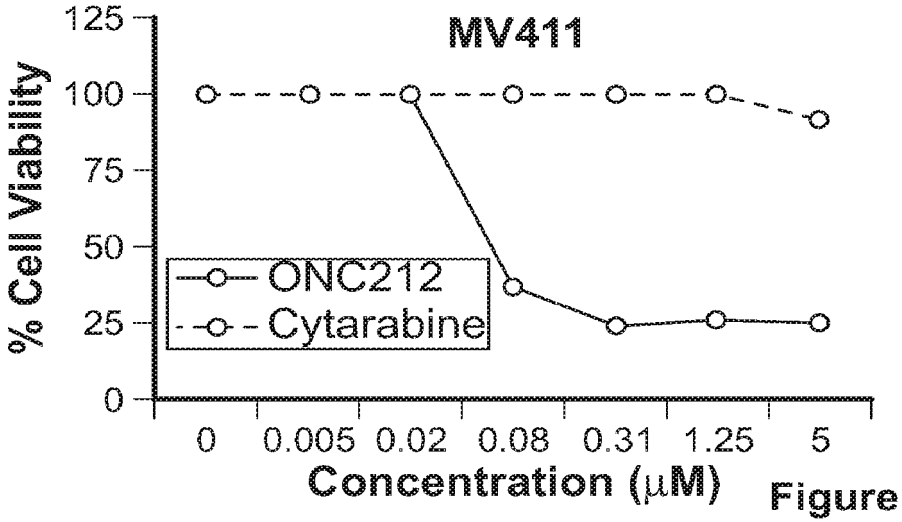
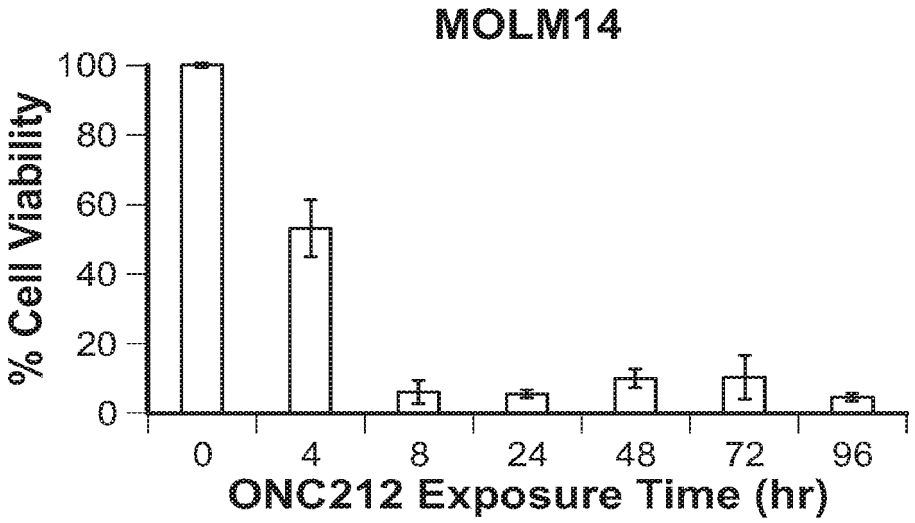


Figure 29A



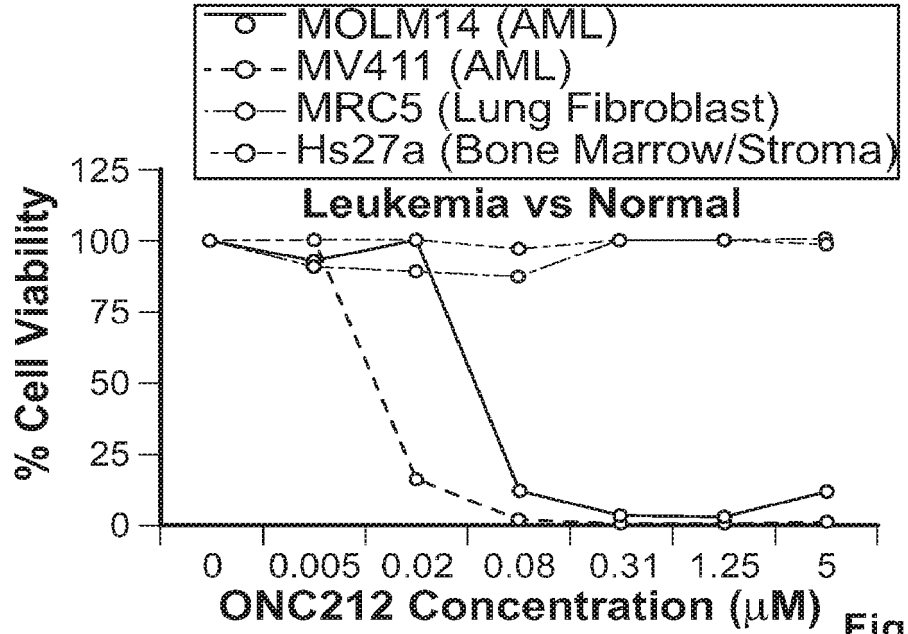


Figure 29B

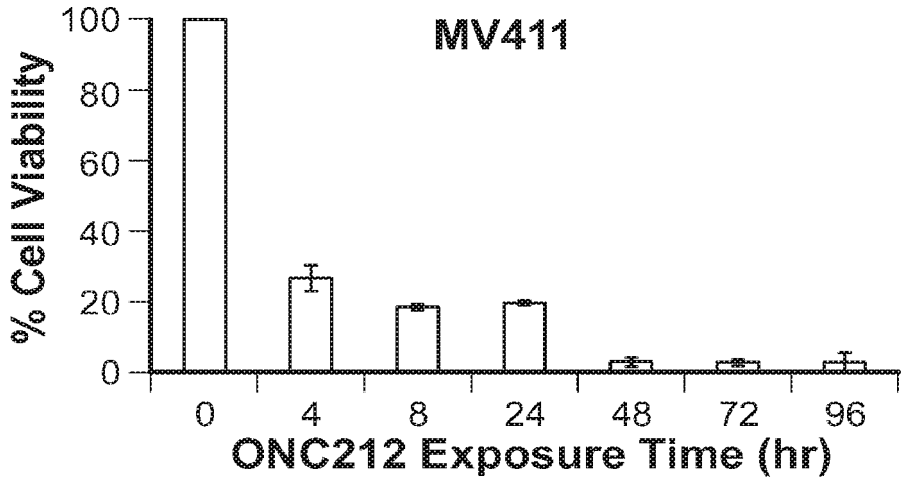


Figure 29C

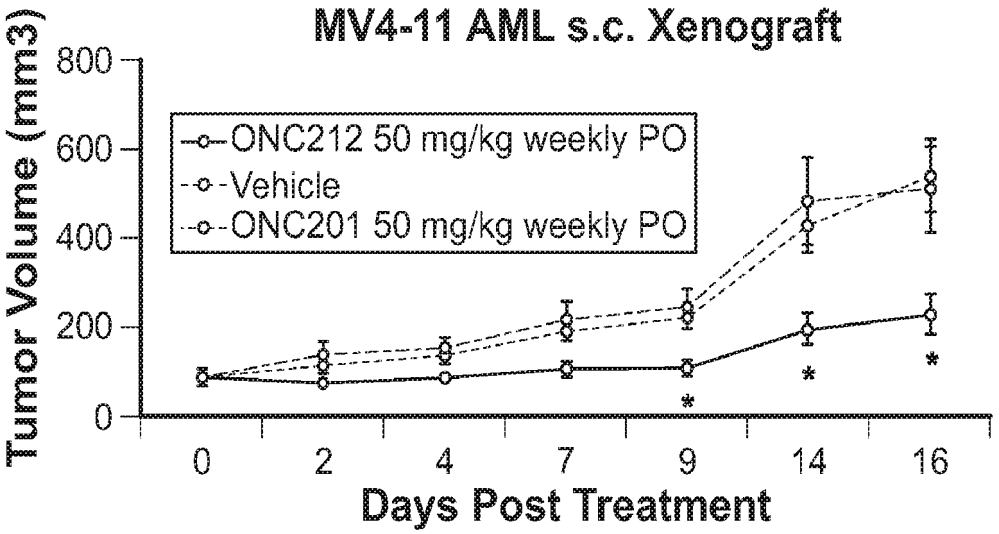


Figure 30A

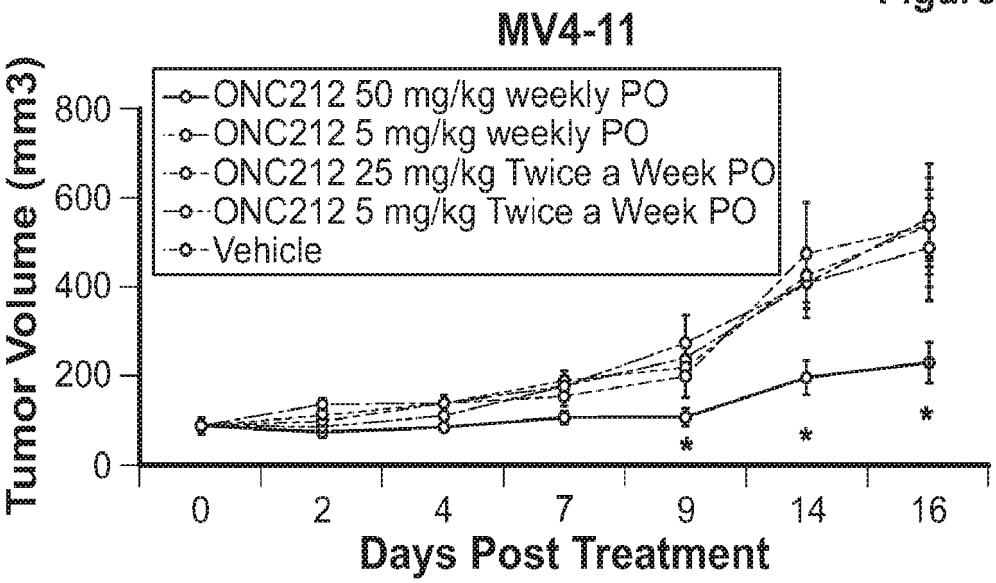


Figure 30B

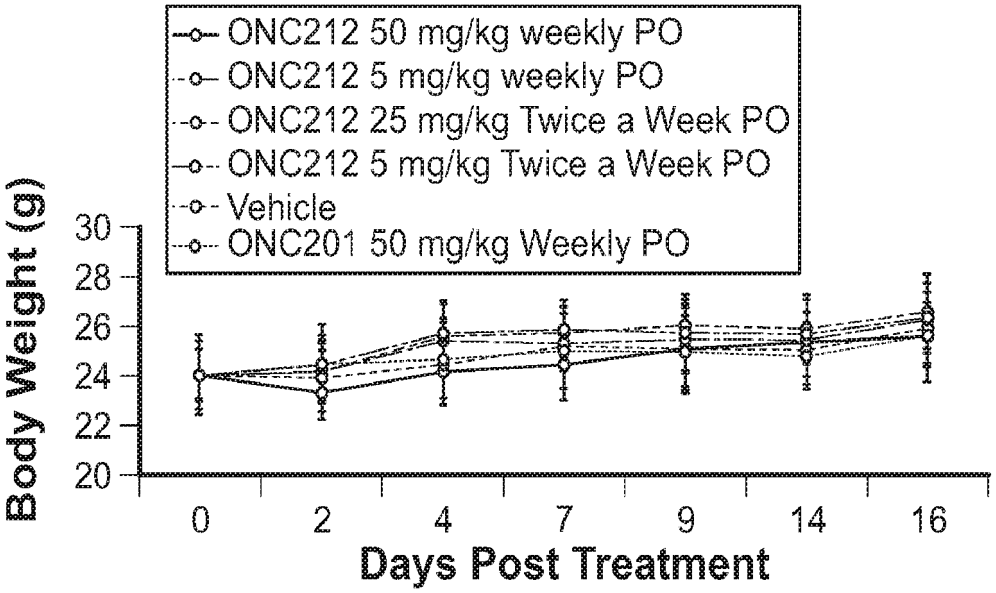
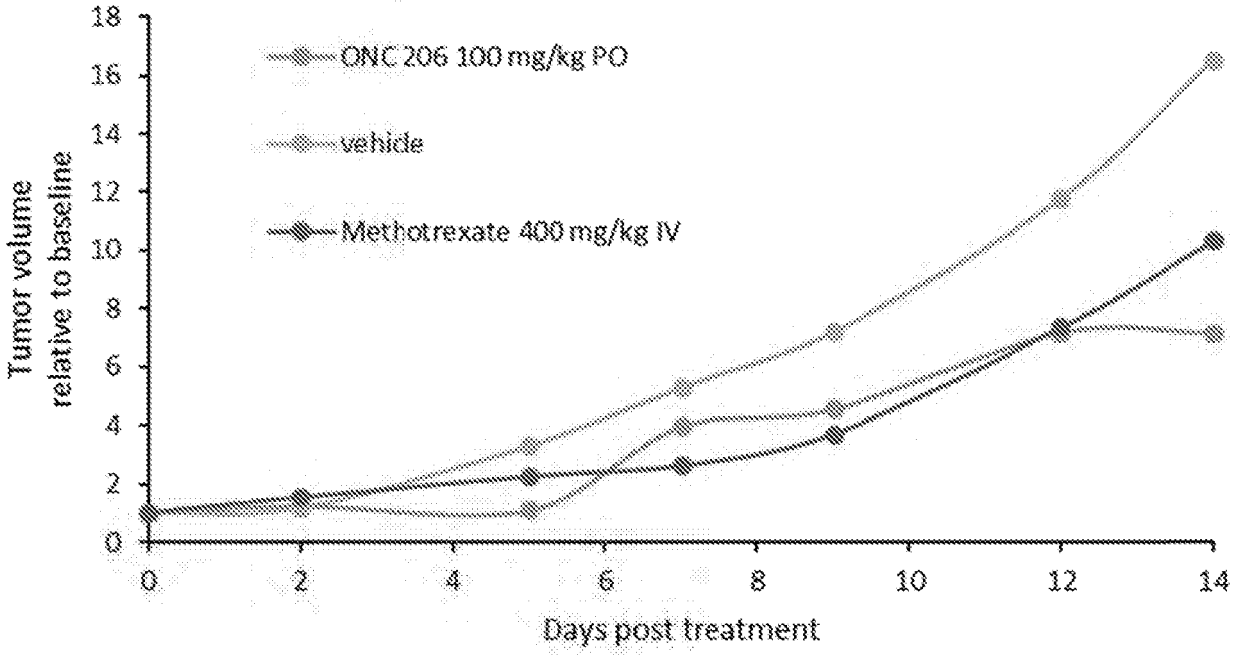


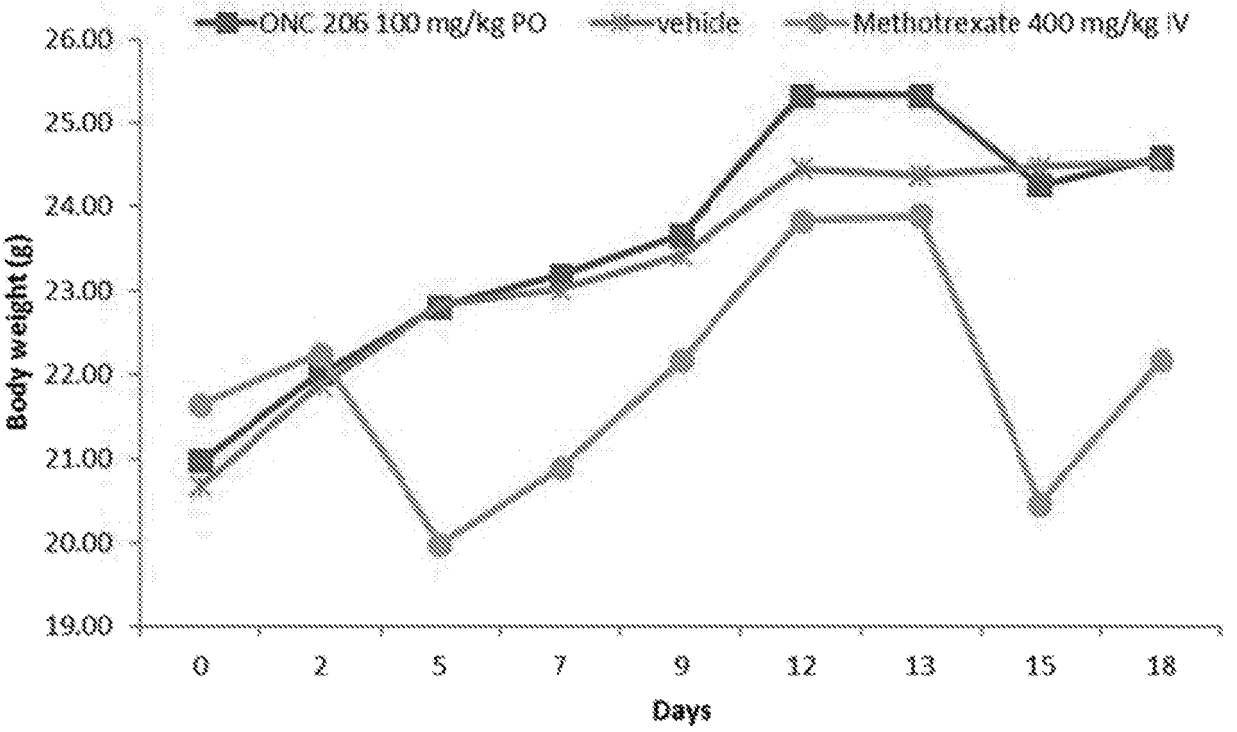
Figure 30C

Figure 31

A


ONC 206 100 mg/kg PO
vehicle
Methotrexate 400 mg/kg IV
Tumor volume relative to baseline
Days post treatment
0
2
4
6
8
10
12
14
16
18

B


ONC 206 100 mg/kg PO
vehicle
Methotrexate 400 mg/kg IV
Body weight (g)
Days
19.00
20.00
21.00
22.00
23.00
24.00
25.00
26.00
0
2
5
7
9
12
13
15
18

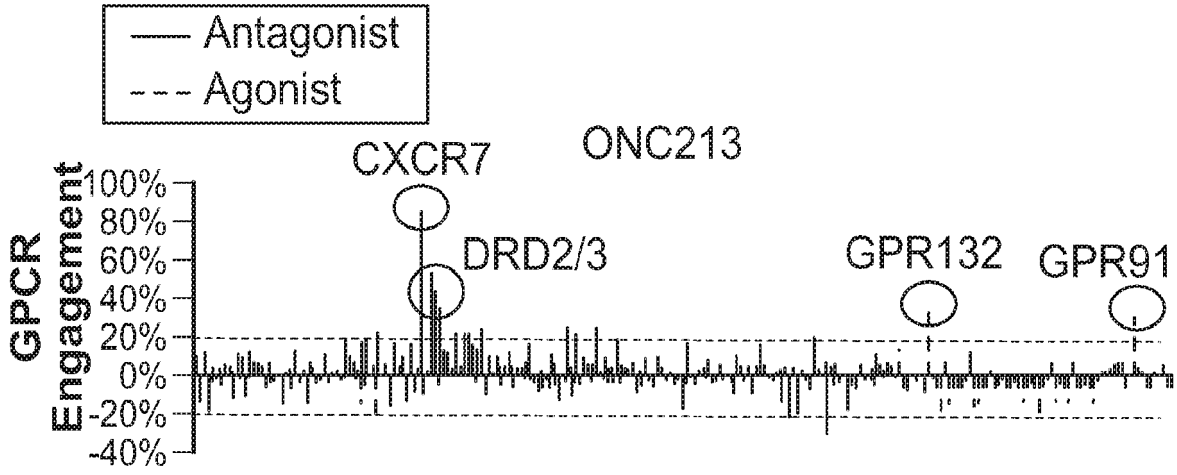

Antagonist
Agonist
ONC213
CXCR7
DRD2/3
GPR132
GPR91
GPCR Engagement
100%
80%
60%
40%
20%
0%
-20%
-40%

Figure 32

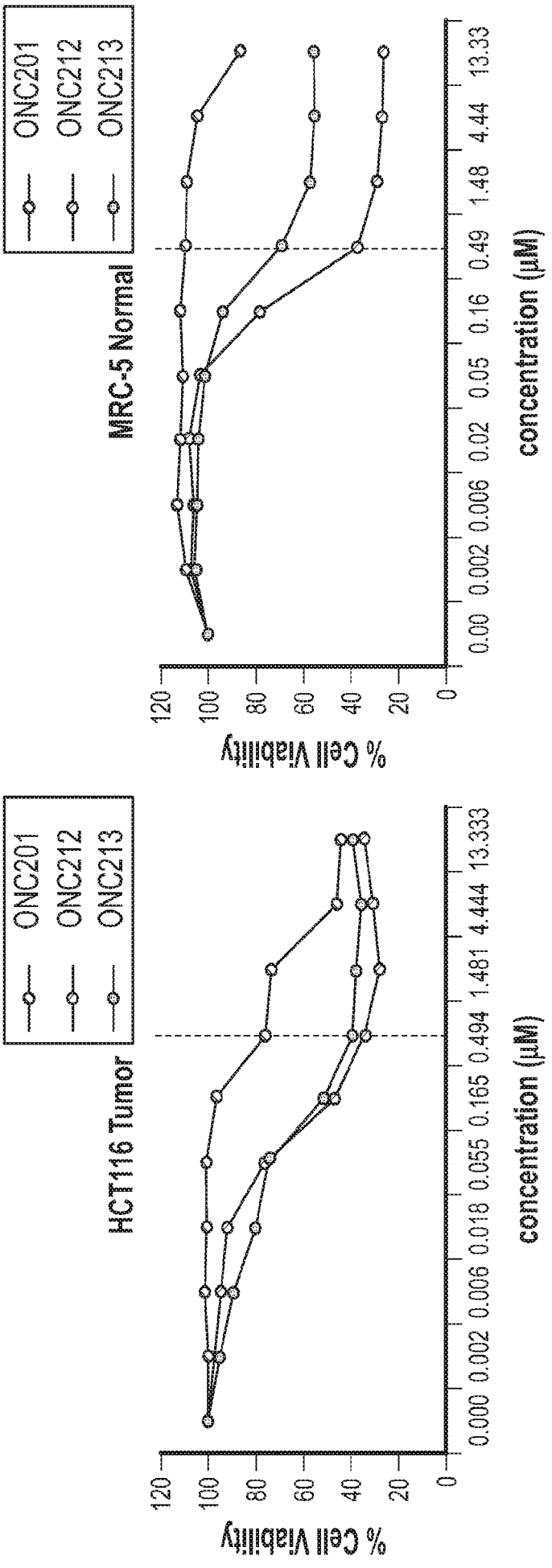

HCT116 Tumor
MRC-5 Normal
ONC201
ONC212
ONC213
% Cell Viability
concentration (µM)
0
20
40
60
80
100
120
0.000
0.002
0.006
0.018
0.055
0.165
0.494
1.481
4.444
13.333
0.00
0.002
0.006
0.02
0.05
0.16
0.49
1.48
4.44
13.33

Figure 33

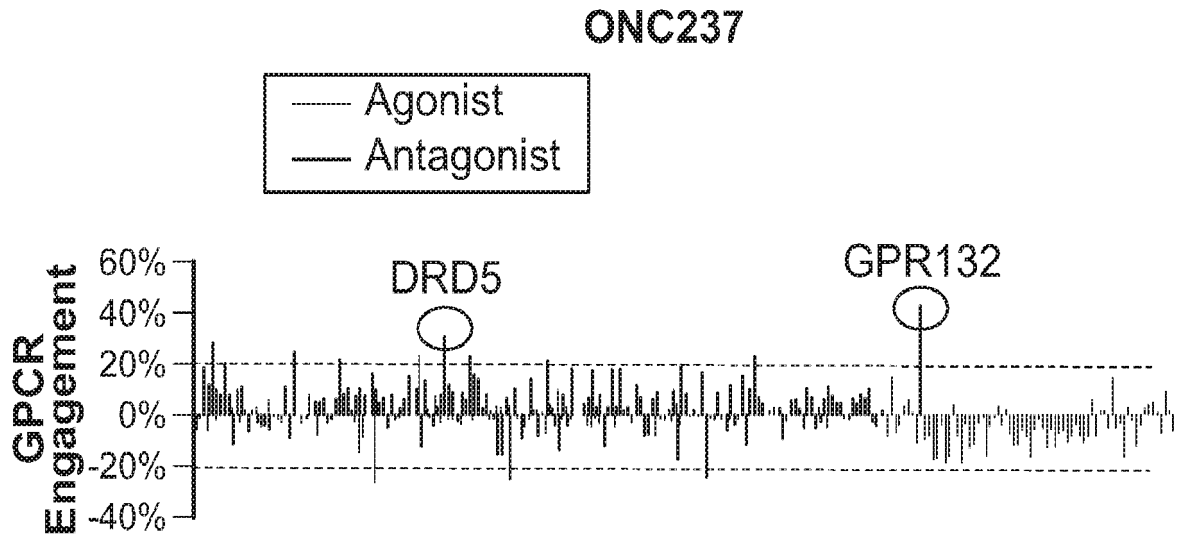


Figure 34

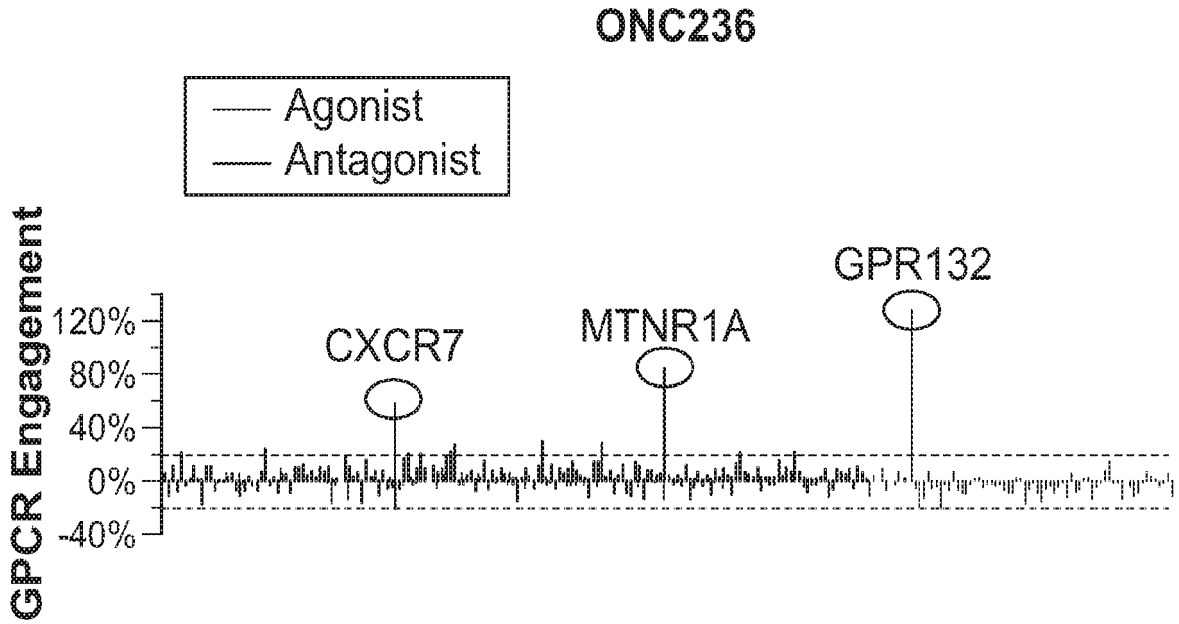


Figure 35

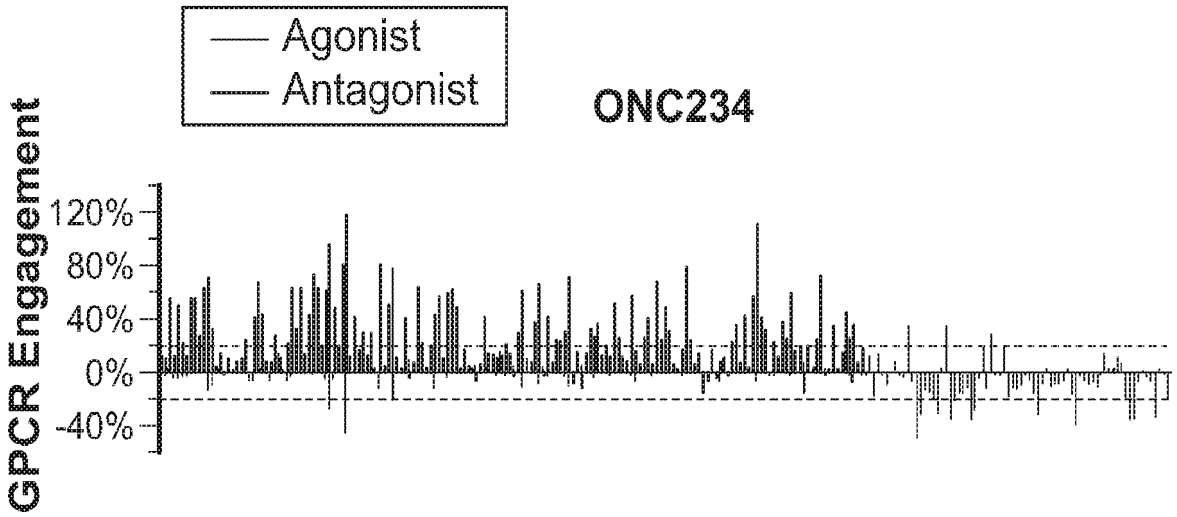


Figure 36

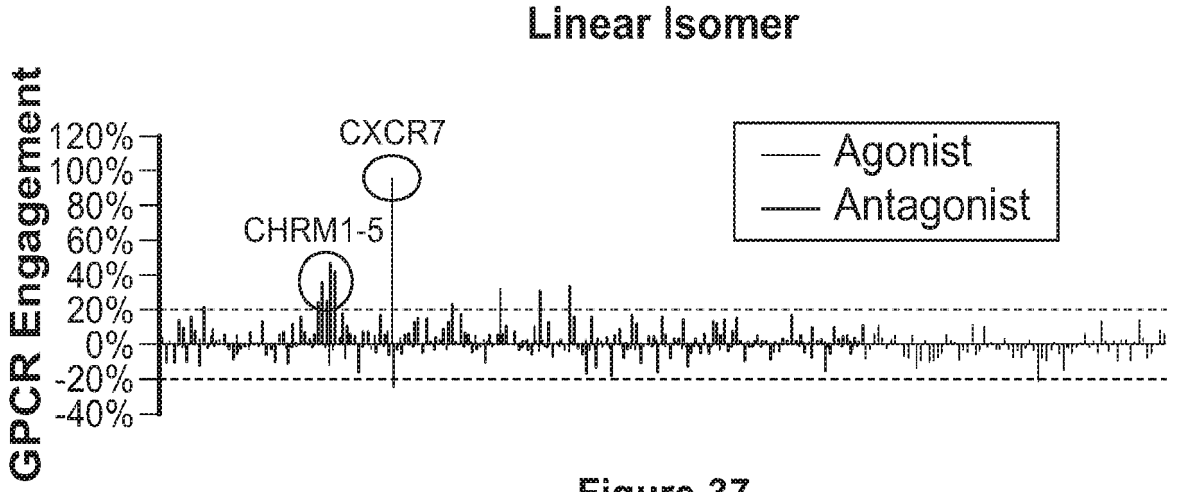
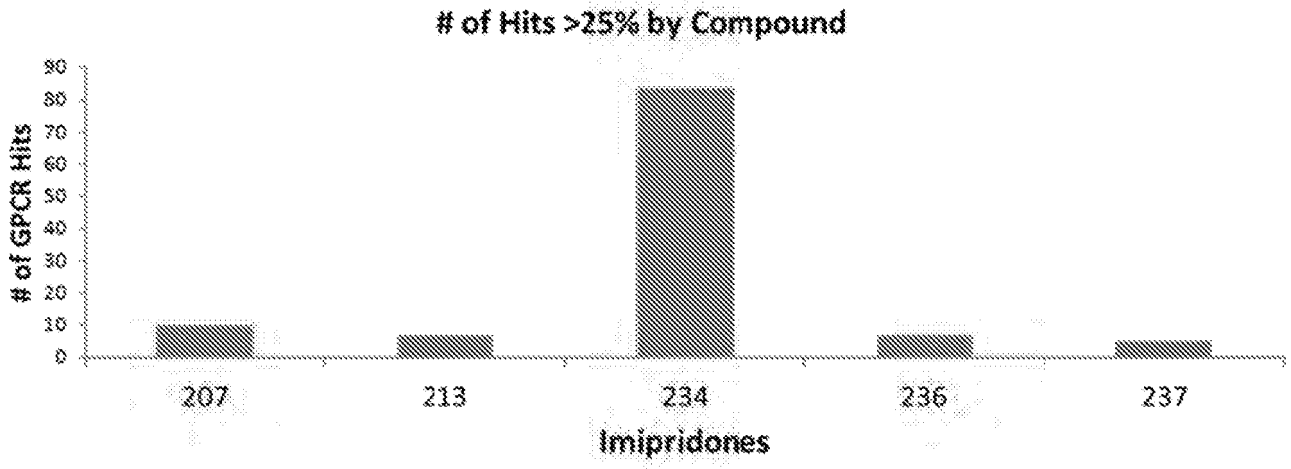


Figure 37

Figure 38


# of Hits >25% by Compound
# of GPCR Hits
90
80
70
60
50
40
30
20
10
0
207
213
234
236
237
Imipridones