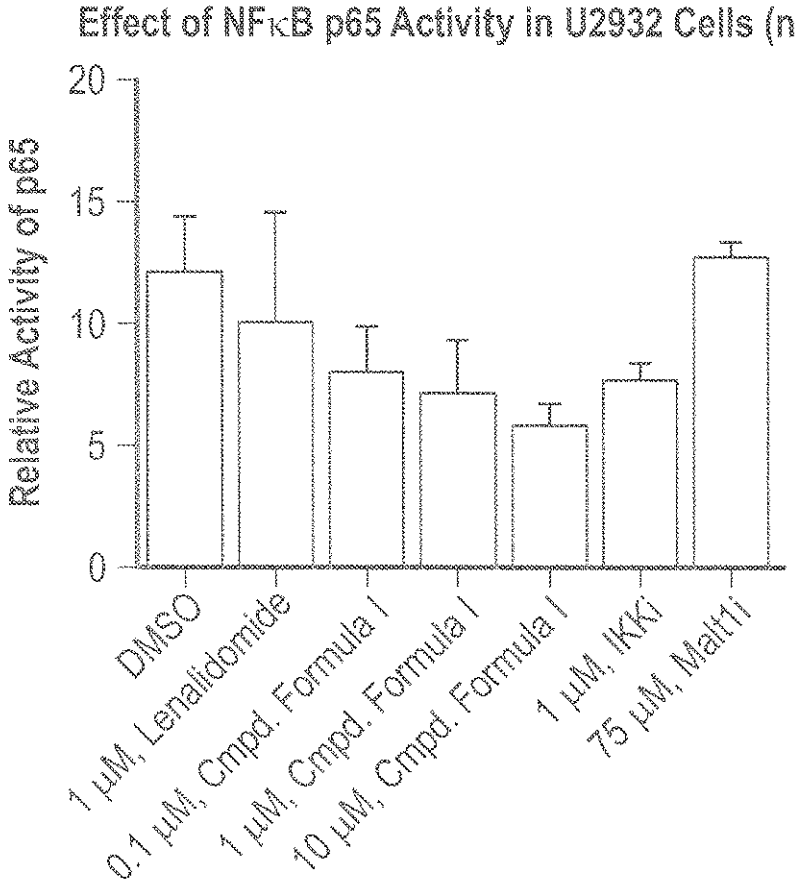

Effect of NFκB p65 Activity in U2932 Cells (n=2)
Relative Activity of p65
20
15
10
5
0
DMSO
1 μM, Lenalidomide
0.1 μM, Cmpd. Formula I
1 μM, Cmpd. Formula I
10 μM, Cmpd. Formula I
1 μM, IKKi
75 μM, Malt1i

FIG. 1A

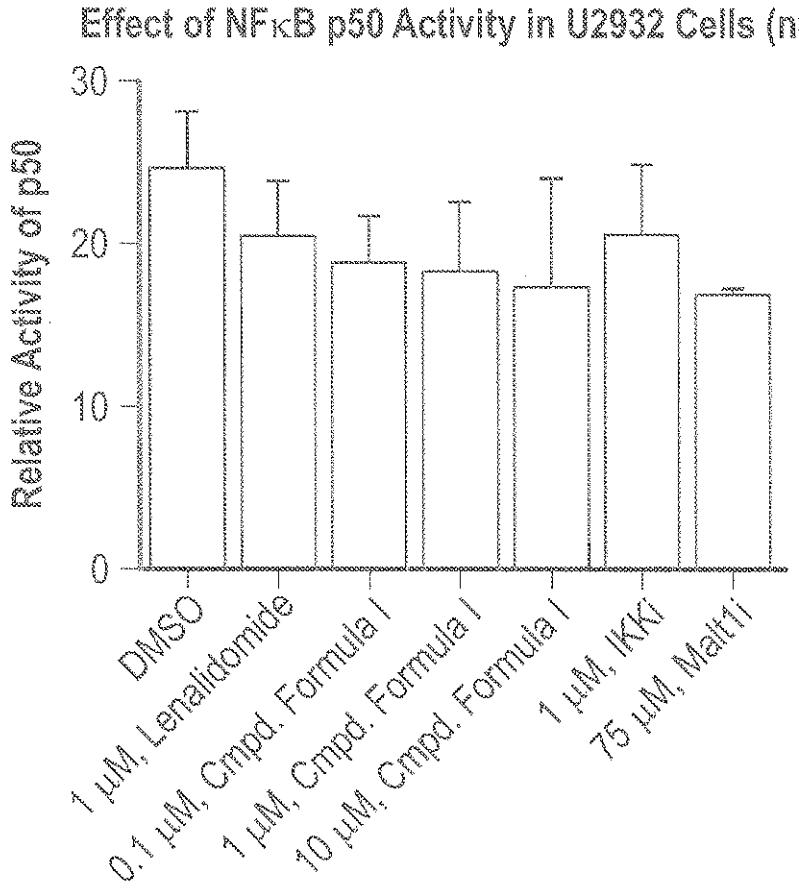

Effect of NFκB p50 Activity in U2932 Cells (n=2)
Relative Activity of p50
30
20
10
0
DMSO
1 μM, Lenalidomide
0.1 μM, Cmpd. Formula I
1 μM, Cmpd. Formula I
10 μM, Cmpd. Formula I
1 μM, IKKi
75 μM, Malt1i

FIG. 1B

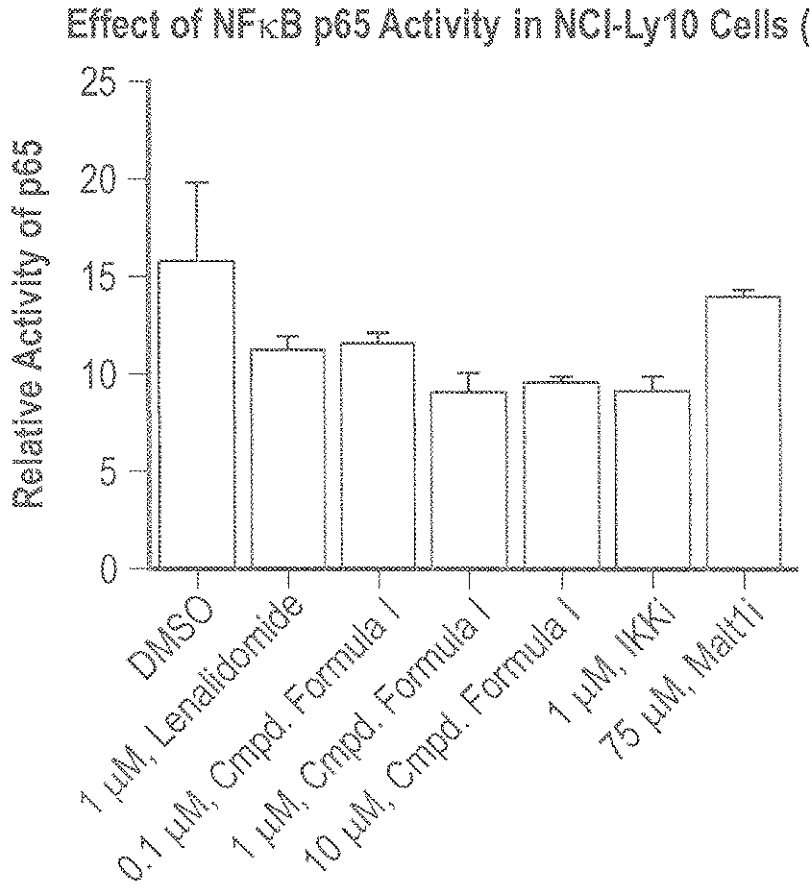

Effect of NFκB p65 Activity in NCI-Ly10 Cells (n=2)
Relative Activity of p65
25
20
15
10
5
0
DMSO
1 μM, Lenalidomide
0.1 μM, Cmpd. Formula I
1 μM, Cmpd. Formula I
10 μM, Cmpd. Formula I
1 μM, IKKi
75 μM, Malt1i

FIG. 1C

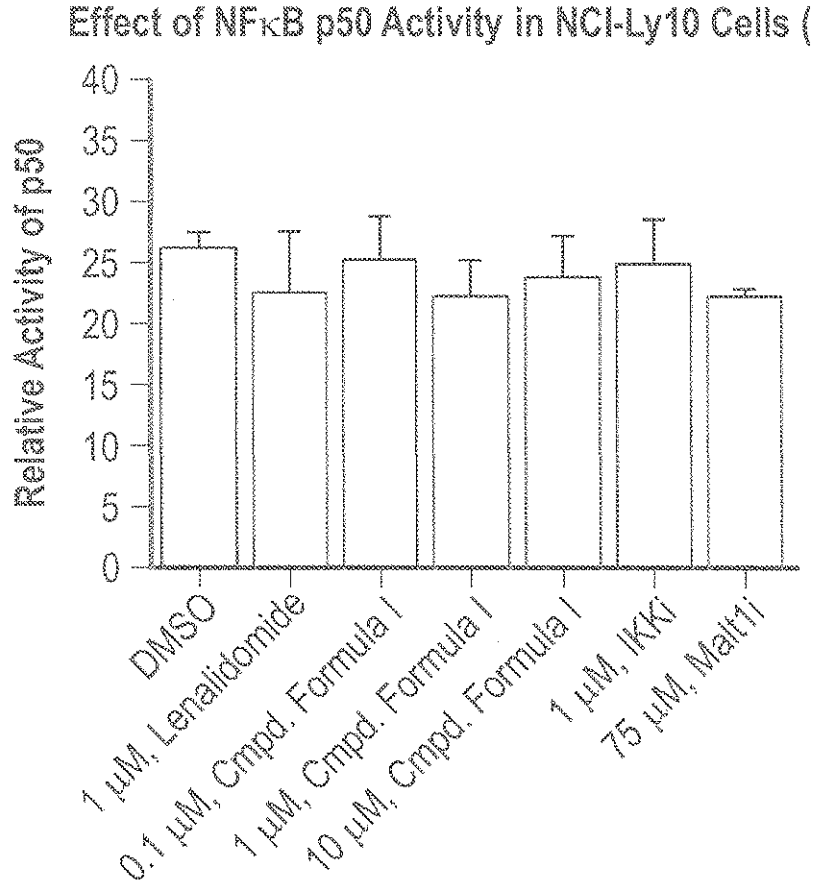

Effect of NFκB p50 Activity in NCI-Ly10 Cells (n=2)
Relative Activity of p50
40
35
30
25
20
15
10
5
0
DMSO
1 μM, Lenalidomide
0.1 μM, Cmpd. Formula I
1 μM, Cmpd. Formula I
10 μM, Cmpd. Formula I
1 μM, IKKi
75 μM, Malt1i

FIG. 1D

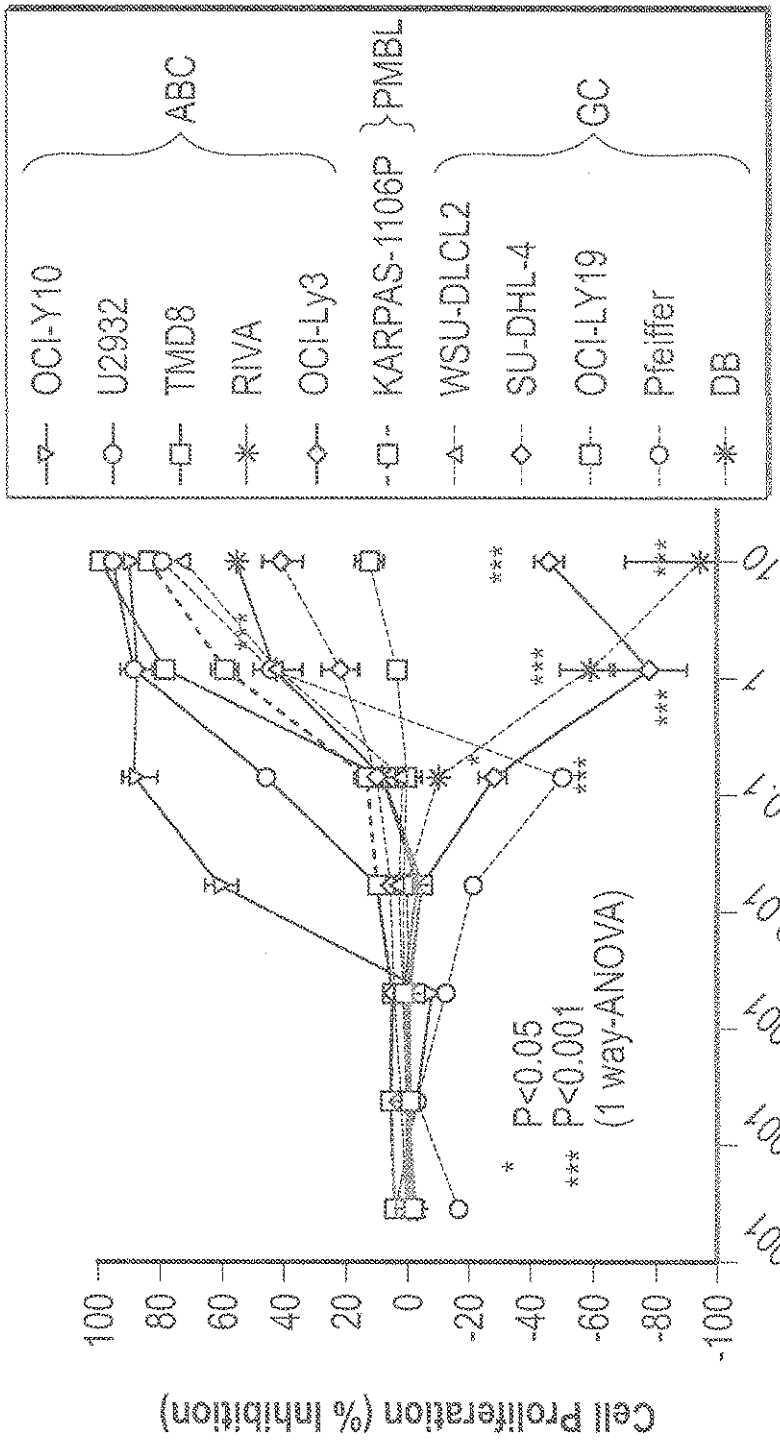

ABC
PMBL
GC
OCI-Y10
U2932
TMD8
RIVA
OCI-Ly3
KARPAS-1106P
WSU-DLCL2
SU-DHL-4
OCI-LY19
Pfeiffer
DB
P<0.05
P<0.001
(1 way-ANOVA)
Cell Proliferation (% Inhibition)
Compound of Formula I (mM)

FIG. 2

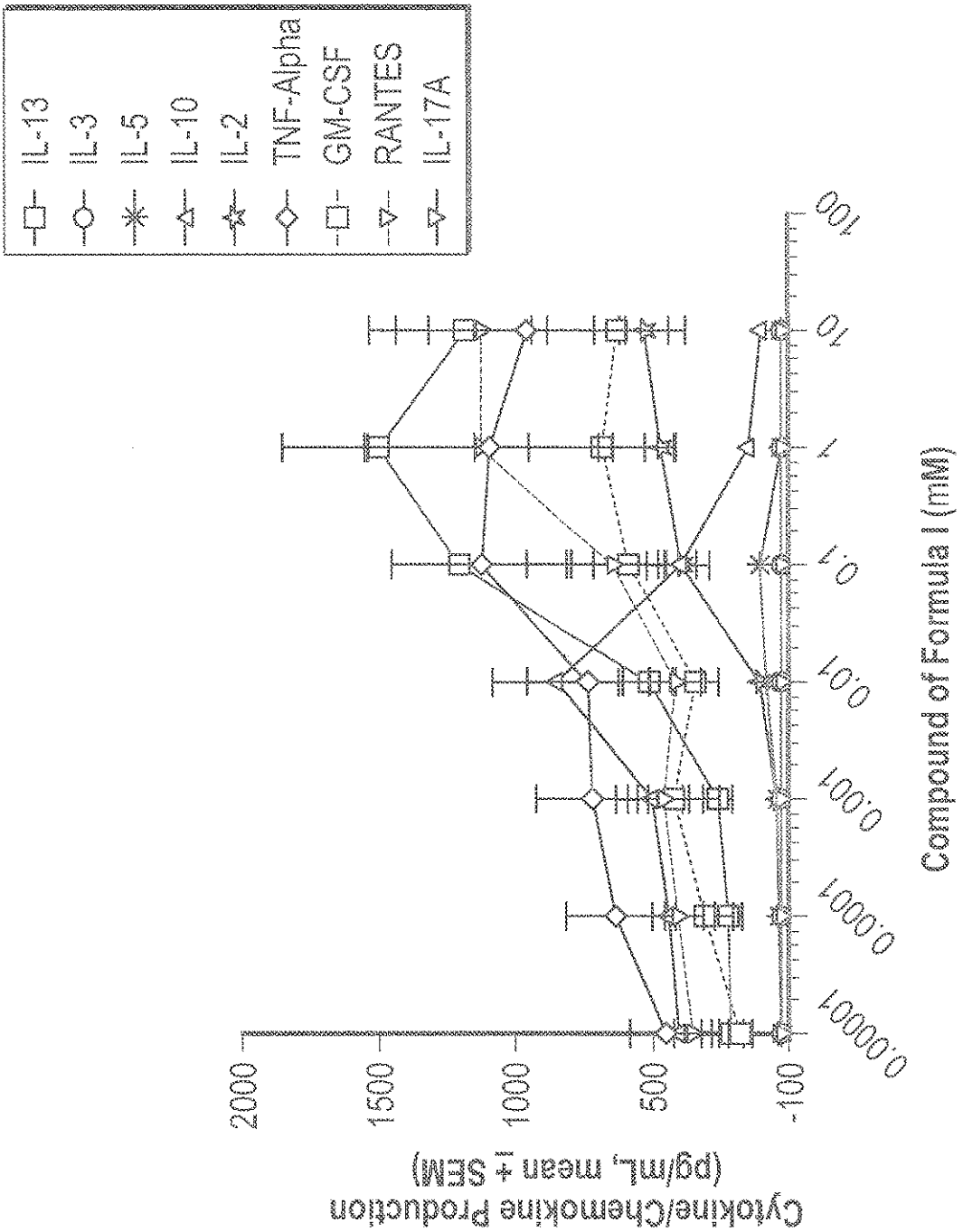

IL-13
IL-3
IL-5
IL-10
IL-2
TNF-Alpha
GM-CSF
RANTES
IL-17A
2000
1500
1000
500
-100
Cytokine/Chemokine Production
(pg/mL, mean ± SEM)
100
10
1
0.1
0.01
0.001
0.0001
0.00001
Compound of Formula I (mM)

FIG. 3

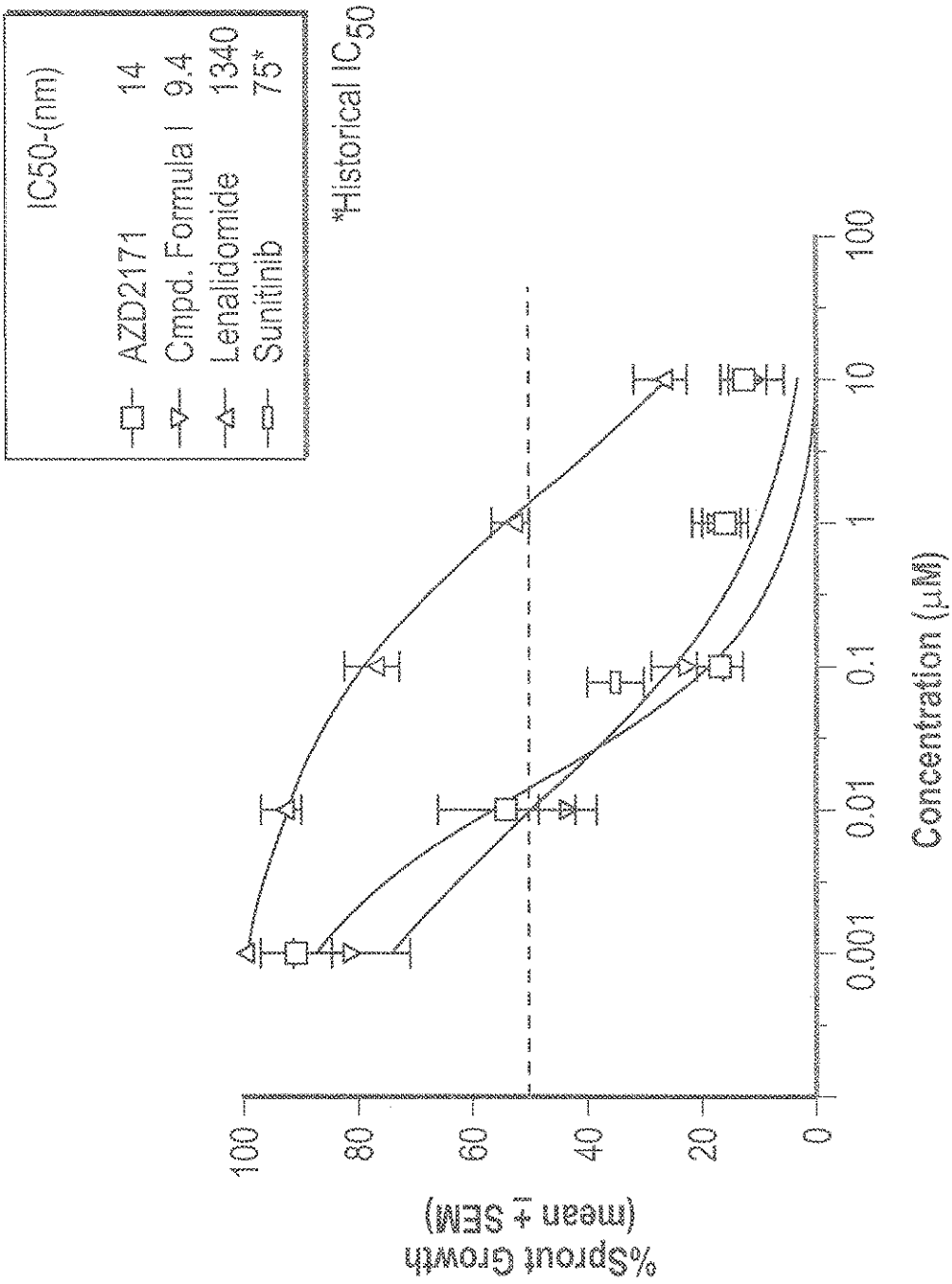

IC50-(nm)
AZD2171 14
Cmpd. Formula I 9.4
Lenalidomide 1340
Sunitinib 75*
*Historical IC50
%Sprout Growth (mean + SEM)
100
80
60
40
20
0
0.001
0.01
0.1
1
10
100
Concentration (μM)

FIG. 4

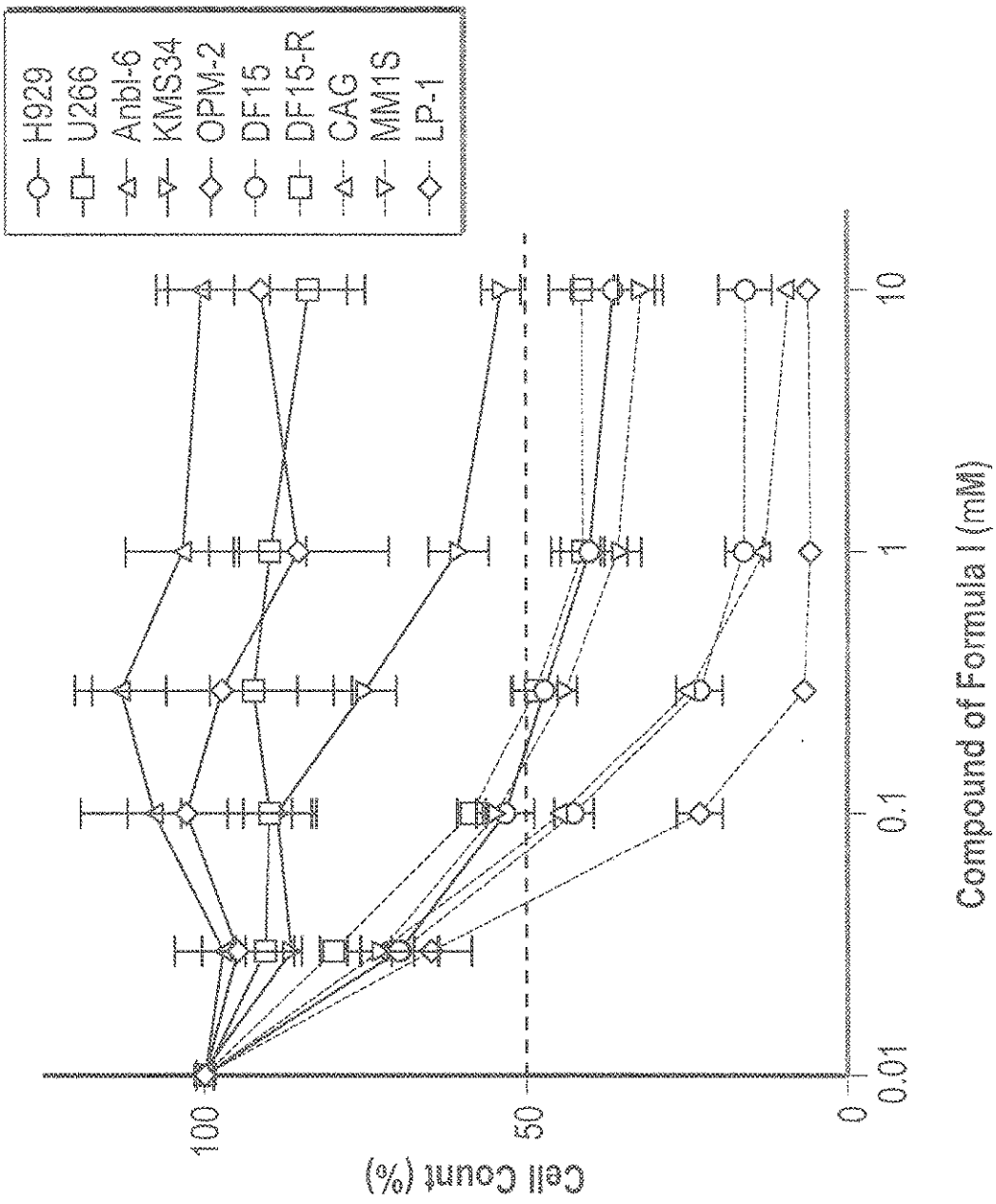
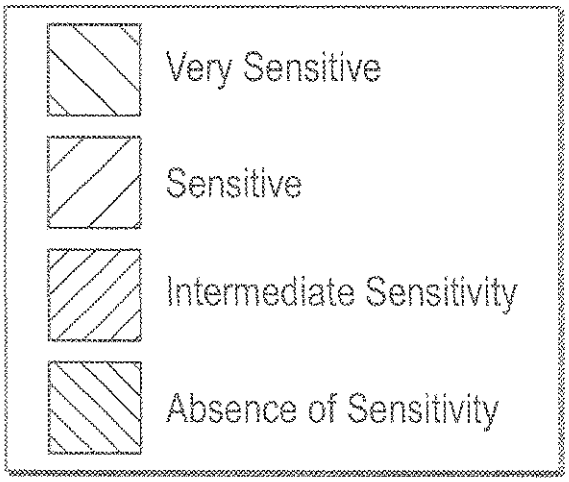

H929
U266
Anbl-6
KMS34
OPM-2
DF15
DF15-R
CAG
MM1S
LP-1
cell count (%)
100
50
0
0.01
0.1
1
10
Compound of Formula I (mM)

FIG. 5A



Proliferation	CC-122	CC-5013
OPM2 (n=2)	0.04	0.3
H929 (n=3)	0.07	10.5
CAG (n=3)	0.085	12.2
MM1.S (n=3)	0.3	8.6
DF15 (n=3)	0.4	19.23
U266 (n=3)	0.4	12.6
KMS34 (n=3)	9.7	>10
LP-1 (n=3)	>10	>10
DF15R (n=3)	>10	>10
Anbl-6 (n=4)	>10	>10

FIG. 5B

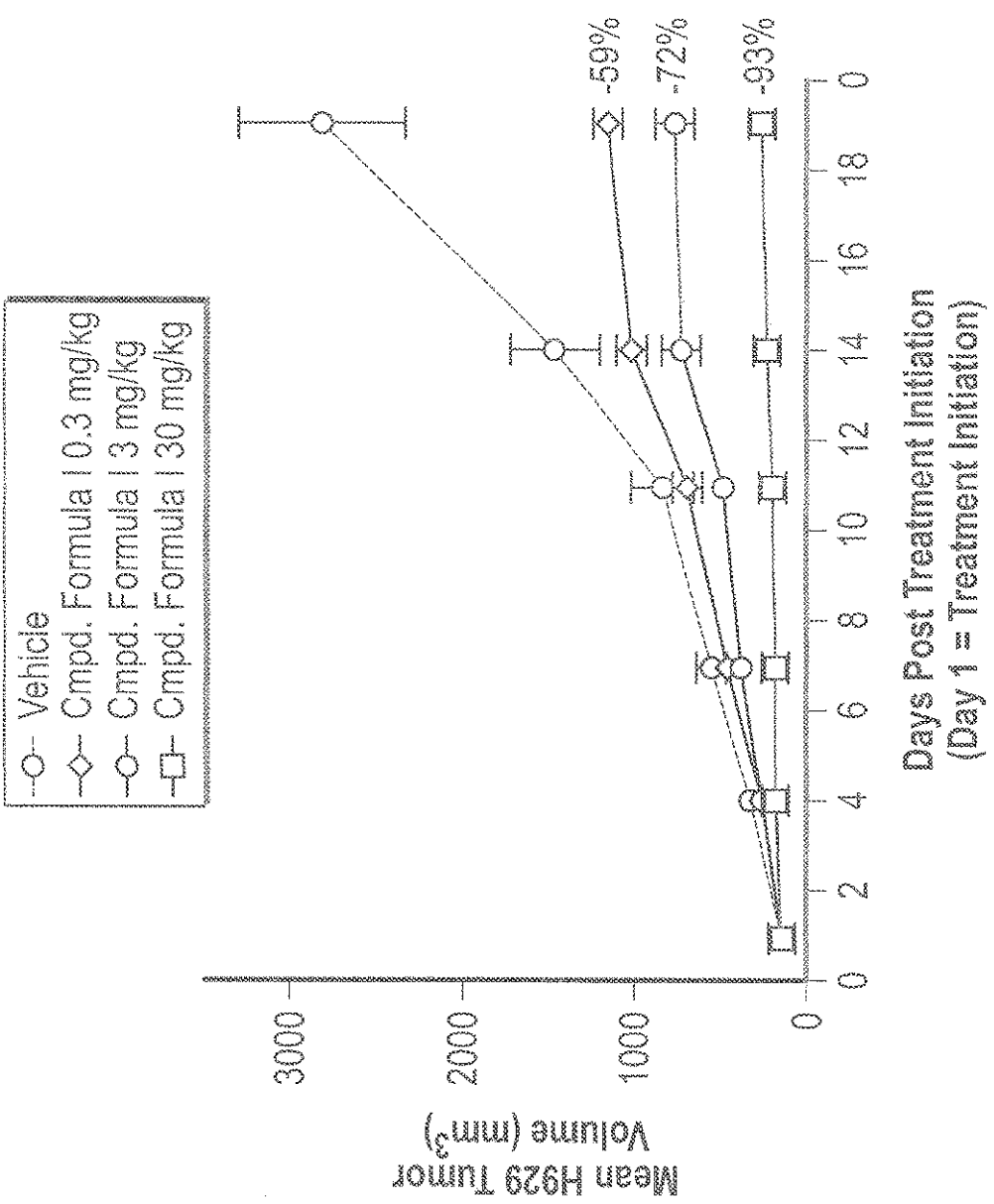
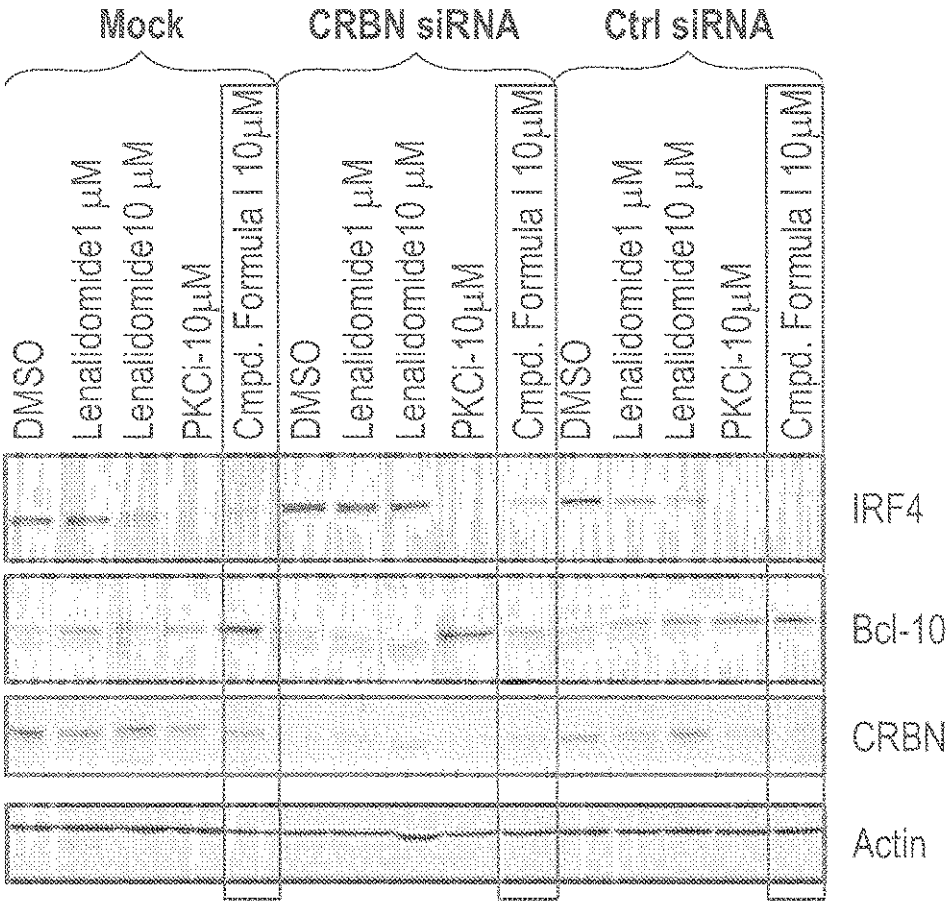

Vehicle
Cmpd. Formula I 0.3 mg/kg
Cmpd. Formula I 3 mg/kg
Cmpd. Formula I 30 mg/kg
-59%
-72%
-93%
Mean H929 Tumor Volume (mm³)
3000
2000
1000
0
0
2
4
6
8
10
12
14
16
18
0
Days Post Treatment Initiation
(Day 1 = Treatment Initiation)

FIG. 6

FIG. 7A


Mock
CRBN siRNA
Ctrl siRNA
DMSO
Lenalidomide1 µM
Lenalidomide10 µM
PKCi-10µM
Cmpd. Formula I 10µM
IRF4
Bcl-10
CRBN
Actin

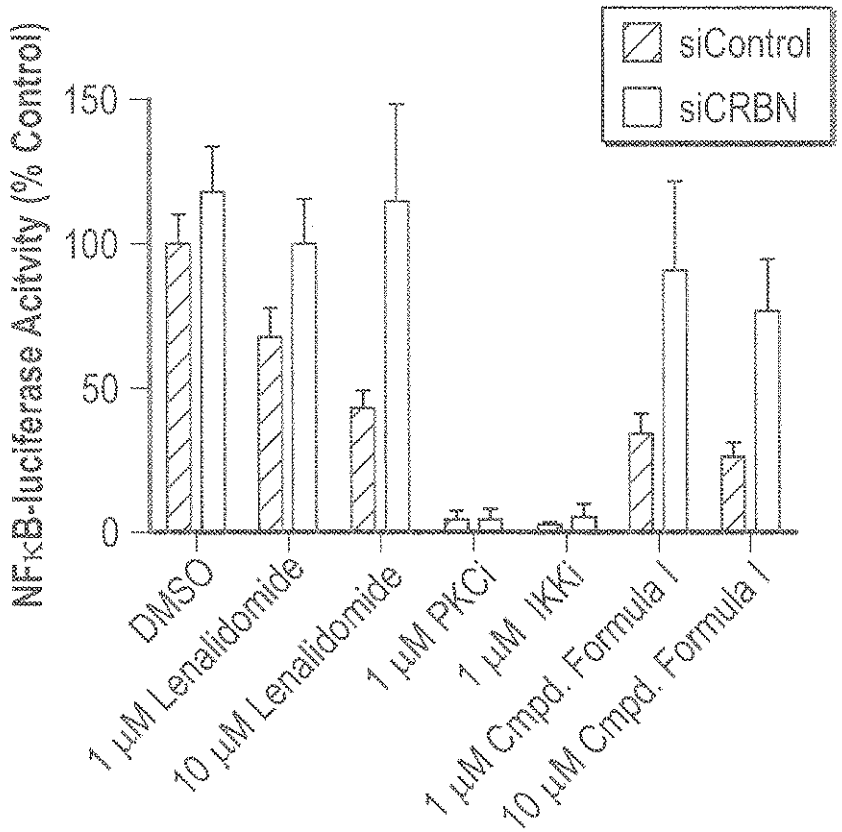

siControl
siCRBN
NFκB-luciferase Acitvity (% Control)
150
100
50
0
DMSO
1 µM Lenalidomide
10 µM Lenalidomide
1 µM PKCi
1 µM IKKi
1 µM Cmpd. Formula I
10 µM Cmpd. Formula I

FIG. 7B

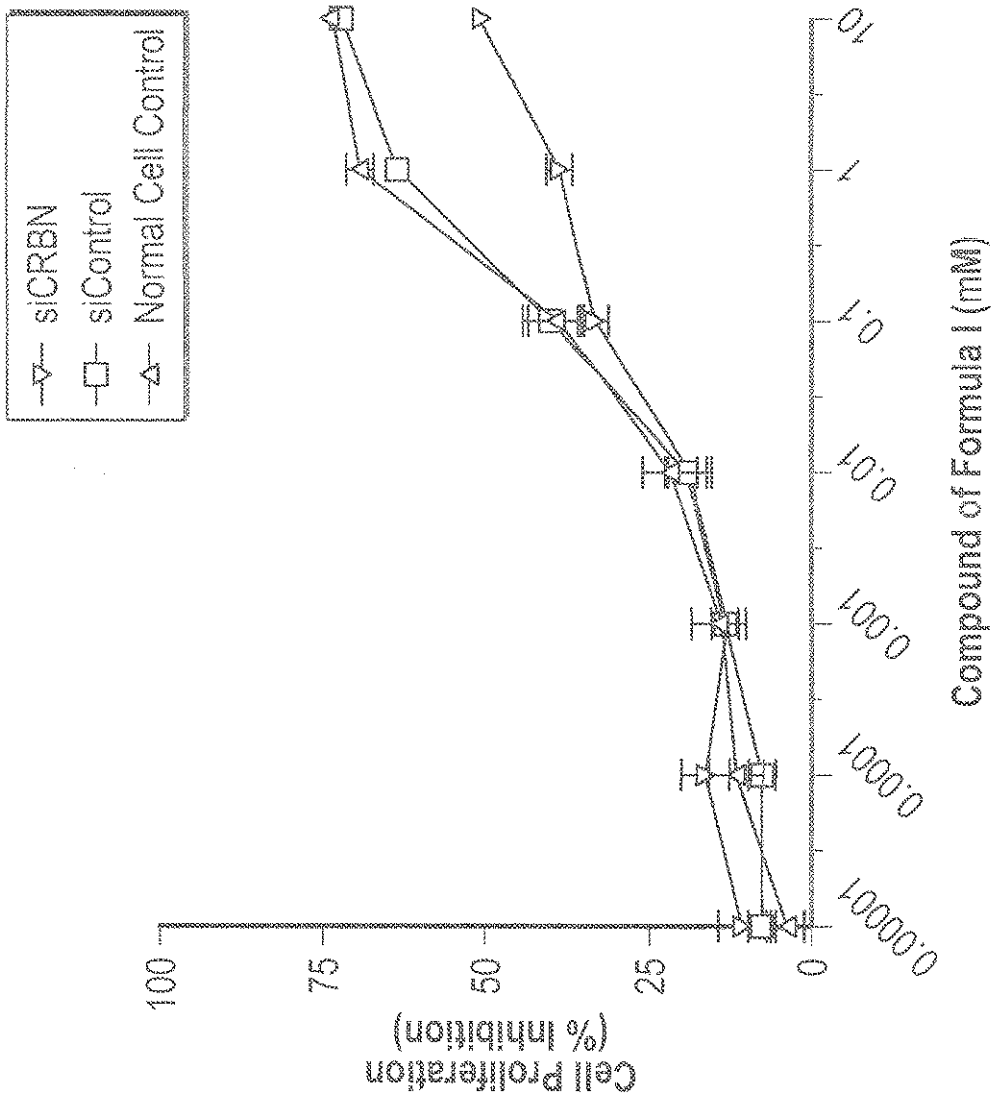

siCREBN
siControl
Normal Cell Control
Cell Proliferation
(% Inhibition)
100
75
50
25
0
10
1
0.1
0.01
0.001
0.0001
0.00001
Compound of Formula I (mM)

FIG. 7C

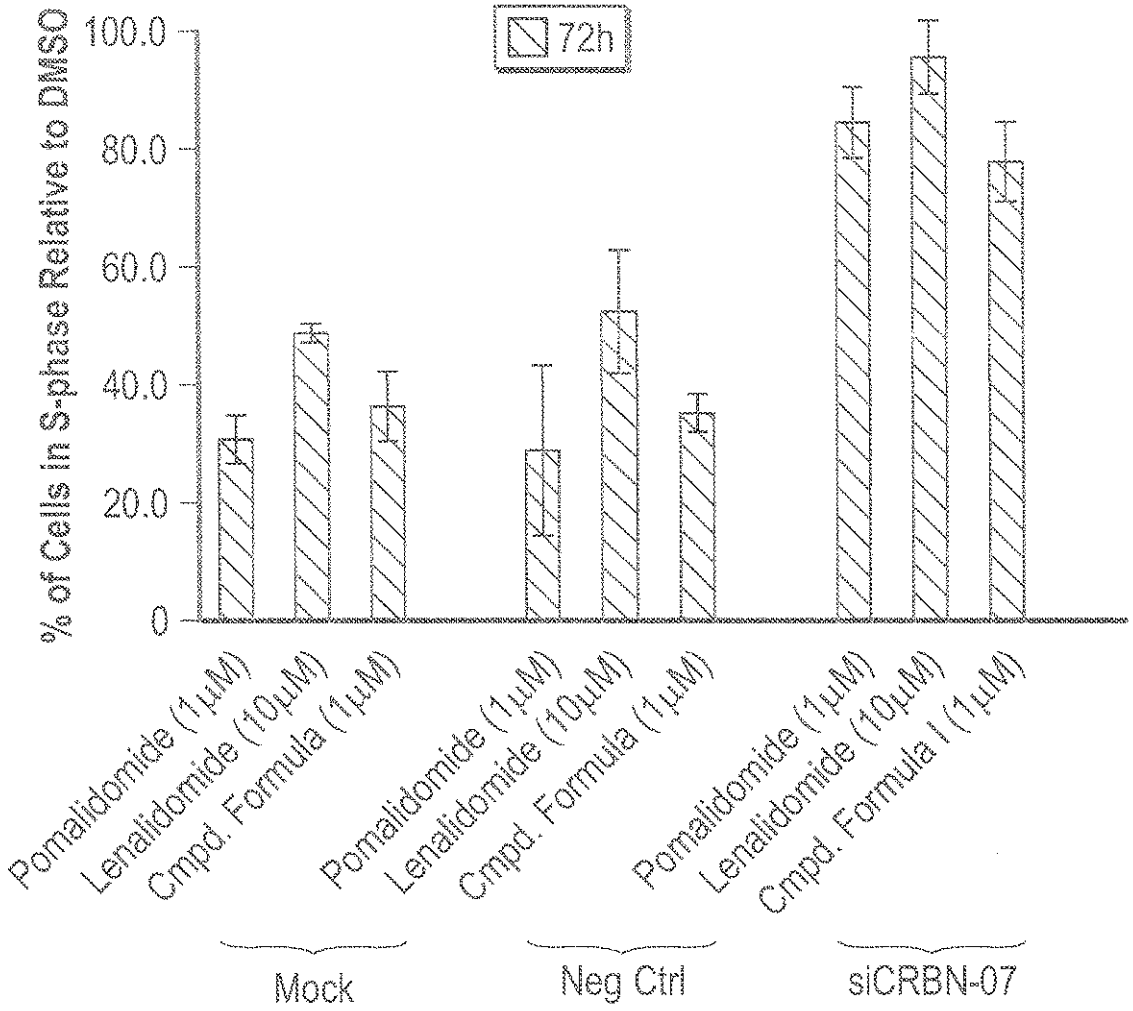

% of Cells in S-phase Relative to DMSO
100.0
80.0
60.0
40.0
20.0
0
72h
Pomalidomide (1μM)
Lenalidomide (10μM)
Cmpd. Formula I (1μM)
Pomalidomide (1μM)
Lenalidomide (10μM)
Cmpd. Formula I (1μM)
Pomalidomide (1μM)
Lenalidomide (10μM)
Cmpd. Formula I (1μM)
Mock
Neg Ctrl
siCRBN-07

FIG. 8

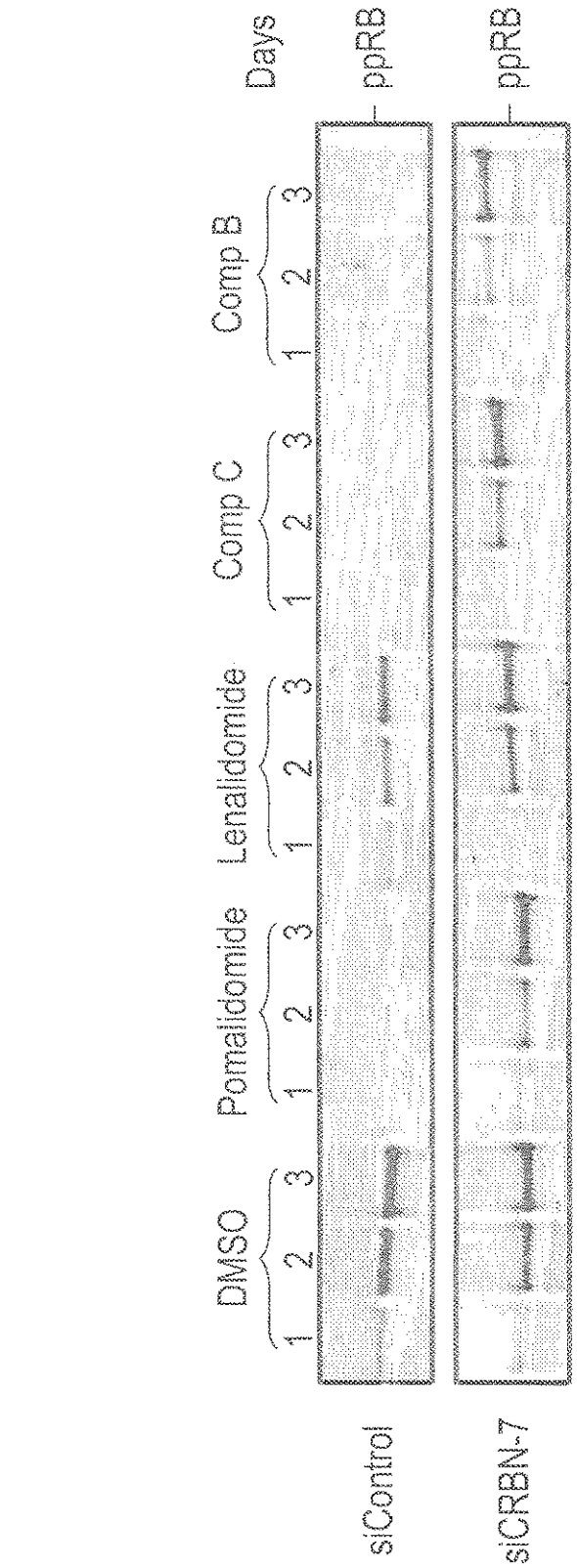

siControl
siCRBN-7
DMSO
Pomalidomide
Lenalidomide
Comp C
Comp B
1 2 3
Days
ppRB
ppRB

FIG. 9A

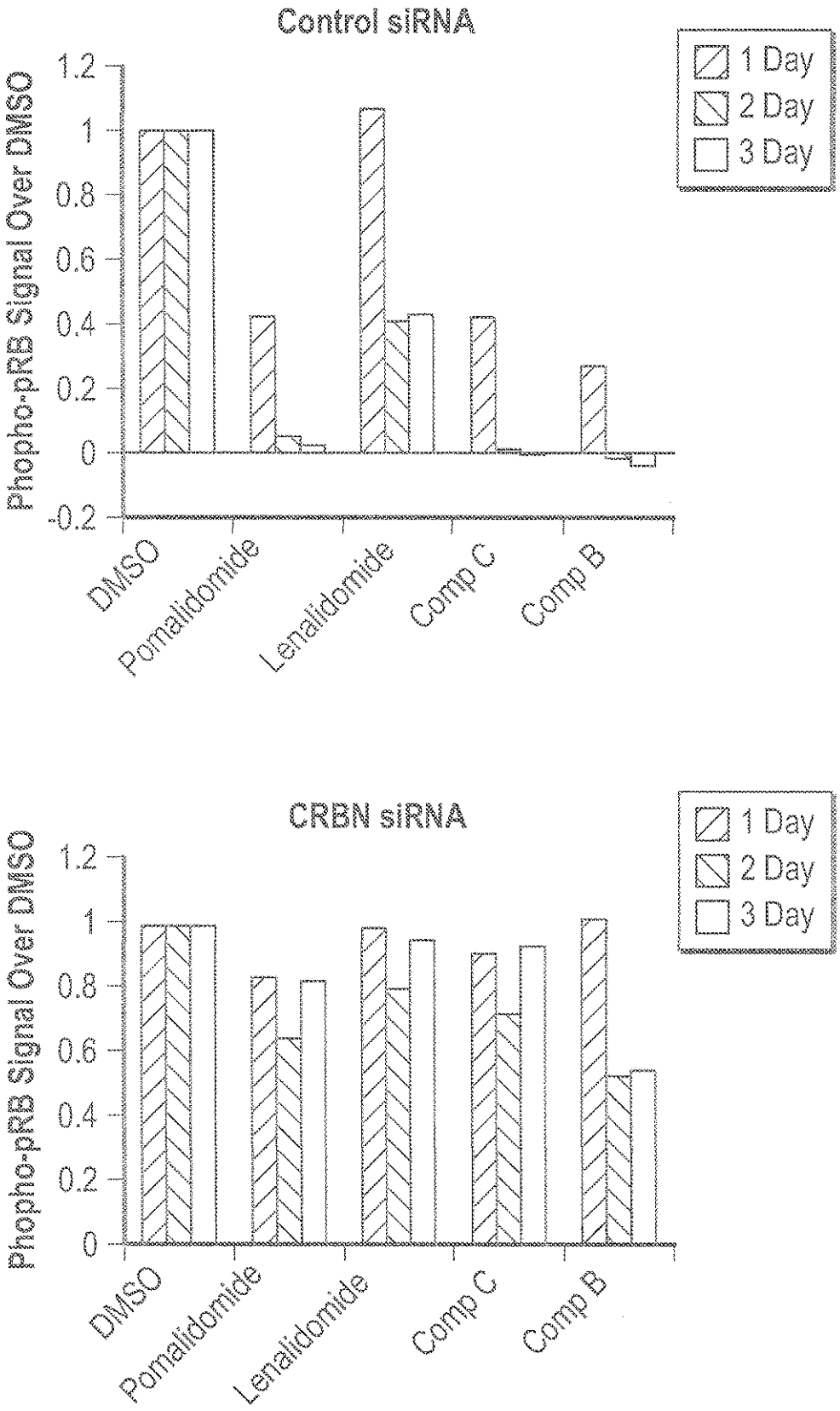

Control siRNA
Phopho-pRB Signal Over DMSO
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
1 Day
2 Day
3 Day
DMSO
Pomalidomide
Lenalidomide
Comp C
Comp B
CRBN siRNA
Phopho-pRB Signal Over DMSO
1.2
1
0.8
0.6
0.4
0.2
0
1 Day
2 Day
3 Day
DMSO
Pomalidomide
Lenalidomide
Comp C
Comp B

FIG. 9B

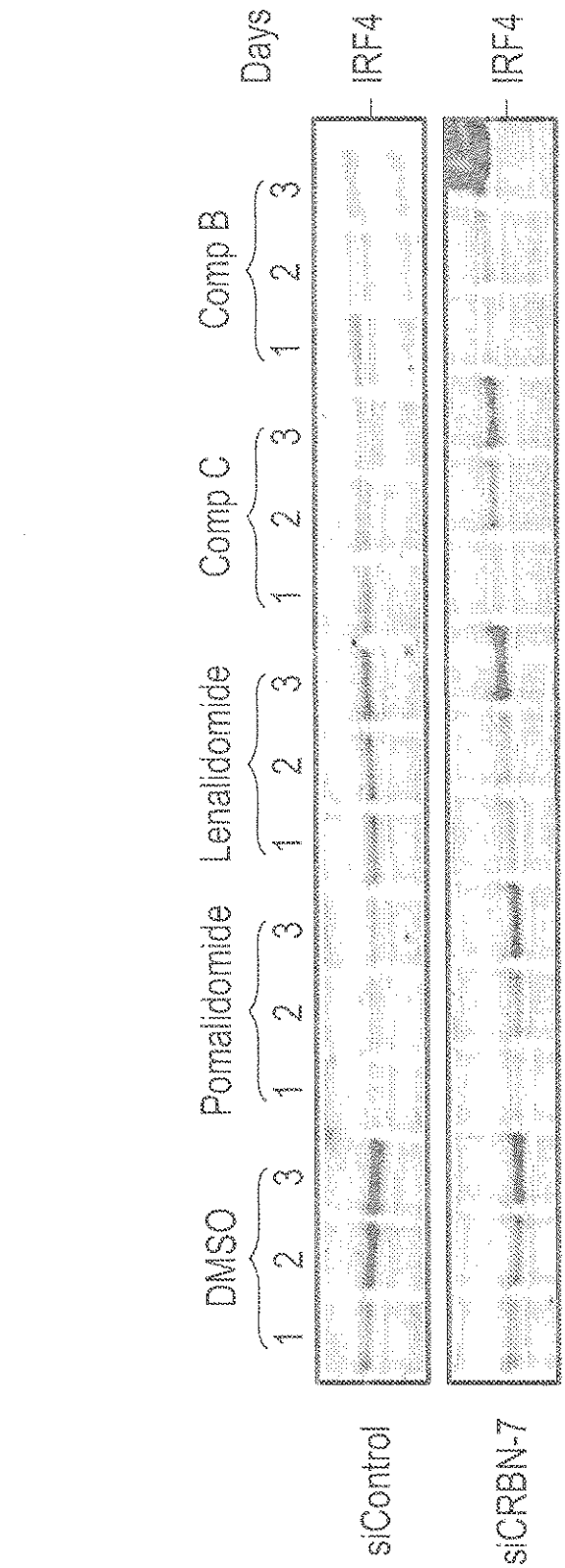
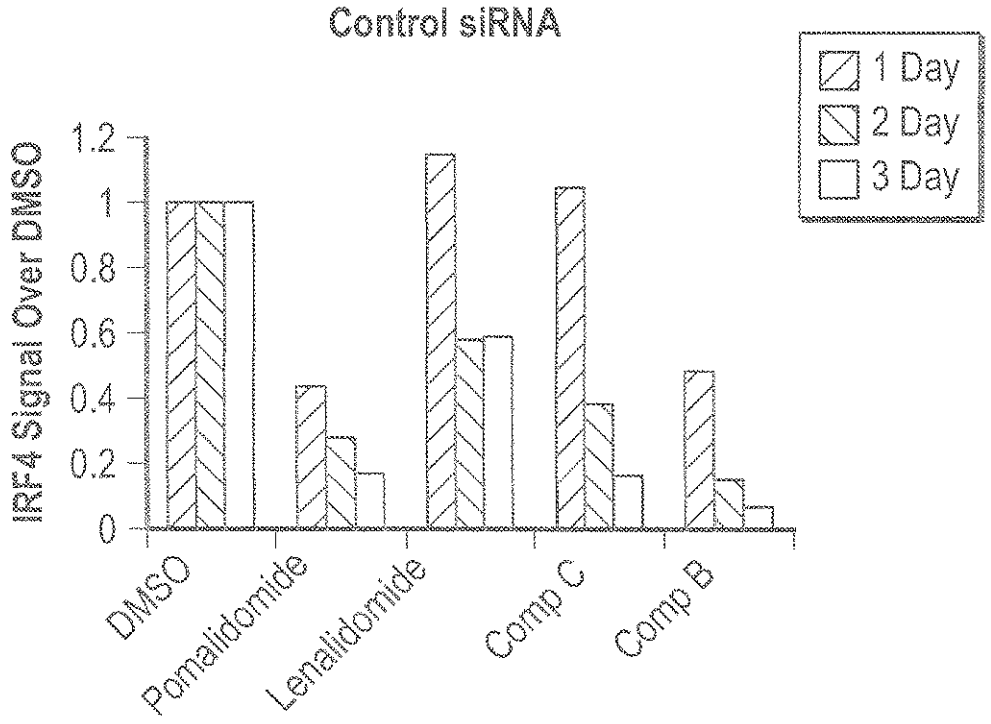

siControl
siCRBN-7
DMSO
Pomalidomide
Lenalidomide
Comp C
Comp B
1 2 3
Days
IRF4
IRF4

FIG. 9C


Control siRNA
1 Day
2 Day
3 Day
IRF4 Signal Over DMSO
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
Pomalidomide
Lenalidomide
Comp C
Comp B

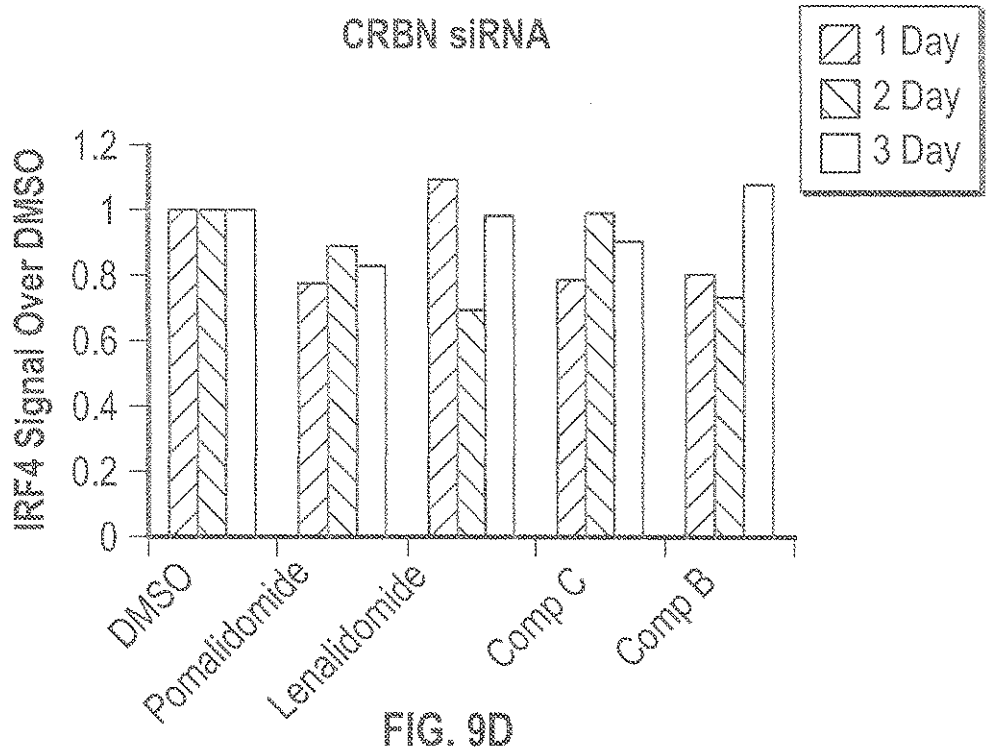

CRBN siRNA
1 Day
2 Day
3 Day
IRF4 Signal Over DMSO
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
Pomalidomide
Lenalidomide
Comp C
Comp B

FIG. 9D

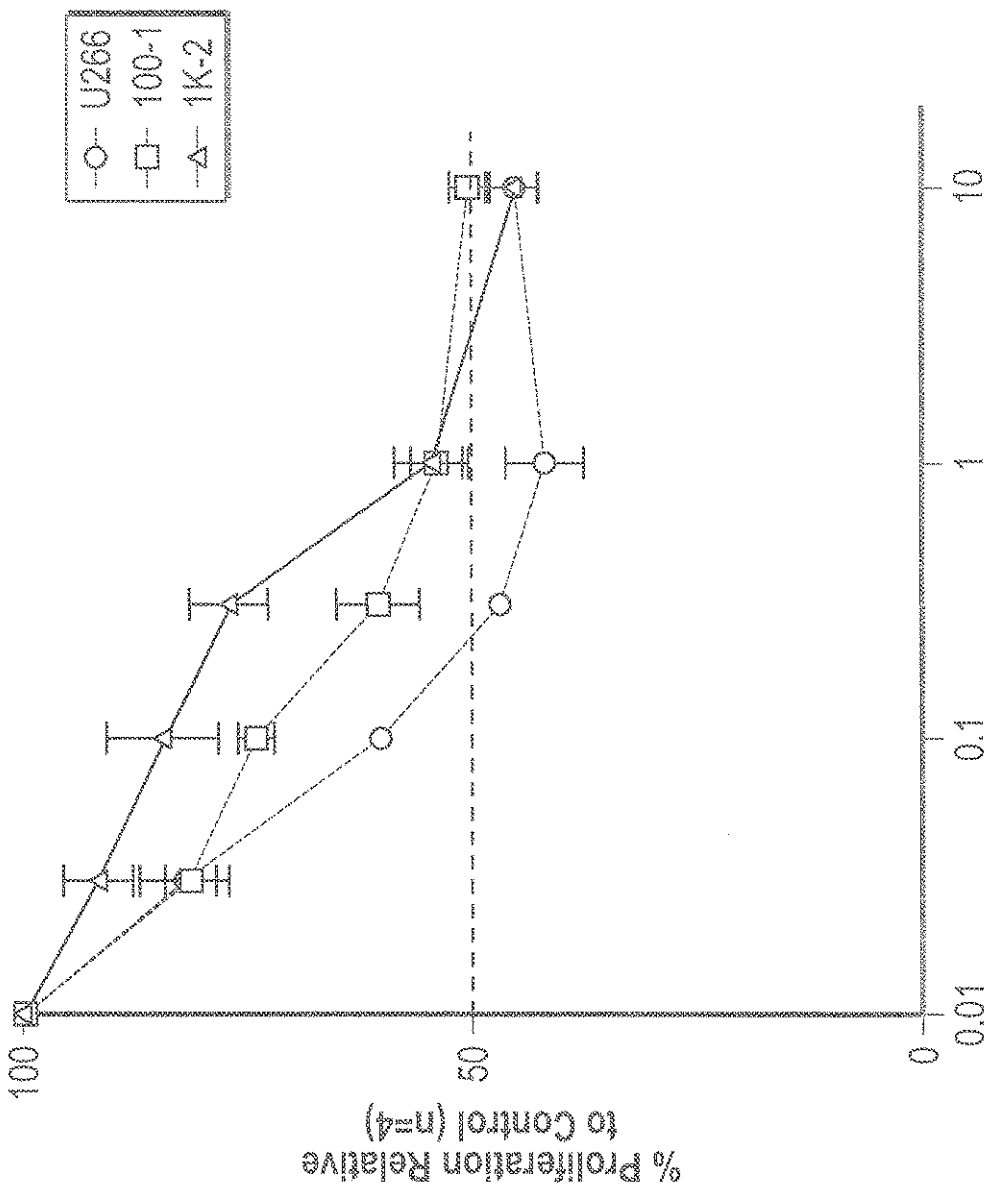
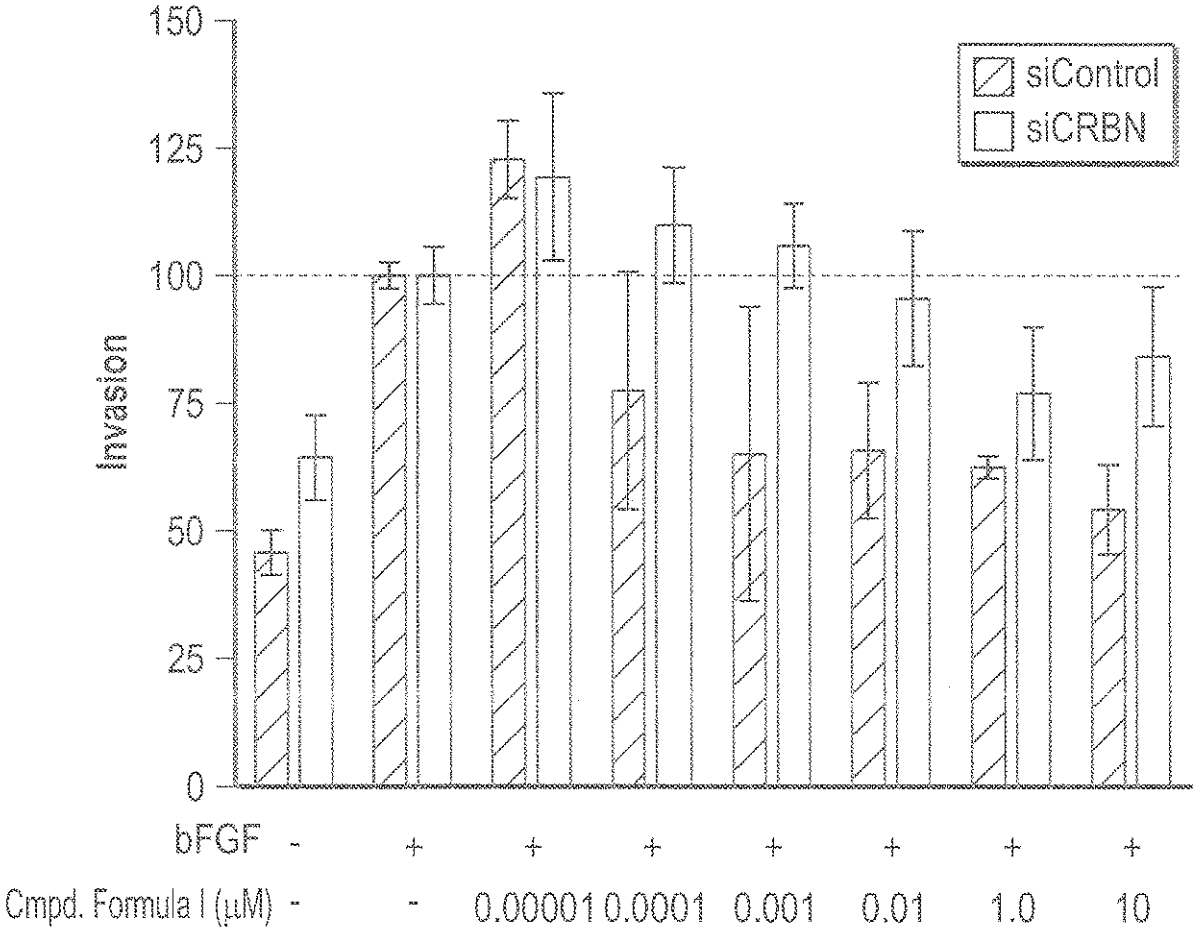

U266
100-1
1K-2
% Proliferation Relative to Control (n=4)
100
50
0
0.01
0.1
1
10
Compound of Formula I (mM)

FIG. 10


150
125
100
75
50
25
0
Invasion
siControl
siCRBN
bFGF - + + + + + + +
Cmpd. Formula I (μM) - - 0.00001 0.0001 0.001 0.01 1.0 10

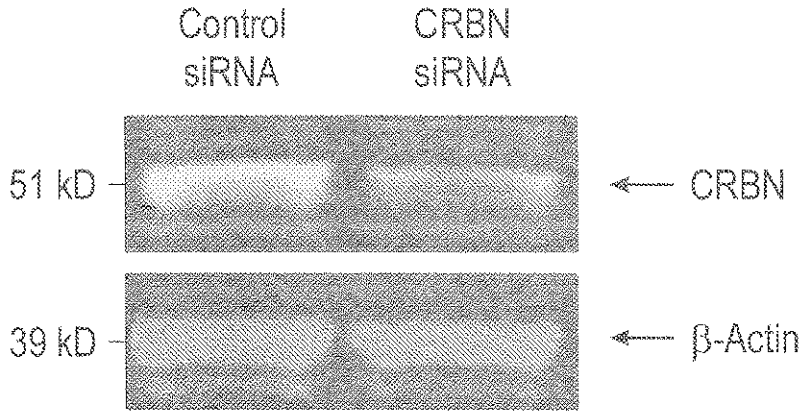

Control siRNA
CRBN siRNA
51 kD
CRBN
39 kD
β-Actin

FIG. 11

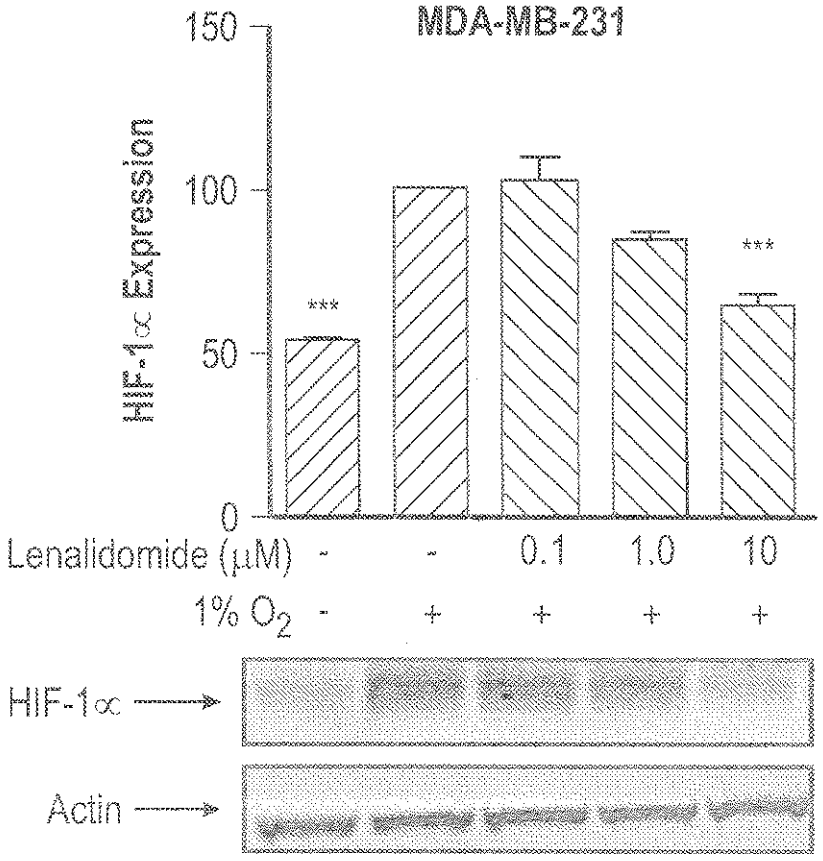


FIG. 12A

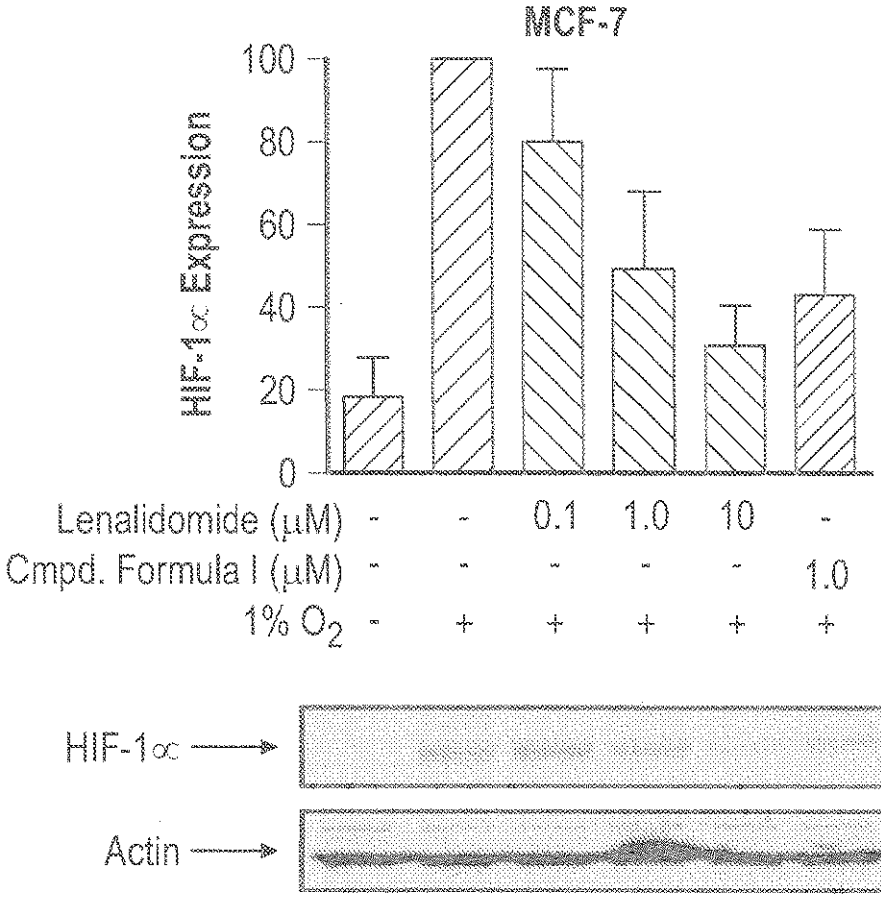


FIG. 12B

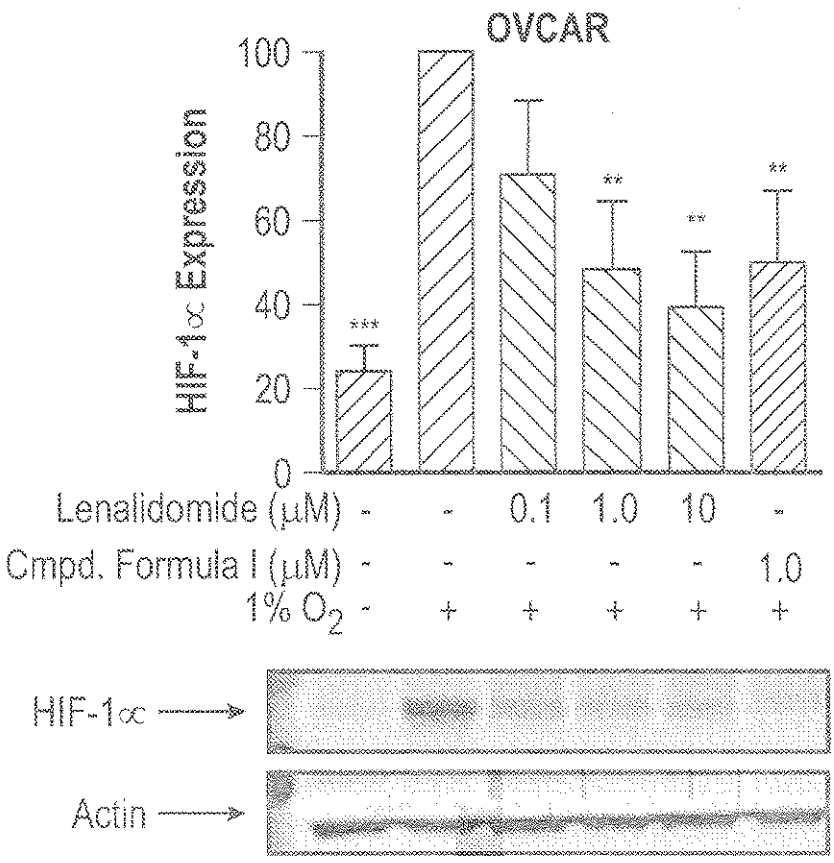


FIG. 12C

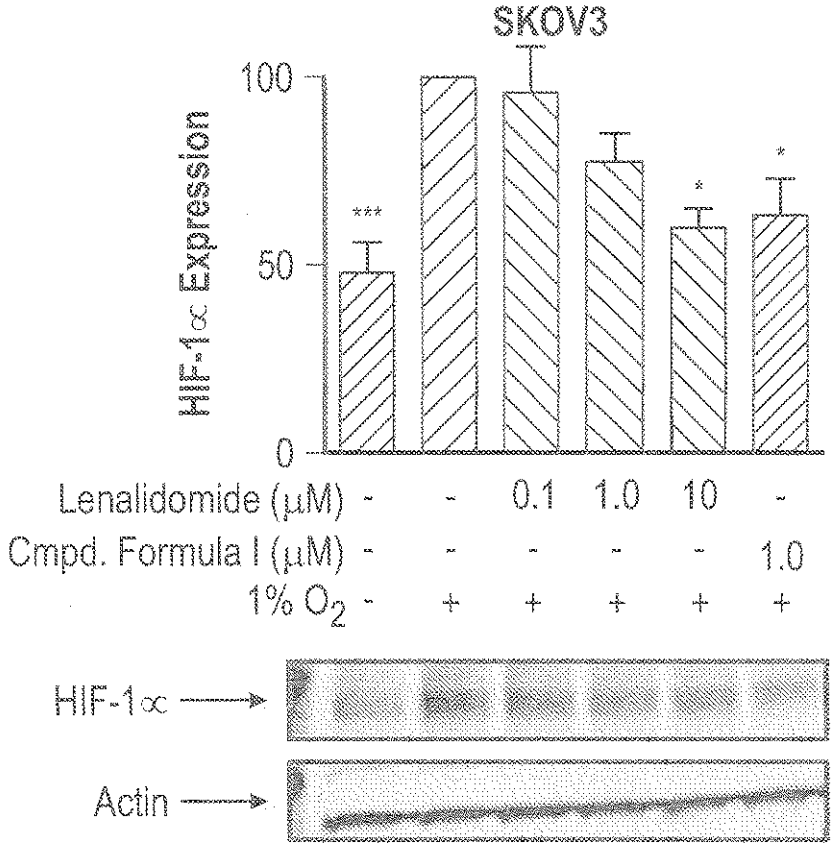


FIG. 12D

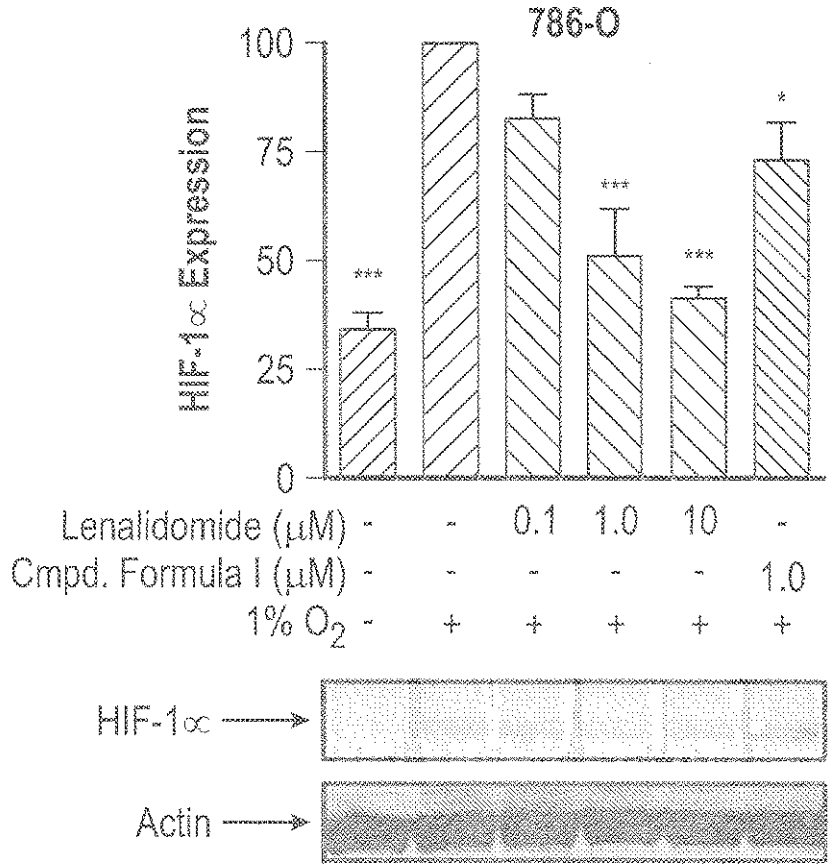


FIG. 12E

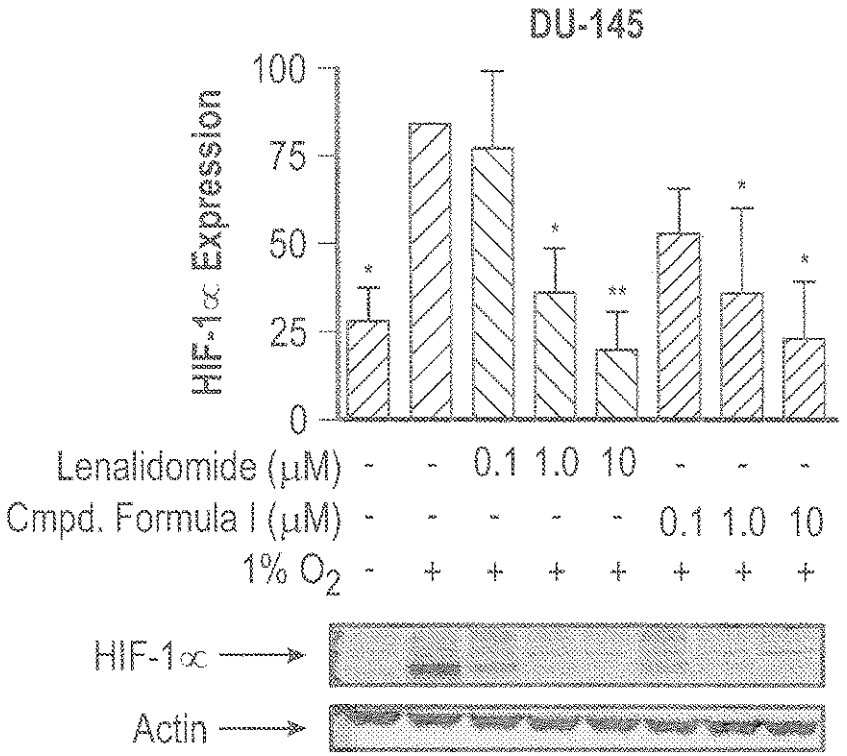


FIG. 12F

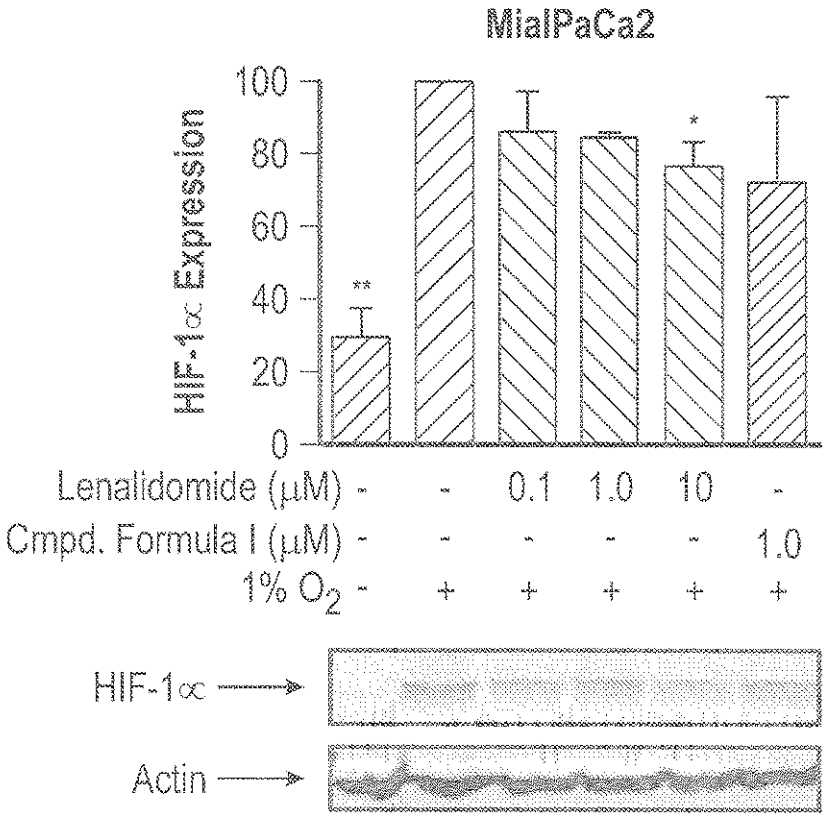


FIG. 12G

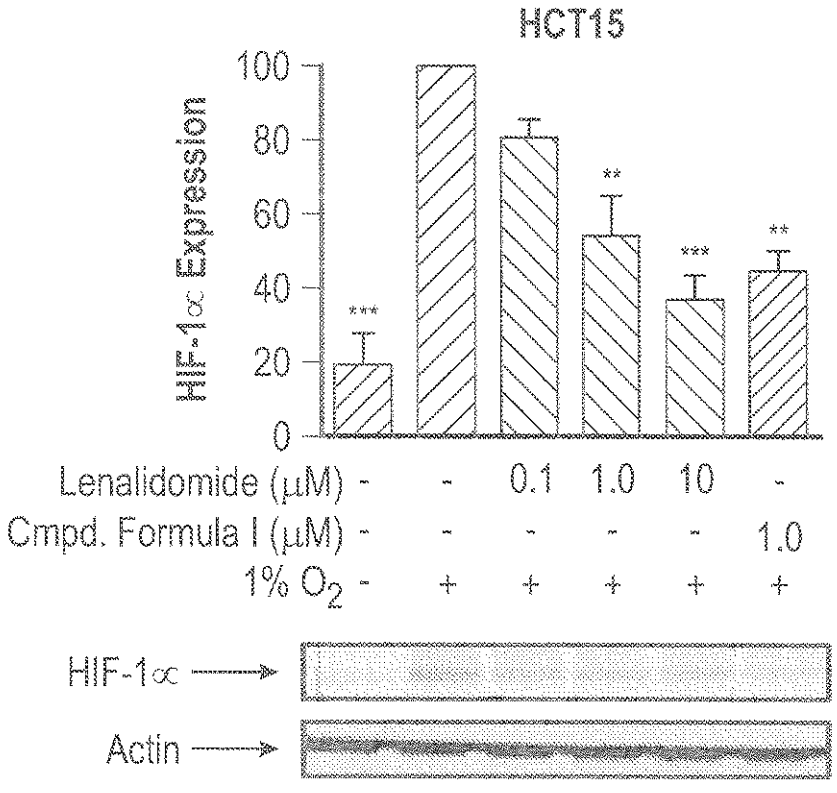


FIG. 12H

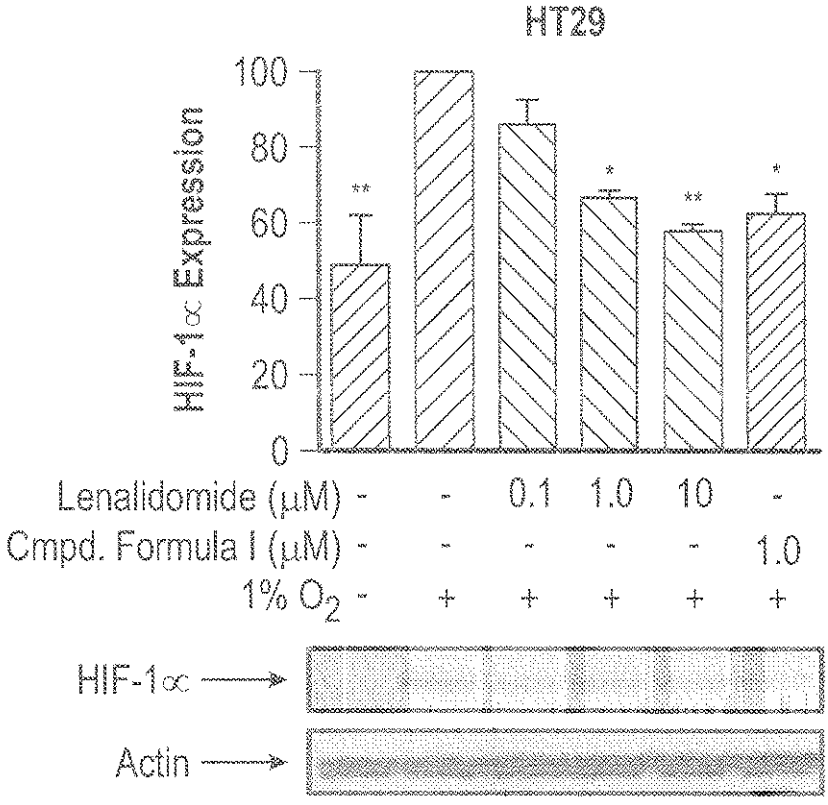

HT29
HIF-1∝ Expression
100
80
60
40
20
0
**
*
**
*
Lenalidomide (μM) - - 0.1 1.0 10 -
Cmpd. Formula I (μM) - - - - - 1.0
1% O2 - + + + + +
HIF-1∝
Actin

FIG. 12I

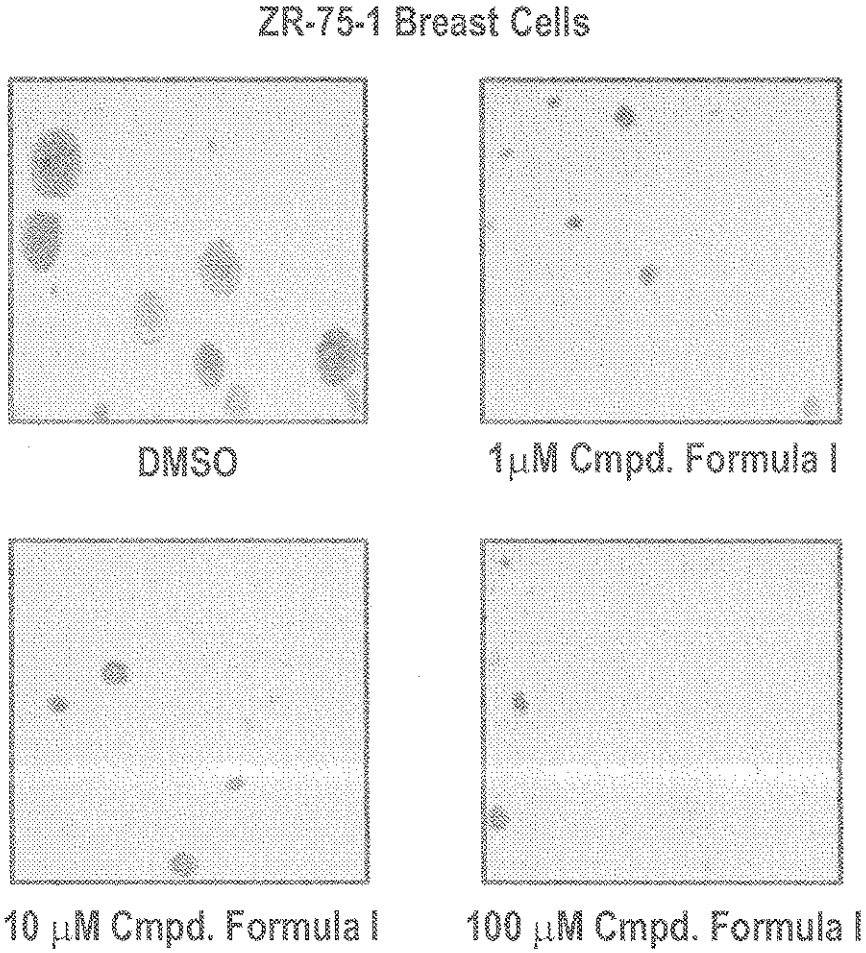


FIG. 13A

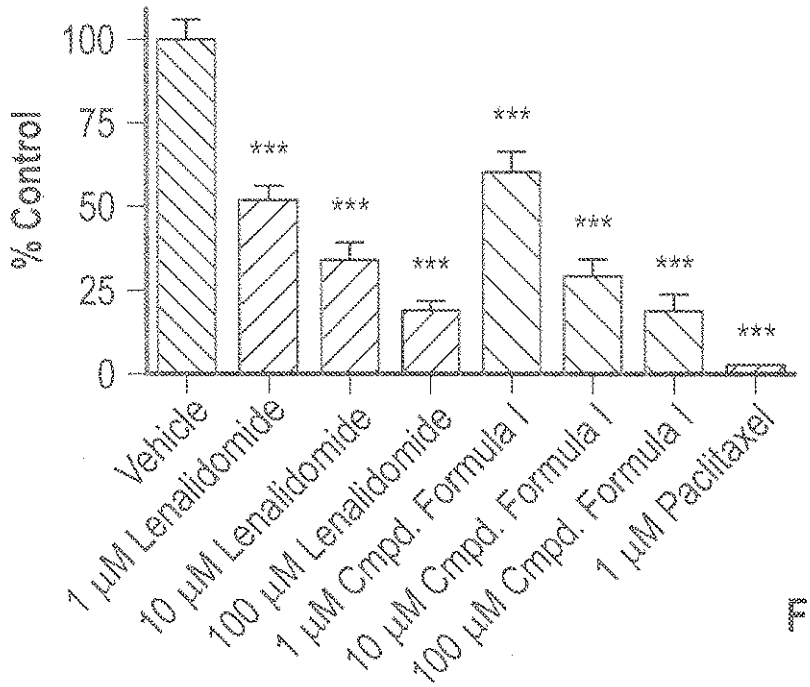


FIG. 13B

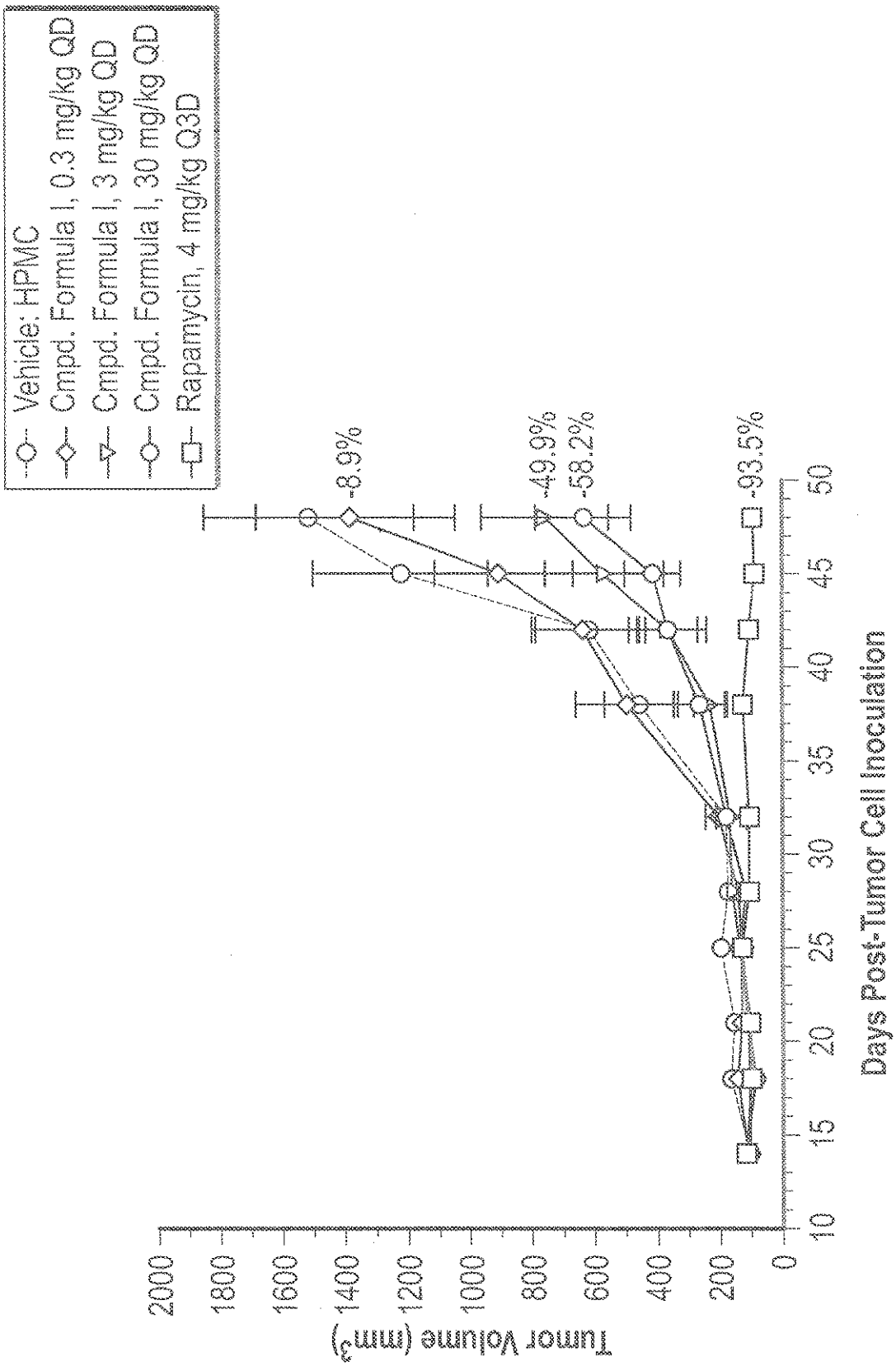

Vehicle: HPMC
Cmpd. Formula I, 0.3 mg/kg QD
Cmpd. Formula I, 3 mg/kg QD
Cmpd. Formula I, 30 mg/kg QD
Rapamycin, 4 mg/kg Q3D
-8.9%
-49.9%
-58.2%
-93.5%
Tumor Volume (mm³)
Days Post-Tumor Cell Inoculation
0
200
400
600
800
1000
1200
1400
1600
1800
2000
10
15
20
25
30
35
40
45
50

FIG. 14