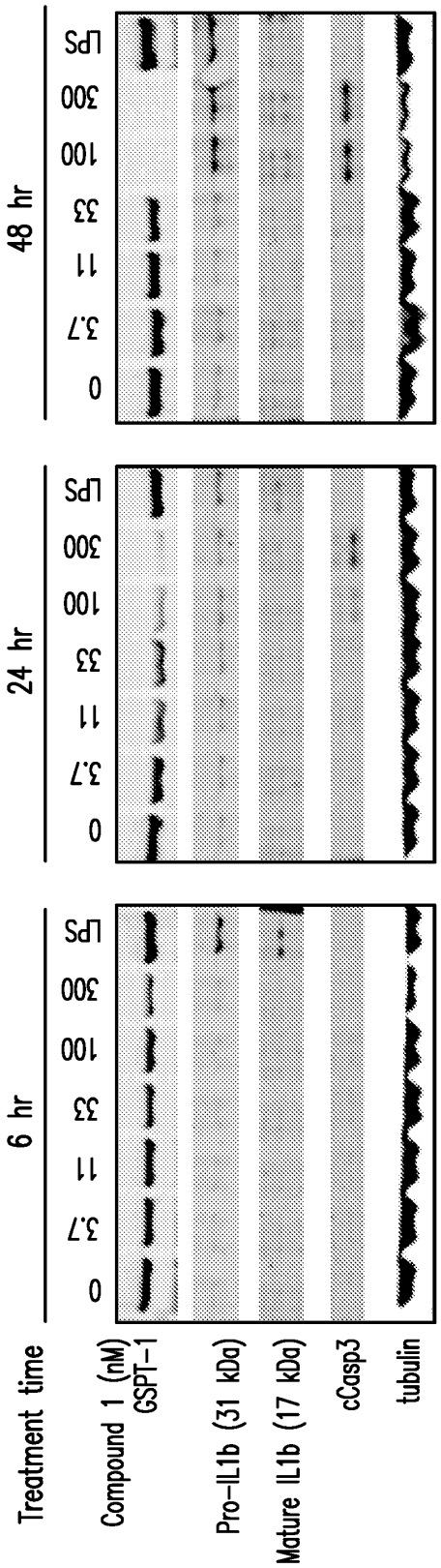

Treatment time
6 hr
24 hr
48 hr
0
3.7
11
33
100
300
LPS
Compound 1 (nM)
GSPT-1
Pro-IL1b (31 kDa)
Mature IL1b (17 kDa)
cCasp3
tubulin

FIG. 1A

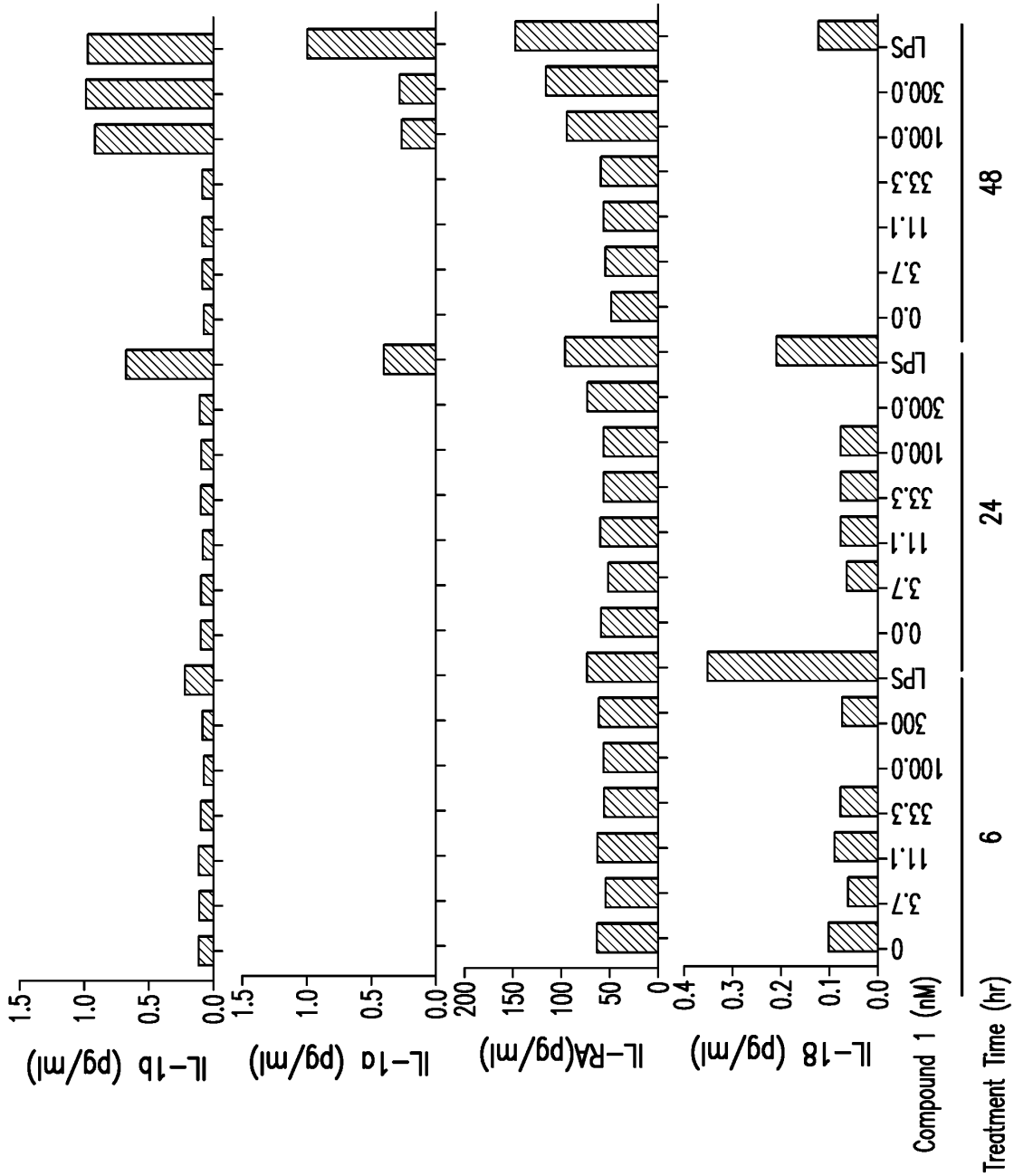

IL-1b (pg/ml)
IL-1a (pg/ml)
IL-RA(pg/ml)
IL-18 (pg/ml)
Compound 1 (nM)
0
3.7
11.1
33.3
100.0
300
LPS
0.0
3.7
11.1
33.3
100.0
300.0
LPS
0.0
3.7
11.1
33.3
100.0
300.0
LPS
Treatment Time (hr)
6
24
48

FIG. 1B

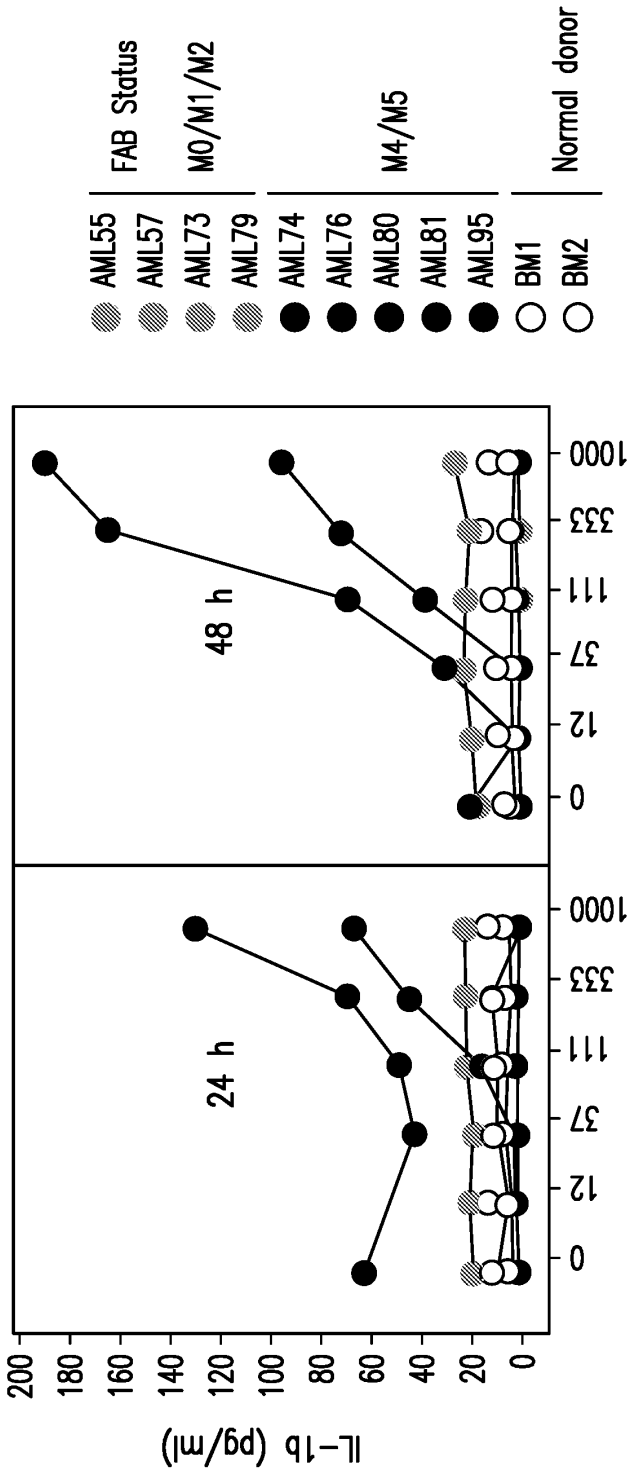
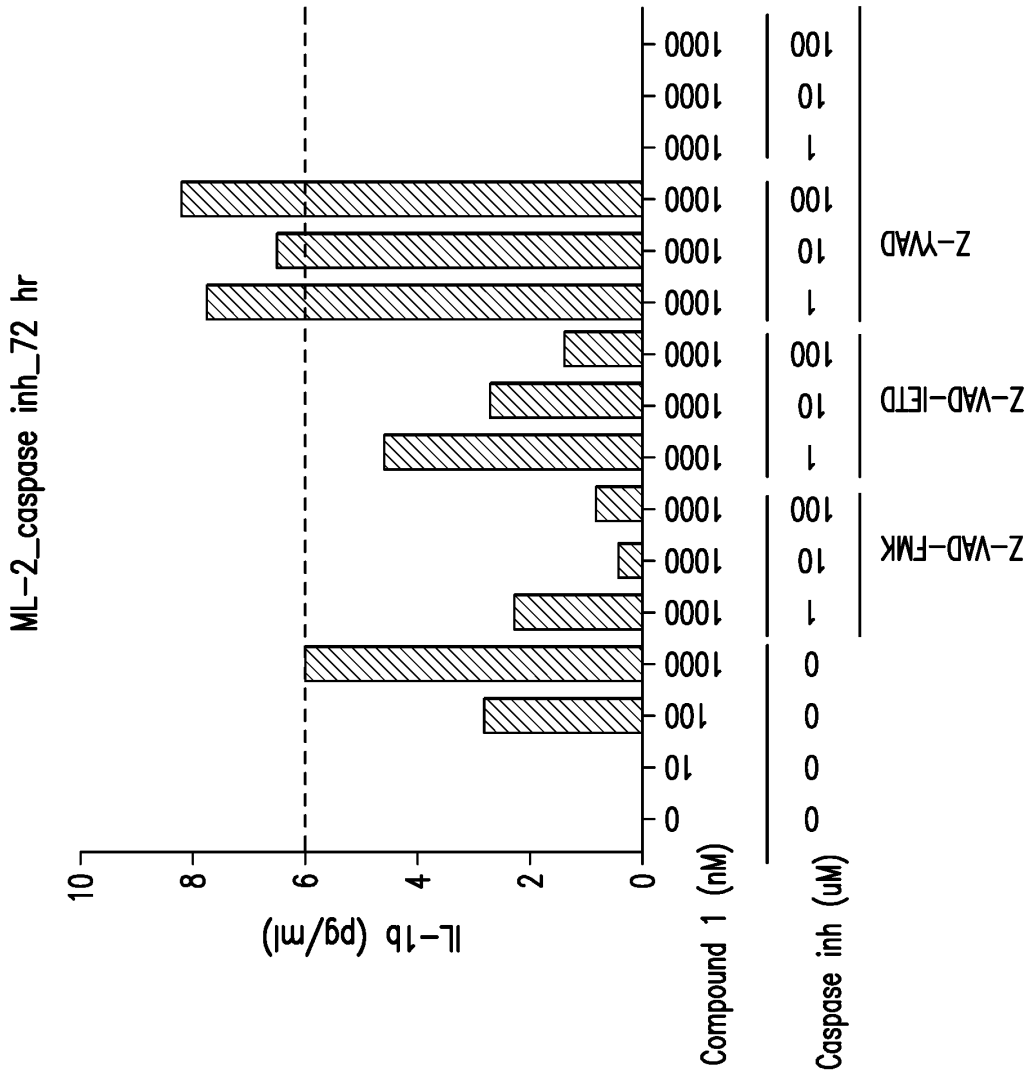

FAB Status
M0/M1/M2
M4/M5
Normal donor
AML55
AML57
AML73
AML79
AML74
AML76
AML80
AML81
AML95
BM1
BM2
48 h
24 h
0
12
37
111
333
1000
IL-1b (pg/ml)
0
20
40
60
80
100
120
140
160
180
200

FIG. 1C

FIG. 2A


ML-2_caspase inh_72 hr
IL-1b (pg/ml)
0
2
4
6
8
10
Compound 1 (nM)
0
10
100
1000
Caspase inh (uM)
0
0
0
0
Z-VAD-FMK
1
10
100
Z-VAD-IETD
1
10
100
Z-YVAD
1
10
100

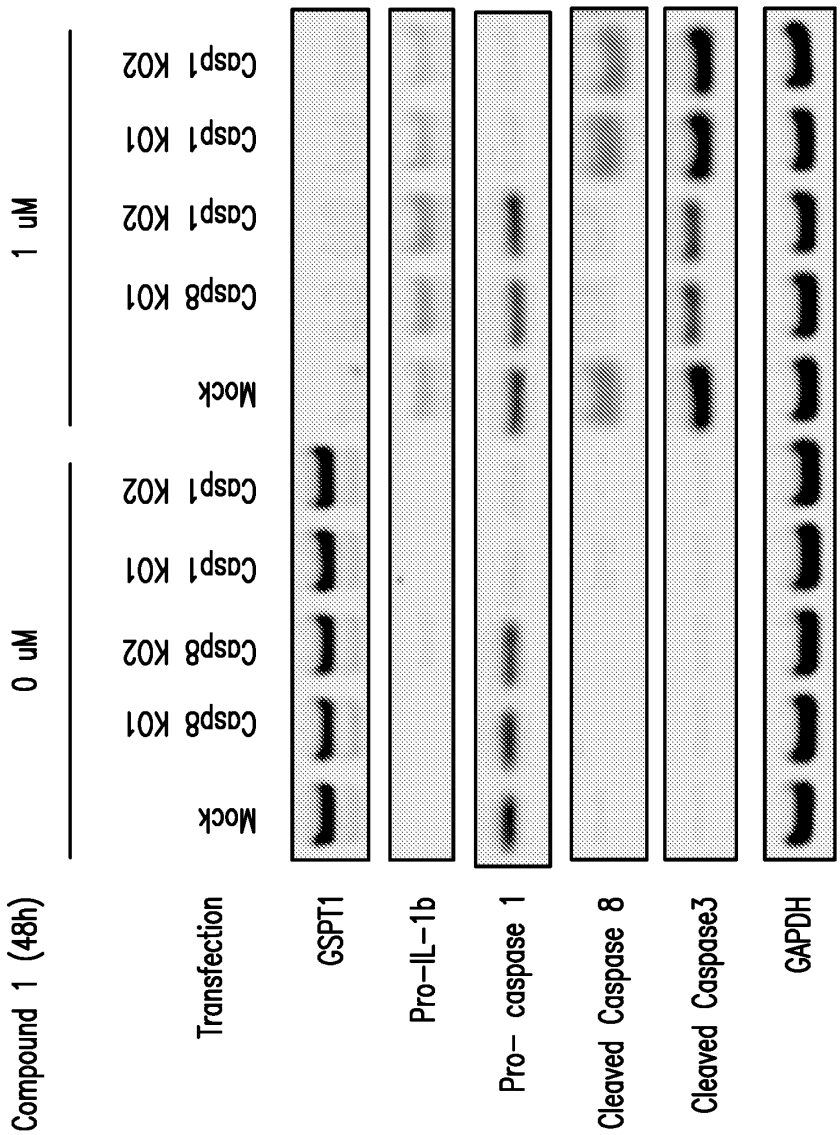

Compound 1 (48h)
0 uM
1 uM
Transfection
Mock
Casp8 KO1
Casp8 KO2
Casp1 KO1
Casp1 KO2
Mock
Casp8 KO1
Casp1 KO1
Casp1 KO2
GSPT1
Pro-IL-1b
Pro- caspase 1
Cleaved Caspase 8
Cleaved Caspase3
GAPDH

FIG. 2B

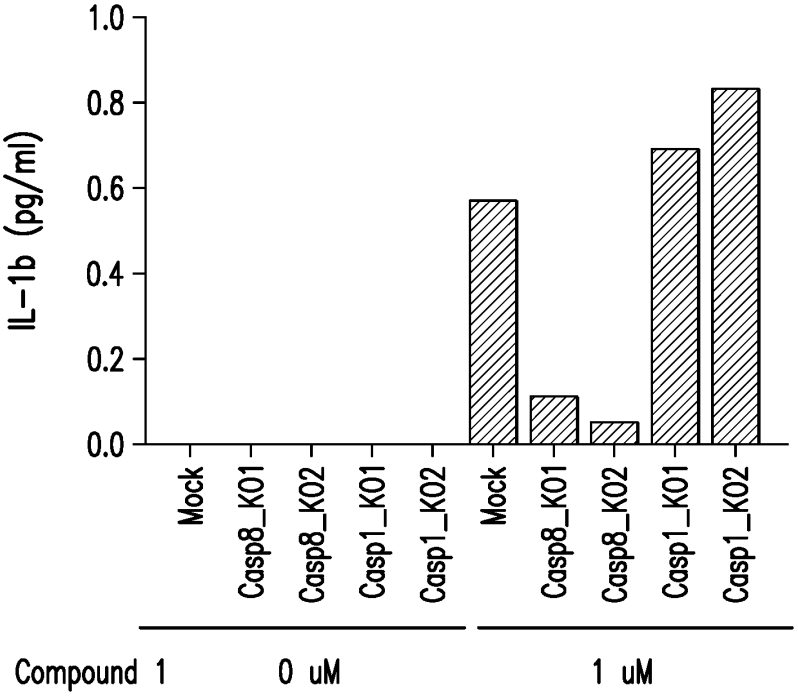

IL-1b (pg/ml)
1.0
0.8
0.6
0.4
0.2
0.0
Mock
Casp8_K01
Casp8_K02
Casp1_K01
Casp1_K02
Mock
Casp8_K01
Casp8_K02
Casp1_K01
Casp1_K02
Compound 1
0 uM
1 uM

FIG. 2C

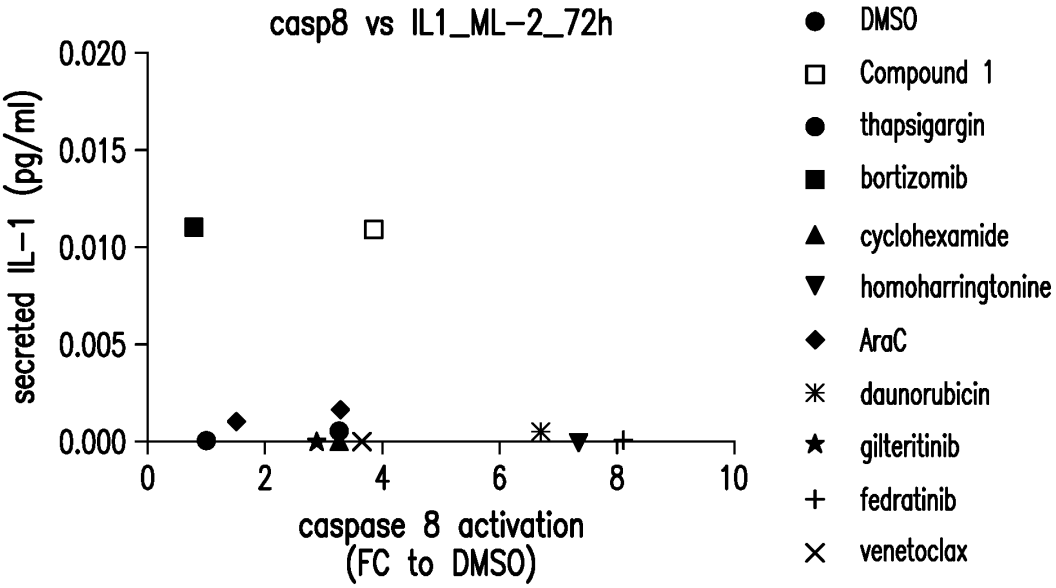

casp8 vs IL1_ML-2_72h
secreted IL-1 (pg/ml)
0.020
0.015
0.010
0.005
0.000
0
2
4
6
8
10
caspase 8 activation
(FC to DMSO)
DMSO
Compound 1
thapsigargin
bortizomib
cyclohexamide
homoharringtonine
AraC
daunorubicin
gilteritinib
fedratinib
venetoclax

FIG. 2D

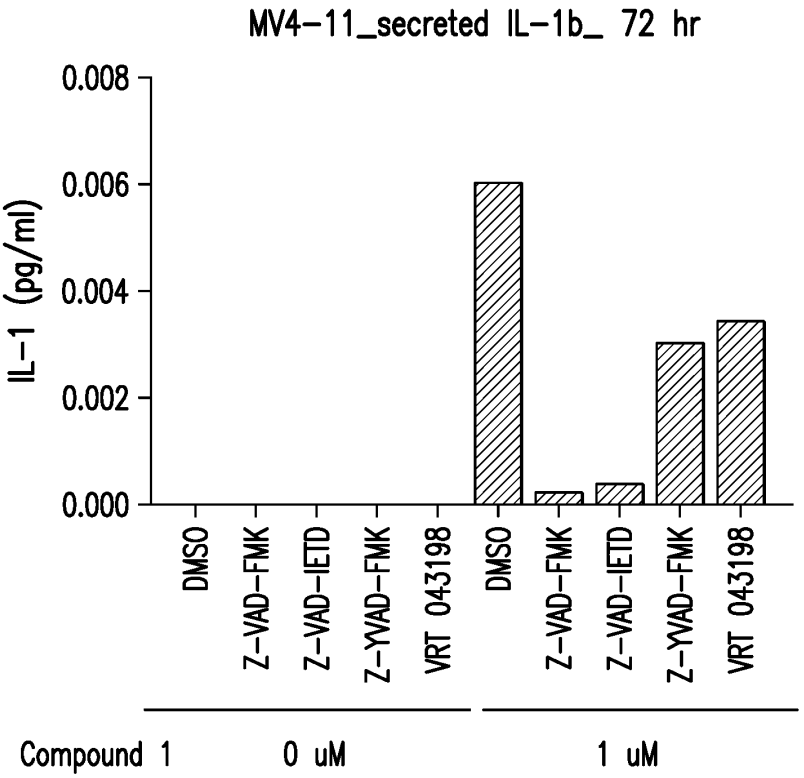

MV4-11_secreted IL-1b_ 72 hr
IL-1 (pg/ml)
0.008
0.006
0.004
0.002
0.000
DMSO
Z-VAD-FMK
Z-VAD-IETD
Z-YVAD-FMK
VRT 043198
DMSO
Z-VAD-FMK
Z-VAD-IETD
Z-YVAD-FMK
VRT 043198
Compound 1
0 uM
1 uM

FIG. 3A

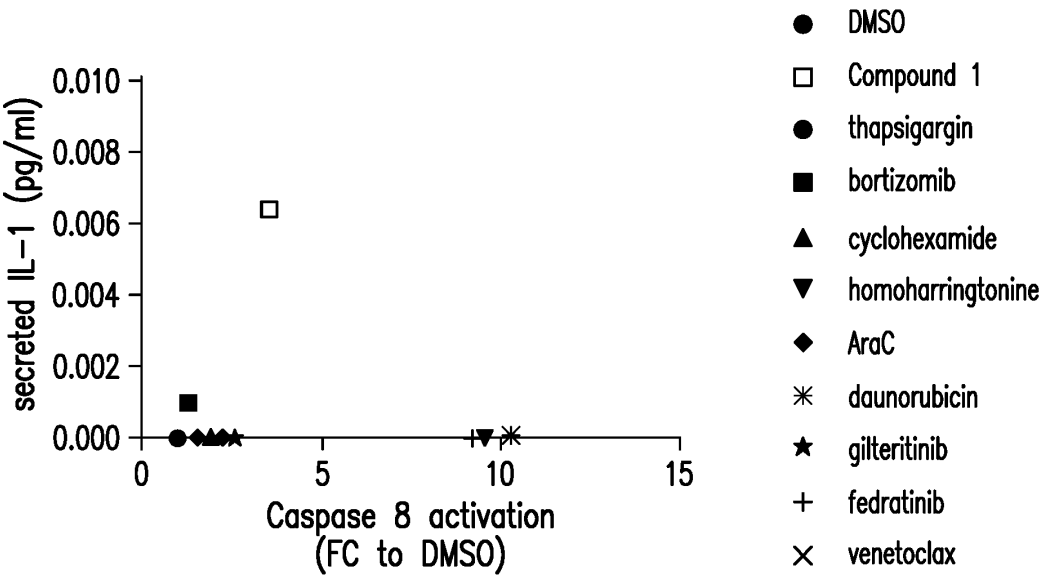

secreted IL-1 (pg/ml)
0.010
0.008
0.006
0.004
0.002
0.000
0
5
10
15
Caspase 8 activation
(FC to DMSO)
DMSO
Compound 1
thapsigargin
bortizomib
cyclohexamide
homoharringtonine
AraC
daunorubicin
gilteritinib
fedratinib
venetoclax

FIG. 3B

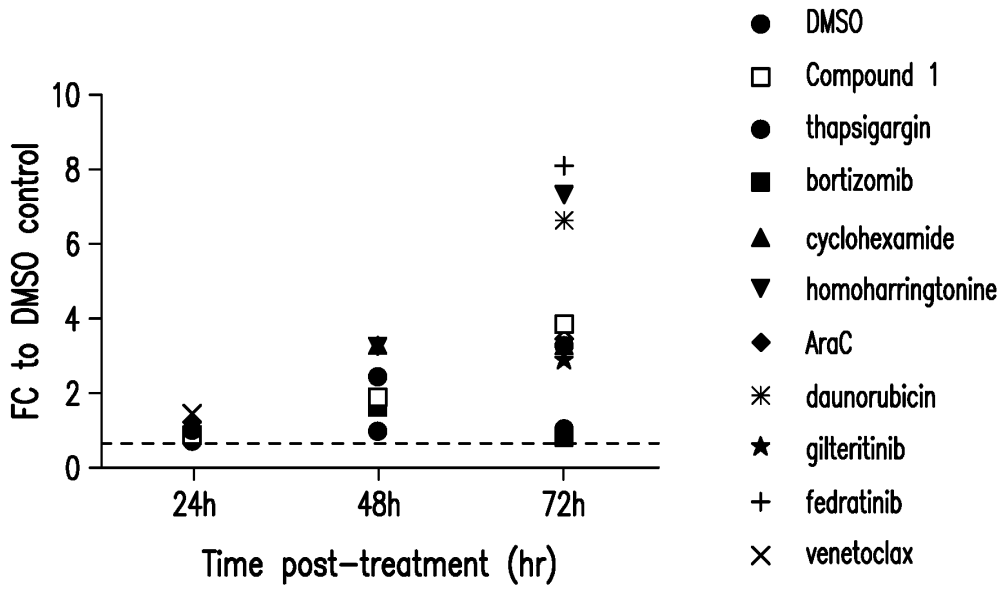

FC to DMSO control
10
8
6
4
2
0
24h
48h
72h
Time post-treatment (hr)
DMSO
Compound 1
thapsigargin
bortizomib
cyclohexamide
homoharringtonine
AraC
daunorubicin
gilteritinib
fedratinib
venetoclax

FIG. 3C

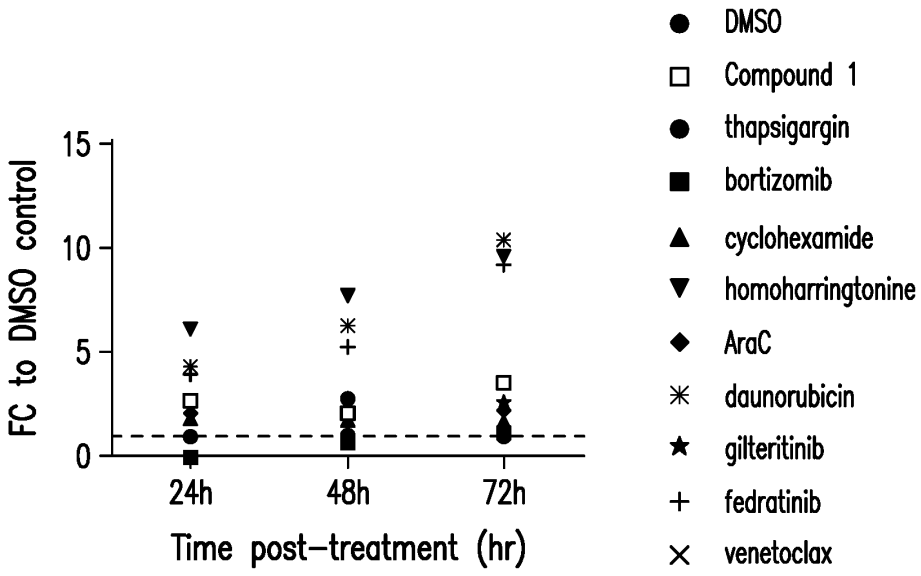

FC to DMSO control
15
10
5
0
24h
48h
72h
Time post-treatment (hr)
DMSO
Compound 1
thapsigargin
bortizomib
cyclohexamide
homoharringtonine
AraC
daunorubicin
gilteritinib
fedratinib
venetoclax

FIG. 3D

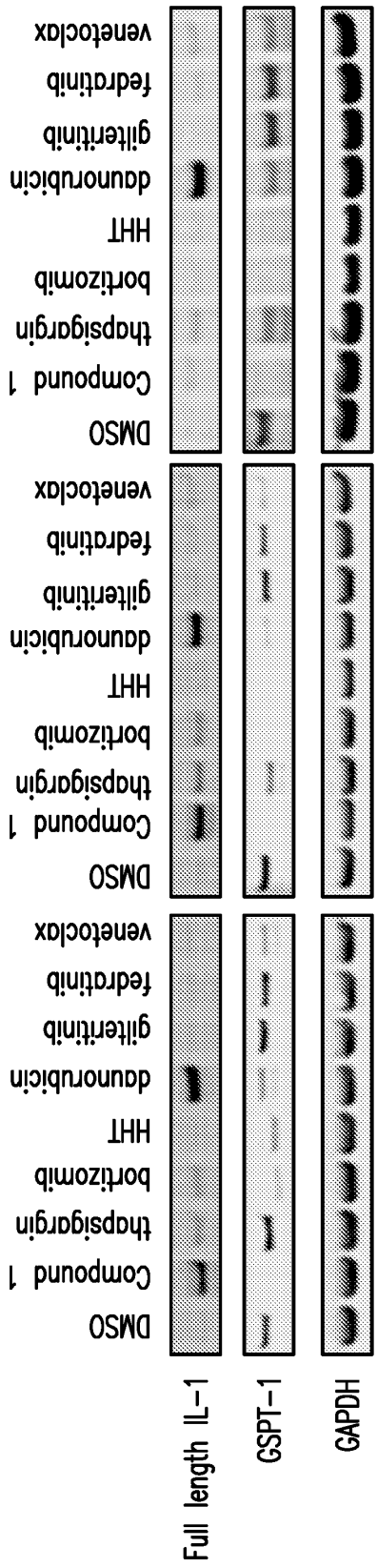

Full length IL-1
GSPT-1
GAPDH
DMSO
Compound 1
thapsigargin
bortizomib
HHT
daunorubicin
gilteritinib
fedratinib
venetoclax
DMSO
Compound 1
thapsigargin
bortizomib
HHT
daunorubicin
gilteritinib
fedratinib
venetoclax
DMSO
Compound 1
thapsigargin
bortizomib
HHT
daunorubicin
gilteritinib
fedratinib
venetoclax

FIG. 4A

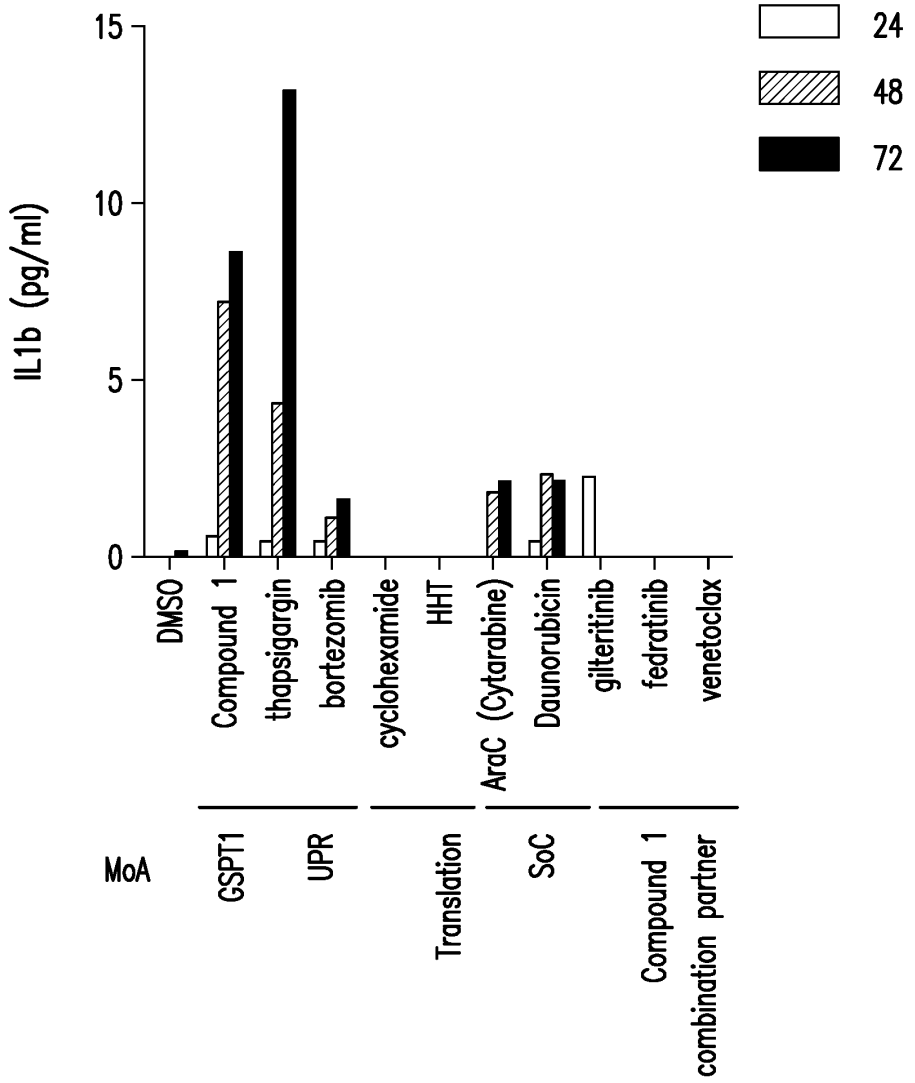

24
48
72
IL1b (pg/ml)
15
10
5
0
DMSO
Compound 1
thapsigargin
bortezomib
cyclohexamide
HHT
AraC (Cytarabine)
Daunorubicin
gilteritinib
fedratinib
venetoclax
MoA
GSPT1
UPR
Translation
SoC
Compound 1 combination partner

FIG. 4B

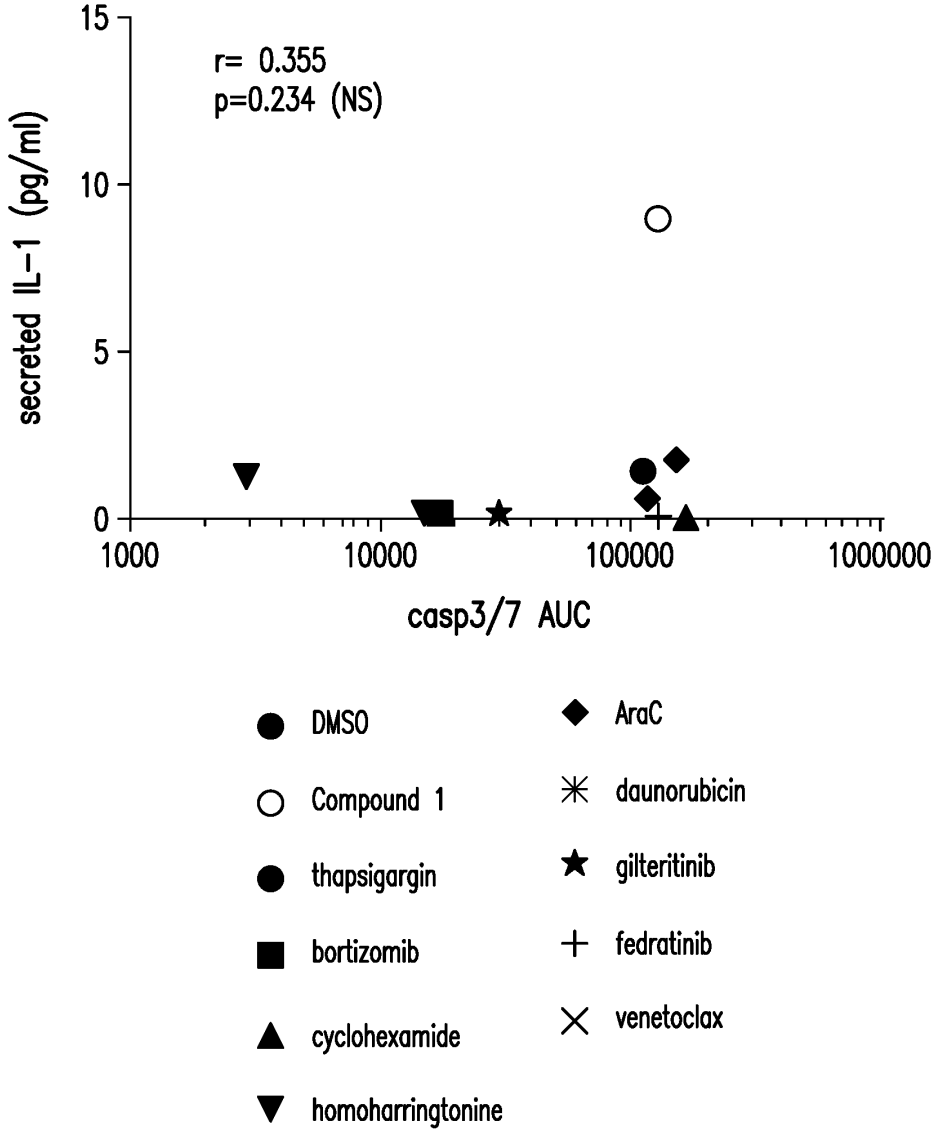

15
10
5
0
r= 0.355
p=0.234 (NS)
secreted IL-1 (pg/ml)
1000
10000
100000
1000000
casp3/7 AUC
DMSO
Compound 1
thapsigargin
bortizomib
cyclohexamide
homoharringtonine
AraC
daunorubicin
gilteritinib
fedratinib
venetoclax

FIG. 4C

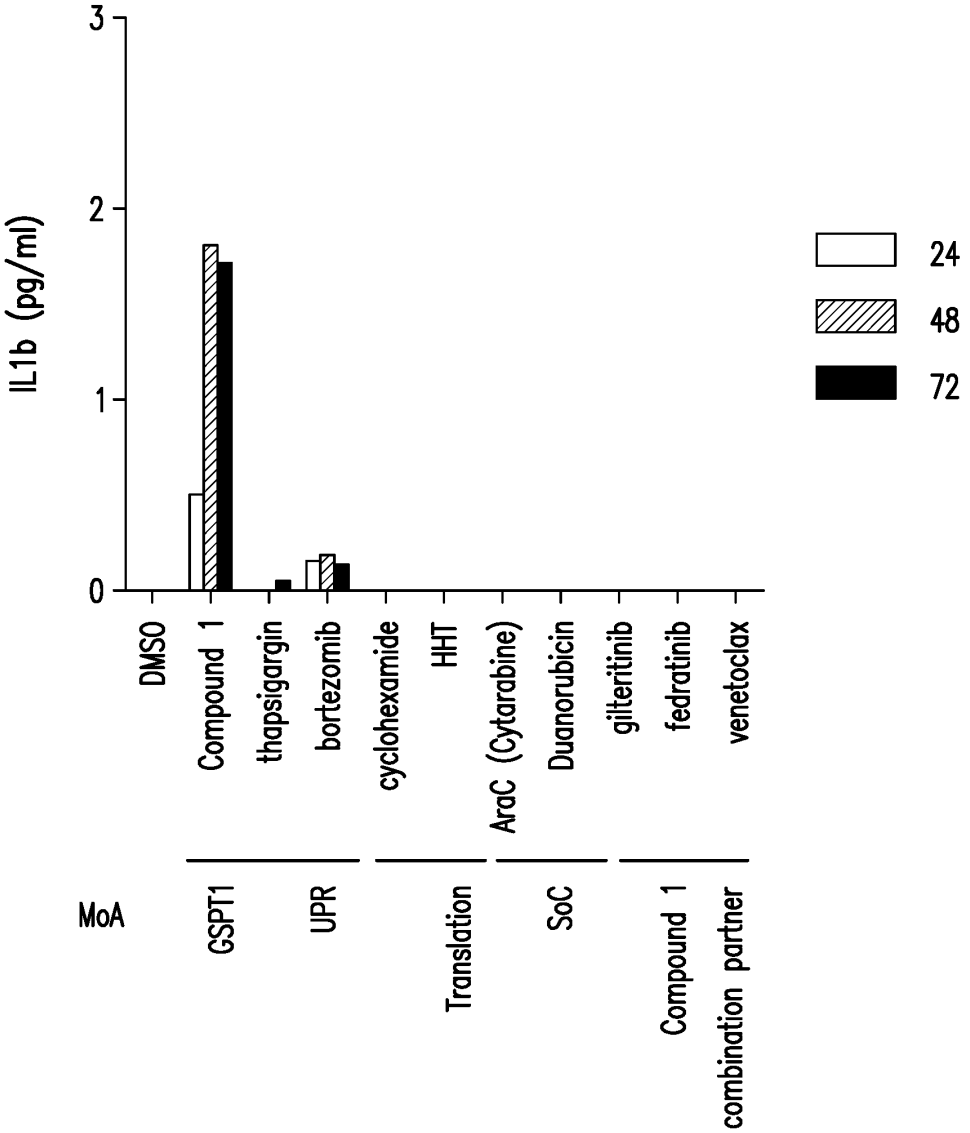

IL1b (pg/ml)
3
2
1
0
24
48
72
DMSO
Compound 1
thapsigargin
bortezomib
cycloheximide
HHT
AraC (Cytarabine)
Duanorubicin
gilteritinib
fedratinib
venetoclax
MoA
GSPT1
UPR
Translation
SoC
Compound 1 combination partner

FIG. 5A

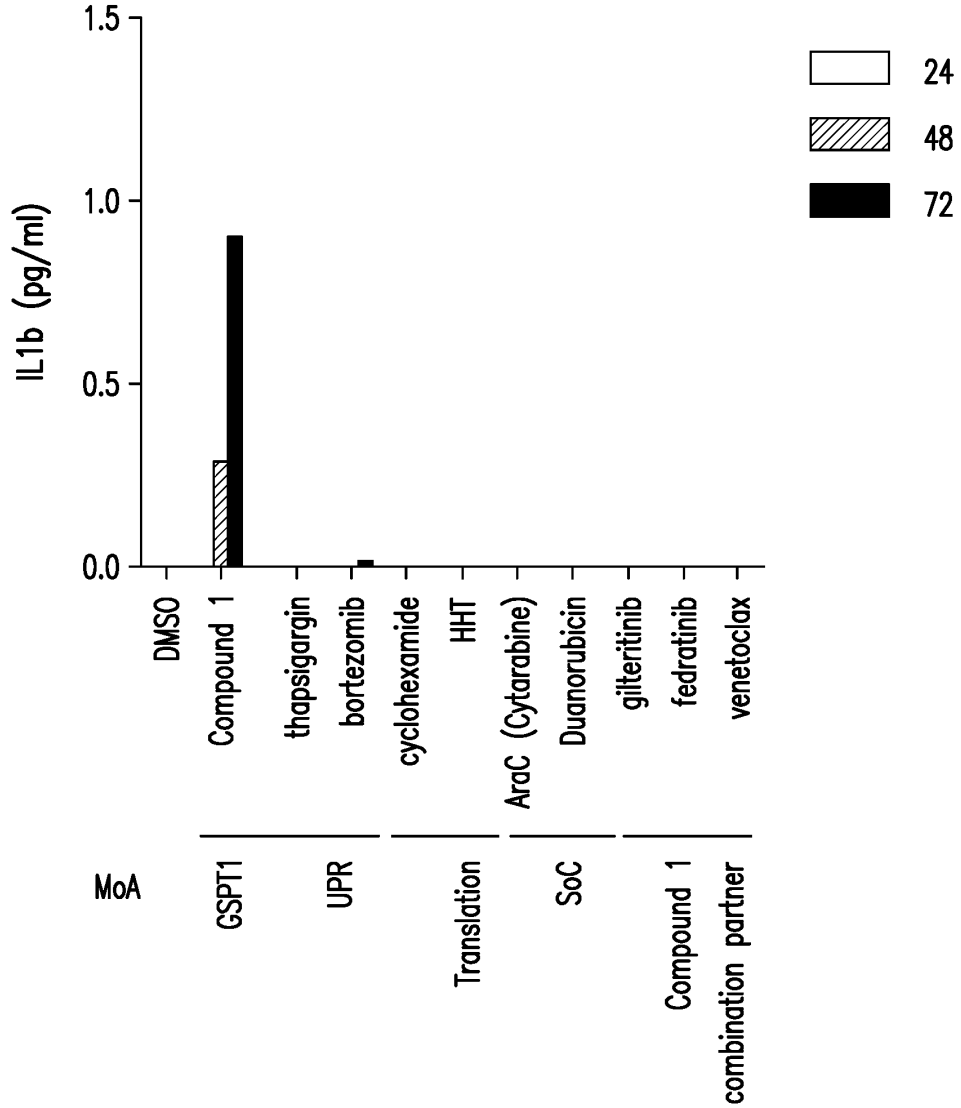

1.5
1.0
0.5
0.0
IL1b (pg/ml)
24
48
72
DMSO
Compound 1
thapsigargin
bortezomib
cyclohexamide
HHT
AraC (Cytarabine)
Duanorubicin
gilteritinib
fedratinib
venetoclax
MoA
GSPT1
UPR
Translation
SoC
Compound 1 combination partner

FIG. 5B

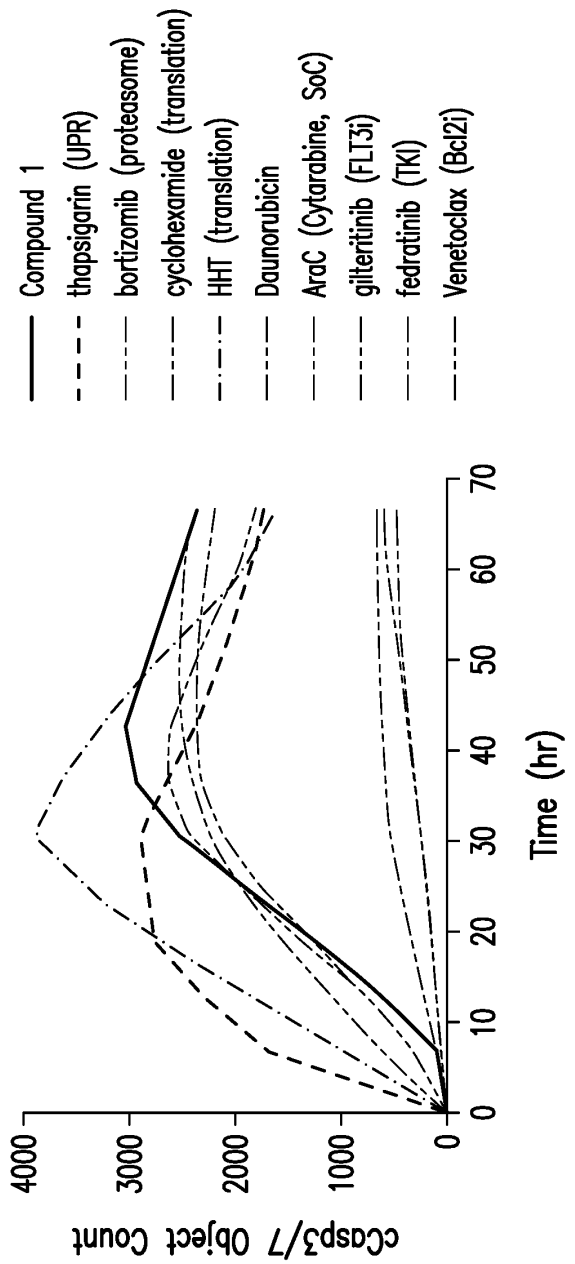

Compound 1
thapsigarin (UPR)
bortizomib (proteasome)
cyclohexamide (translation)
HHT (translation)
Daunorubicin
AraC (Cytarabine, SoC)
gilteritinib (FLT3i)
fedratinib (TKI)
Venetoclax (Bcl2i)
cCasp3/7 Object Count
4000
3000
2000
1000
0
0
10
20
30
40
50
60
70
Time (hr)

FIG. 6A

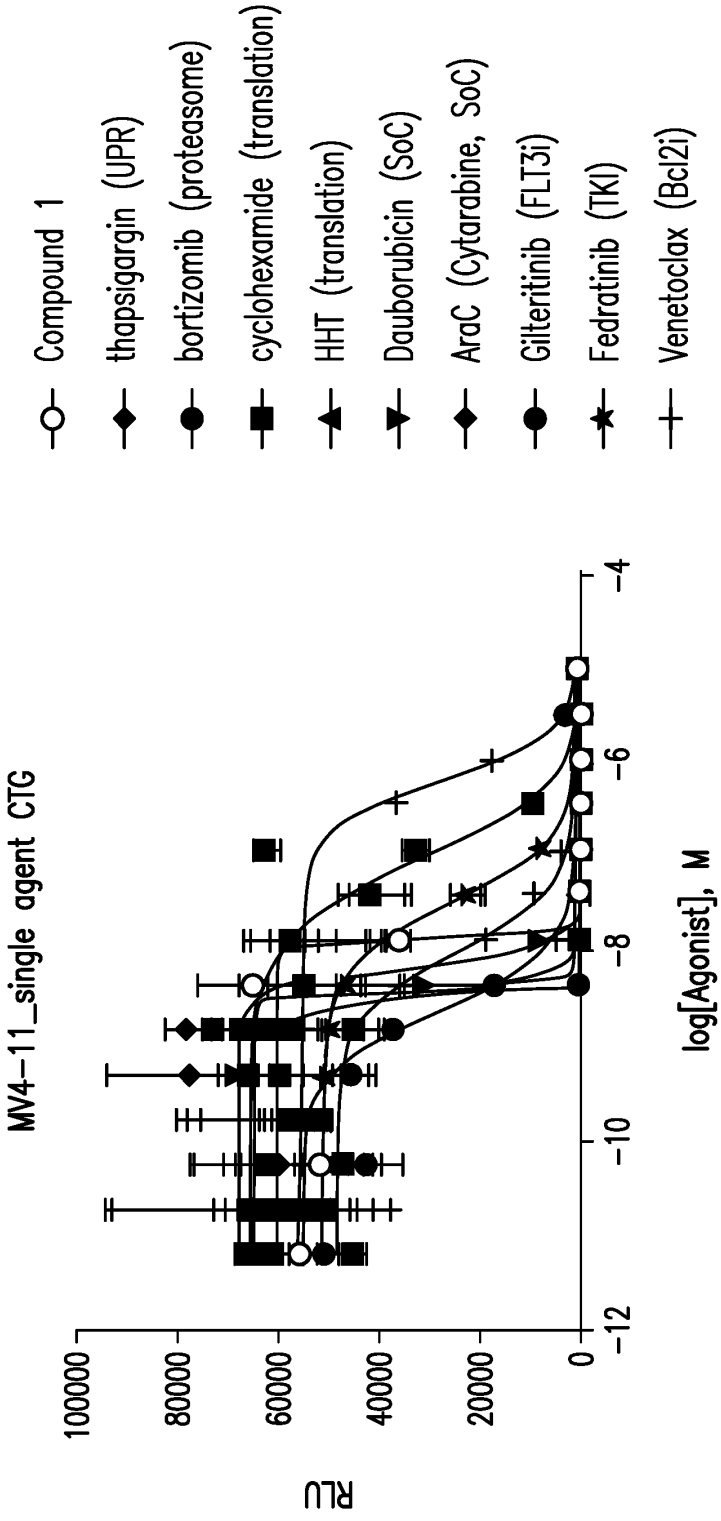

Compound 1
thapsigargin (UPR)
bortizomib (proteasome)
cyclohexamide (translation)
HHT (translation)
Dauborubicin (SoC)
AraC (Cytarabine, SoC)
Gilteritinib (FLT3i)
Fedratinib (TKI)
Venetoclax (Bcl2i)
MV4-11_single agent CTG
RLU
100000
80000
60000
40000
20000
0
-12
-10
-8
-6
-4
log[Agonist], M

FIG. 6B

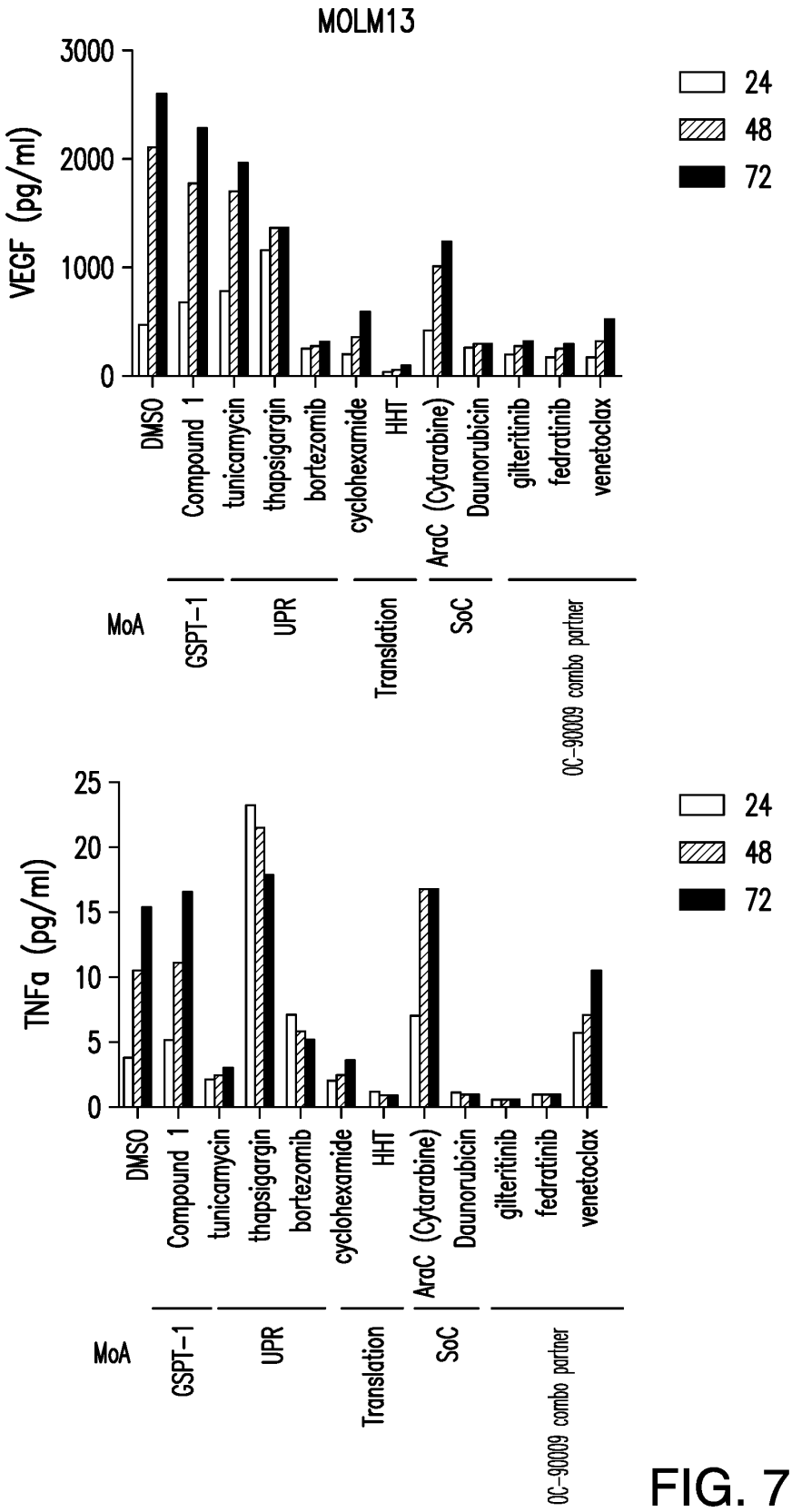

MOLM13
VEGF (pg/ml)
3000
2000
1000
0
24
48
72
DMSO
Compound 1
tunicamycin
thapsigargin
bortezomib
cyclohexamide
HHT
AraC (Cytarabine)
Daunorubicin
gilteritinib
fedratinib
venetoclax
MoA
GSPT-1
UPR
Translation
SoC
OC-90009 combo partner
TNFa (pg/ml)
25
20
15
10
5
0
24
48
72
DMSO
Compound 1
tunicamycin
thapsigargin
bortezomib
cyclohexamide
HHT
AraC (Cytarabine)
Daunorubicin
gilteritinib
fedratinib
venetoclax
MoA
GSPT-1
UPR
Translation
SoC
OC-90009 combo partner

FIG. 7

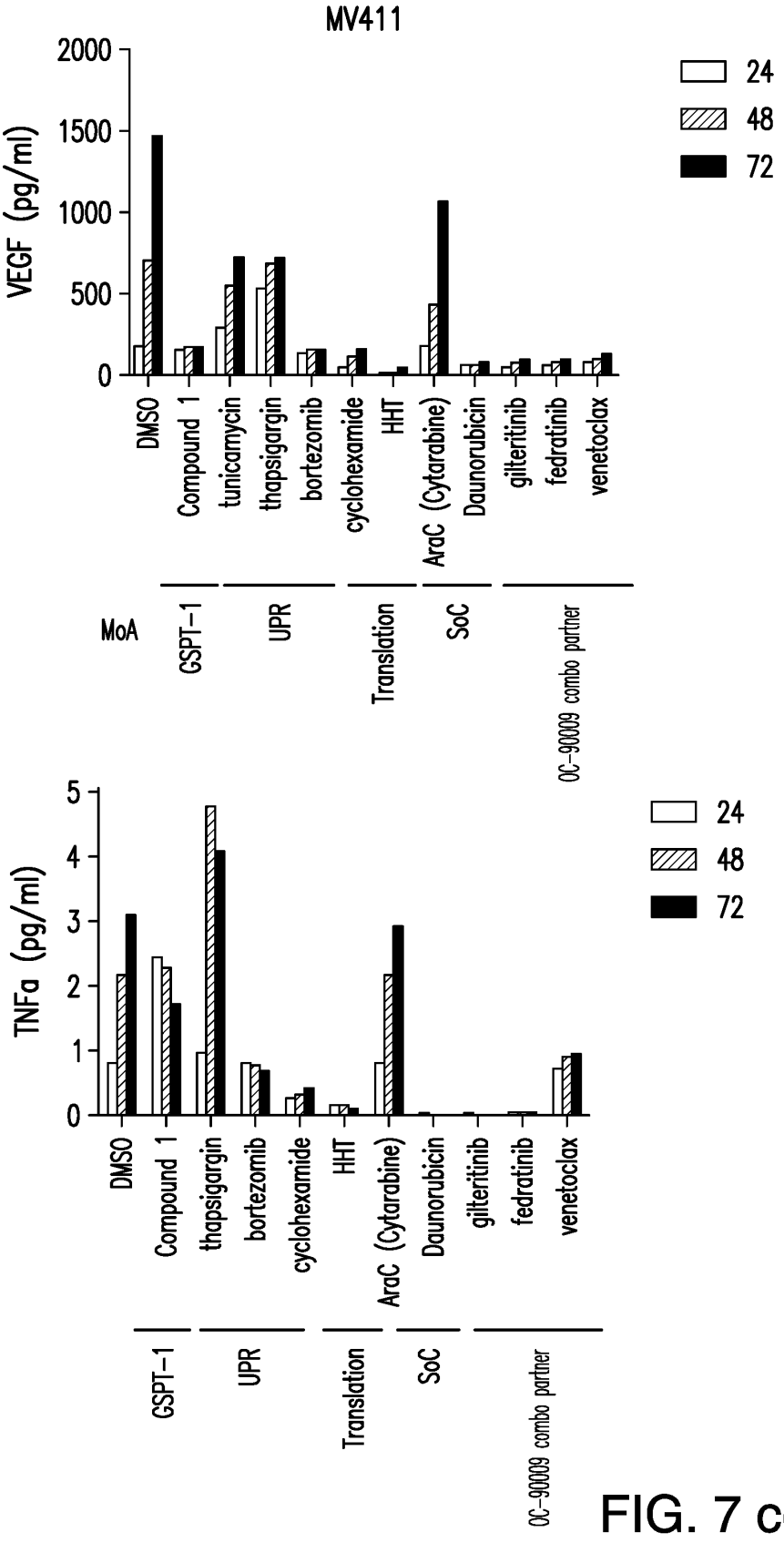


FIG. 7 continued

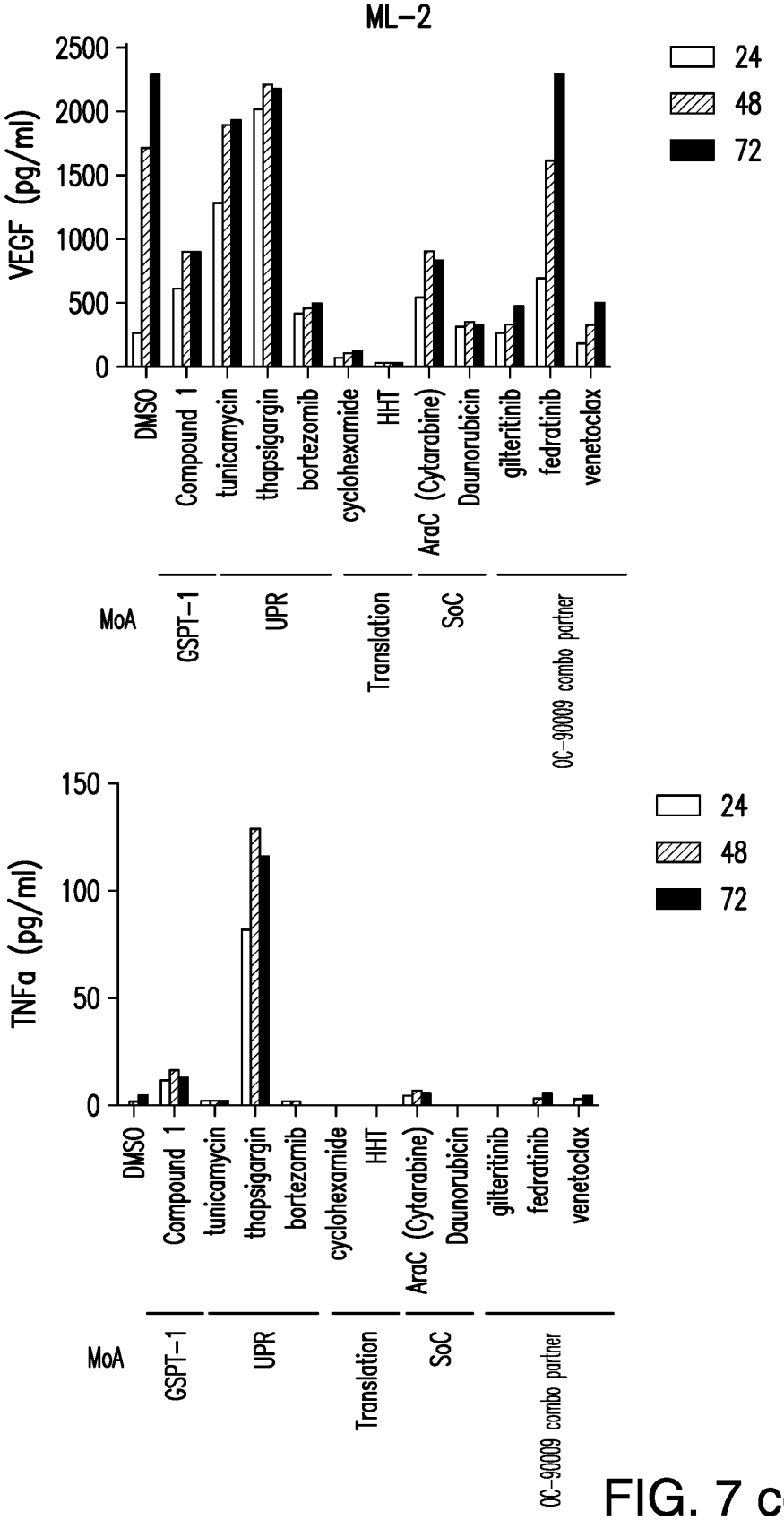


FIG. 7 continued

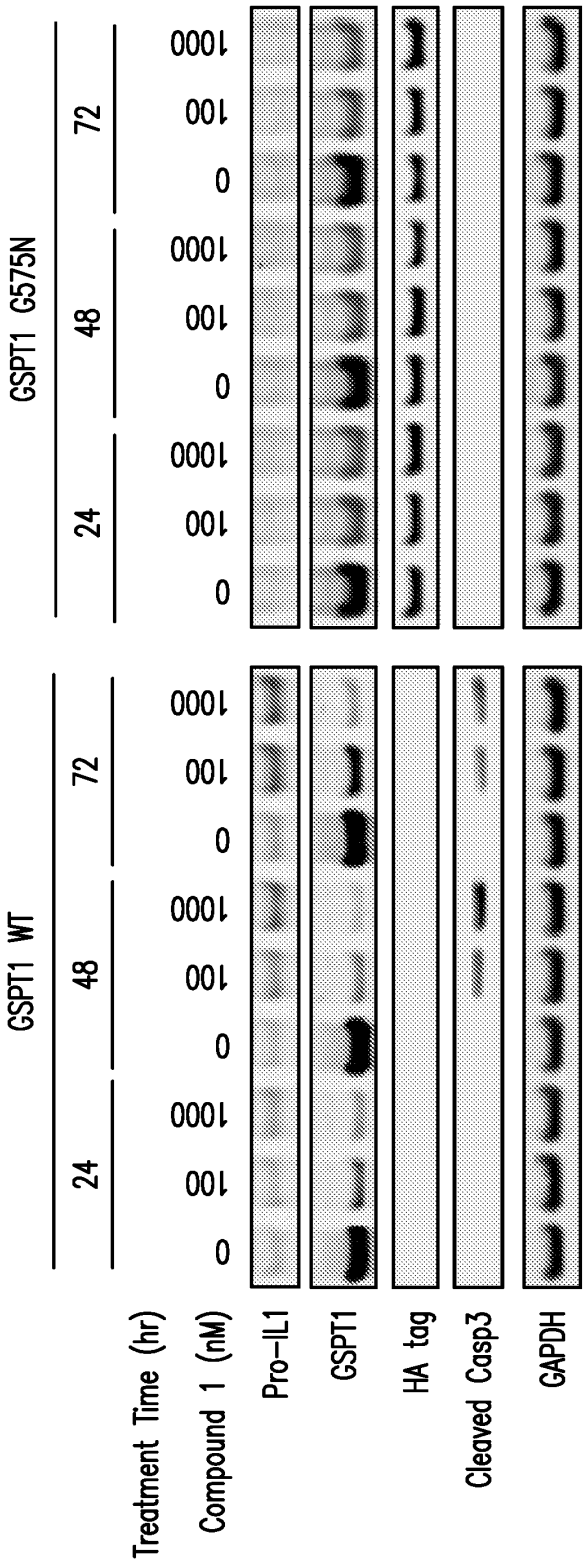

GSPT1 WT
GSPT1 G575N
24
48
72
0
100
1000
Treatment Time (hr)
Compound 1 (nM)
Pro-IL1
GSPT1
HA tag
Cleaved Casp3
GAPDH

FIG. 8A

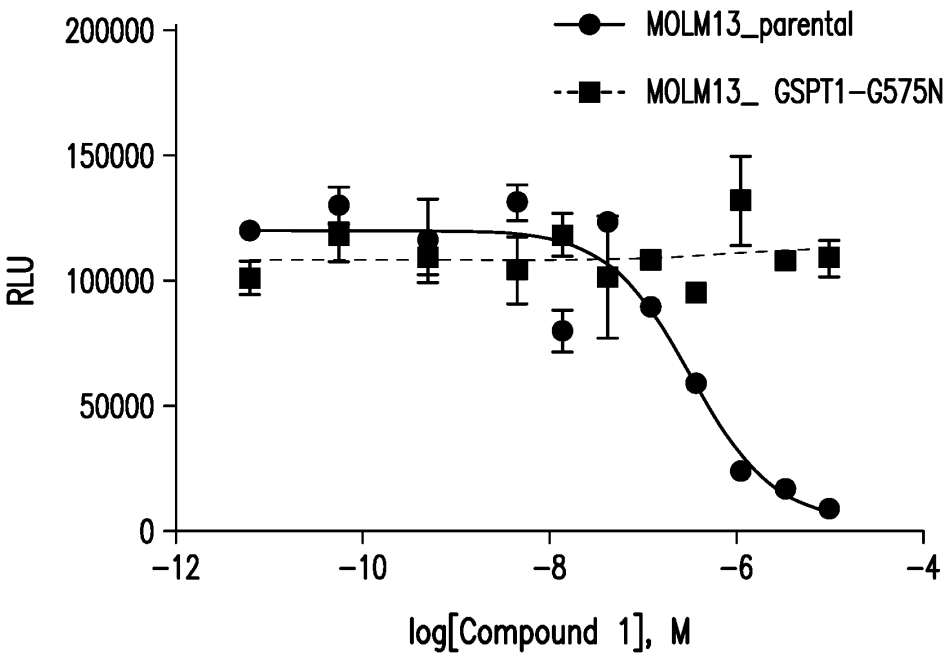

MOLM13_parental
MOLM13_ GSPT1-G575N
RLU
200000
150000
100000
50000
0
-12
-10
-8
-6
-4
log[Compound 1], M

FIG. 8B

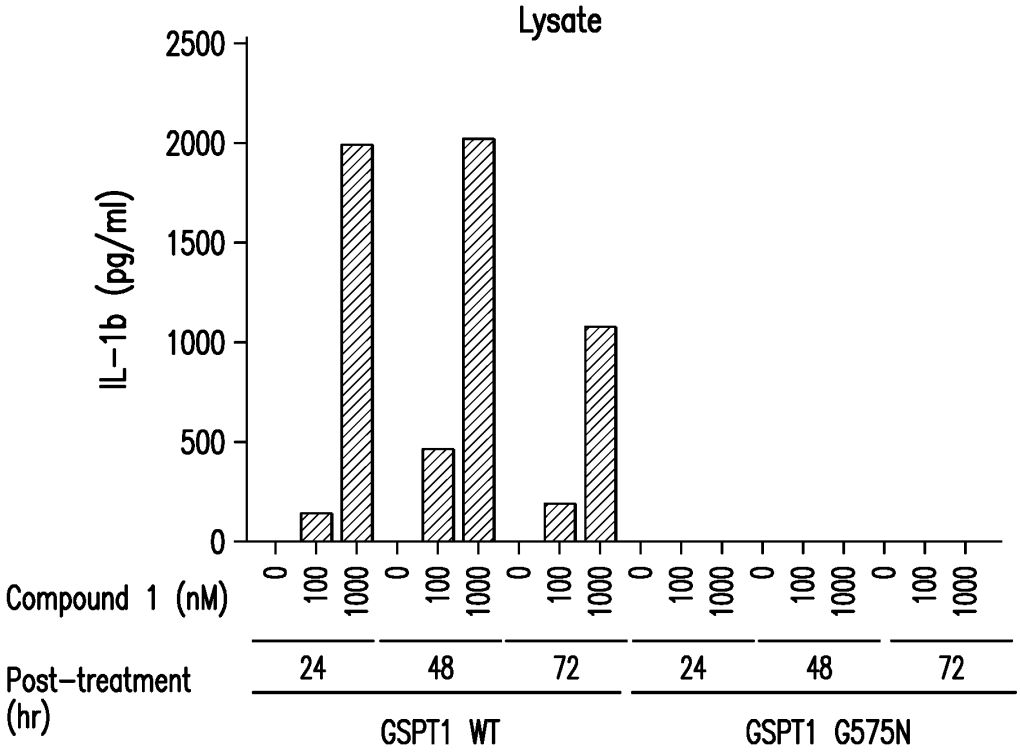

Lysate
IL-1b (pg/ml)
2500
2000
1500
1000
500
0
Compound 1 (nM)
0
100
1000
Post-treatment (hr)
24
48
72
GSPT1 WT
GSPT1 G575N

FIG. 8C

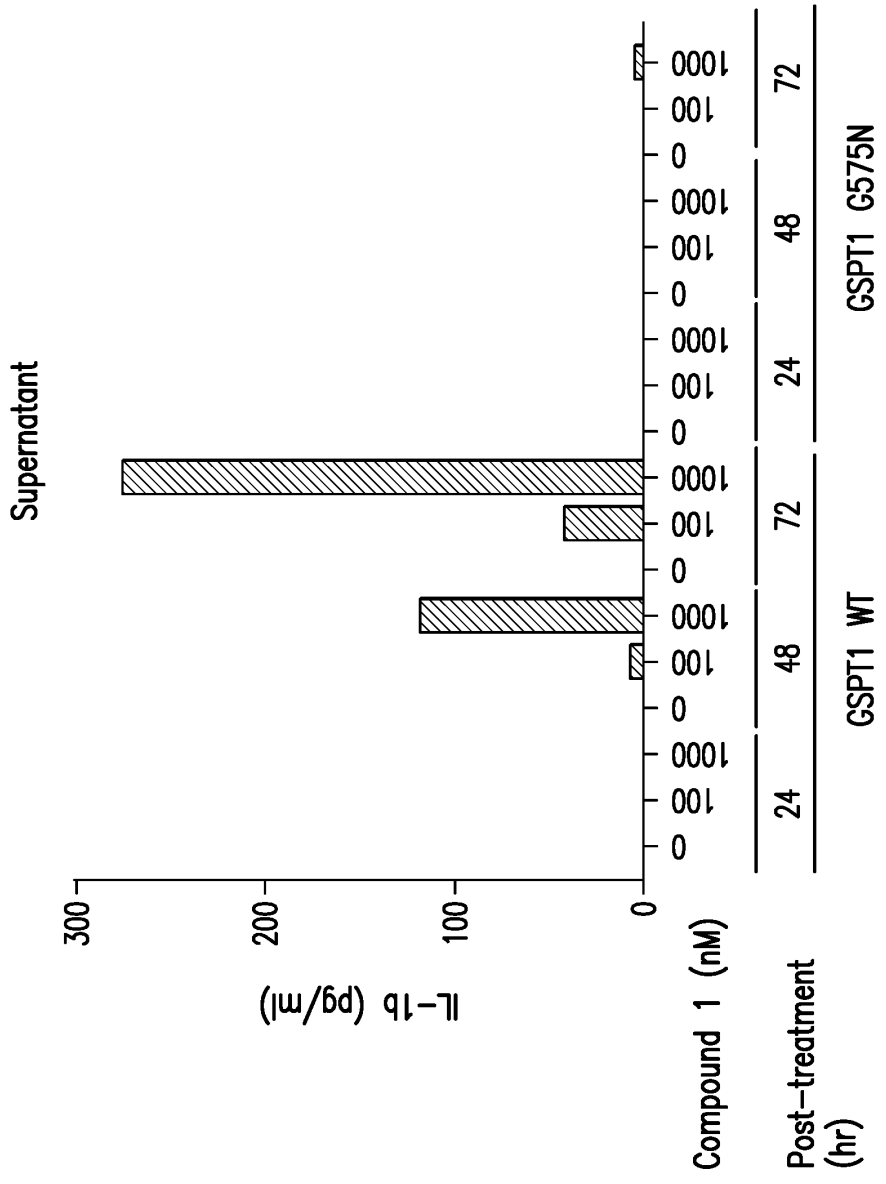

Supernatant
IL-1b (pg/ml)
300
200
100
0
Compound 1 (nM)
0
100
1000
Post-treatment (hr)
24
48
72
GSPT1 WT
GSPT1 G575N

FIG. 8D

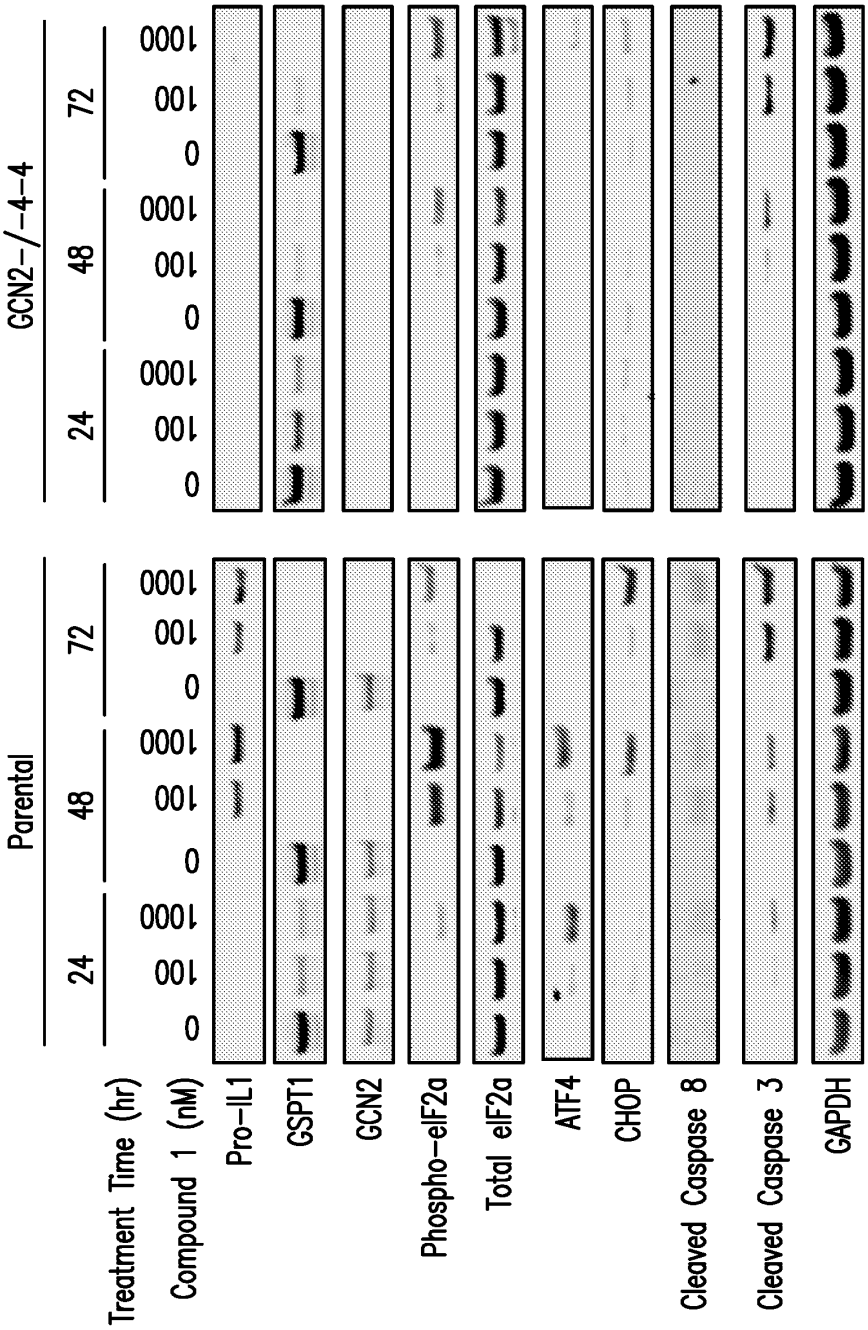

Parental
GCN2-/-4-4
Treatment Time (hr)
24
48
72
Compound 1 (nM)
0
100
1000
Pro-IL1
GSPT1
GCN2
Phospho-eIF2a
Total eIF2a
ATF4
CHOP
Cleaved Caspase 8
Cleaved Caspase 3
GAPDH

FIG. 9A

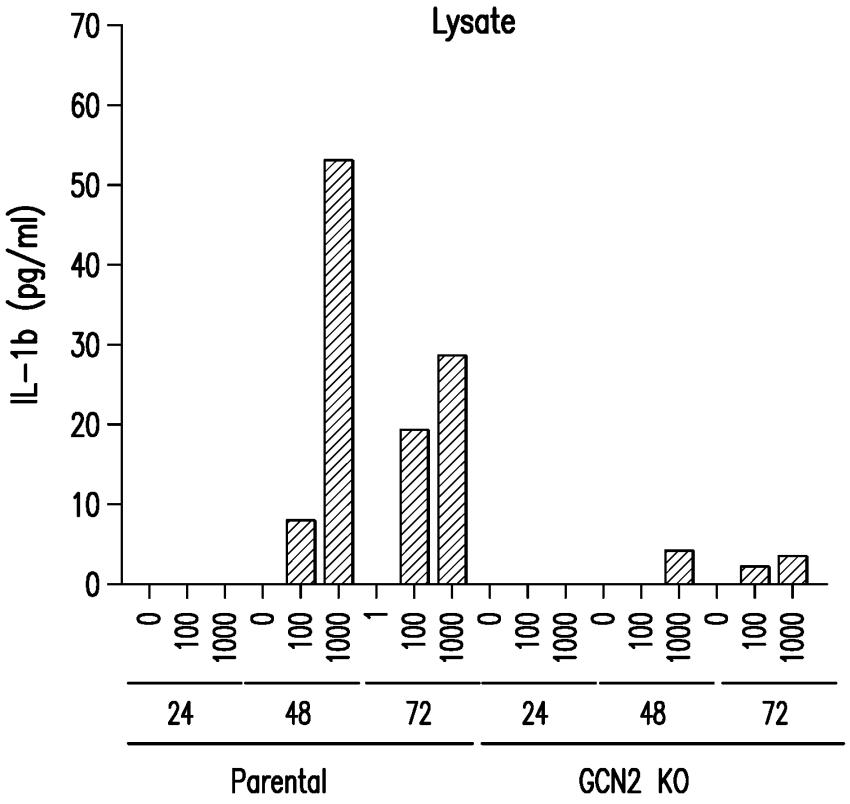

Lysate
IL-1b (pg/ml)
70
60
50
40
30
20
10
0
0 100 1000 0 100 1000 1 100 1000 0 100 1000 0 100 1000 0 100 1000
24 48 72 24 48 72
Parental
GCN2 KO

FIG. 9B

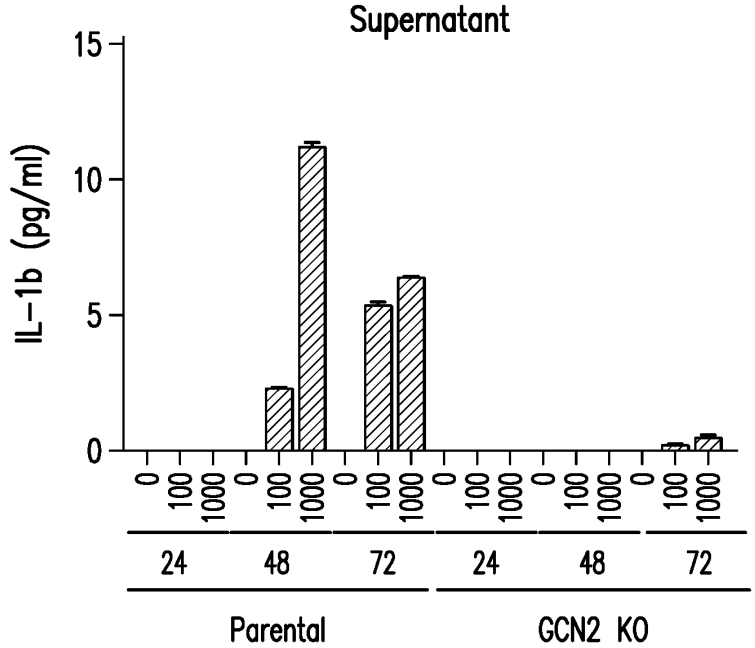

Supernatant
IL-1b (pg/ml)
15
10
5
0
0 100 1000 0 100 1000 0 100 1000 0 100 1000 0 100 1000 0 100 1000
24 48 72 24 48 72
Parental
GCN2 KO

FIG. 9C

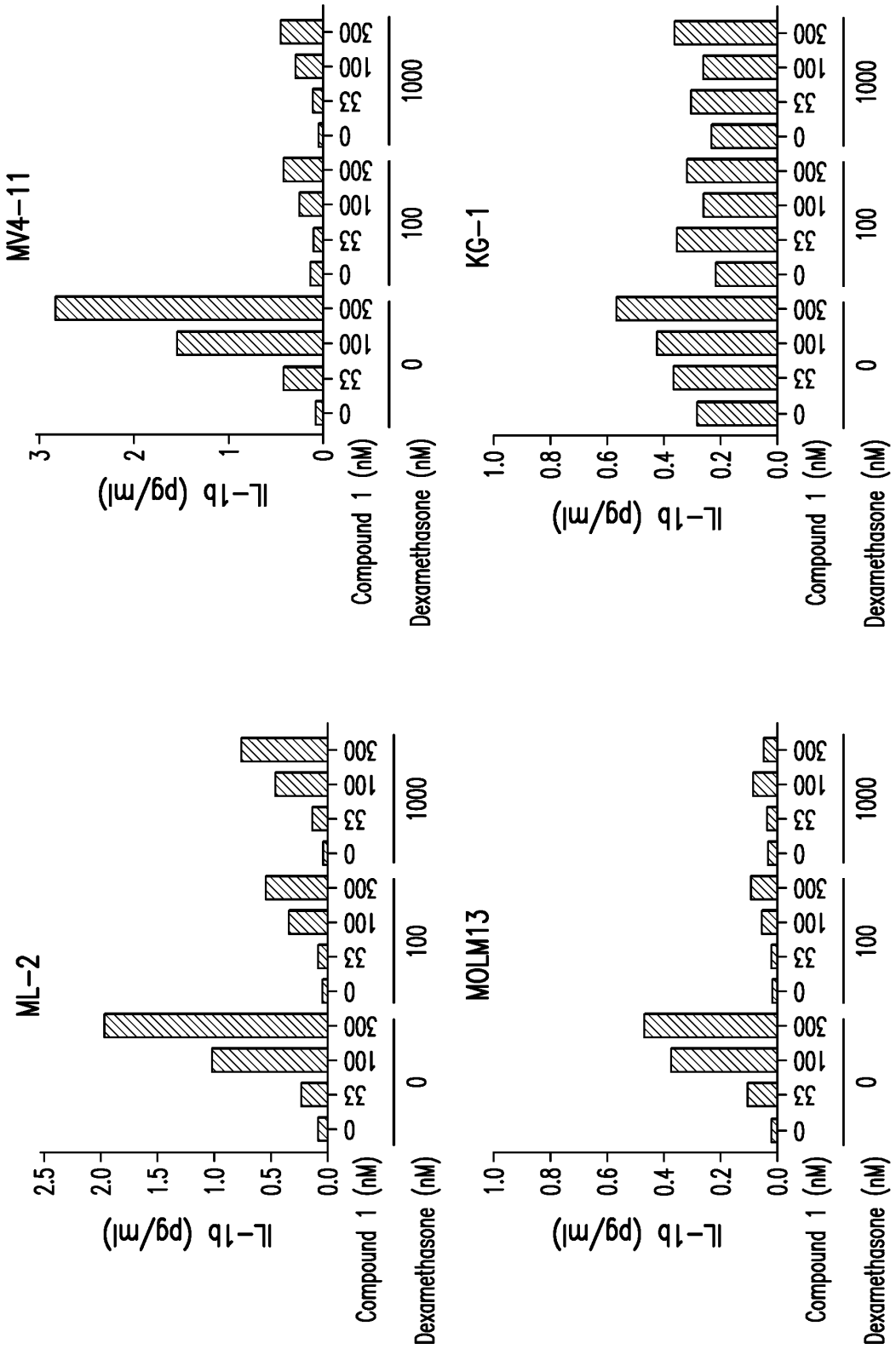

MV4-11
KG-1
ML-2
MOLM13
IL-1b (pg/ml)
Compound 1 (nM)
Dexamethasone (nM)
0
33
100
300
0
100
1000

FIG. 10A

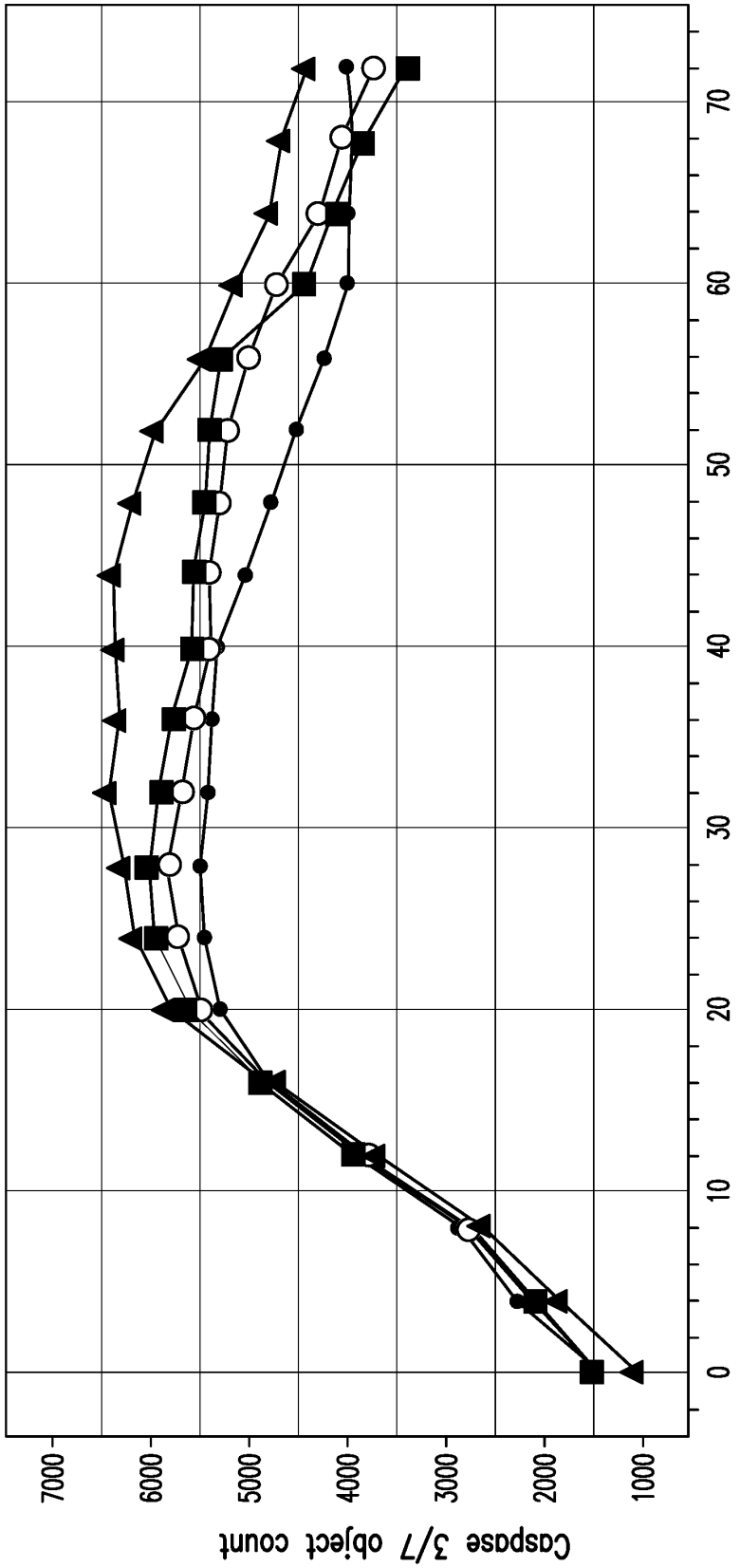

Caspase 3/7 object count
7000
6000
5000
4000
3000
2000
1000
0
10
20
30
40
50
60
70
Time (hours)

FIG. 10B

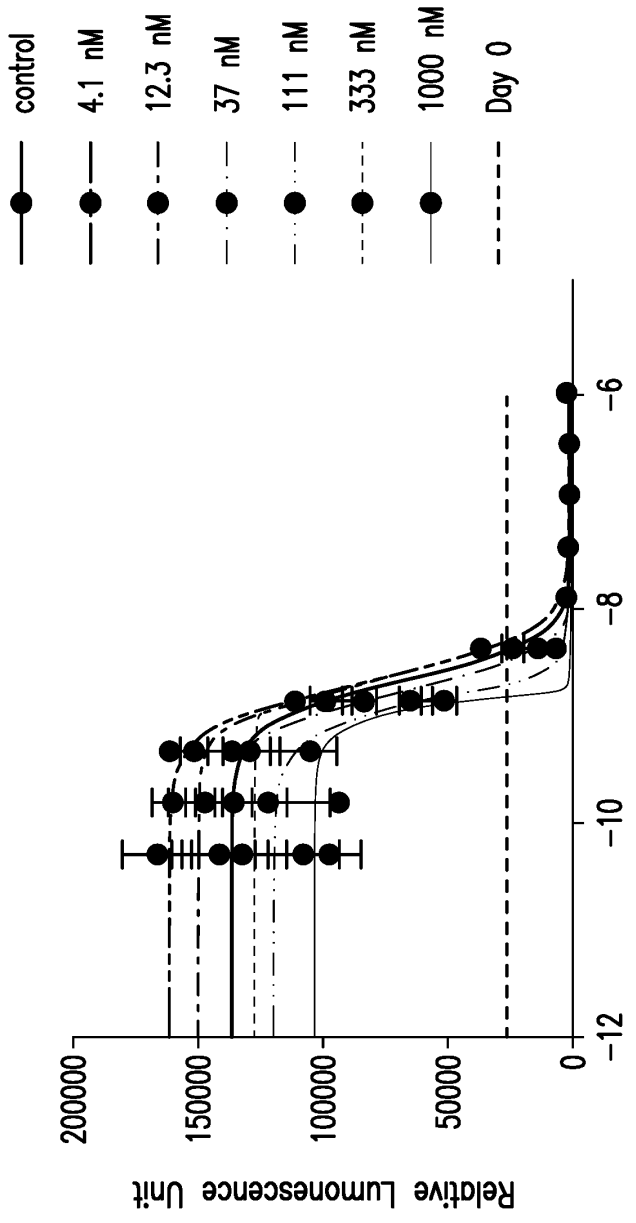

control
4.1 nM
12.3 nM
37 nM
111 nM
333 nM
1000 nM
Day 0
Relative Luminescence Unit
200000
150000
100000
50000
0
−12
−10
−8
−6
Compound 1(logM)

FIG. 10C

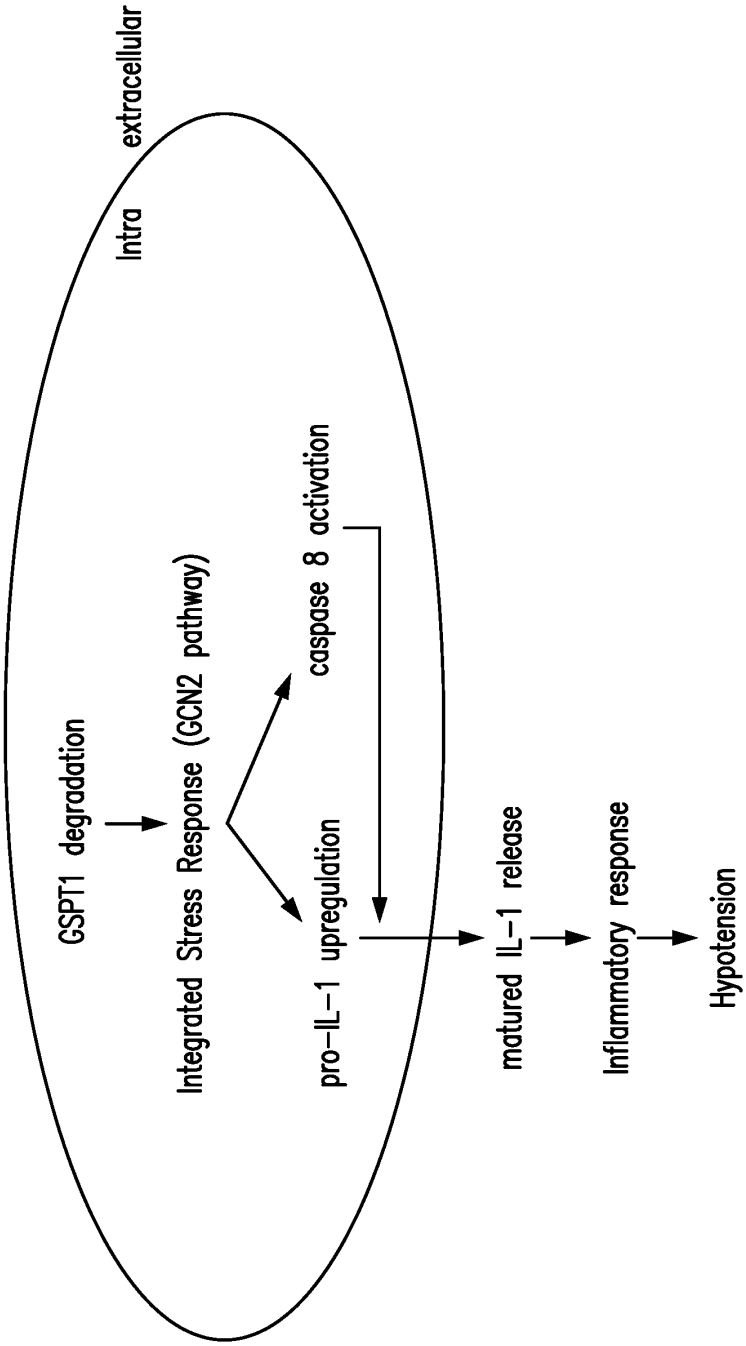

extracellular
Intra
GSPT1 degradation
Integrated Stress Response (GCN2 pathway)
caspase 8 activation
pro-IL-1 upregulation
matured IL-1 release
Inflammatory response
Hypotension

FIG. 11

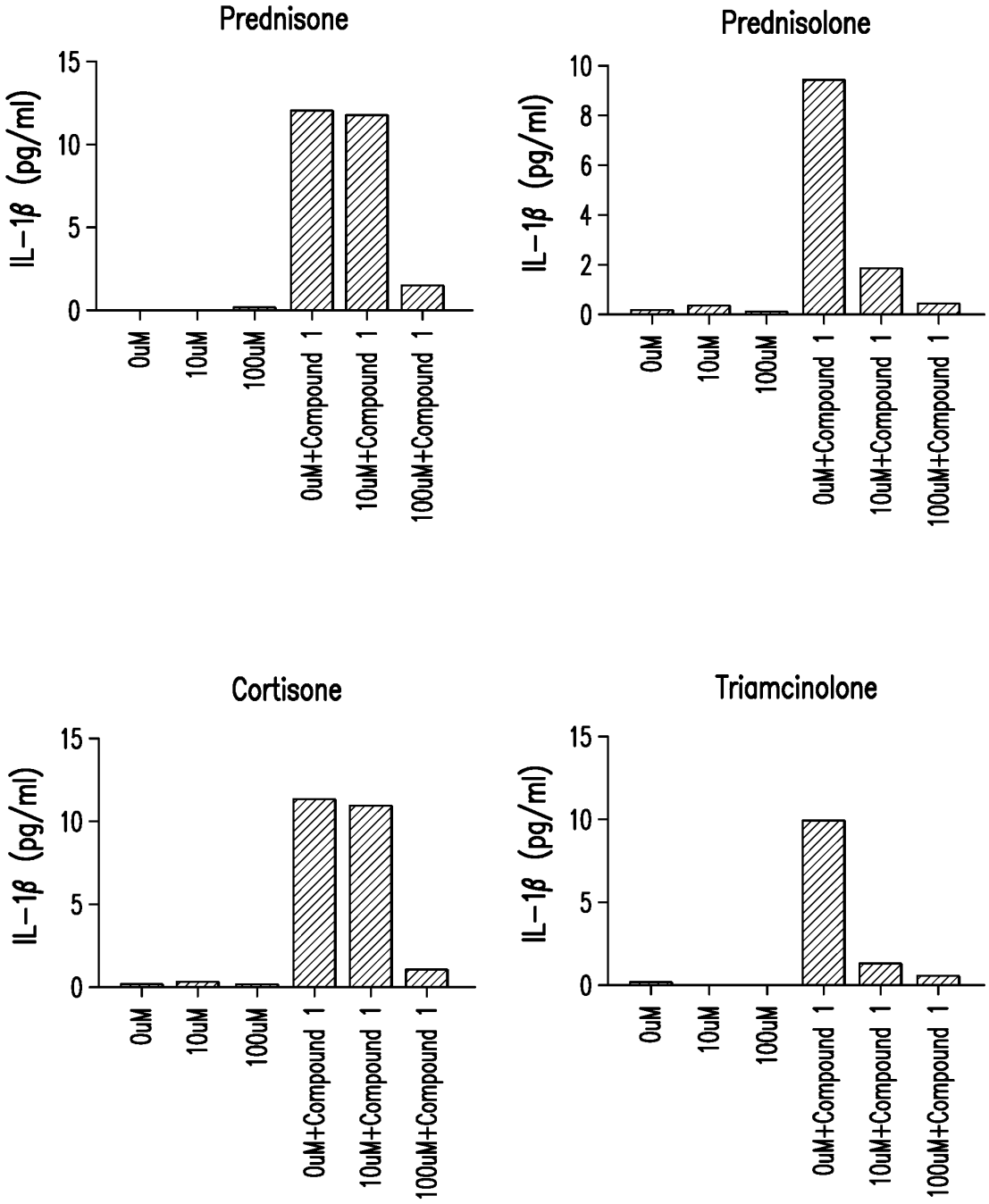

Prednisone
IL-1β (pg/ml)
15
10
5
0
0uM
10uM
100uM
0uM+Compound 1
10uM+Compound 1
100uM+Compound 1
Prednisolone
IL-1β (pg/ml)
10
8
6
4
2
0
0uM
10uM
100uM
0uM+Compound 1
10uM+Compound 1
100uM+Compound 1
Cortisone
IL-1β (pg/ml)
15
10
5
0
0uM
10uM
100uM
0uM+Compound 1
10uM+Compound 1
100uM+Compound 1
Triamcinolone
IL-1β (pg/ml)
15
10
5
0
0uM
10uM
100uM
0uM+Compound 1
10uM+Compound 1
100uM+Compound 1

FIG. 12

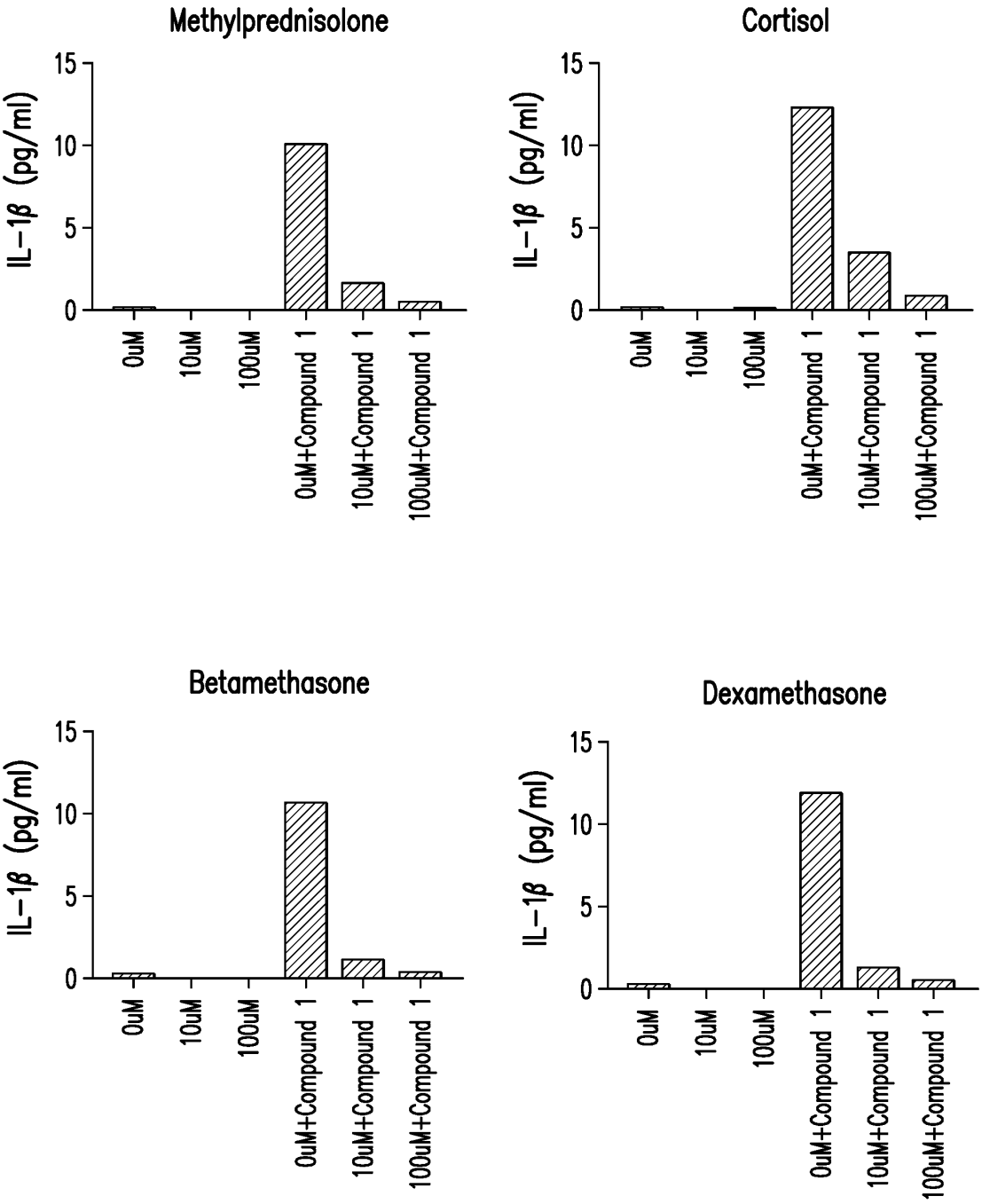


FIG. 12 continued

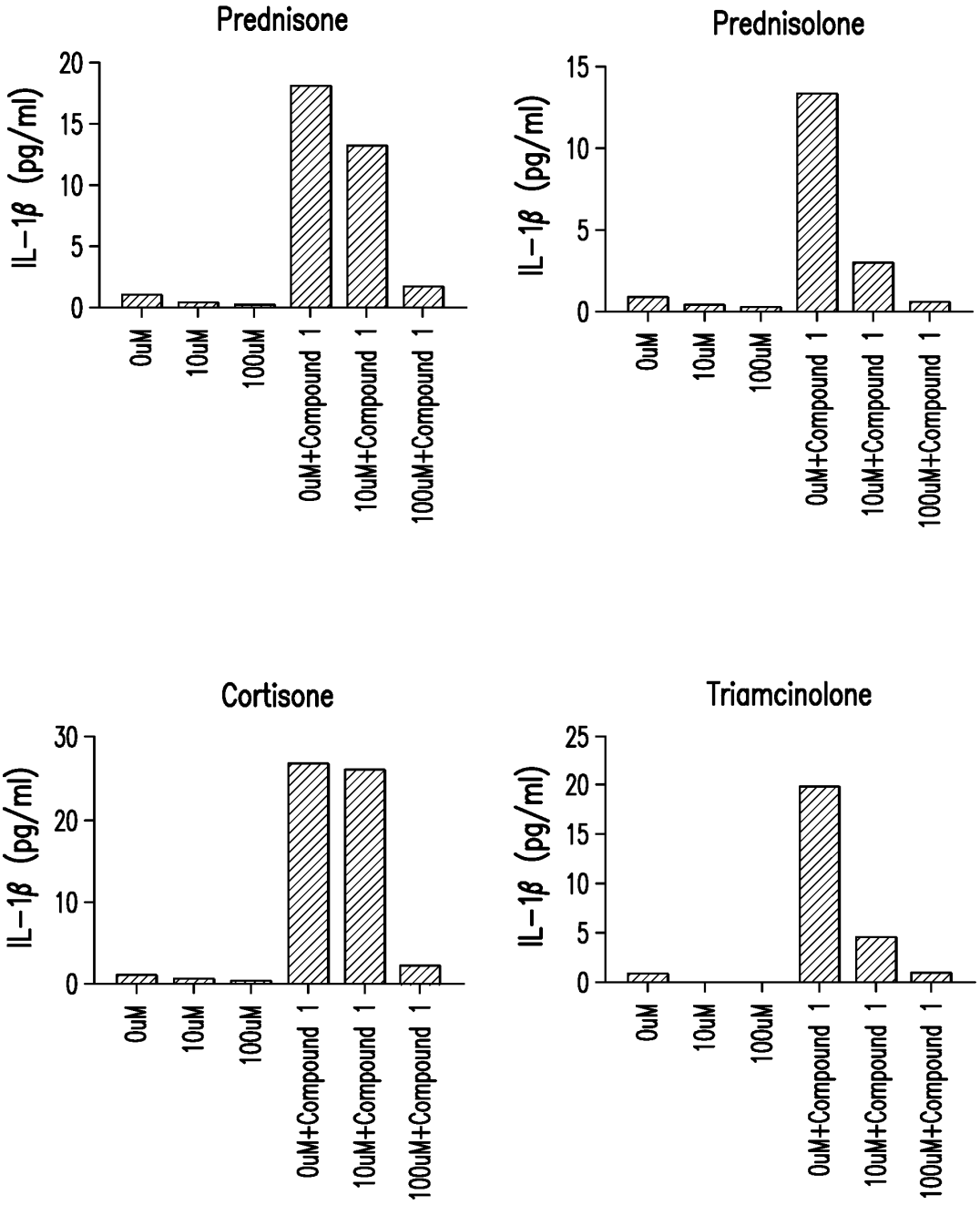

Prednisone
IL-1β (pg/ml)
20
15
10
5
0
0uM
10uM
100uM
0uM+Compound 1
10uM+Compound 1
100uM+Compound 1
Prednisolone
IL-1β (pg/ml)
15
10
5
0
0uM
10uM
100uM
0uM+Compound 1
10uM+Compound 1
100uM+Compound 1
Cortisone
IL-1β (pg/ml)
30
20
10
0
0uM
10uM
100uM
0uM+Compound 1
10uM+Compound 1
100uM+Compound 1
Triamcinolone
IL-1β (pg/ml)
25
20
15
10
5
0
0uM
10uM
100uM
0uM+Compound 1
10uM+Compound 1
100uM+Compound 1

FIG. 13

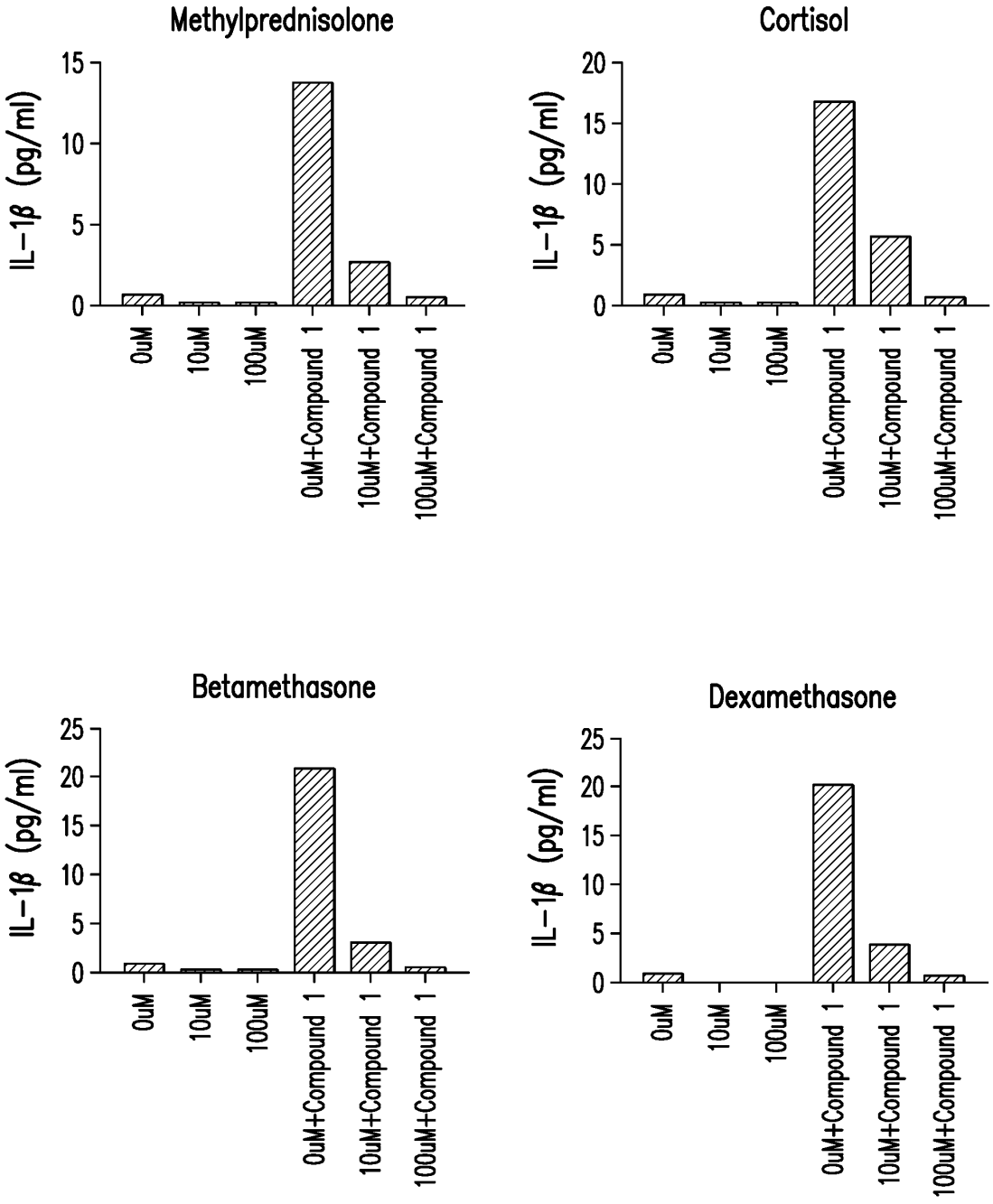


FIG. 13 continued