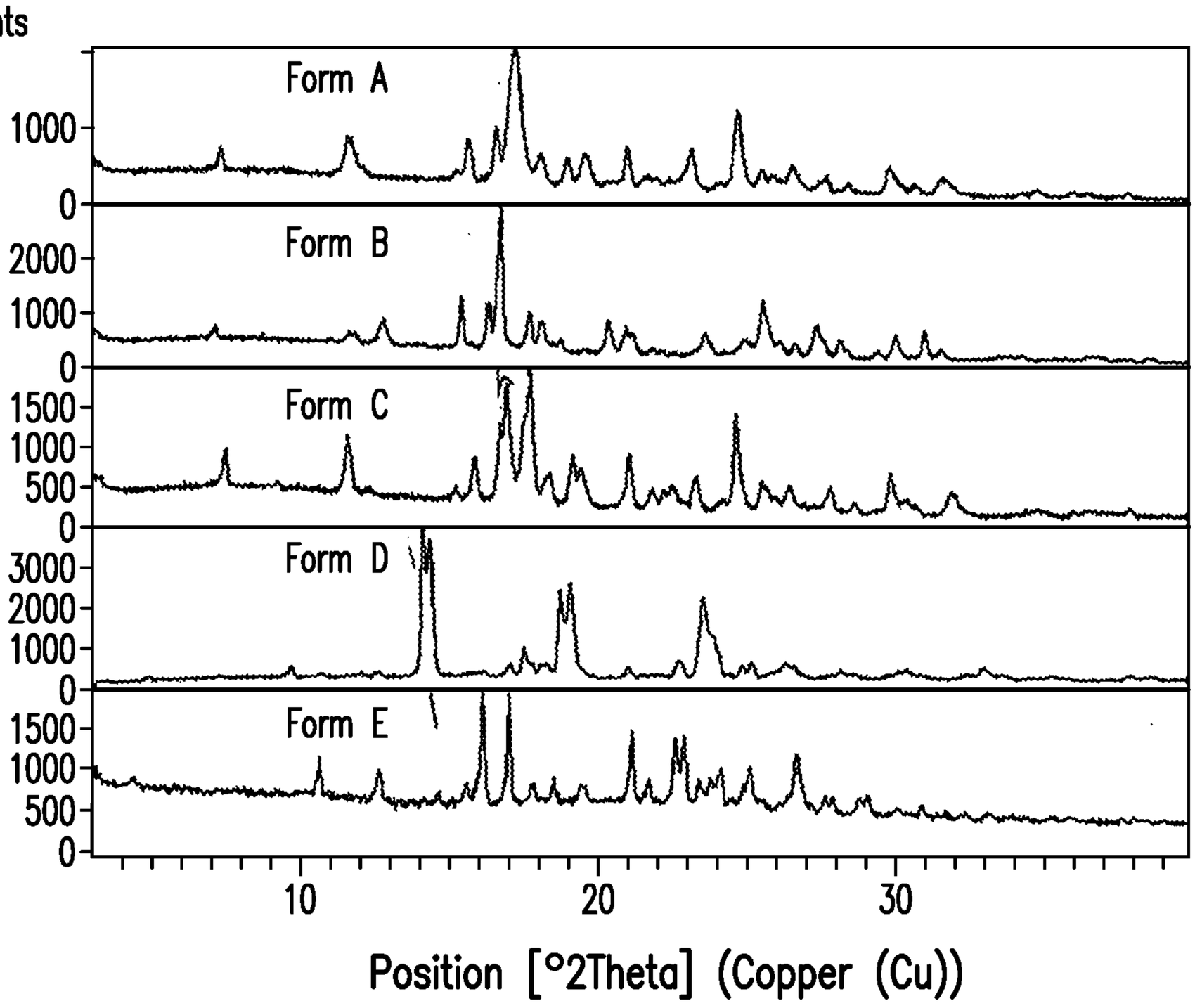

Counts
Form A
1000
0
Form B
2000
1000
0
Form C
1500
1000
500
0
Form D
3000
2000
1000
0
Form E
1500
1000
500
0
10
20
30
Position [°2Theta] (Copper (Cu))

FIG. 1

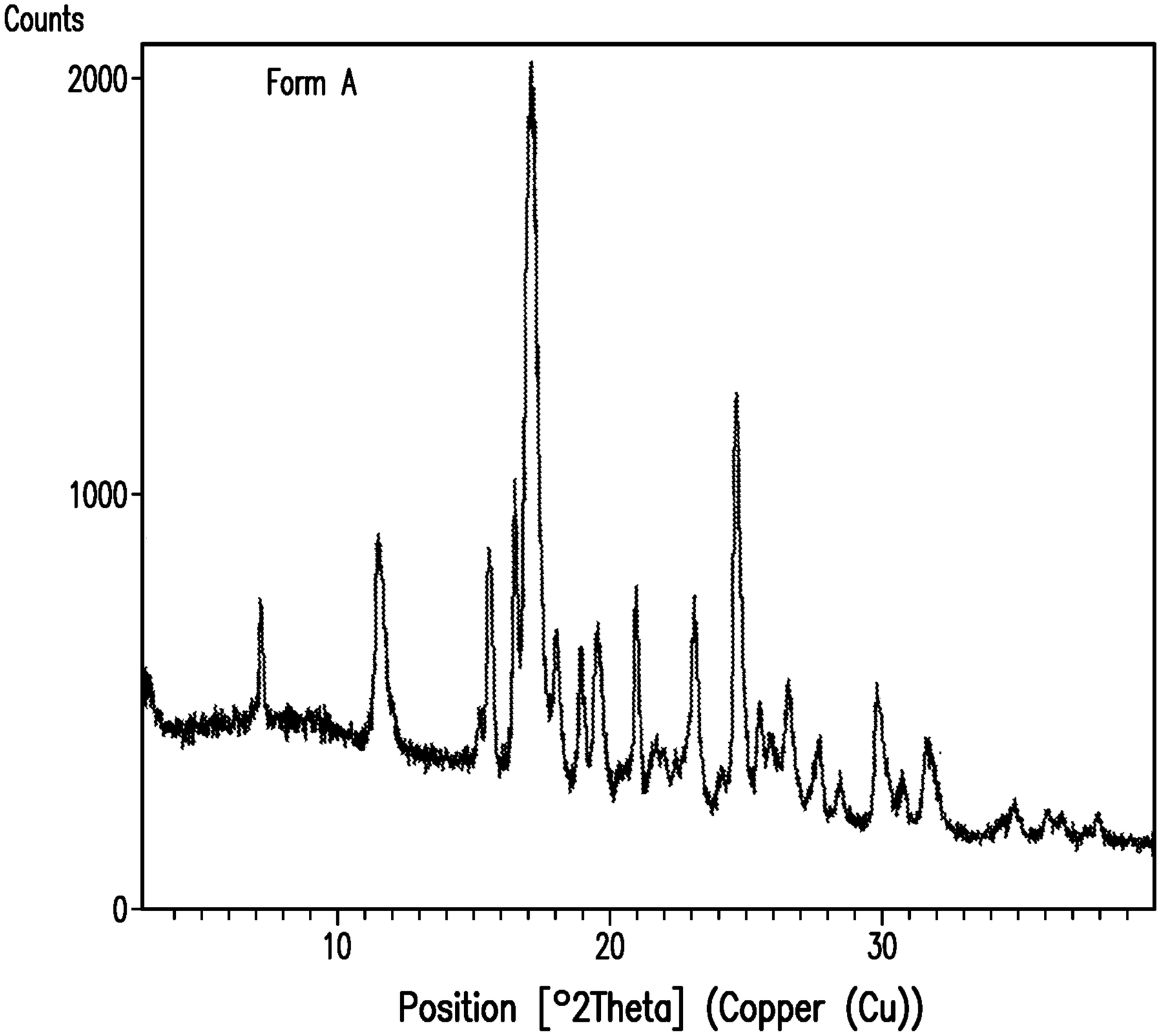


FIG. 2

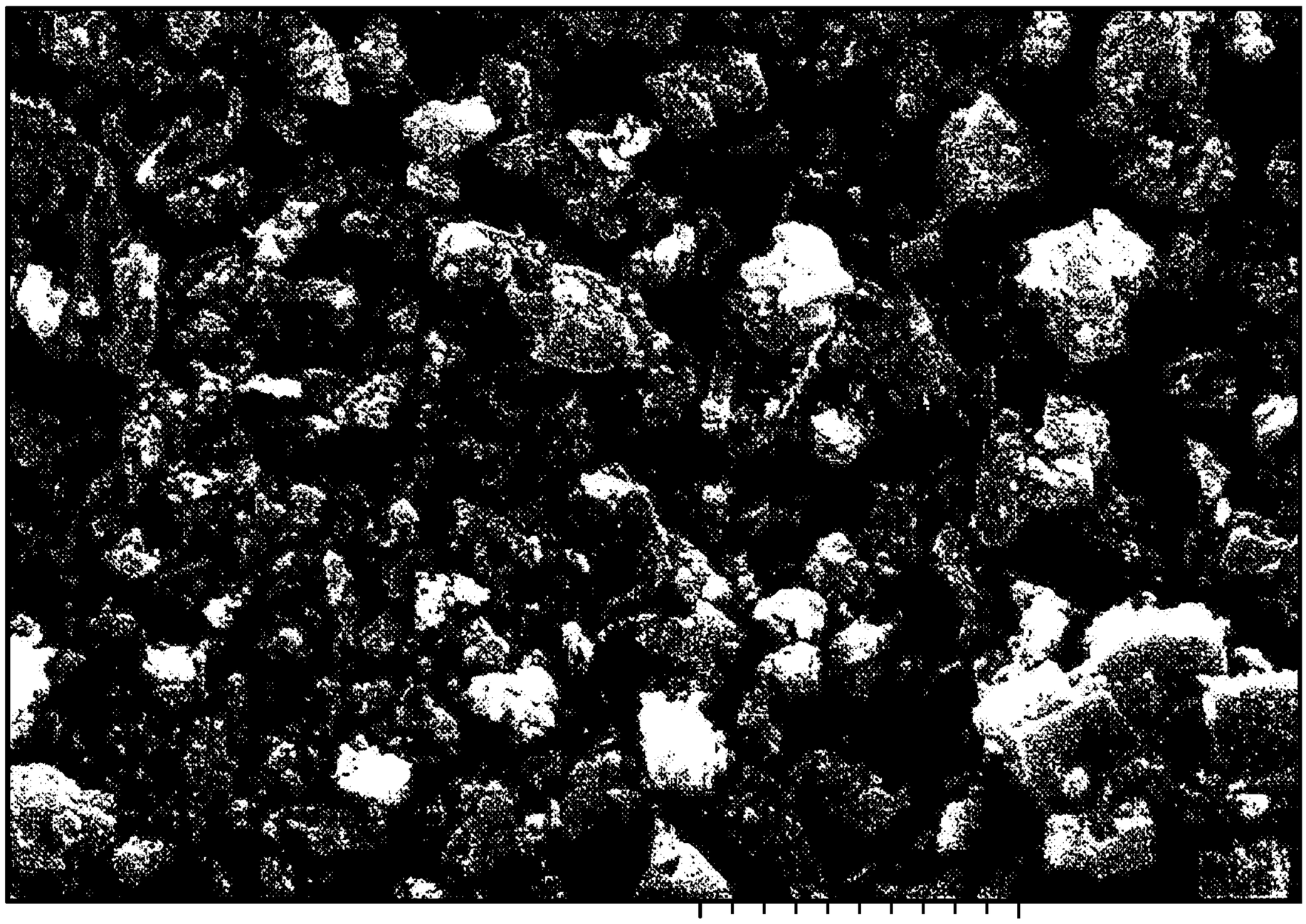


FIG. 3

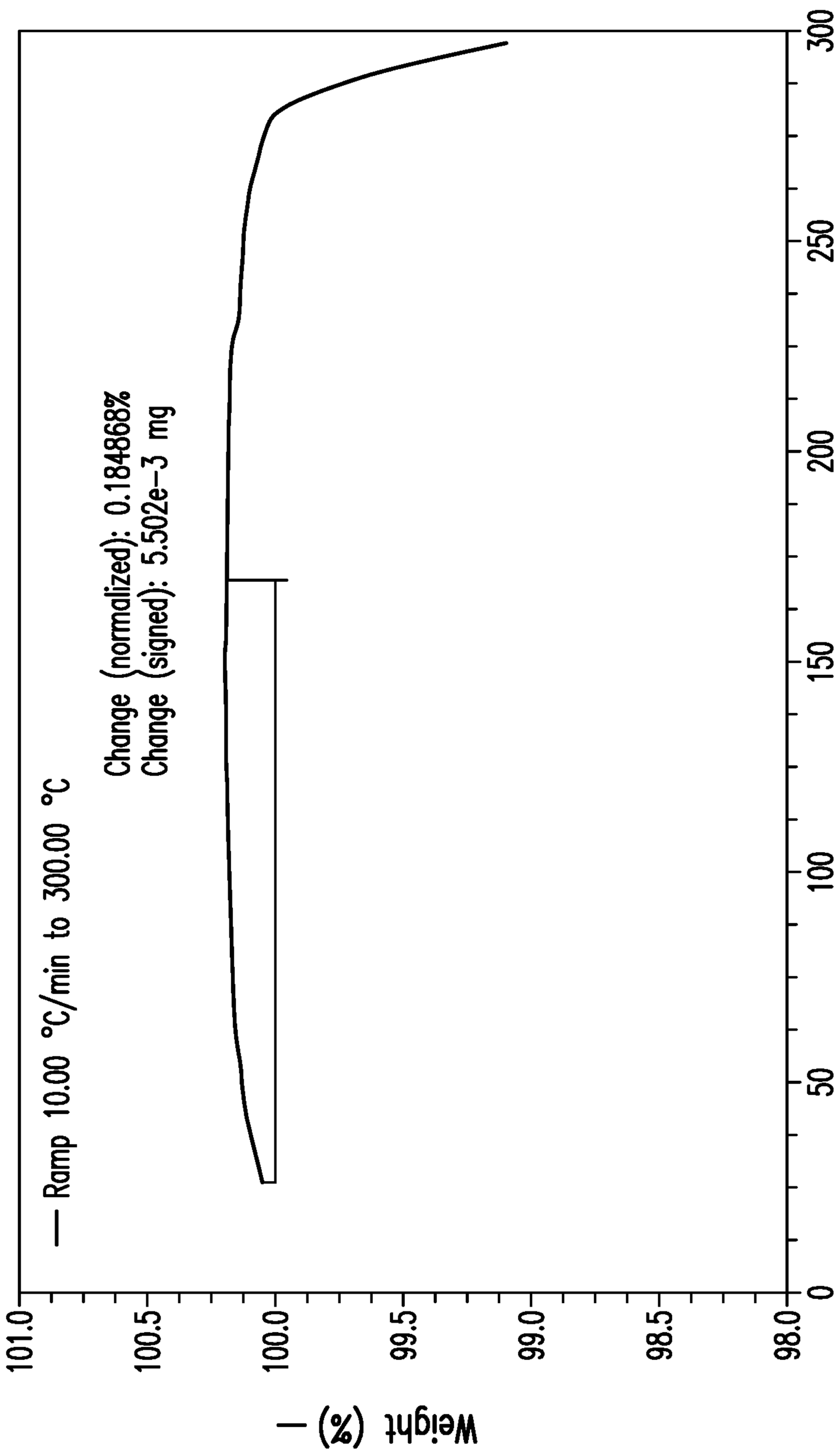

— Ramp 10.00 °C/min to 300.00 °C
Change (normalized): 0.184868%
Change (signed): 5.502e−3 mg
Weight (%) —
101.0
100.5
100.0
99.5
99.0
98.5
98.0
0
50
100
150
200
250
300
(°C)

FIG. 4

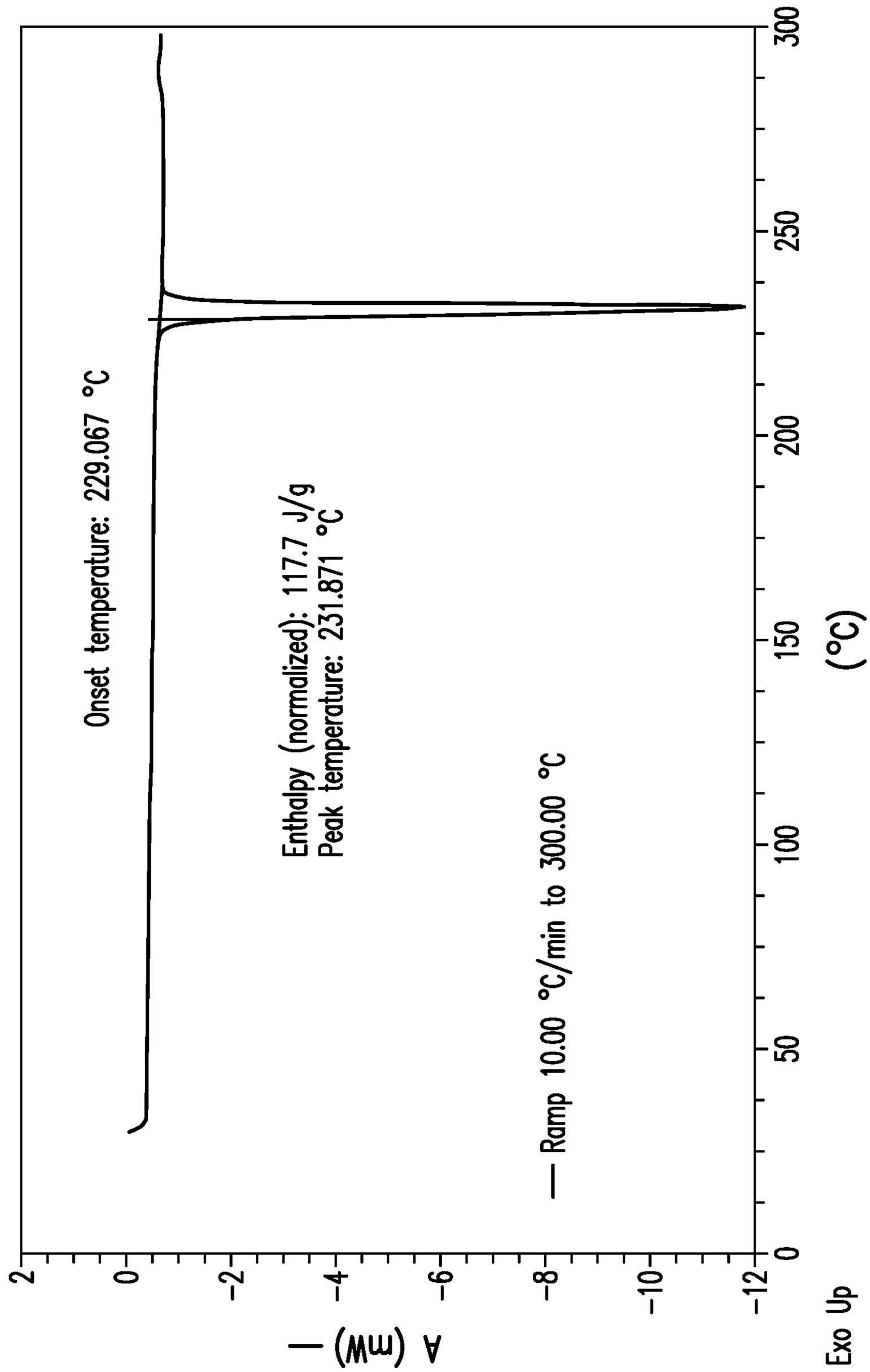
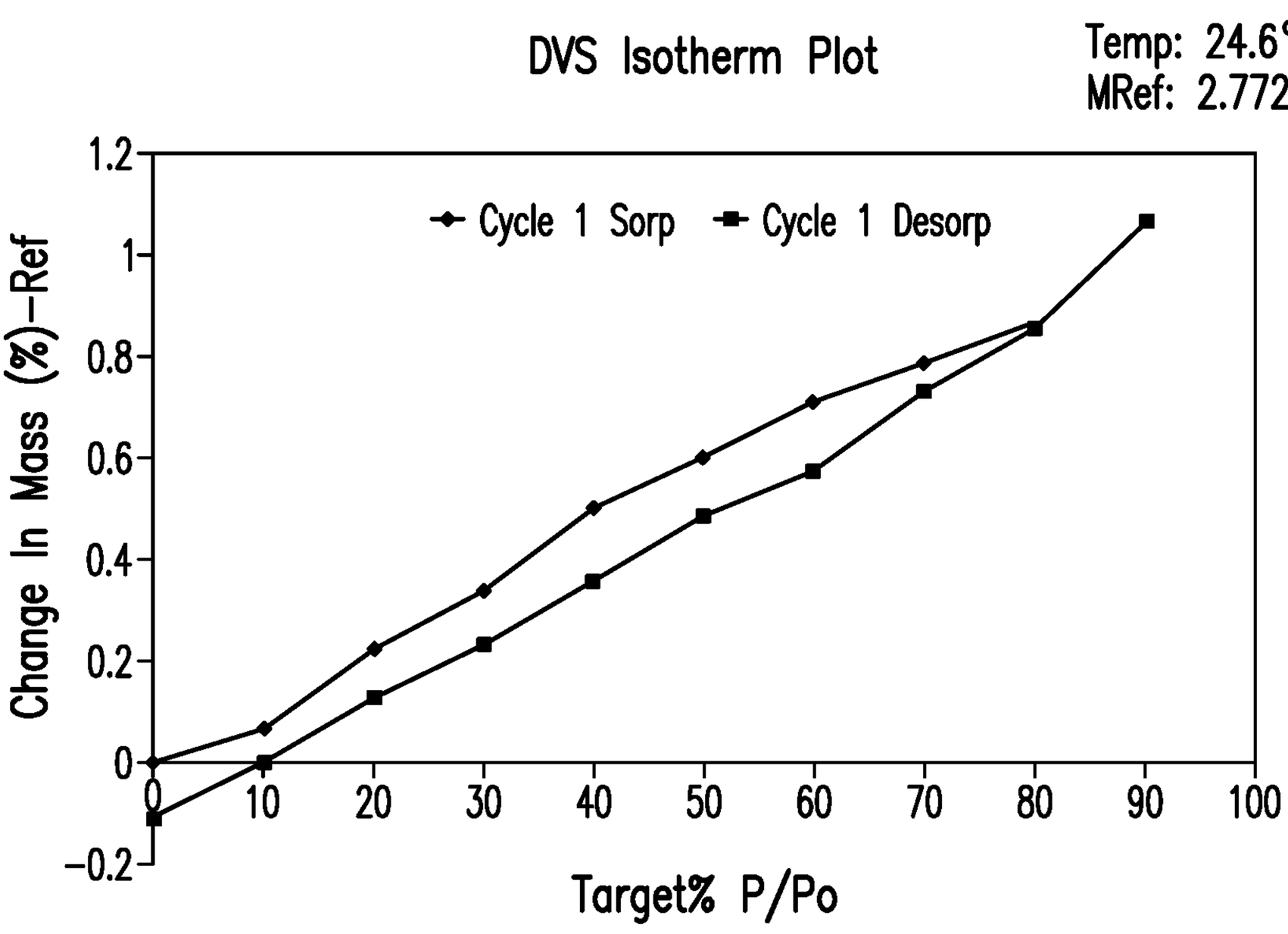

Onset temperature: 229.067 °C
Enthalpy (normalized): 117.7 J/g
Peak temperature: 231.871 °C
Ramp 10.00 °C/min to 300.00 °C
Exo Up
mW
°C
300
250
200
150
100
50
0
2
0
-2
-4
-6
-8
-10
-12

FIG. 5



	Target % P/Po	Change In Mass (%)–ref Sorption	Desorption	Hysteresis
Cycle 1	0.0	–0.004	–0.111	
	10.0	0.063	–0.002	–0.066
	20.0	0.221	0.126	–0.094
	30.0	0.339	0.231	–0.108
	40.0	0.509	0.360	–0.149
	50.0	0.614	0.496	–0.118
	60.0	0.726	0.586	–0.139
	70.0	0.808	0.751	–0.057
	80.0	0.887	0.880	–0.007
	90.0	1.099	1.099	

FIG. 6

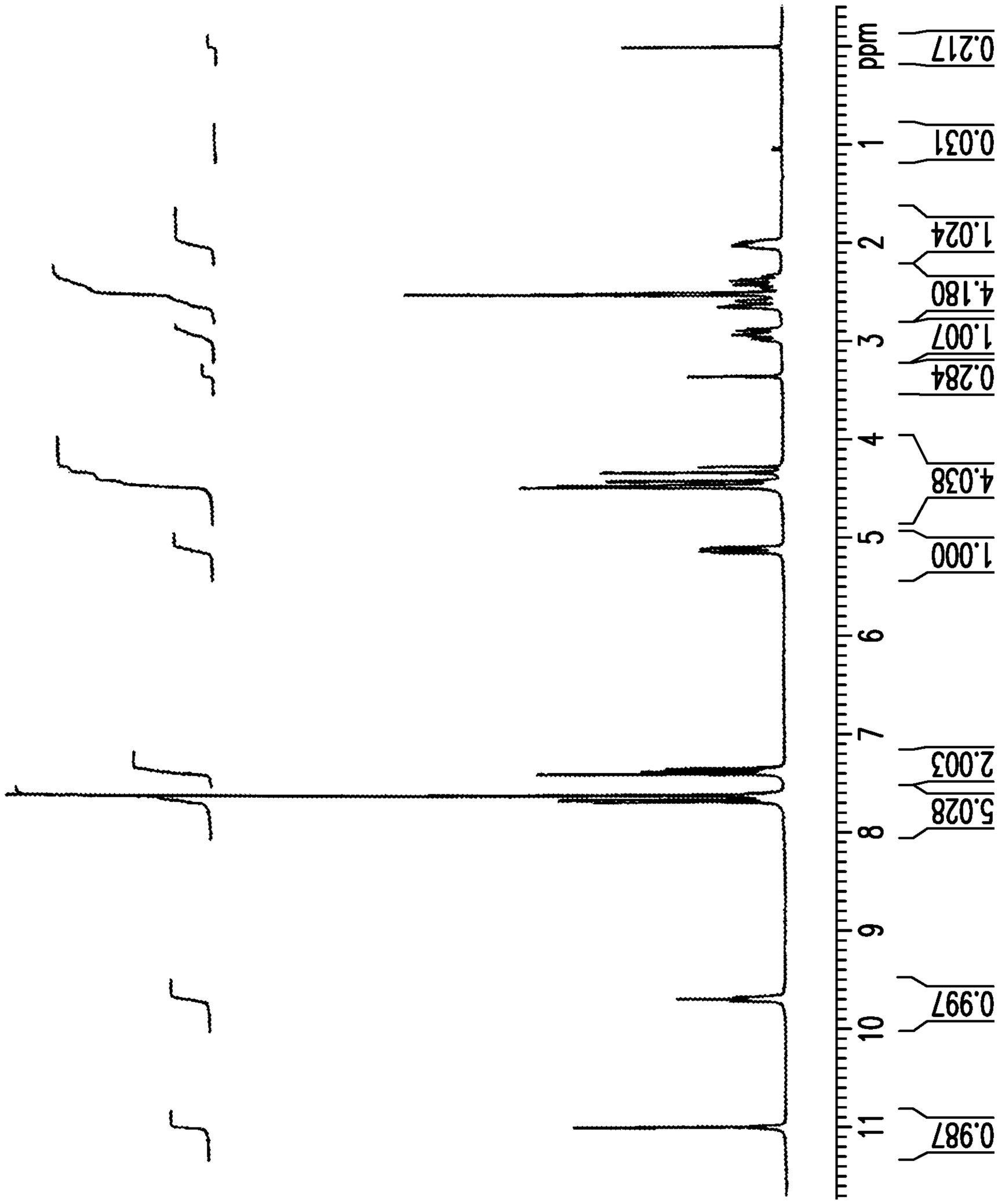

ppm
0.217
0.031
1.024
4.180
1.007
0.284
4.038
1.000
2.003
5.028
0.997
0.987

FIG. 7

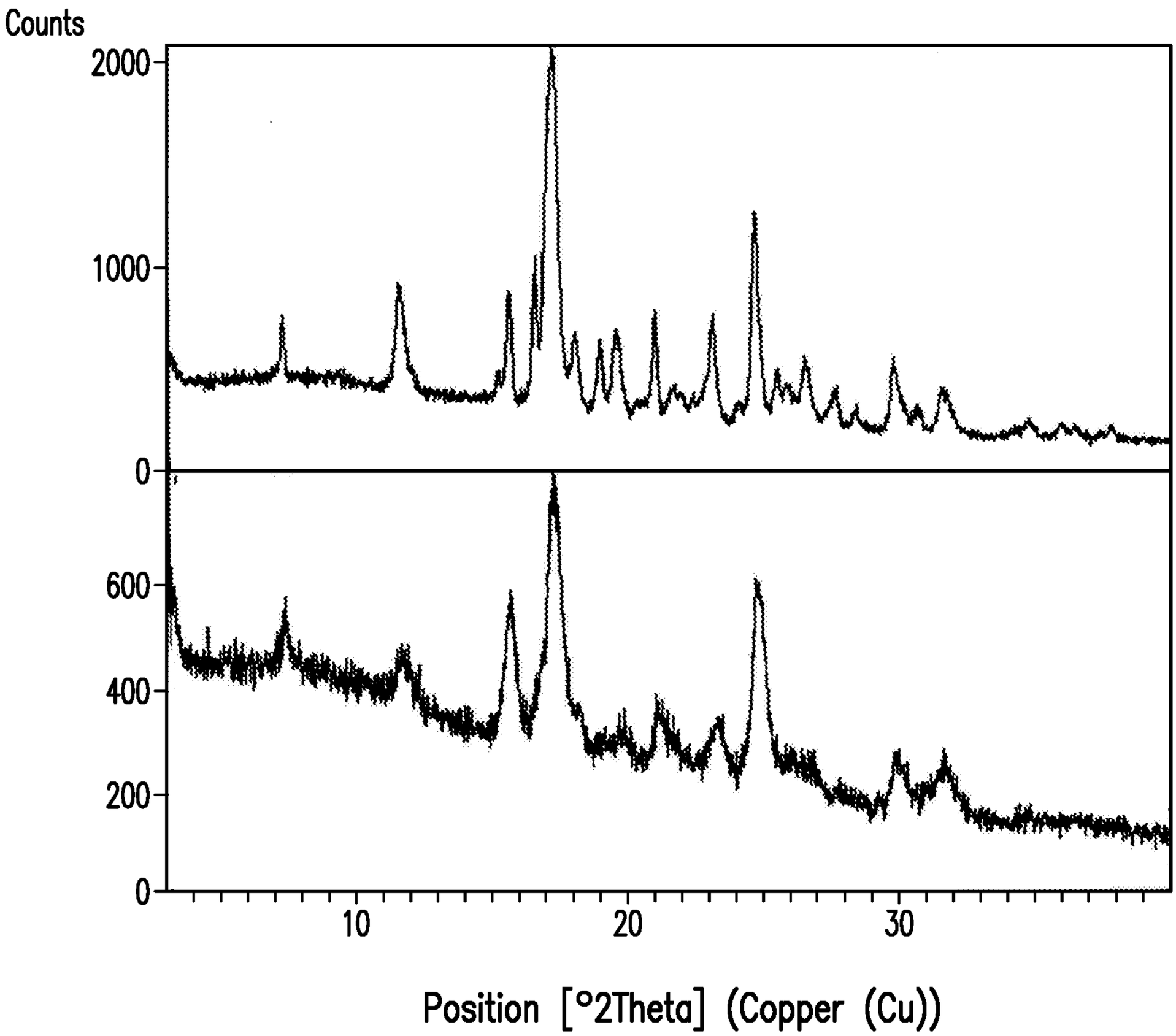

Counts
2000
1000
0
600
400
200
0
10
20
30
Position [°2Theta] (Copper (Cu))

FIG. 8

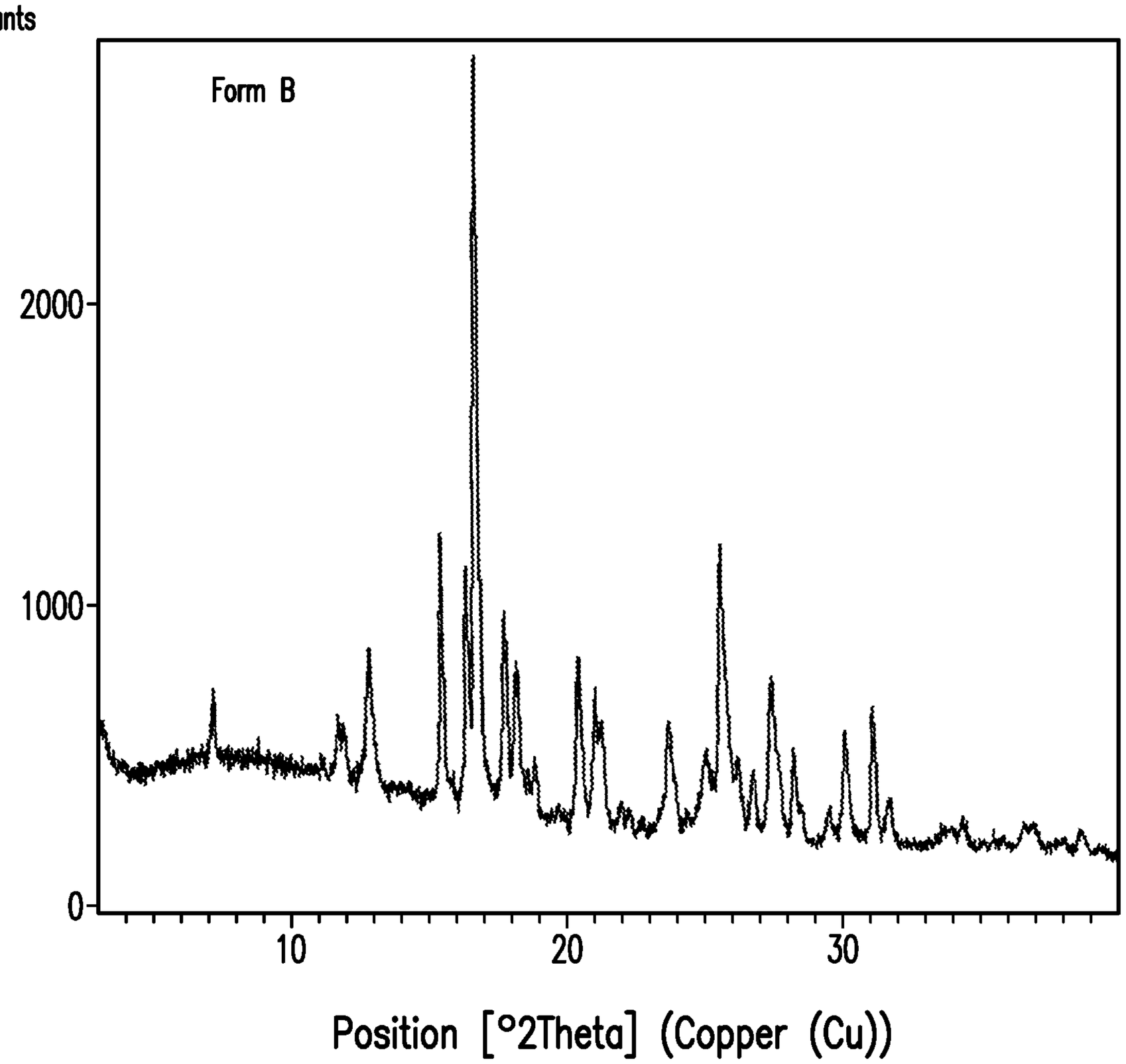


FIG. 9

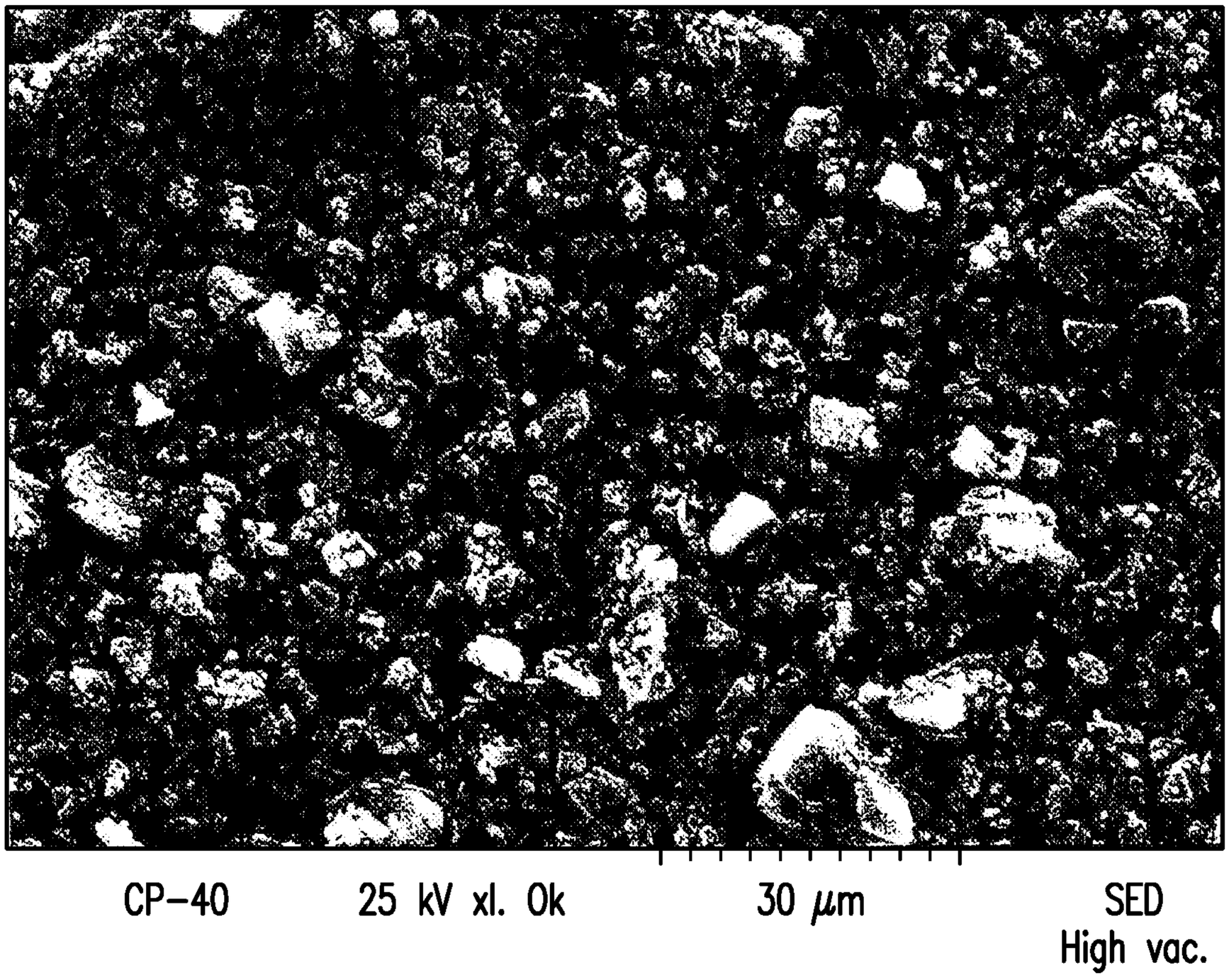


FIG. 10

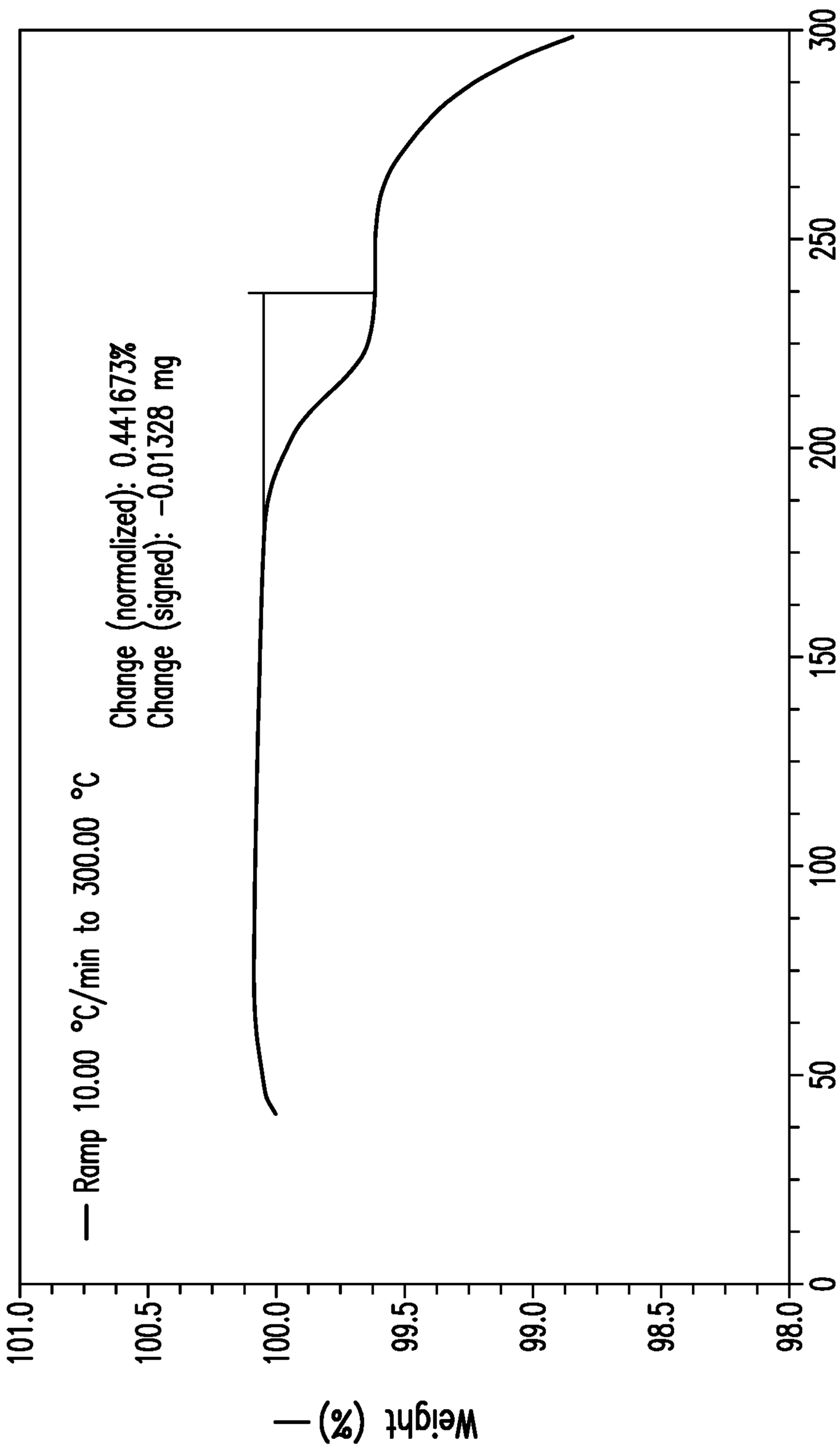

Change (normalized): 0.441673%
Change (signed): −0.01328 mg
— Ramp 10.00 °C/min to 300.00 °C
Weight (%) —
101.0
100.5
100.0
99.5
99.0
98.5
98.0
0
50
100
150
200
250
300
(°C)

FIG. 11

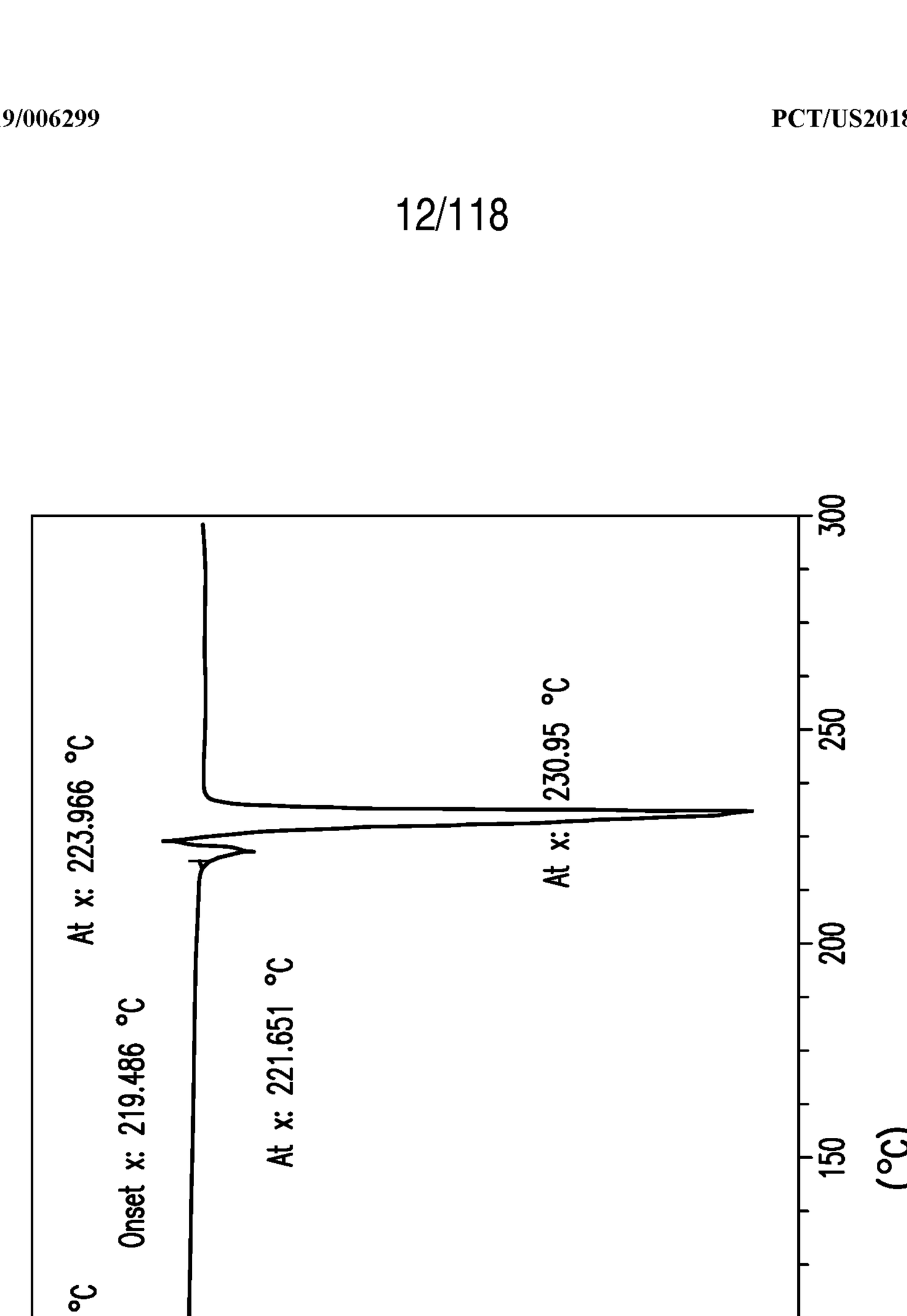
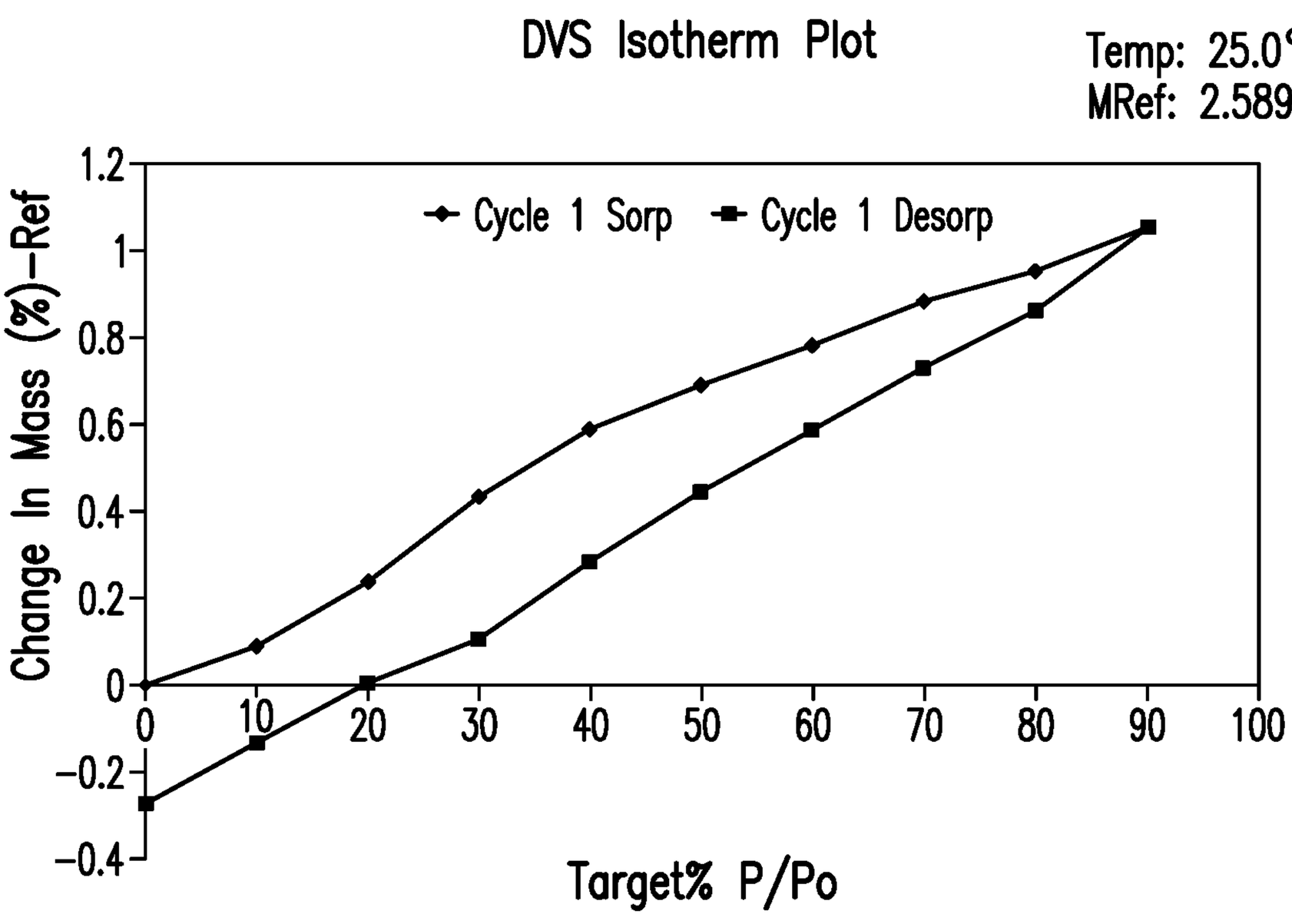

Ramp 10.00 °C/min to 300.00 °C
Onset x: 219.486 °C
At x: 221.651 °C
At x: 223.966 °C
At x: 230.95 °C
A (mW)
Exo Up
(°C)

FIG. 12



	Target % P/Po	Change In Mass (%)–ref Sorption	Desorption	Hysteresis
Cycle 1	0.0	0.000	–0.270	
	10.0	0.093	–0.120	–0.213
	20.0	0.241	0.009	–0.232
	30.0	0.439	0.112	–0.327
	40.0	0.595	0.292	–0.303
	50.0	0.700	0.456	–0.244
	60.0	0.798	0.599	–0.198
	70.0	0.903	0.748	–0.154
	80.0	0.977	0.886	–0.091
	90.0	1.085	1.085	

FIG. 13

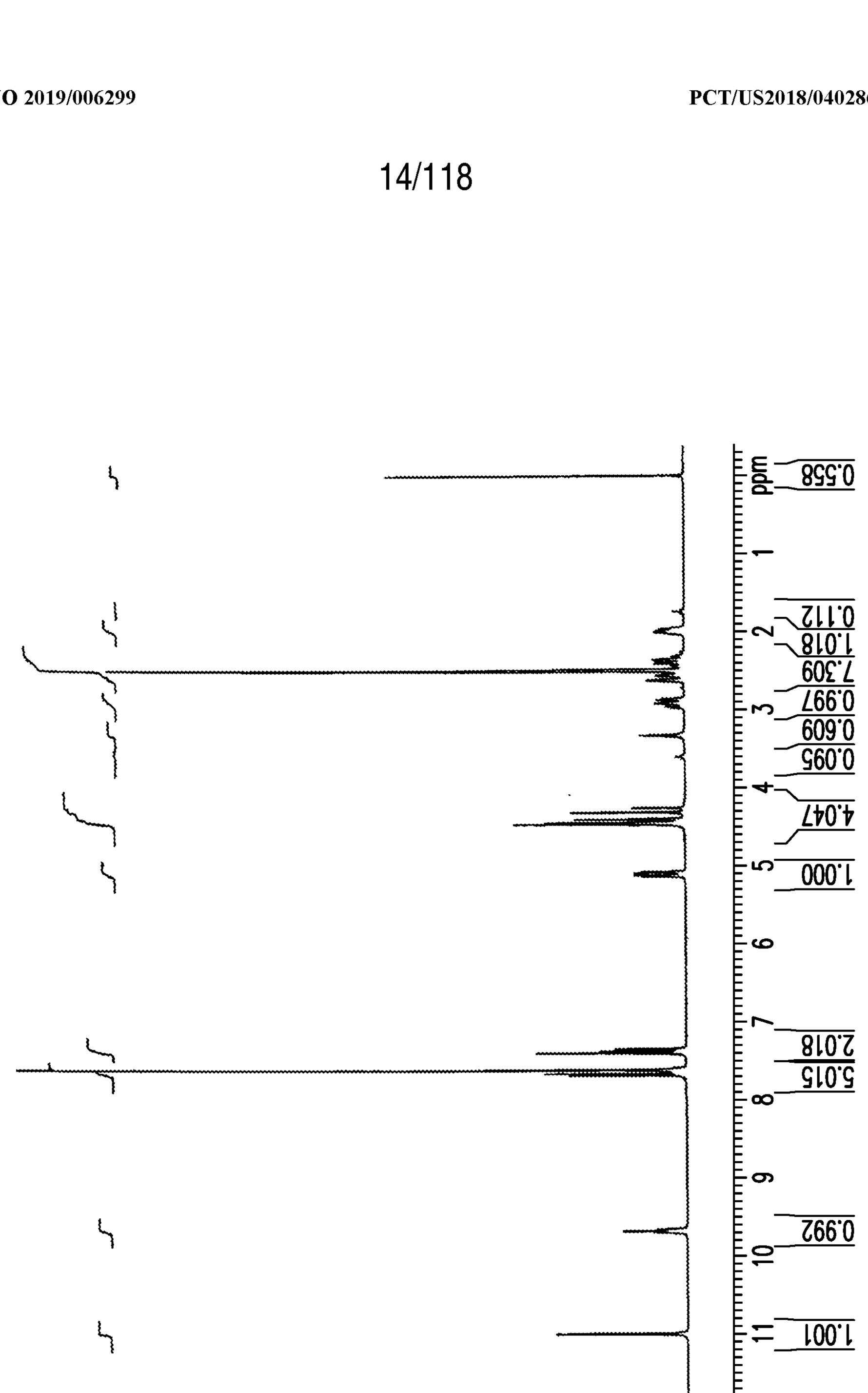

ppm
0.558
1.000
4.047
0.095
0.609
0.997
7.309
1.018
0.112
2.018
5.015
0.992
1.001

FIG. 14

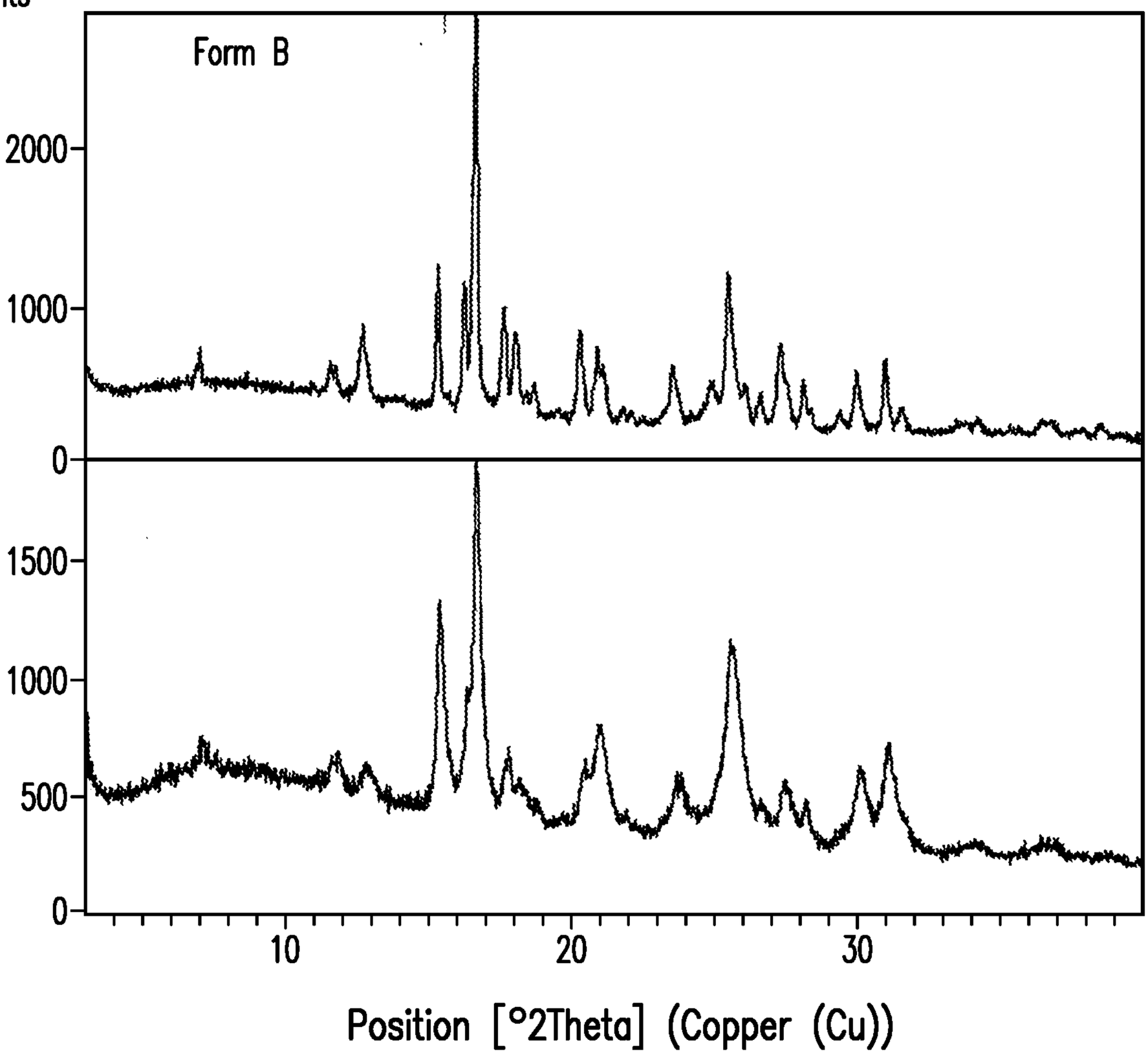

Counts
Form B
2000
1000
0
1500
1000
500
0
10
20
30
Position [°2Theta] (Copper (Cu))

FIG. 15

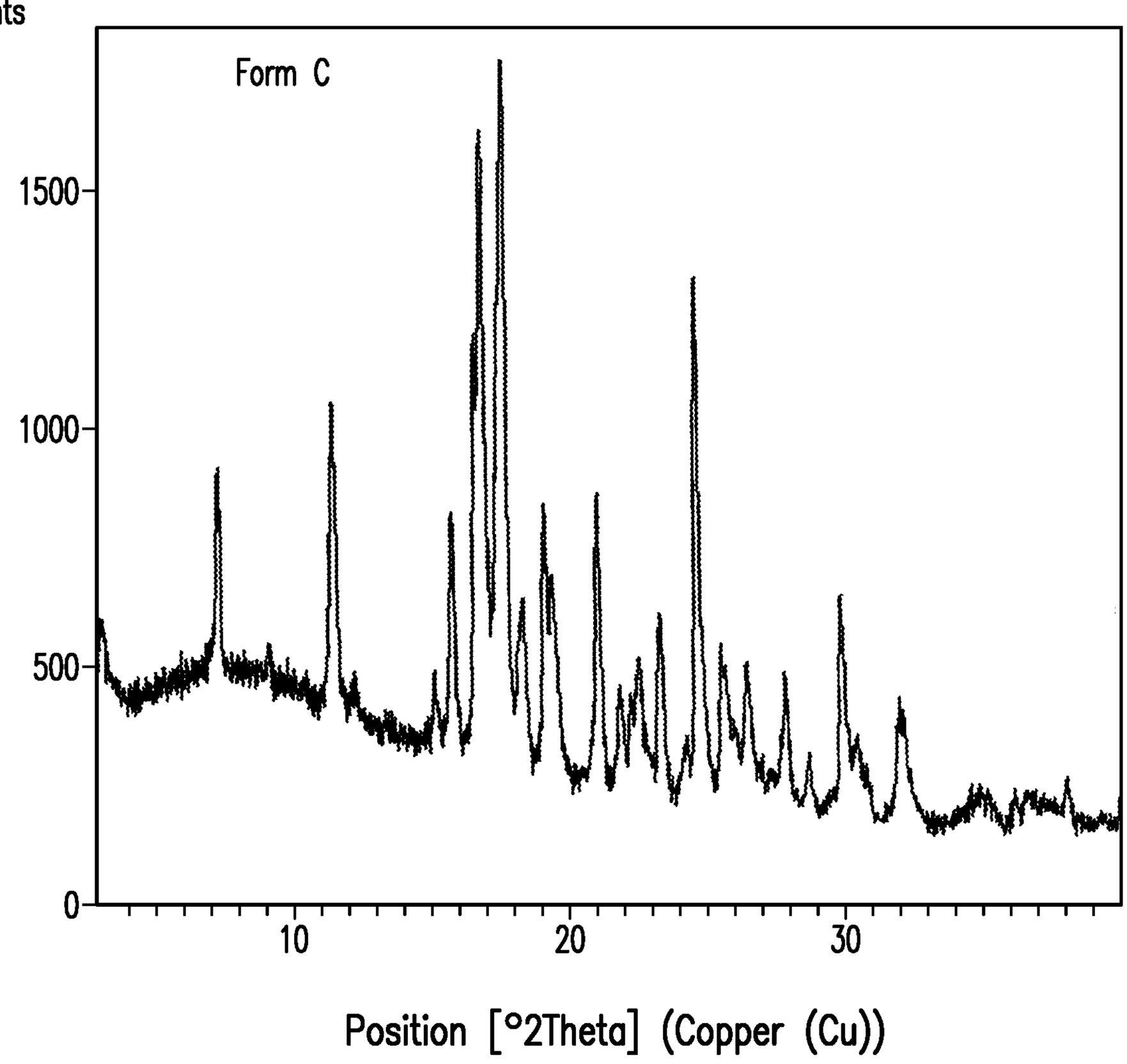

Counts
Form C
1500
1000
500
0
10
20
30
Position [°2Theta] (Copper (Cu))

FIG. 16

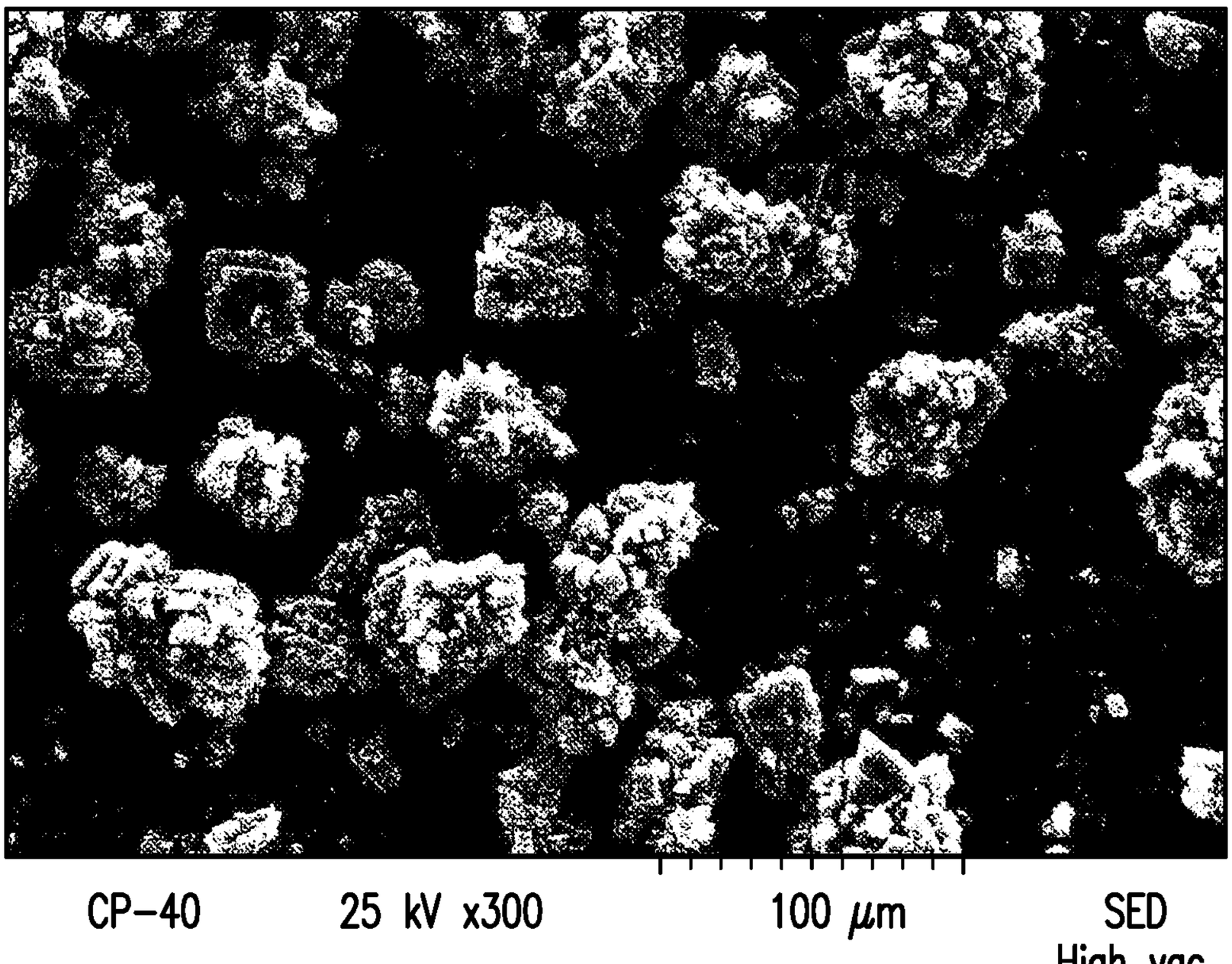


FIG. 17

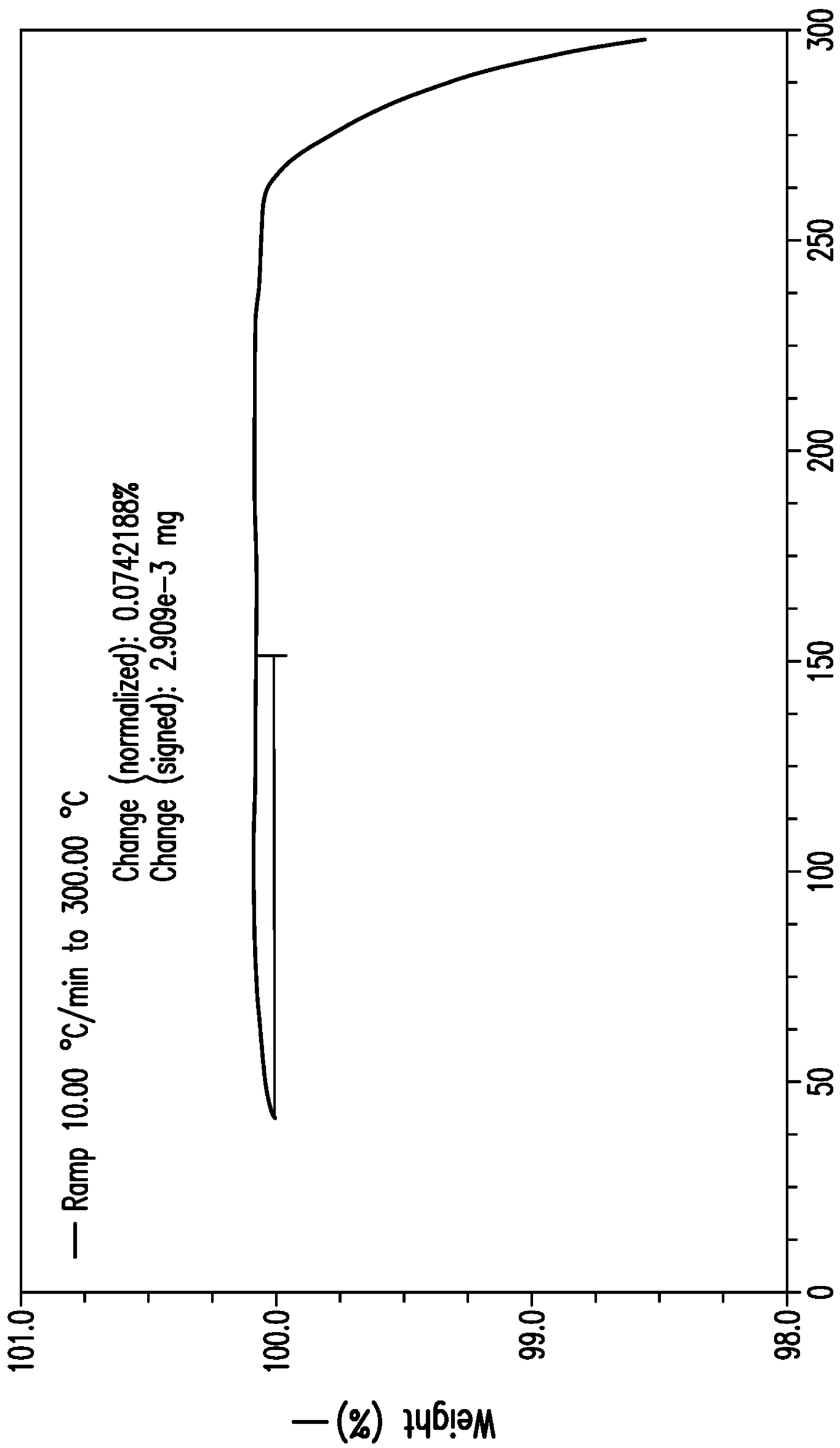

— Ramp 10.00 °C/min to 300.00 °C
Change (normalized): 0.0742188%
Change (signed): 2.909e−3 mg
Weight (%) —
101.0
100.0
99.0
98.0
0
50
100
150
200
250
300
(°C)

FIG. 18

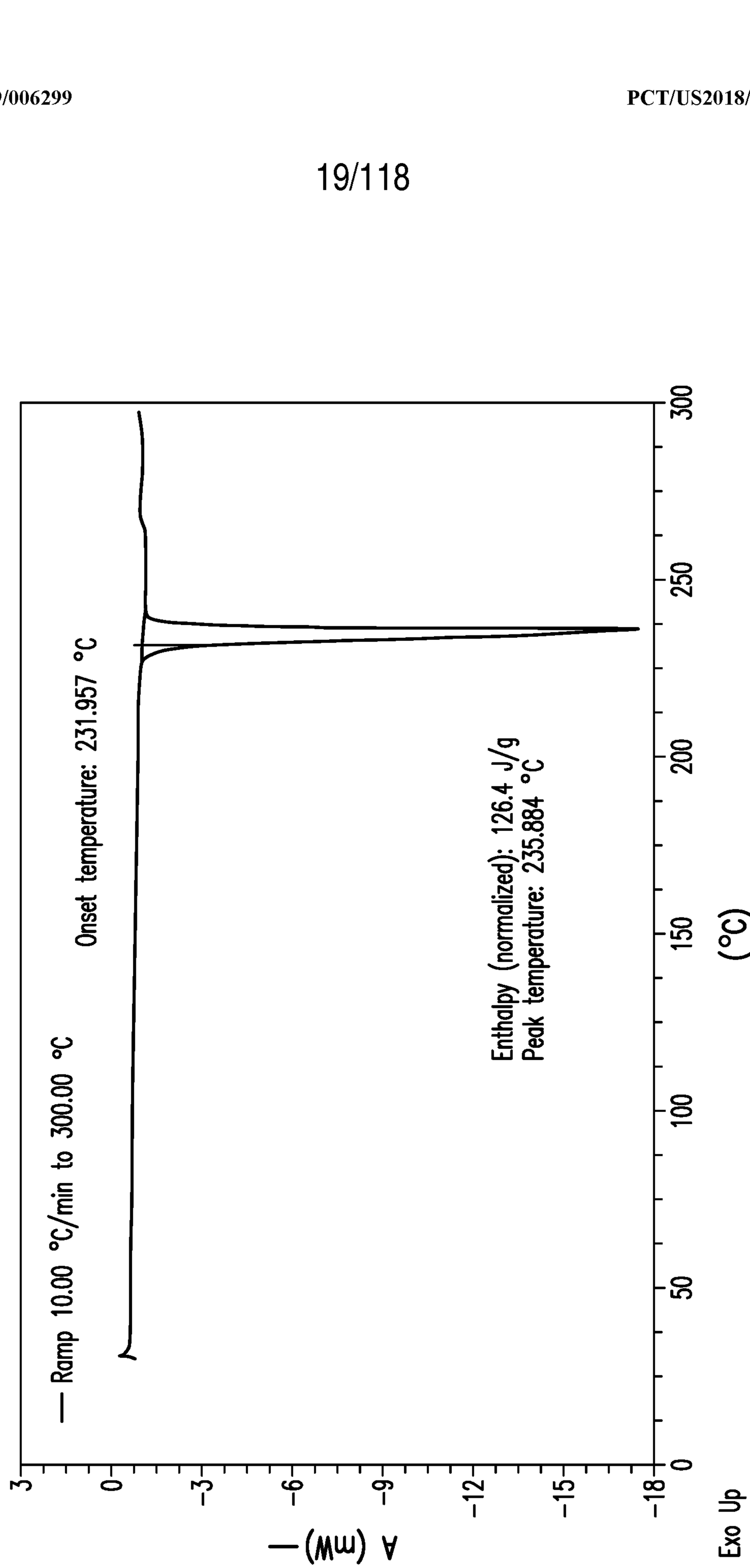
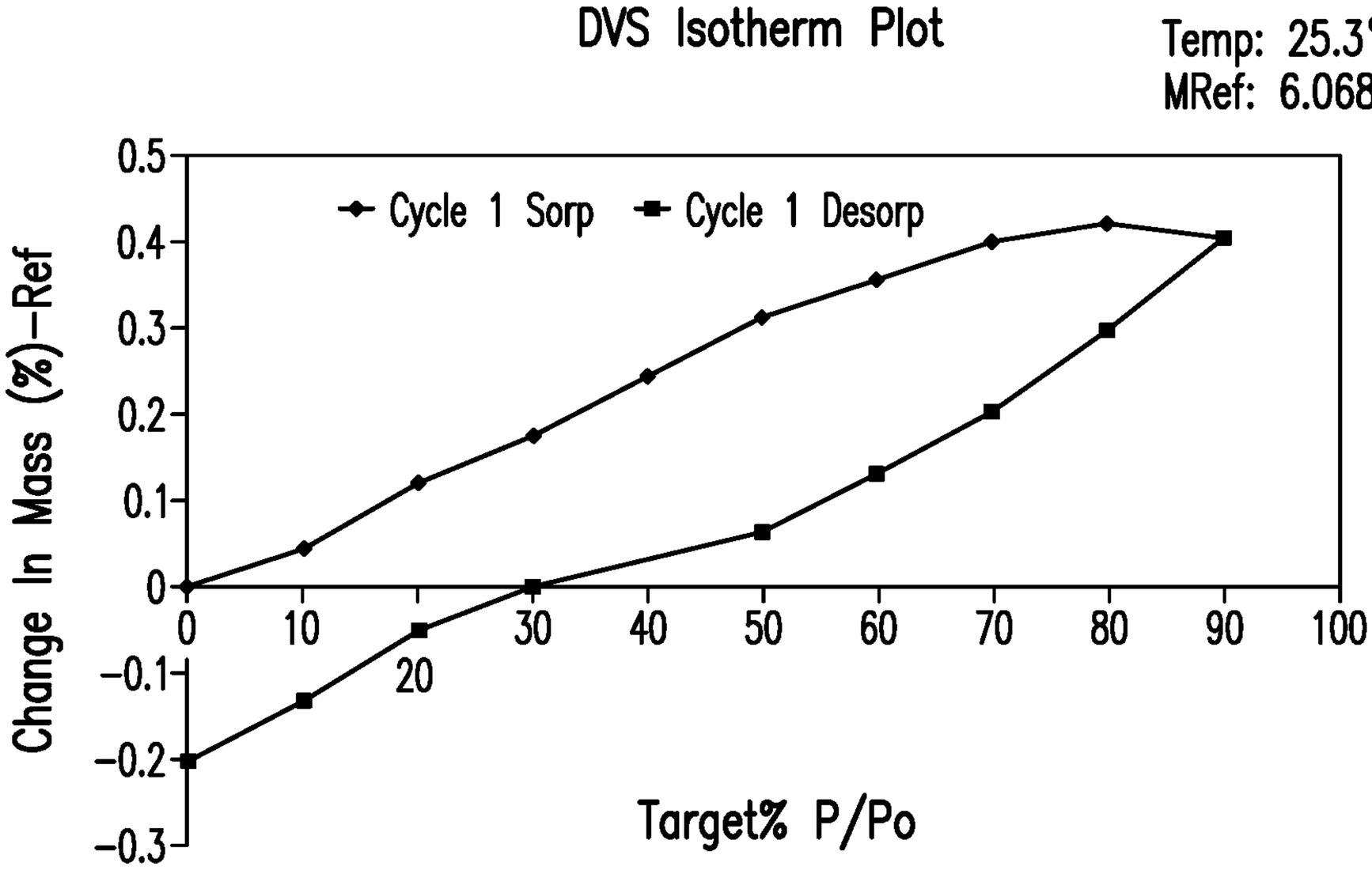

Ramp 10.00 °C/min to 300.00 °C
Onset temperature: 231.957 °C
Enthalpy (normalized): 126.4 J/g
Peak temperature: 235.884 °C
A (mW)
Exo Up
(°C)
3
0
-3
-6
-9
-12
-15
-18
0
50
100
150
200
250
300

FIG. 19



	Target % P/Po	Change In Mass (%)–ref Sorption	Desorption	Hysteresis
Cycle 1	0.0	–0.0020	–0.2070	
	10.0	0.0409	–0.1368	–0.1776
	20.0	0.1186	0.0547	–0.1734
	30.0	0.1730	0.0049	–0.1780
	40.0	0.2409	0.0395	–0.2805
	50.0	0.3114	0.0606	–0.2508
	60.0	0.3559	0.1305	–0.2254
	70.0	0.4014	0.2027	–0.1987
	80.0	0.4235	0.2983	–0.1252
	90.0	0.4087	0.4087	

FIG. 20

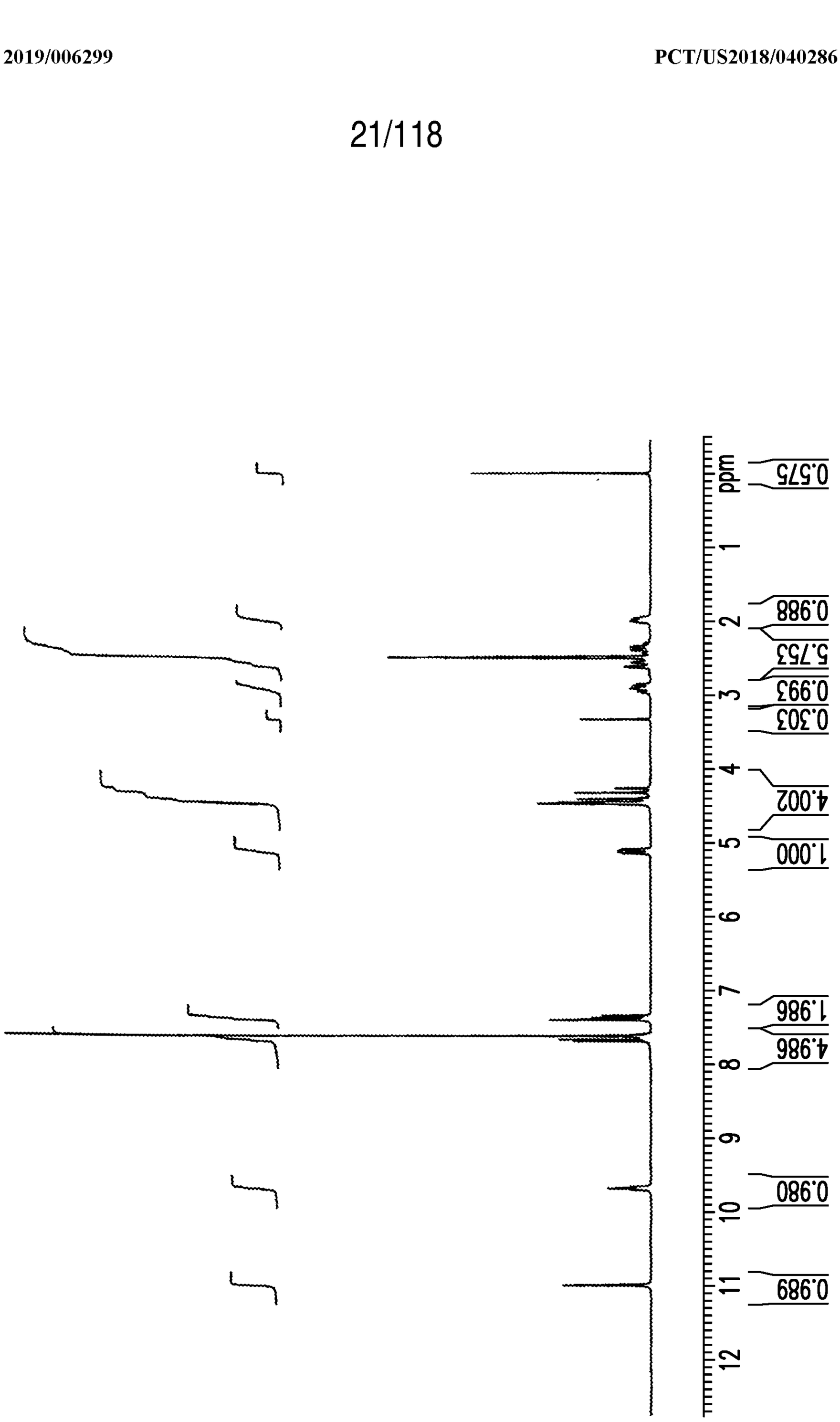


FIG. 21

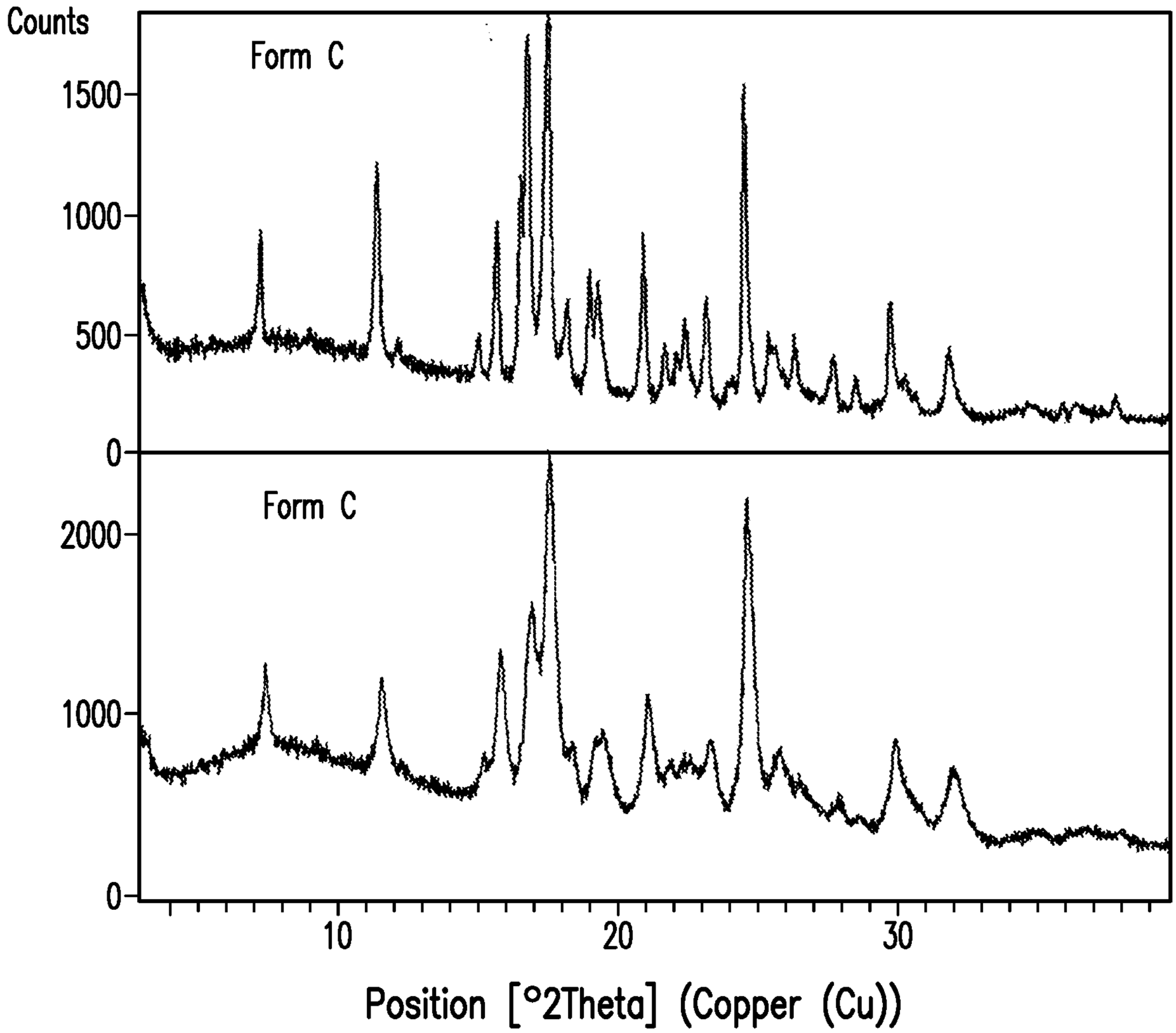

Counts
Form C
1500
1000
500
0
Form C
2000
1000
0
10
20
30
Position [°2Theta] (Copper (Cu))

FIG. 22

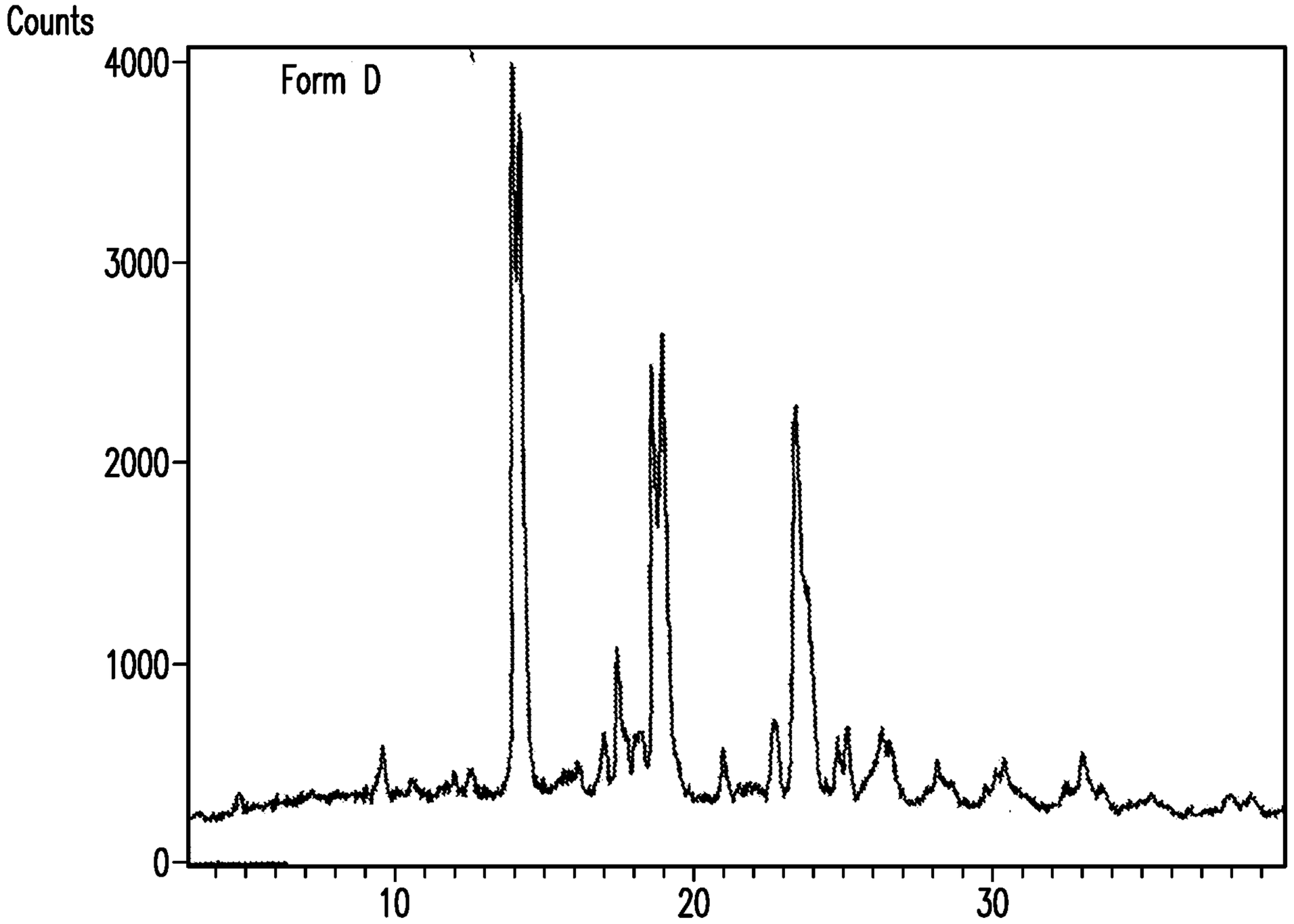

Counts
4000
3000
2000
1000
0
Form D
10
20
30
Position [°2Theta] (Copper (Cu))

FIG. 23

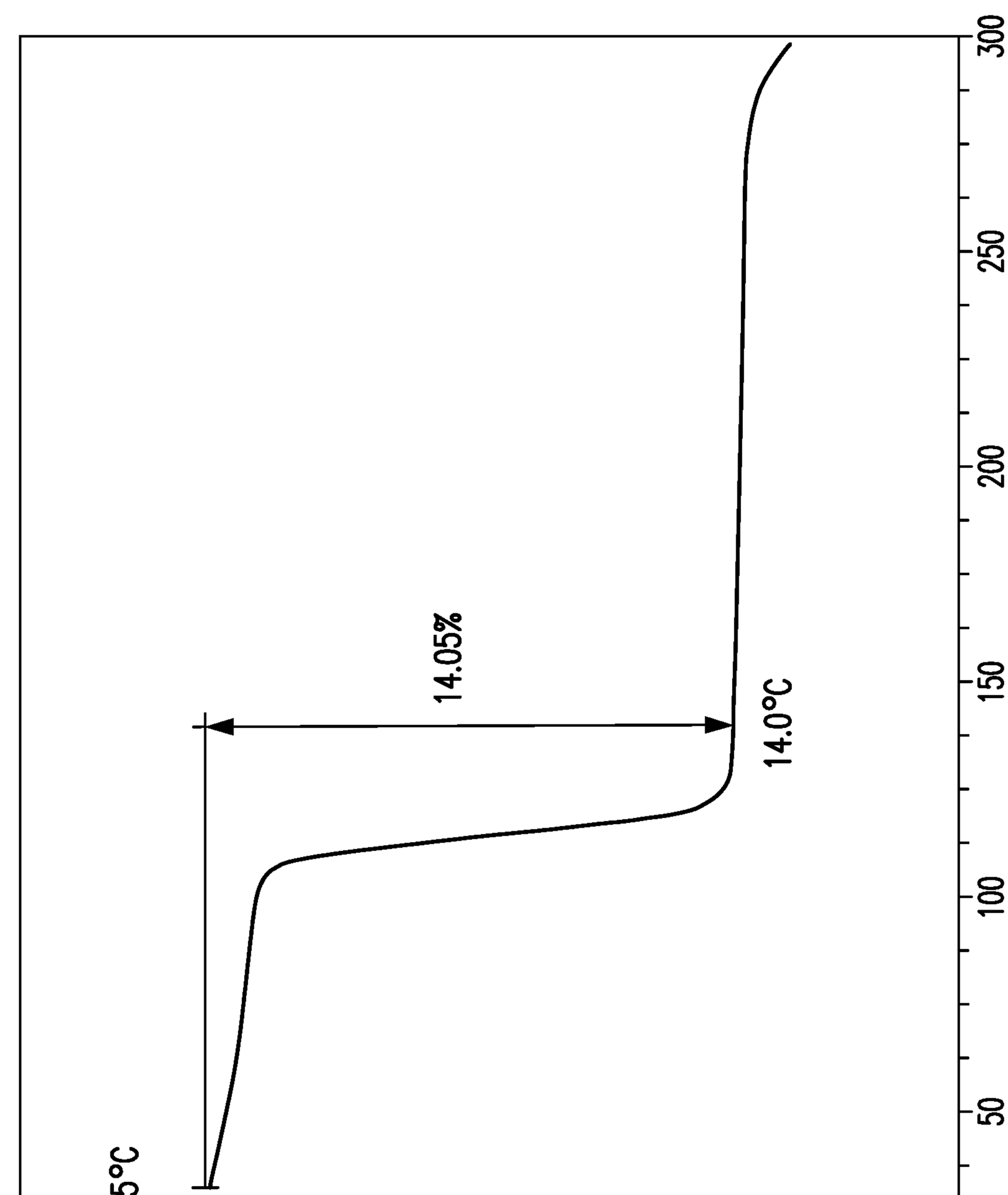

32.5°C
14.05%
14.0°C
Weight (%)
105
100
95
90
85
80
Temperature (°C)
0
50
100
150
200
250
300

FIG. 24

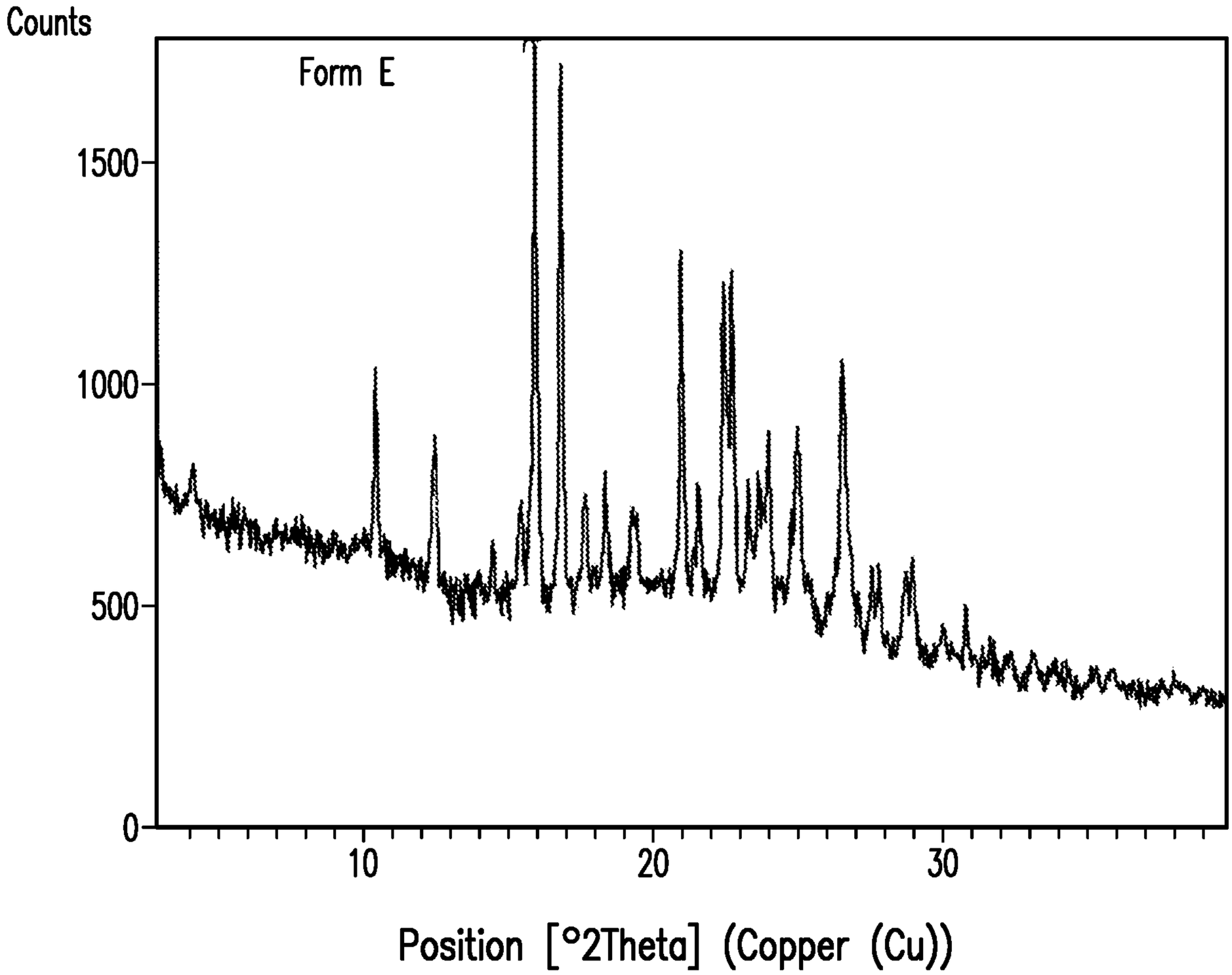

Counts
Form E
1500
1000
500
0
10
20
30
Position [°2Theta] (Copper (Cu))

FIG. 25

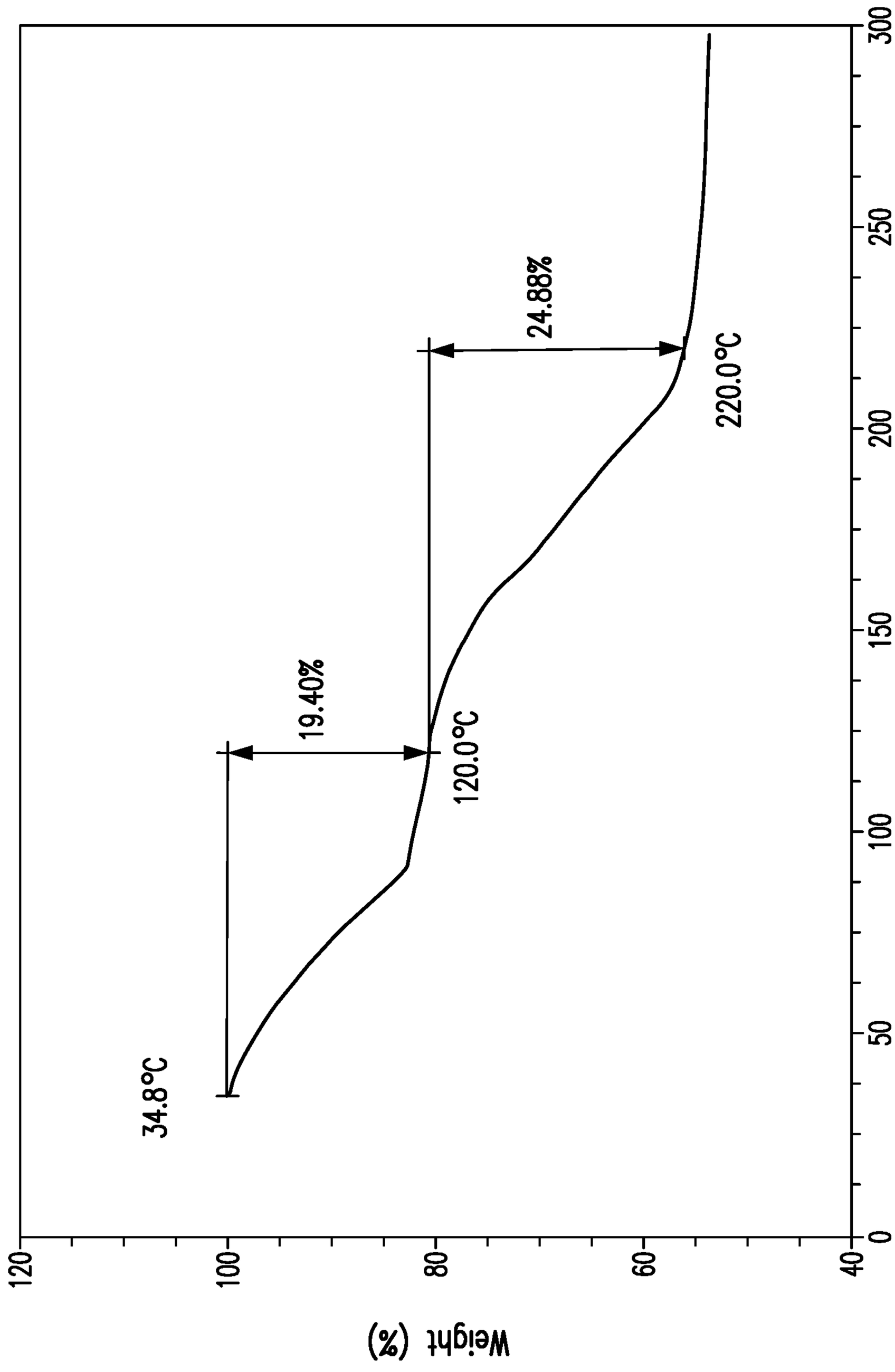

Weight (%)
120
100
80
60
40
0
50
100
150
200
250
300
Temperature (°C)
34.8°C
19.40%
120.0°C
24.88%
220.0°C

FIG. 26

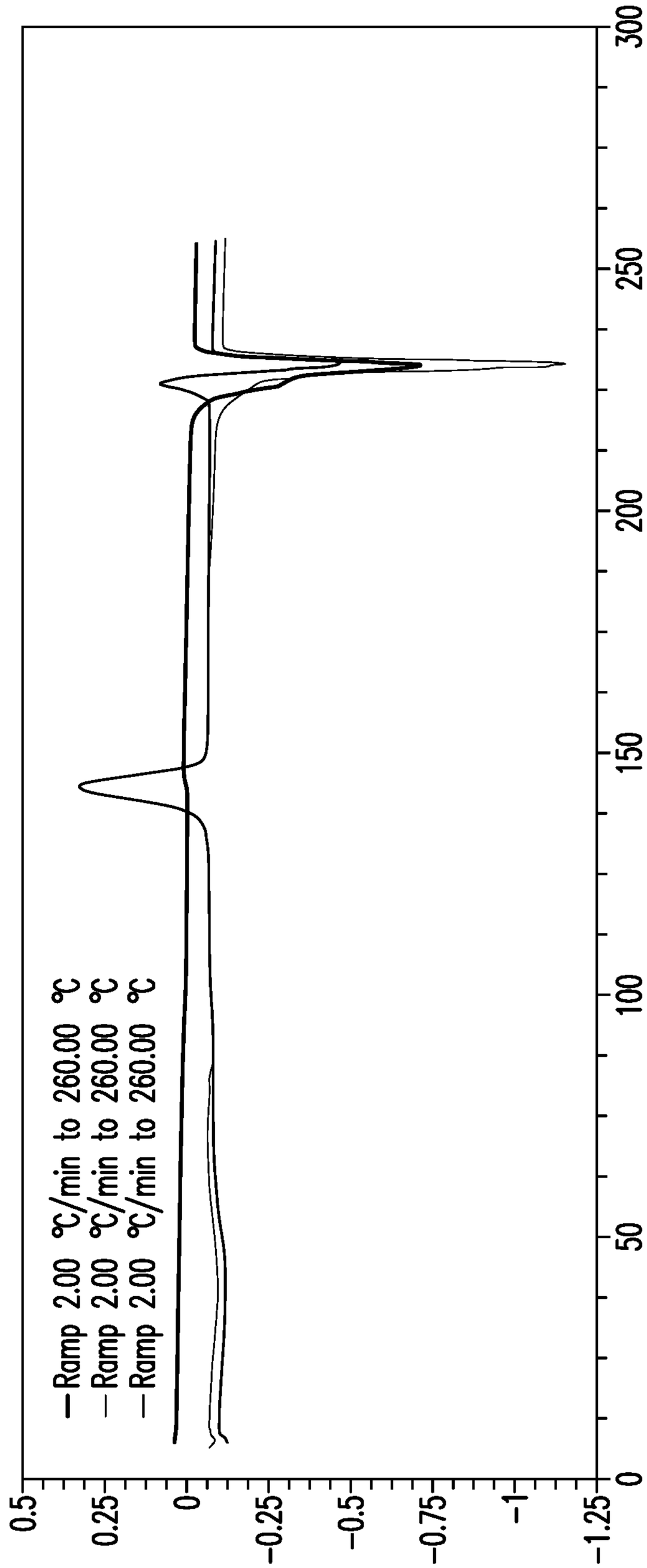

Reversing Heat Flow (mW)– Non–Reversing Heat Flow Am (mW)–
Total Heat Flow A (mW)–
Temperature (°C)
Ramp 2.00 °C/min to 260.00 °C
Ramp 2.00 °C/min to 260.00 °C
Ramp 2.00 °C/min to 260.00 °C
300
250
200
150
100
50
0
0.5
0.25
0
–0.25
–0.5
–0.75
–1
–1.25

FIG. 27

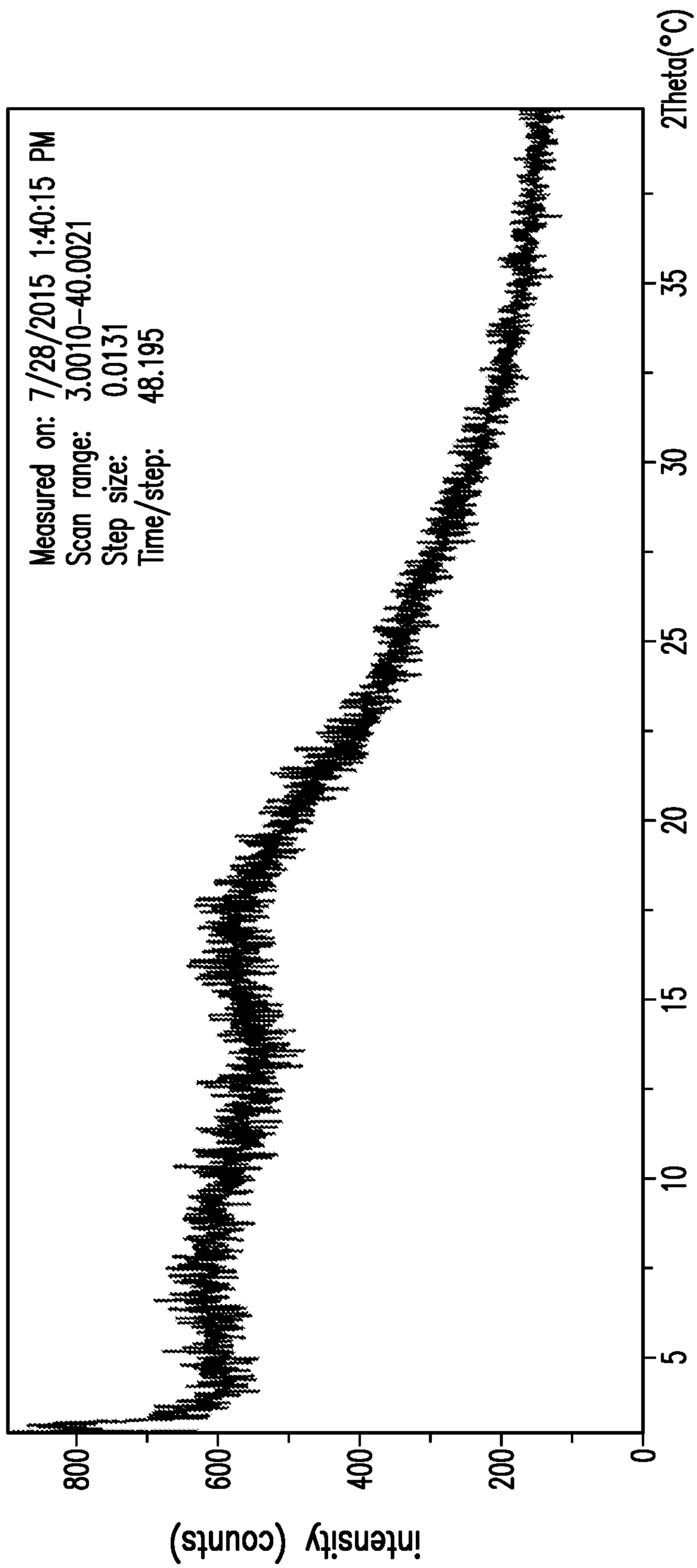

Measured on: 7/28/2015 1:40:15 PM
Scan range: 3.0010–40.0021
Step size: 0.0131
Time/step: 48.195
eta(°C)
2Th
intensity (counts)
800
600
400
200
0
5
10
15
20
25
30
35

FIG. 28

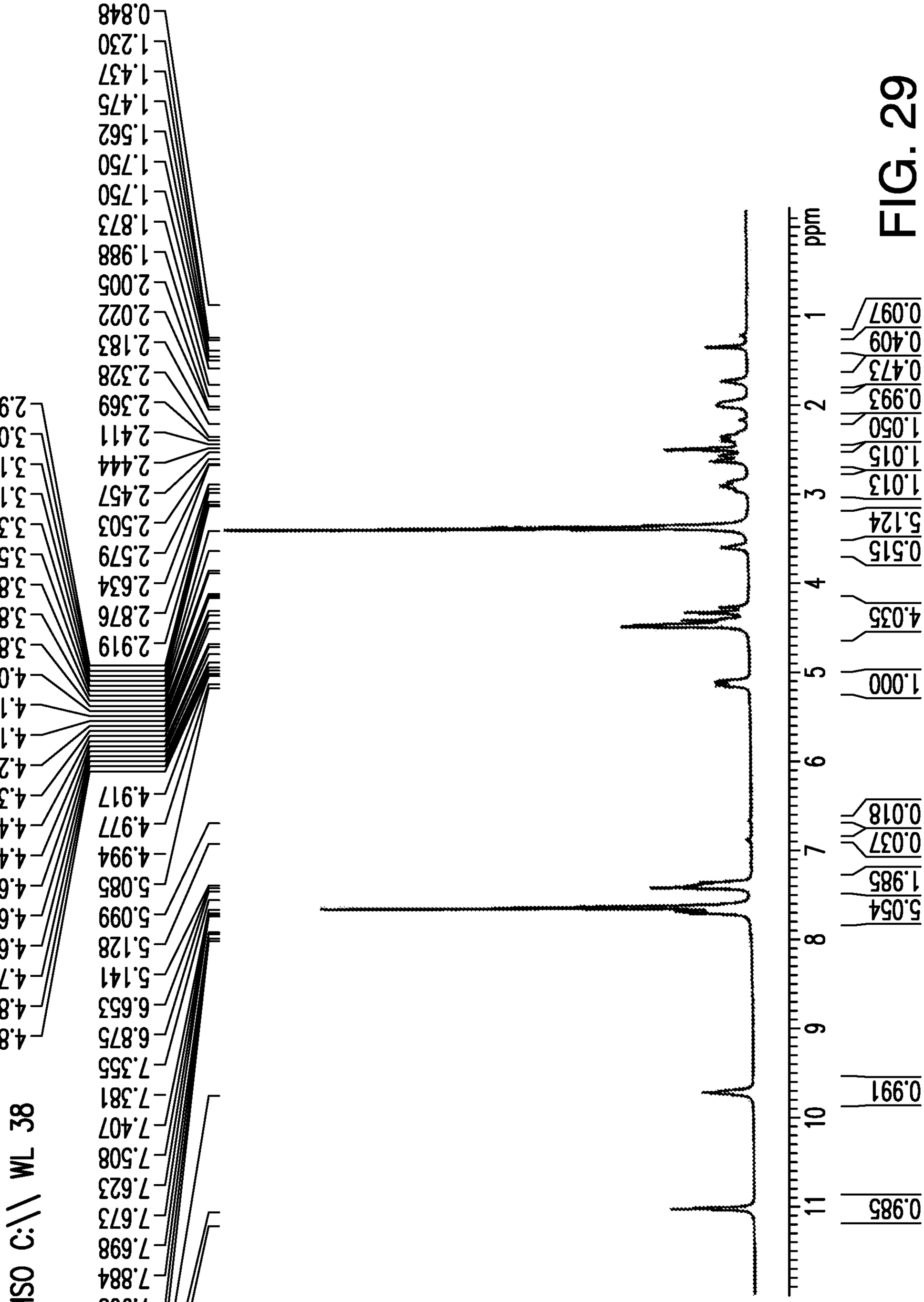

PROTON DMSO C:\\ WL 38
0.848
1.230
1.437
1.475
1.562
1.750
1.750
1.873
1.988
2.005
2.022
2.183
2.328
2.369
2.411
2.444
2.457
2.503
2.579
2.634
2.876
2.919
2.962
3.055
3.109
3.124
3.371
3.596
3.813
3.829
3.842
4.073
4.105
4.125
4.260
4.317
4.401
4.463
4.635
4.675
4.682
4.751
4.852
4.899
4.917
4.977
4.994
5.085
5.099
5.128
5.141
6.653
6.875
7.355
7.381
7.407
7.508
7.623
7.673
7.698
7.884
7.905
7.965
9.705
11.006
11.165
ppm
1.000
4.035
0.515
5.124
1.013
1.015
1.050
0.993
0.473
0.409
0.097
5.054
1.985
0.037
0.018
0.991
0.985

FIG. 29

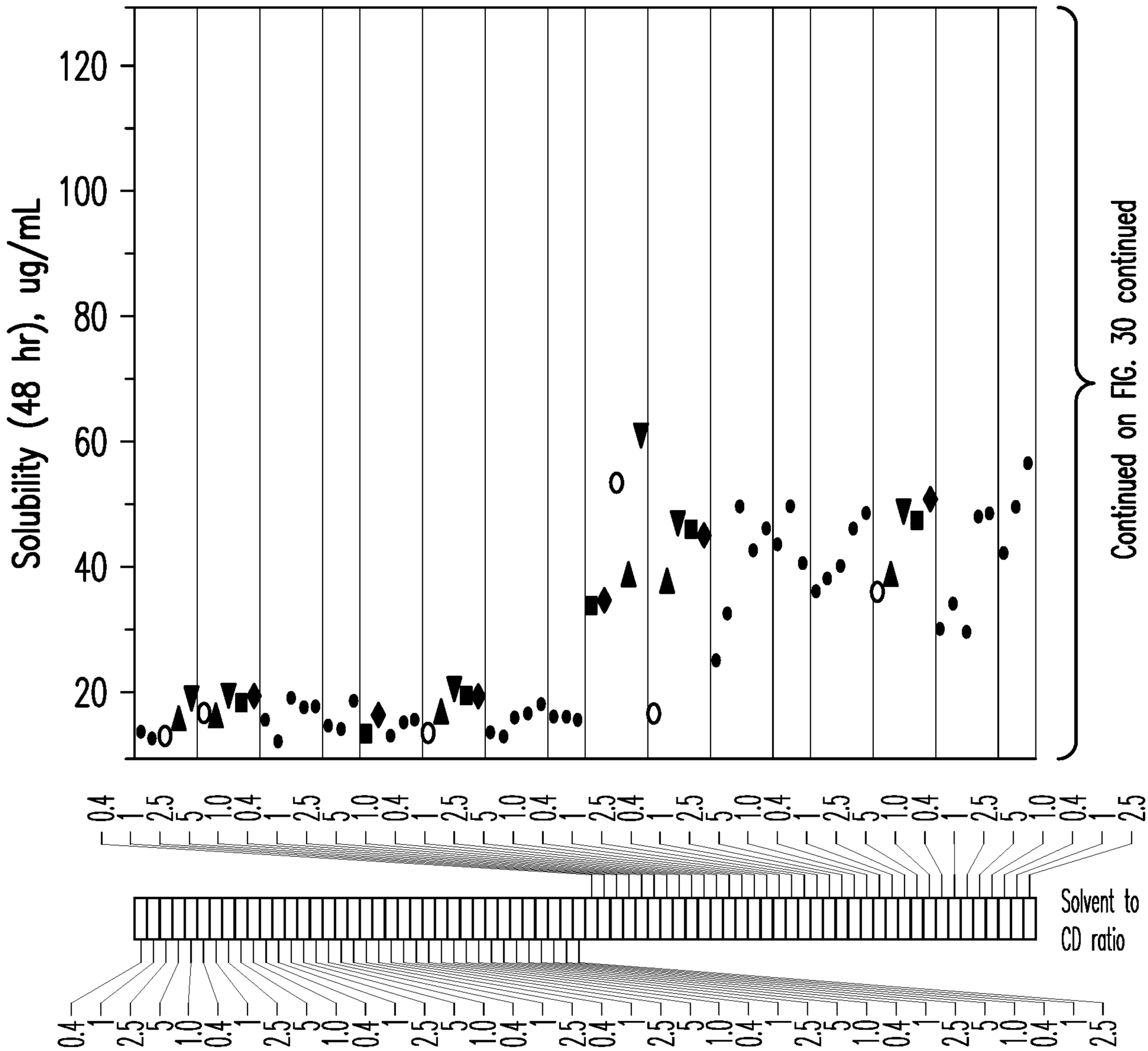

Solubility (48 hr), ug/mL
120
100
80
60
40
20
Continued on FIG. 30 continued
0.4 1 2.5 5 1.0
Solvent to CD ratio
Captisol
Dexolve
HP-B-CD
Kleptose
Brand
DMSO
Formic Acid
Solvent type
0.03
0.09
CD conc %

FIG. 30

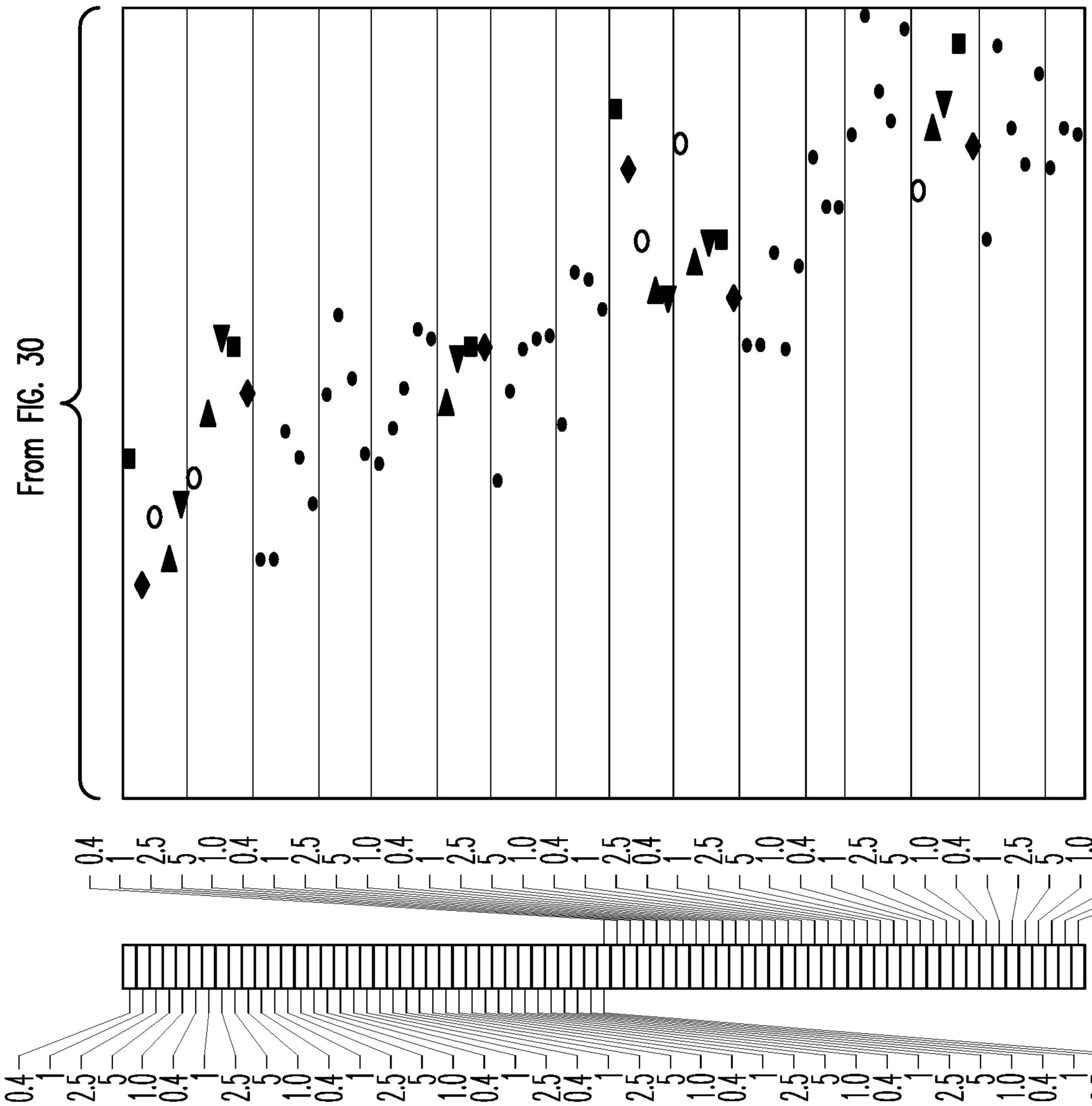


FIG. 30 continued

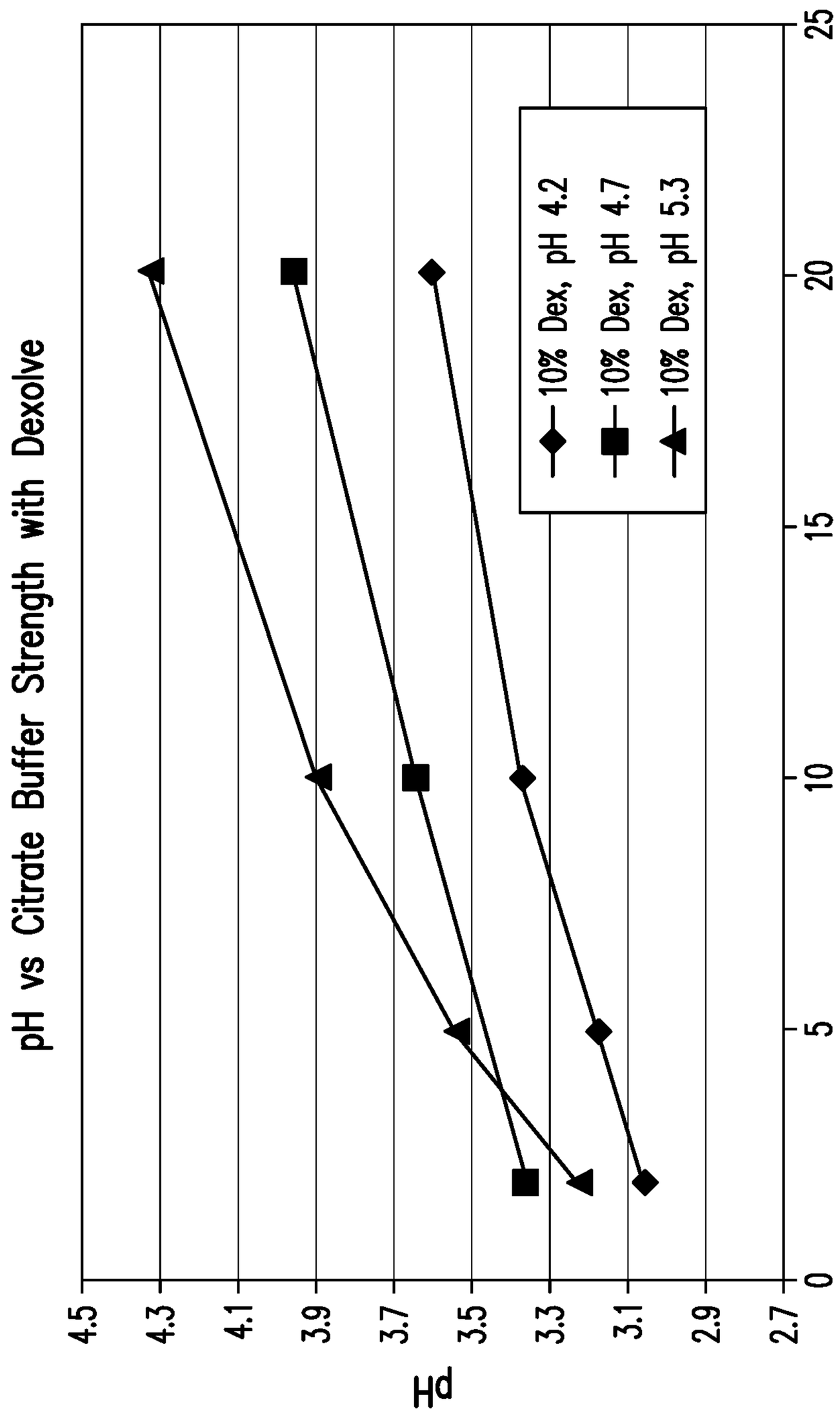

pH vs Citrate Buffer Strength with Dexolve
10% Dex, pH 4.2
10% Dex, pH 4.7
10% Dex, pH 5.3
Buffer Strength (mM)
pH
4.5
4.3
4.1
3.9
3.7
3.5
3.3
3.1
2.9
2.7
0
5
10
15
20
25

FIG. 31

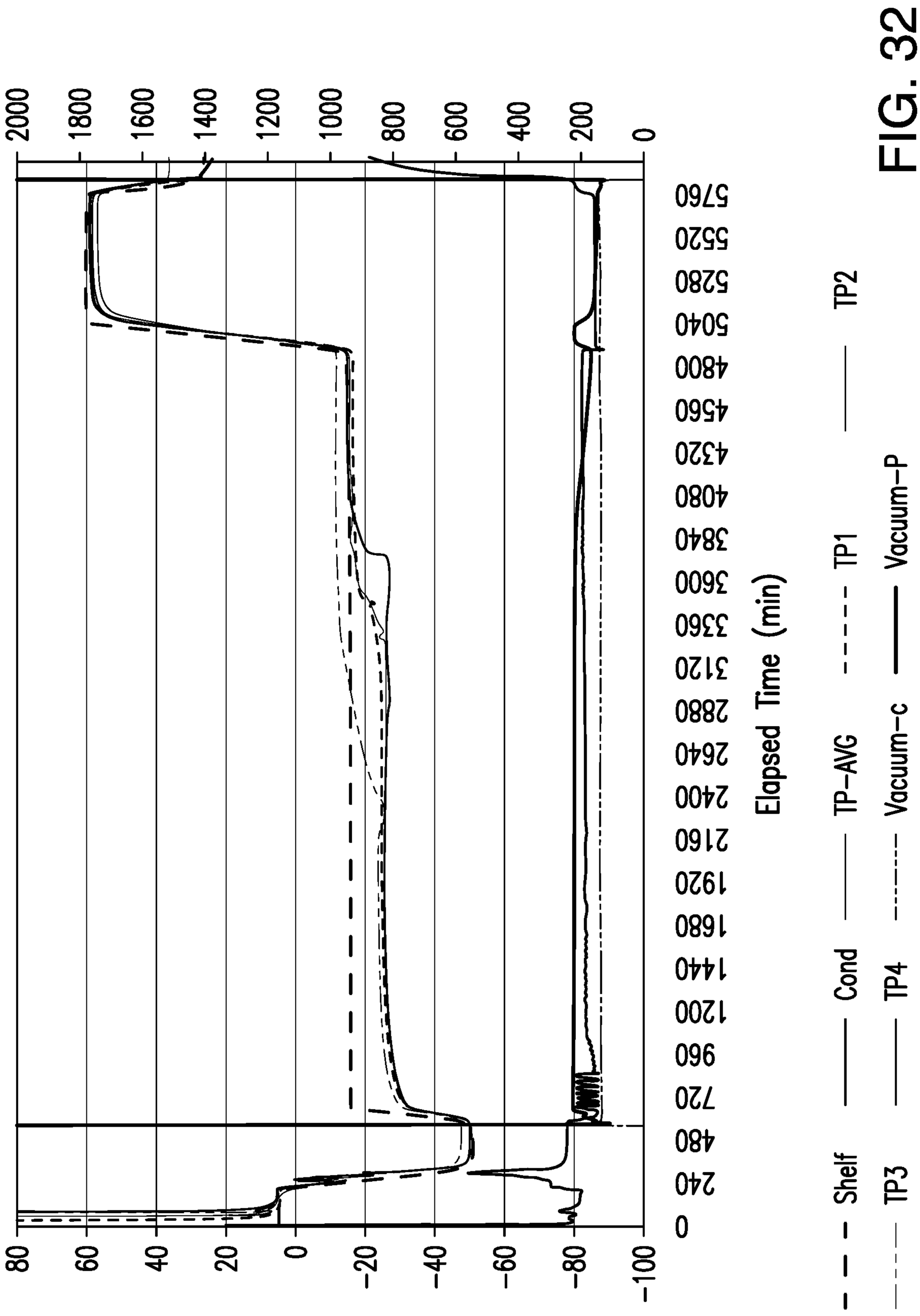

Temperature (°C)
80
60
40
20
0
-20
-40
-60
-80
-100
Elapsed Time (min)
0
240
480
720
960
1200
1440
1680
1920
2160
2400
2640
2880
3120
3360
3600
3840
4080
4320
4560
4800
5040
5280
5520
5760
Cond
TP-AVG
TP4
Vacuum-c
Shelf
TP3
TP1
TP2
Vacuum-P

FIG. 32

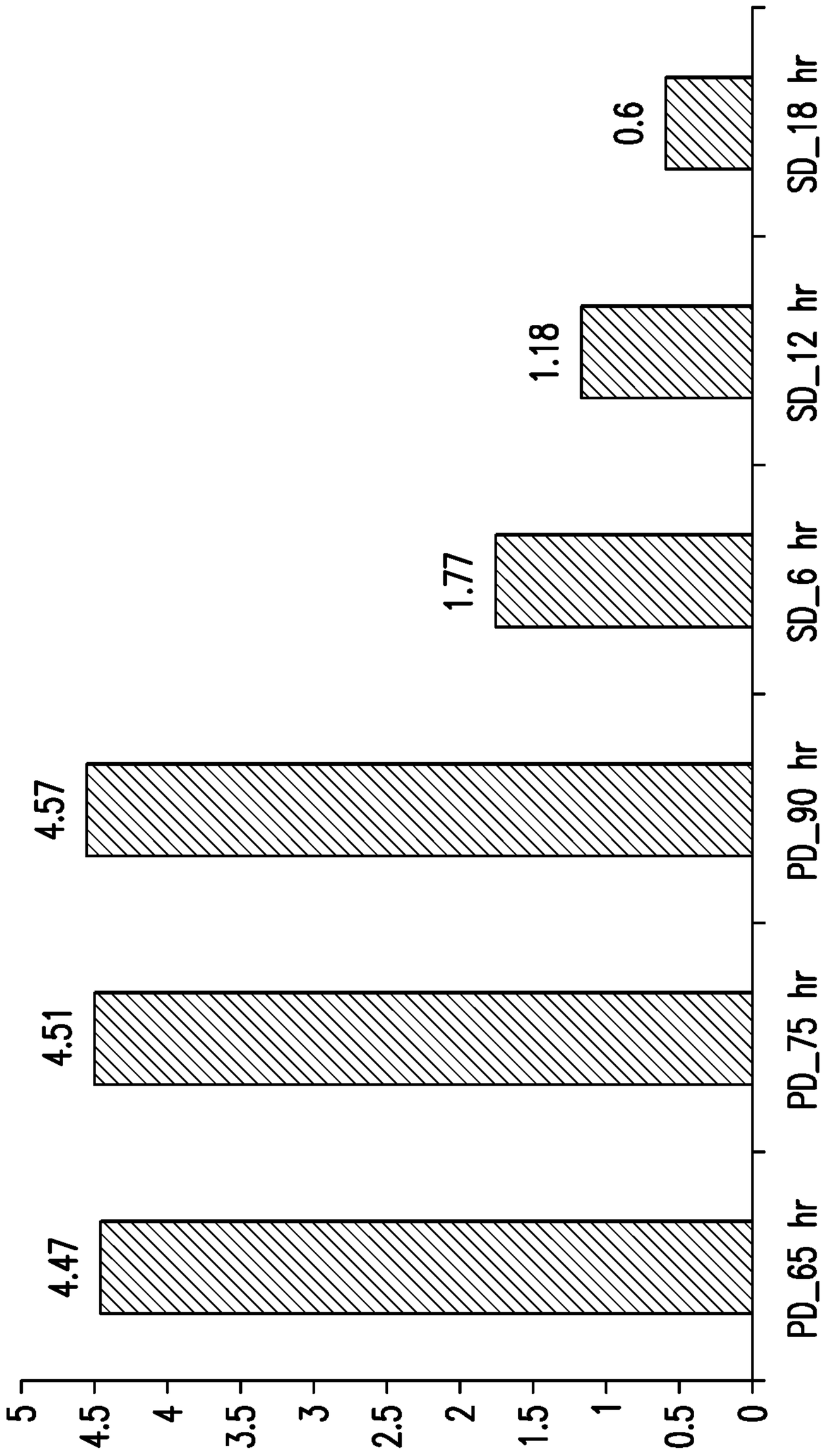

Residual Formate Acid (mg/vial)
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
4.47
4.51
4.57
1.77
1.18
0.6
PD_65 hr
PD_75 hr
PD_90 hr
SD_6 hr
SD_12 hr
SD_18 hr
Lyo Cycle Time

FIG. 33

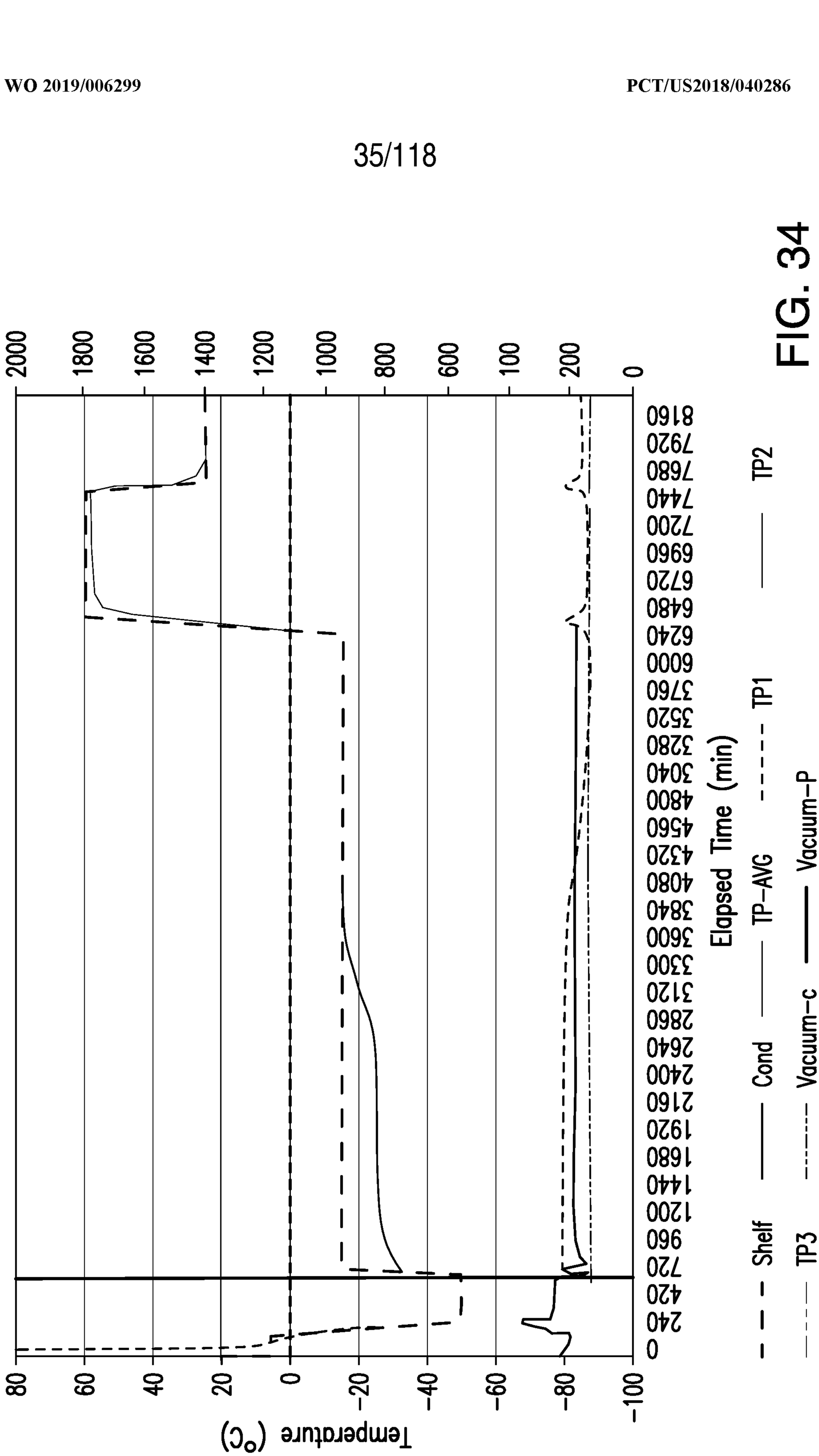

Temperature (°C)
80
60
40
20
0
-20
-40
-60
-80
-100
Elapsed Time (min)
0
240
420
720
960
1200
1440
1680
1920
2160
2400
2640
2860
3120
3300
3600
3840
4080
4320
4560
4800
3040
3280
3520
3760
6000
6240
6480
6720
6960
7200
7440
7680
7920
8160
2000
1800
1600
1400
1200
1000
800
600
100
200
0
Cond
TP-AVG
Vacuum-P
Vacuum-c
Shelf
TP3
TP1
TP2

FIG. 34

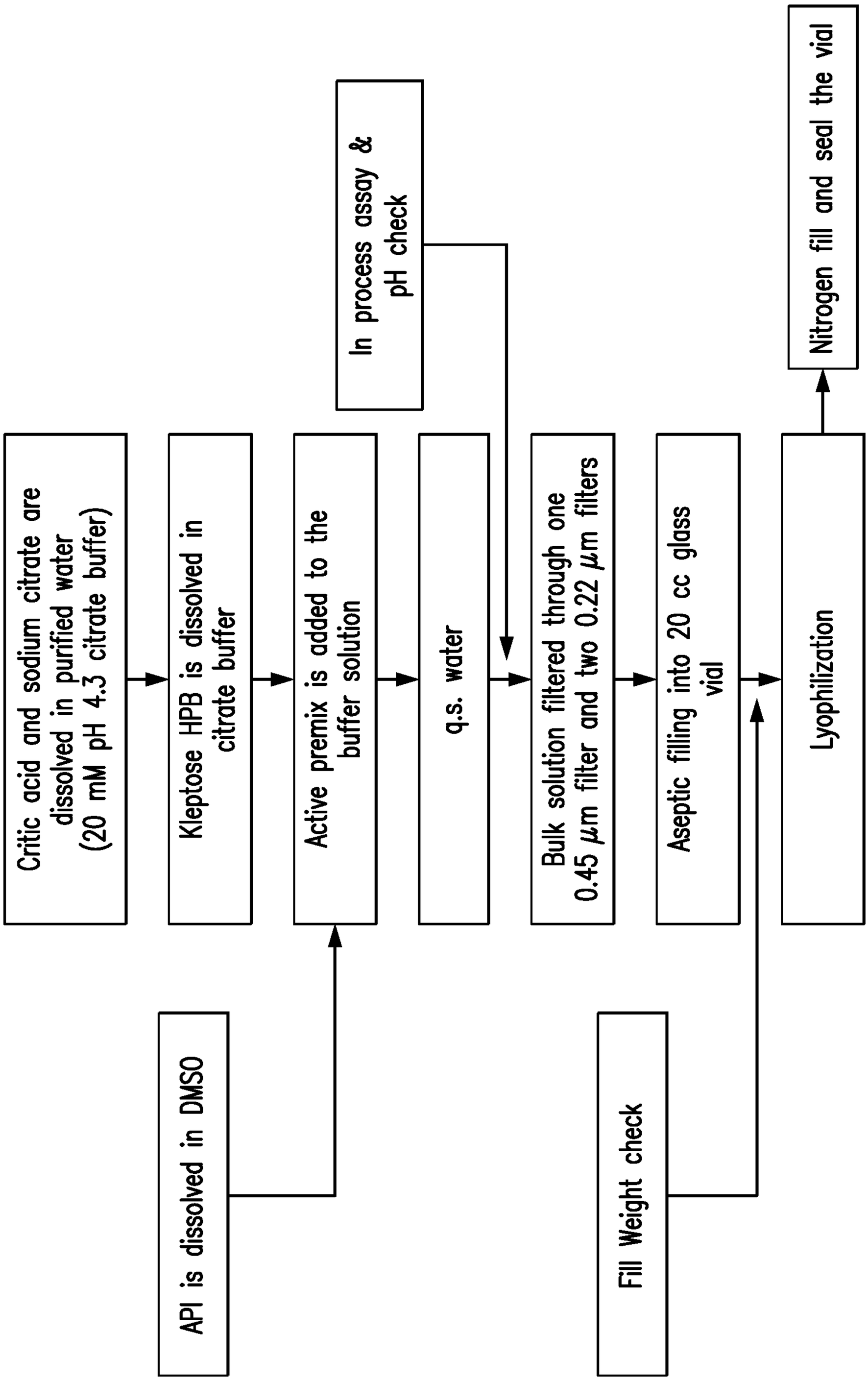

Critic acid and sodium citrate are dissolved in purified water (20 mM pH 4.3 citrate buffer)
Kleptose HPB is dissolved in citrate buffer
Active premix is added to the buffer solution
q.s. water
In process assay & pH check
Bulk solution filtered through one 0.45 μm filter and two 0.22 μm filters
Aseptic filling into 20 cc glass vial
Nitrogen fill and seal the vial
Lyophilization
API is dissolved in DMSO
Fill Weight check

FIG. 35

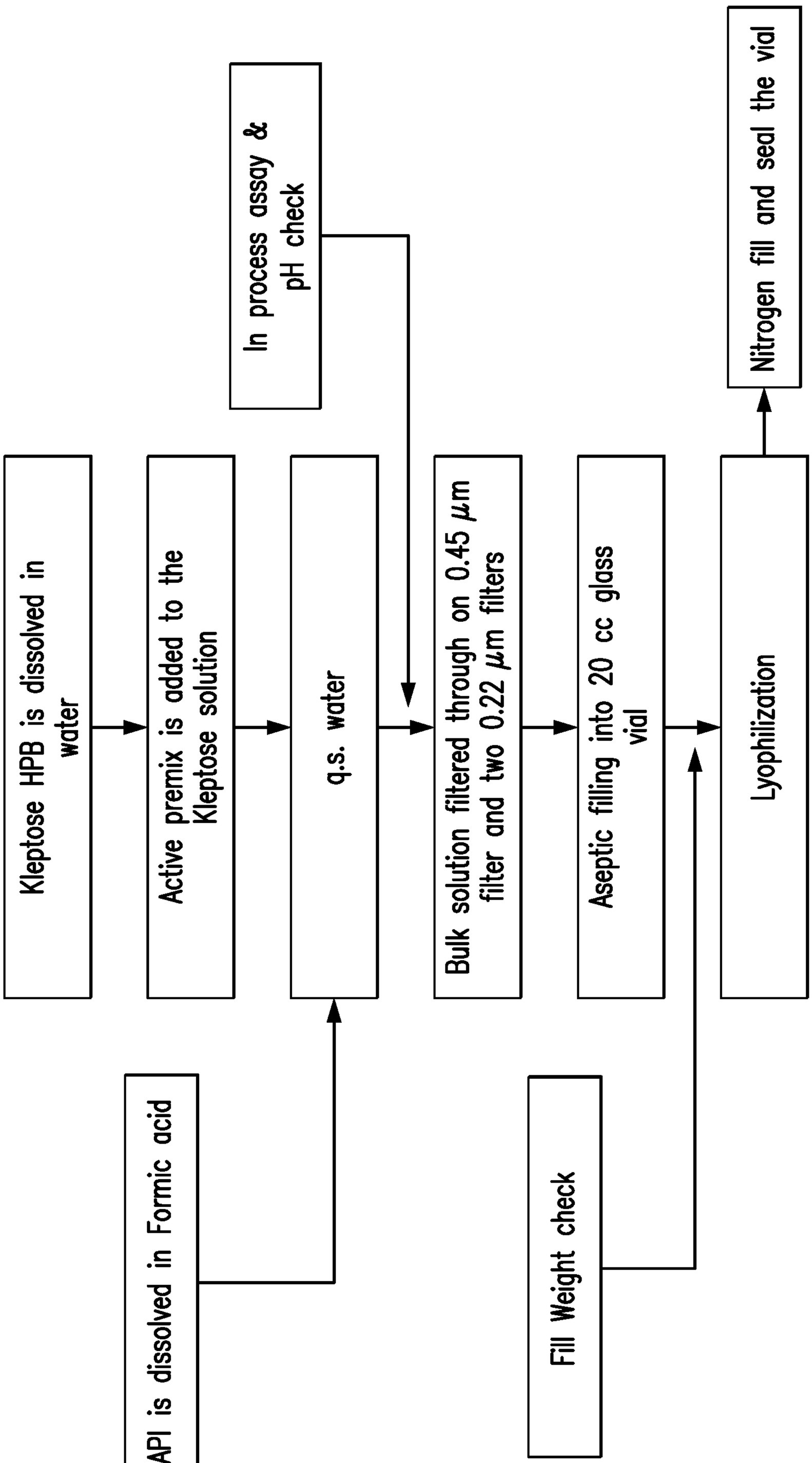

Kleptose HPB is dissolved in water
Active premix is added to the Kleptose solution
q.s. water
In process assay & pH check
Bulk solution filtered through on 0.45 μm filter and two 0.22 μm filters
Aseptic filling into 20 cc glass vial
Nitrogen fill and seal the vial
Lyophilization
API is dissolved in Formic acid
Fill Weight check

FIG. 36

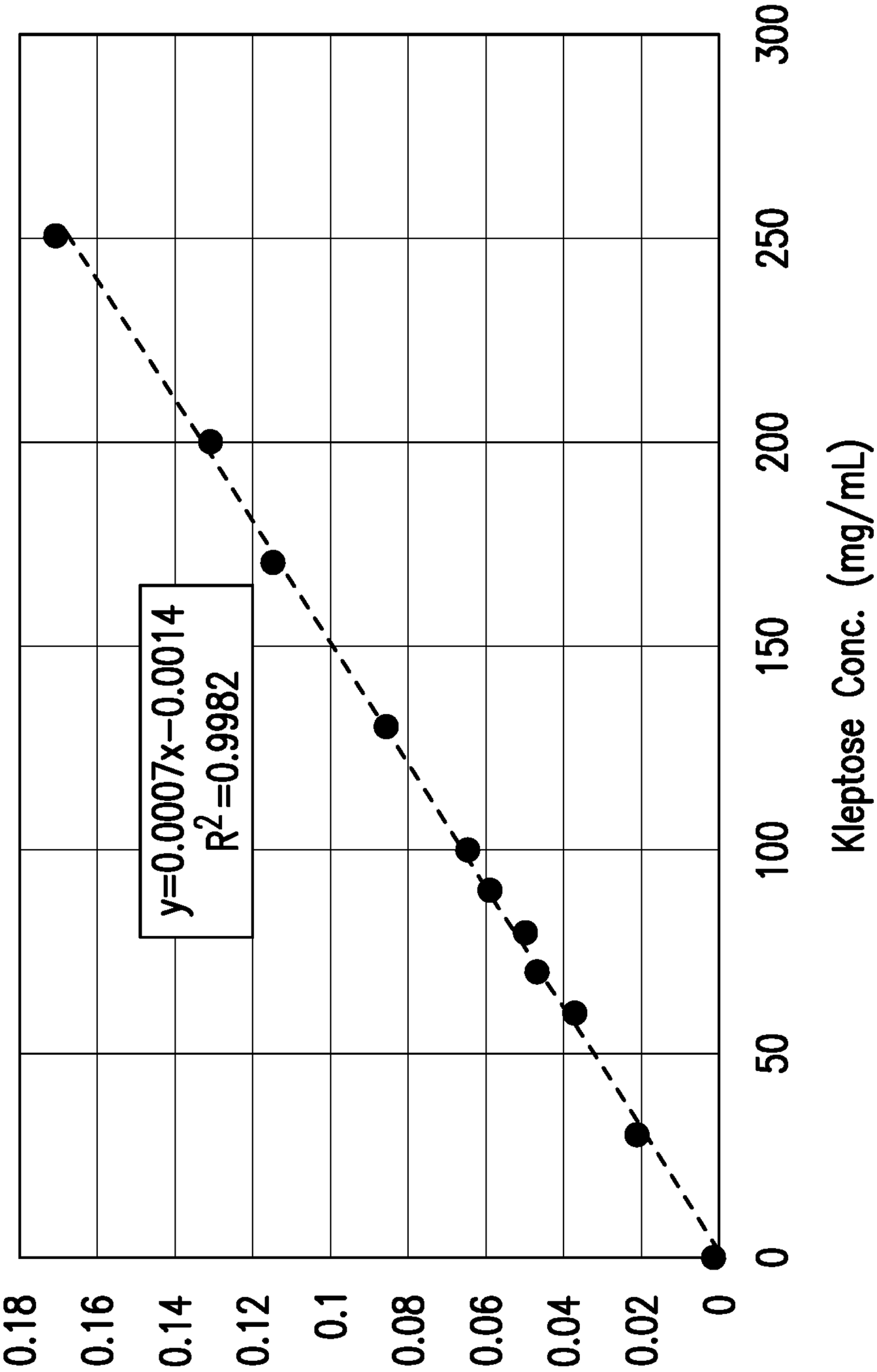

y=0.0007x−0.0014
R2=0.9982
Kleptose Conc. (mg/mL)
Compound 1 solubility (mg/mL)
0
50
100
150
200
250
300
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0

FIG. 37

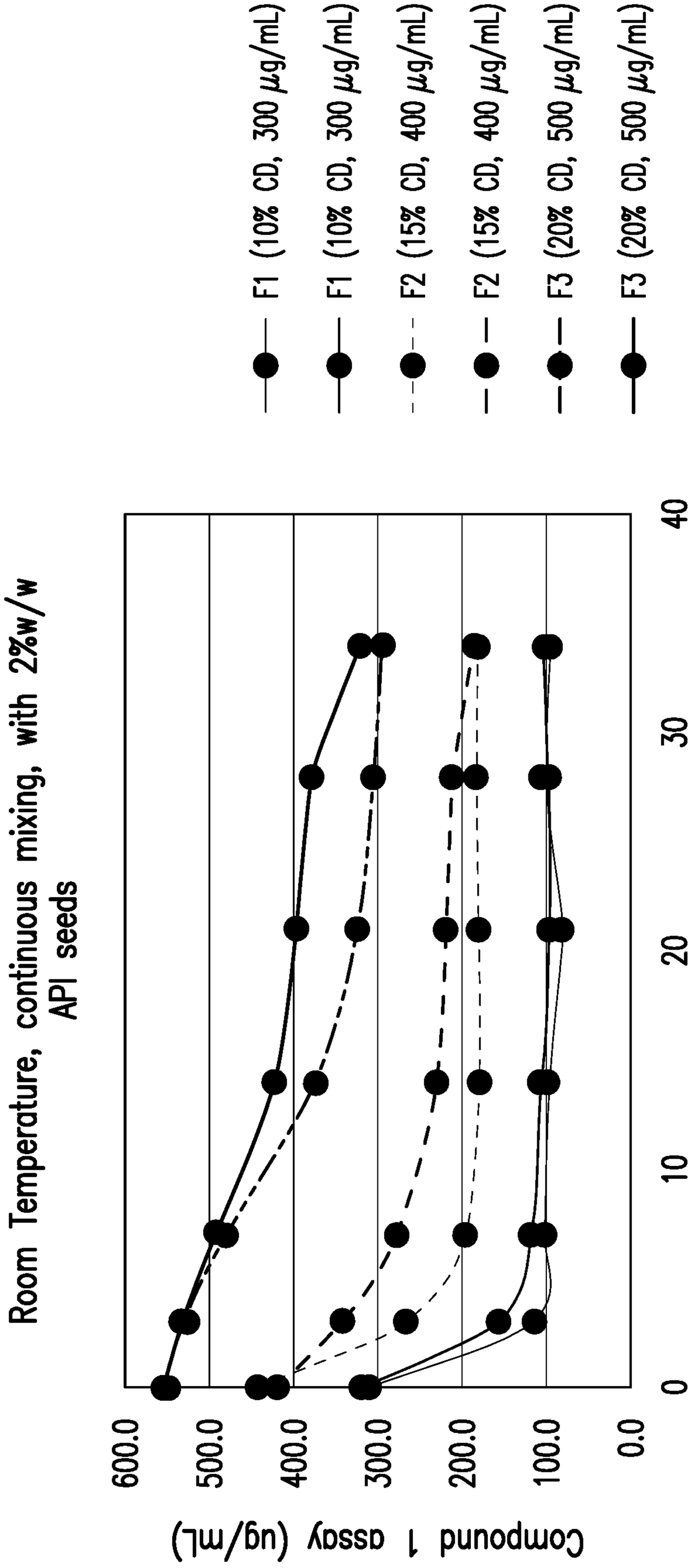

Compound 1 assay (ug/mL)
600.0
500.0
400.0
300.0
200.0
100.0
0.0
0
10
20
30
40
Time (days)
Room Temperature, continuous mixing, with 2%w/w API seeds
F1 (10% CD, 300 µg/mL)
F1 (10% CD, 300 µg/mL)
F2 (15% CD, 400 µg/mL)
F2 (15% CD, 400 µg/mL)
F3 (20% CD, 500 µg/mL)
F3 (20% CD, 500 µg/mL)

FIG. 38

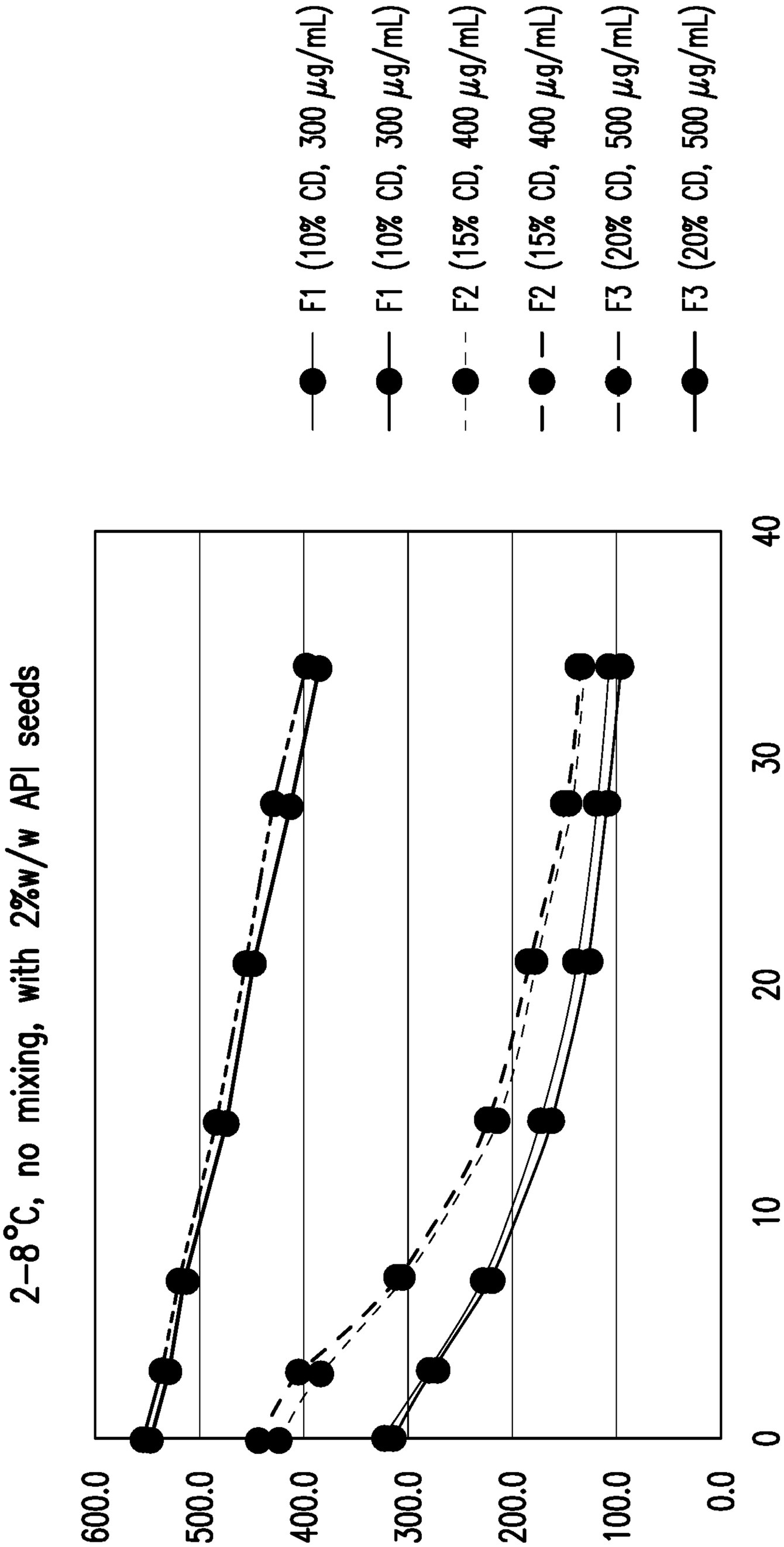

F1 (10% CD, 300 µg/mL)
F1 (10% CD, 300 µg/mL)
F2 (15% CD, 400 µg/mL)
F2 (15% CD, 400 µg/mL)
F3 (20% CD, 500 µg/mL)
F3 (20% CD, 500 µg/mL)
2–8°C, no mixing, with 2%w/w API seeds
Compound 1 assay (µg/mL)
600.0
500.0
400.0
300.0
200.0
100.0
0.0
Time (days)
0
10
20
30
40

FIG. 39

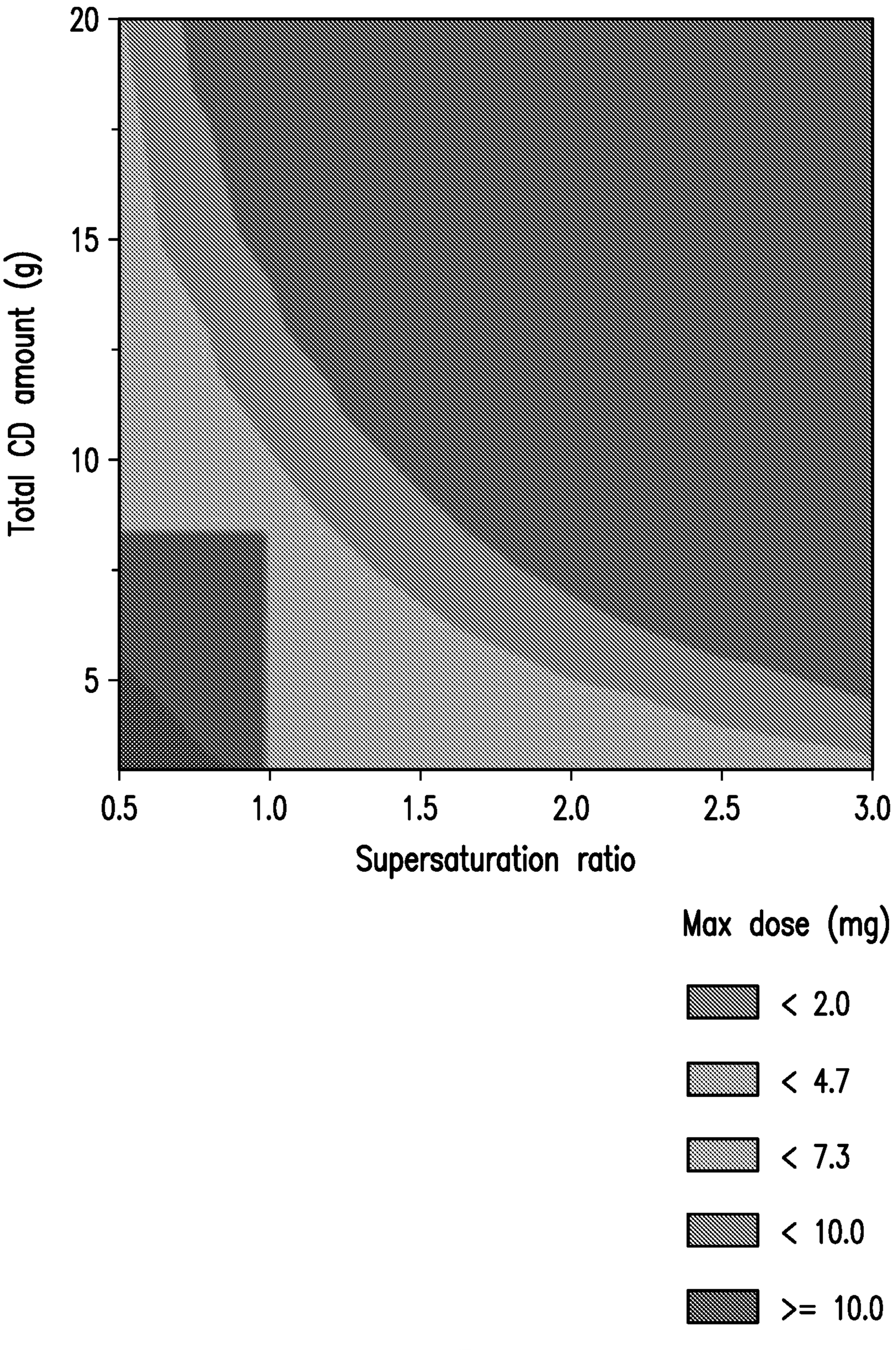

20
15
10
5
Total CD amount (g)
0.5
1.0
1.5
2.0
2.5
3.0
Supersaturation ratio
Max dose (mg)
< 2.0
< 4.7
< 7.3
< 10.0
>= 10.0

FIG. 40

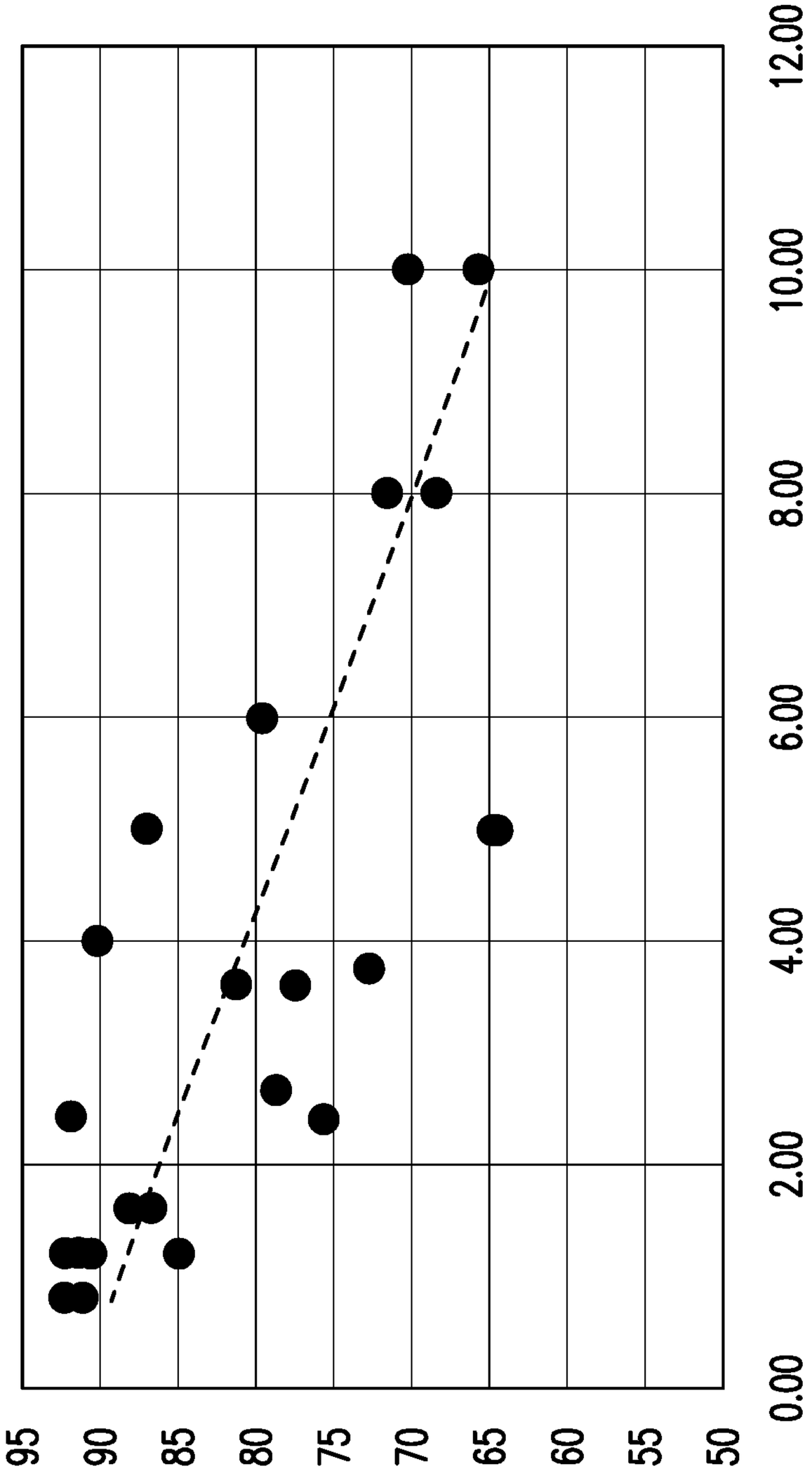

12.00
10.00
8.00
6.00
4.00
2.00
0.00
Total Kleptose Amount (g/vial)
95
90
85
80
75
70
65
60
55
50
% Formic Acid Removed

FIG. 41

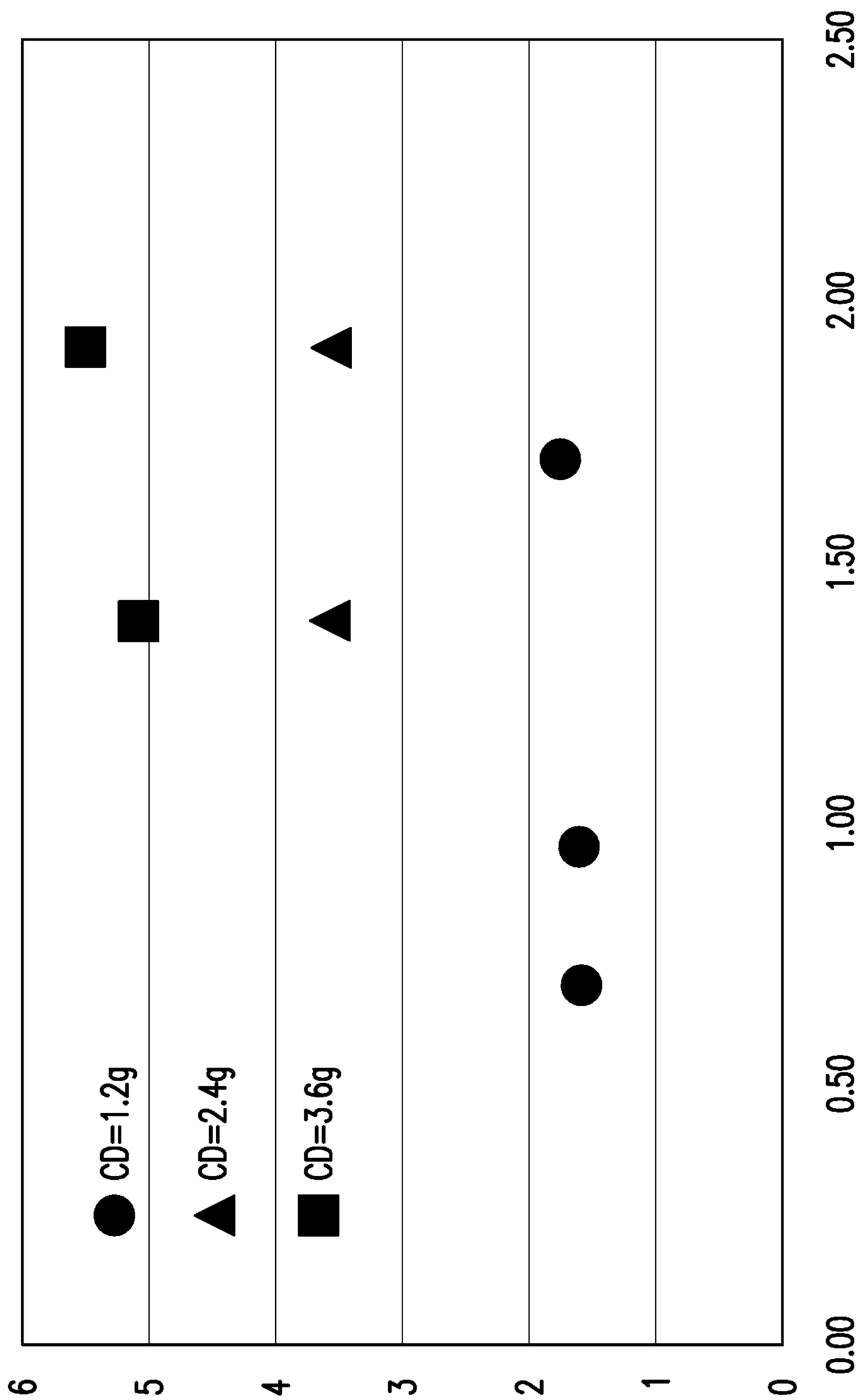

CD=1.2g
CD=2.4g
CD=3.6g
0
1
2
3
4
5
6
Residual Formic Acid (mg/vial)
0.00
0.50
1.00
1.50
2.00
2.50
Fill Height (cm)

FIG. 42

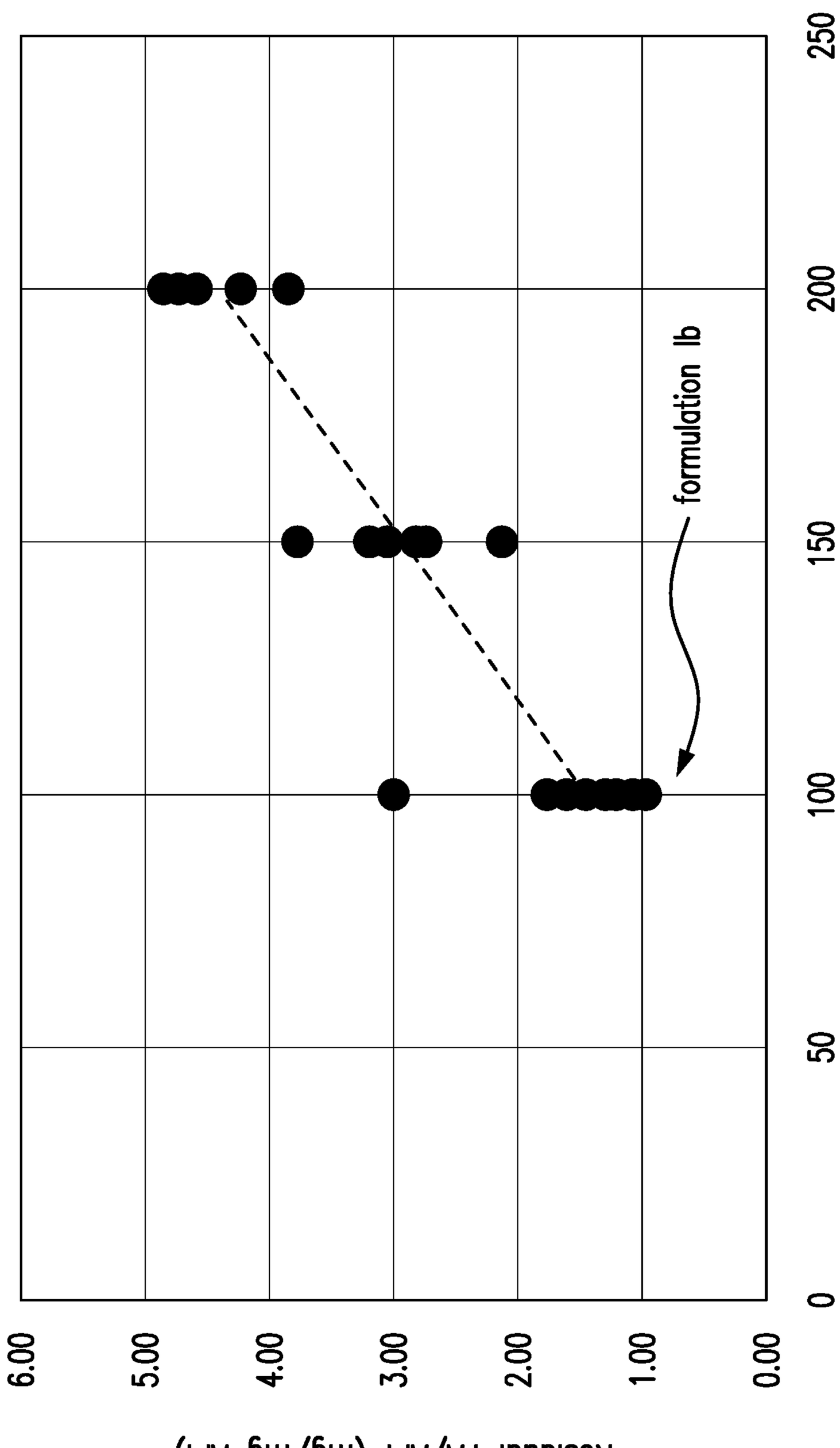

Residual FA/API (mg/mg API)
6.00
5.00
4.00
3.00
2.00
1.00
0.00
Kleptose concentration (mg/mL)
0
50
100
150
200
250
formulation Ib

FIG. 43

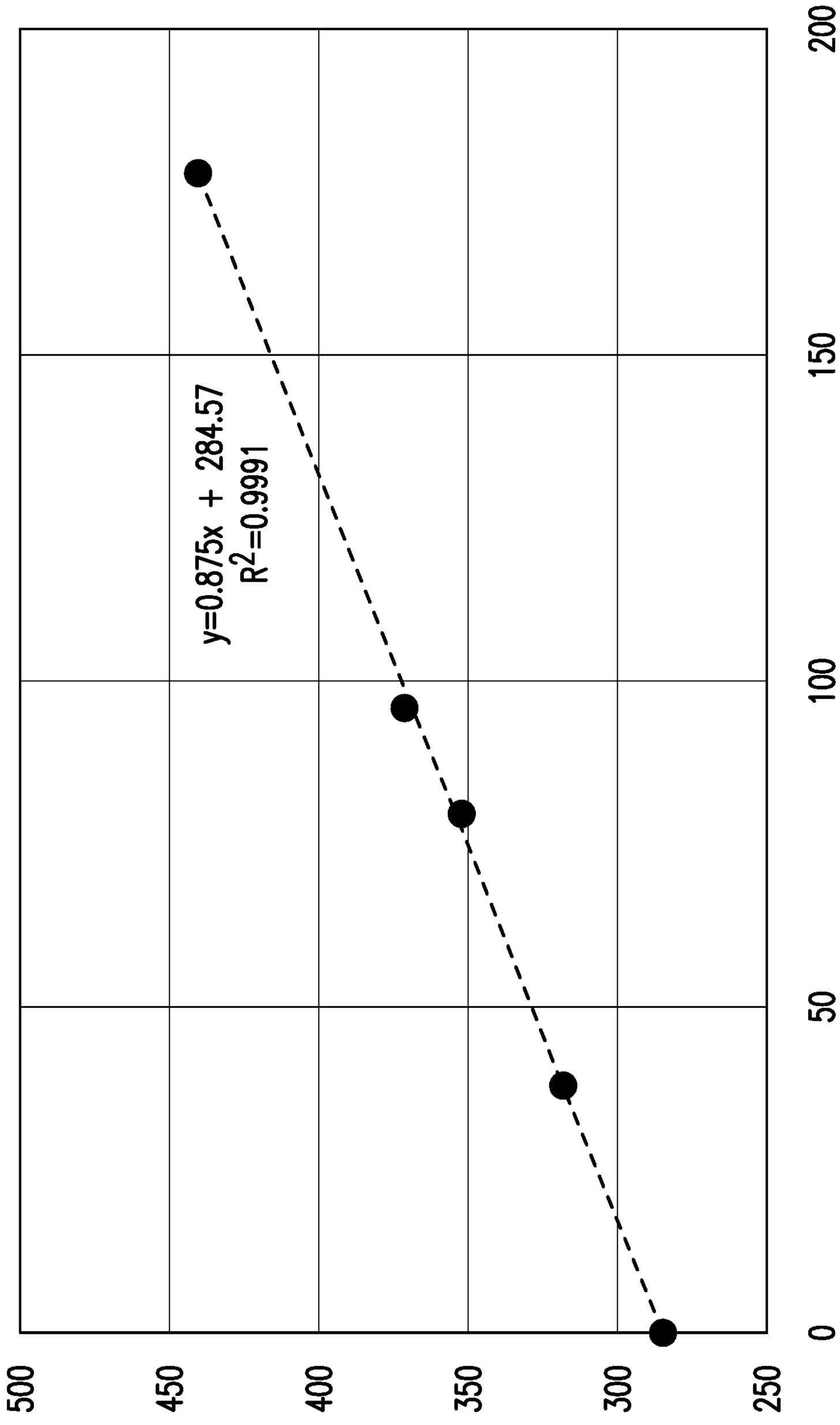

y=0.875x + 284.57
R2=0.9991
Kleptose Conc. (mg/mL)
0
50
100
150
200
Osmolality (mOsm/kg)
500
450
400
350
300
250

FIG. 44

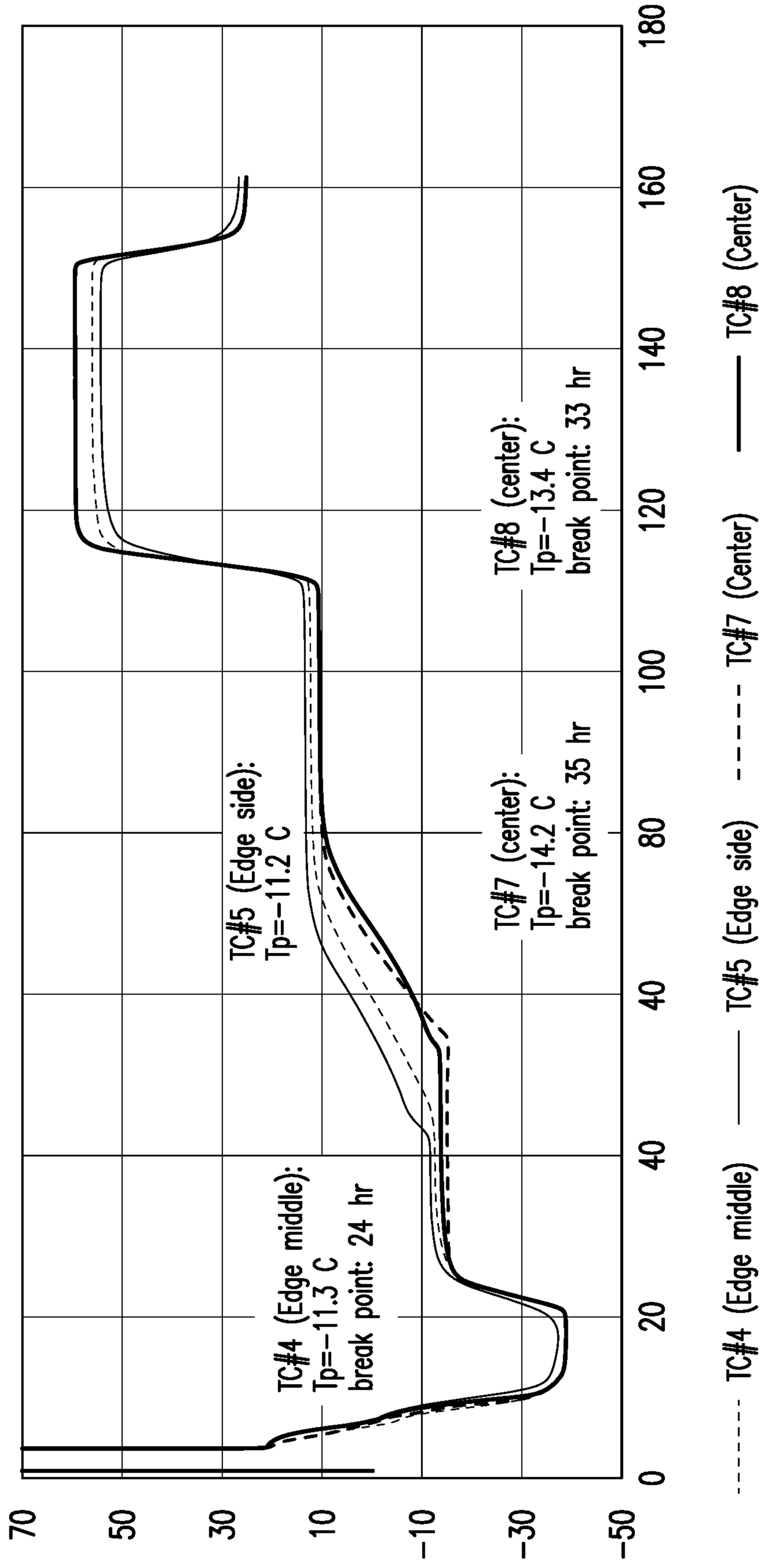

TC#4 (Edge middle):
Tp=−11.3 C
break point: 24 hr
TC#5 (Edge side):
Tp=−11.2 C
TC#7 (center):
Tp=−14.2 C
break point: 35 hr
TC#8 (center):
Tp=−13.4 C
break point: 33 hr
TC#4 (Edge middle) —— TC#5 (Edge side) - - - - TC#7 (Center) —— TC#8 (Center)
70
50
30
10
−10
−30
−50
0
20
40
60
80
100
120
140
160
180

FIG. 45

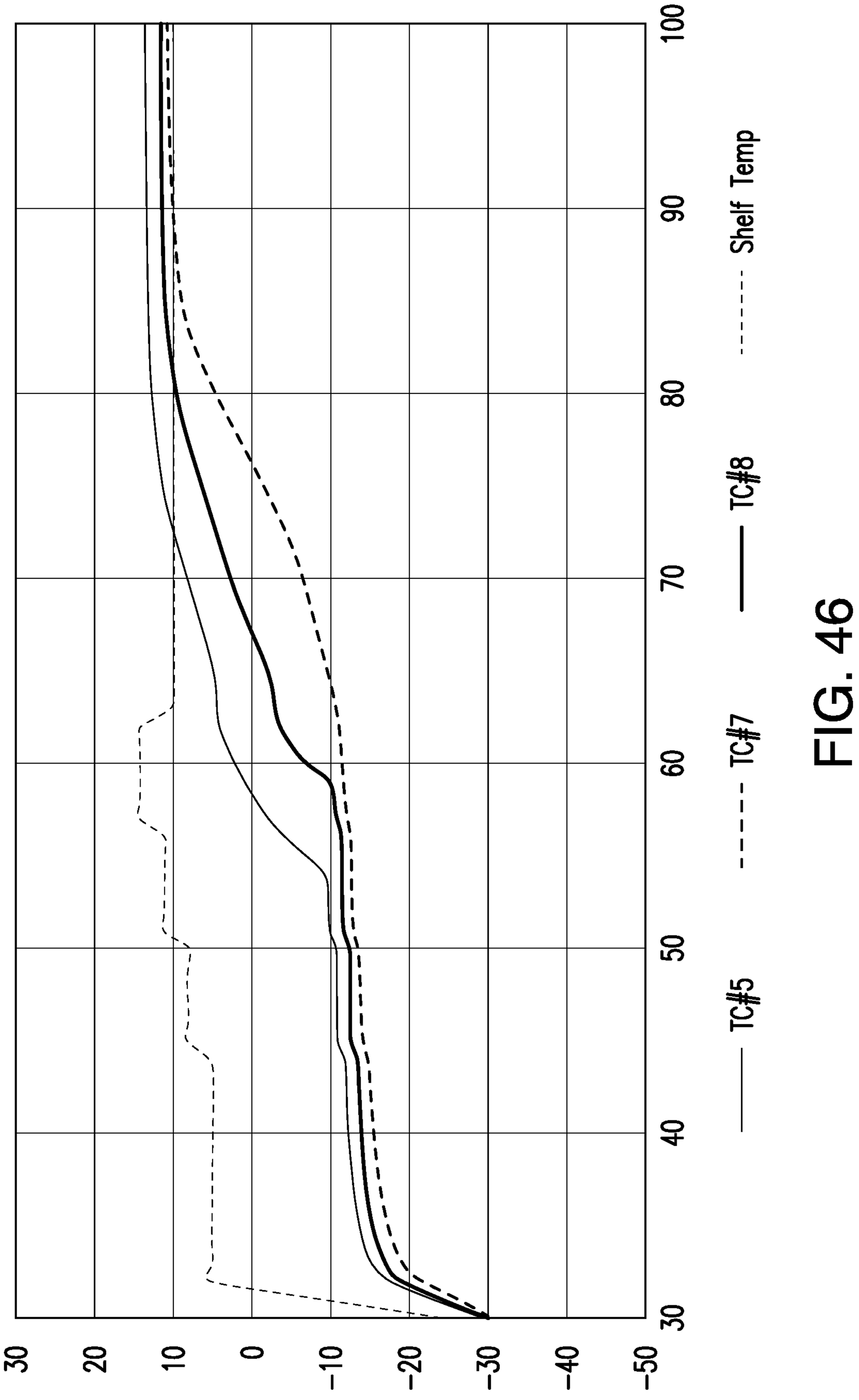

100
90
80
70
60
50
40
30
30
20
10
0
−10
−20
−30
−40
−50
Shelf Temp
TC#8
TC#7
TC#5

FIG. 46

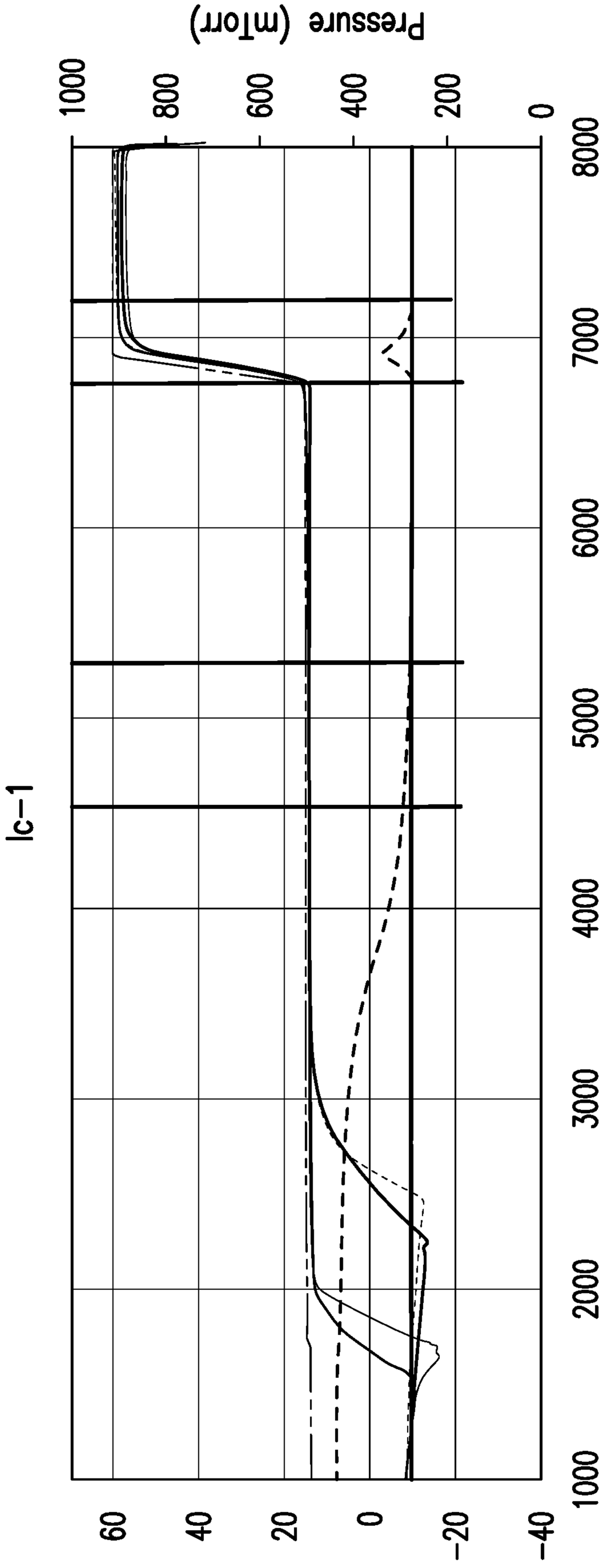

Pressure (mTorr)
1000
800
600
400
200
0
8000
7000
6000
5000
4000
3000
2000
1000
Ic–1
Cycle Time (min)
TP1
TP2
Shelf
Cond
60
40
20
0
–20
–40
Temperature (°C)

FIG. 47

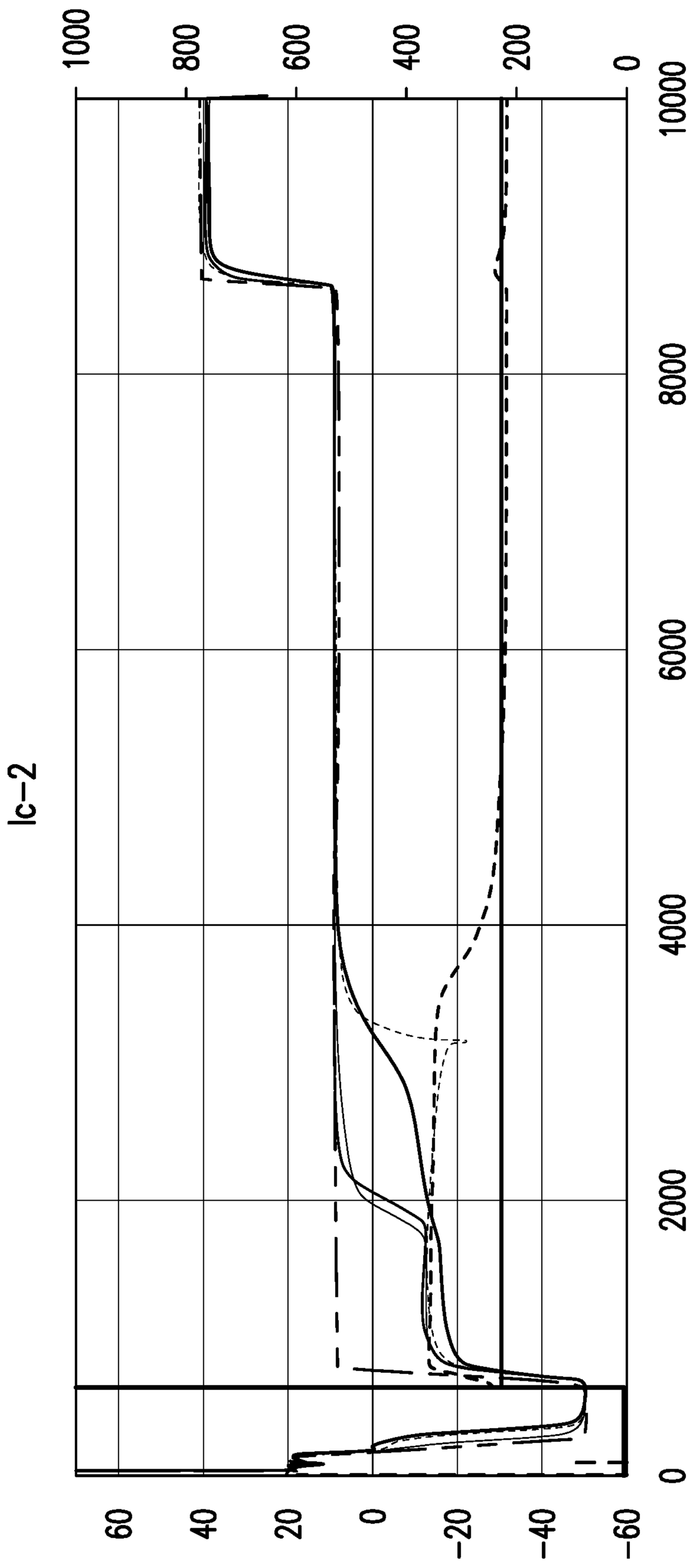

Pressure (mTorr)
1000
800
600
400
200
0
10000
8000
6000
4000
2000
0
Cycle Time (min)
Ic-2
TP2
Shelf
Cond
TP1
60
40
20
0
-20
-40
-60
Temperature (°C)

FIG. 48

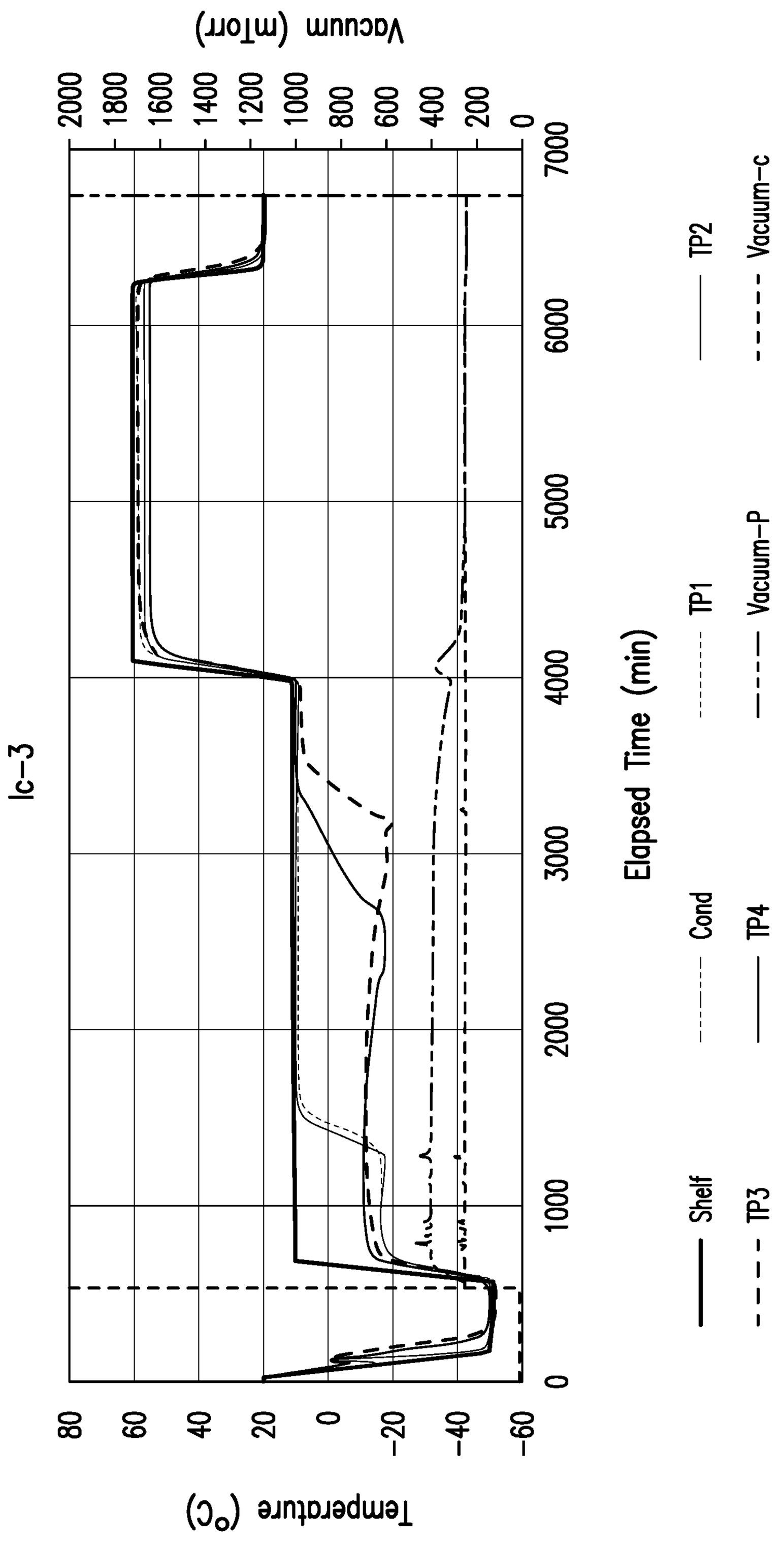
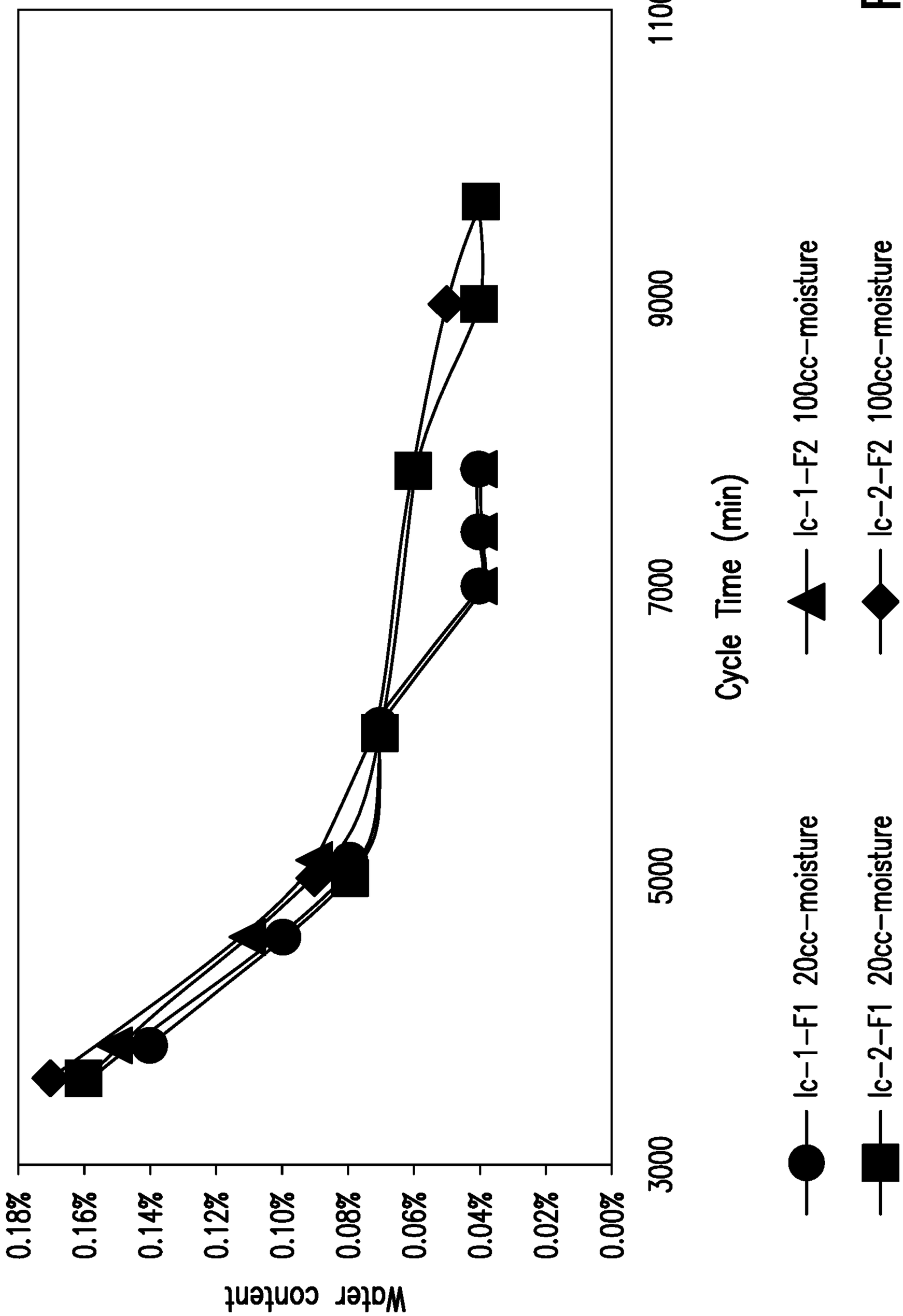

Vacuum (mTorr)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
Ic–3
7000
6000
5000
4000
3000
2000
1000
0
Elapsed Time (min)
80
60
40
20
0
–20
–40
–60
Temperature (°C)
TP1
TP2
Cond
TP4
Shelf
TP3
Vacuum–P
Vacuum–c

FIG. 49

FIG. 50


Water content
0.18%
0.16%
0.14%
0.12%
0.10%
0.08%
0.06%
0.04%
0.02%
0.00%
Cycle Time (min)
3000
5000
7000
9000
11000
lc-1-F1 20cc-moisture
lc-2-F1 20cc-moisture
lc-1-F2 100cc-moisture
lc-2-F2 100cc-moisture

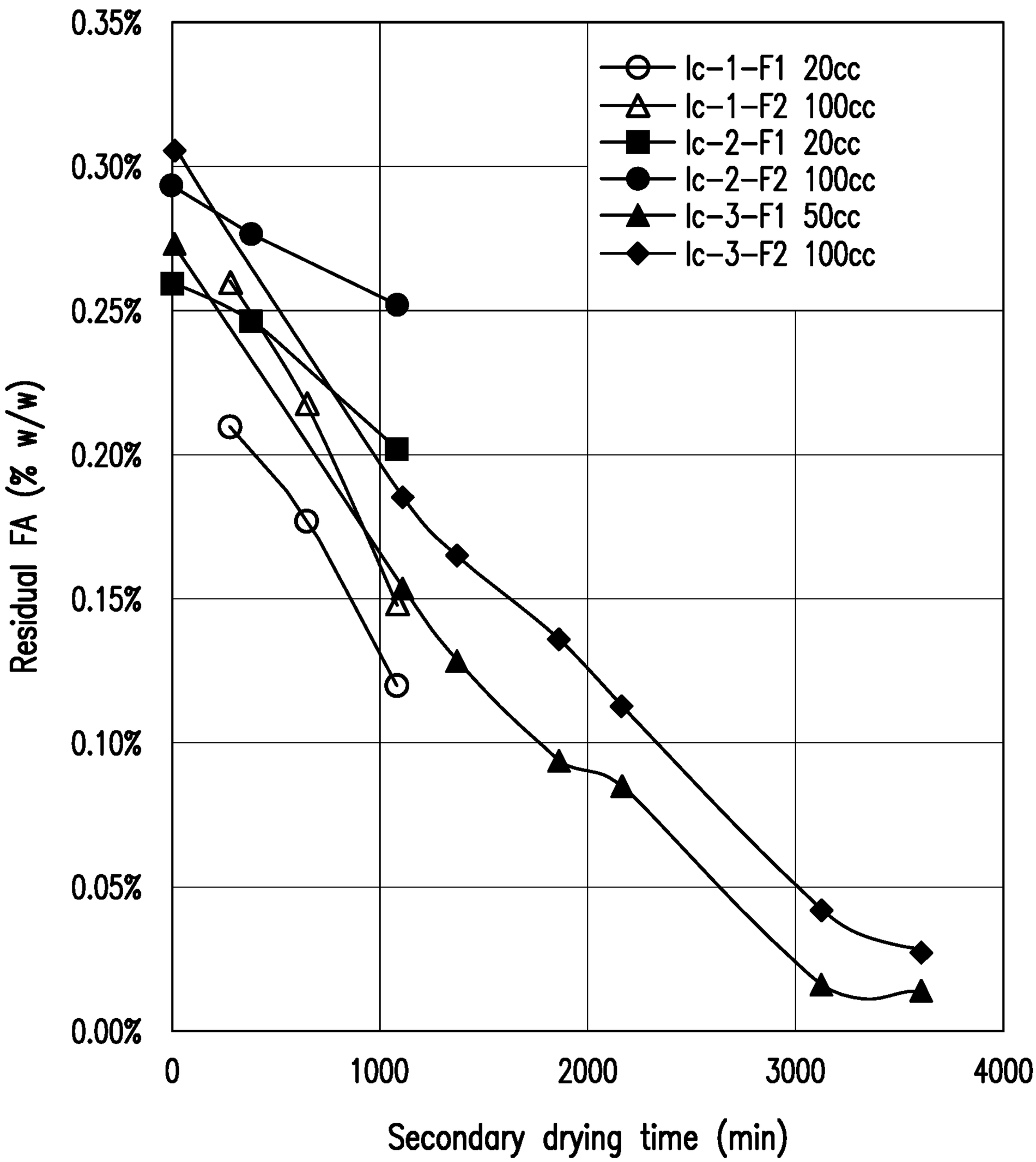

0.35%
0.30%
0.25%
0.20%
0.15%
0.10%
0.05%
0.00%
Residual FA (% w/w)
0
1000
2000
3000
4000
Secondary drying time (min)
lc-1-F1 20cc
lc-1-F2 100cc
lc-2-F1 20cc
lc-2-F2 100cc
lc-3-F1 50cc
lc-3-F2 100cc

FIG. 51

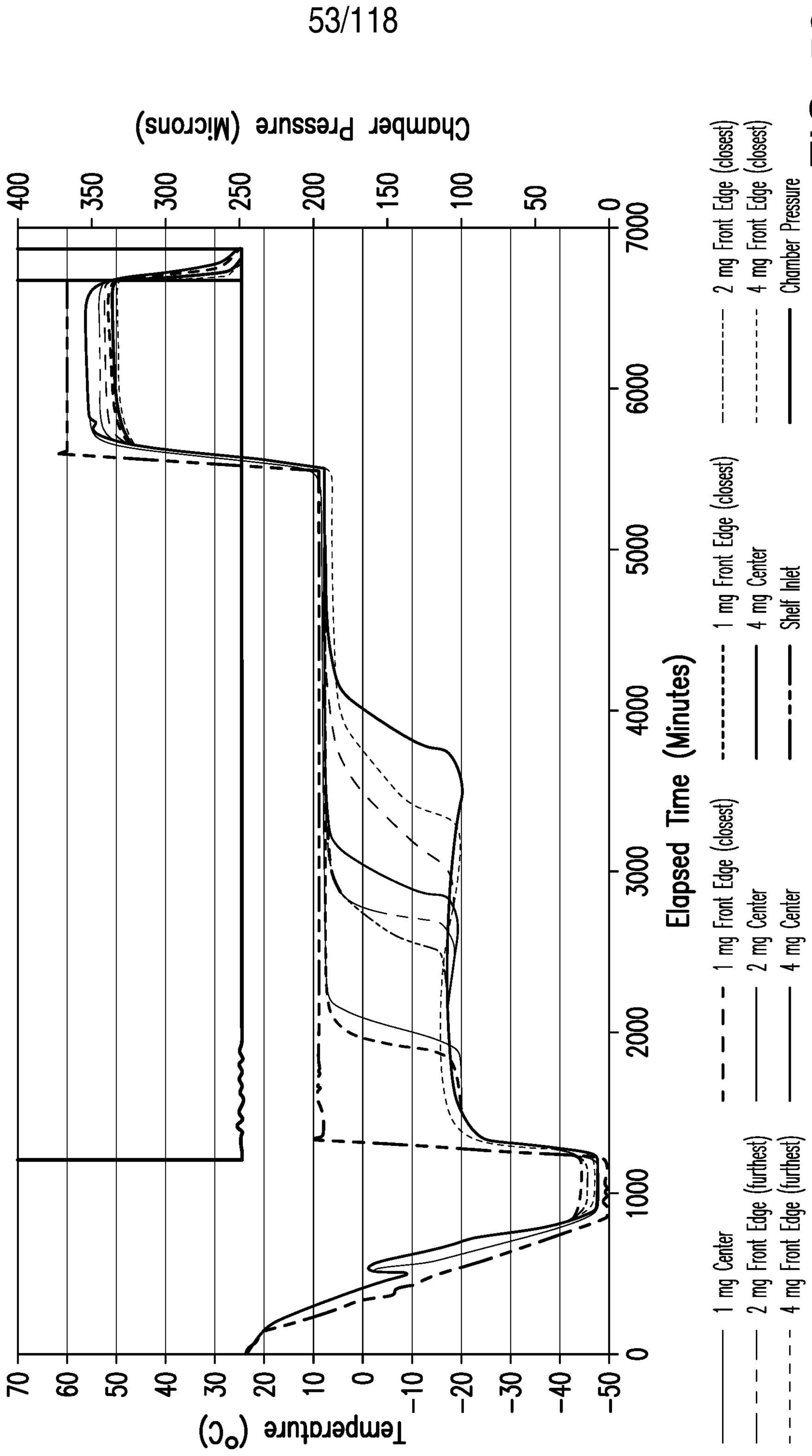

Compound 1 (0.080mg/mL) in Formic Acid
(0.1 °C/minute freezing ramp)
Chamber Pressure (Microns)
400
350
300
250
200
150
100
50
0
Elapsed Time (Minutes)
0
1000
2000
3000
4000
5000
6000
7000
1 mg Front Edge (closest)
4 mg Center
Shelf Inlet
2 mg Front Edge (closest)
4 mg Front Edge (closest)
Chamber Pressure
Temperature (°C)
70
60
50
40
30
20
10
0
−10
−20
−30
−40
−50
1 mg Front Edge (closest)
2 mg Center
4 mg Center
1 mg Center
2 mg Front Edge (furthest)
4 mg Front Edge (furthest)

FIG. 52

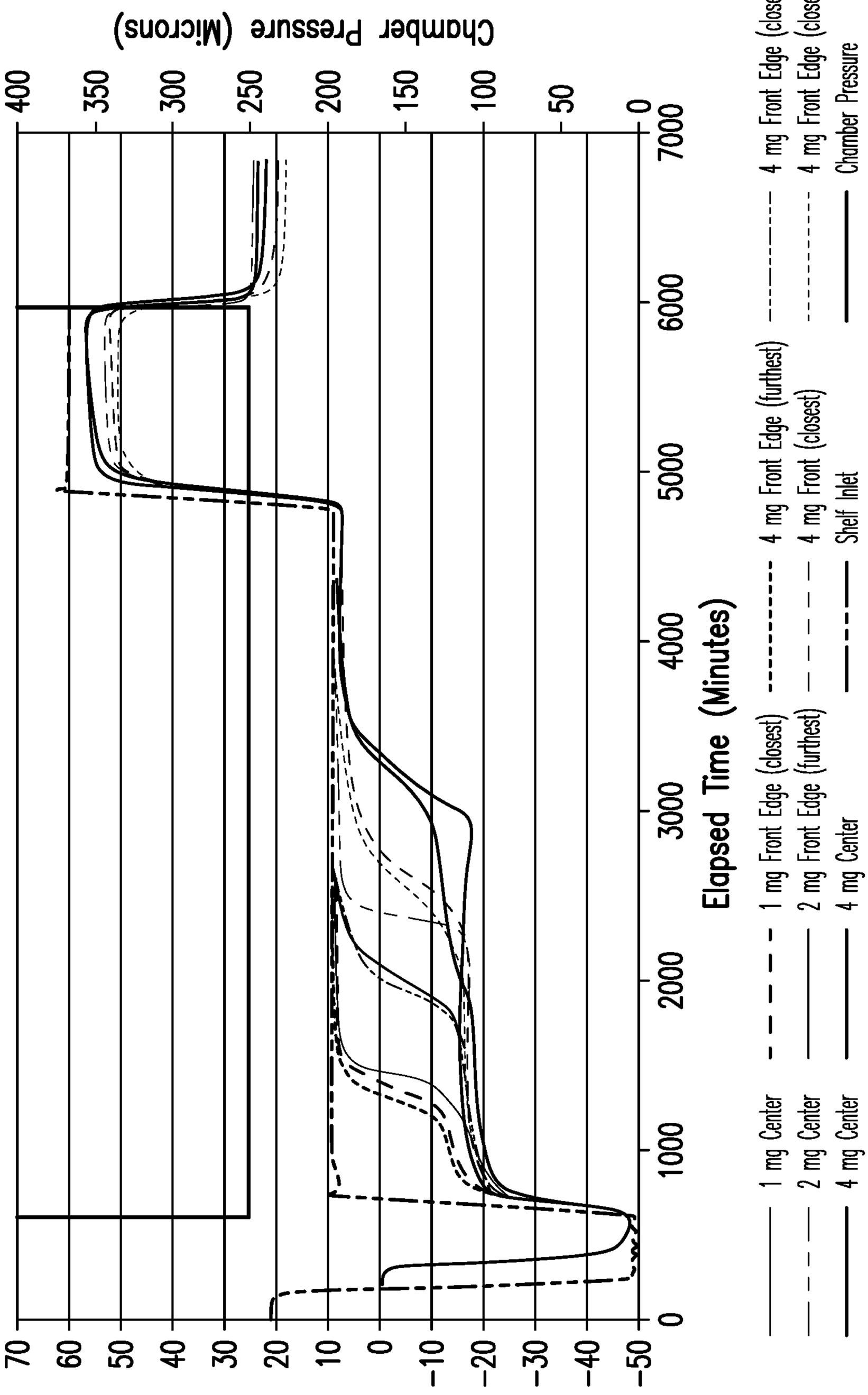

Compound 1 (0.080mg/mL) in Formic Acid
(0.1 °C/minute freezing ramp)
Temperature (°C)
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
Chamber Pressure (Microns)
400
350
300
250
200
150
100
50
0
Elapsed Time (Minutes)
0
1000
2000
3000
4000
5000
6000
7000
1 mg Front Edge (closest)
2 mg Front Edge (furthest)
4 mg Center
4 mg Front Edge (furthest)
4 mg Front (closest)
Shelf Inlet
4 mg Front Edge (closest)
4 mg Front Edge (closest)
Chamber Pressure

FIG. 53

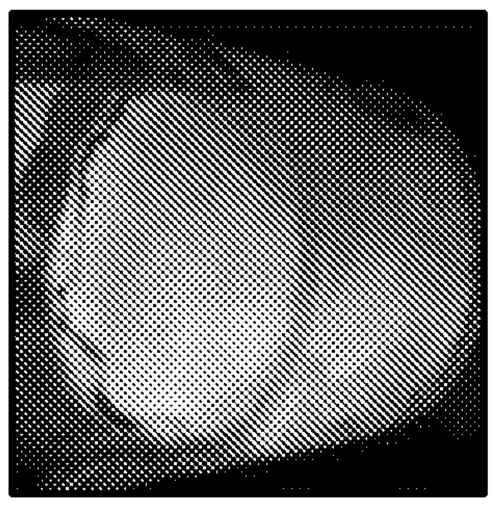
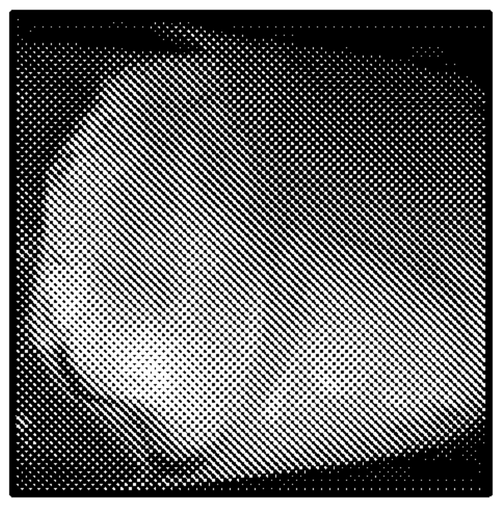
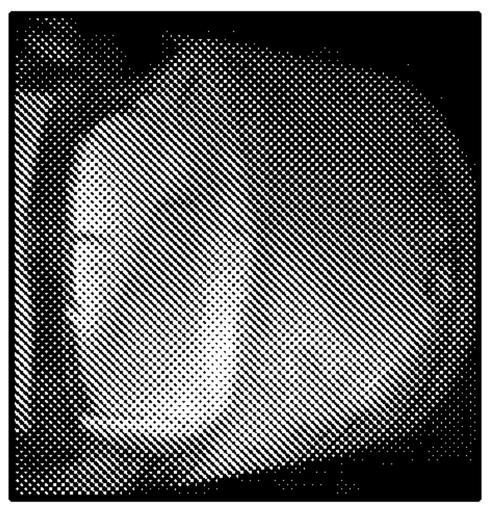
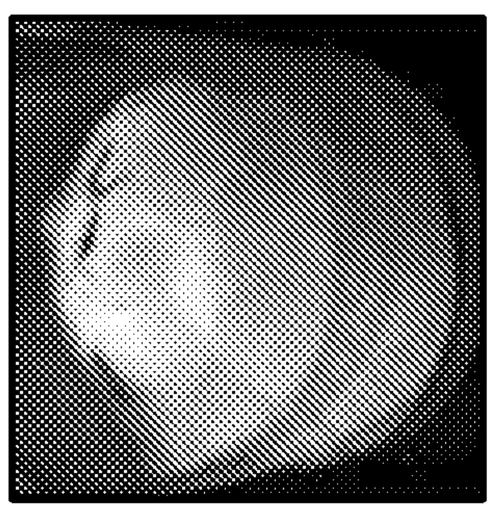
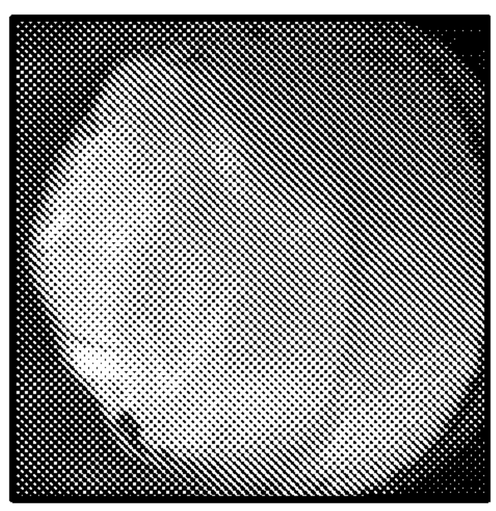
 4 mg/vial	 4 mg/vial
 2 mg/vial	 2 mg/vial
 1 mg/vial	 1 mg/vial
Picture (Batch C1)	Picture (Batch C2)

FIG. 54

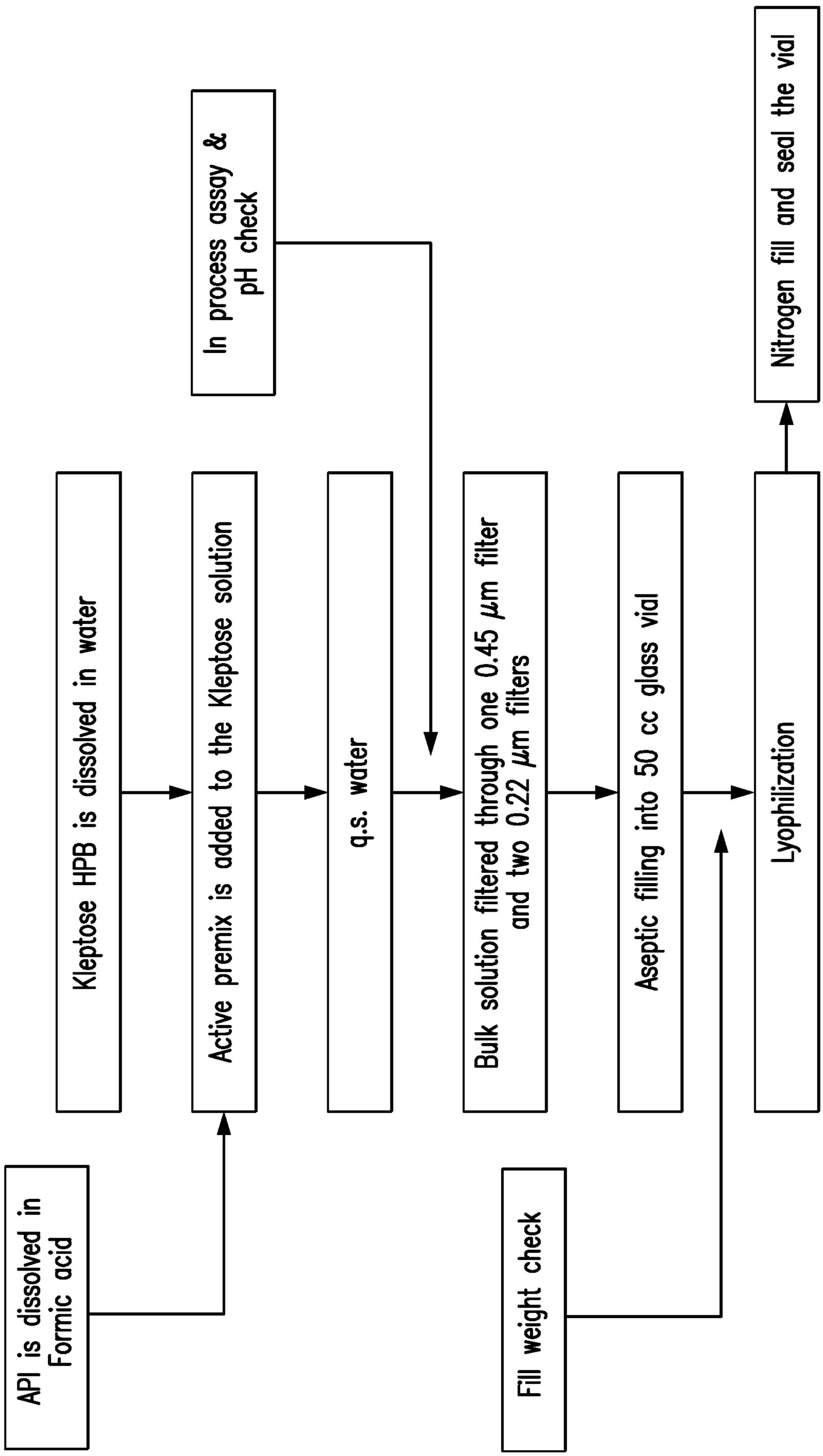

Kleptose HPB is dissolved in water
Active premix is added to the Kleptose solution
q.s. water
In process assay & pH check
Bulk solution filtered through one 0.45 μm filter and two 0.22 μm filters
Aseptic filling into 50 cc glass vial
Lyophilization
Nitrogen fill and seal the vial
API is dissolved in Formic acid
Fill weight check

FIG. 55

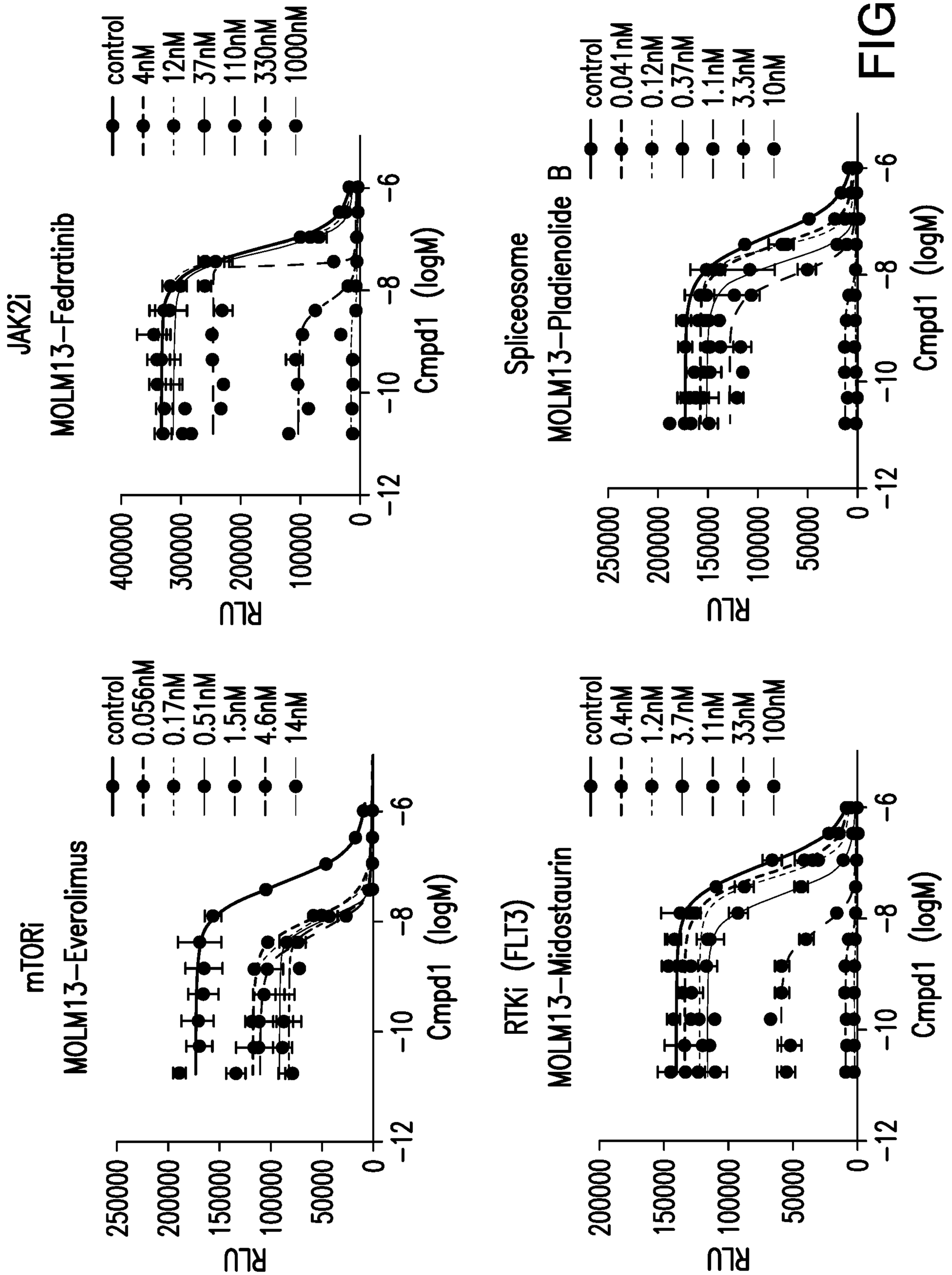

JAK2i
MOLM13–Fedratinib
control
4nM
12nM
37nM
110nM
330nM
1000nM
RLU
Cmpd1 (logM)
Spliceosome
MOLM13–Pladienolide B
control
0.041nM
0.12nM
0.37nM
1.1nM
3.3nM
10nM
RLU
Cmpd1 (logM)
mTORi
MOLM13–Everolimus
control
0.056nM
0.17nM
0.51nM
1.5nM
4.6nM
14nM
RLU
Cmpd1 (logM)
RTKi (FLT3)
MOLM13–Midostaurin
control
0.4nM
1.2nM
3.7nM
11nM
33nM
100nM
RLU
Cmpd1 (logM)

FIG. 56A

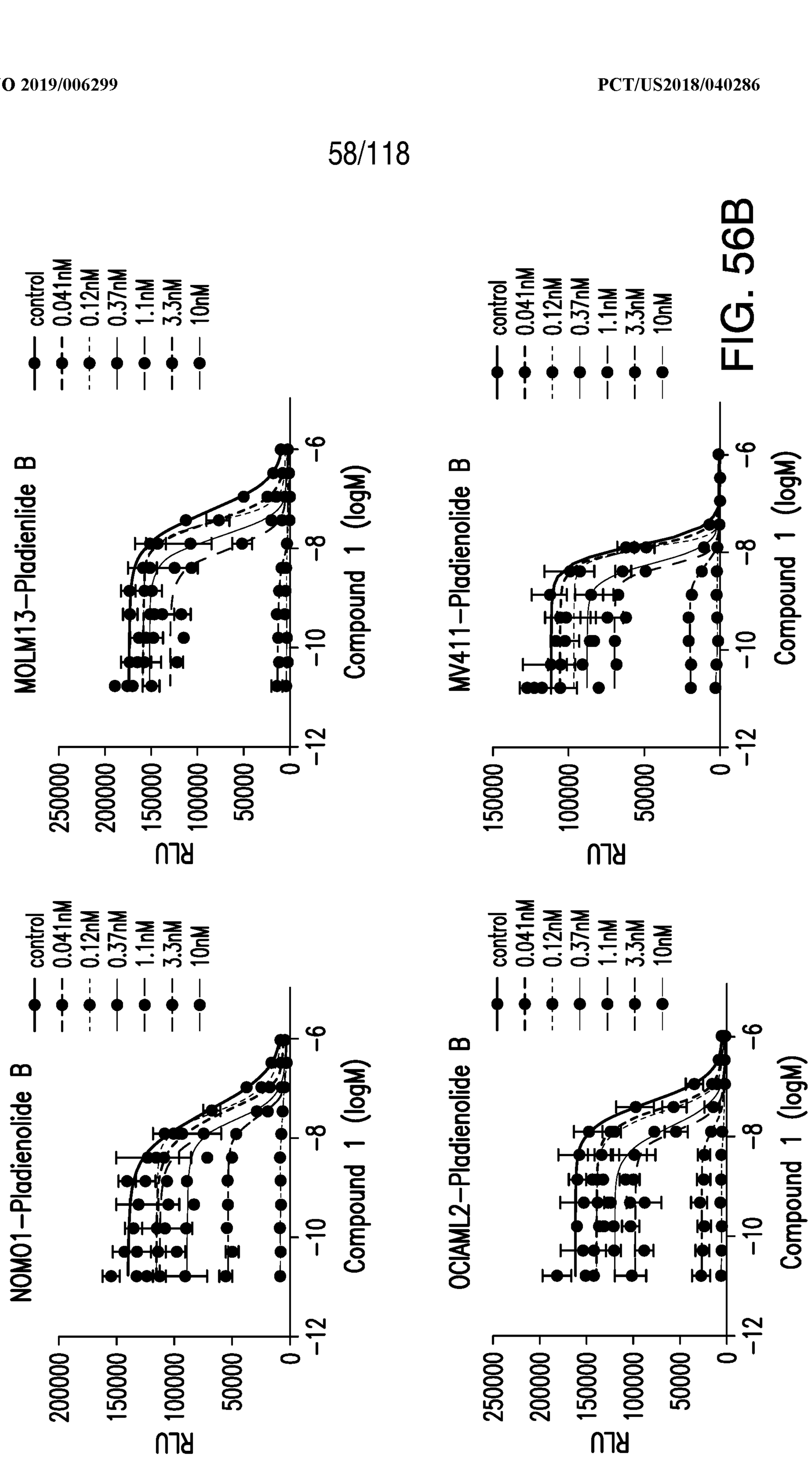

MOLM13–Pladienlide B
MV411–Pladienolide B
NOMO1–Pladienolide B
OCIAML2–Pladienolide B
control
0.041nM
0.12nM
0.37nM
1.1nM
3.3nM
10nM
RLU
Compound 1 (logM)

FIG. 56B

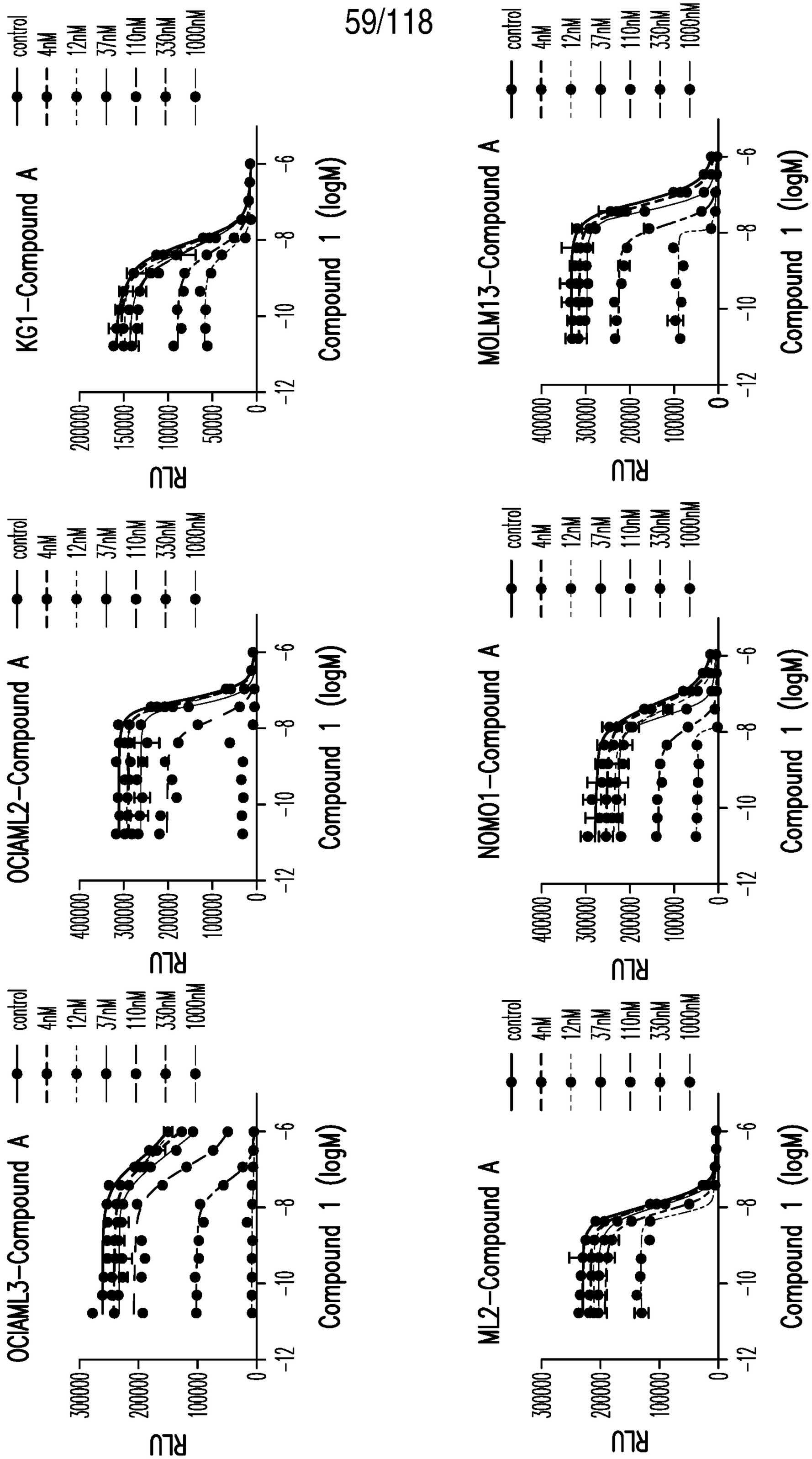
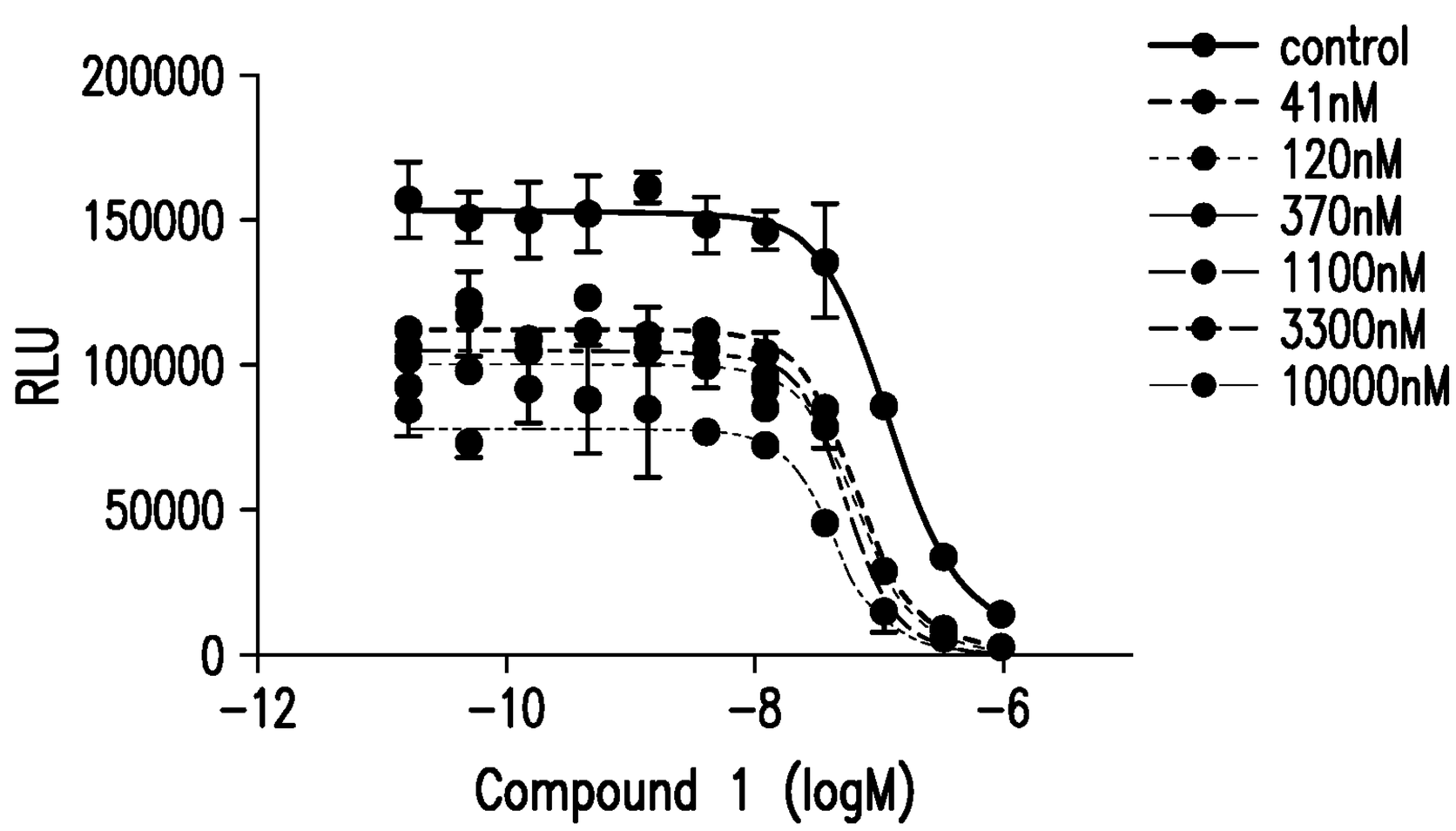

control
4nM
12nM
37nM
110nM
330nM
1000nM
KG1–Compound A
MOLM13–Compound A
OCIAML2–Compound A
NOMO1–Compound A
OCIAML3–Compound A
ML2–Compound A
RLU
Compound 1 (logM)

FIG. 56C


MOLM13–Compound B
200000
150000
100000
50000
0
RLU
–12
–10
–8
–6
Compound 1 (logM)
control
41nM
120nM
370nM
1100nM
3300nM
10000nM

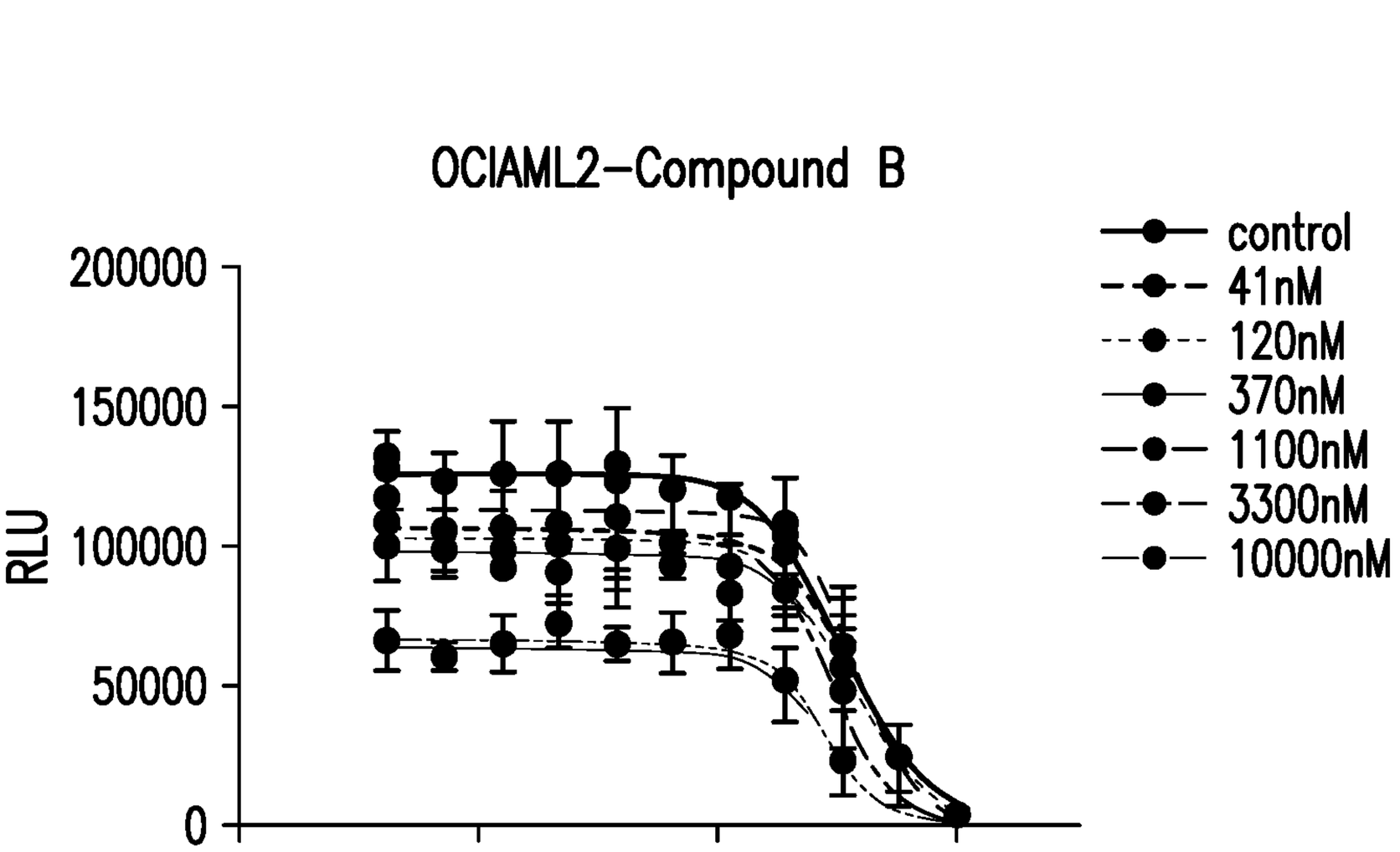
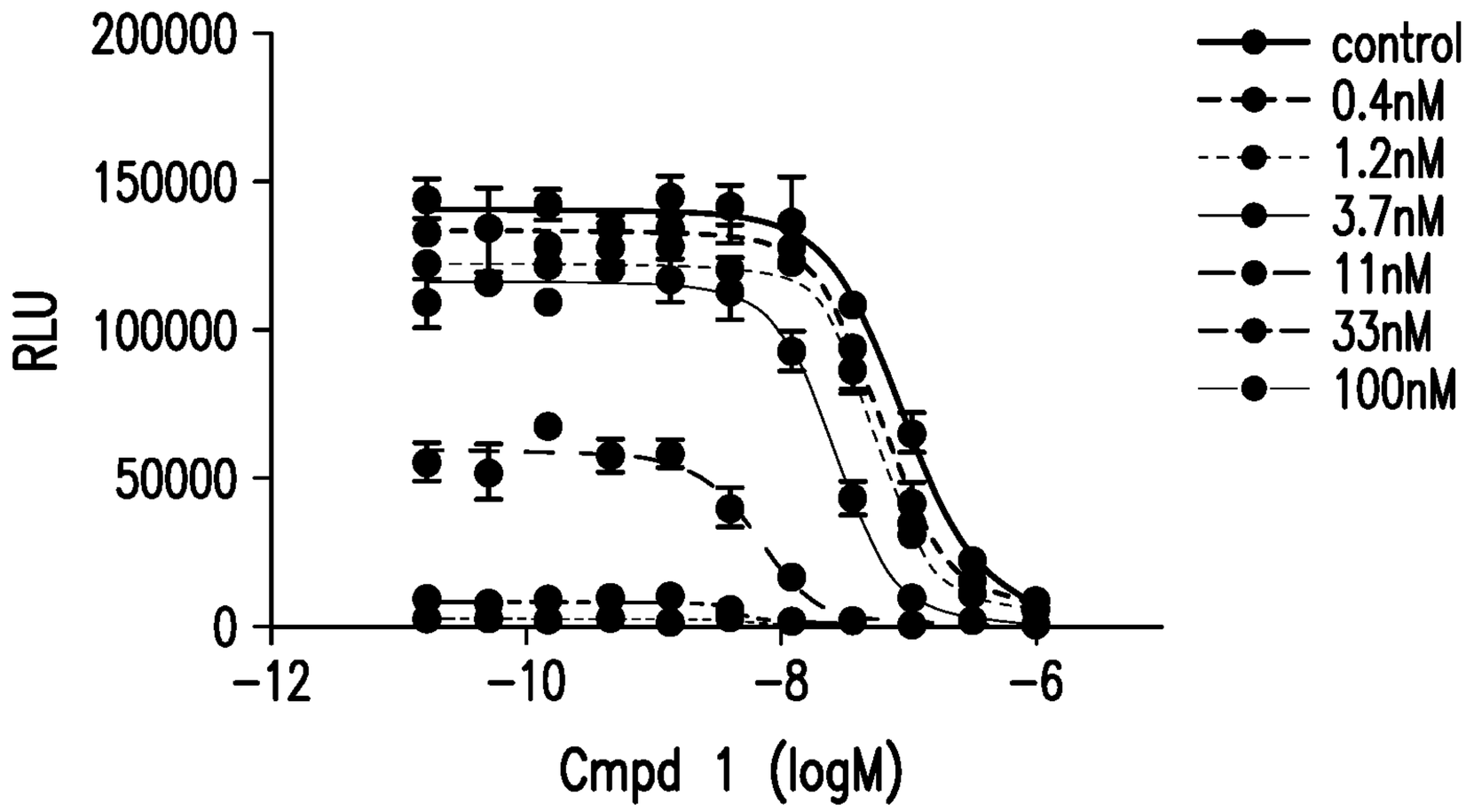

OCIAML2–Compound B
200000
150000
100000
50000
0
RLU
–12
–10
–8
–6
Compound 1 (logM)
control
41nM
120nM
370nM
1100nM
3300nM
10000nM

FIG. 56D


MOLM13–Midostaurin
RLU
200000
150000
100000
50000
0
−12
−10
−8
−6
Cmpd 1 (logM)
control
0.4nM
1.2nM
3.7nM
11nM
33nM
100nM

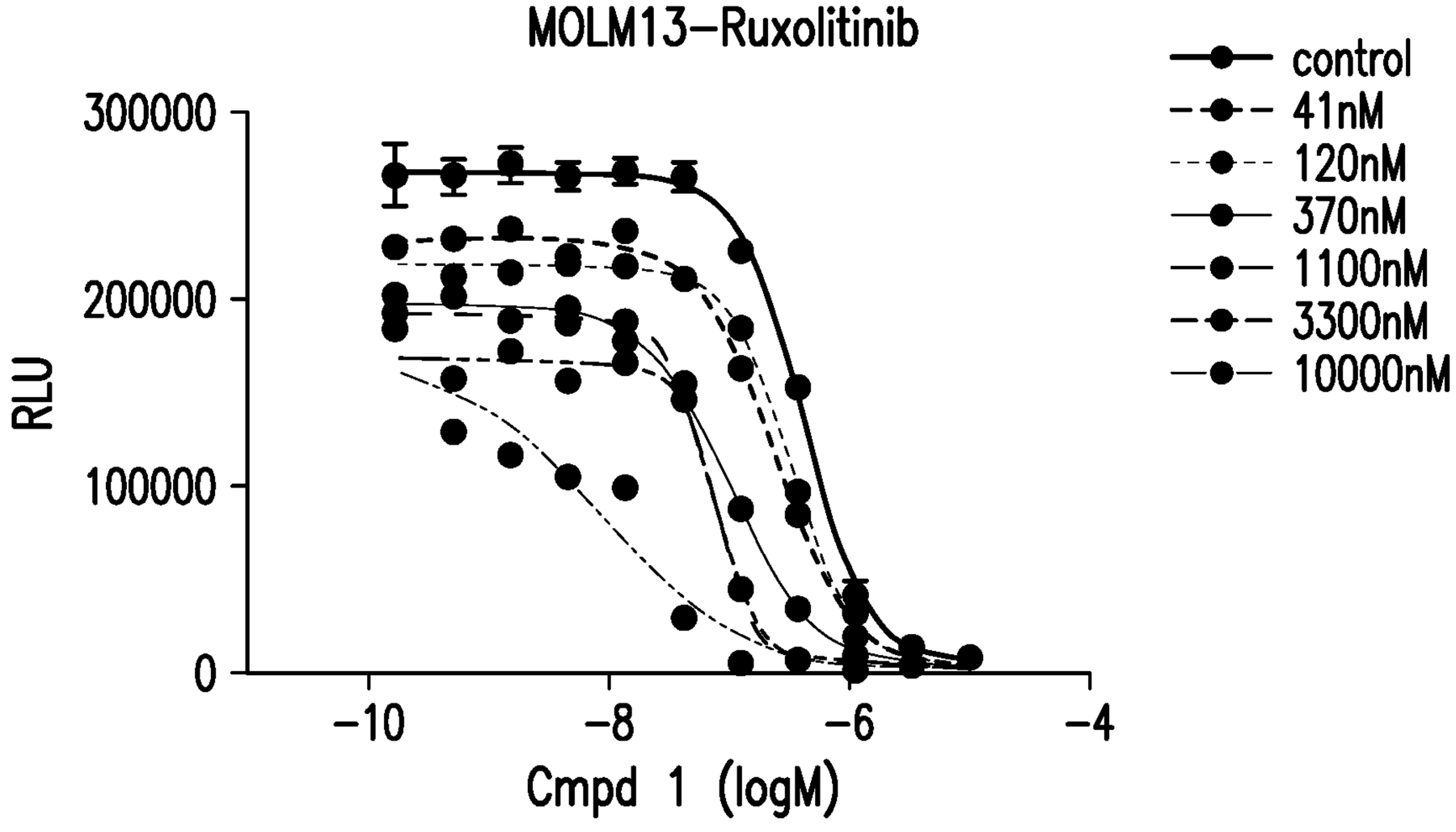

MOLM13–Ruxolitinib
RLU
300000
200000
100000
0
−10
−8
−6
−4
Cmpd 1 (logM)
control
41nM
120nM
370nM
1100nM
3300nM
10000nM

FIG. 57

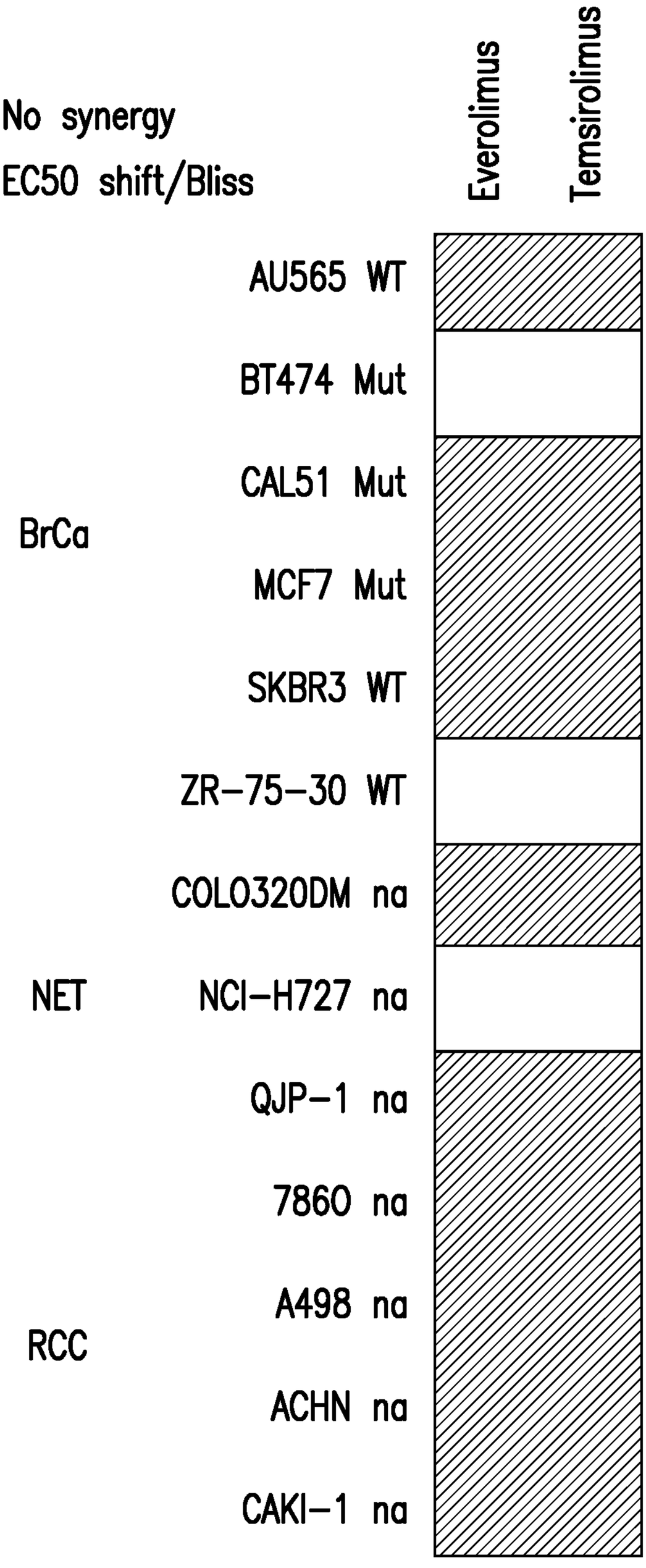

No synergy
EC50 shift/Bliss
Everolimus
Temsirolimus
BrCa
AU565 WT
BT474 Mut
CAL51 Mut
MCF7 Mut
SKBR3 WT
ZR-75-30 WT
NET
COLO320DM na
NCI-H727 na
RCC
QJP-1 na
786O na
A498 na
ACHN na
CAKI-1 na

FIG. 58

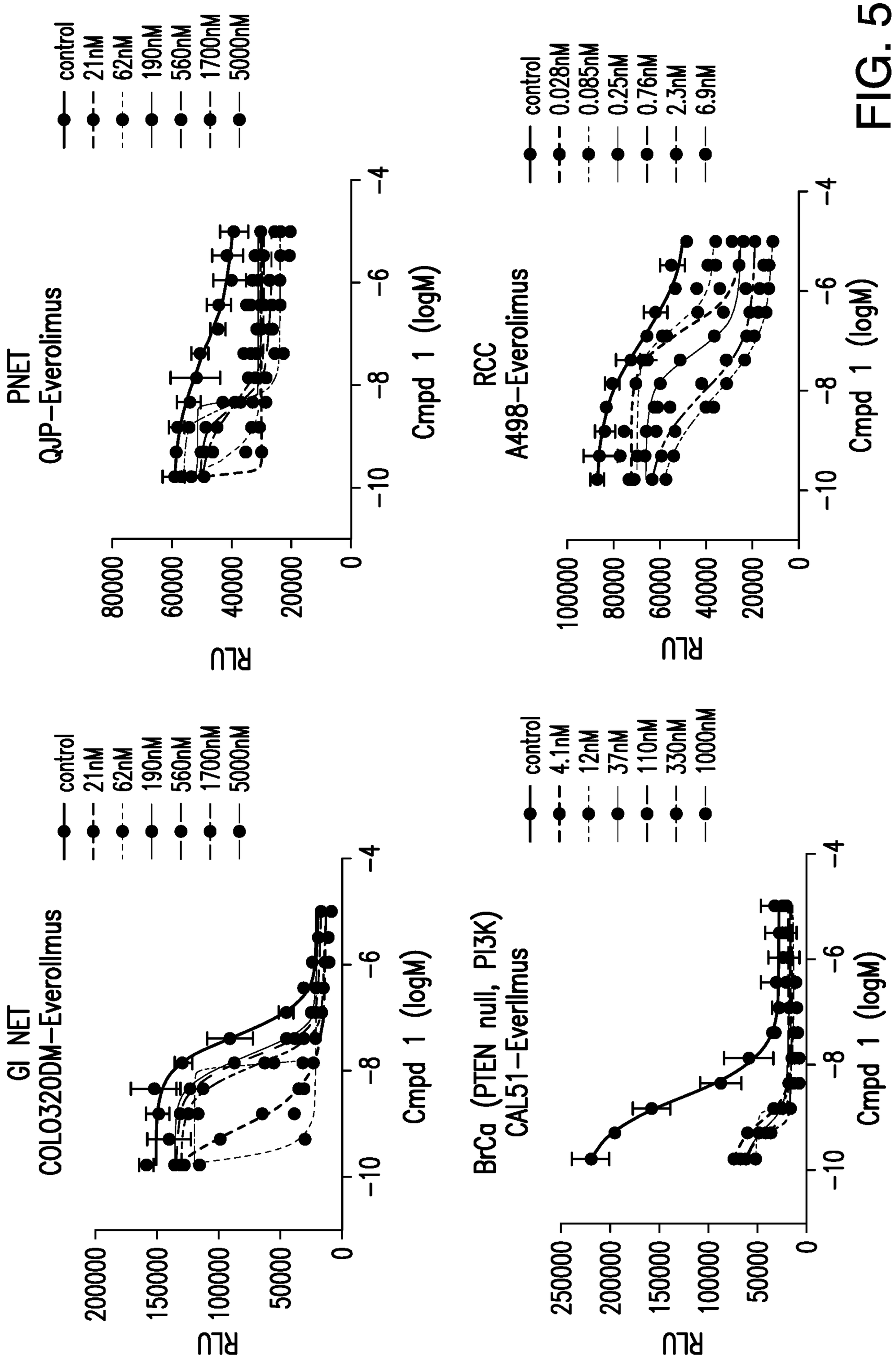

control
21nM
62nM
190nM
560nM
1700nM
5000nM
PNET
QJP−Everolimus
RLU
Cmpd 1 (logM)
control
0.028nM
0.085nM
0.25nM
0.76nM
2.3nM
6.9nM
RCC
A498−Everolimus
RLU
Cmpd 1 (logM)
control
21nM
62nM
190nM
560nM
1700nM
5000nM
GI NET
COLO320DM−Everollmus
RLU
Cmpd 1 (logM)
control
4.1nM
12nM
37nM
110nM
330nM
1000nM
BrCa (PTEN null, PI3K)
CAL51−Everllmus
RLU
Cmpd 1 (logM)

FIG. 59

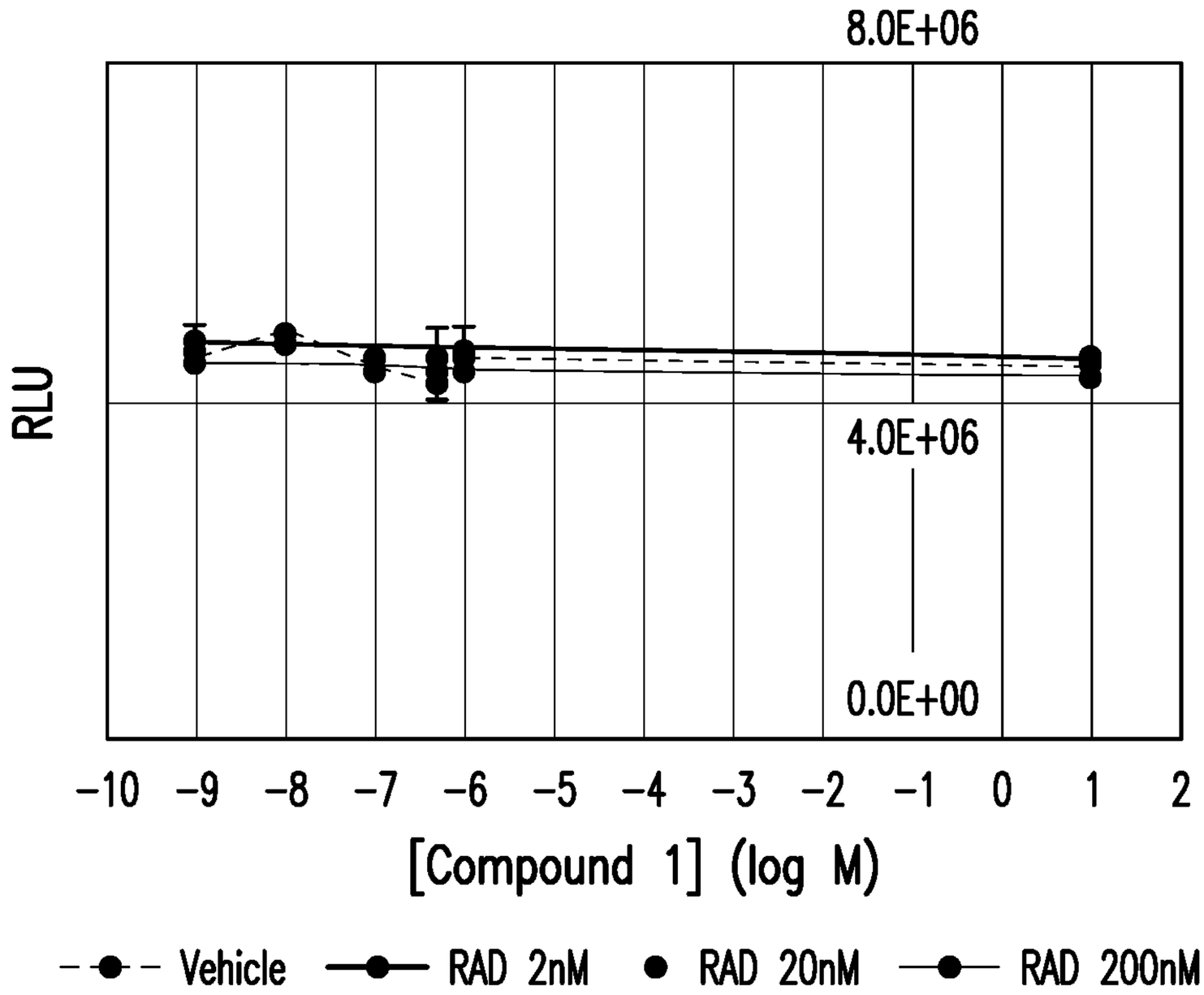

8.0E+06
4.0E+06
0.0E+00
RLU
−10 −9 −8 −7 −6 −5 −4 −3 −2 −1 0 1 2
[Compound 1] (log M)
Vehicle
RAD 2nM
RAD 20nM
RAD 200nM

FIG. 60

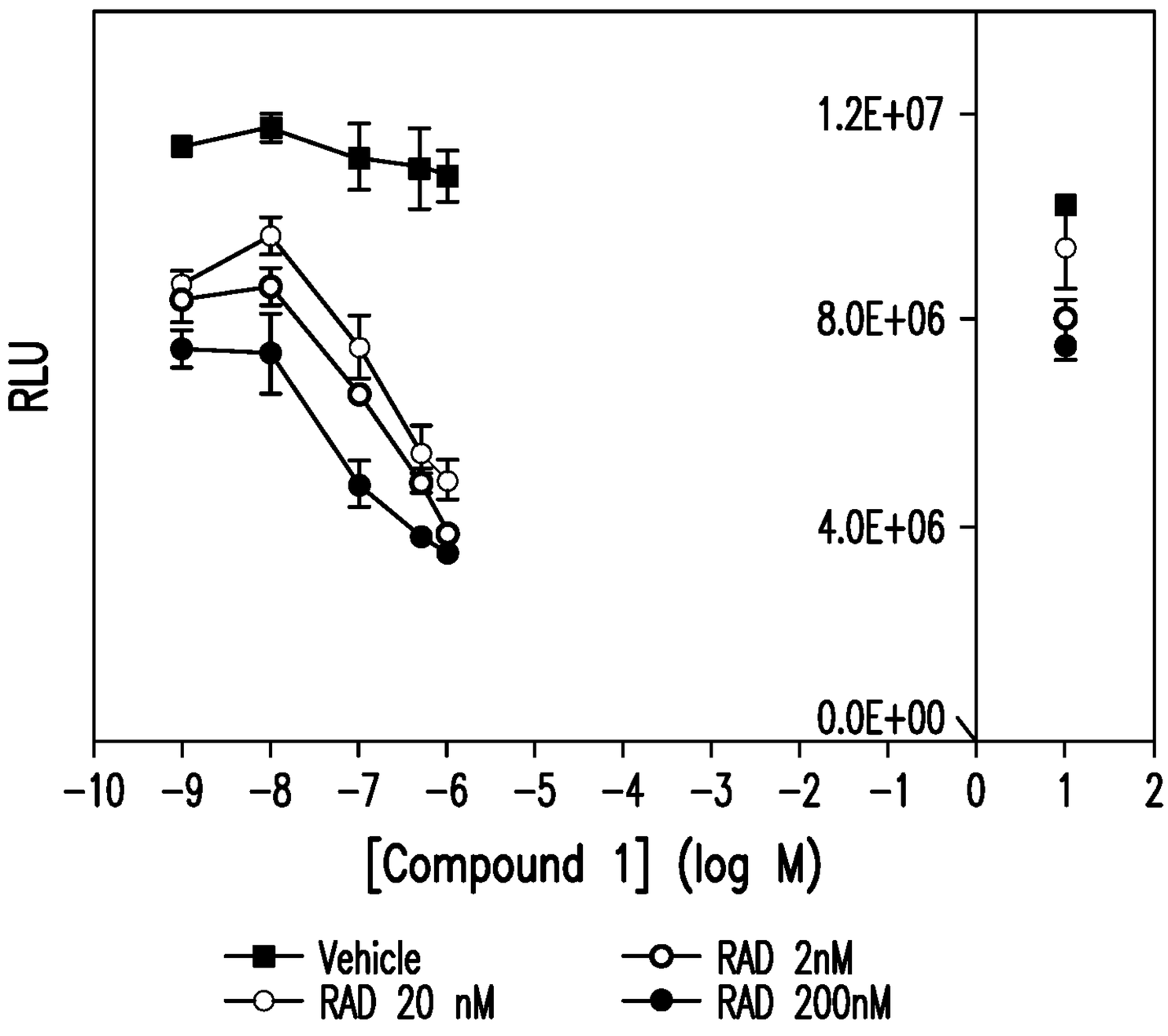

1.2E+07
8.0E+06
4.0E+06
0.0E+00
RLU
−10 −9 −8 −7 −6 −5 −4 −3 −2 −1 0 1 2
[Compound 1] (log M)
Vehicle
RAD 2nM
RAD 20 nM
RAD 200nM

FIG. 61

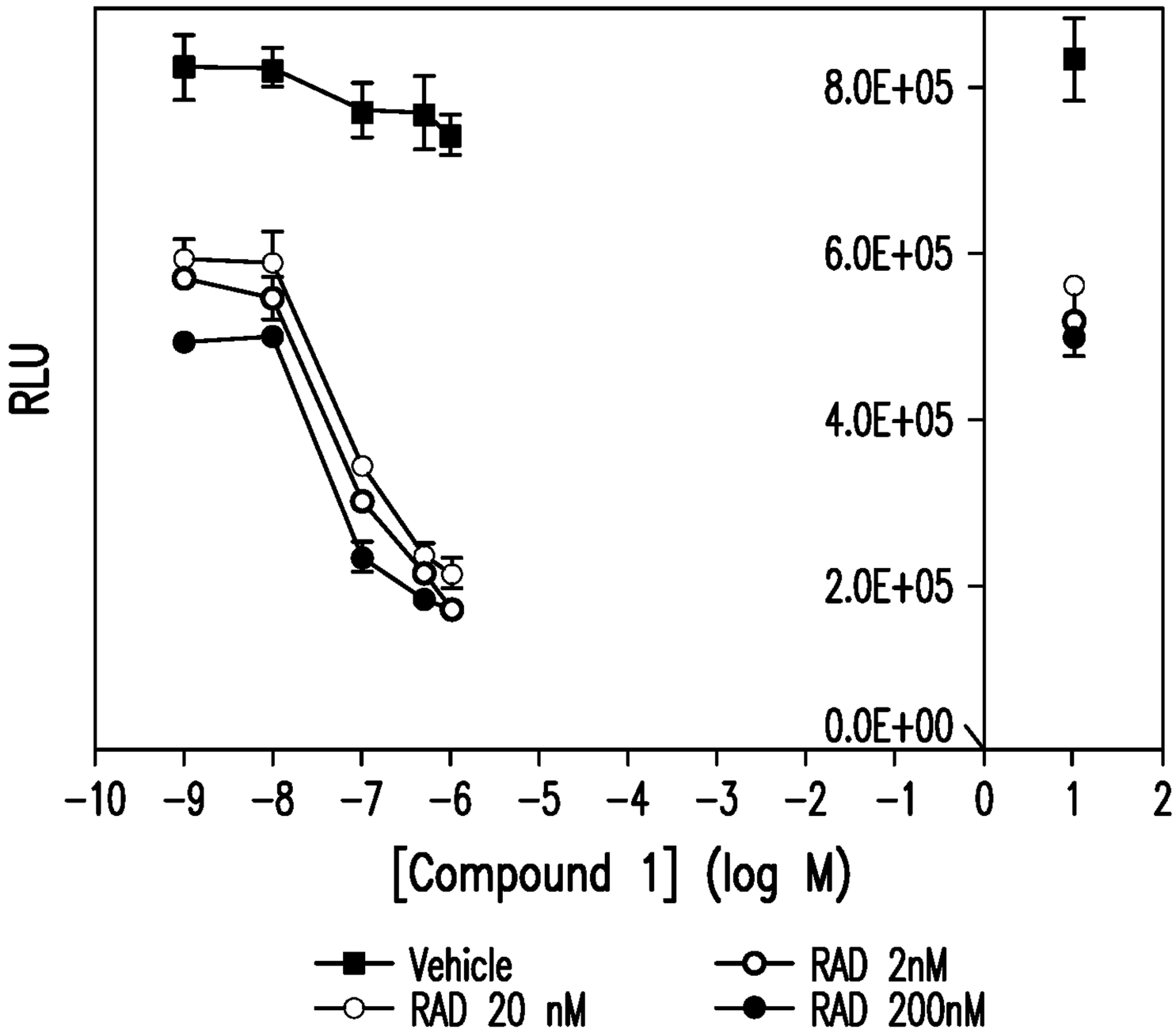

RLU
8.0E+05
6.0E+05
4.0E+05
2.0E+05
0.0E+00
−10 −9 −8 −7 −6 −5 −4 −3 −2 −1 0 1 2
[Compound 1] (log M)
Vehicle
RAD 20 nM
RAD 2nM
RAD 200nM

FIG. 62

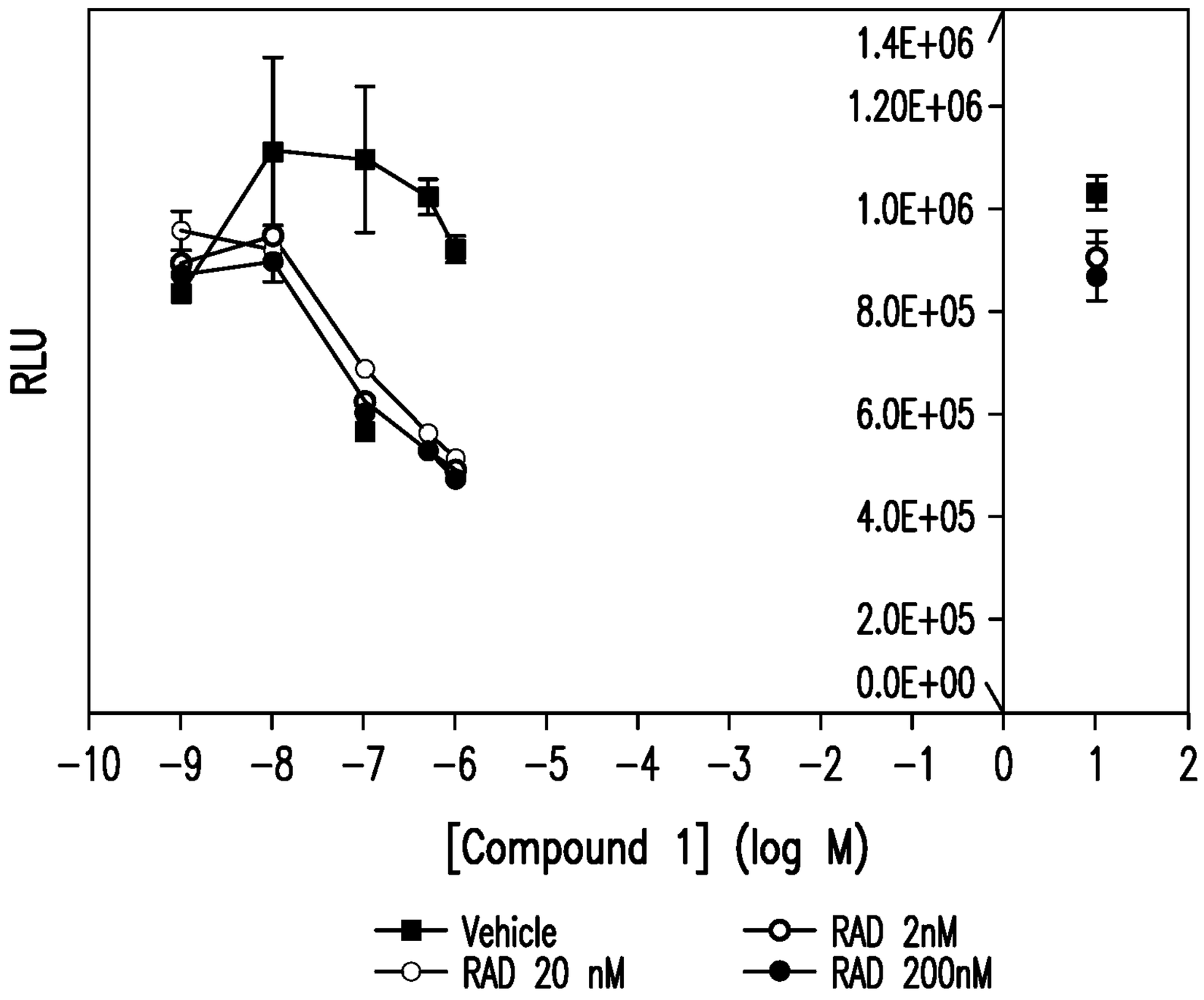

RLU
1.4E+06
1.20E+06
1.0E+06
8.0E+05
6.0E+05
4.0E+05
2.0E+05
0.0E+00
−10 −9 −8 −7 −6 −5 −4 −3 −2 −1 0 1 2
[Compound 1] (log M)
Vehicle
RAD 20 nM
RAD 2nM
RAD 200nM

FIG. 63

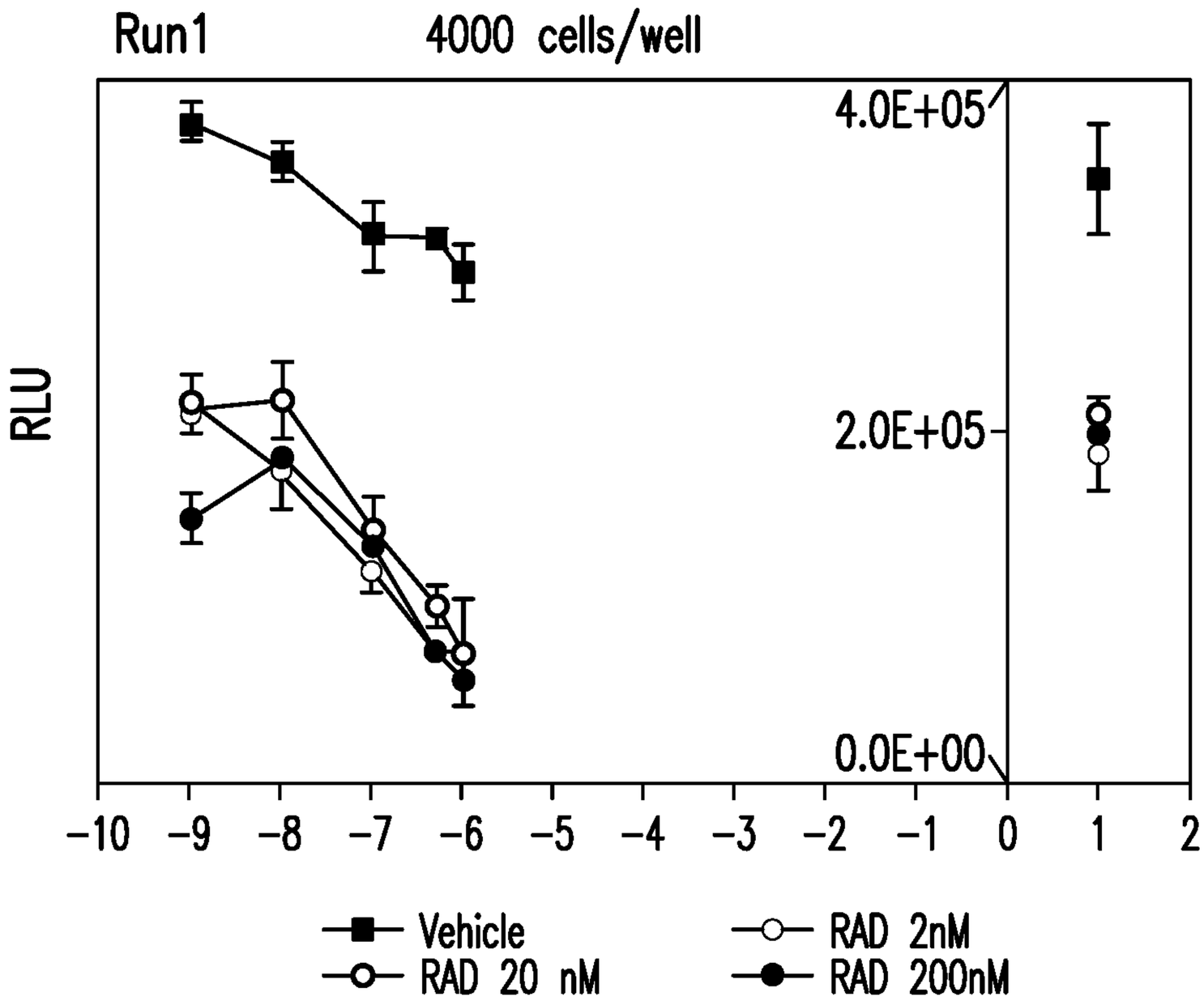


FIG. 64A

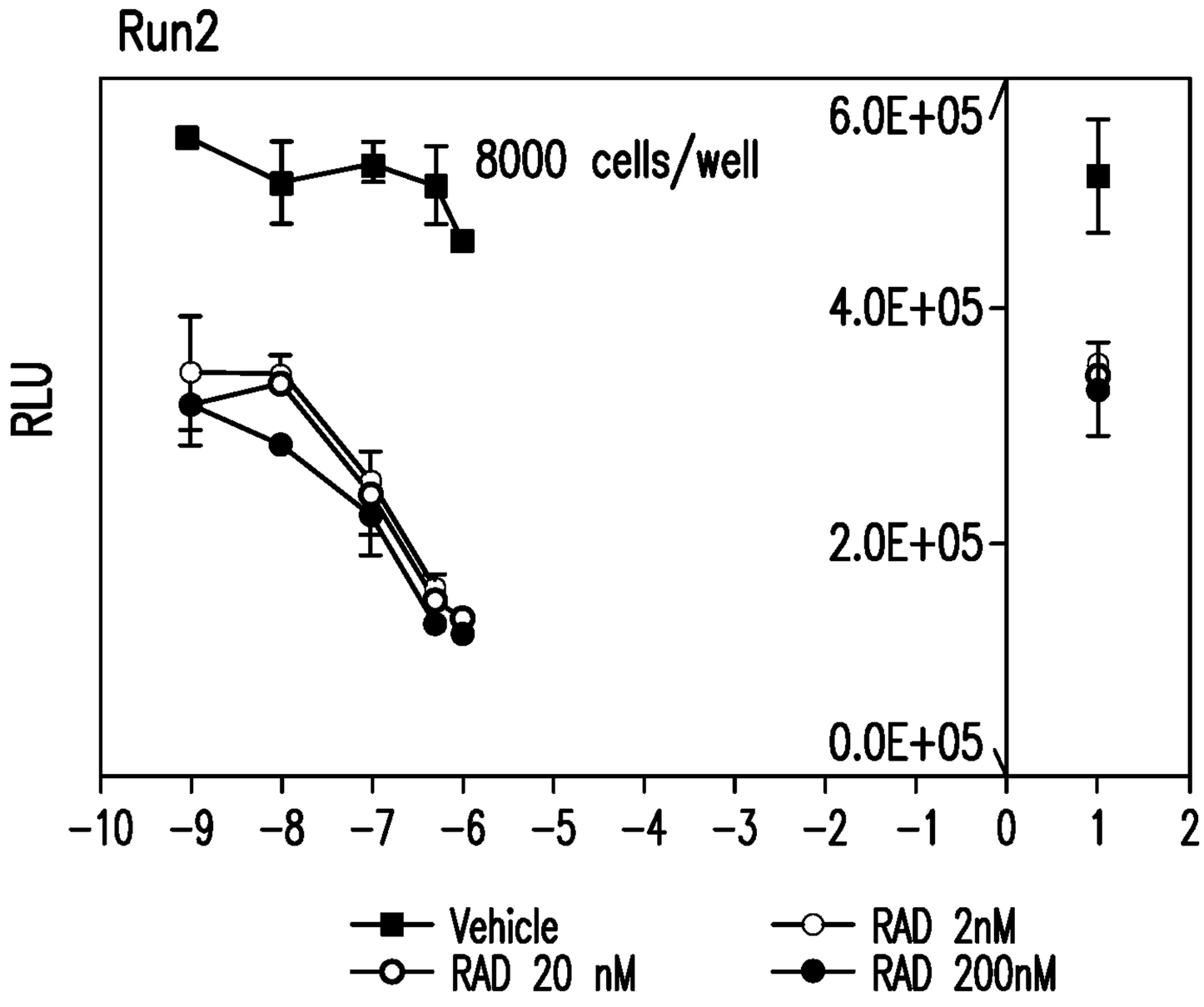


FIG. 64B

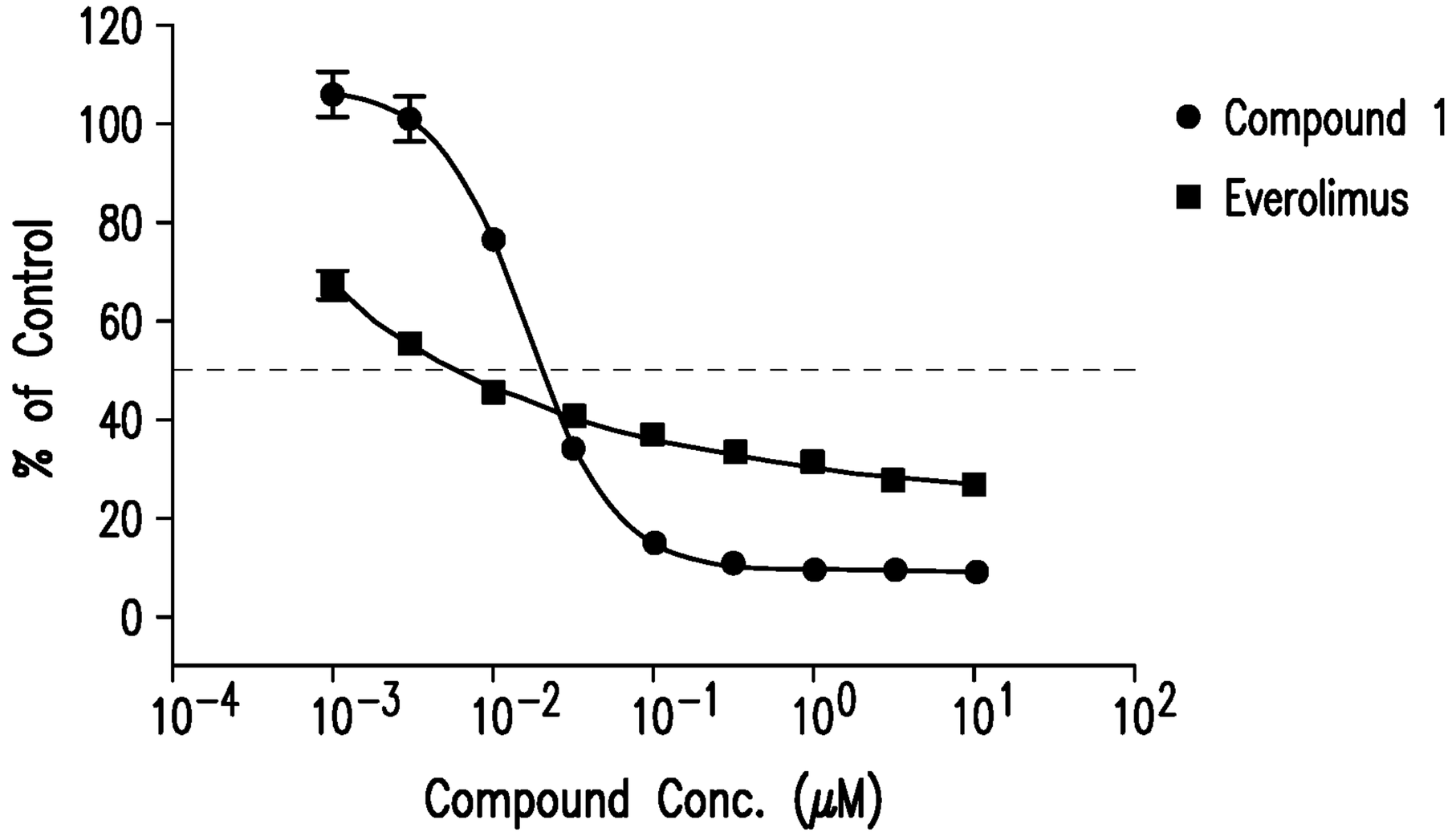


FIG. 65A

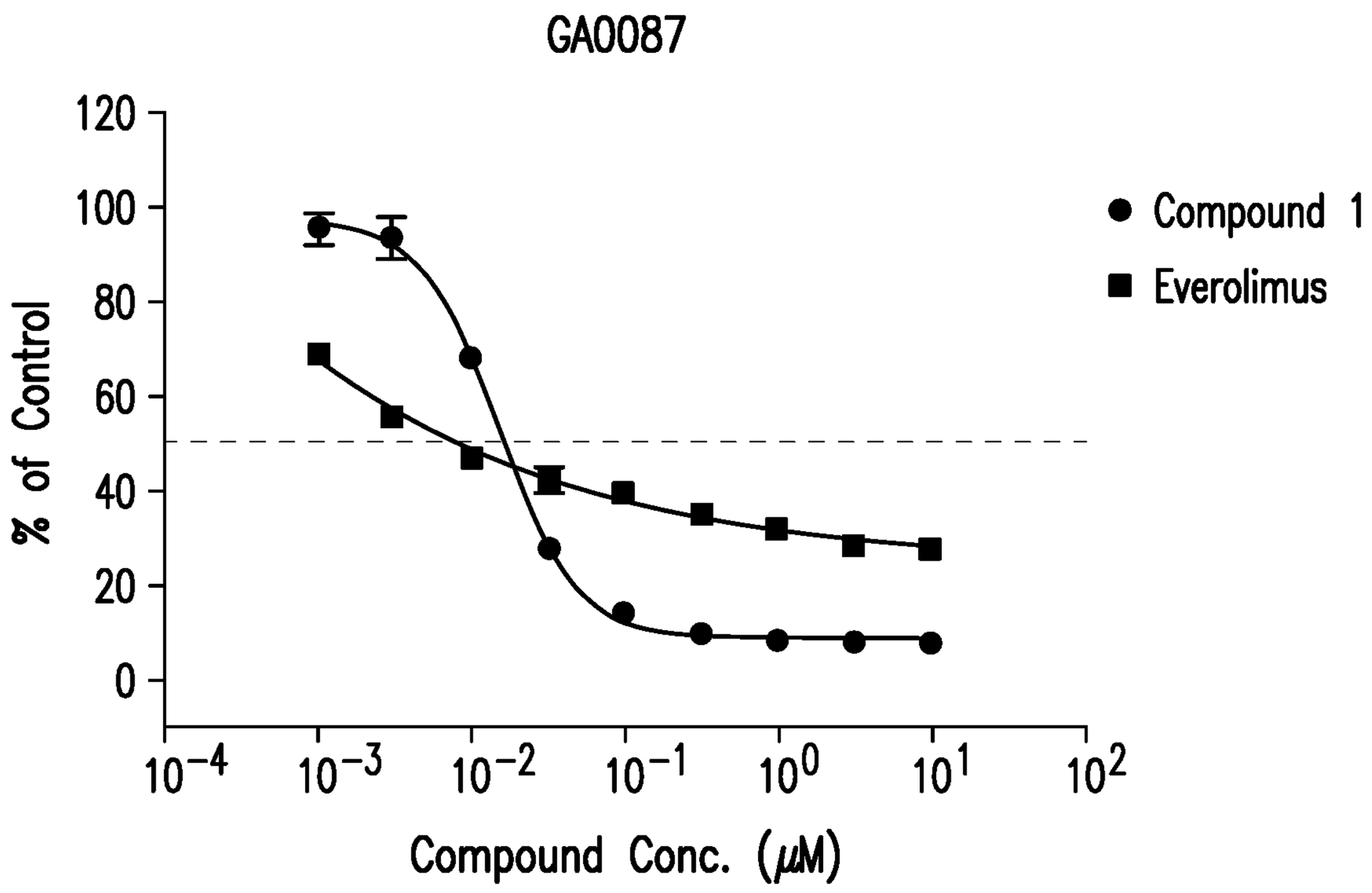


FIG. 65B

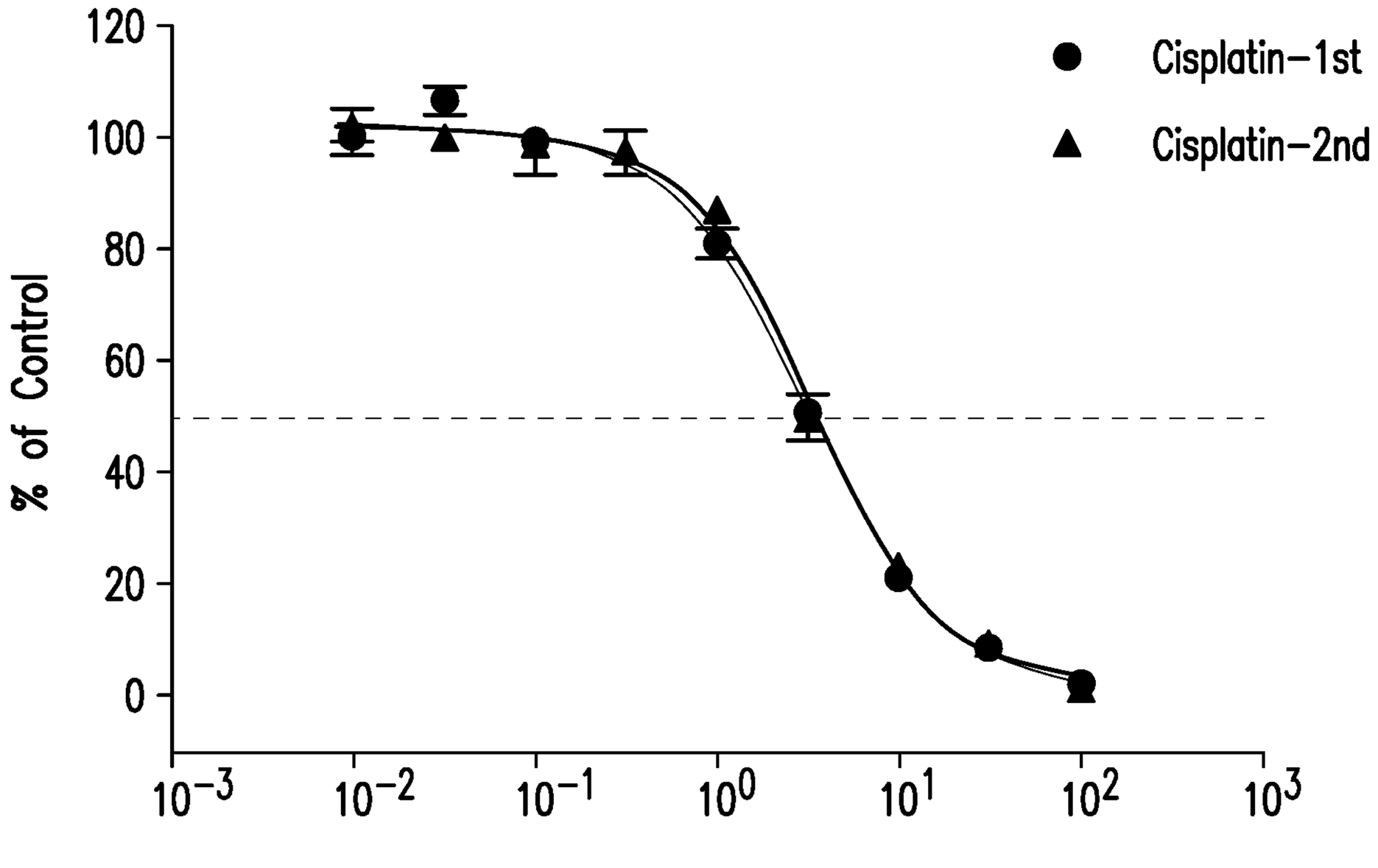

GA0087-cis
Cisplatin-1st
Cisplatin-2nd
% of Control
120
100
80
60
40
20
0
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
10^{3}
Compound Conc. (μM)

FIG. 66

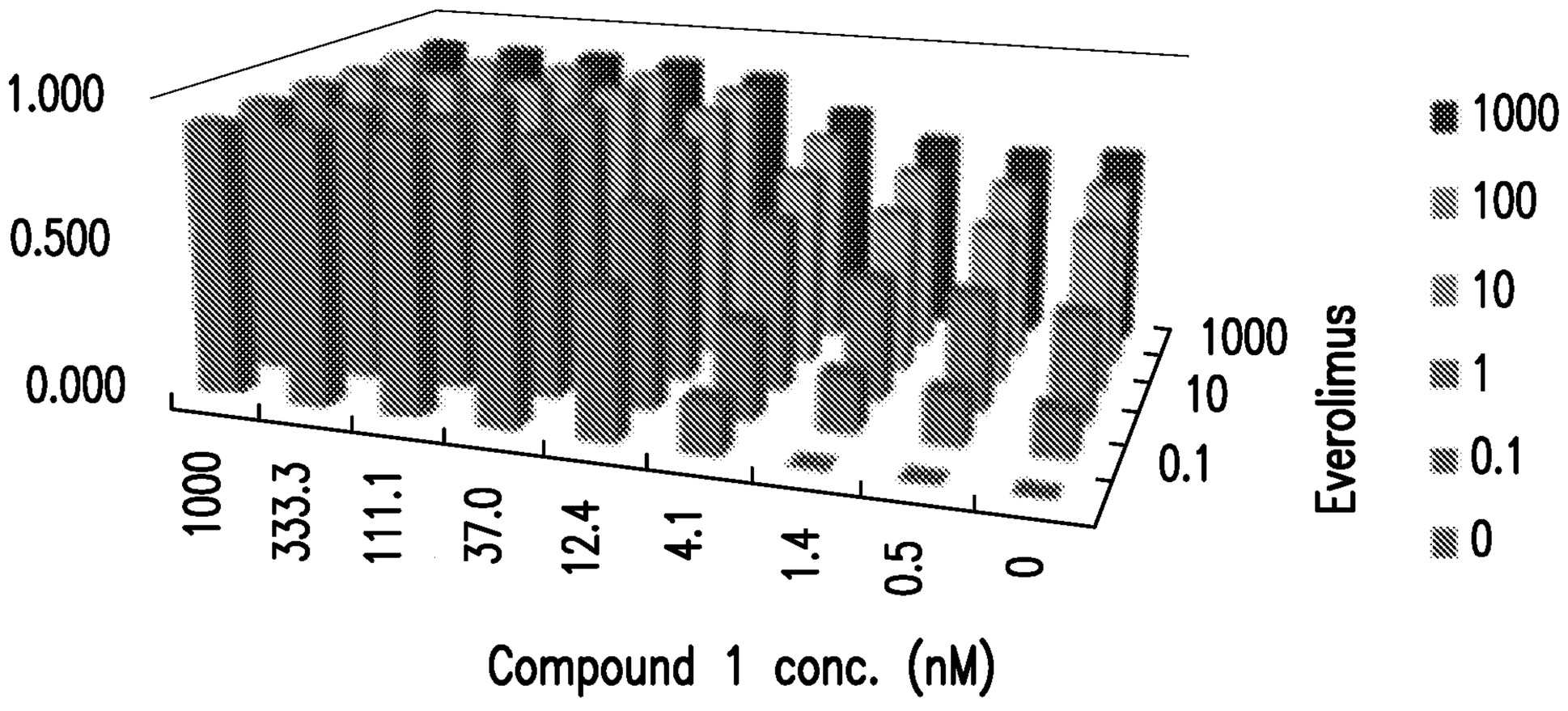


FIG. 67A

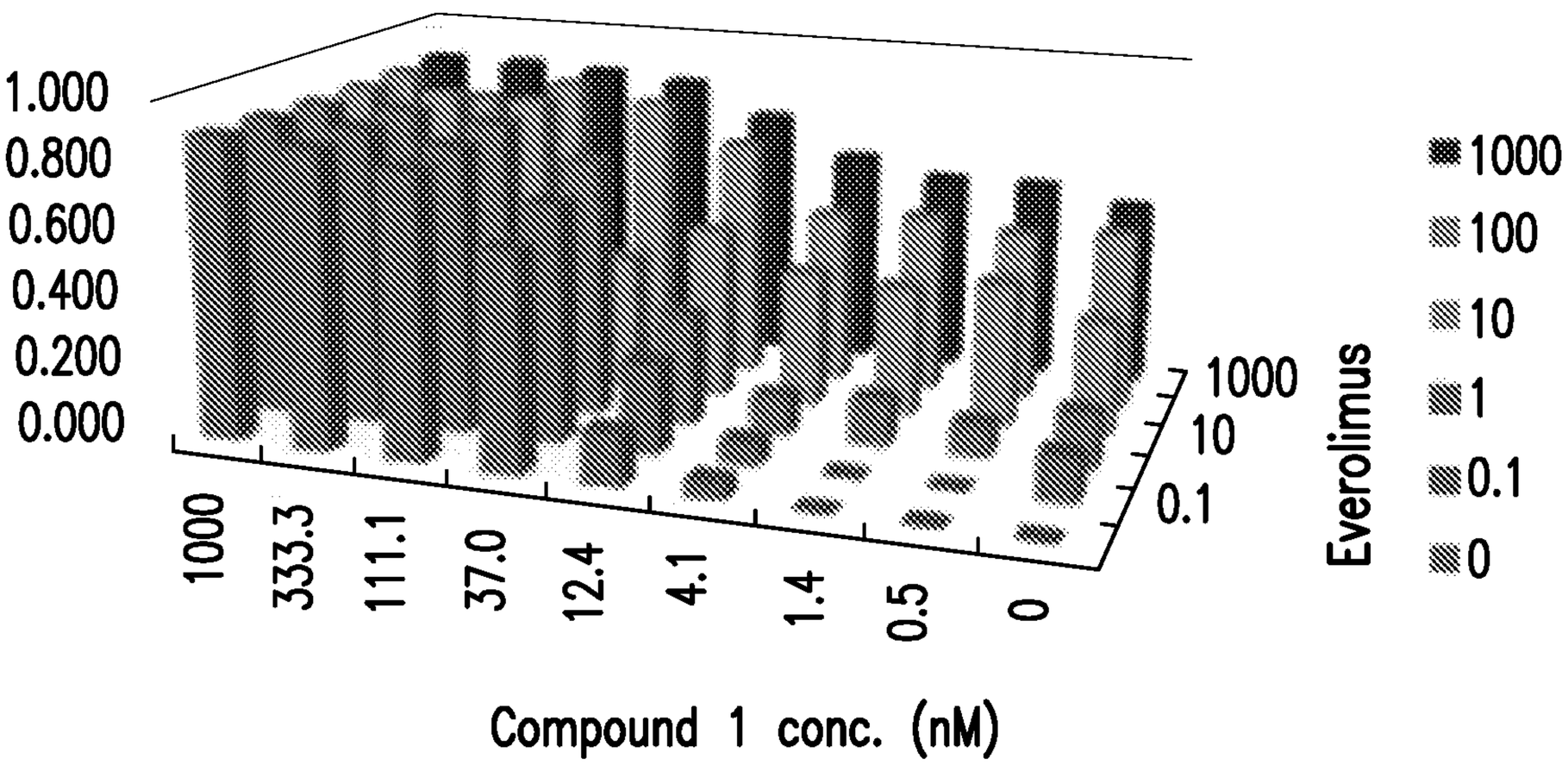


FIG. 67B

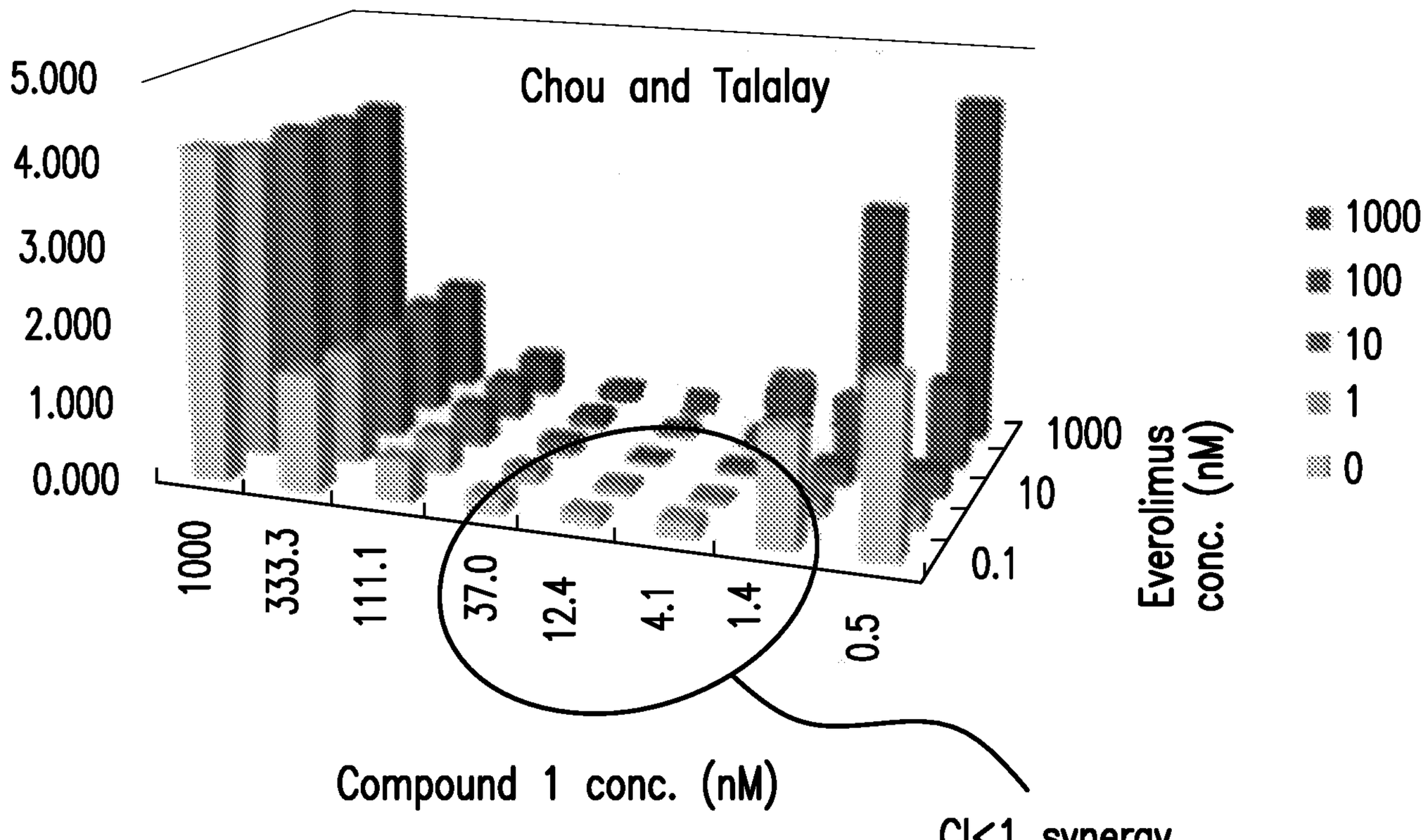


FIG. 68A

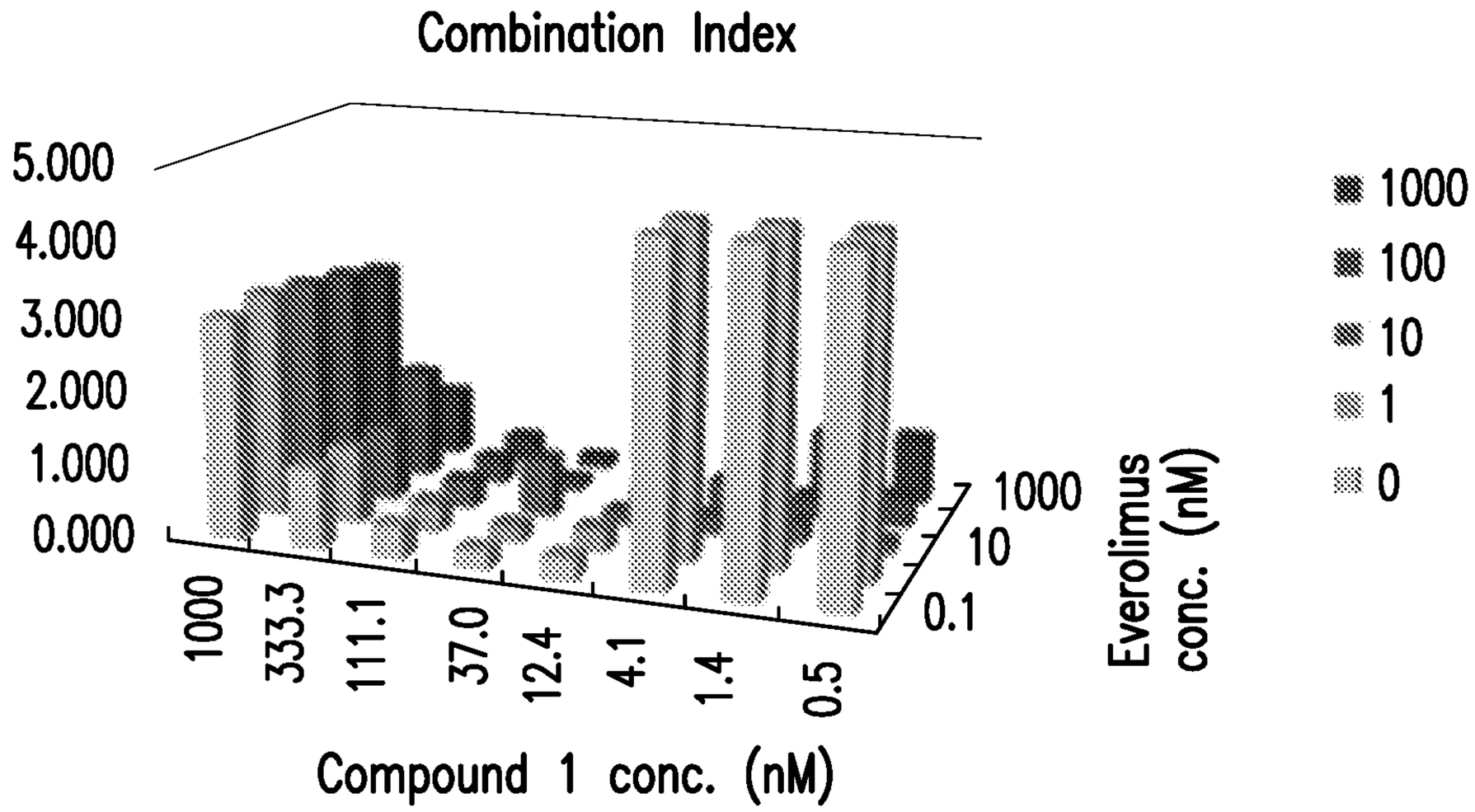


FIG. 68B

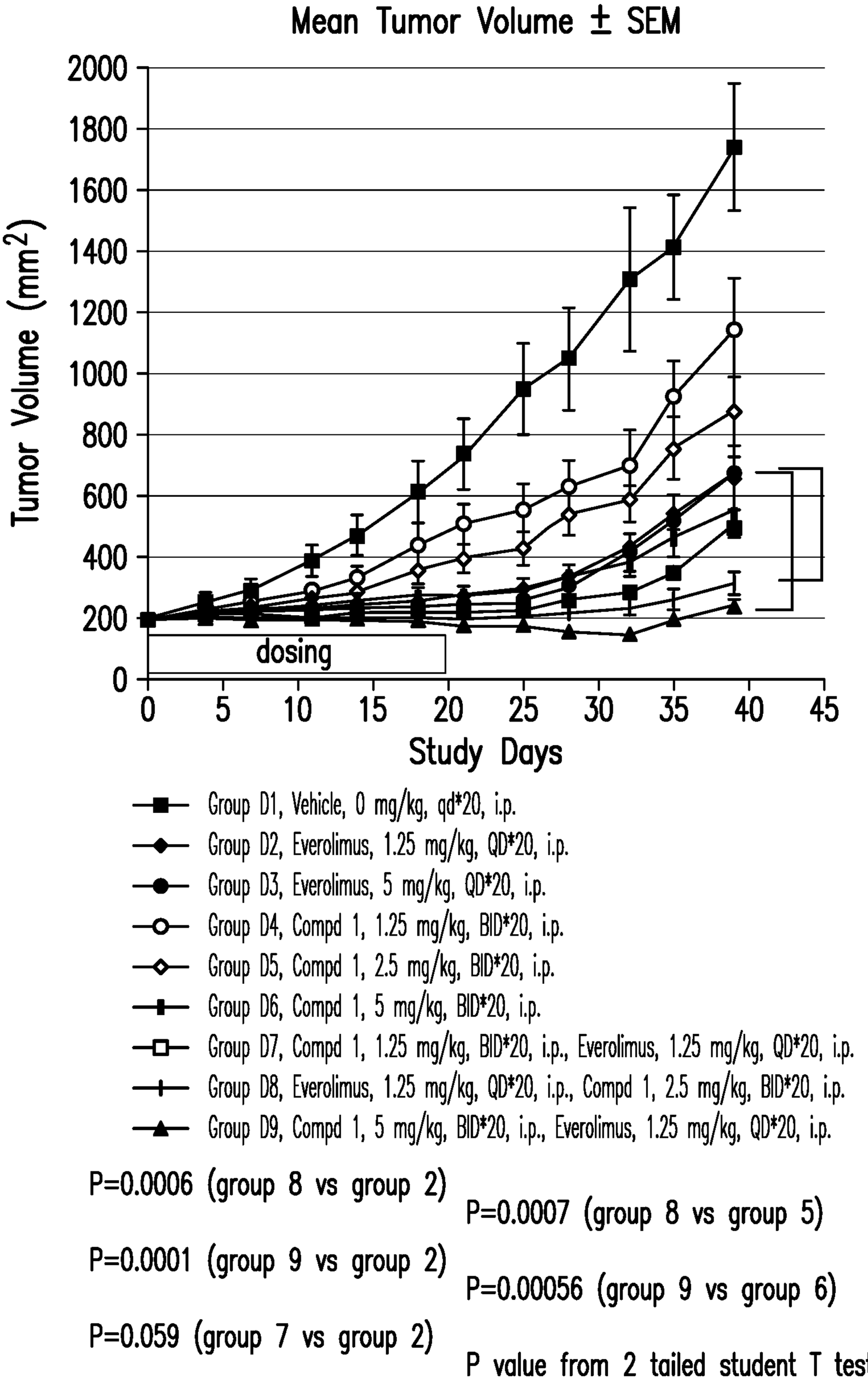

Mean Tumor Volume ± SEM
Tumor Volume (mm2)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
dosing
0
5
10
15
20
25
30
35
40
45
Study Days
Group D1, Vehicle, 0 mg/kg, qd*20, i.p.
Group D2, Everolimus, 1.25 mg/kg, QD*20, i.p.
Group D3, Everolimus, 5 mg/kg, QD*20, i.p.
Group D4, Compd 1, 1.25 mg/kg, BID*20, i.p.
Group D5, Compd 1, 2.5 mg/kg, BID*20, i.p.
Group D6, Compd 1, 5 mg/kg, BID*20, i.p.
Group D7, Compd 1, 1.25 mg/kg, BID*20, i.p., Everolimus, 1.25 mg/kg, QD*20, i.p.
Group D8, Everolimus, 1.25 mg/kg, QD*20, i.p., Compd 1, 2.5 mg/kg, BID*20, i.p.
Group D9, Compd 1, 5 mg/kg, BID*20, i.p., Everolimus, 1.25 mg/kg, QD*20, i.p.
P=0.0006 (group 8 vs group 2)
P=0.0001 (group 9 vs group 2)
P=0.059 (group 7 vs group 2)
P=0.0007 (group 8 vs group 5)
P=0.00056 (group 9 vs group 6)
P value from 2 tailed student T test

FIG. 69

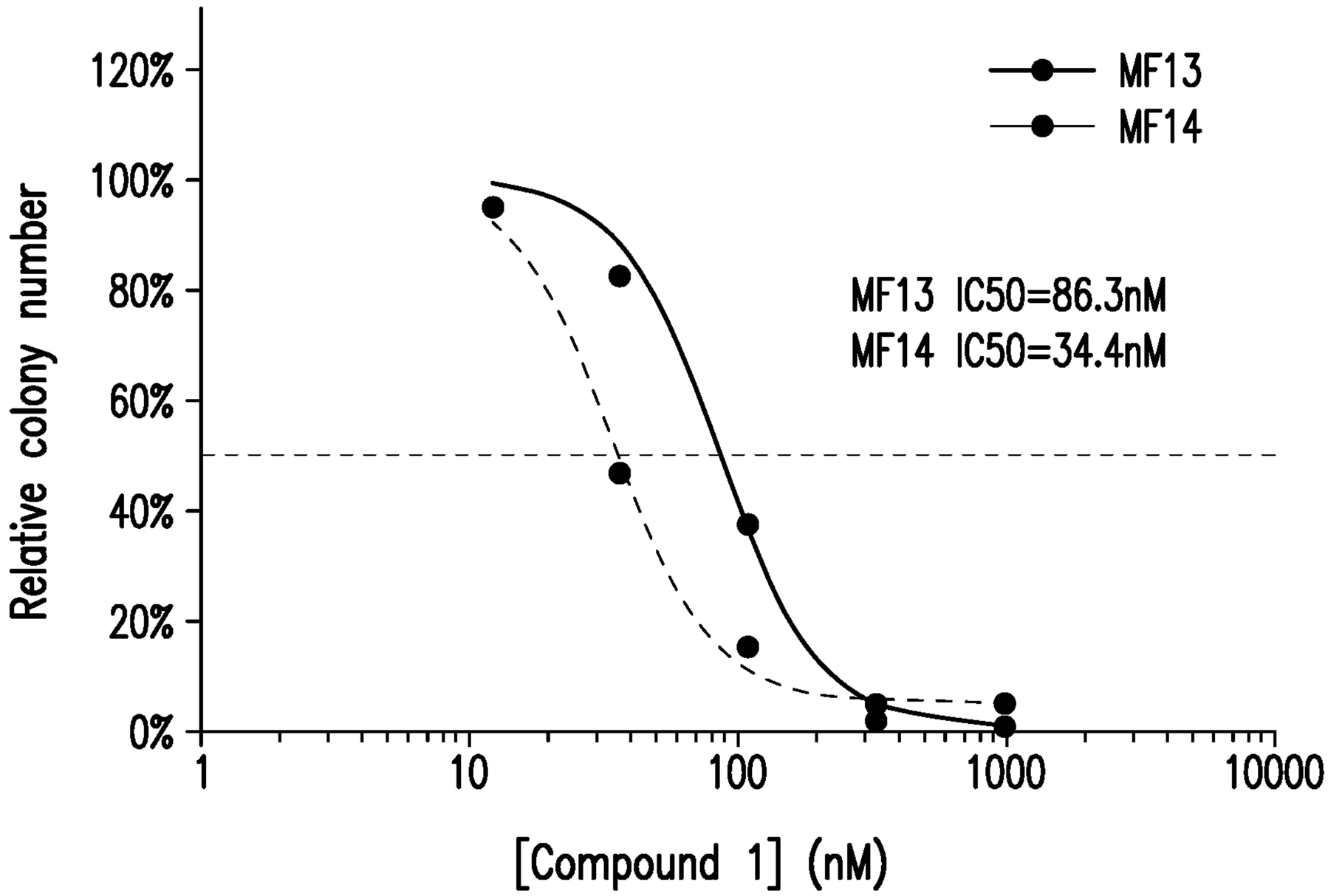
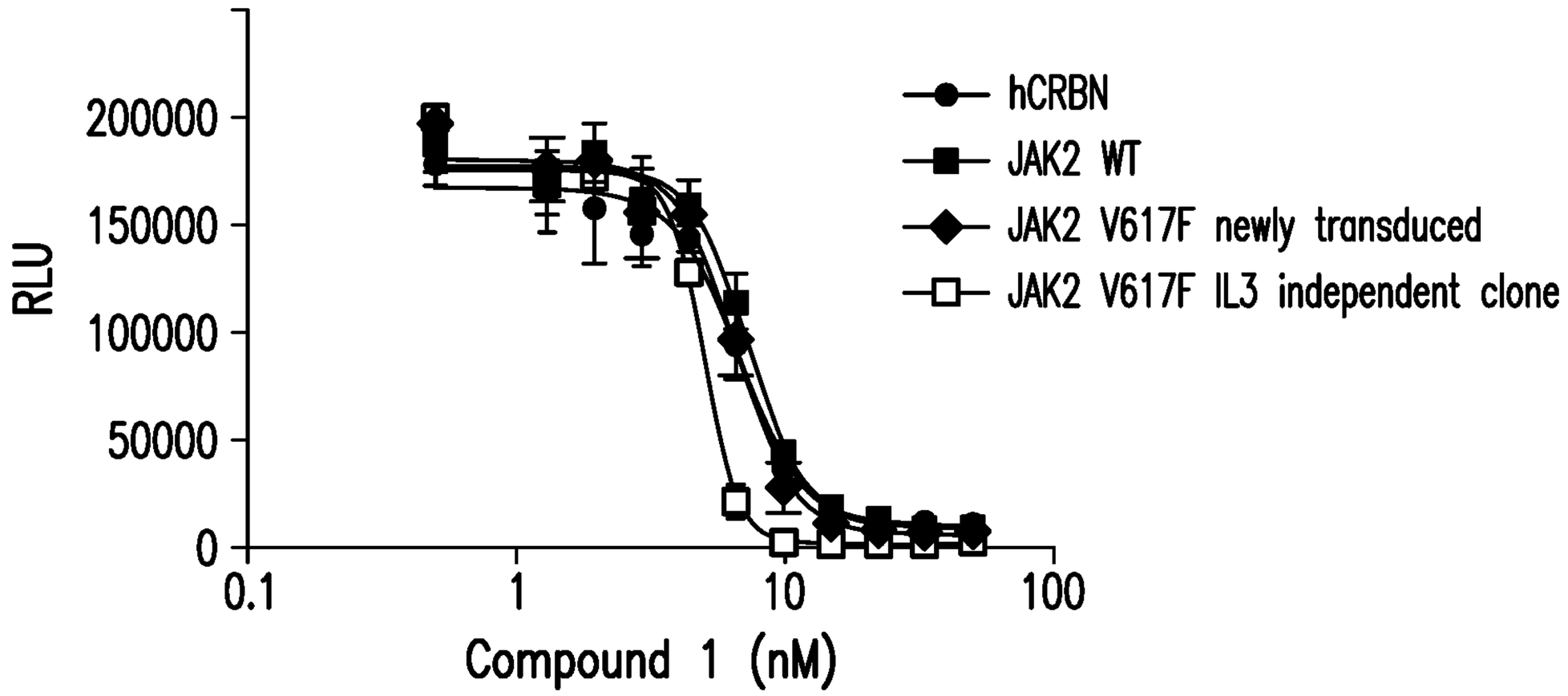
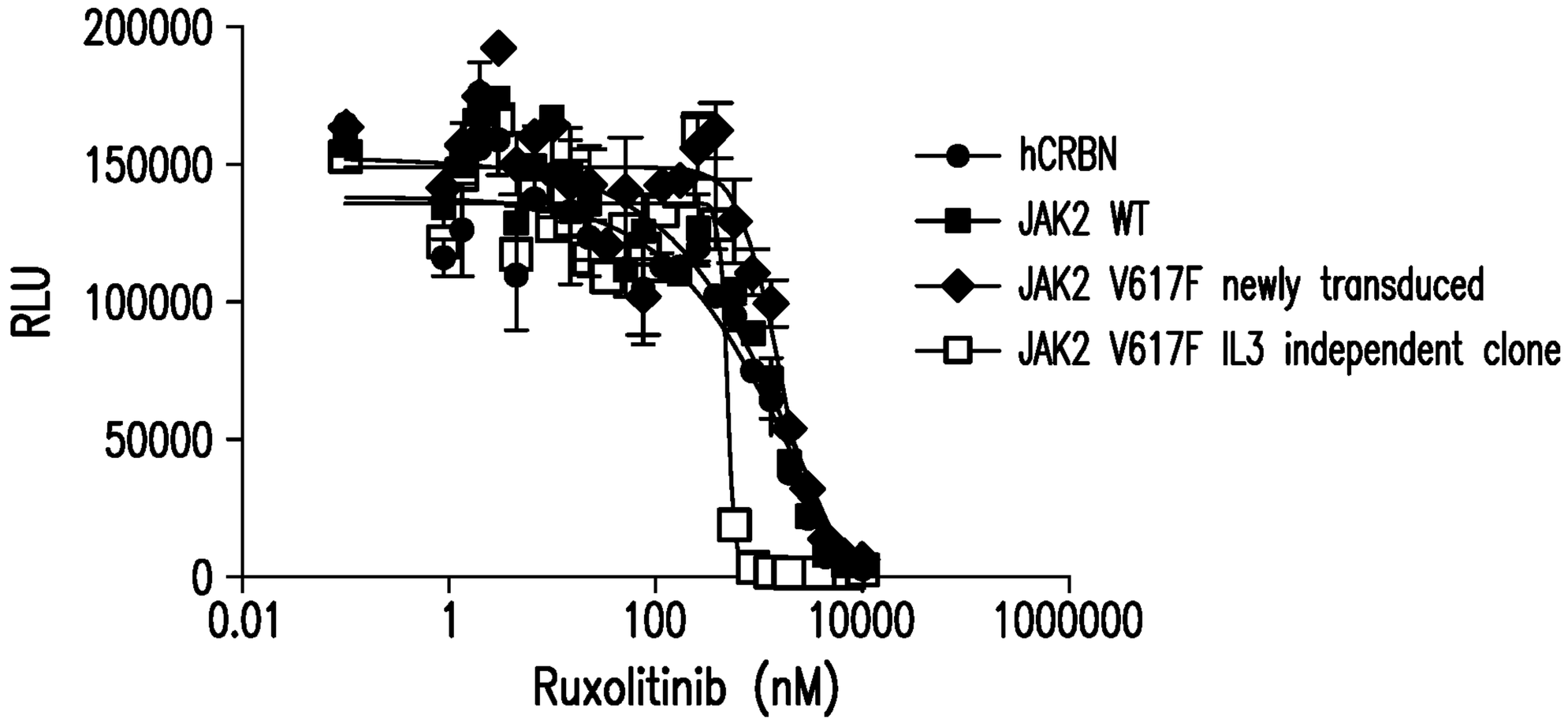

MF13
MF14
MF13 IC50=86.3nM
MF14 IC50=34.4nM
Relative colony number
120%
100%
80%
60%
40%
20%
0%
1
10
100
1000
10000
[Compound 1] (nM)

FIG. 70



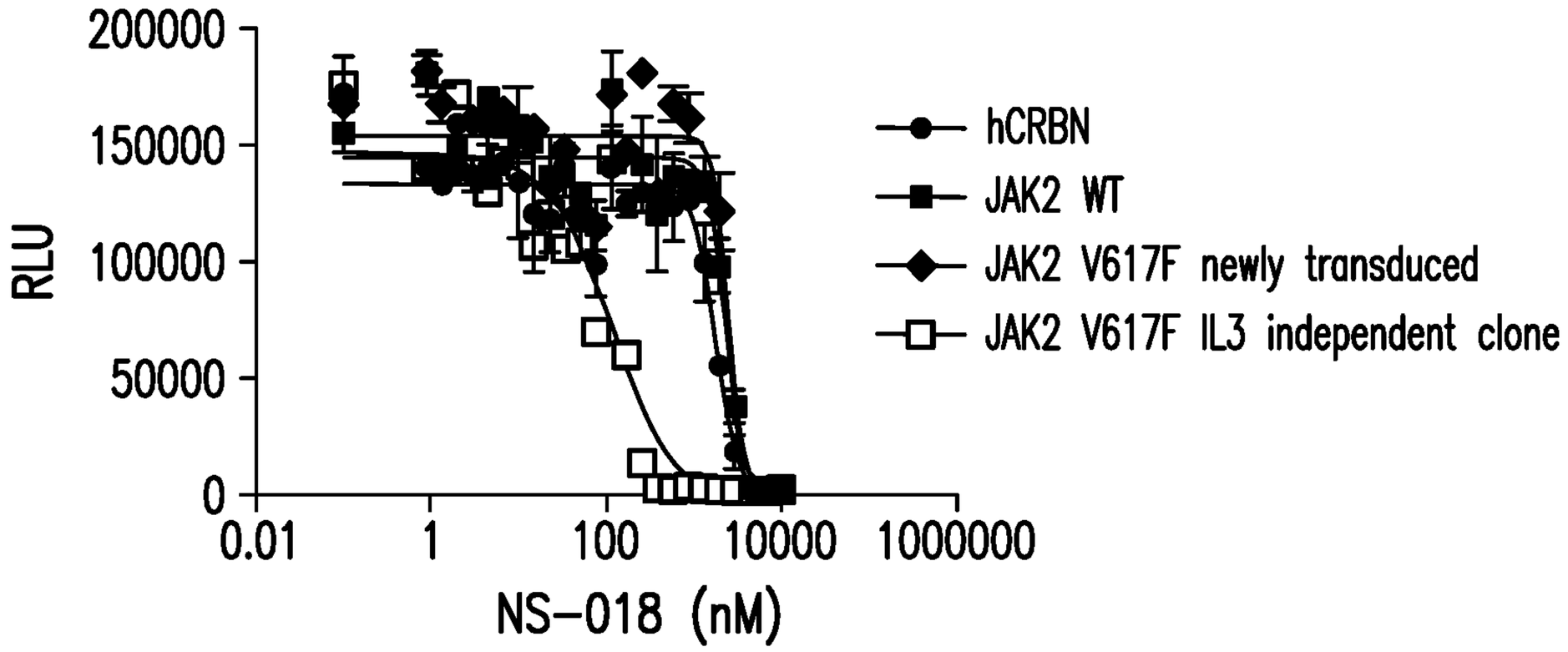
	hCRBN	JAK2 WT	JAK2 V617F newly transduced	JAK2 V617F IL3 independent clone
HillSlope	−3.616	−4.08	−4.001	−6.716
IC50	6.724	7.312	6.553	4.992

FIG. 71



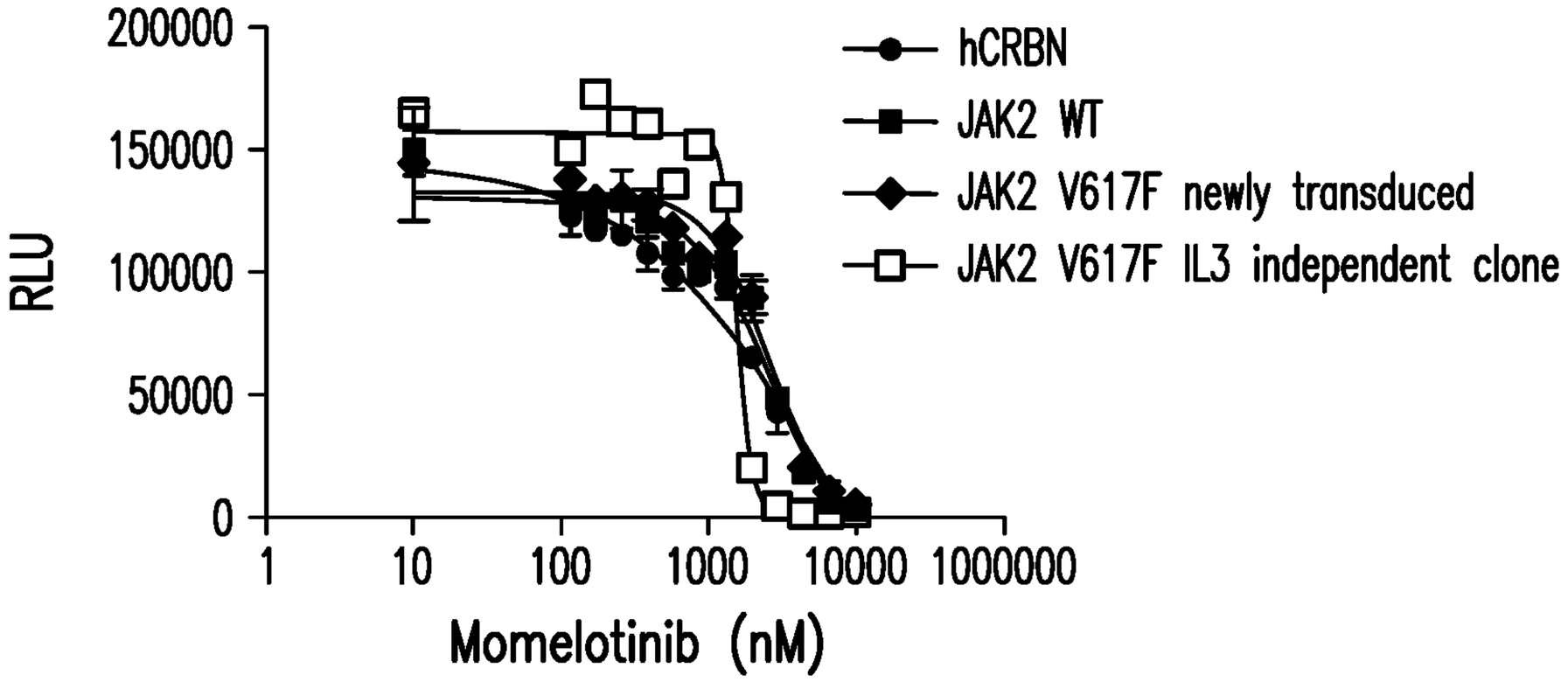
	hCRBN	JAK2 WT	JAK2 V617F newly transduced	JAK2 V617F IL3 independent clone
HillSlope	−0.691	−0.6379	−2.347	−11.79
IC50	2526	3469	1578	496.8

FIG. 72



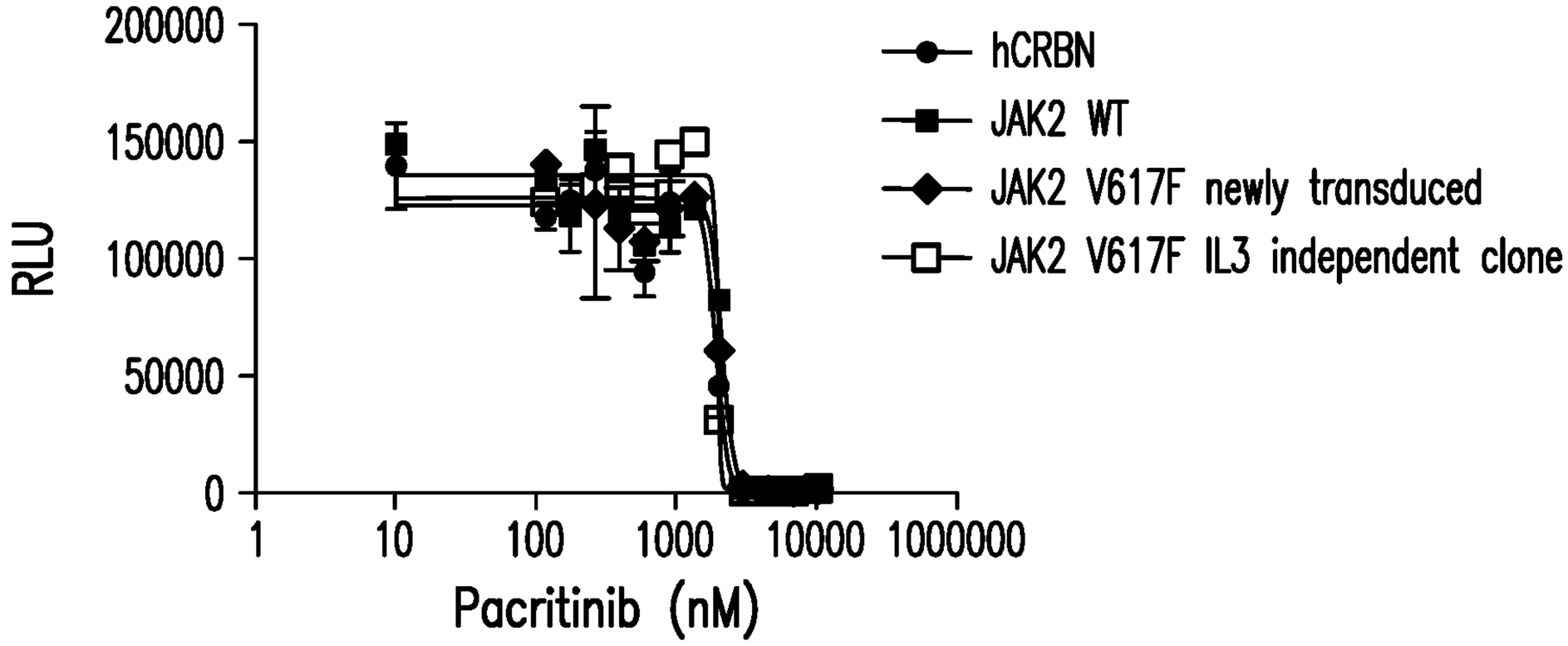
	hCRBN	JAK2 WT	JAK2 V617F newly transduced	JAK2 V617F IL3 independent clone
HillSlope	−3.561	−4.313	−5.53	−1.211
IC50	1780	2321	2443	121.8

FIG. 73



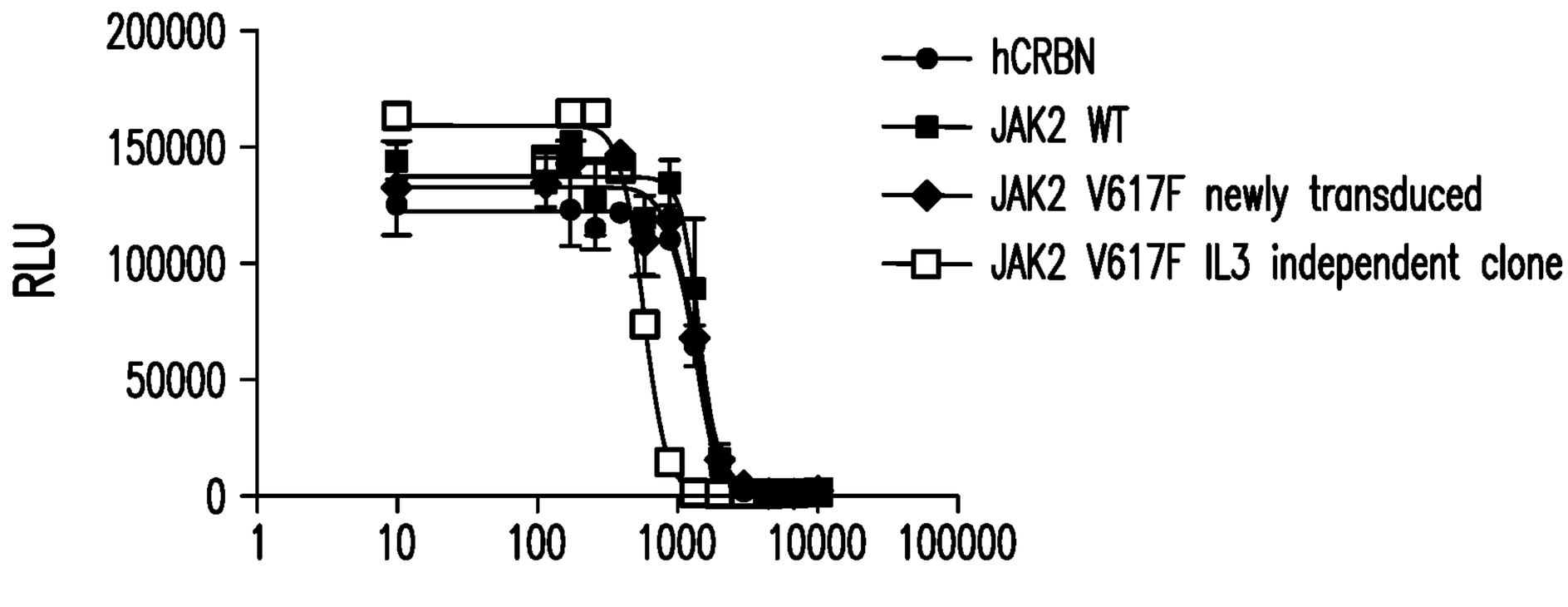
	hCRBN	JAK2 WT	JAK2 V617F newly transduced	JAK2 V617F IL3 independent clone
HillSlope	−0.6718	−1.593	−2.053	−8.822
IC50	6238	2798	2638	1573

FIG. 74



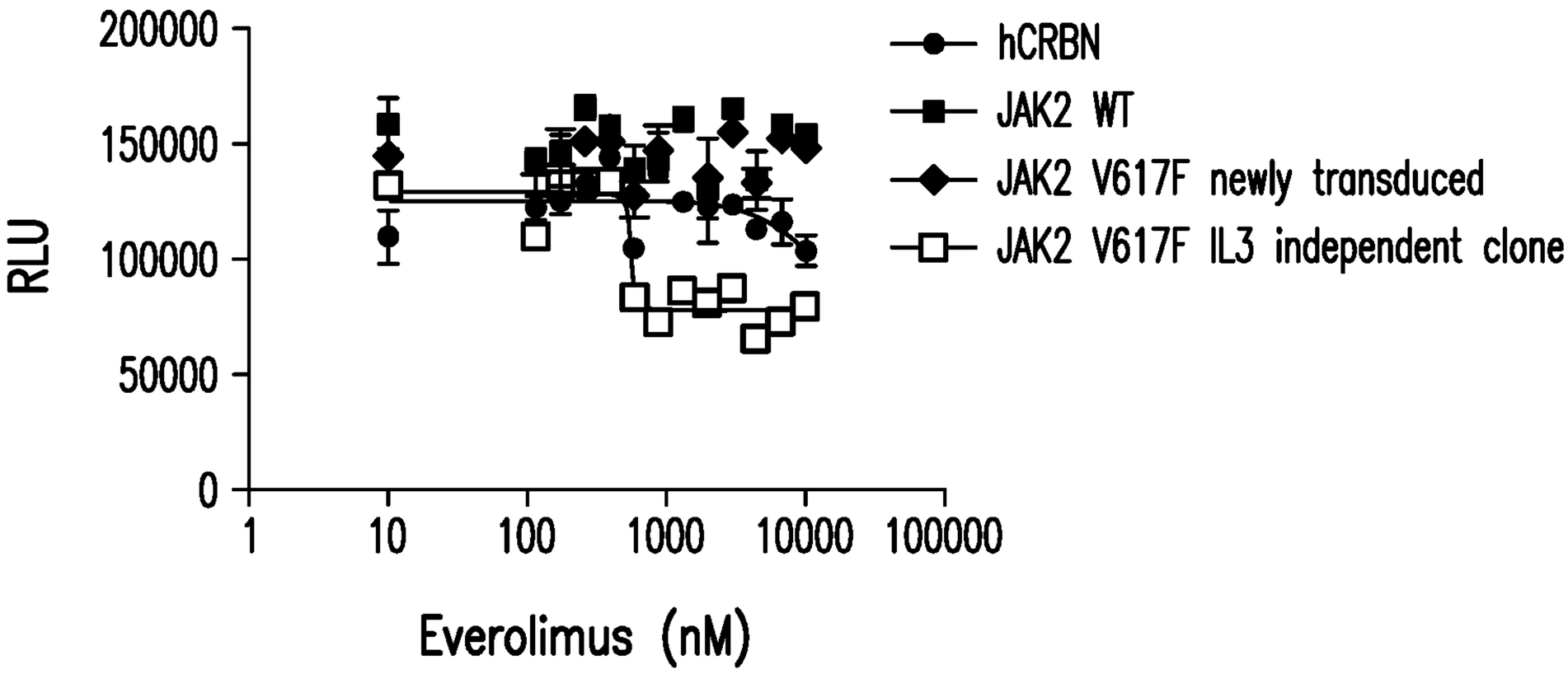
	hCRBN	JAK2 WT	JAK2 V617F newly transduced	JAK2 V617F IL3 independent clone
HillSlope	−11.27	−11.62	−14.02	~ −39.85
IC50	1882	2084	1961	~ 1914

FIG. 75



	hCRBN	JAK2 WT	JAK2 V617F newly transduced	JAK2 V617F IL3 independent clone
HillSlope	−5.401	−6.66	−4.52	−5.578
IC50	1330	1443	1313	567.9

FIG. 76



	hCRBN	JAK2 WT	JAK2 V617F newly transduced	JAK2 V617F IL3 independent clone
HillSlope	−1.959			~ −35.61
IC50	12190			~ 551.7

FIG. 77

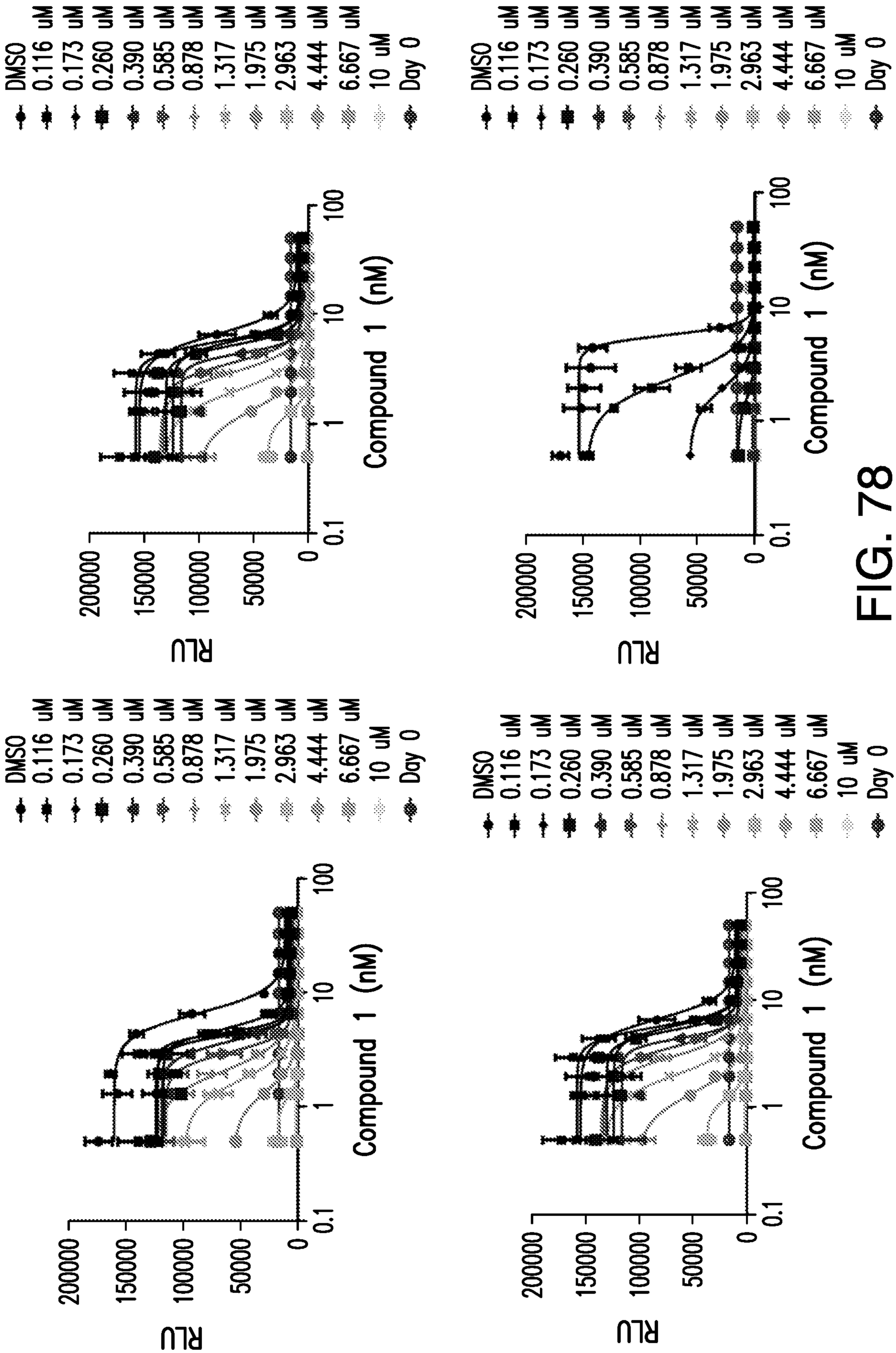

DMSO
0.116 uM
0.173 uM
0.260 uM
0.390 uM
0.585 uM
0.878 uM
1.317 uM
1.975 uM
2.963 uM
4.444 uM
6.667 uM
10 uM
Day 0
RLU
200000
150000
100000
50000
0
0.1
1
10
100
Compound 1 (nM)

FIG. 78

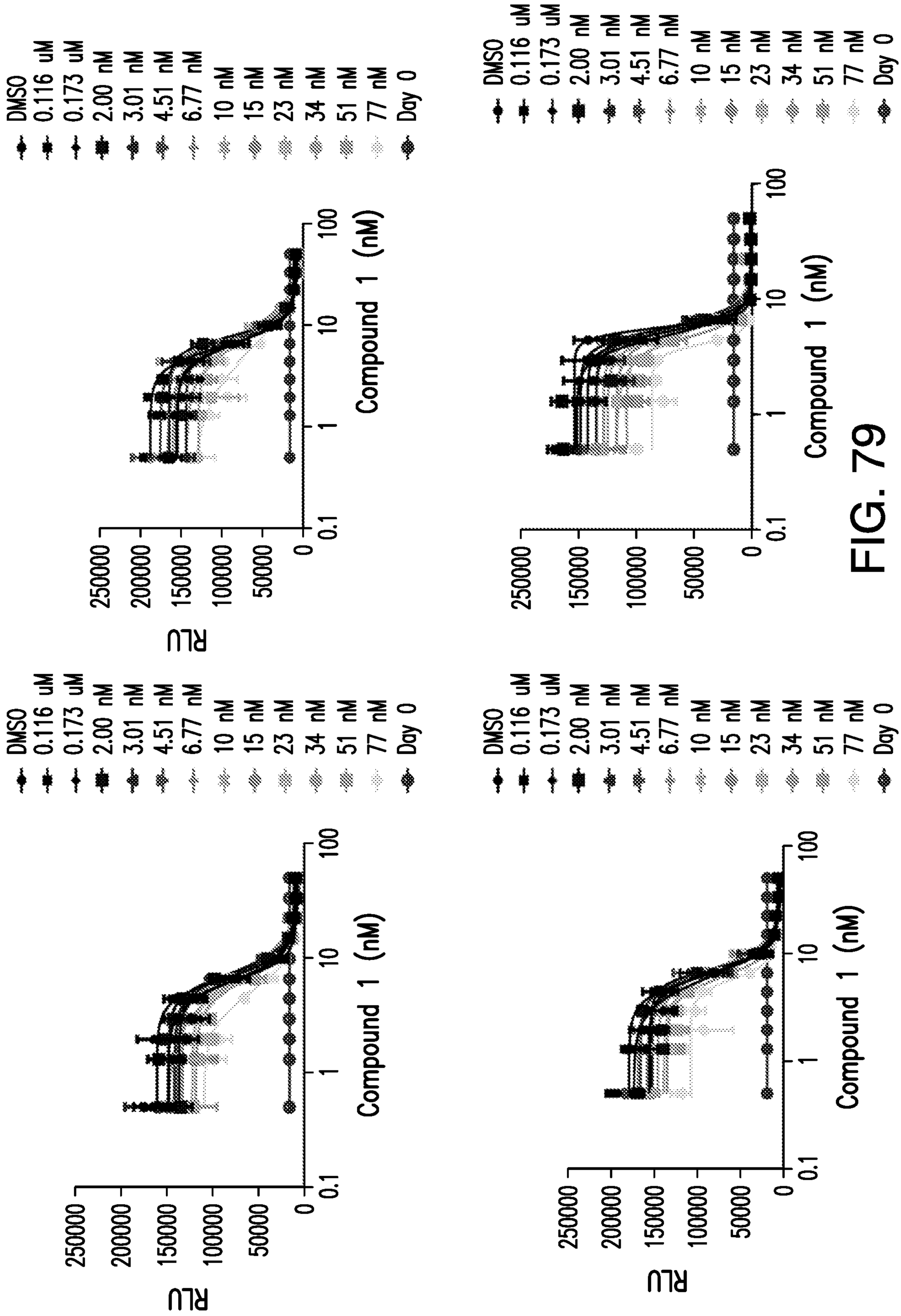

DMSO
0.116 uM
0.173 uM
2.00 nM
3.01 nM
4.51 nM
6.77 nM
10 nM
15 nM
23 nM
34 nM
51 nM
77 nM
Day 0
RLU
250000
200000
150000
100000
50000
0
0.1
1
10
100
Compound 1 (nM)

FIG. 79

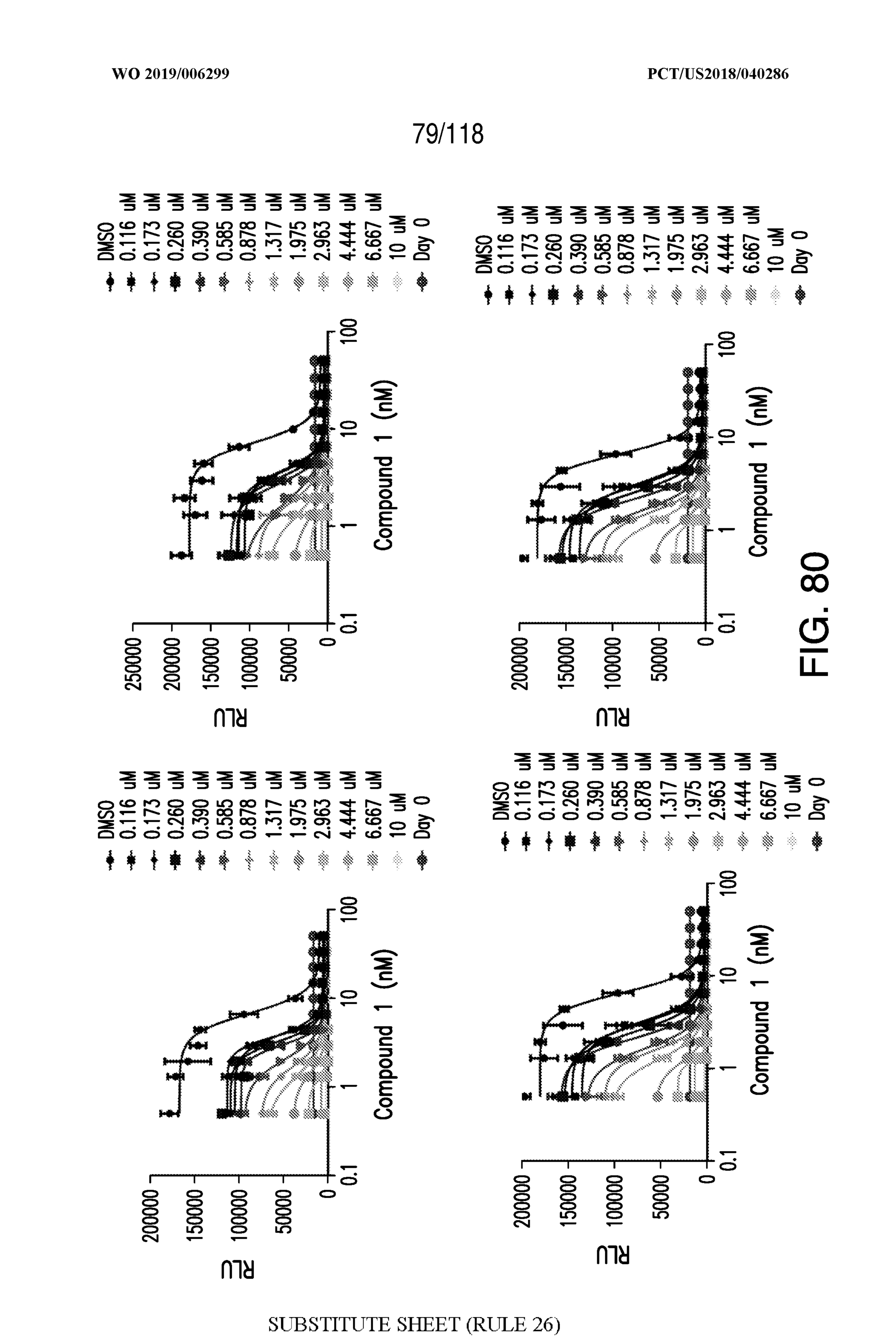
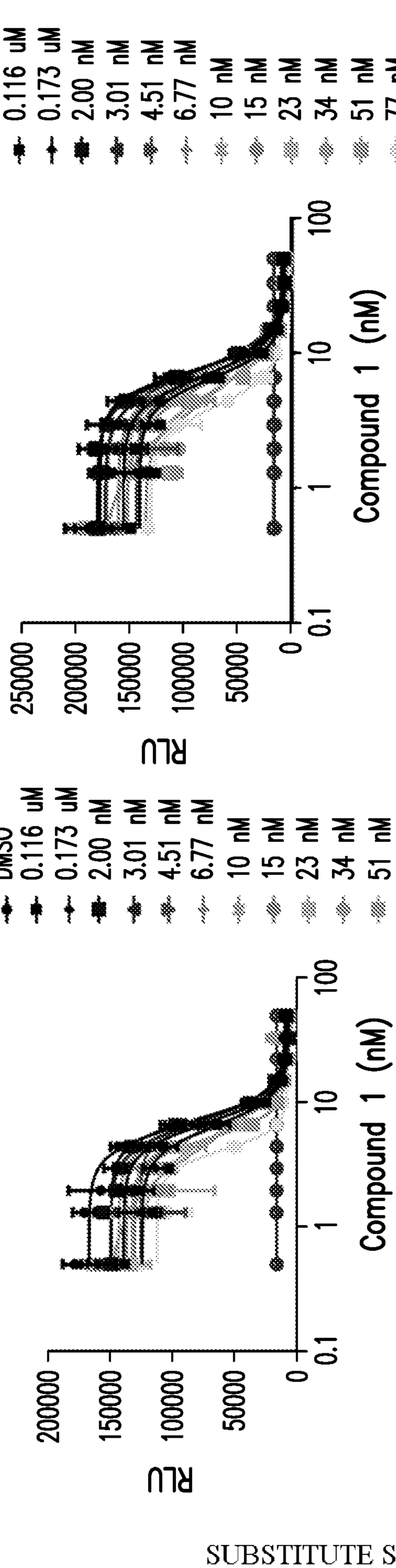

DMSO
0.116 uM
0.173 uM
0.260 uM
0.390 uM
0.585 uM
0.878 uM
1.317 uM
1.975 uM
2.963 uM
4.444 uM
6.667 uM
10 uM
Day 0
RLU
250000
200000
150000
100000
50000
0
0.1
1
10
100
Compound 1 (nM)

FIG. 80


DMSO
0.116 uM
0.173 uM
2.00 nM
3.01 nM
4.51 nM
6.77 nM
10 nM
15 nM
23 nM
34 nM
51 nM
77 nM
Day 0
RLU
250000
200000
150000
100000
50000
0
0.1
1
10
100
Compound 1 (nM)

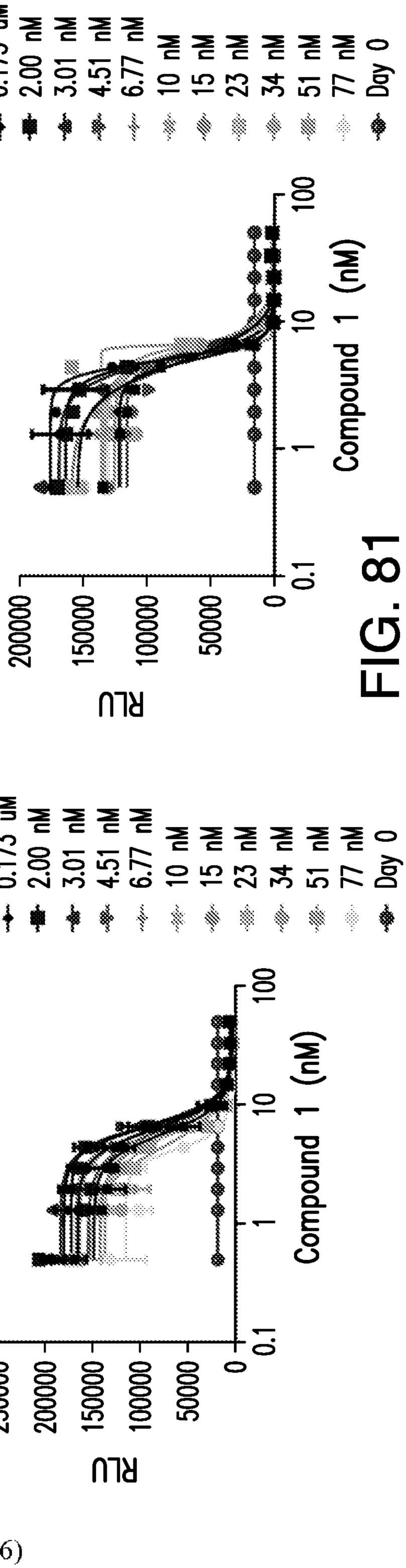

DMSO
0.116 uM
0.173 uM
2.00 nM
3.01 nM
4.51 nM
6.77 nM
10 nM
15 nM
23 nM
34 nM
51 nM
77 nM
Day 0
RLU
200000
150000
100000
50000
0
0.1
1
10
100
Compound 1 (nM)

FIG. 81

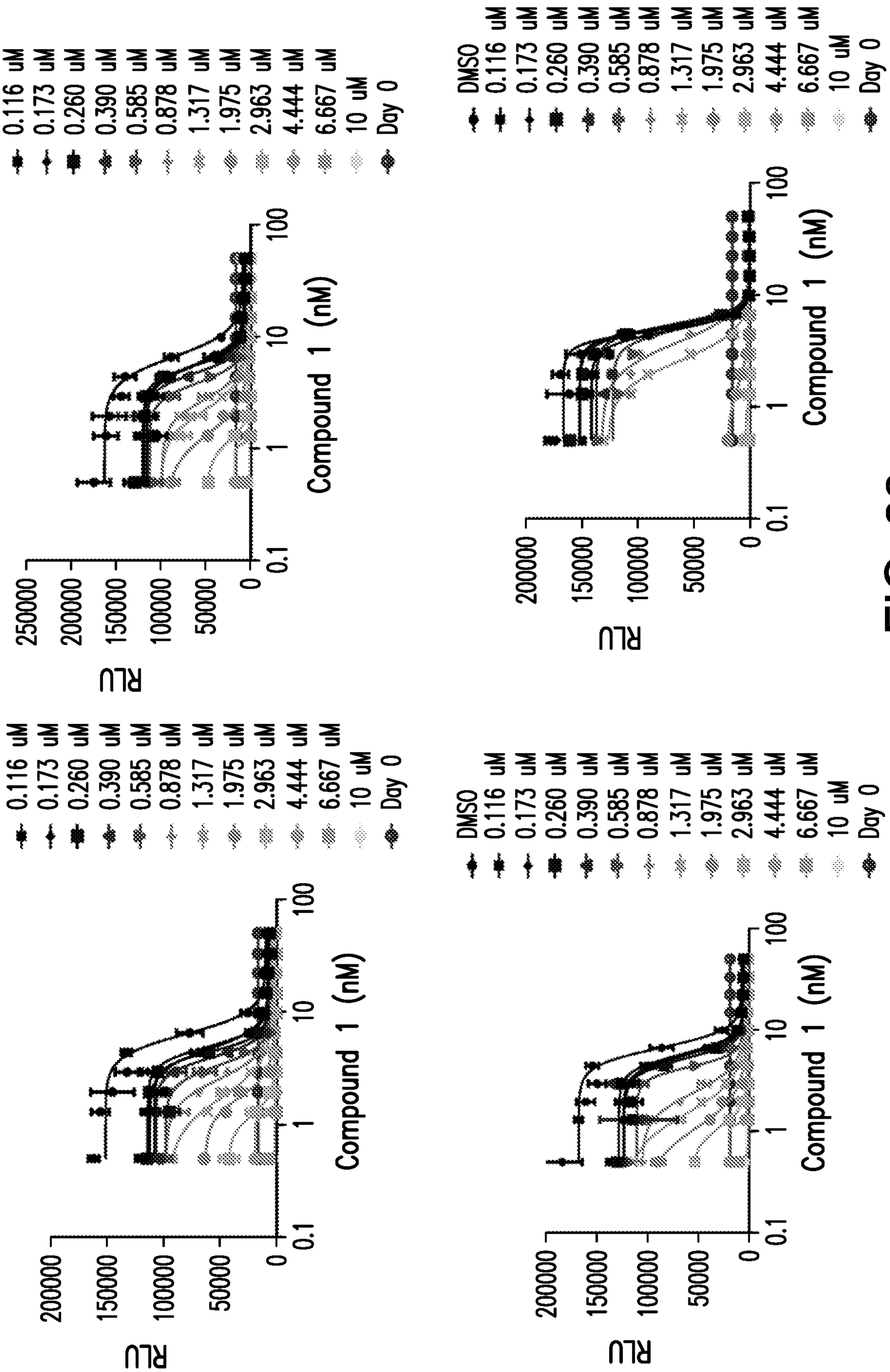
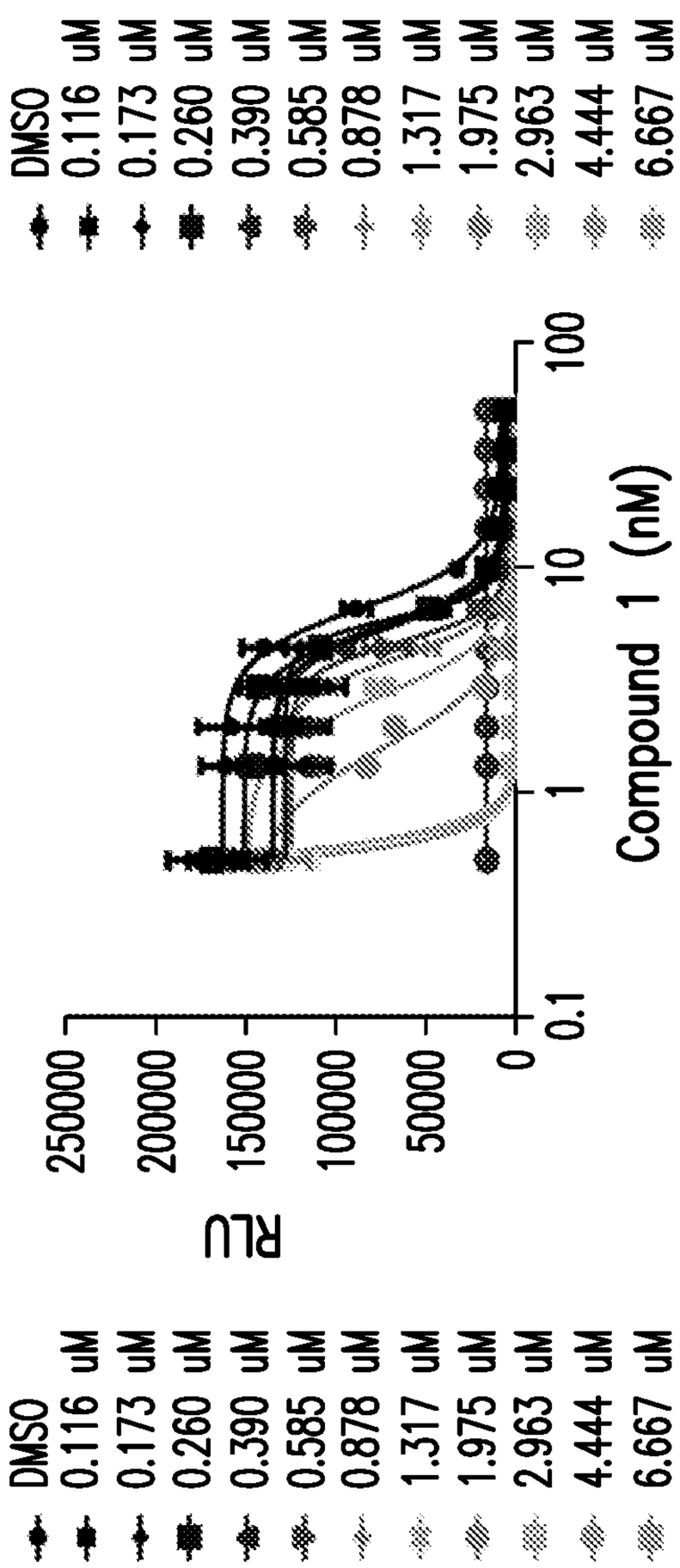

DMSO
0.116 uM
0.173 uM
0.260 uM
0.390 uM
0.585 uM
0.878 uM
1.317 uM
1.975 uM
2.963 uM
4.444 uM
6.667 uM
10 uM
Day 0
RLU
Compound 1 (nM)
0
50000
100000
150000
200000
0.1
1
10
100

FIG. 82


DMSO
0.116 uM
0.173 uM
0.260 uM
0.390 uM
0.585 uM
0.878 uM
1.317 uM
1.975 uM
2.963 uM
4.444 uM
6.667 uM
10 uM
Day 0
RLU
0
50000
100000
150000
200000
0.1
1
10
100
Compound 1 (nM)

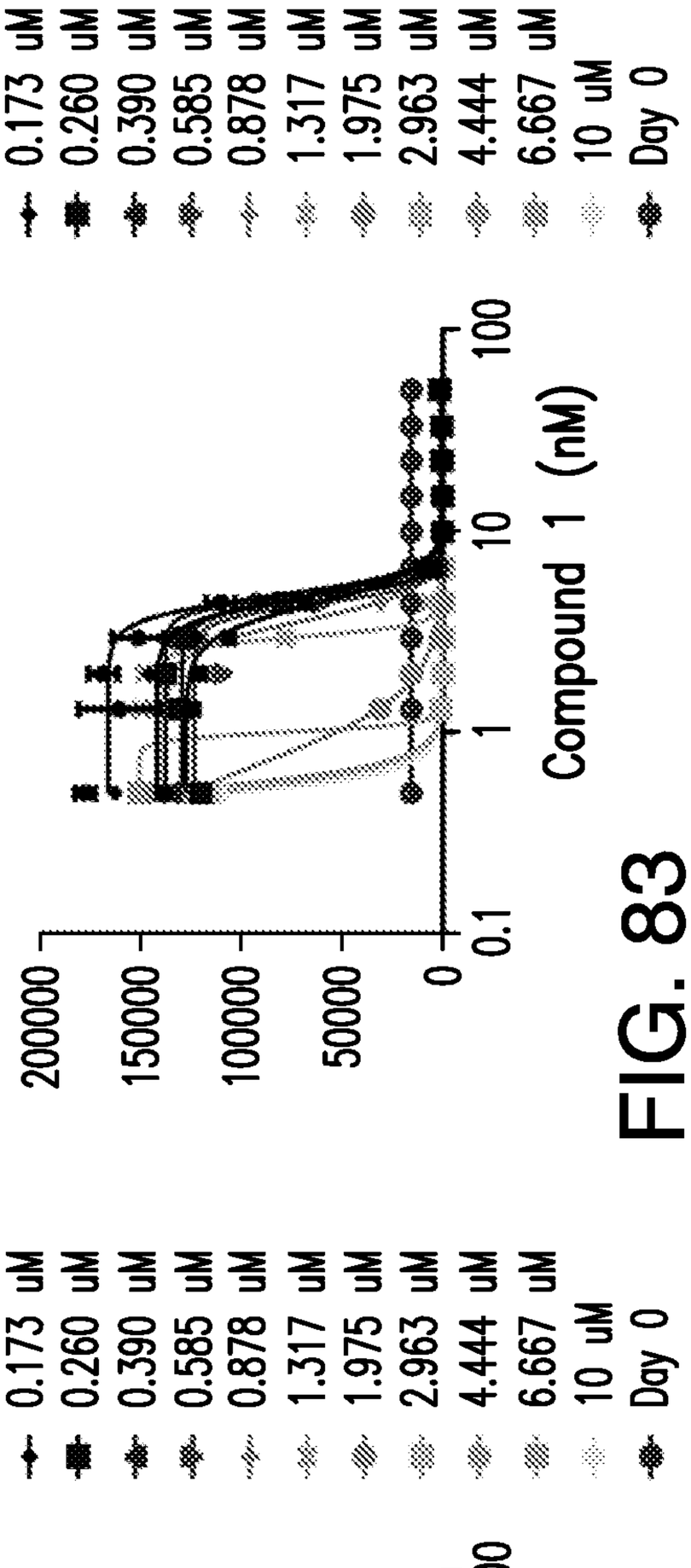
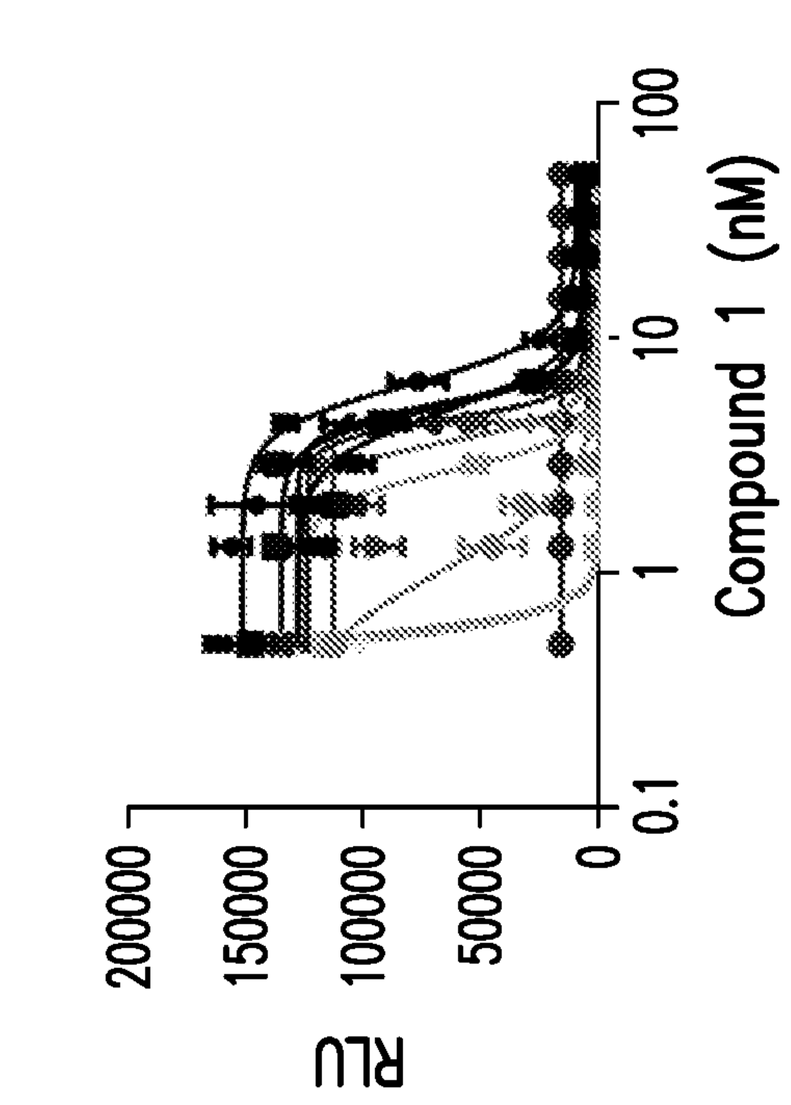
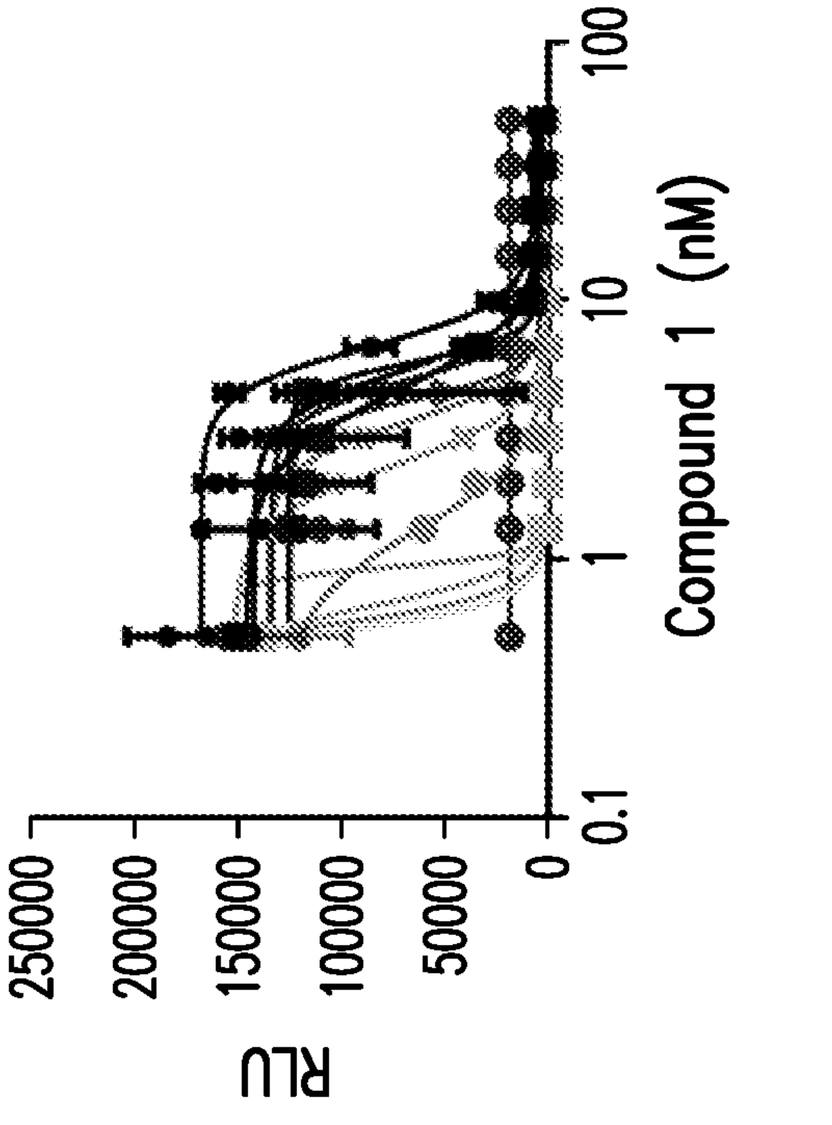

DMSO
0.116 uM
0.173 uM
0.260 uM
0.390 uM
0.585 uM
0.878 uM
1.317 uM
1.975 uM
2.963 uM
4.444 uM
6.667 uM
10 uM
Day 0
RLU
0
50000
100000
150000
200000
0.1
1
10
100
Compound 1 (nM)

FIG. 83


DMSO
0.116 uM
0.173 uM
0.260 uM
0.390 uM
0.585 uM
0.878 uM
1.317 uM
1.975 uM
2.963 uM
4.444 uM
6.667 uM
10 uM
Day 0
RLU
0
50000
100000
150000
200000
0.1
1
10
100
Compound 1 (nM)


DMSO
0.116 uM
0.173 uM
0.260 uM
0.390 uM
0.585 uM
0.878 uM
1.317 uM
1.975 uM
2.963 uM
4.444 uM
6.667 uM
10 uM
Day 0
RLU
0
50000
100000
150000
200000
250000
0.1
1
10
100
Compound 1 (nM)

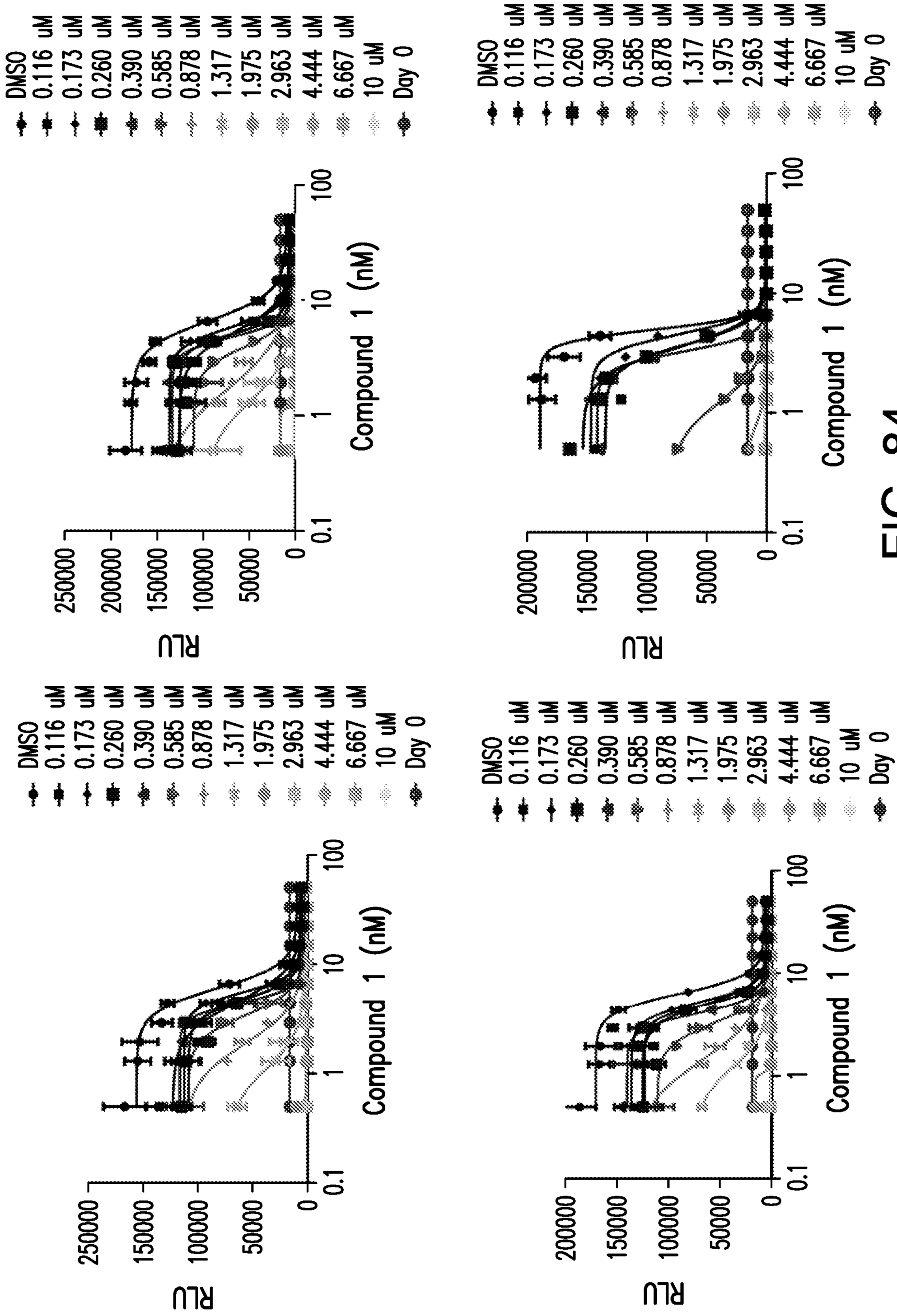

DMSO
0.116 uM
0.173 uM
0.260 uM
0.390 uM
0.585 uM
0.878 uM
1.317 uM
1.975 uM
2.963 uM
4.444 uM
6.667 uM
10 uM
Day 0
RLU
250000
200000
150000
100000
50000
0
0.1
1
10
100
Compound 1 (nM)

FIG. 84

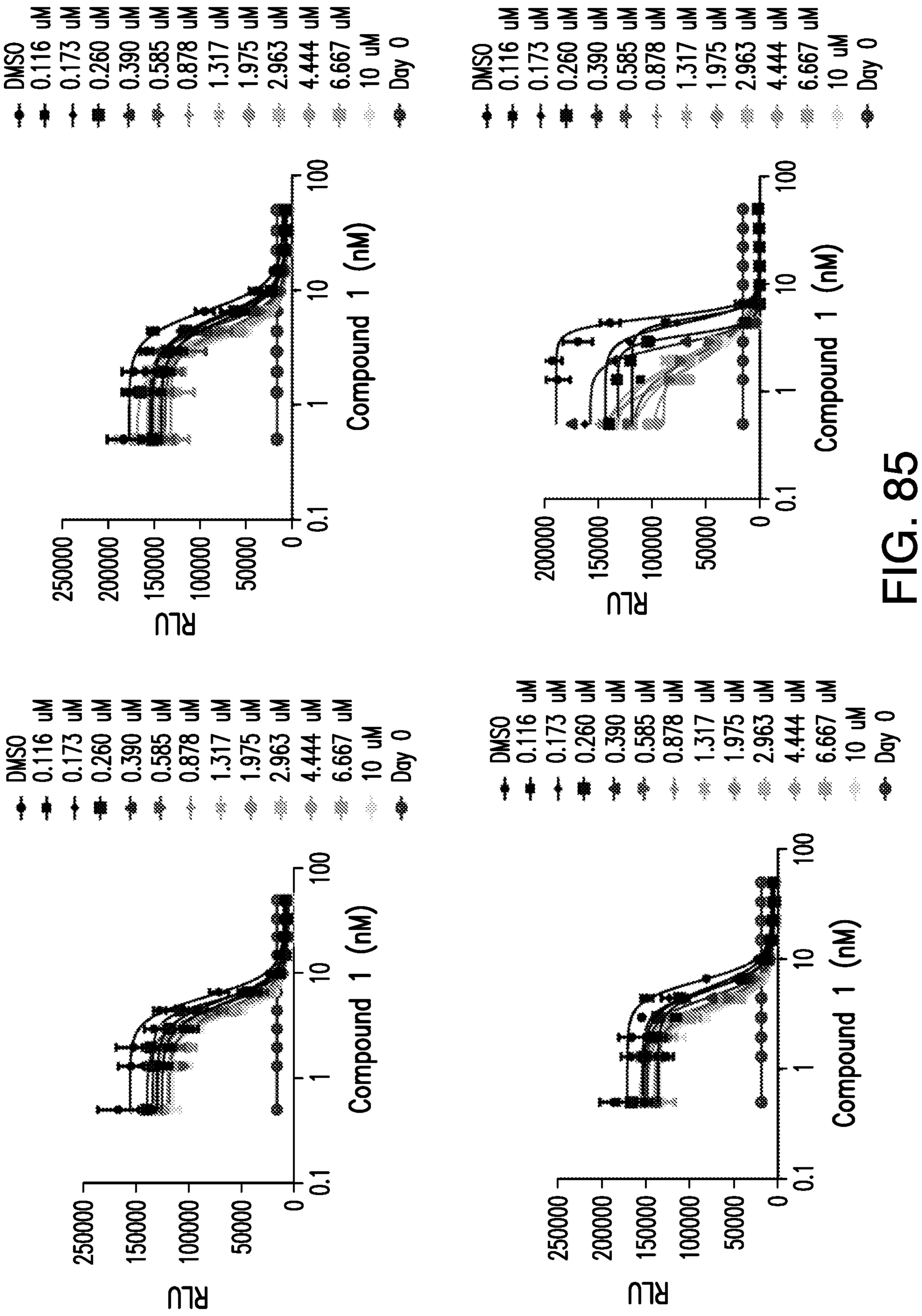

DMSO
0.116 uM
0.173 uM
0.260 uM
0.390 uM
0.585 uM
0.878 uM
1.317 uM
1.975 uM
2.963 uM
4.444 uM
6.667 uM
10 uM
Day 0
RLU
250000
200000
150000
100000
50000
0
0.1
1
10
100
Compound 1 (nM)

FIG. 85

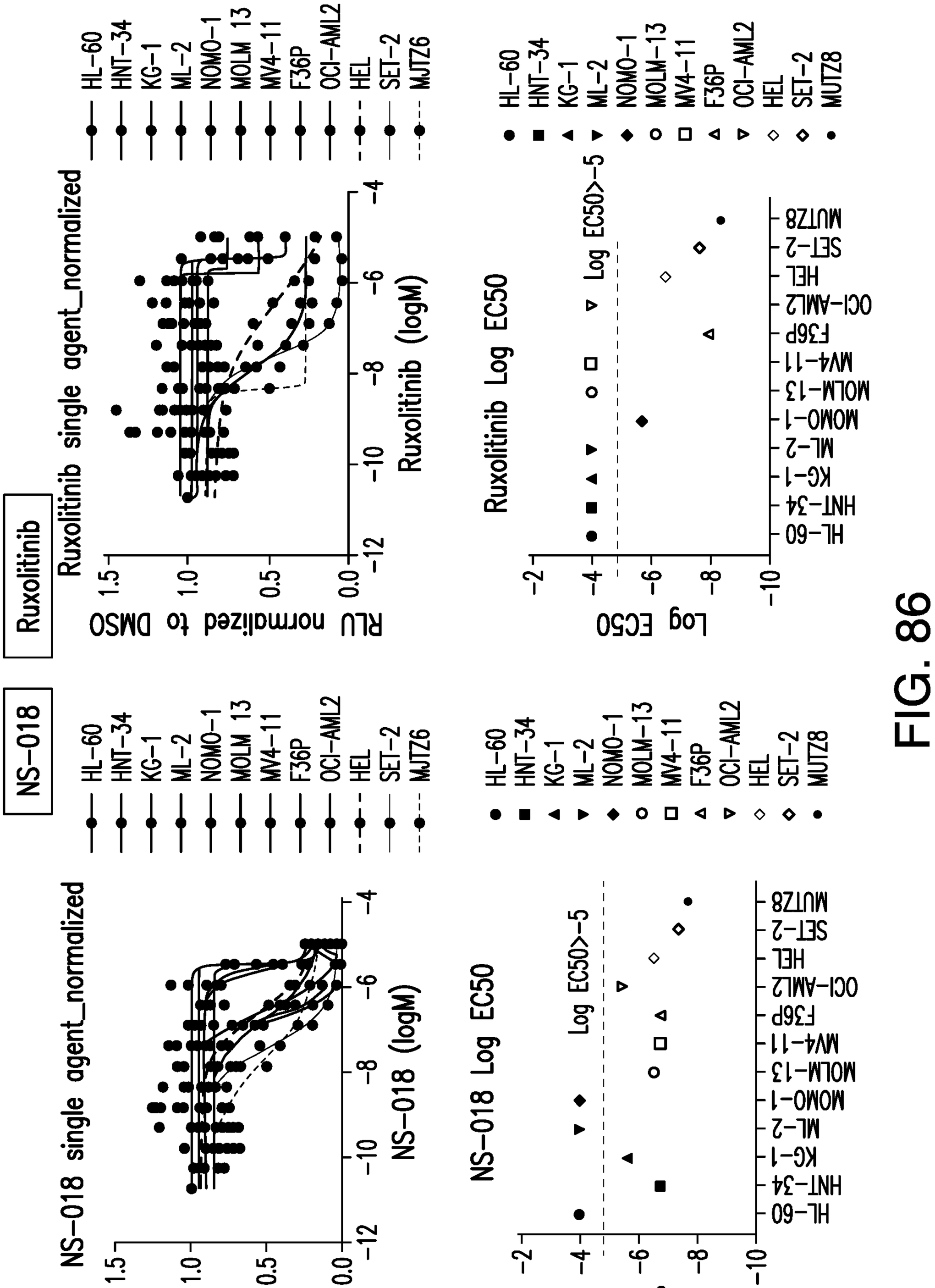

Ruxolitinib
Ruxolitinib single agent_normalized
RLU normalized to DMSO
Ruxolitinib (logM)
HL-60
HNT-34
KG-1
ML-2
NOMO-1
MOLM 13
MV4-11
F36P
OCI-AML2
HEL
SET-2
MJTZ6
Ruxolitinib Log EC50
Log EC50
Log EC50>-5
HL-60
HNT-34
KG-1
ML-2
NOMO-1
MOLM-13
MV4-11
F36P
OCI-AML2
HEL
SET-2
MUTZ8
NS-018
NS-018 single agent_normalized
NS-018 (logM)
NS-018 Log EC50

FIG. 86

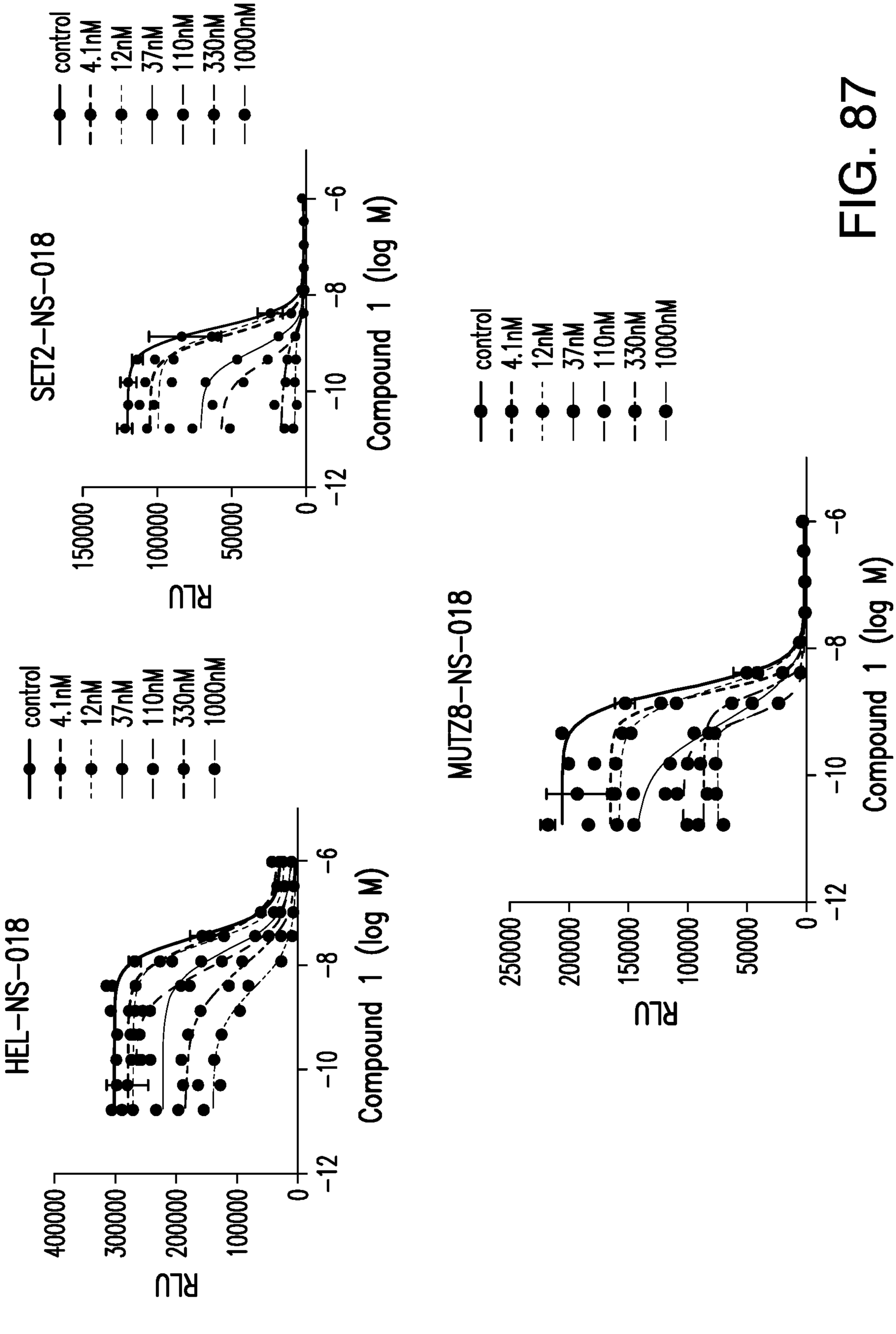

SET2–NS–018
RLU
Compound 1 (log M)
control
4.1nM
12nM
37nM
110nM
330nM
1000nM
MUTZ8–NS–018
HEL–NS–018

FIG. 87

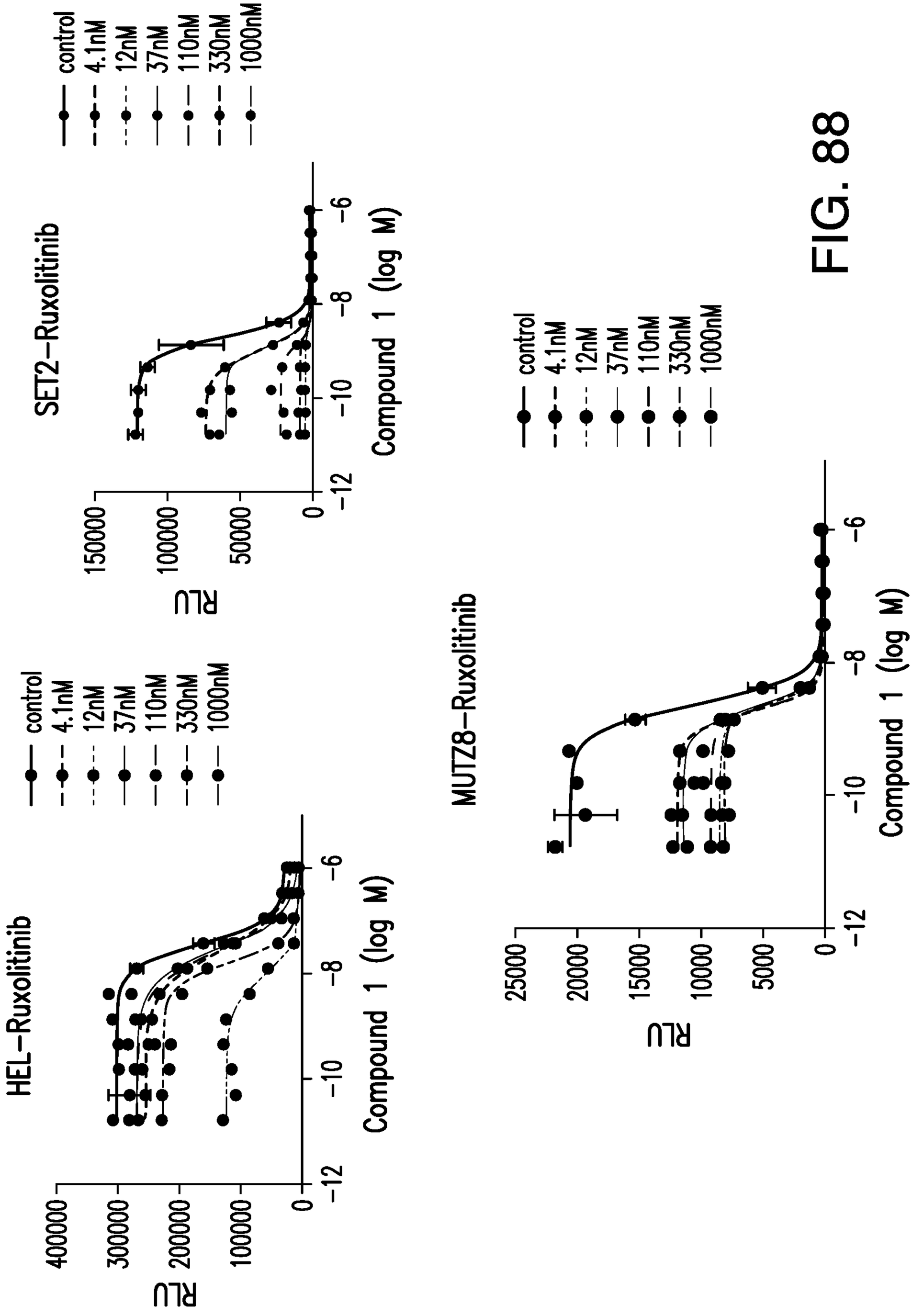

SET2–Ruxolitinib
MUTZ8–Ruxolitinib
HEL–Ruxolitinib
control
4.1nM
12nM
37nM
110nM
330nM
1000nM
RLU
Compound 1 (log M)
150000
100000
50000
0
25000
20000
15000
10000
5000
400000
300000
200000
100000
−12
−10
−8
−6

FIG. 88

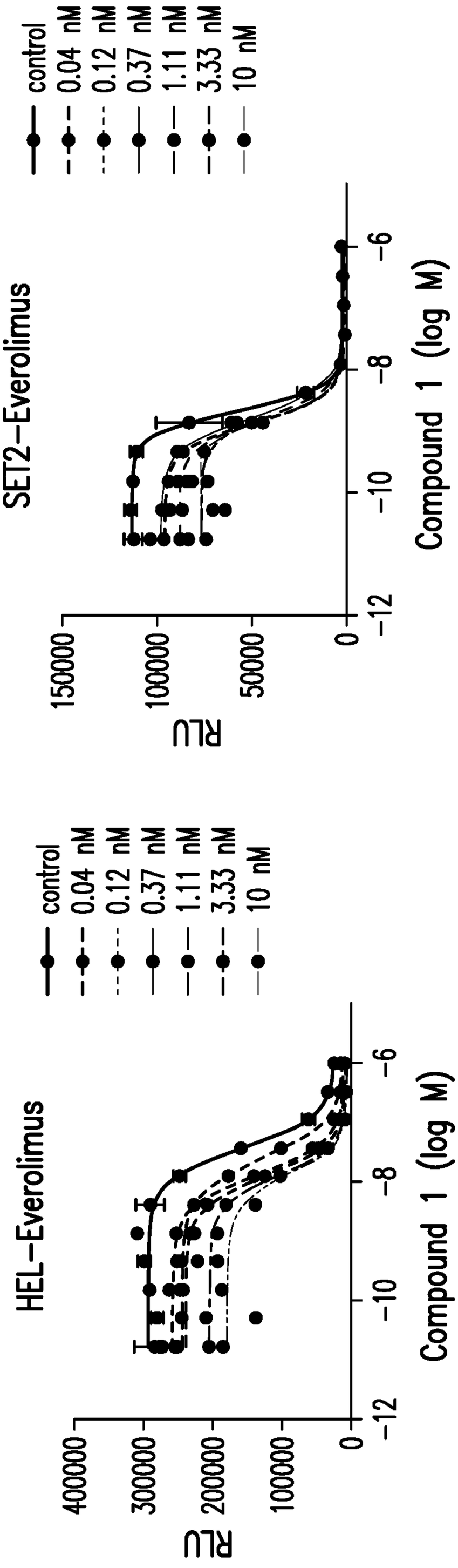

control
0.04 nM
0.12 nM
0.37 nM
1.11 nM
3.33 nM
10 nM
SET2–Everolimus
RLU
Compound 1 (log M)
MUTZ8–Everolimus
HEL–Everolimus

FIG. 89

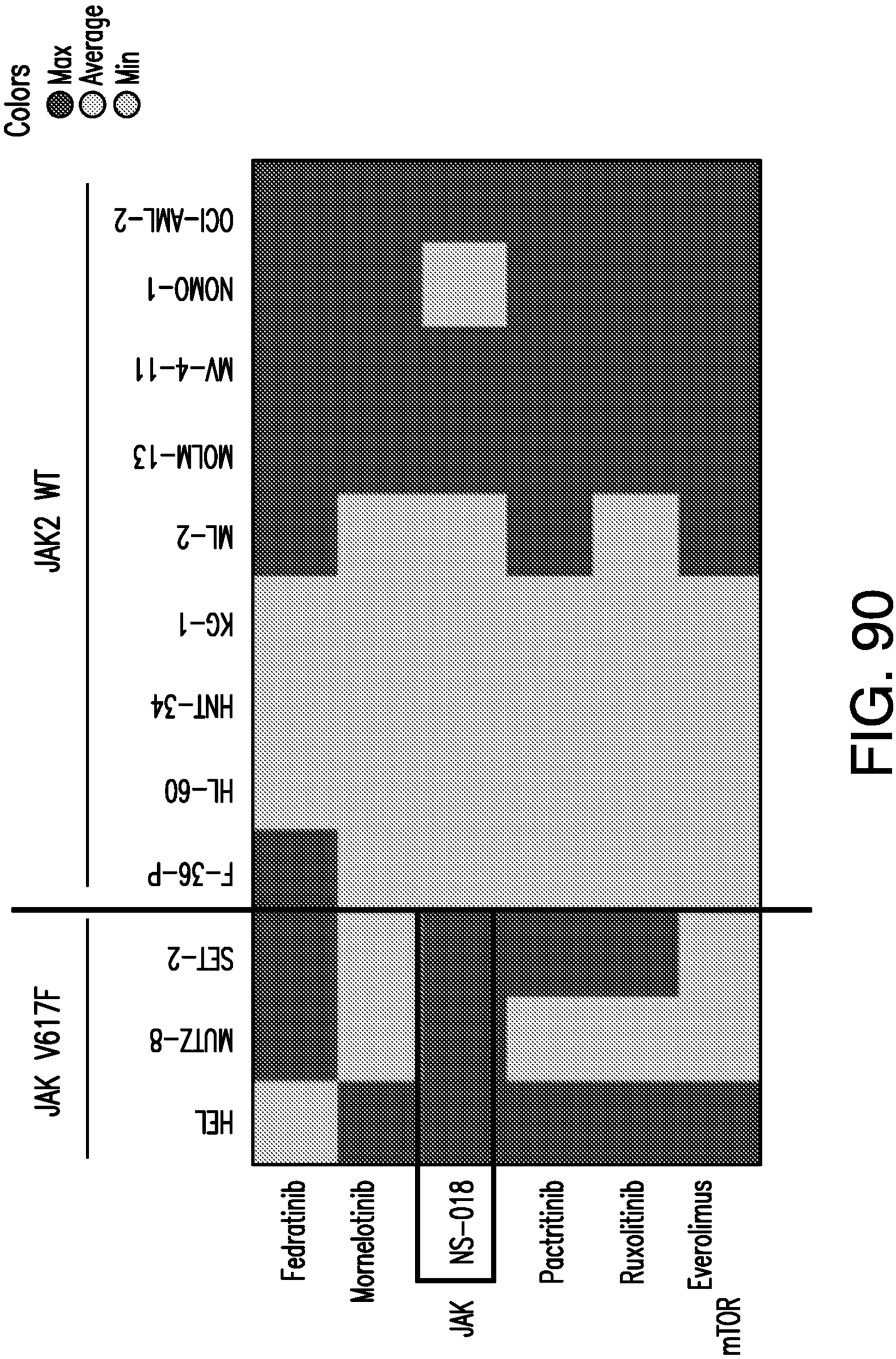

Colors
Max
Average
Min
JAK2 WT
OCI-AML-2
NOMO-1
MV-4-11
MOLM-13
ML-2
JAK V617F
K6-1
HNT-34
HL-60
F-36-P
SET-2
MUTZ-8
HEL
Fedratinib
Momelotinib
NS-018
Pactritinib
Ruxolitinib
Everolimus
JAK
mTOR

FIG. 90

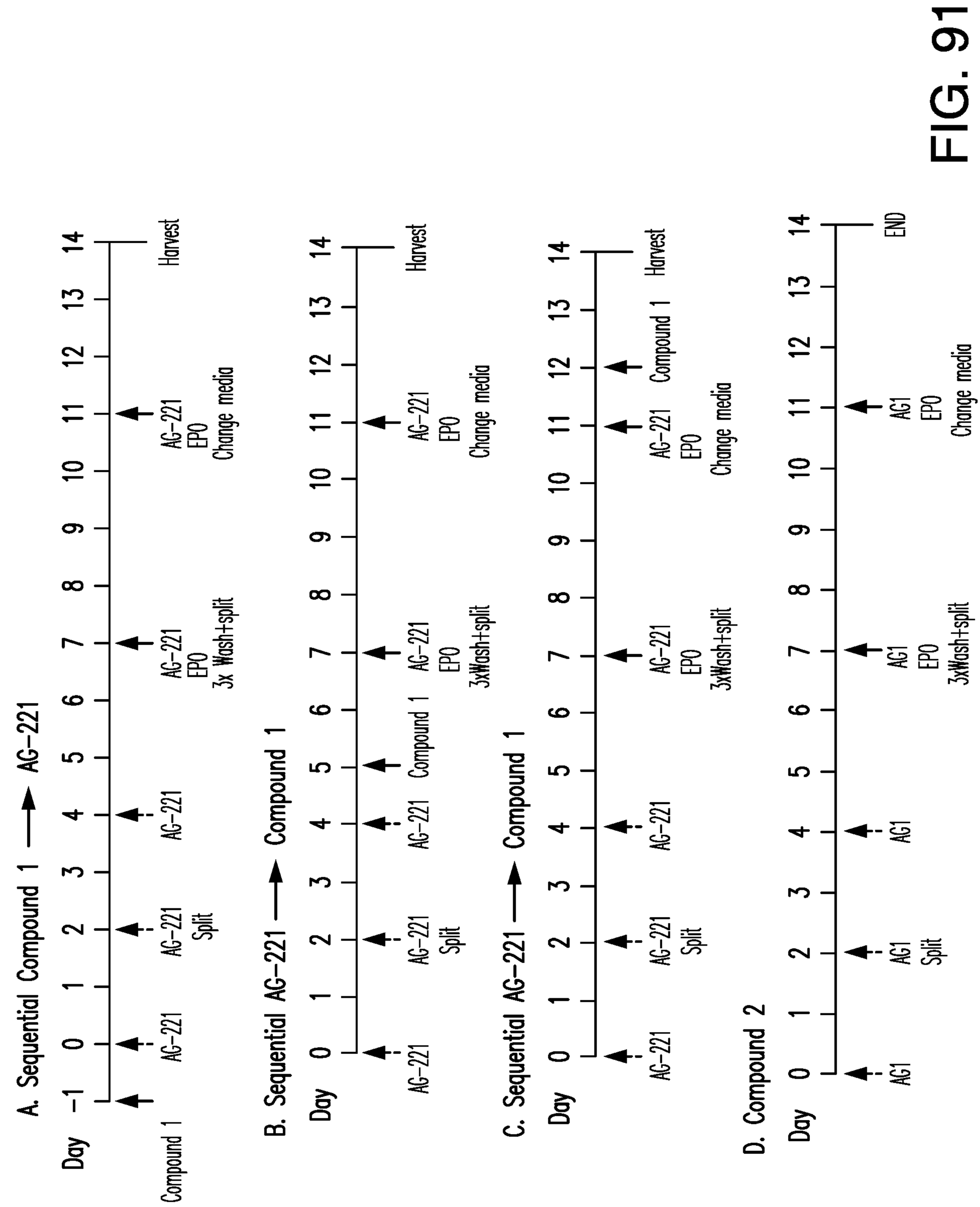

A. Sequential Compound 1 → AG-221
Day −1 0
Compound 1
AG-221
Split
AG-221
EPO
3x Wash+split
B. Sequential AG-221 → Compound 1
Day 0
AG-221
Split
AG-221
Compound 1
AG-221
EPO
3xWash+split
C. Sequential AG-221 → Compound 1
Day 0
AG-221
Split
AG-221
EPO
3xWash+split
D. Compound 2
Day 0
AG1
Split
AG1
EPO
3xWash+split
1 2 3 4 5 6 7 8 9 10 11 12 13 14
AG-221
EPO
Change media
Harvest
Compound 1
AG-221
EPO
Change media
Harvest
AG1
EPO
Change media
END

FIG. 91

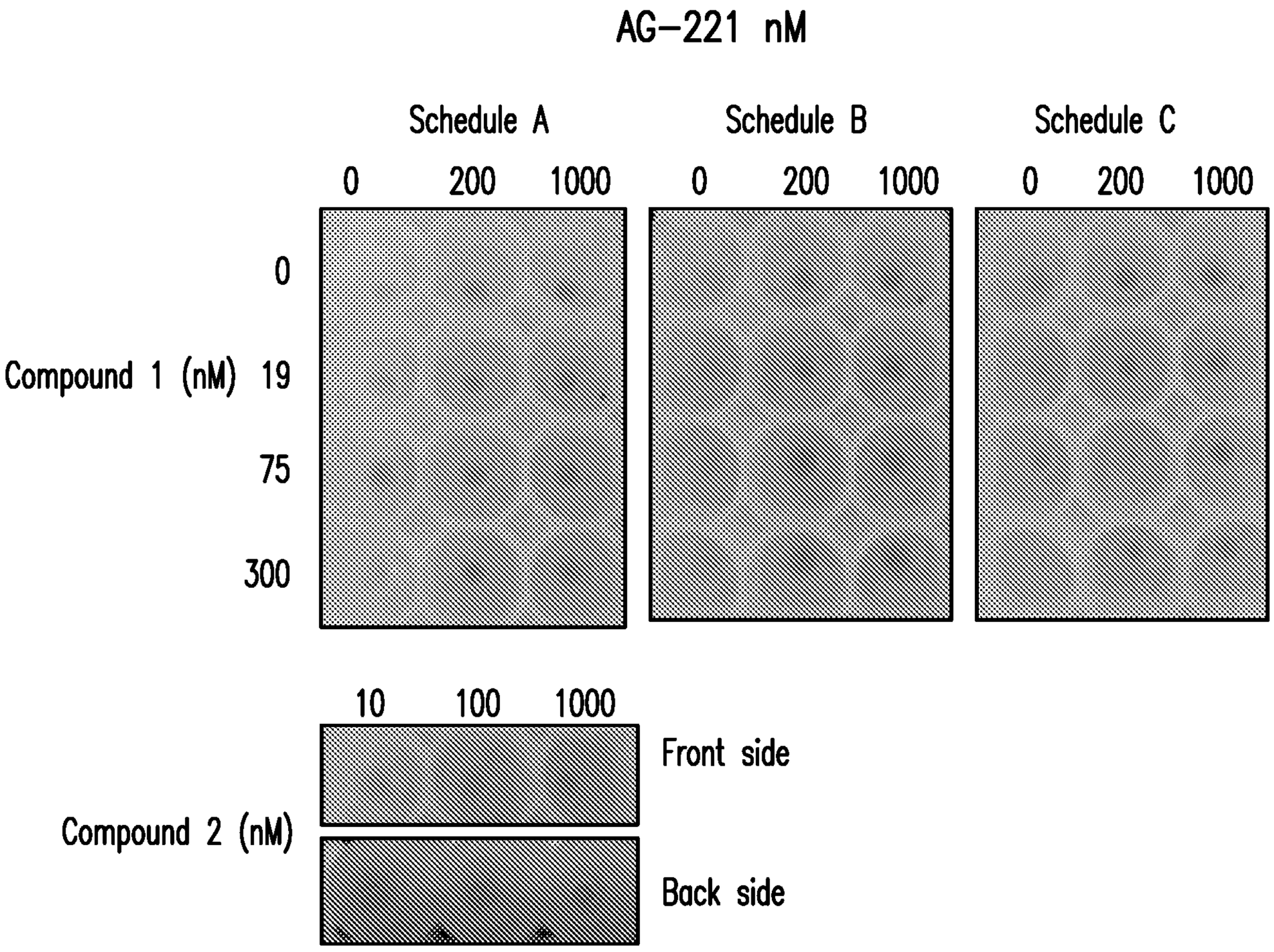

AG-221 nM
Schedule A
Schedule B
Schedule C
0
200
1000
0
200
1000
0
200
1000
Compound 1 (nM)
0
19
75
300
10
100
1000
Front side
Compound 2 (nM)
Back side

FIG. 92

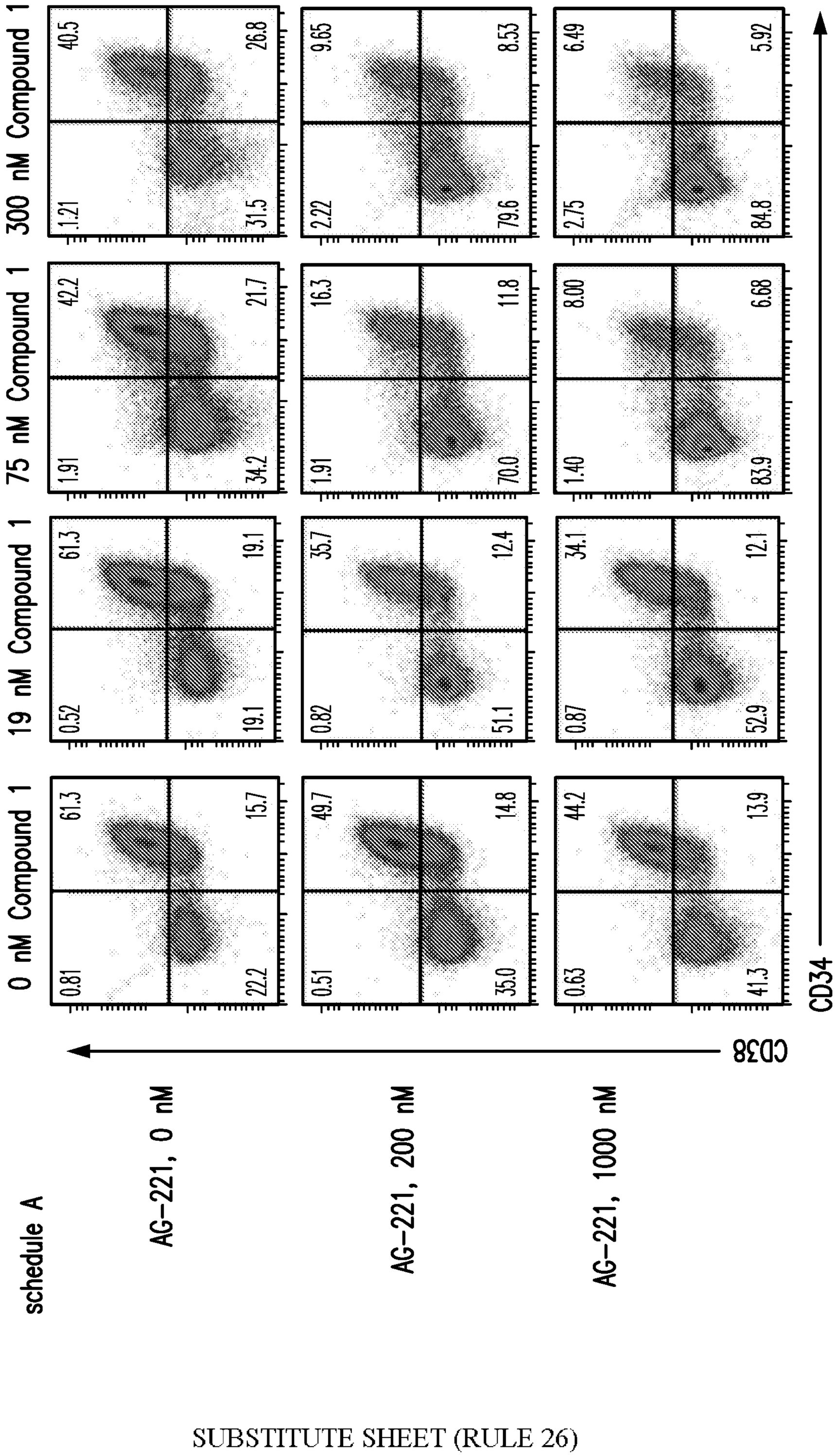

schedule A
AG-221, 0 nM
AG-221, 200 nM
AG-221, 1000 nM
CD38
CD34
0 nM Compound 1
19 nM Compound 1
75 nM Compound 1
300 nM Compound 1
0.81 61.3 22.2 15.7
0.51 49.7 35.0 14.8
0.63 44.2 41.3 13.9
0.52 61.3 19.1 19.1
0.82 35.7 51.1 12.4
0.87 34.1 52.9 12.1
1.91 42.2 34.2 21.7
1.91 16.3 70.0 11.8
1.40 8.00 83.9 6.68
1.21 40.5 31.5 26.8
2.22 9.65 79.6 8.53
2.75 6.49 84.8 5.92

FIG. 93

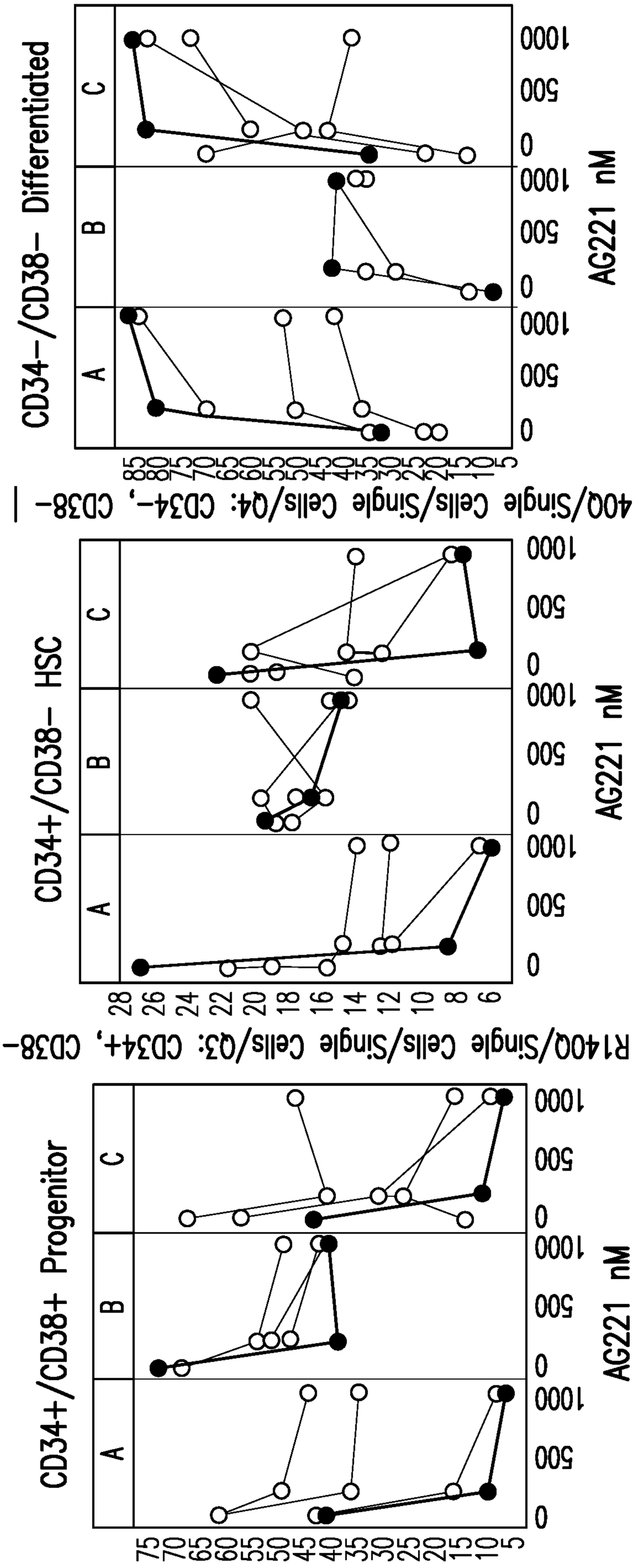

CD34-/CD38- Differentiated
A
B
C
AG221 nM
0
500
1000
TF1R1400/Single Cells/Single Cells/04: CD34-, CD38- | Freq...
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
CD34+/CD38- HSC
TF1R1400/Single Cells/Single Cells/03: CD34+, CD38- |...
6 8 10 12 14 16 18 20 22 24 26 28
CD34+/CD38+ Progenitor
TF1R1400/Single Cells/Single Cells/02: CD34+, CD38+...
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75
Color by
Compound 1 nM
Max (300.00)
Min (0.00)

FIG. 94

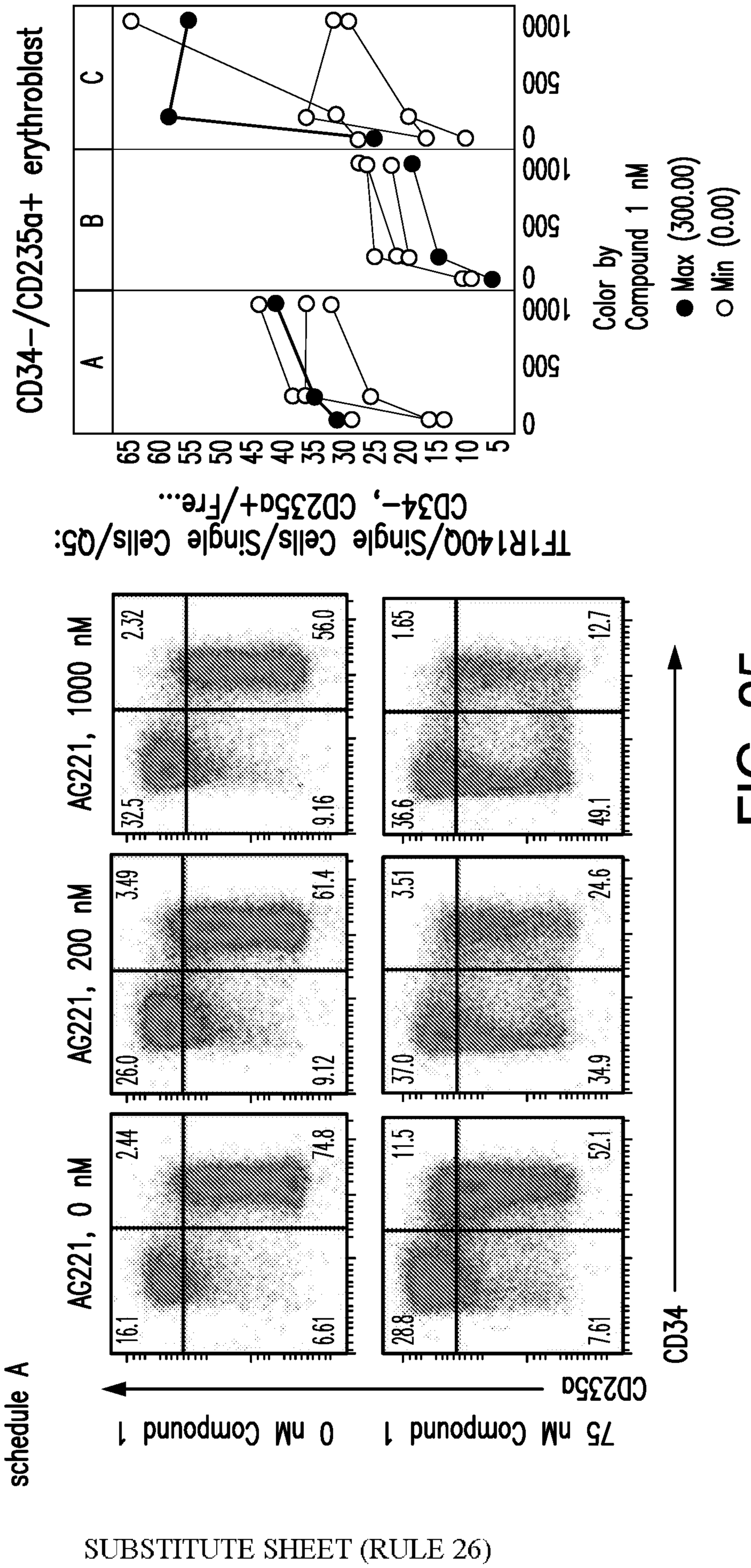

TF1R1400/Single Cells/Single Cells/05:
CD34−, CD235a+/Fre...
CD34−/CD235a+ ery...
A
B
C
0
500
1000
65 60 55 50 45 40 35 30 25 20 15 10 5
Color by
Compound 1 nM
Max (300.00)
Min (0.00)
AG221, 1000 nM
AG221, 200 nM
AG221, 0 nM
32.5
2.32
56.0
9.16
36.6
1.65
12.7
49.1
26.0
3.49
61.4
9.12
37.0
3.51
24.6
34.9
16.1
2.44
74.8
6.61
28.8
11.5
52.1
7.61
schedule A
0 nM Compound 1
75 nM Compound 1
CD235a
CD34

FIG. 95

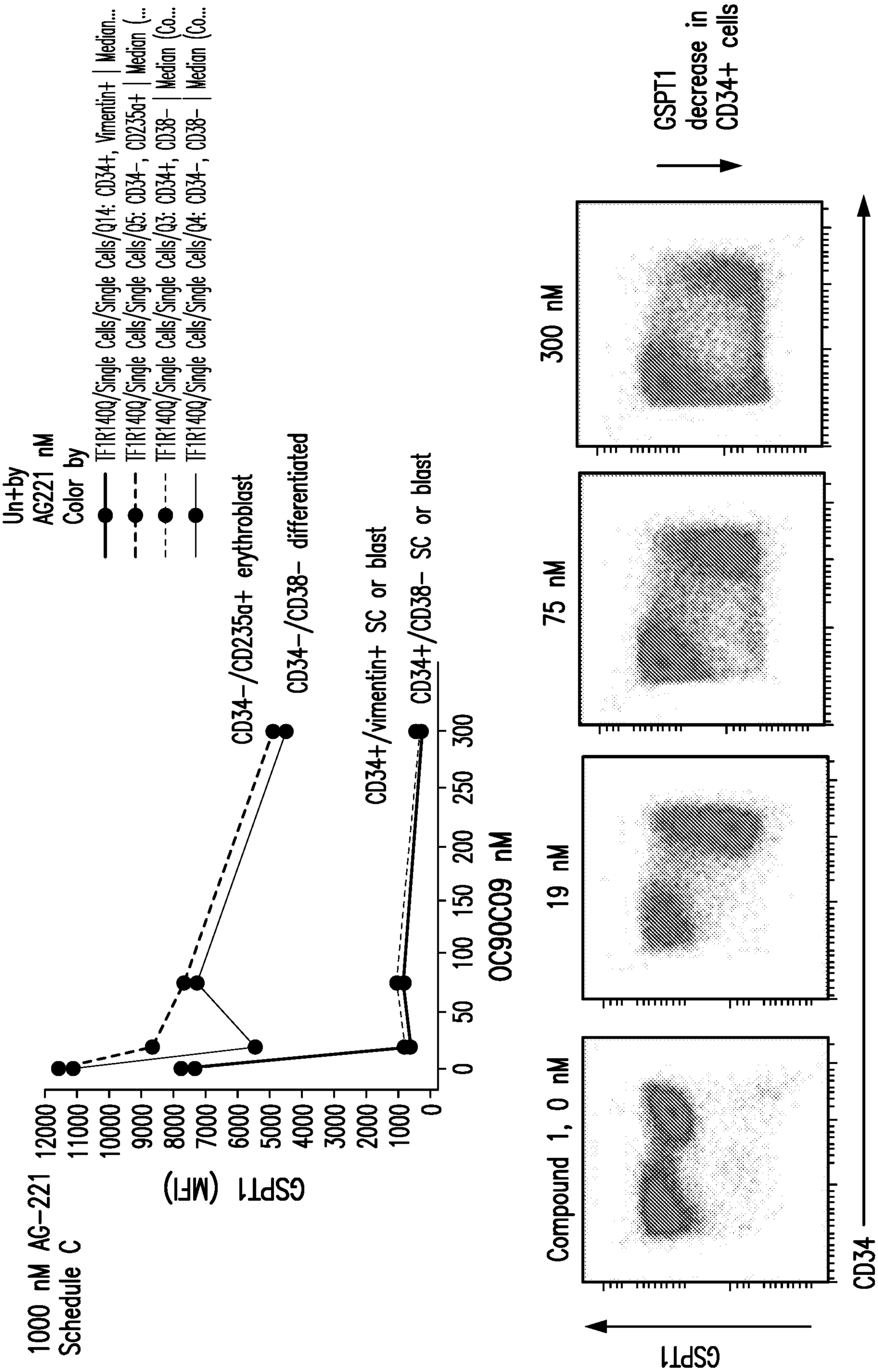

GSPT1
decrease in
CD34+ cells
300 nM
75 nM
19 nM
Compound 1, 0 nM
GSPT1
CD34
Un+by
AG221 nM
Color by
TF1R140Q/Single Cells/Single Cells/Q14: CD...
TF1R140Q/Single Cells/Single Cells/Q5: CD3...
TF1R140Q/Single Cells/Single Cells/Q3: CD3...
TF1R140Q/Single Cells/Single Cells/Q4: CD3...
CD34+, Vimentin+ | Median...
CD34−, CD235a+ | Median (...
CD34+, CD38− | Median (Co...
CD34−, CD38− | Median (Co...
CD34−/CD38− differentiated
CD34+/vimentin+ SC or blast
CD34+/CD38− SC or blast
OC90C09 nM
0
50
100
150
200
250
300
GSPT1 (MFI)
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
10000
11000
12000
1000 nM AG−221
Schedule C

FIG. 96

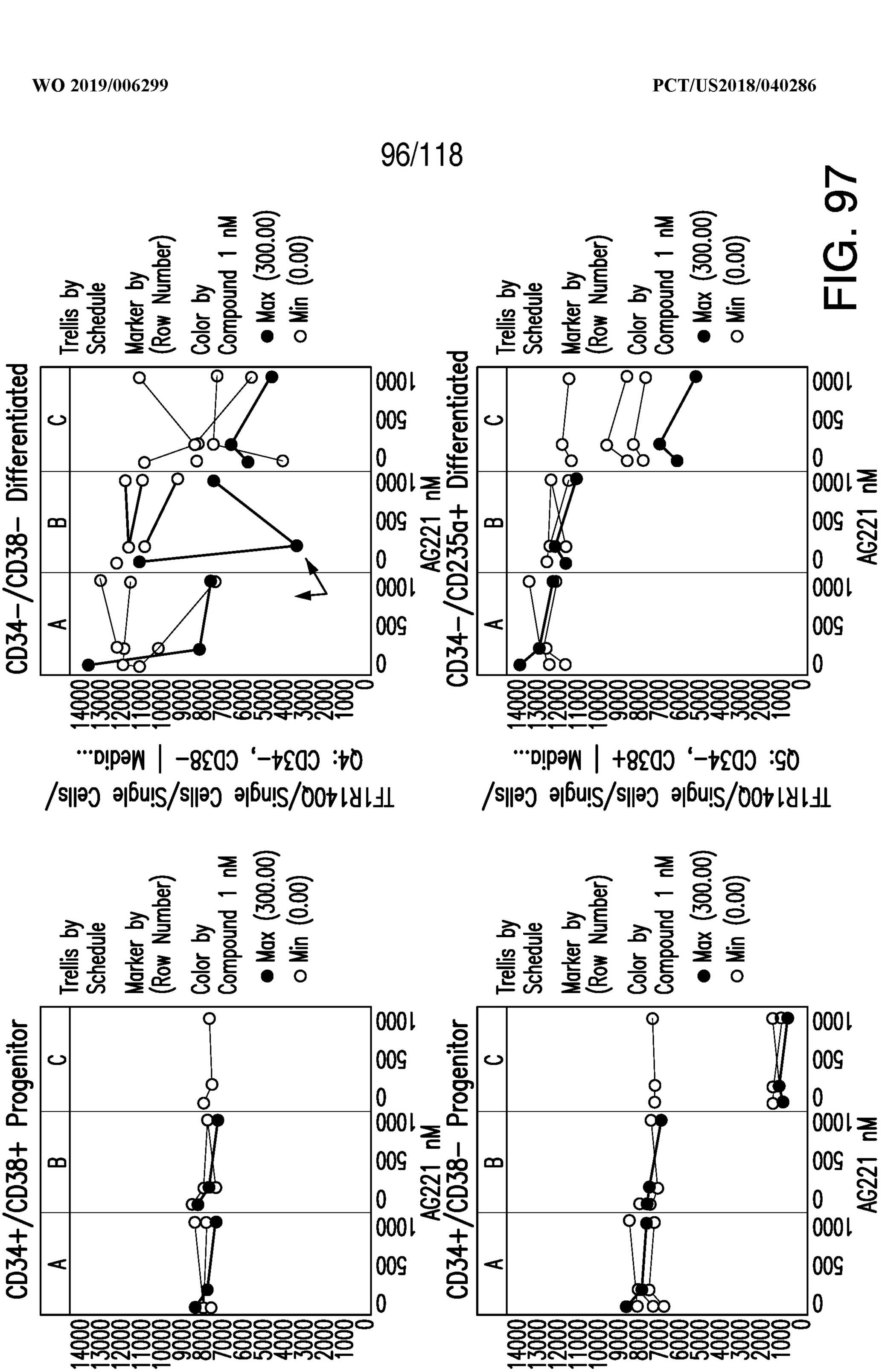
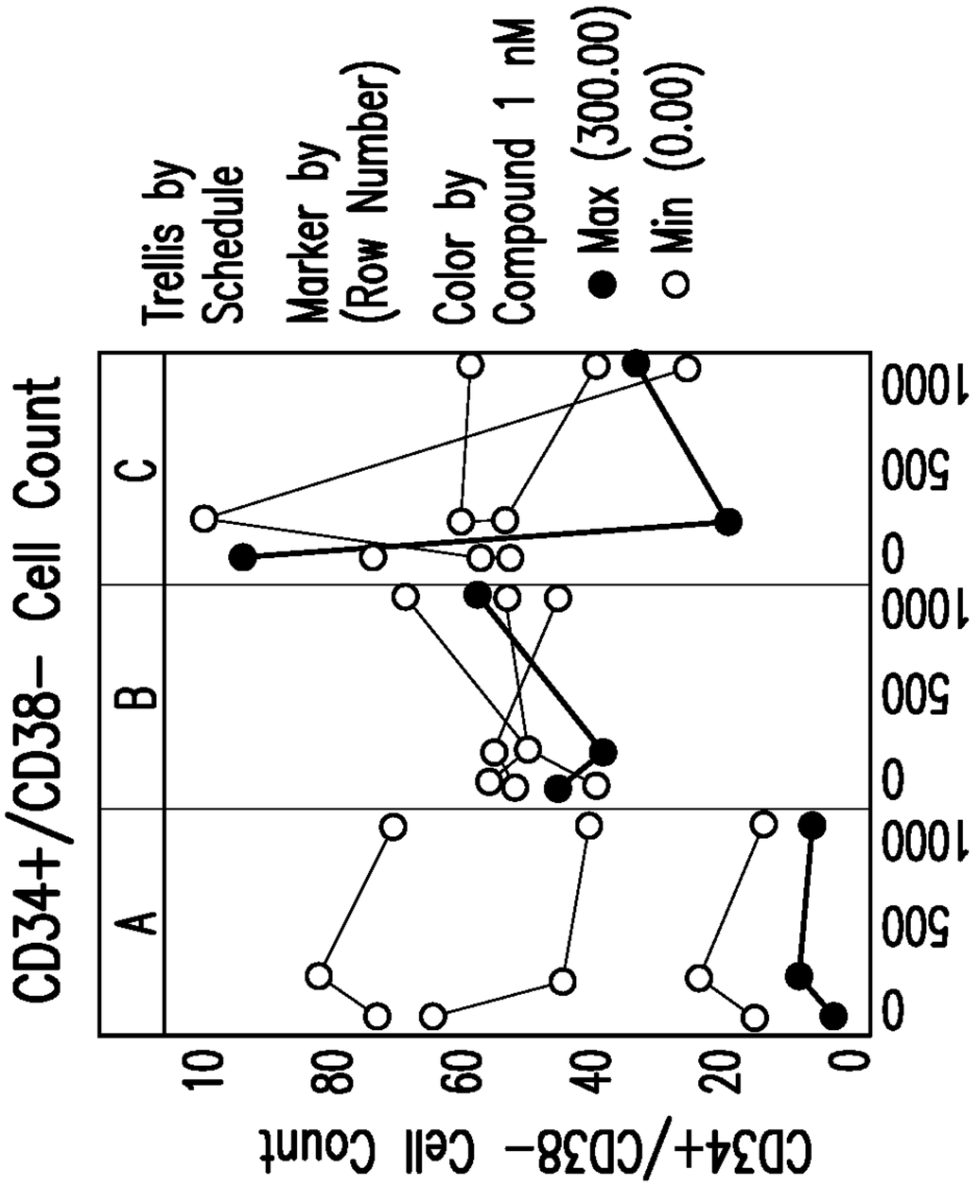
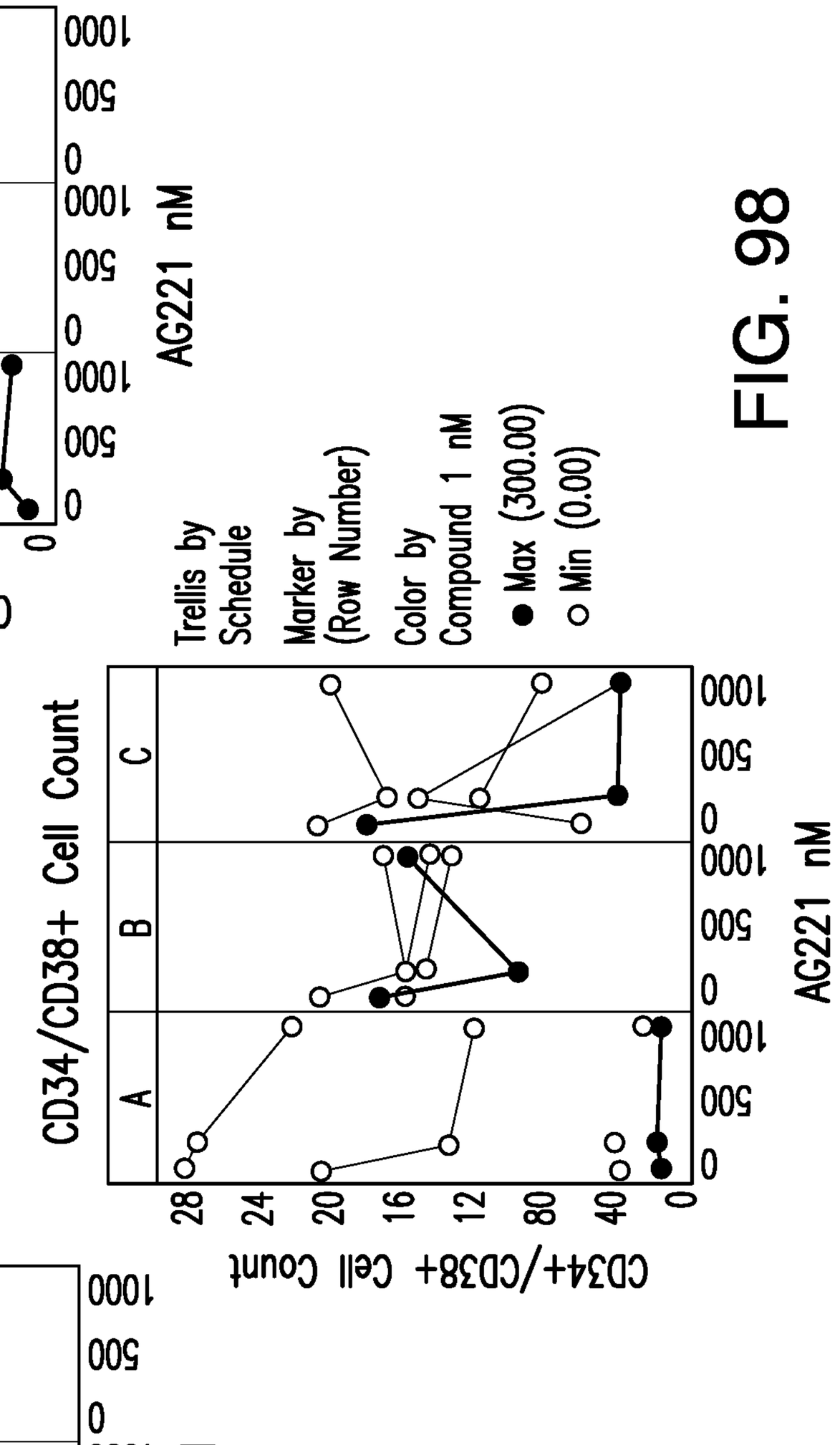

Trellis by Schedule
Marker by (Row Number)
Color by Compound 1 nM
● Max (300.00)
○ Min (0.00)
CD34−/CD38− Differentiated
CD34−/CD235a+ Differentiate
CD34+/CD38+ Progenitor
CD34+/CD38− Progenitor
A
B
C
AG221 nM
0
500
1000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
04: CD34−, CD38− | Media... TF1R140Q/Single Cells/Single Cells/
05: CD34−, CD38+ | Media... TF1R140Q/Single Cells/Single Cells/
02: CD34+, CD38+ | Media... TF1R140Q/Single Cells/Single Cells/
03: CD34+, CD38− | Media... TF1R140Q/Single Cells/Single Cells/

FIG. 97


Trellis by Schedule
Marker by (Row Number)
Color by Compound 1 nM
● Max (300.00)
○ Min (0.00)
CD34+/CD38− Cell Count
A
B
C
0
20
40
60
80
100
0
500
1000
AG221 nM


Trellis by Schedule
Marker by (Row Number)
Color by Compound 1 nM
● Max (300.00)
○ Min (0.00)
CD34/CD38+ Cell Count
A
B
C
0
40
80
12
16
20
24
28
0
500
1000
AG221 nM

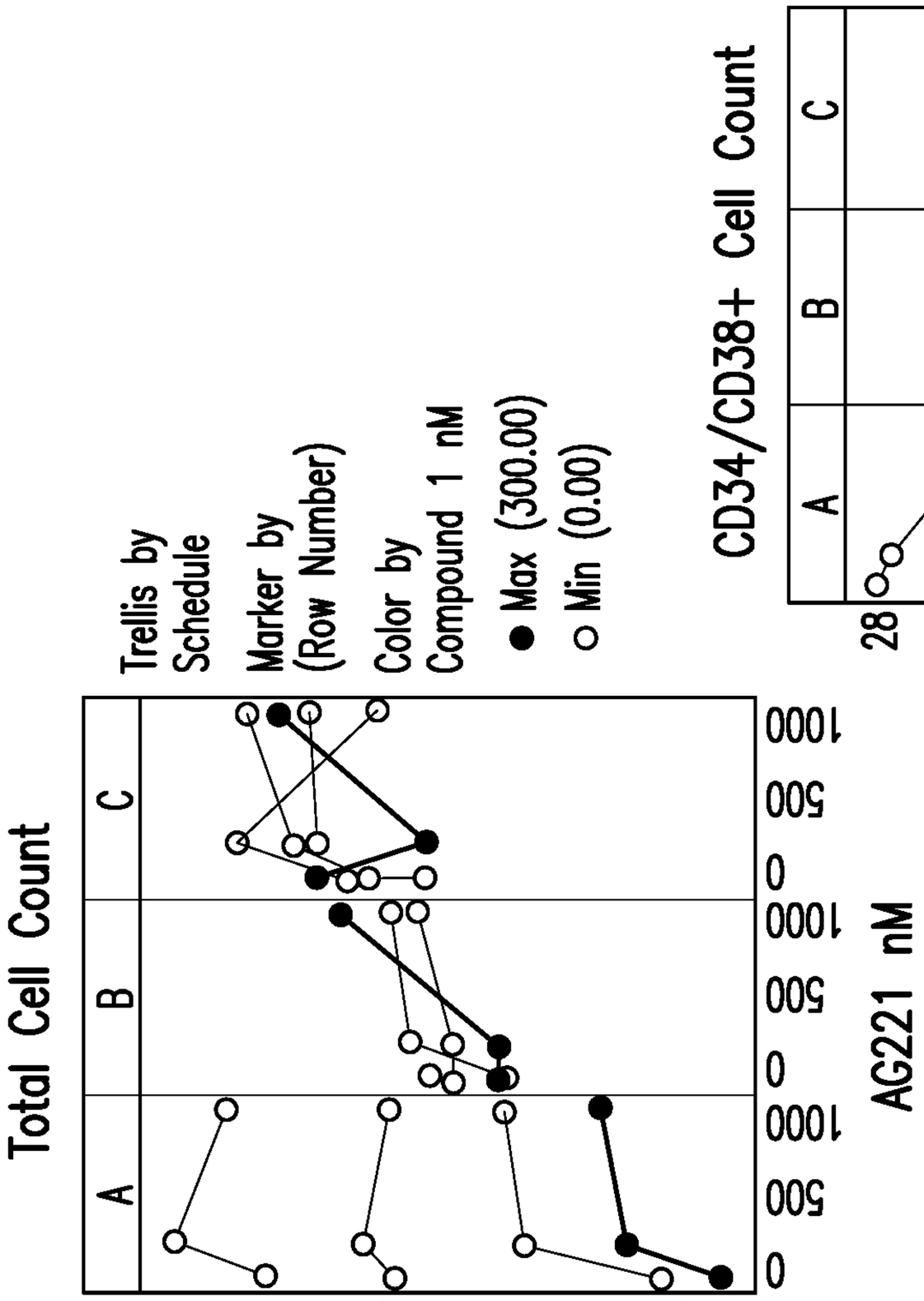

Trellis by Schedule
Marker by (Row Number)
Color by Compound 1 nM
● Max (300.00)
○ Min (0.00)
Total Cell Count
A
B
C
0
10
15
20
25
30
35
40
45
50
55
0
500
1000
AG221 nM

FIG. 98

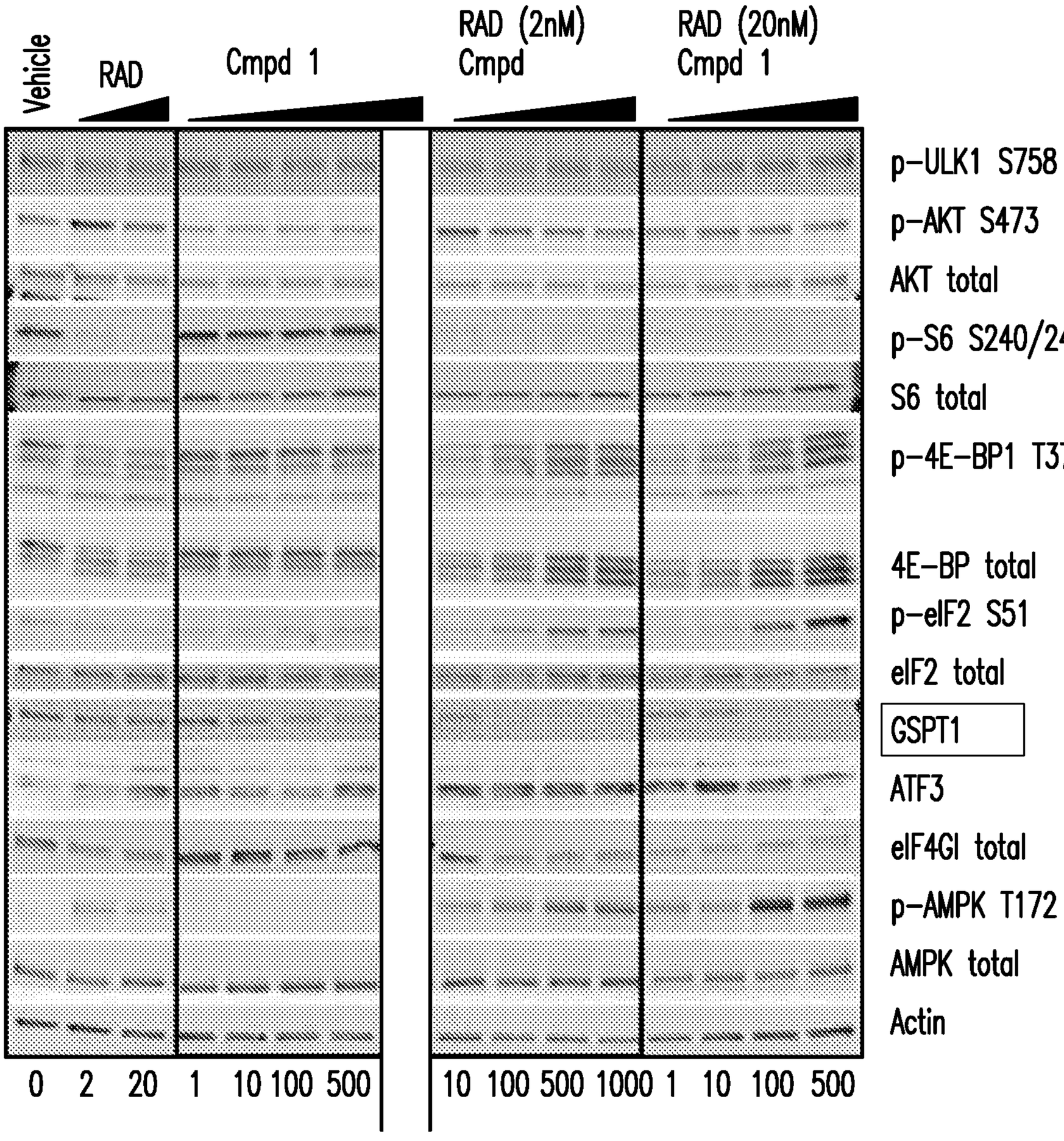

Vehicle
RAD
Cmpd 1
RAD (2nM) Cmpd
RAD (20nM) Cmpd 1
p-ULK1 S758
p-AKT S473
AKT total
p-S6 S240/244
S6 total
p-4E-BP1 T37/46
4E-BP total
p-eIF2 S51
eIF2 total
GSPT1
ATF3
eIF4GI total
p-AMPK T172
AMPK total
Actin
0 2 20 1 10 100 500
10 100 500 1000 1 10 100 500

FIG. 99

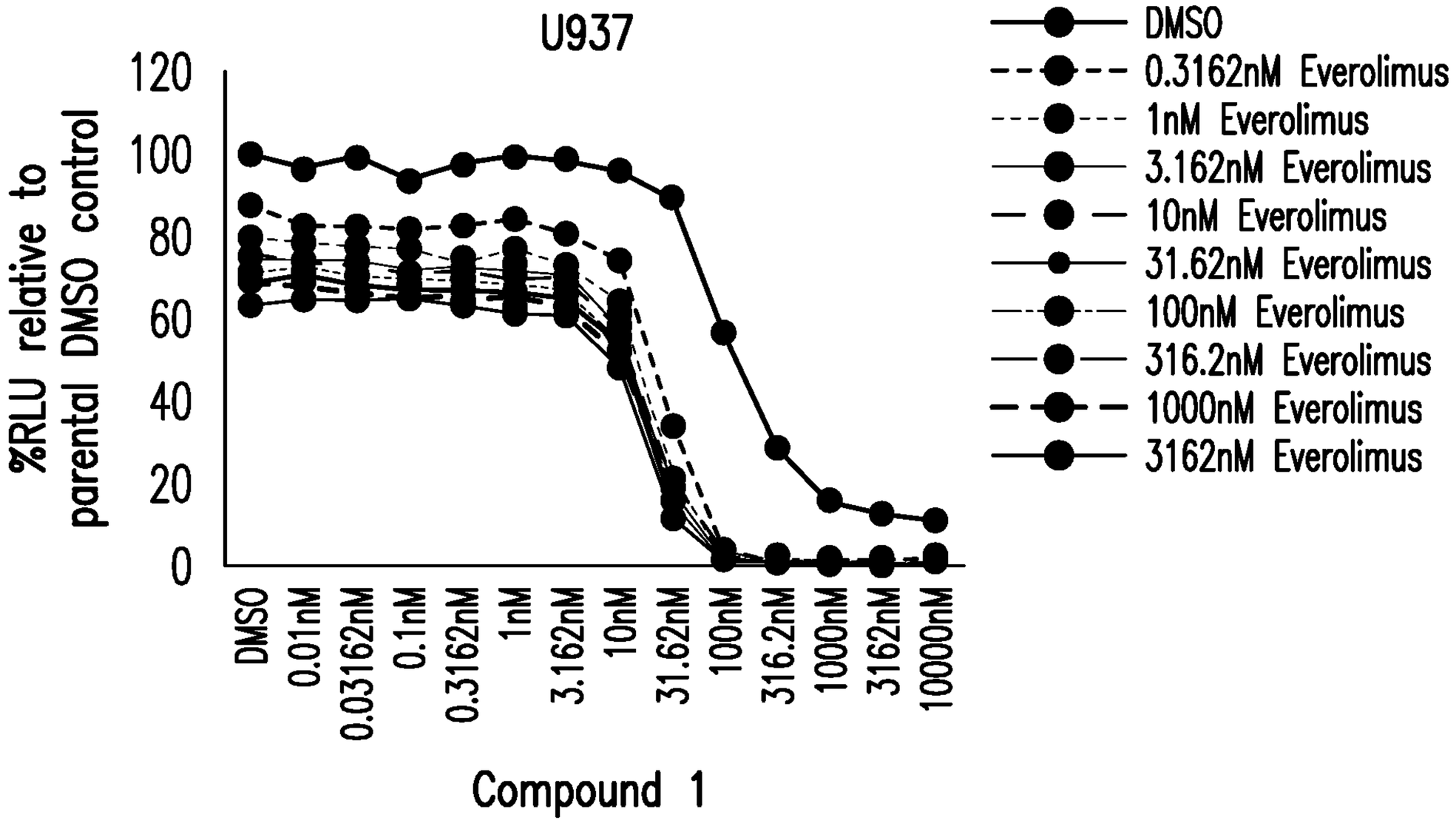


FIG. 100A

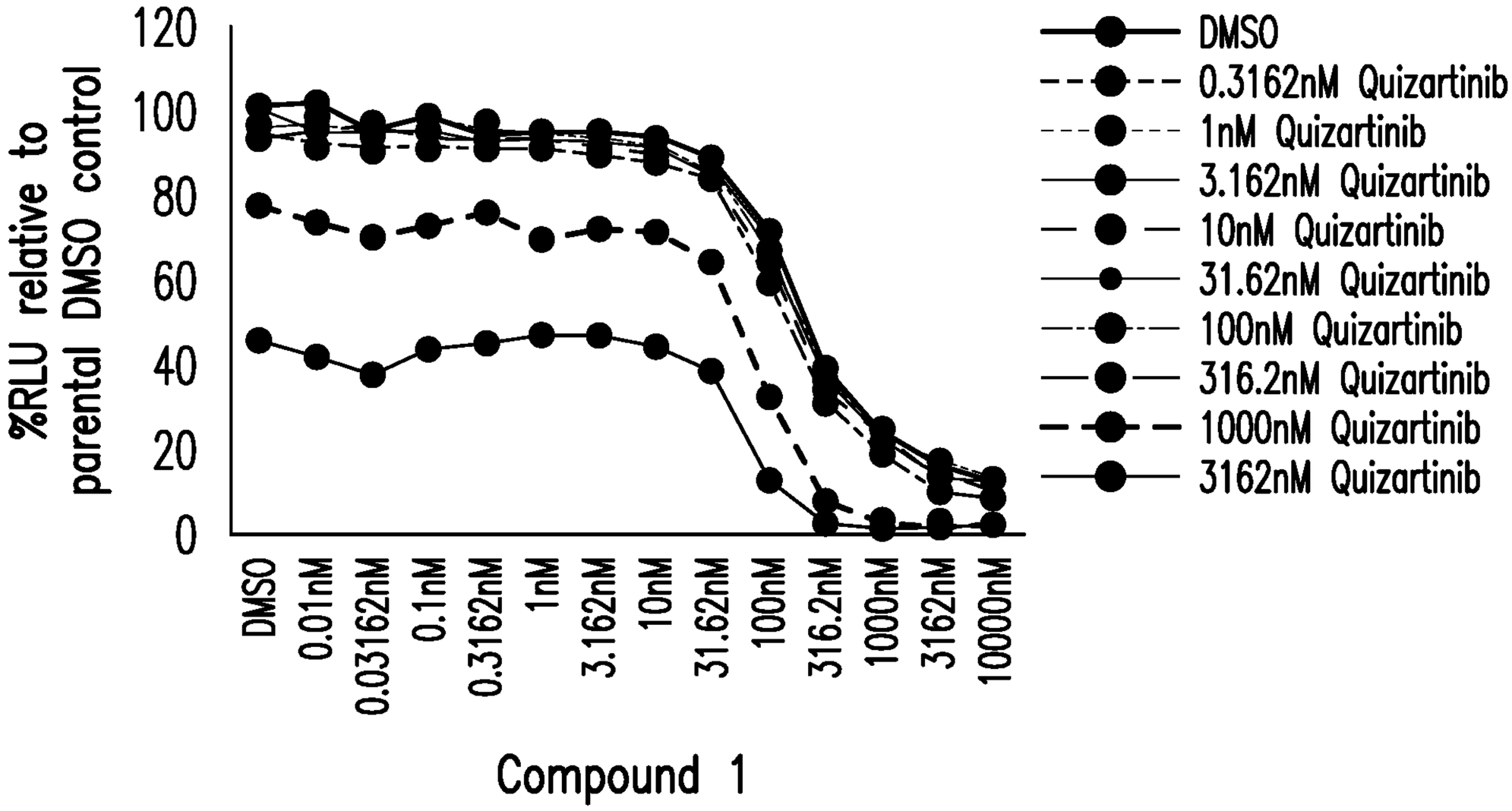


FIG. 100B

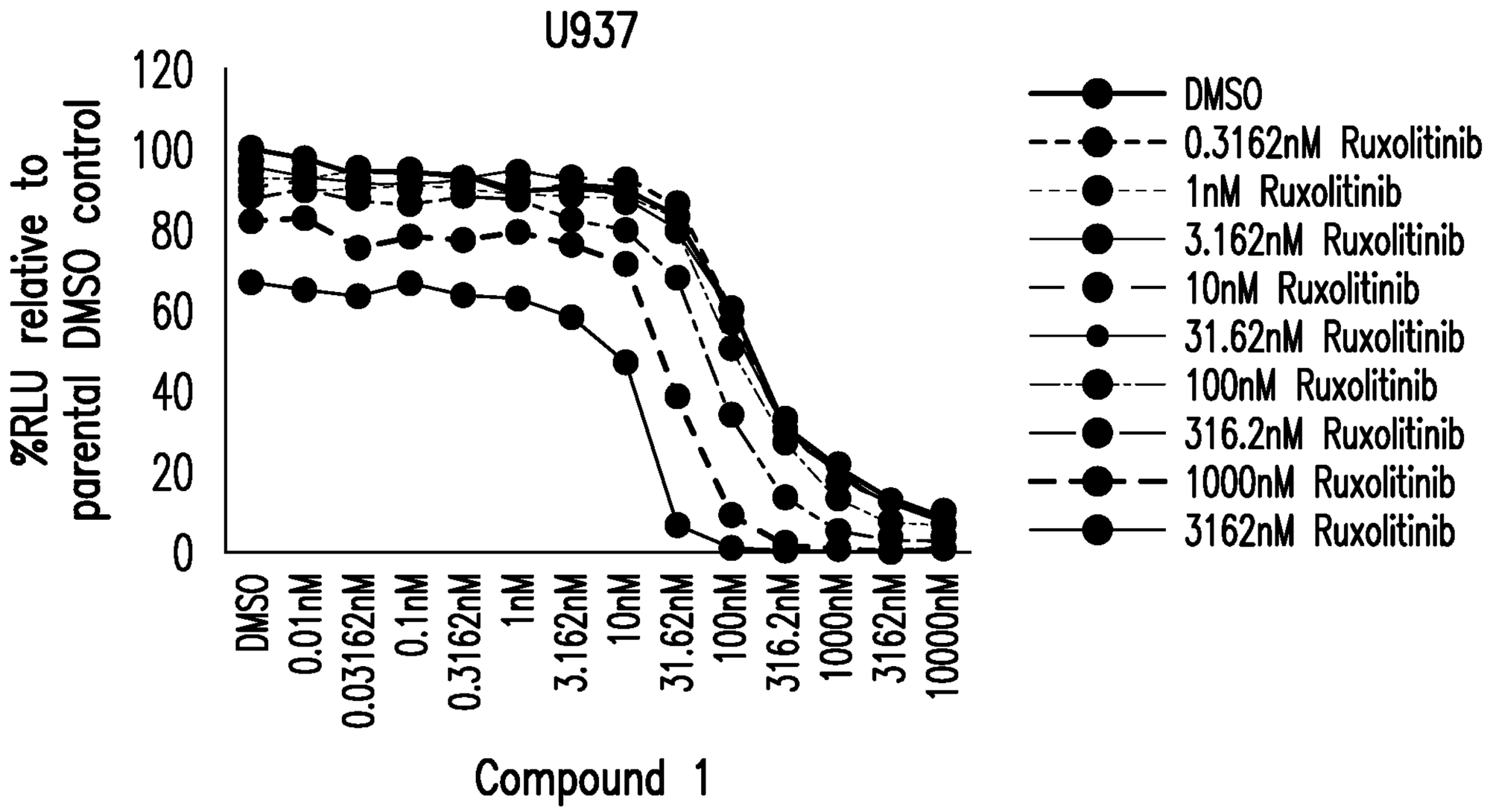


FIG. 100C

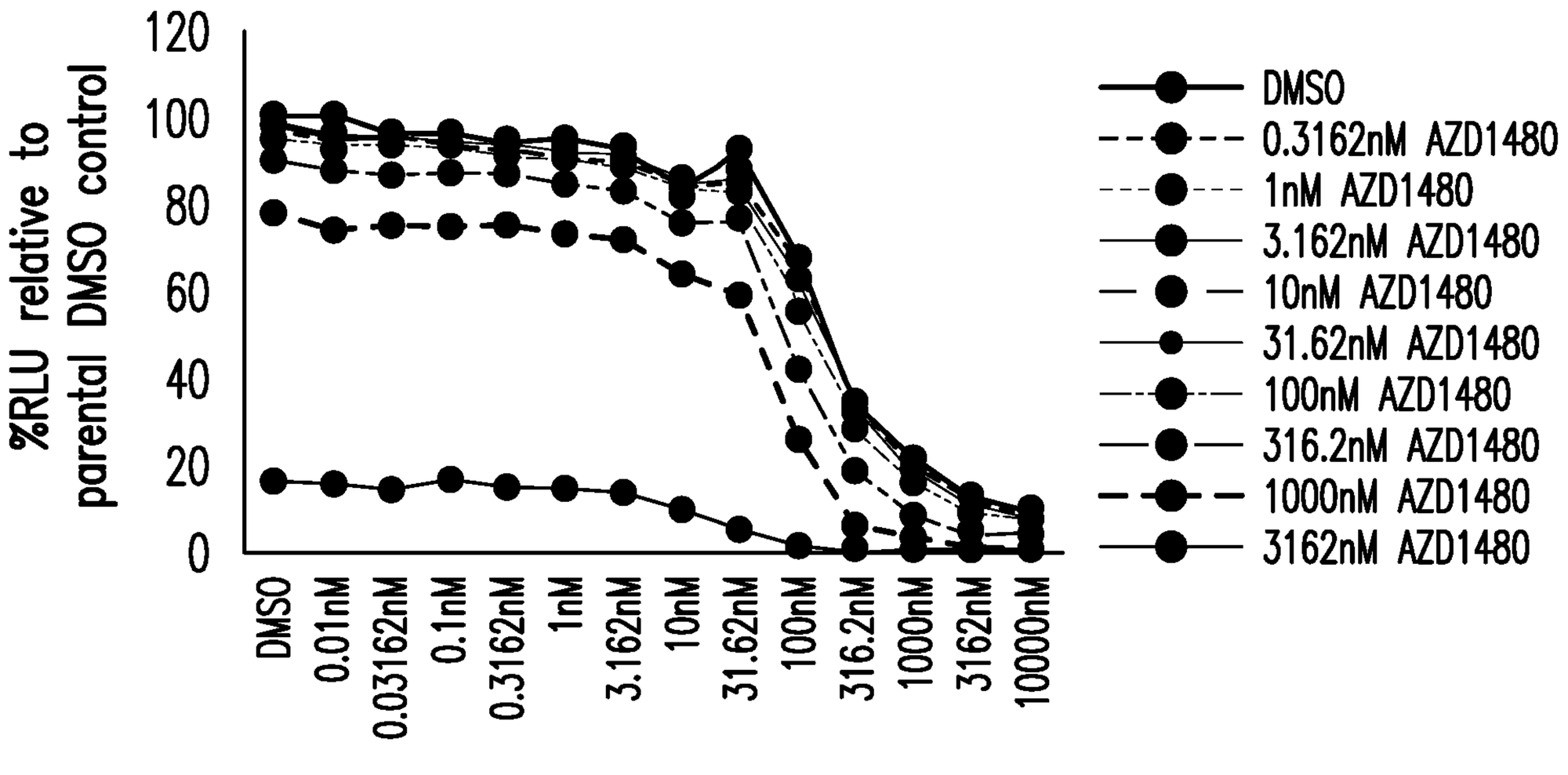


FIG. 100D

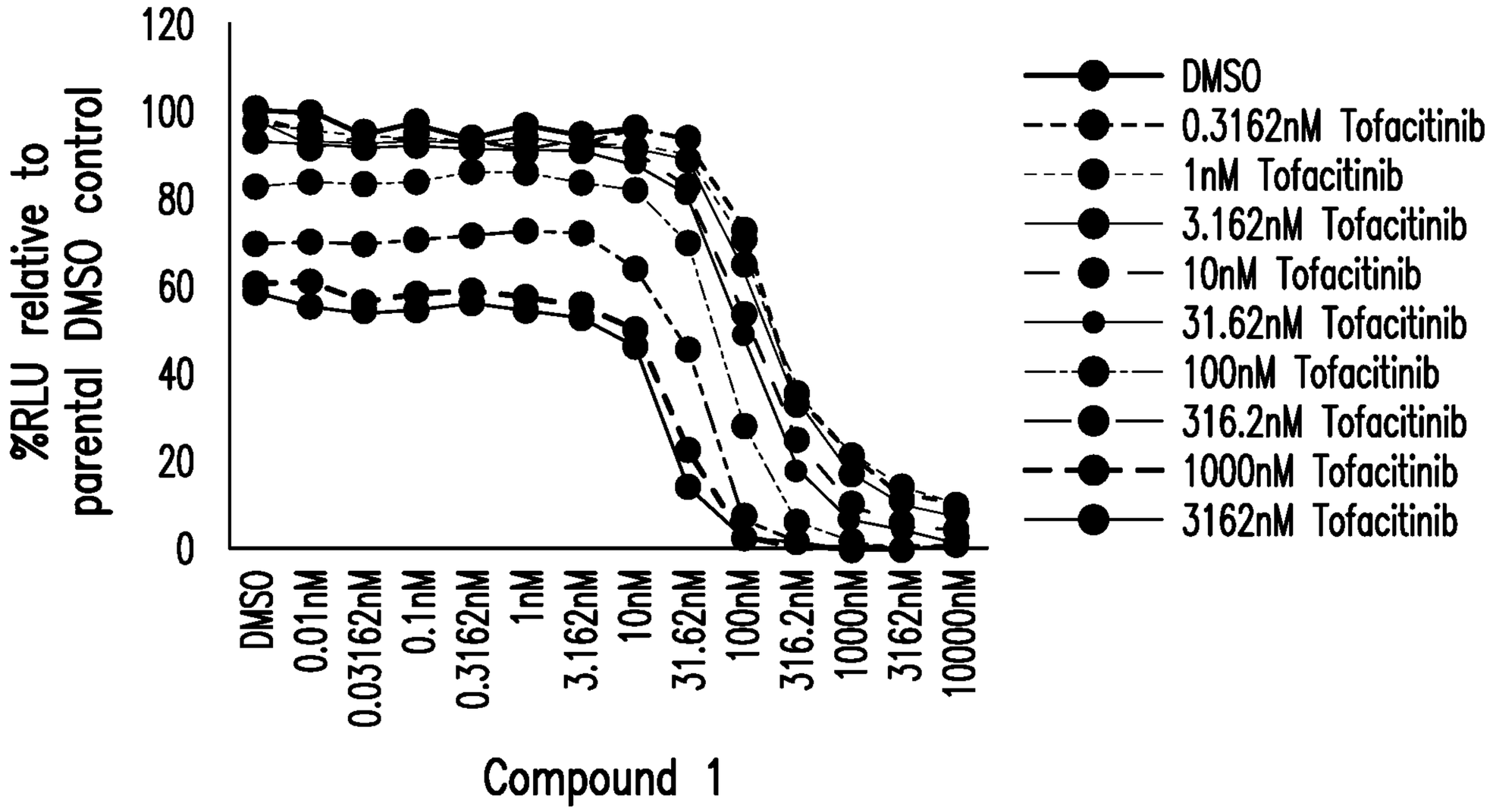

U937
%RLU relative to parental DMSO control
120
100
80
60
40
20
0
DMSO
0.01nM
0.03162nM
0.1nM
0.3162nM
1nM
3.162nM
10nM
31.62nM
100nM
316.2nM
1000nM
3162nM
10000nM
Compound 1
DMSO
0.3162nM Tofacitinib
1nM Tofacitinib
3.162nM Tofacitinib
10nM Tofacitinib
31.62nM Tofacitinib
100nM Tofacitinib
316.2nM Tofacitinib
1000nM Tofacitinib
3162nM Tofacitinib

FIG. 100E

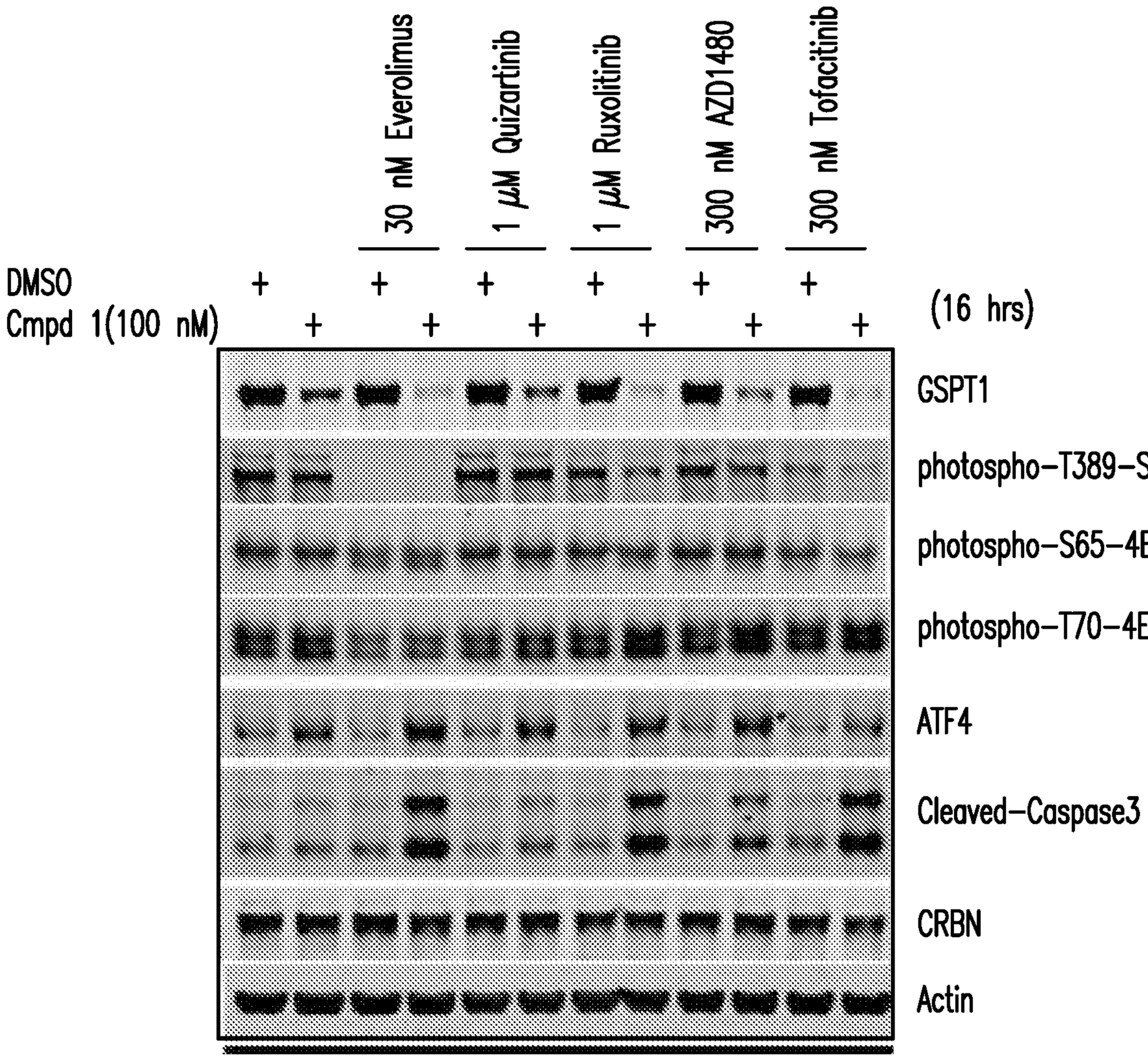

3 nM Everolimus
1 μM Quizartinib
1 μM Ruxolitinib
3 nM AZD1480
3 nM Tofacitinib
DMSO
Cmpd 1(100 nM)
(16 hrs)
GSPT1
photospho-T389-S6K1
photospho-S65-4E-BP1
photospho-T70-4E-BP1
ATF4
Cleaved-Caspase3
CRBN
Actin
U937

FIG. 101

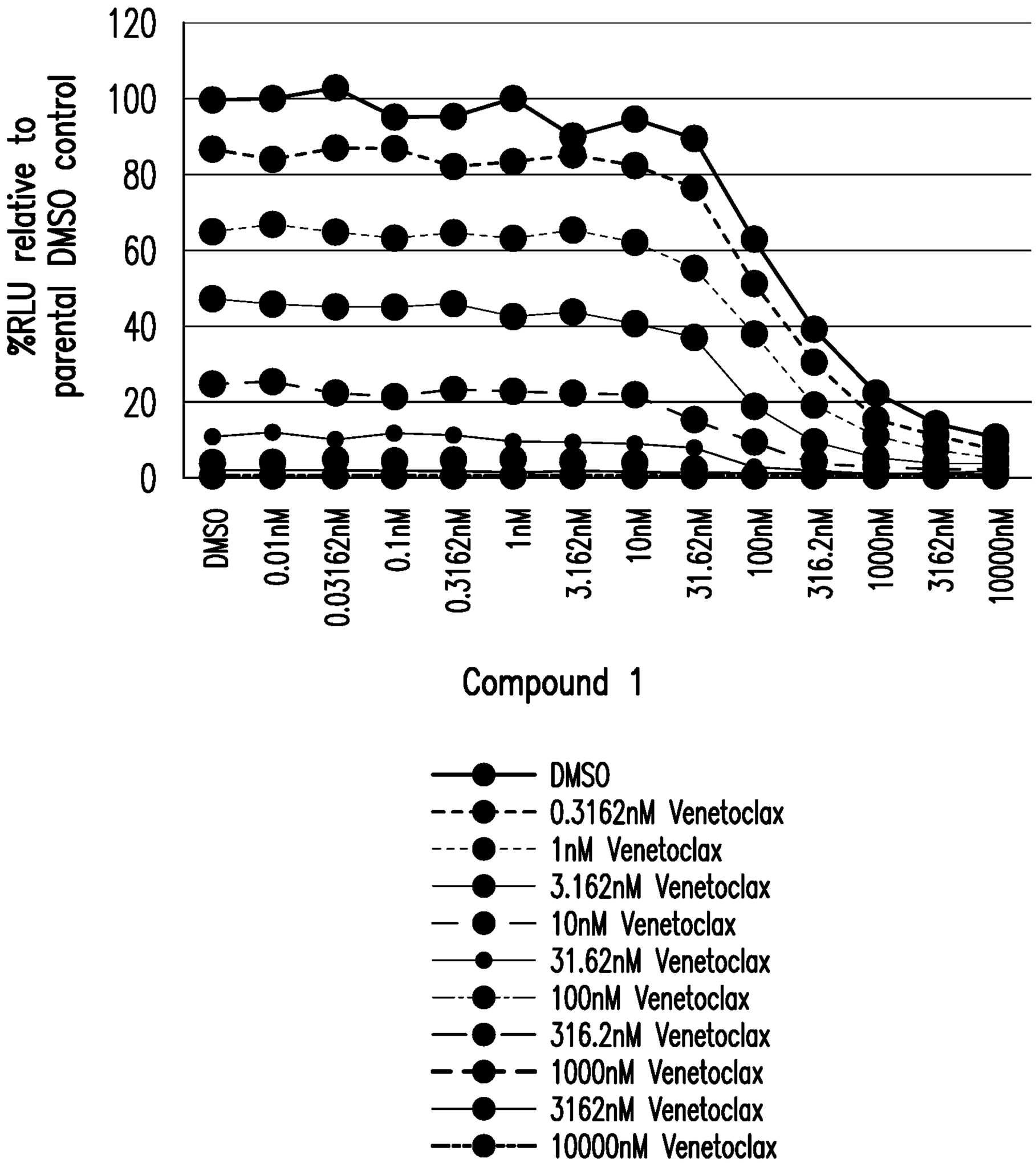

OCI-AML2
%RLU relative to parental DMSO control
120
100
80
60
40
20
0
DMSO
0.01nM
0.03162nM
0.1nM
0.3162nM
1nM
3.162nM
10nM
31.62nM
100nM
316.2nM
1000nM
3162nM
10000nM
Compound 1
DMSO
0.3162nM Venetoclax
1nM Venetoclax
3.162nM Venetoclax
10nM Venetoclax
31.62nM Venetoclax
100nM Venetoclax
316.2nM Venetoclax
1000nM Venetoclax
3162nM Venetoclax
10000nM Venetoclax

FIG. 102A

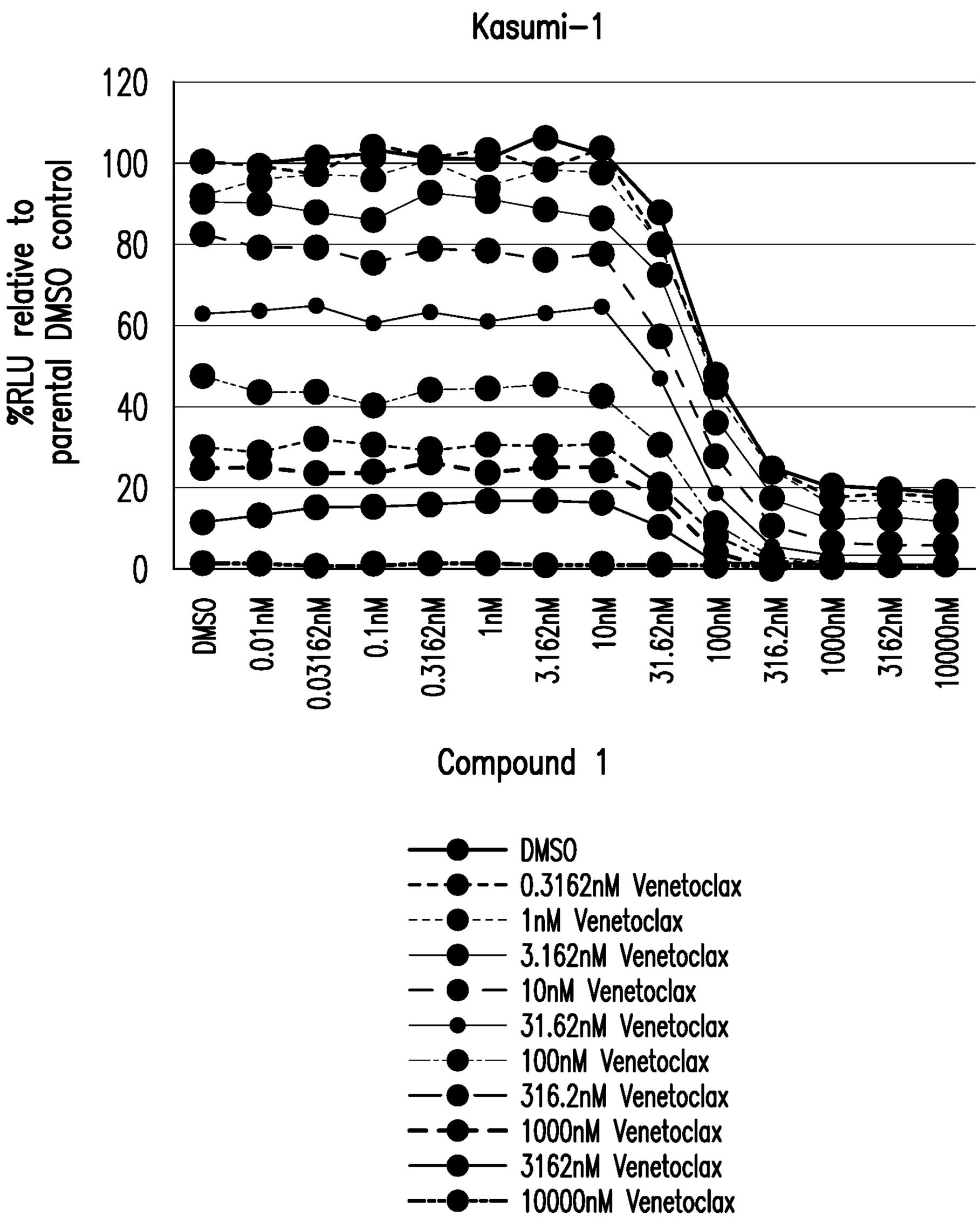

Kasumi-1
120
100
80
60
40
20
0
%RLU relative to parental DMSO control
DMSO
0.01nM
.03162nM
0.1nM
0.3162nM
1nM
3.162nM
10nM
31.62nM
100nM
316.2nM
1000nM
3162nM
10000nM
Compound 1
DMSO
0.3162nM Venetoclax
1nM Venetoclax
3.162nM Venetoclax
10nM Venetoclax
31.62nM Venetoclax
100nM Venetoclax
316.2nM Venetoclax
1000nM Venetoclax
3162nM Venetoclax
10000nM Venetoclax

FIG. 102B

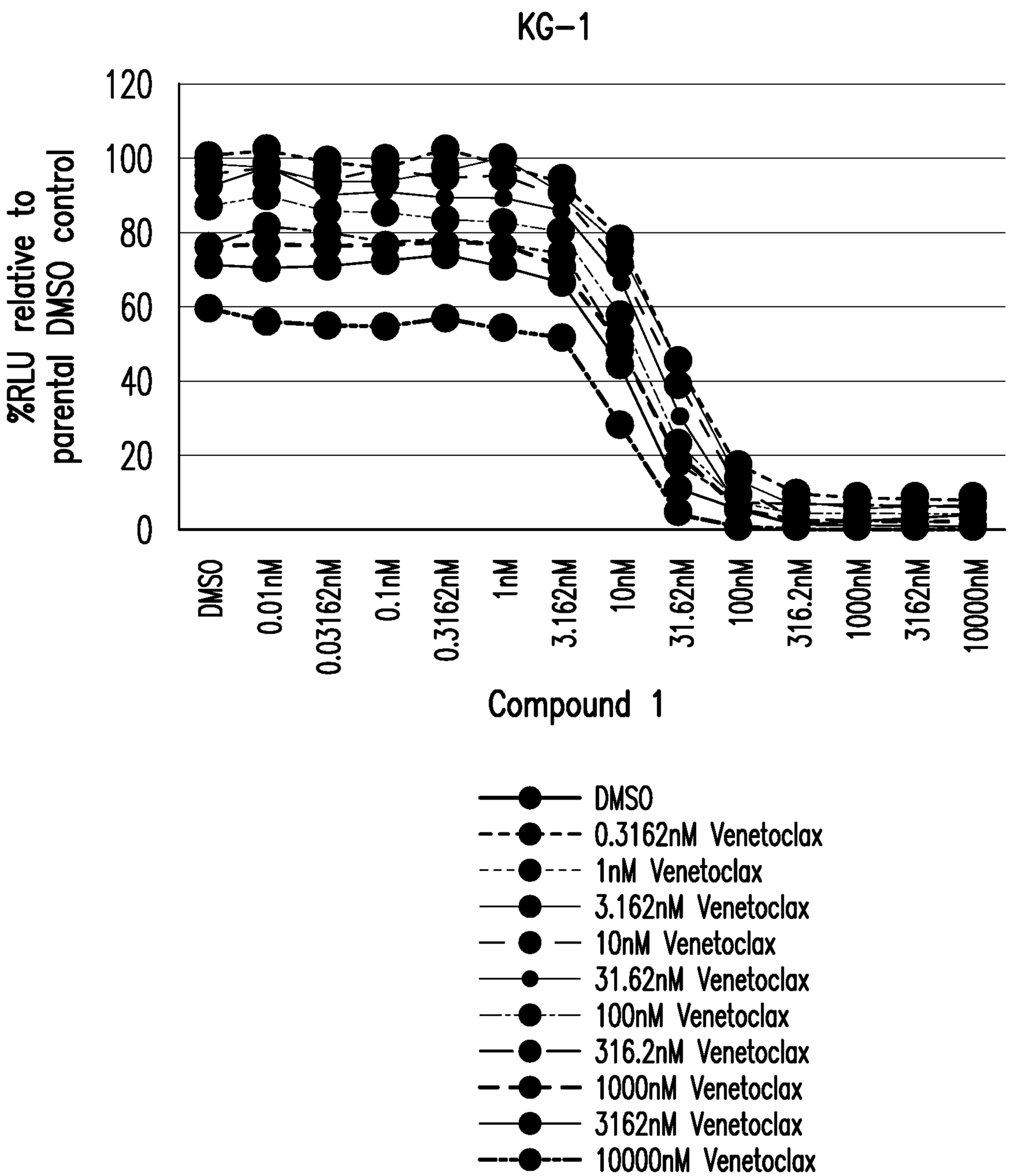

KG-1
%RLU relative to parental DMSO control
120
100
80
60
40
20
0
DMSO
0.01nM
0.03162nM
0.1nM
0.3162nM
1nM
3.162nM
10nM
31.62nM
100nM
316.2nM
1000nM
3162nM
10000nM
Compound 1
DMSO
0.3162nM Venetoclax
1nM Venetoclax
3.162nM Venetoclax
10nM Venetoclax
31.62nM Venetoclax
100nM Venetoclax
316.2nM Venetoclax
1000nM Venetoclax
3162nM Venetoclax
10000nM Venetoclax

FIG. 102C

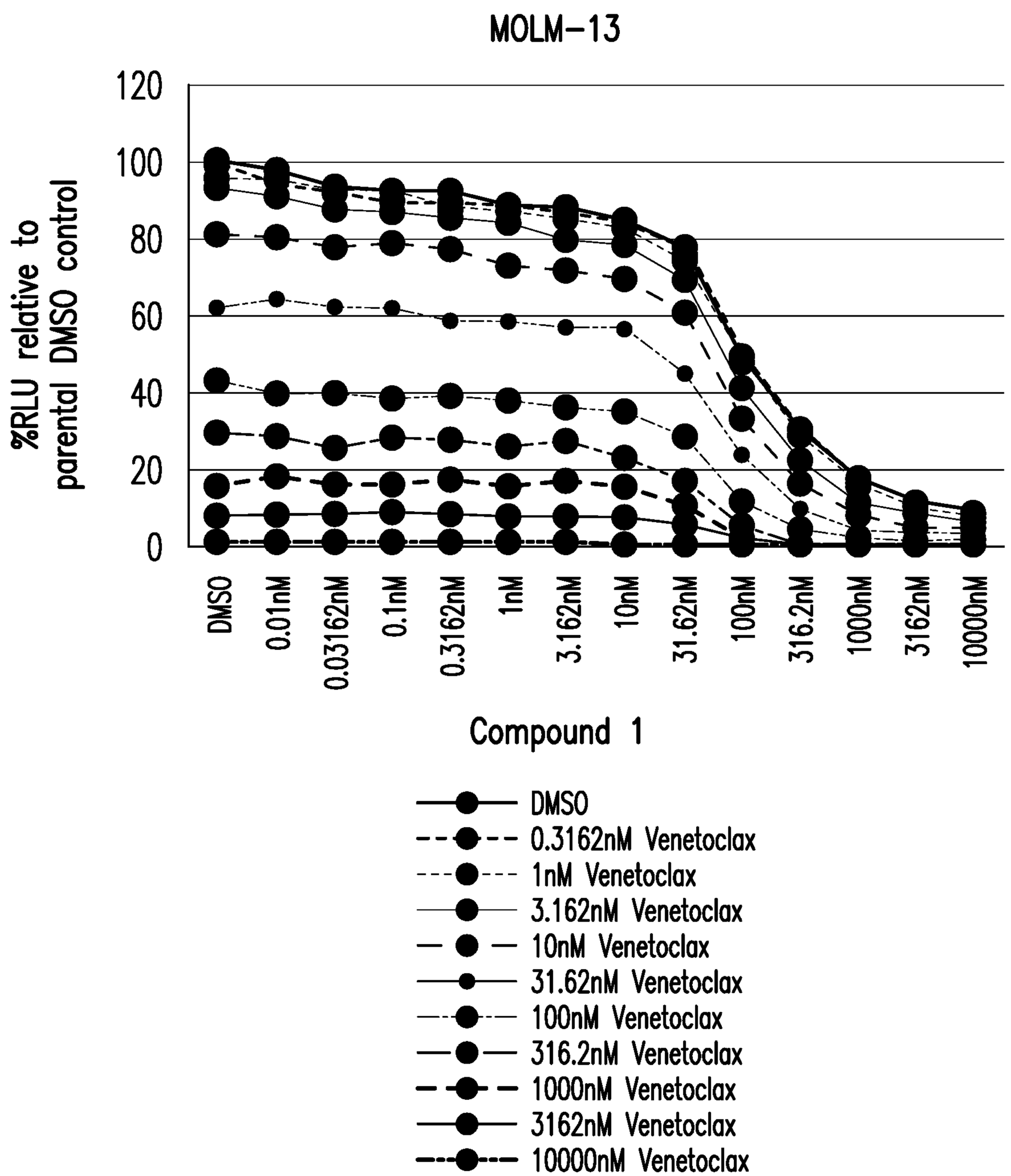

MOLM-13
%RLU relative to parental DMSO control
120
100
80
60
40
20
0
DMSO
0.01nM
.03162nM
0.1nM
0.3162nM
1nM
3.162nM
10nM
31.62nM
100nM
316.2nM
1000nM
3162nM
10000nM
Compound 1
DMSO
0.3162nM Venetoclax
1nM Venetoclax
3.162nM Venetoclax
10nM Venetoclax
31.62nM Venetoclax
100nM Venetoclax
316.2nM Venetoclax
1000nM Venetoclax
3162nM Venetoclax
10000nM Venetoclax

FIG. 102D

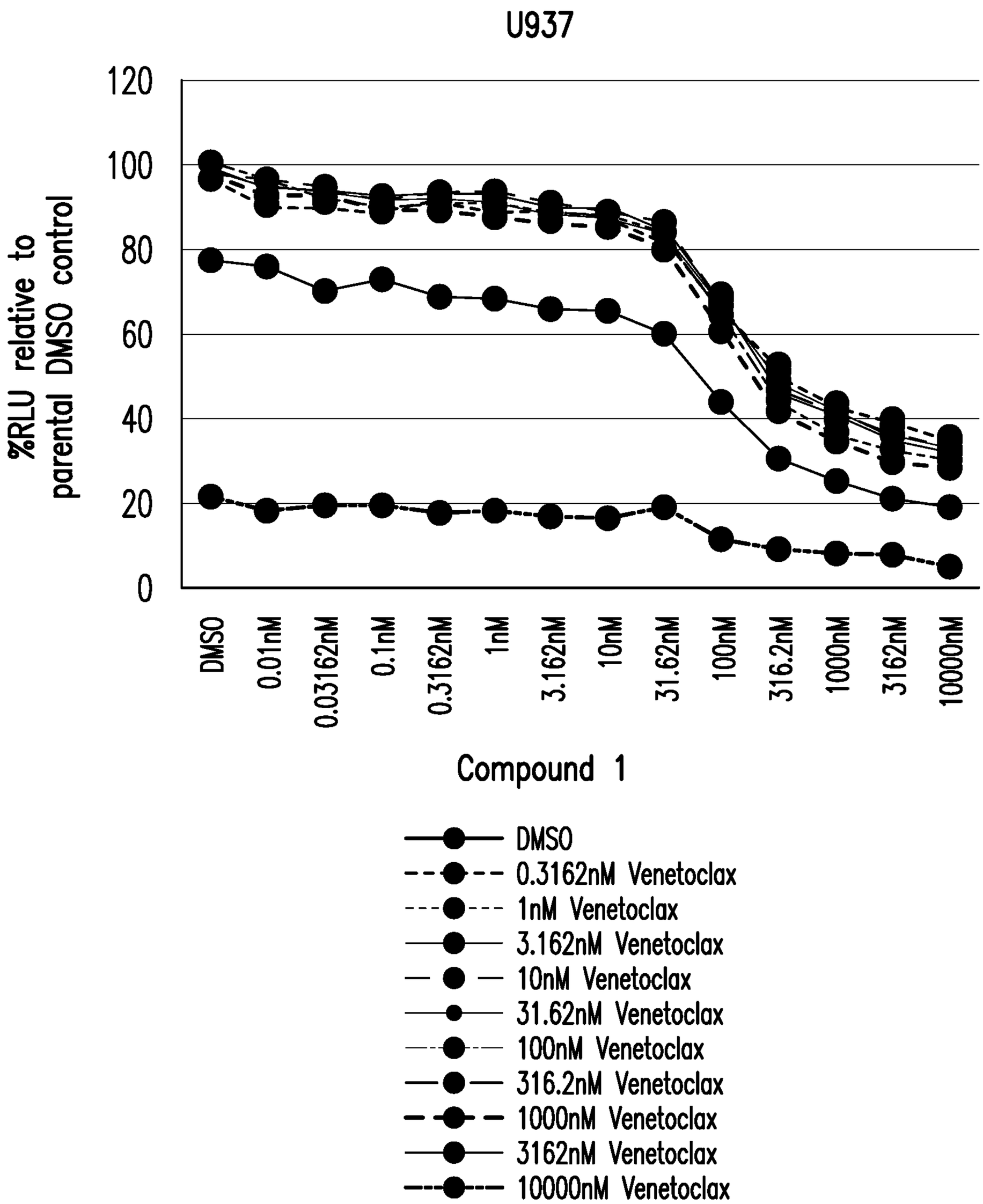

U937
120
100
80
60
40
20
0
%RLU relative to parental DMSO control
DMSO
0.01 nM
0.03162 nM
0.1 nM
0.3162 nM
1 nM
3.162 nM
10 nM
31.62 nM
100 nM
316.2 nM
1000 nM
3162 nM
10000 nM
Compound 1
DMSO
0.3162nM Venetoclax
1nM Venetoclax
3.162nM Venetoclax
10nM Venetoclax
31.62nM Venetoclax
100nM Venetoclax
316.2nM Venetoclax
1000nM Venetoclax
3162nM Venetoclax
10000nM Venetoclax

FIG. 102E

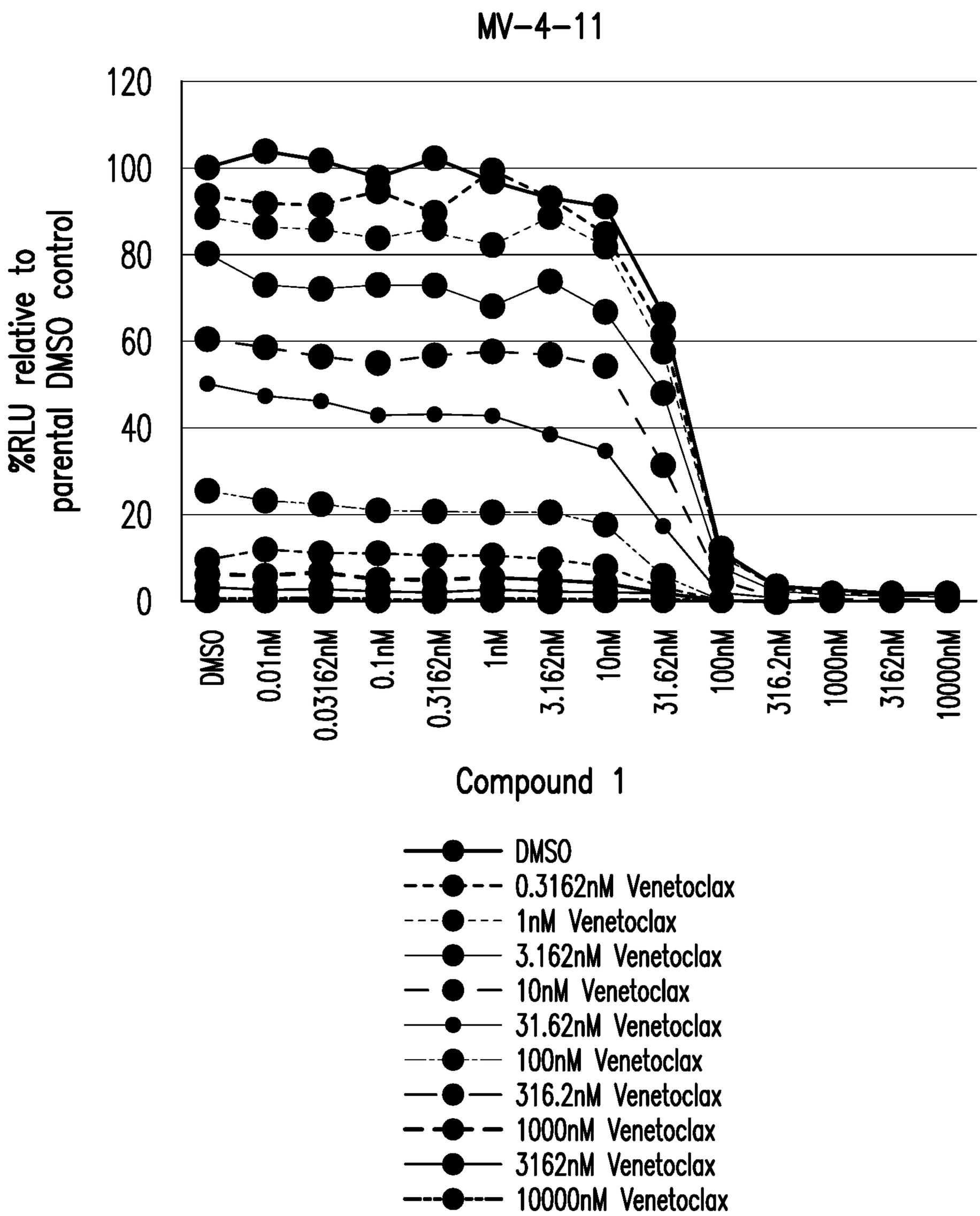

MV-4-11
%RLU relative to parental DMSO control
120
100
80
60
40
20
0
DMSO
0.01 nM
0.03162 nM
0.1 nM
0.3162 nM
1 nM
3.162 nM
10 nM
31.62 nM
100 nM
316.2 nM
1000 nM
3162 nM
10000 nM
Compound 1
DMSO
0.3162nM Venetoclax
1nM Venetoclax
3.162nM Venetoclax
10nM Venetoclax
31.62nM Venetoclax
100nM Venetoclax
316.2nM Venetoclax
1000nM Venetoclax
3162nM Venetoclax
10000nM Venetoclax

FIG. 102F

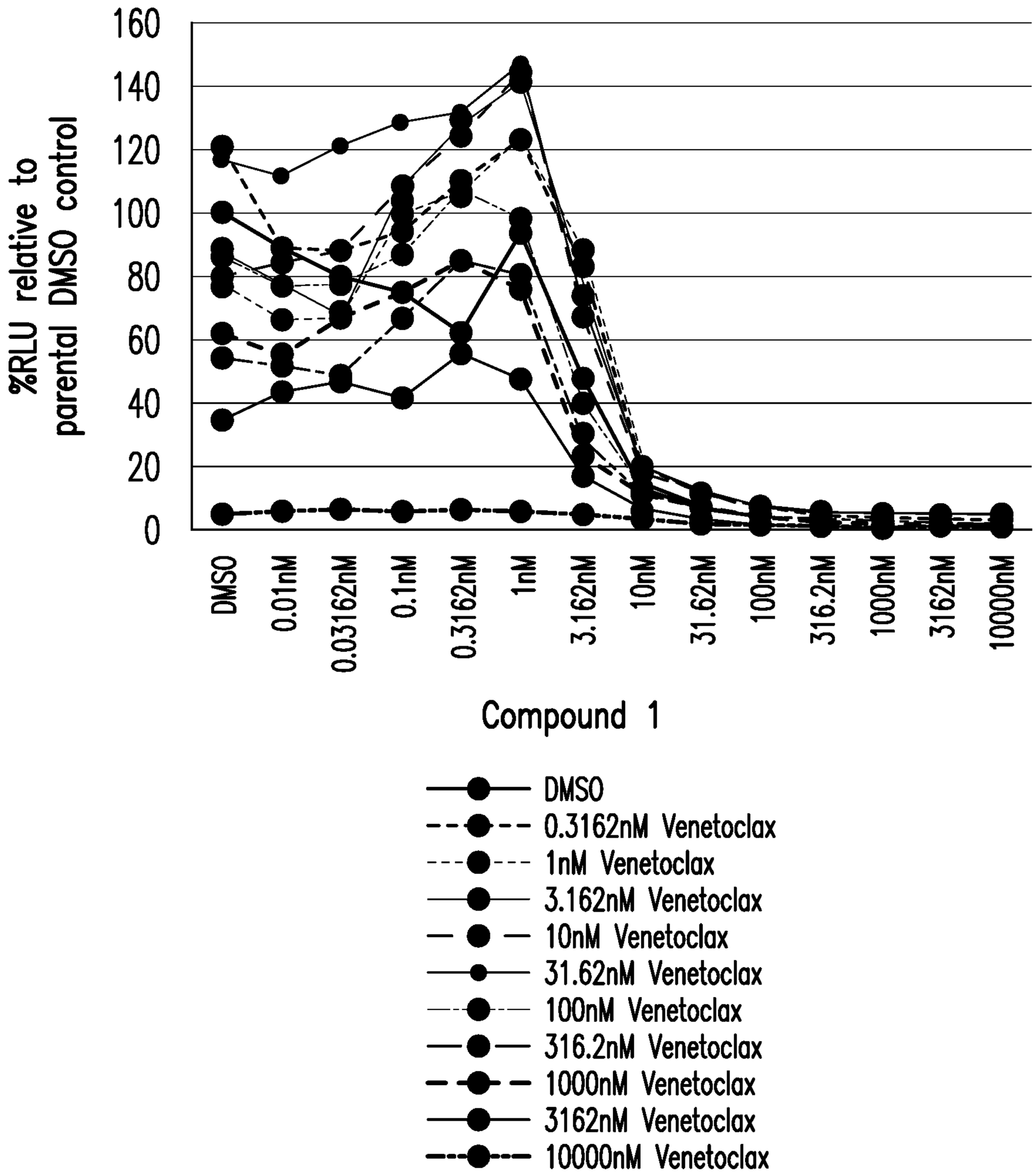

HNT-34
%RLU relative to parental DMSO control
160
140
120
100
80
60
40
20
0
DMSO
0.01nM
.03162nM
0.1nM
0.3162nM
1nM
3.162nM
10nM
31.62nM
100nM
316.2nM
1000nM
3162nM
10000nM
Compound 1
DMSO
0.3162nM Venetoclax
1nM Venetoclax
3.162nM Venetoclax
10nM Venetoclax
31.62nM Venetoclax
100nM Venetoclax
316.2nM Venetoclax
1000nM Venetoclax
3162nM Venetoclax
10000nM Venetoclax

FIG. 102G

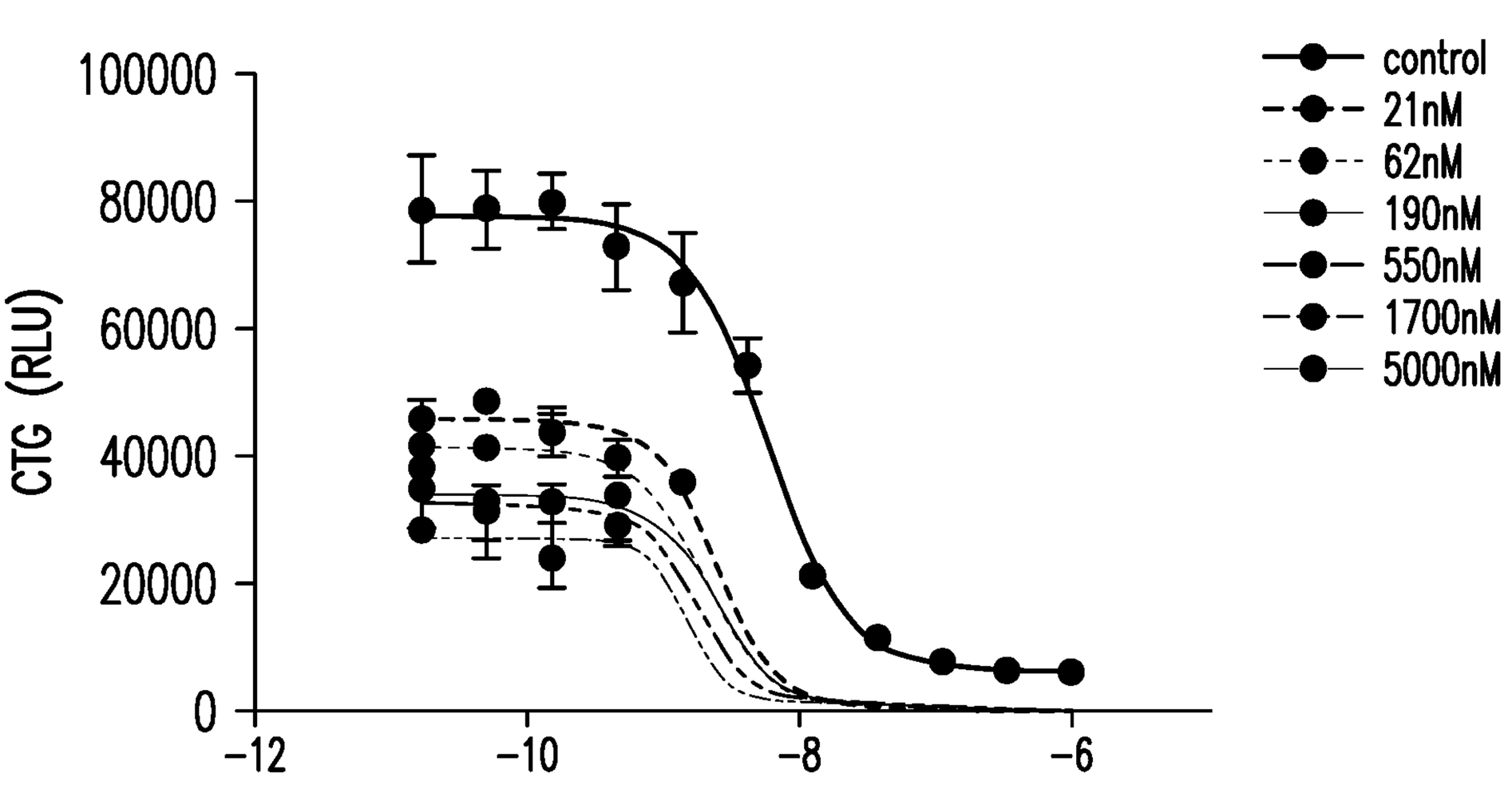

KG1–Venetoclax
CTG (RLU)
100000
80000
60000
40000
20000
0
−12
−10
−8
−6
Compound 1 (logM)
control
21nM
62nM
190nM
550nM
1700nM
5000nM

FIG. 103

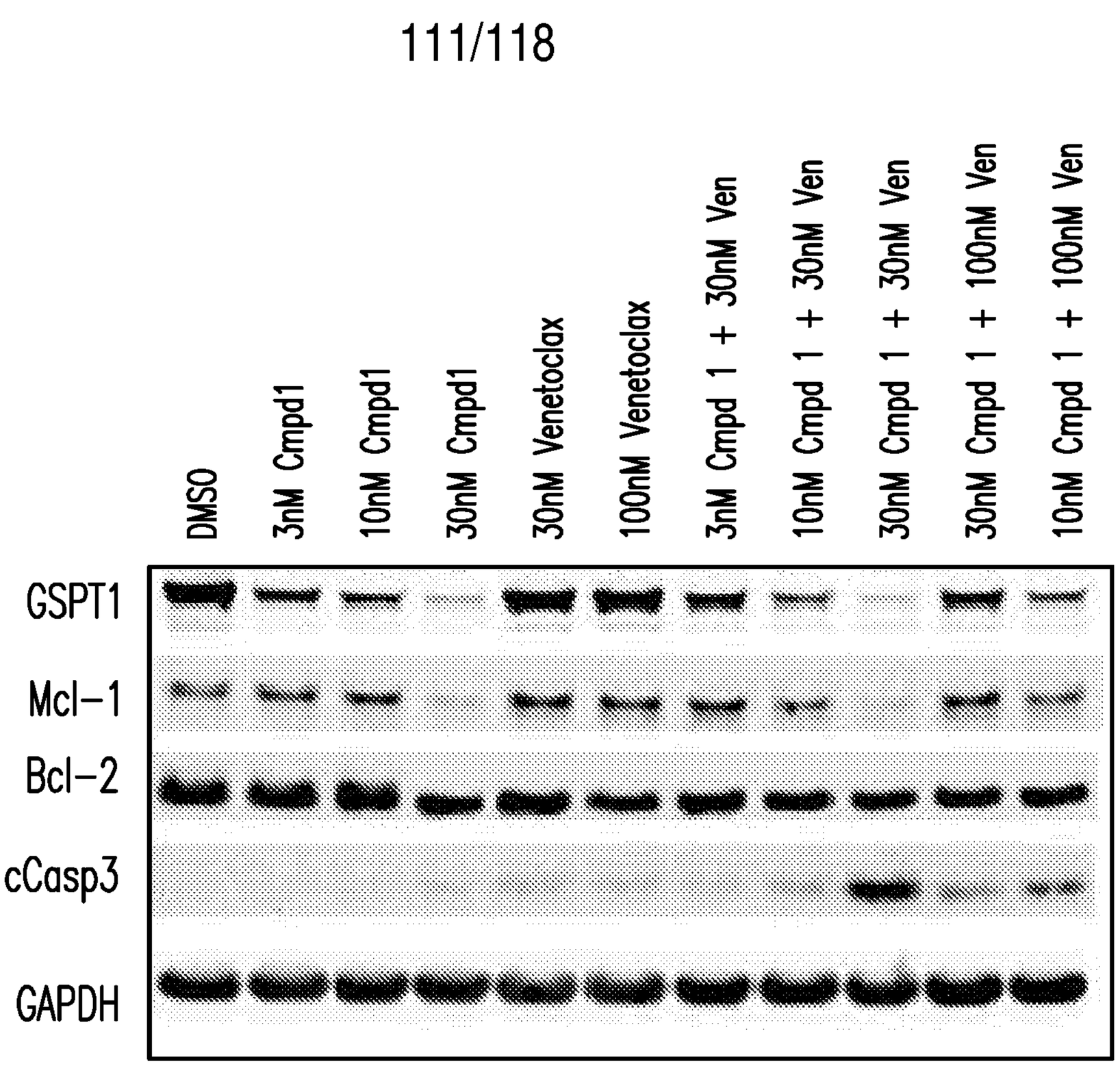

DMSO
3nM Cmpd1
10nM Cmpd1
30nM Cmpd1
30nM Venetoclax
100nM Venetoclax
3nM Cmpd 1 + 30nM Ven
10nM Cmpd 1 + 30nM Ven
30nM Cmpd 1 + 30nM Ven
30nM Cmpd 1 + 100nM Ven
10nM Cmpd 1 + 100nM Ven
GSPT1
Mcl-1
Bcl-2
cCasp3
GAPDH

FIG. 104

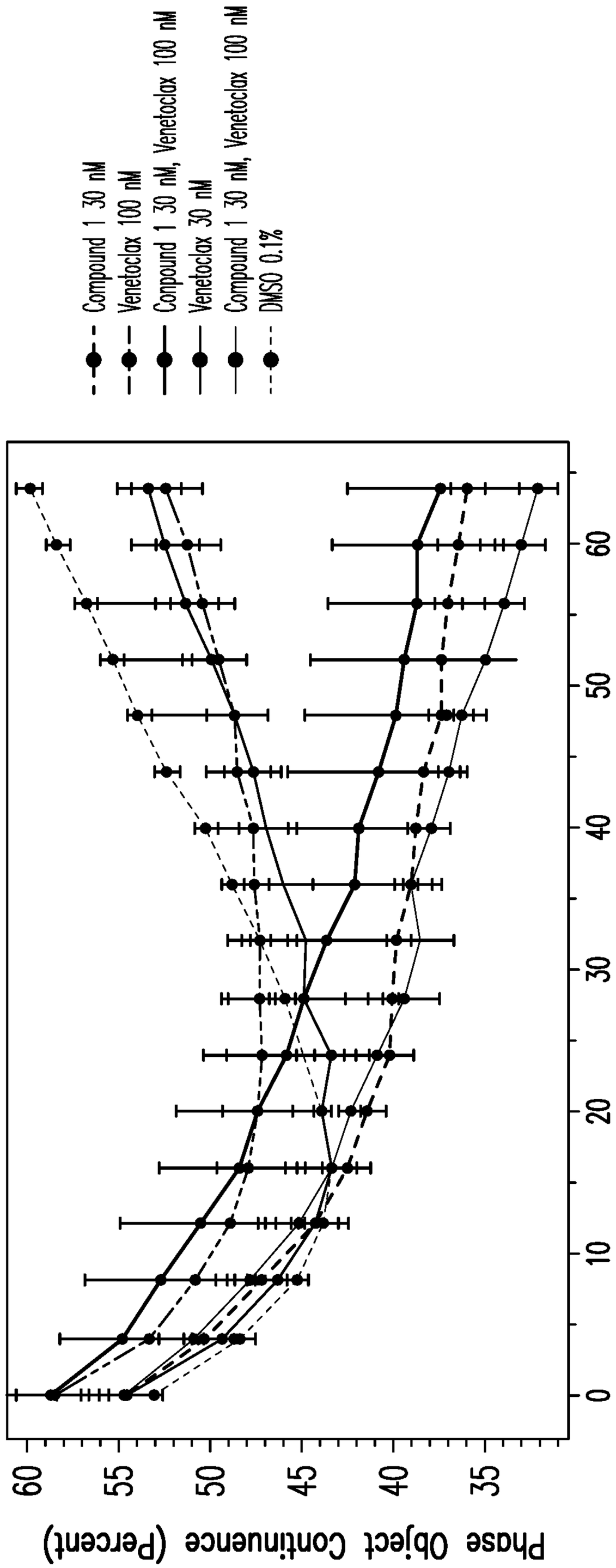

Compound 1 30 nM
Venetoclax 100 nM
Compound 1 30 nM, Venetoclax 100 nM
Venetoclax 30 nM
Compound 1 30 nM, Venetoclax 100 nM
DMSO 0.1%
Phase Object Continuence (Percent)
60
55
50
45
40
35
Time (Hours)
0
10
20
30
40
50
60

FIG. 105A

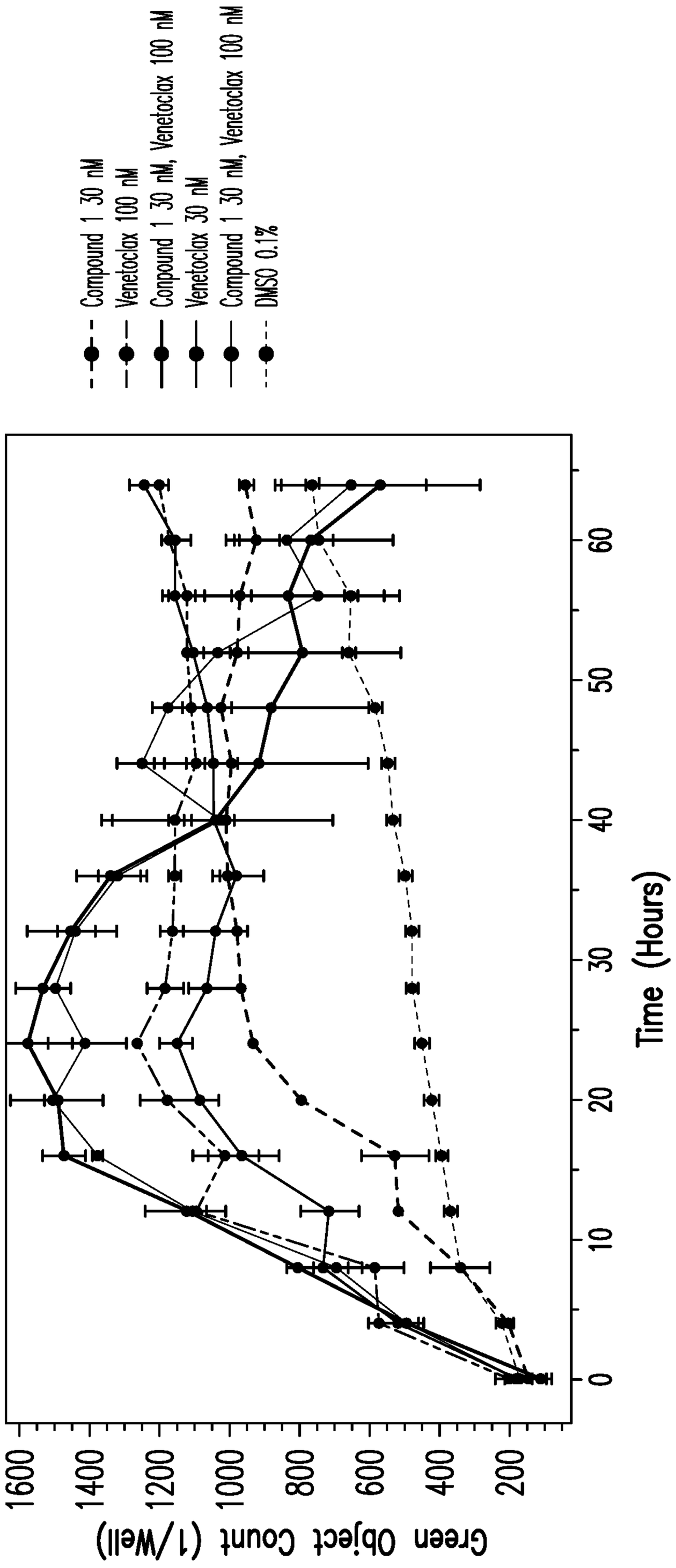

Compound 1 30 nM
Venetoclax 100 nM
Compound 1 30 nM, Venetoclax 100 nM
Venetoclax 30 nM
Compound 1 30 nM, Venetoclax 100 nM
DMSO 0.1%
Green Object Count (1/Well)
1600
1400
1200
1000
800
600
400
200
Time (Hours)
0
10
20
30
40
50
60

FIG. 105B

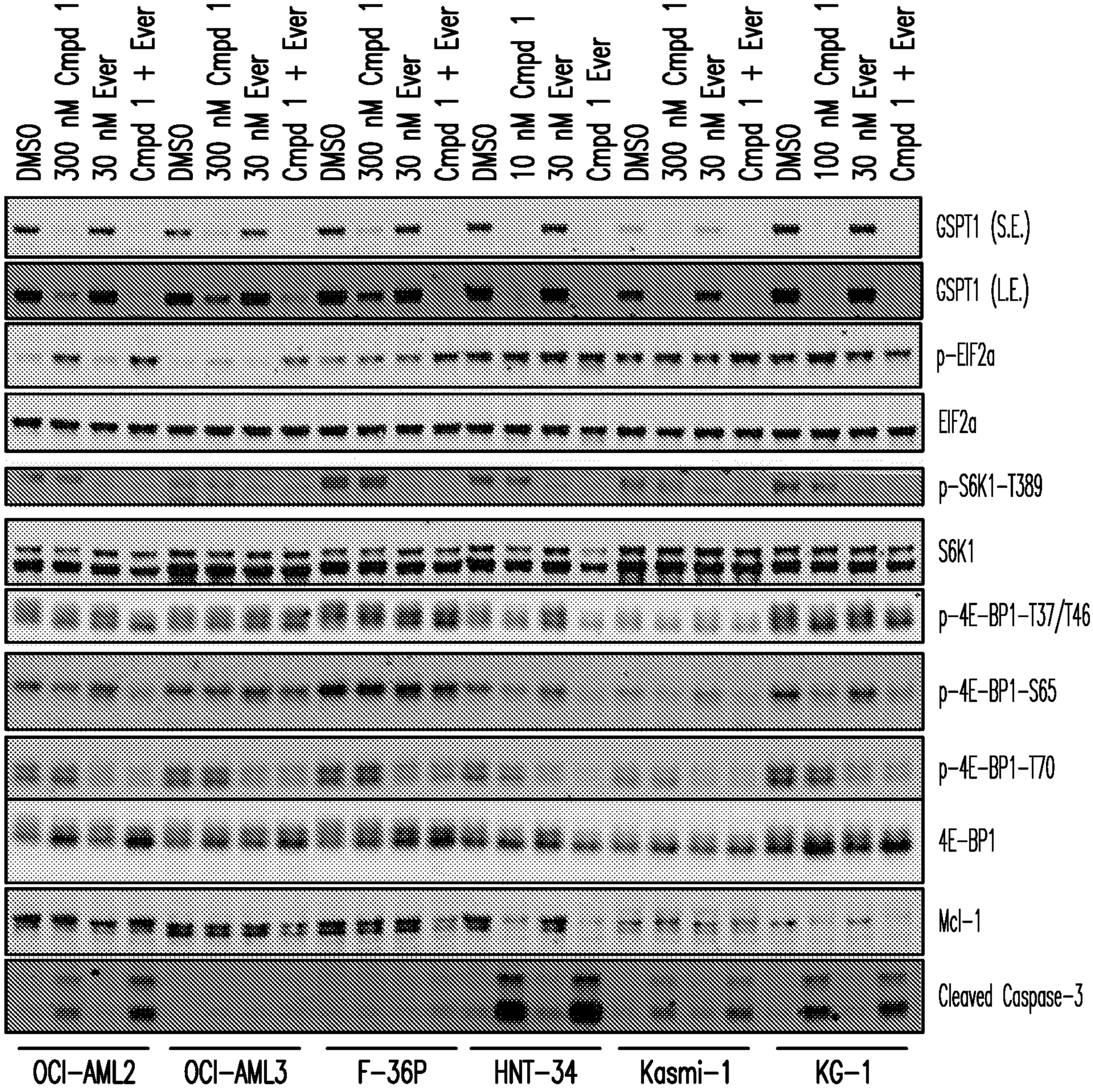

DMSO
300 nM Cmpd 1
30 nM Ever
Cmpd 1 + Ever
DMSO
300 nM Cmpd 1
30 nM Ever
Cmpd 1 + Ever
DMSO
300 nM Cmpd 1
30 nM Ever
Cmpd 1 + Ever
DMSO
10 nM Cmpd 1
30 nM Ever
Cmpd 1 Ever
DMSO
300 nM Cmpd 1
30 nM Ever
Cmpd 1 + Ever
DMSO
100 nM Cmpd 1
30 nM Ever
Cmpd 1 + Ever
GSPT1 (S.E.)
GSPT1 (L.E.)
p-EIF2a
EIF2a
p-S6K1-T389
S6K1
p-4E-BP1-T37/T46
p-4E-BP1-S65
p-4E-BP1-T70
4E-BP1
Mcl-1
Cleaved Caspase-3
OCI-AML2
OCI-AML3
F-36P
HNT-34
Kasmi-1
KG-1

FIG. 106

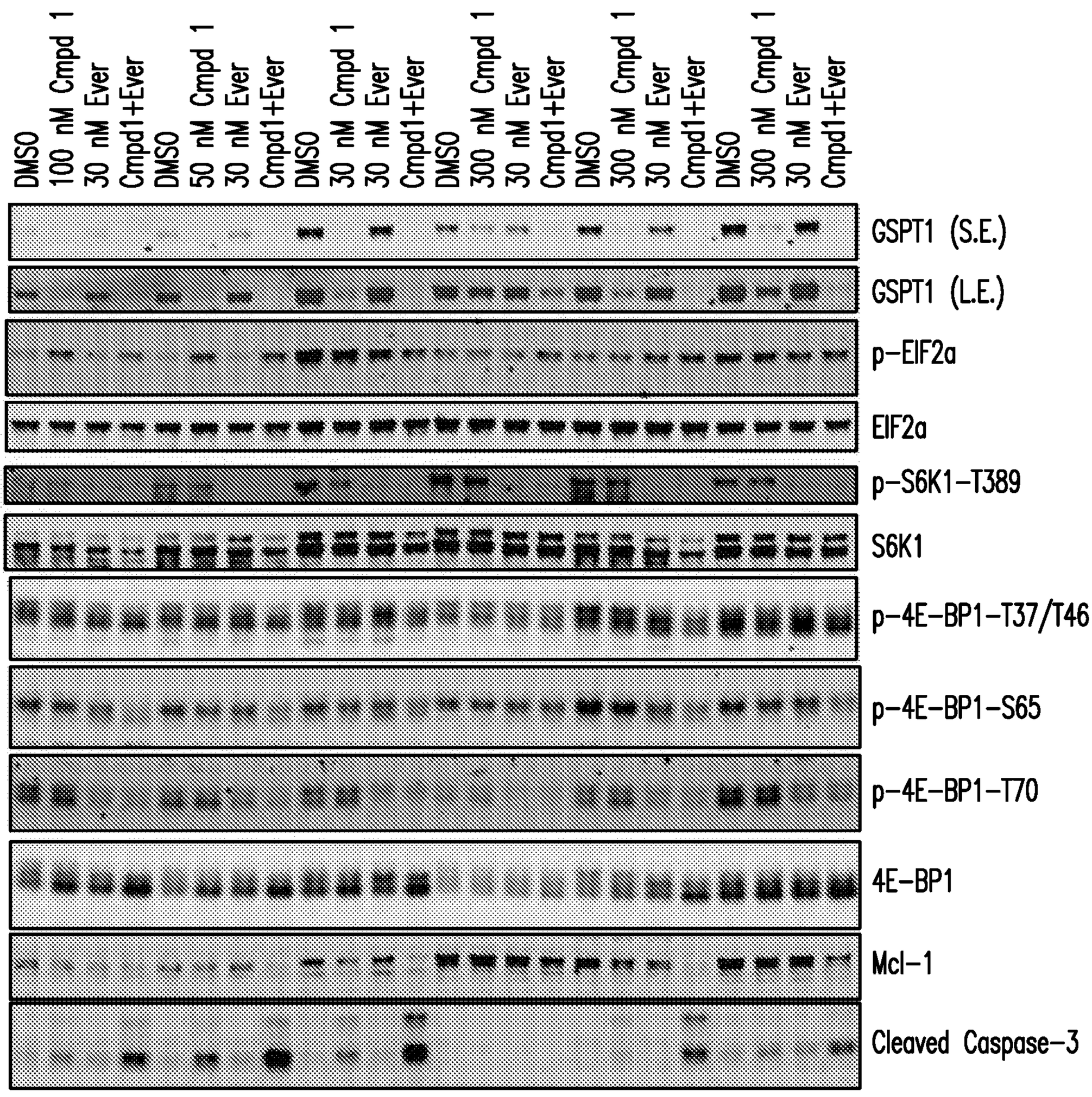


FIG. 106 (continued)

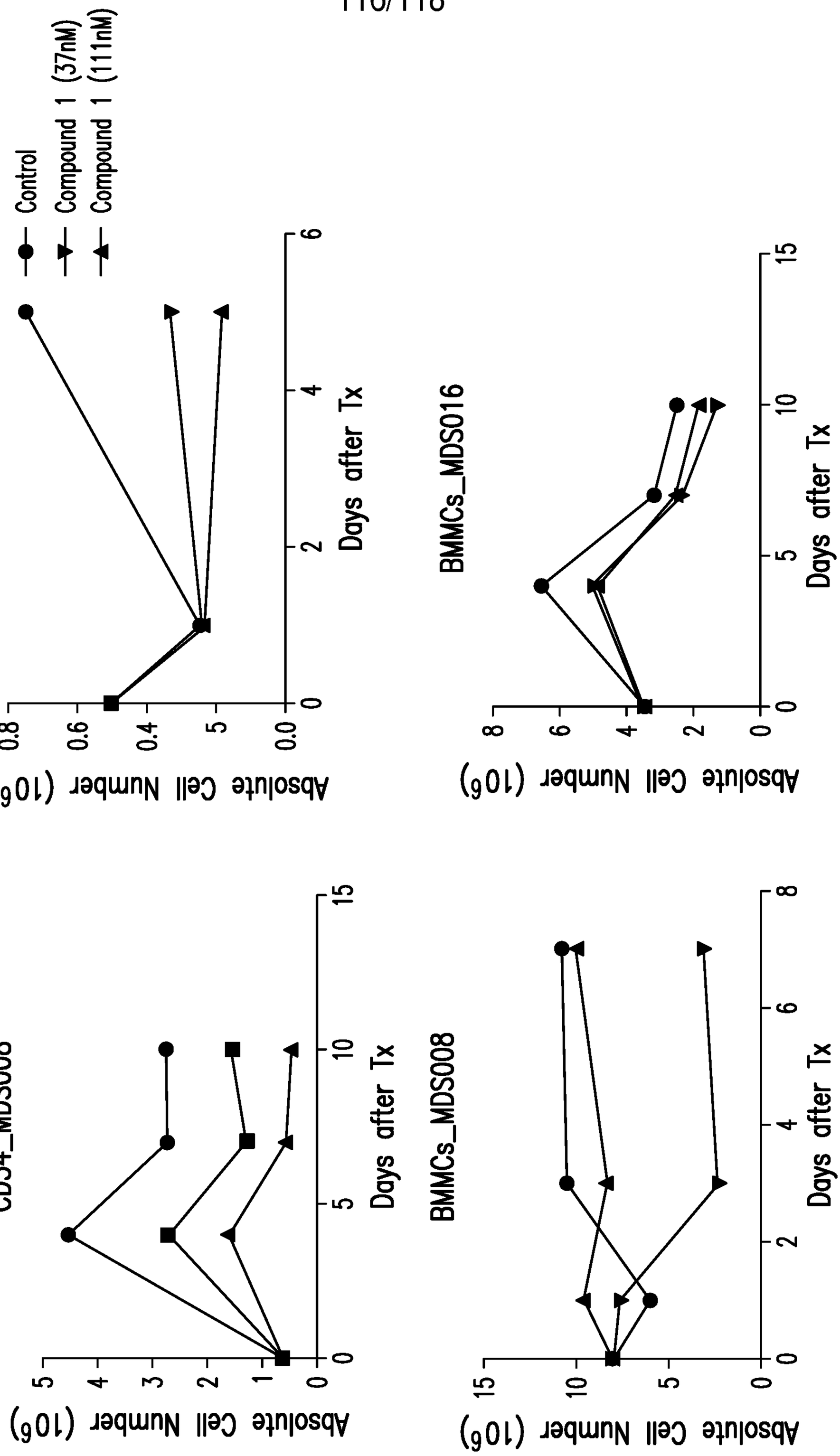

Control
Compound 1 (37nM)
Compound 1 (111nM)
CD34_MDS016
BMMCs_MDS016
CD34_MDS008
BMMCs_MDS008
Days after Tx
Absolute Cell Number (10^6)

FIG. 107

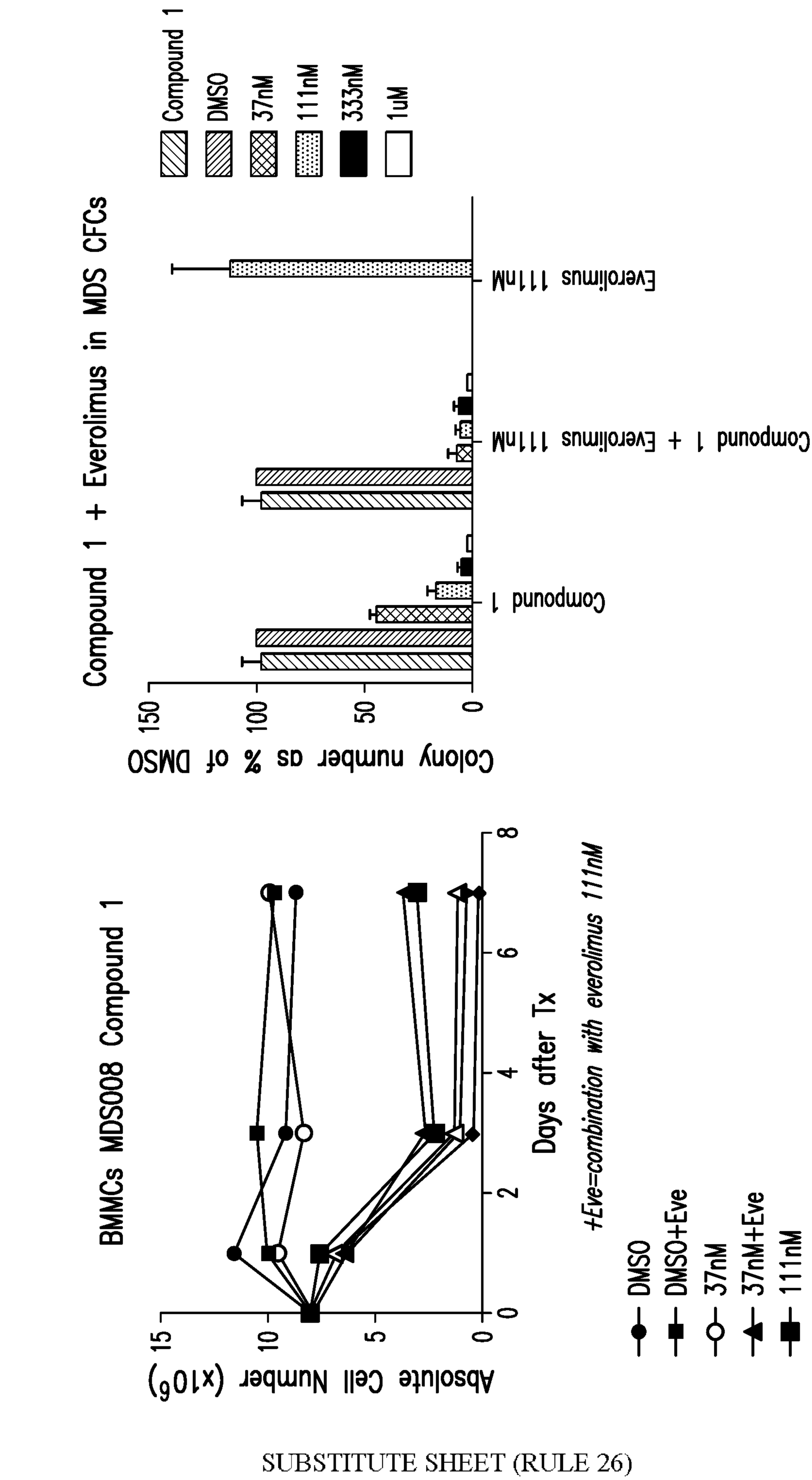


FIG. 108B

FIG. 108A

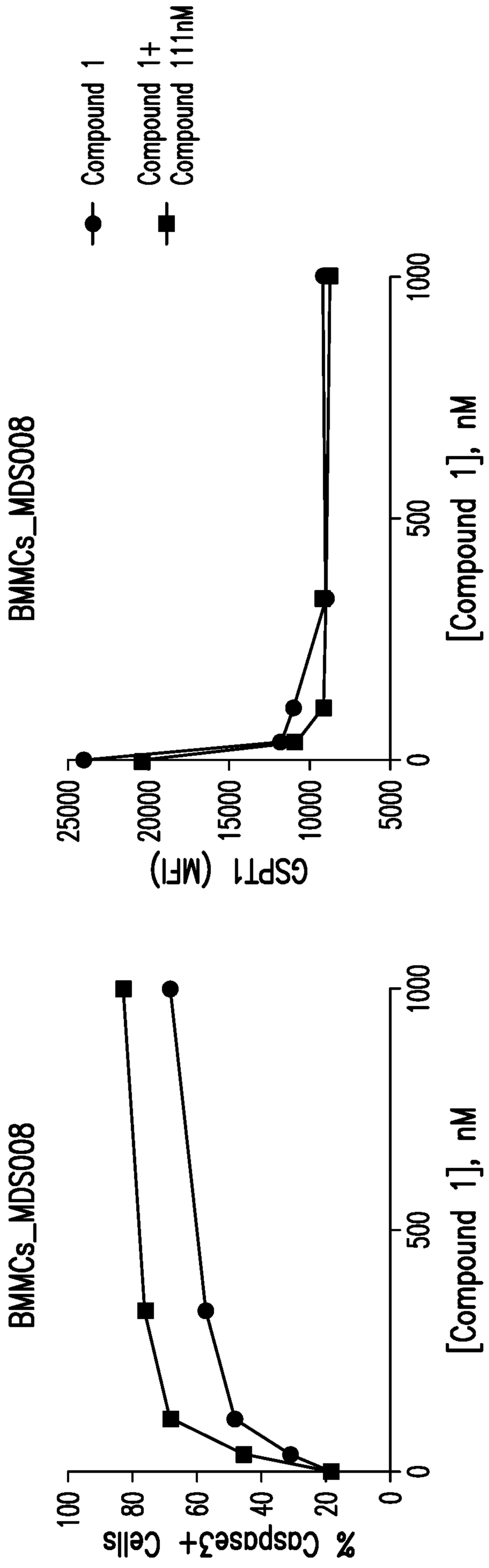

Compound 1
Compound 1+ Compound 111nM
BMMCs_MDS008
GSPT1 (MFI)
25000
20000
15000
10000
5000
0
500
1000
[Compound 1], nM
BMMCs_MDS008
% Caspase3+ Cells
100
80
60
40
20
0
500
1000
[Compound 1], nM

FIG. 109