Figure 1-Example 1; A204 cells

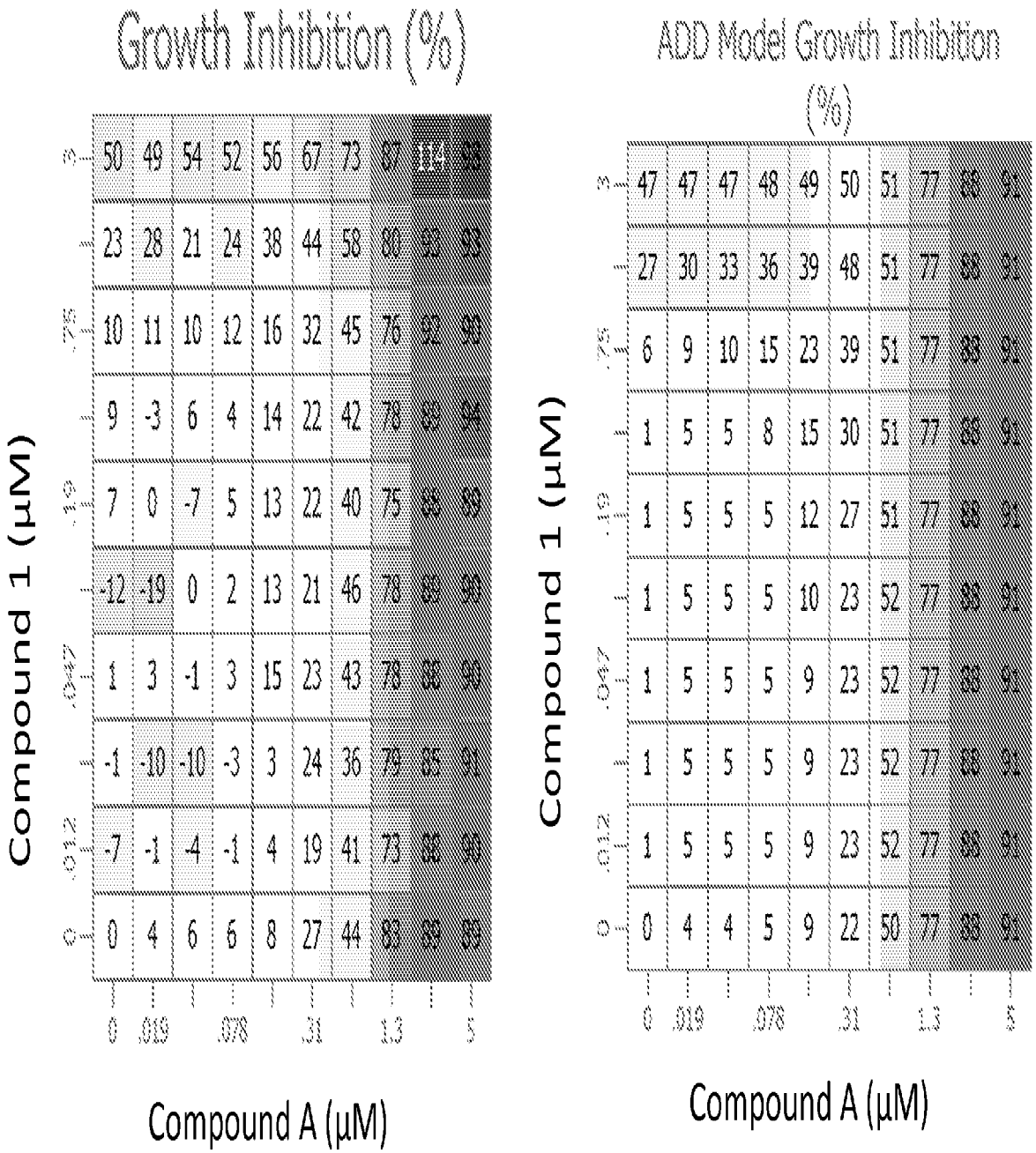
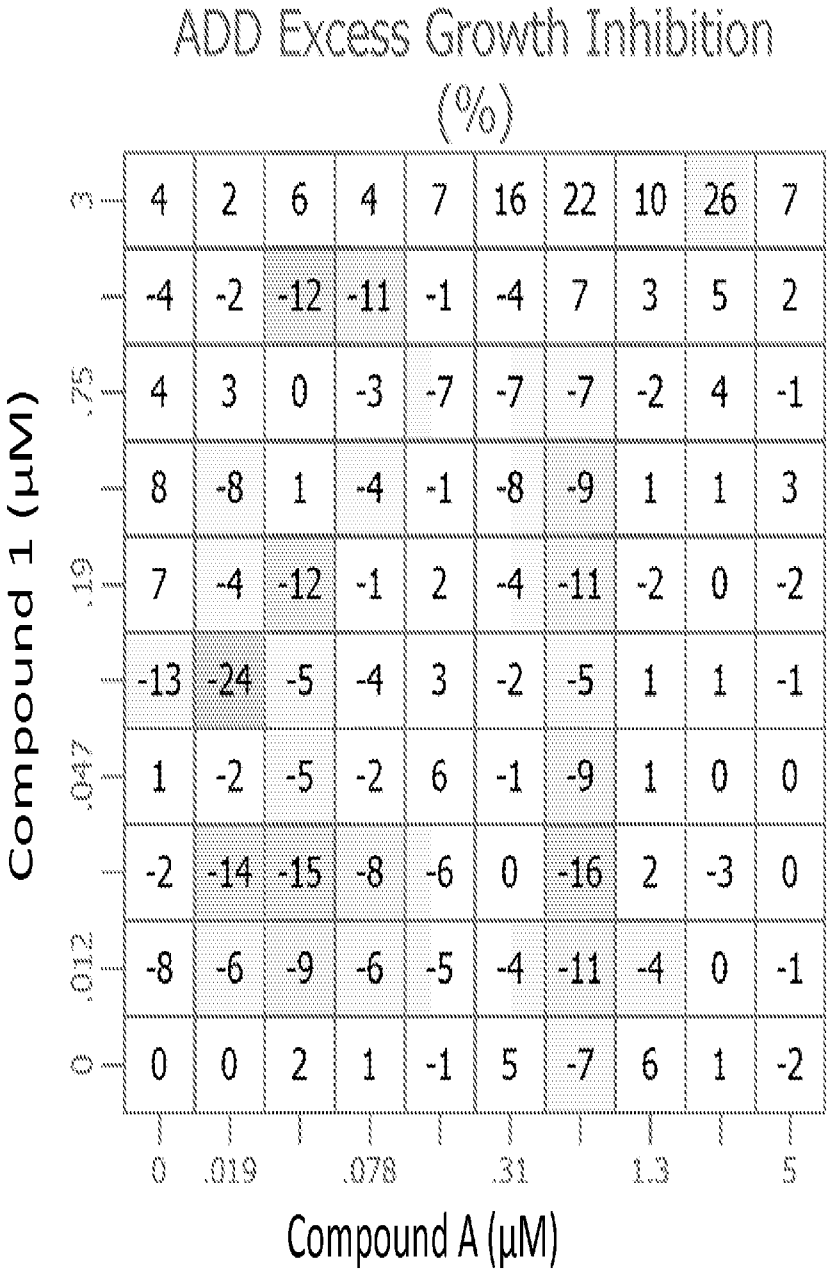


Figure 1a-Example 1; A204 cells



	Synergy Score
A x 1	0.532
A self-cross	0.621
1 self-cross	0.432

Figure 2-Example 2; A375sq2

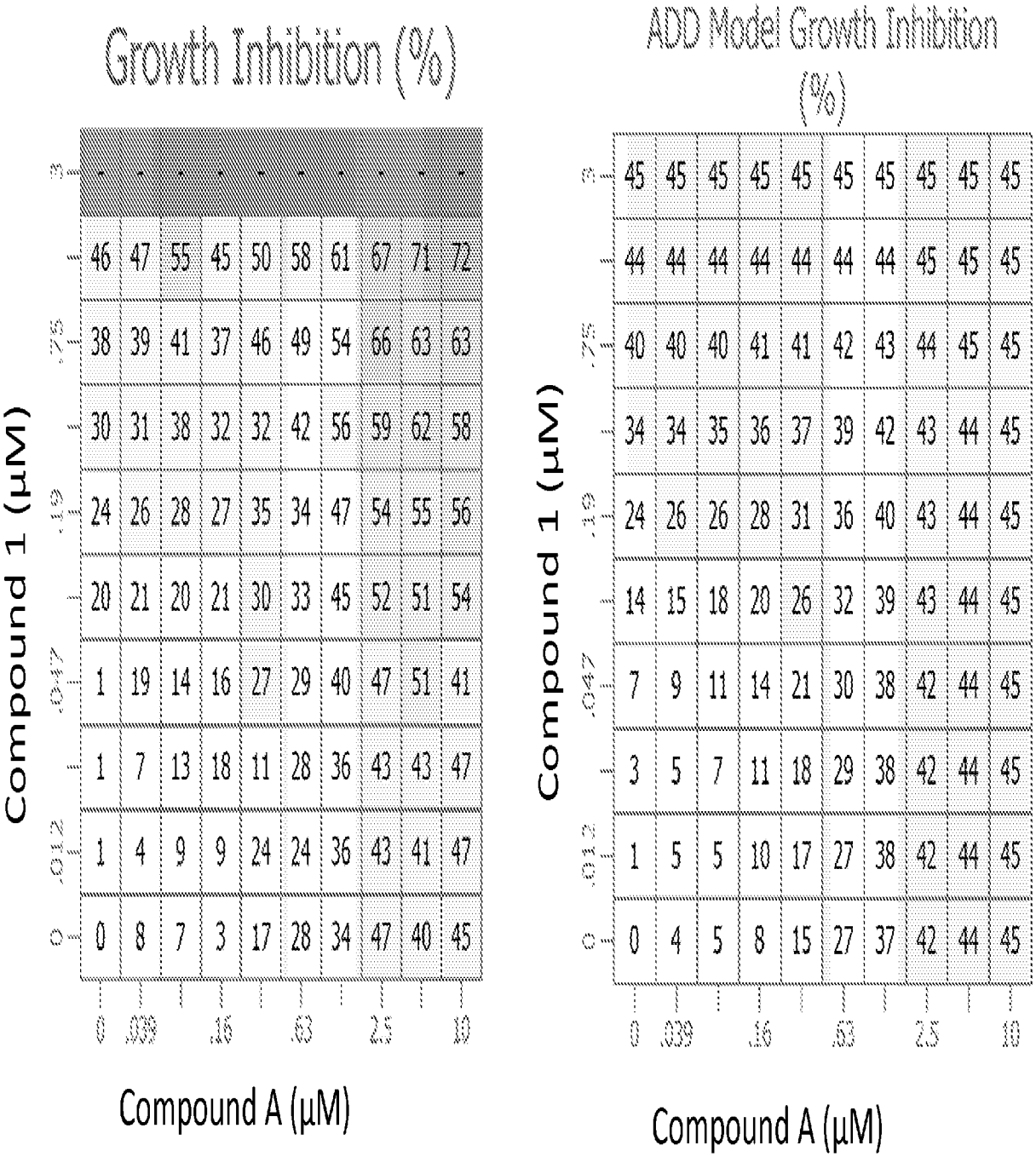
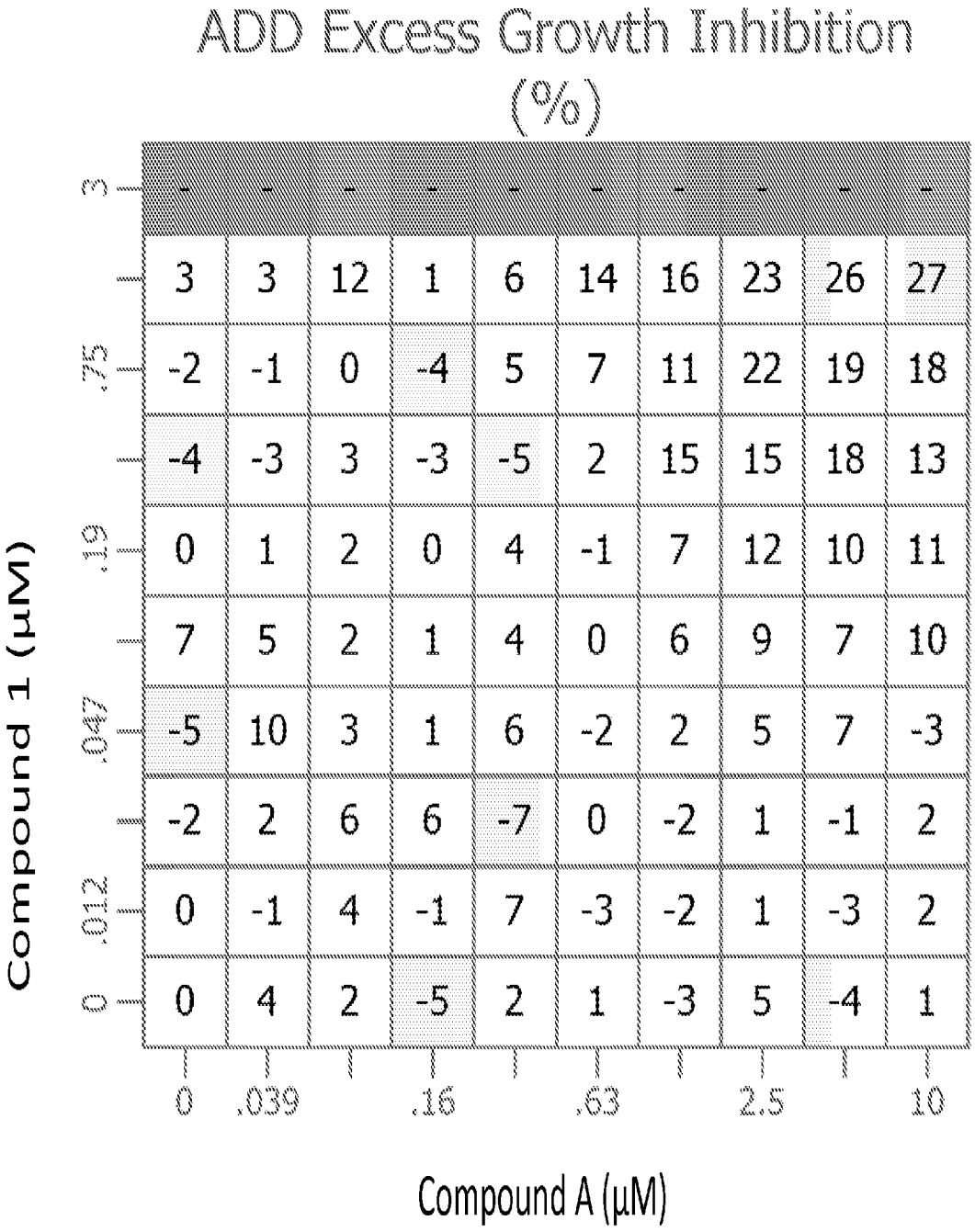


Figure 2a-Example 2; A375sq2 cells



	Synergy Score
A x 1	1.25
A self-cross	0.333
1 x self-cross	0.226

Figure 3-Example 3; A-427 cells

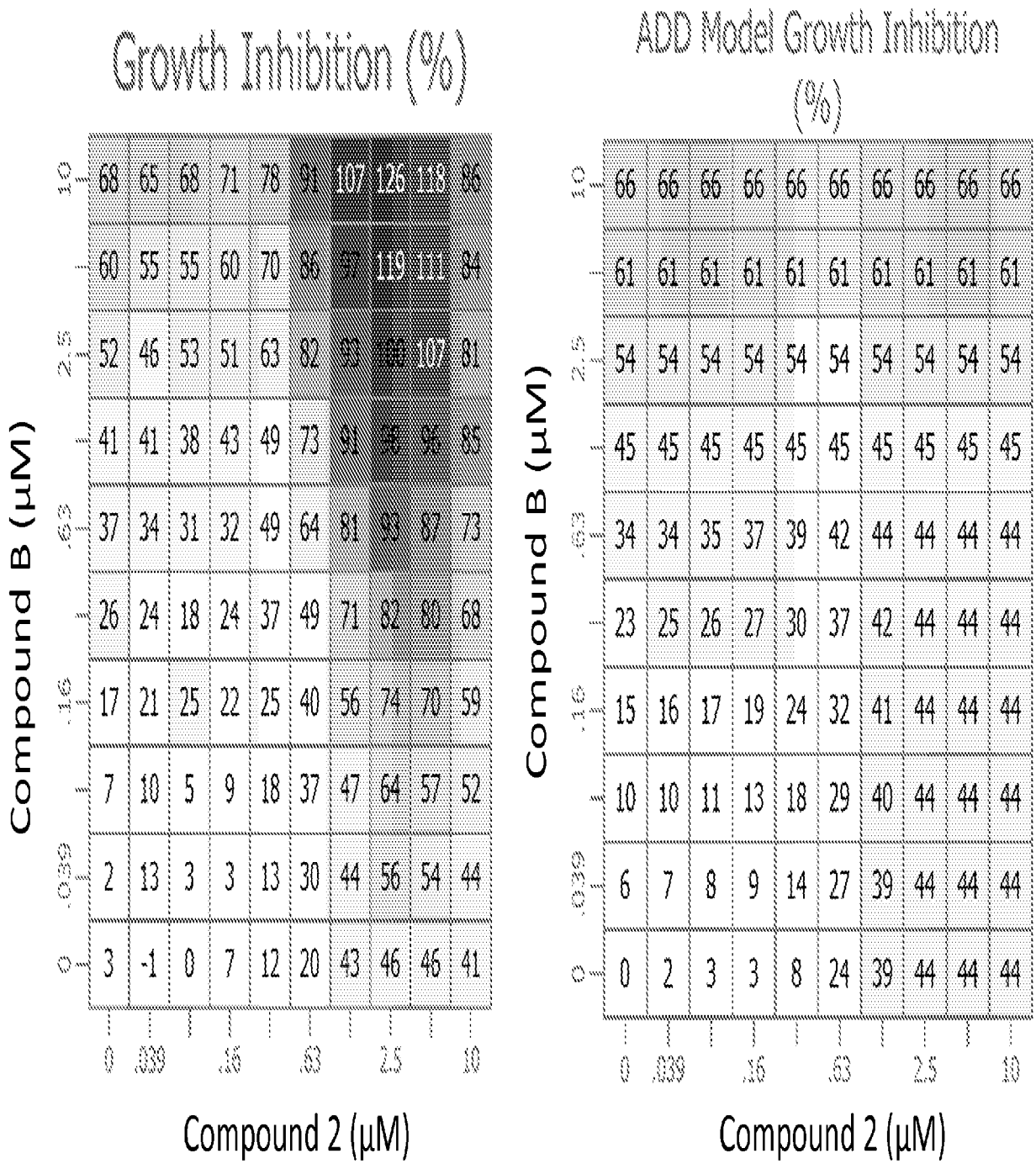
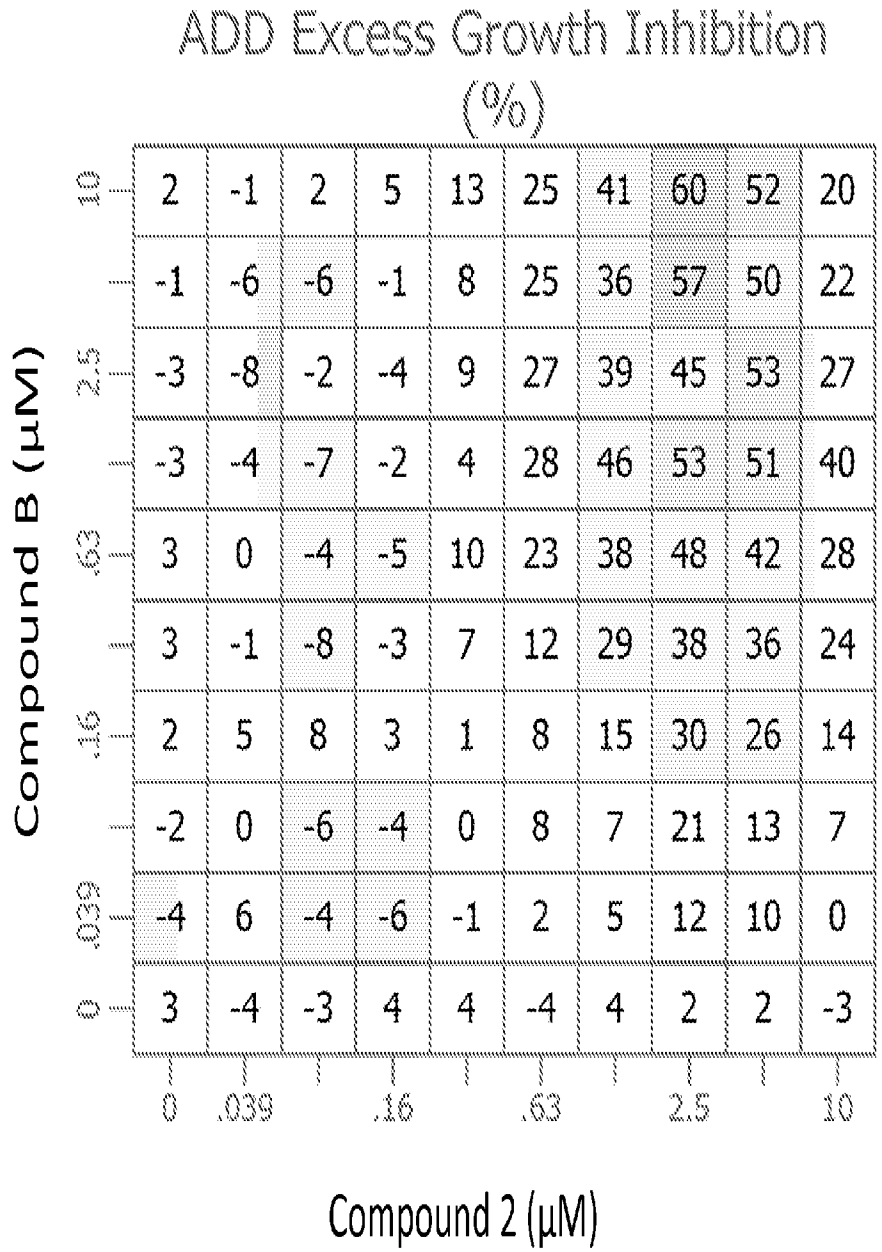


Figure 3a-Example 3; A-427 cells



	Synergy Score
B x 2	5.73
B self-cross	0.712
2 self-cross	0.169

Figure 4-Example 4; C32 cells

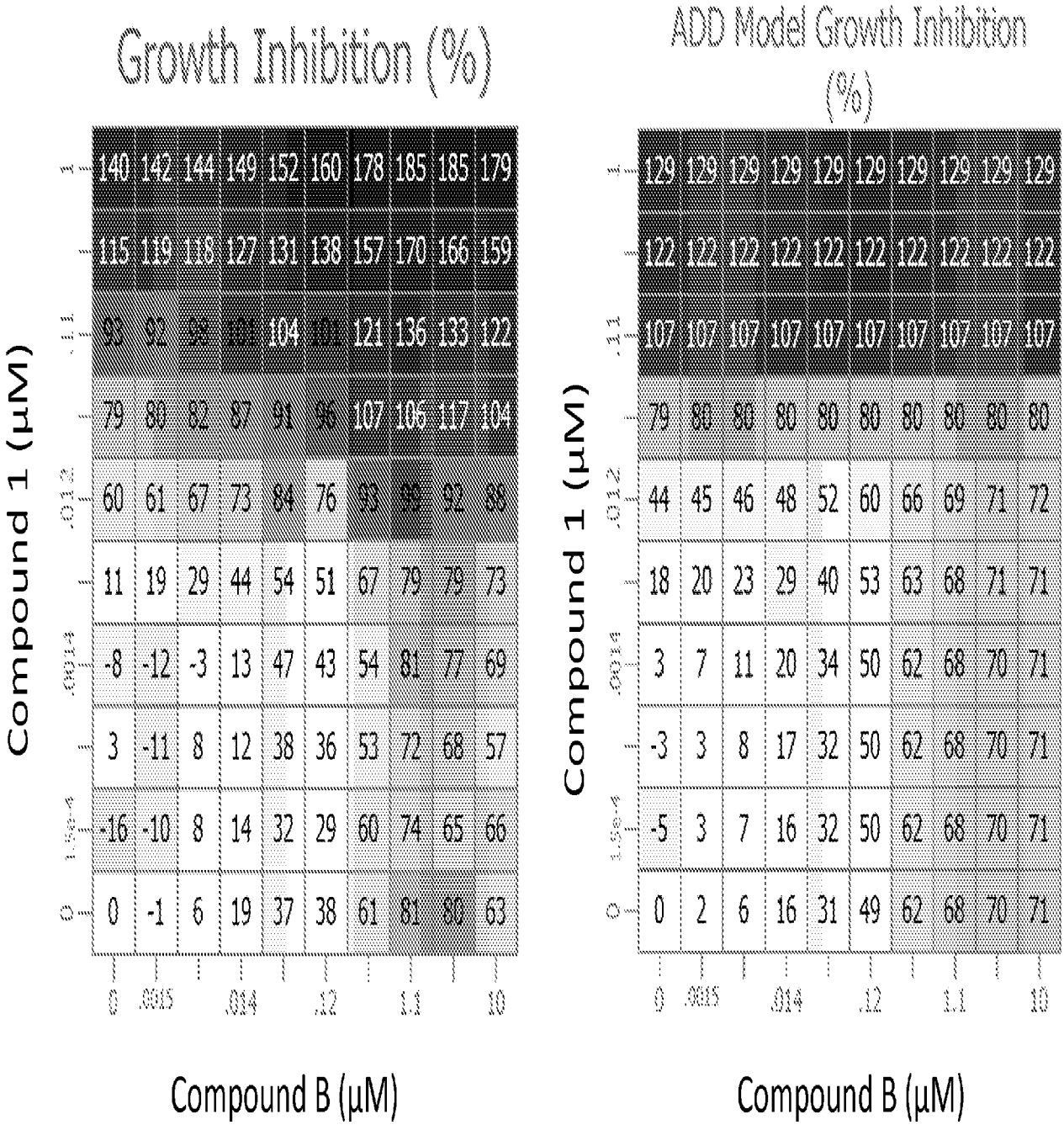
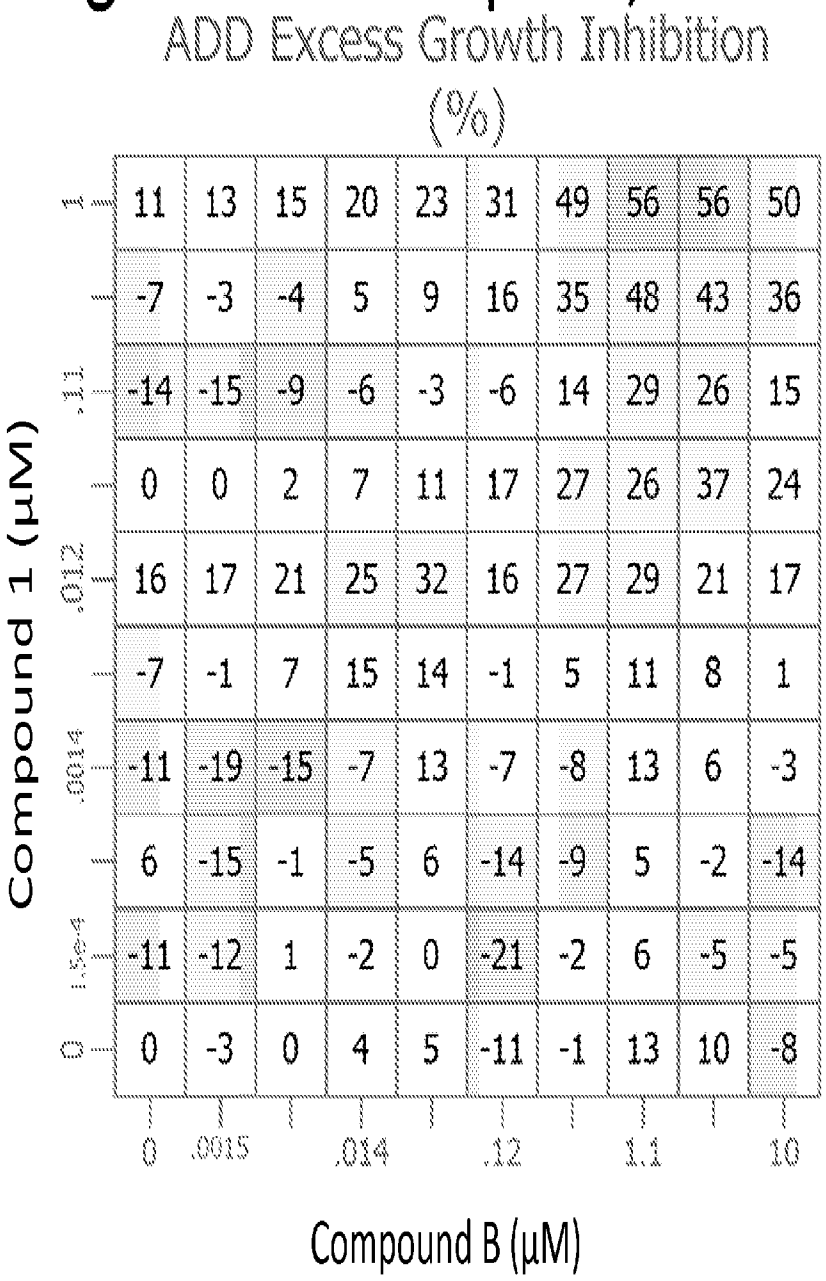


Figure 4a-Example 4; C32 cells



	Synergy Score
2653149 x 2112819	16.3
2653149 self	0.886
2112819 self	4.74

Figure 5-Example 5; C32 cells

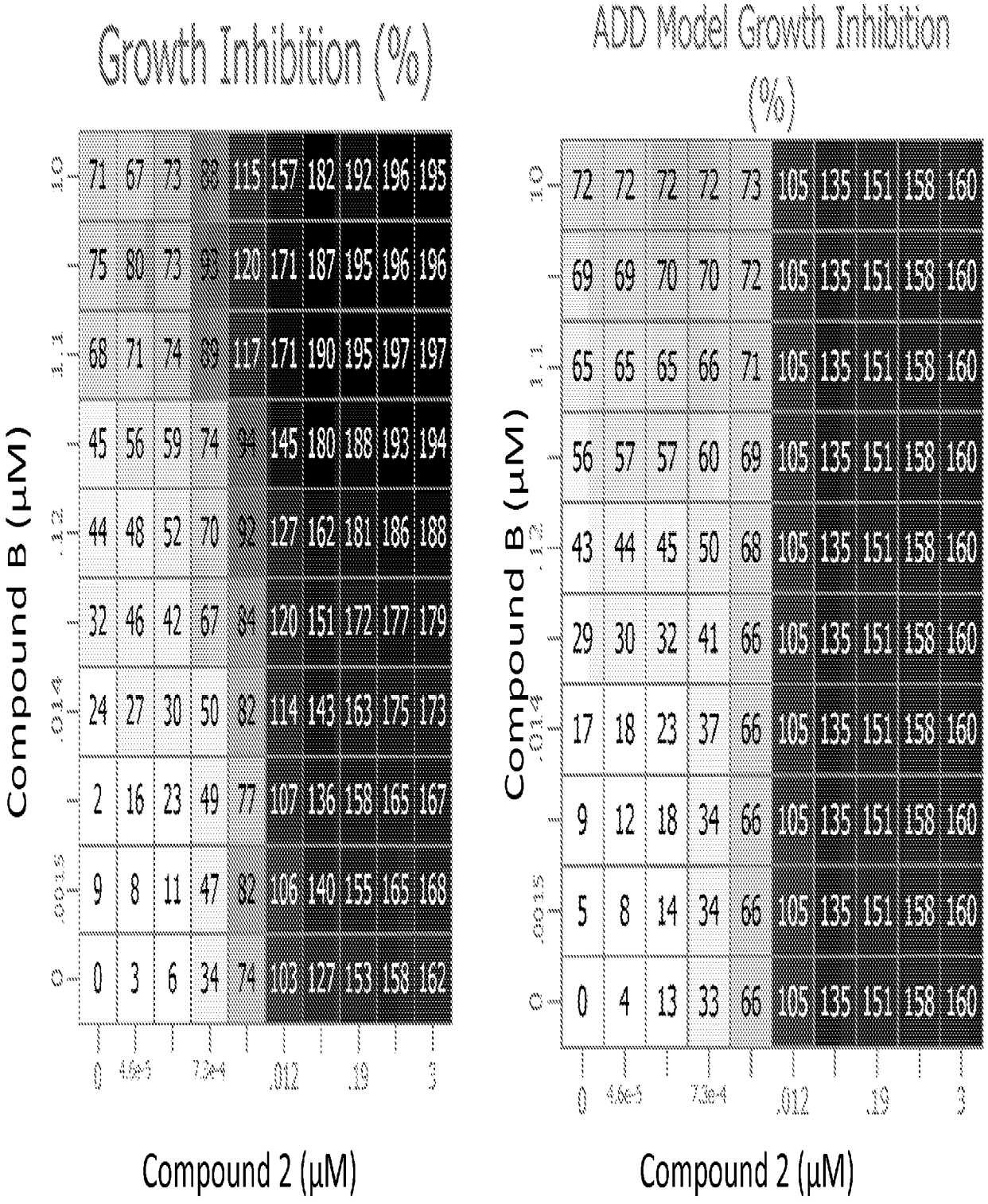
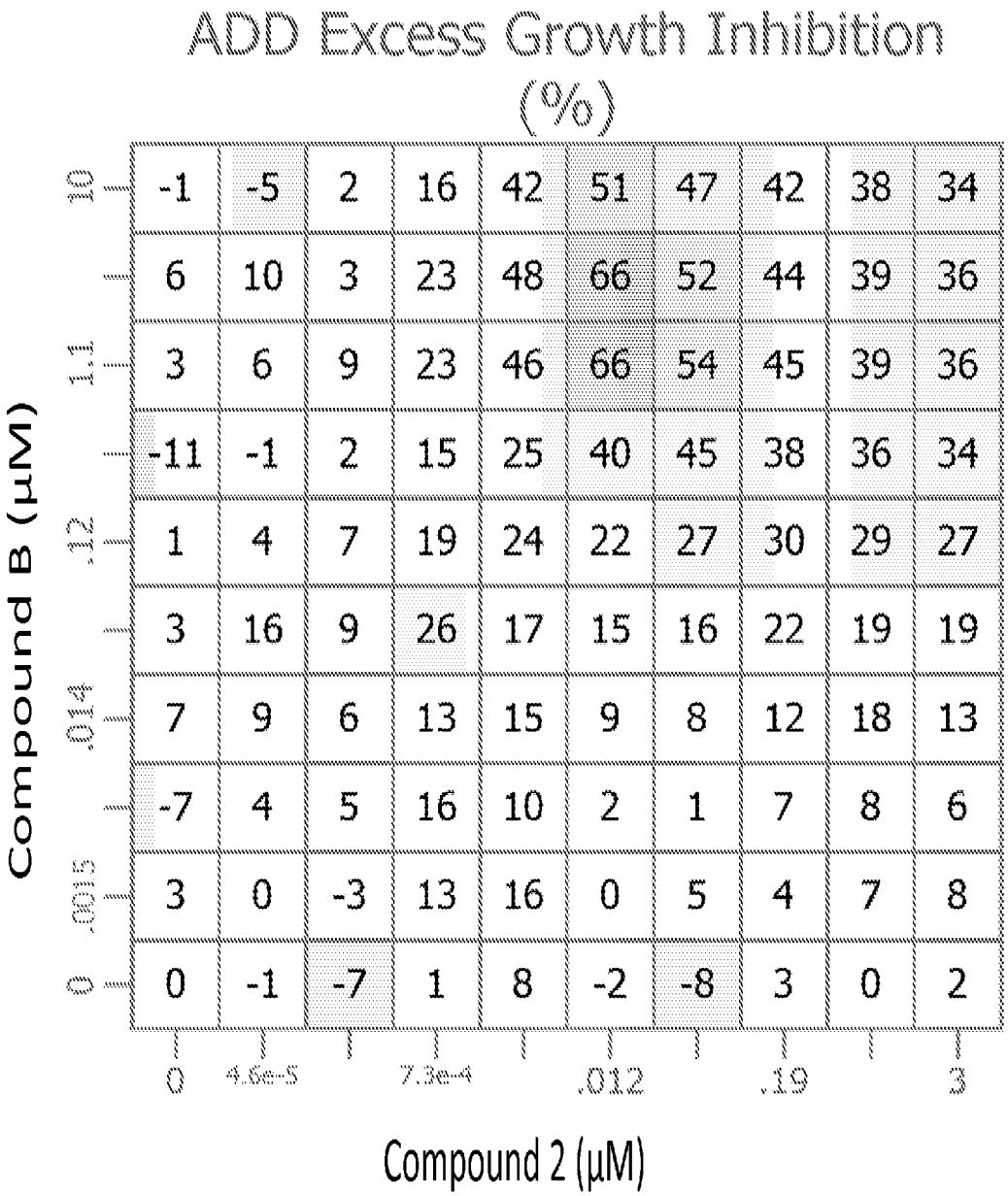


Figure 5a-Example 5; C32 cells



	Synergy Score
B x 2	39.4
B self-cross	0.73
2 self-cross	3.27

Figure 6-Example 6; G-361 cells

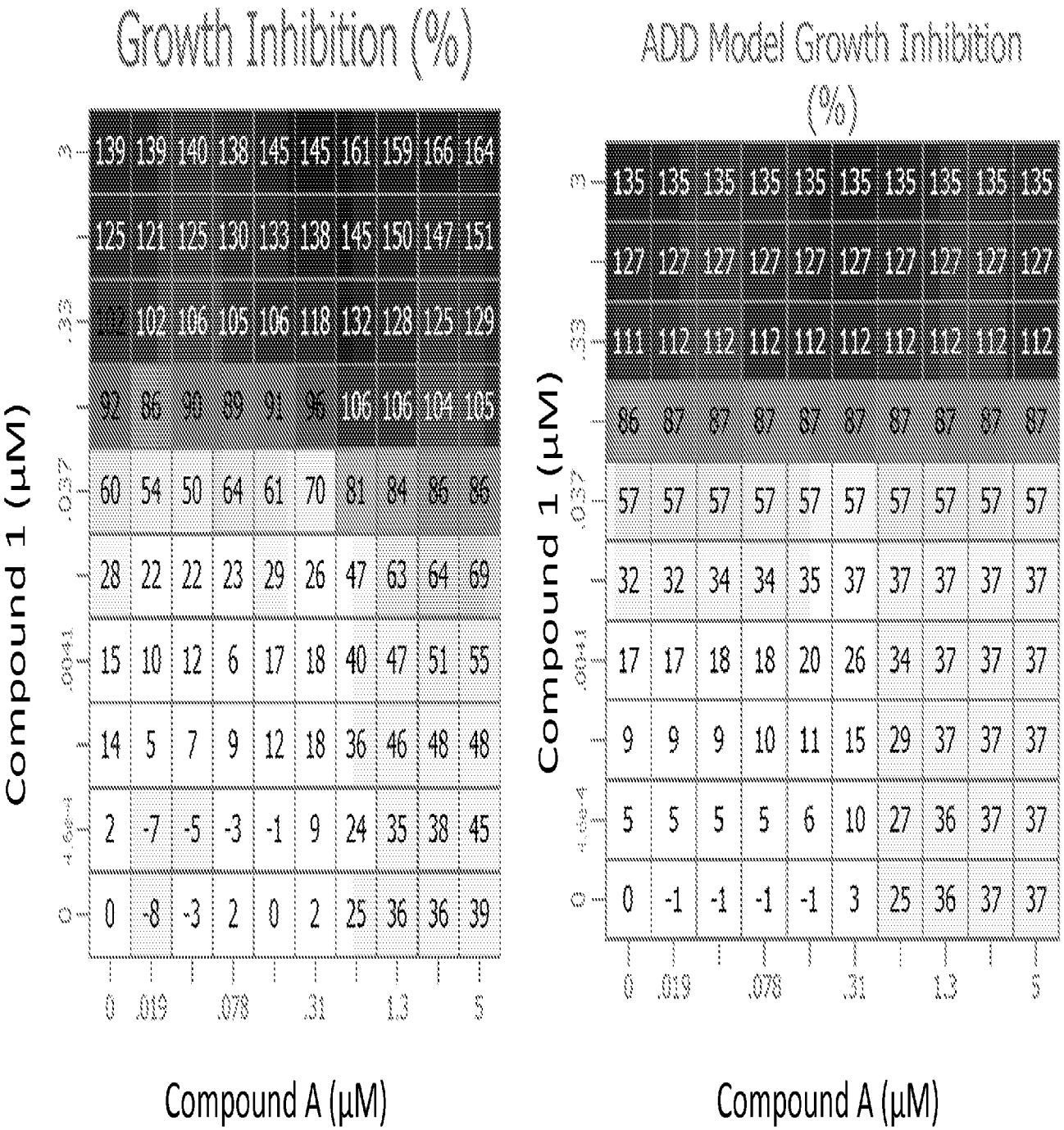
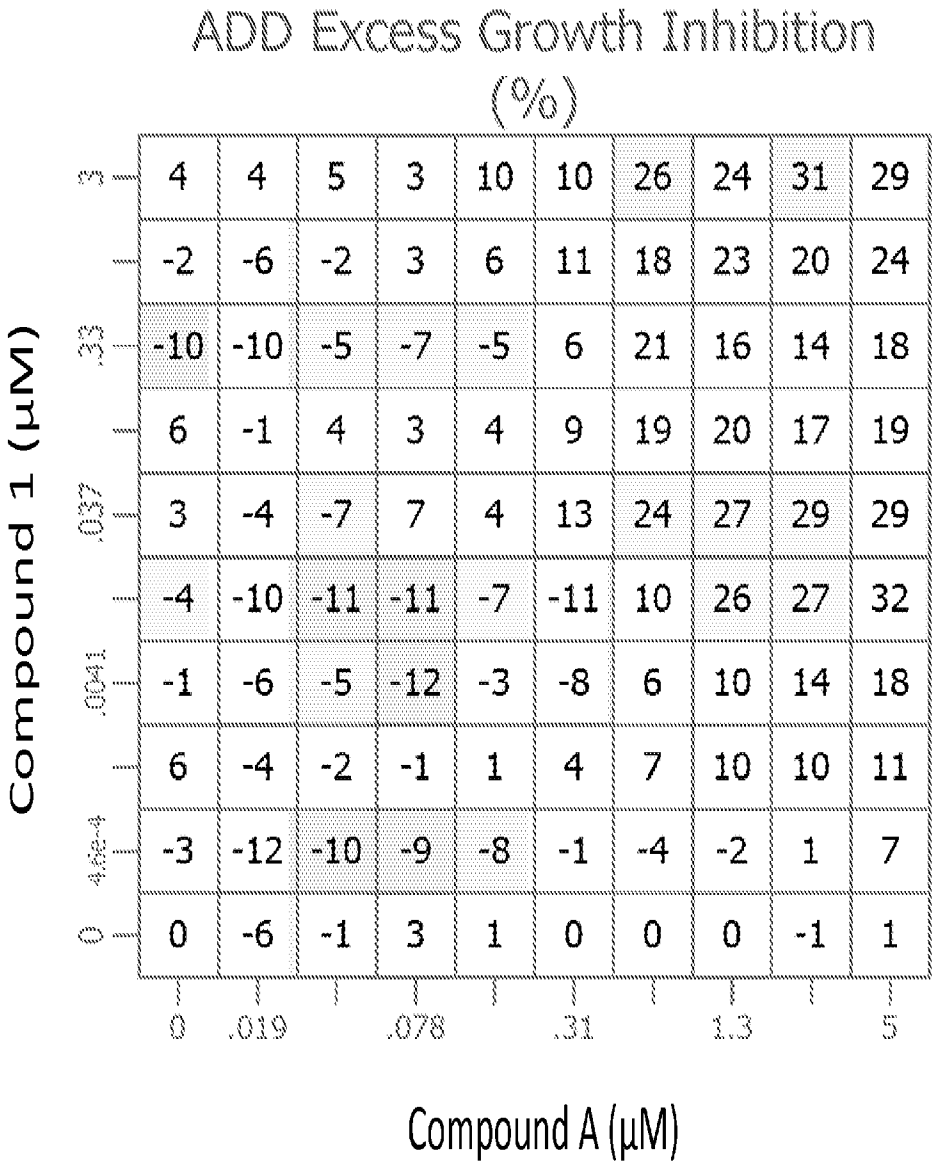


Figure 6a-Example 6; G-361 cells



	Synergy Score
A x 1	5.97
A self-cross	0.0953
1 self-cross	2.26

Figure 7-Example 7; LS 174T cells

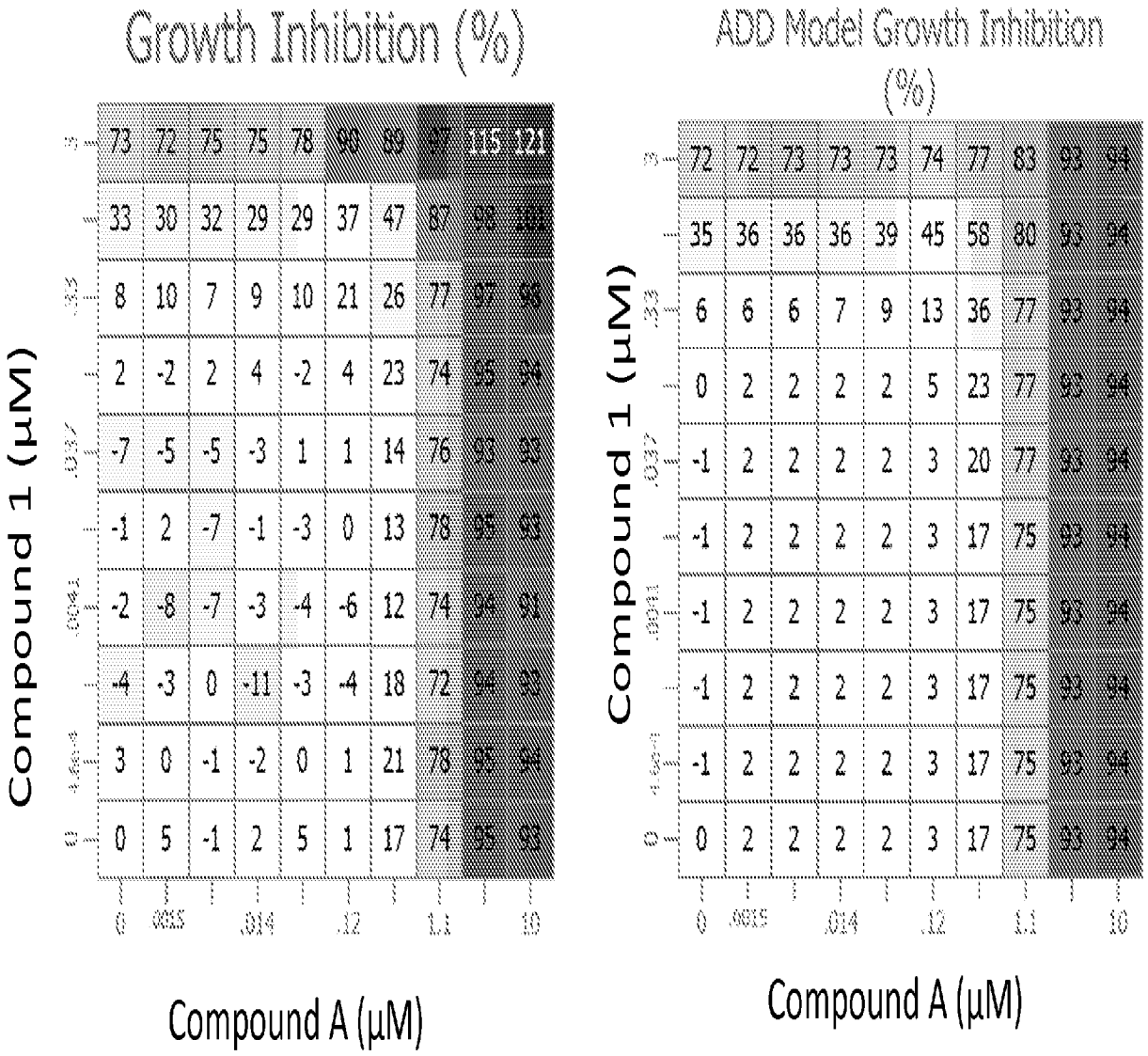
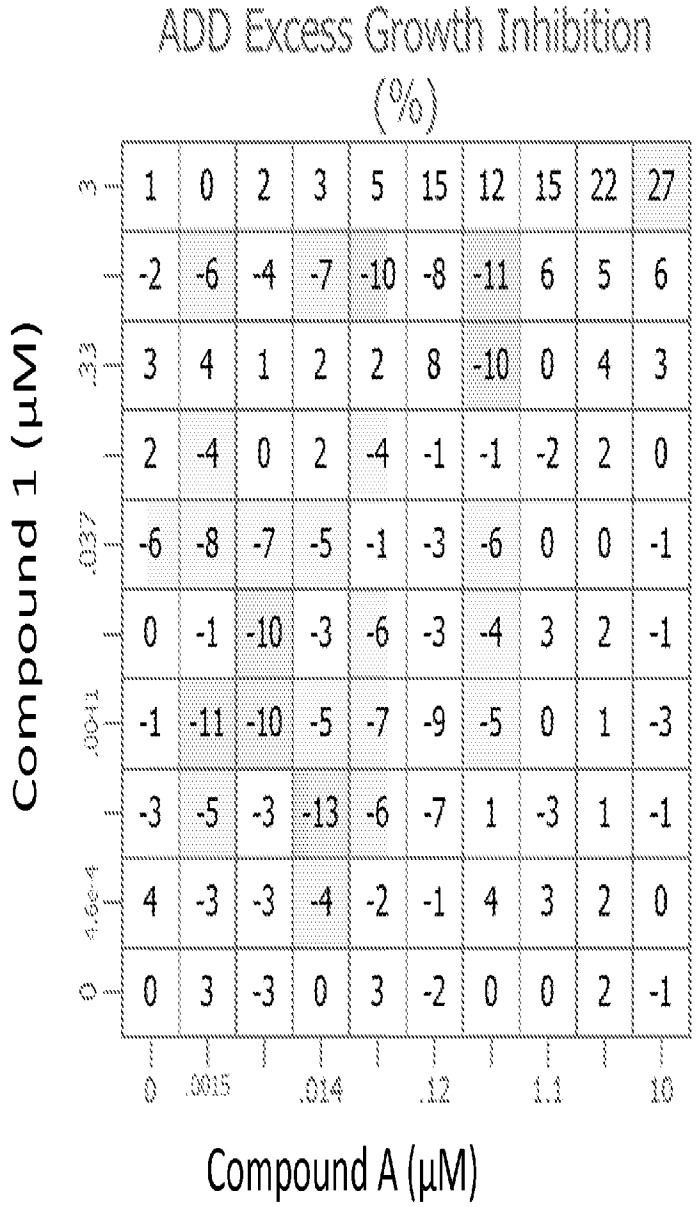


Figure 7a-Example 7; LS 174T cells



	Synergy Score
A x 1	1.76
A self-cross	0.578
1 self-cross	1.43

Figure 8-Example 8; MCF7 cells

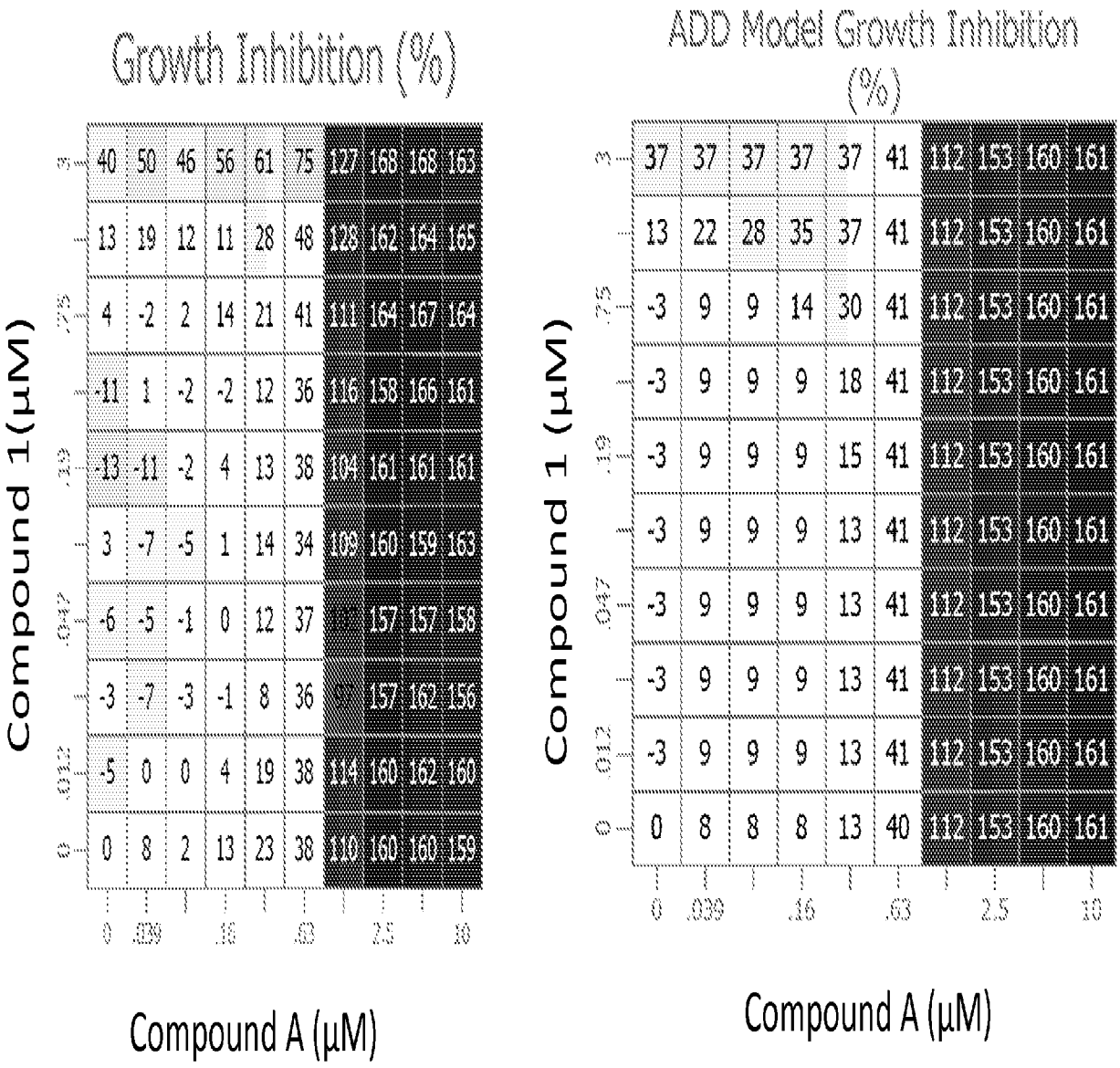
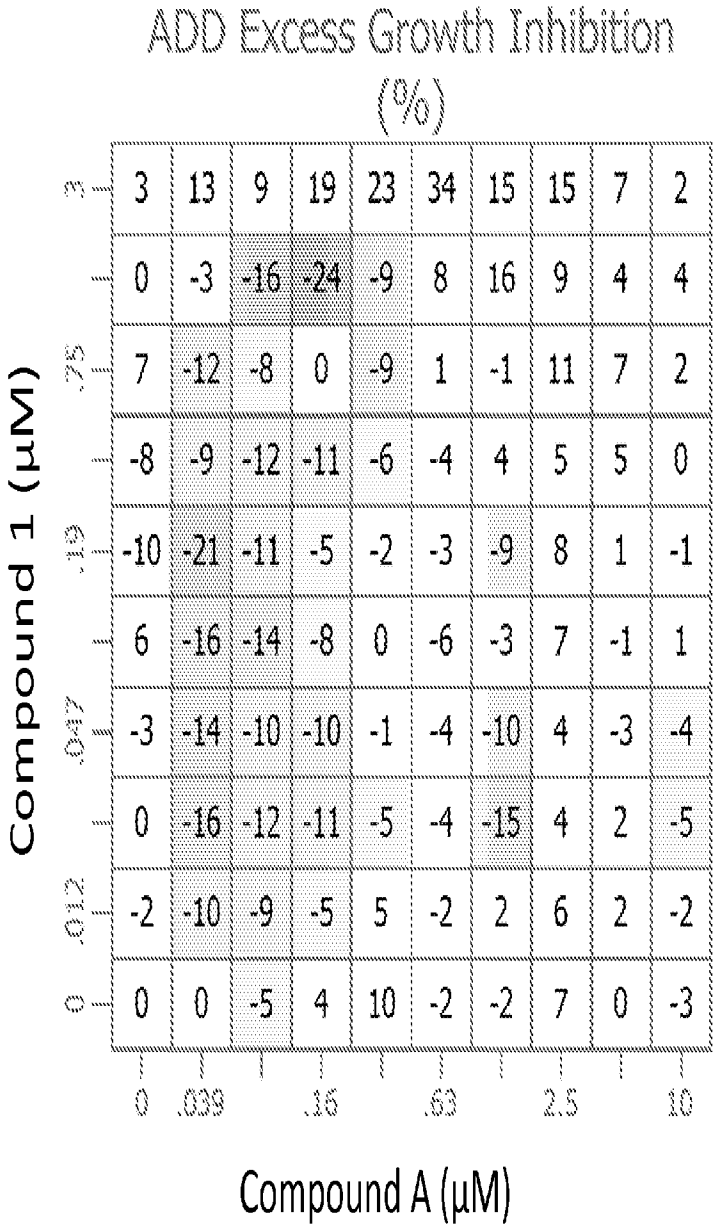


Figure 8a-Example 8, MCF7 cells



	Synergy Score
A x 1	1.36
A self-cross	0.753
1 self-cross	0.955

Figure 9-Example 9; NCI-H1666 cells

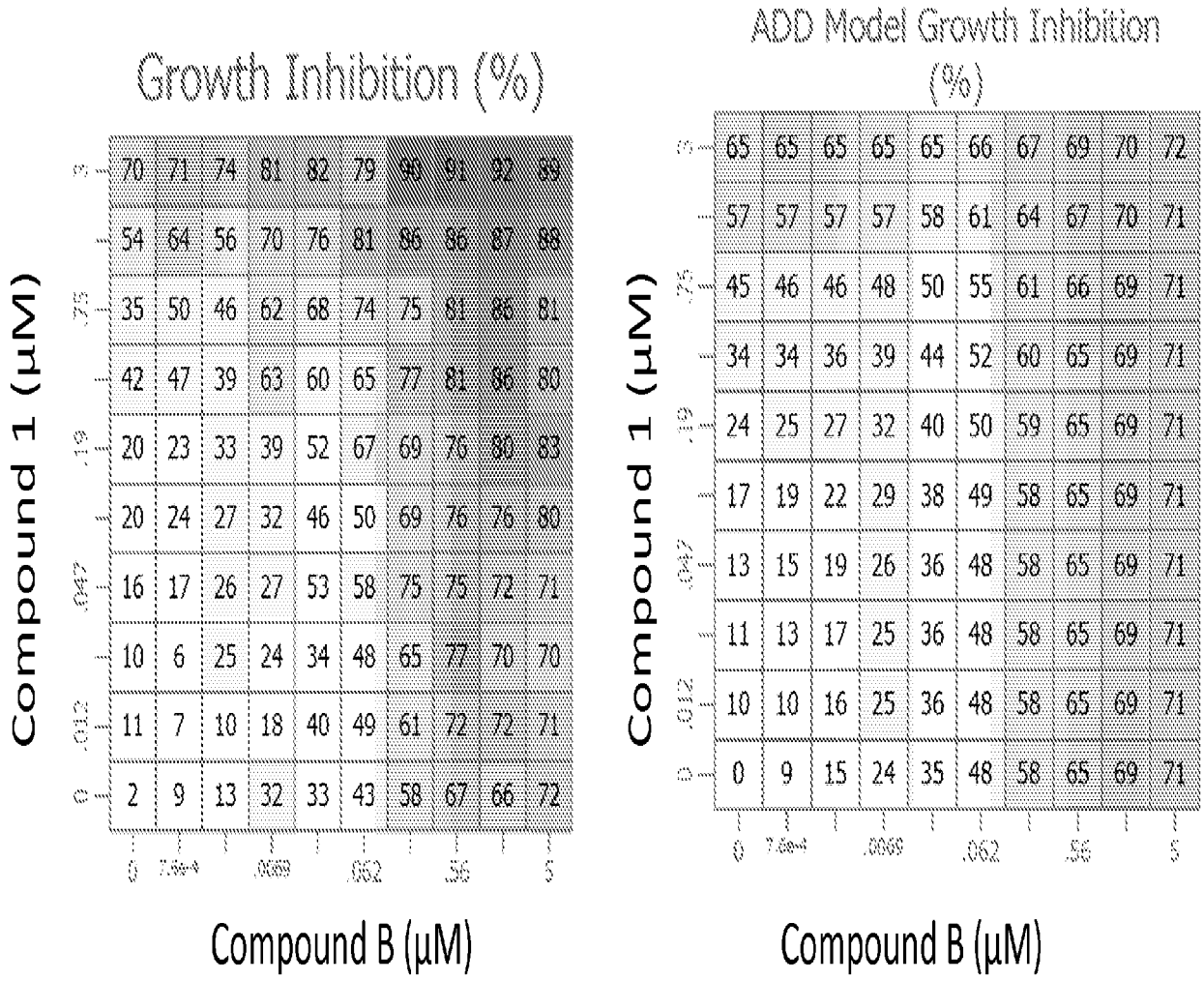
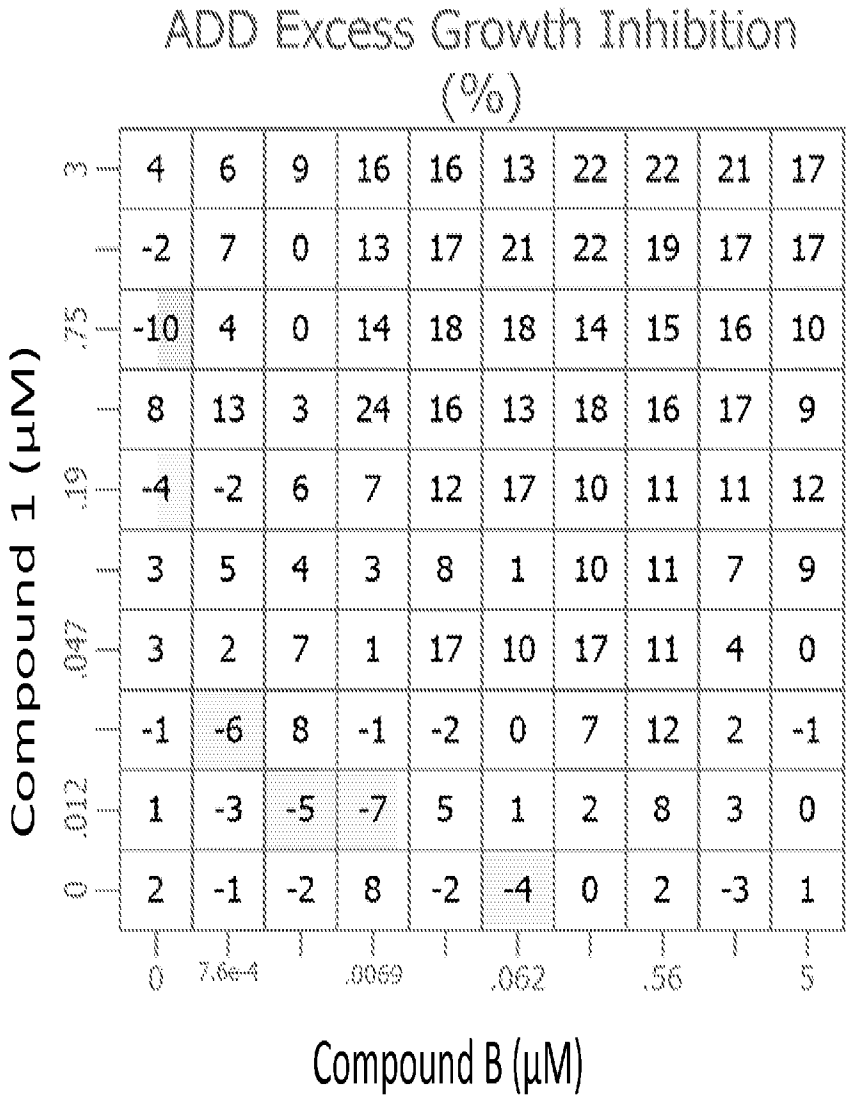


Figure 9a-Example 9; NCI-H1666 cells



	Synergy Score
B x 1	4.3
B self-cross	0.117
1 self-cross	0.532

Figure 10-Example 10; NCI-H1666 cells

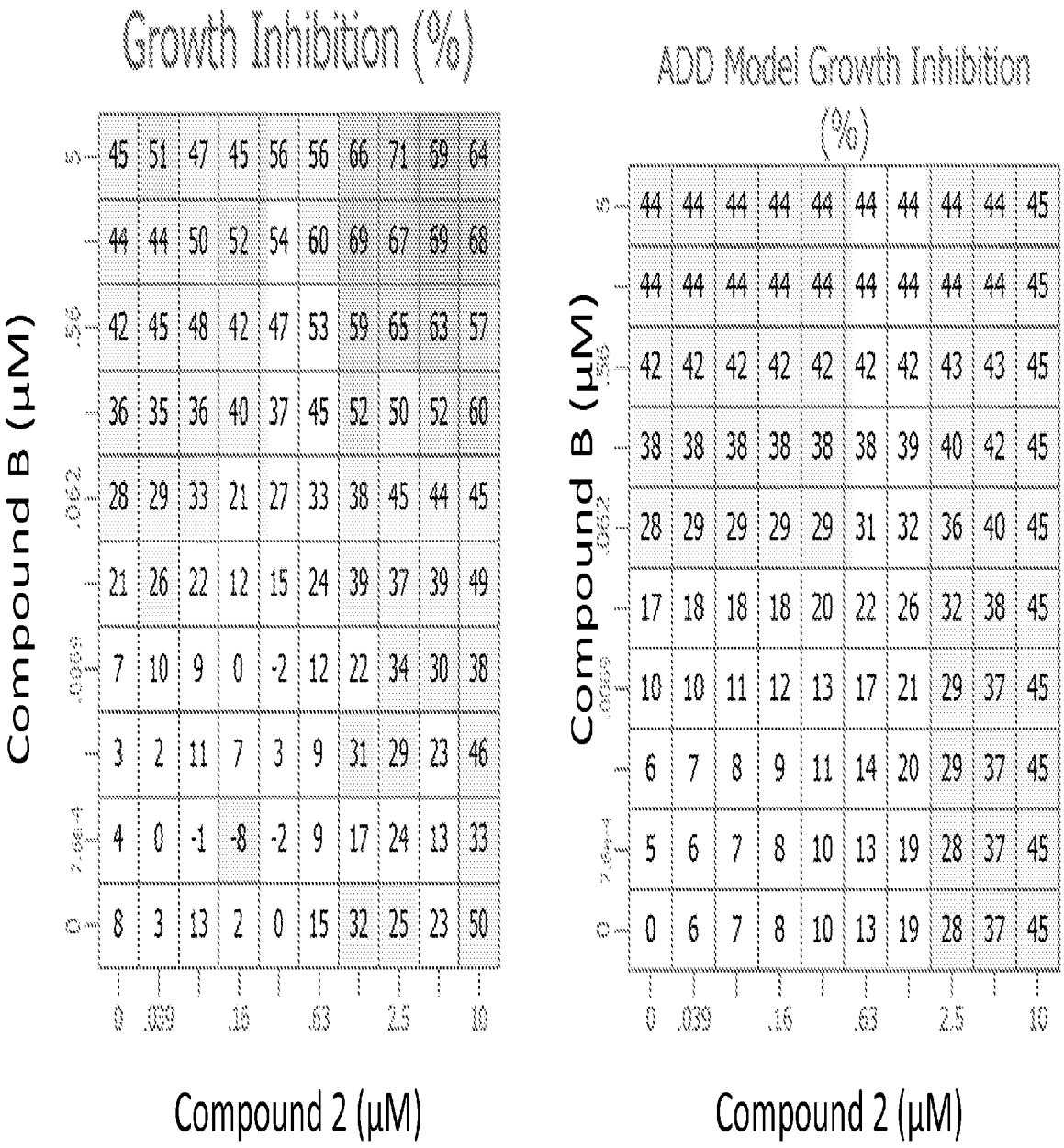
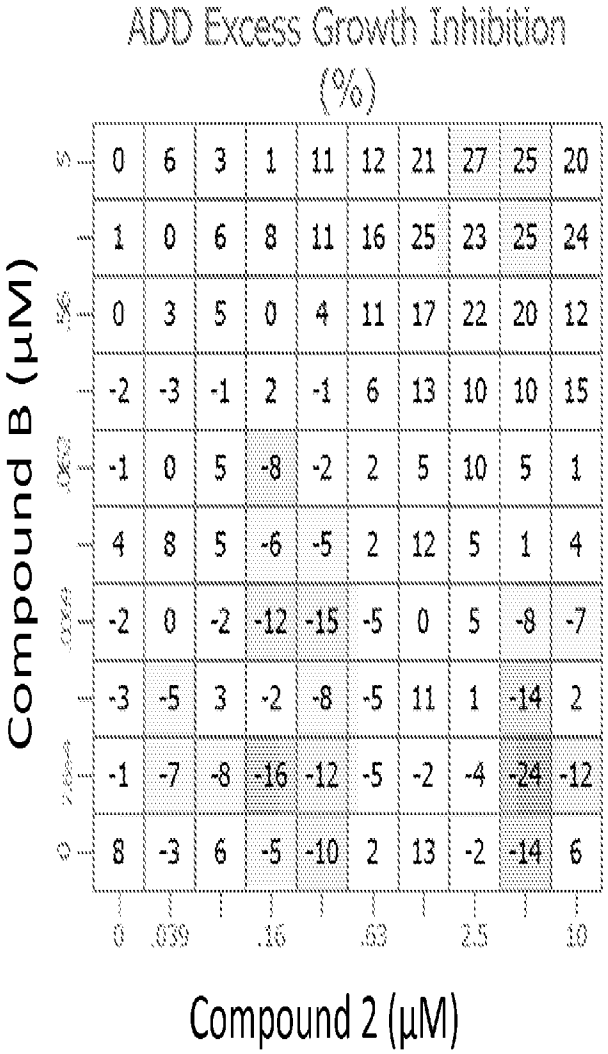


Figure 10a-Example 10; NCI-H1666 cells



B x 2	2.18
B self-cross	0.117
2 self-cross	0.233

Figure 11-Example 11; RKO cells

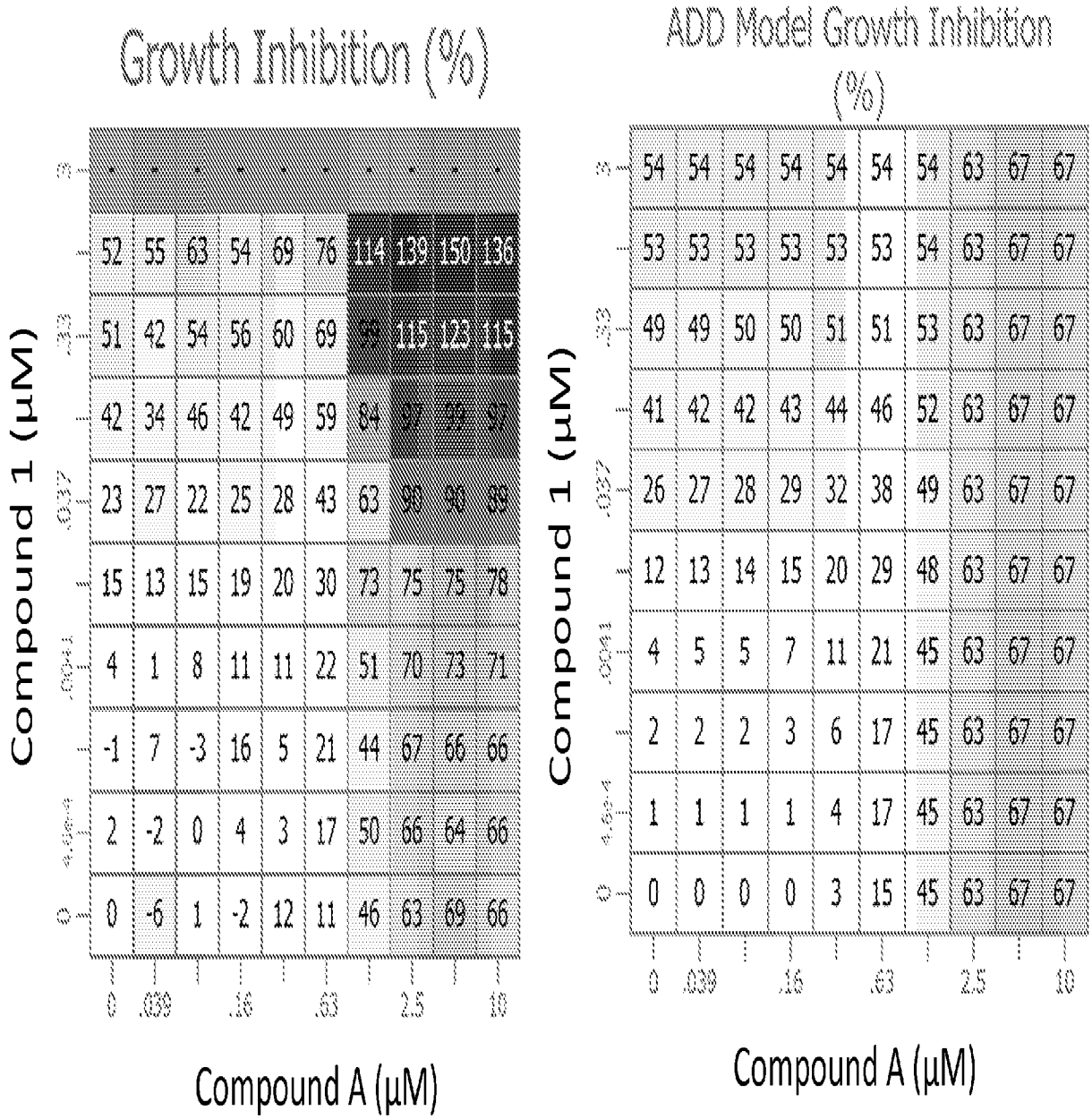
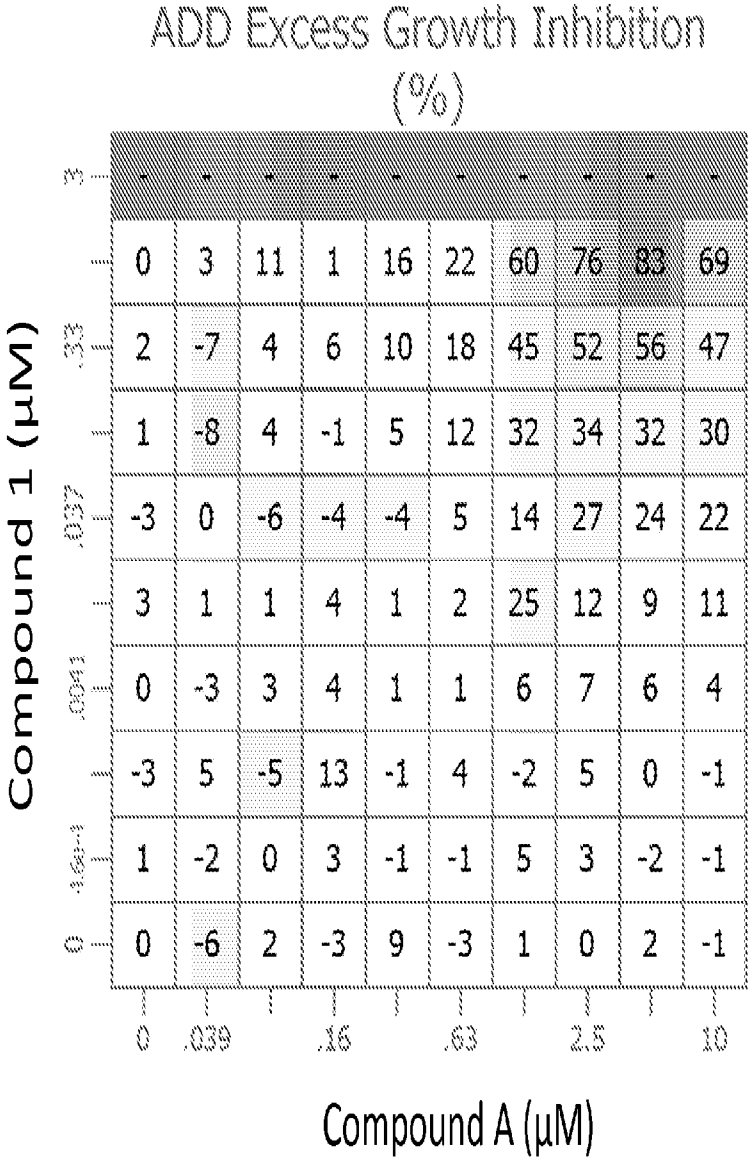
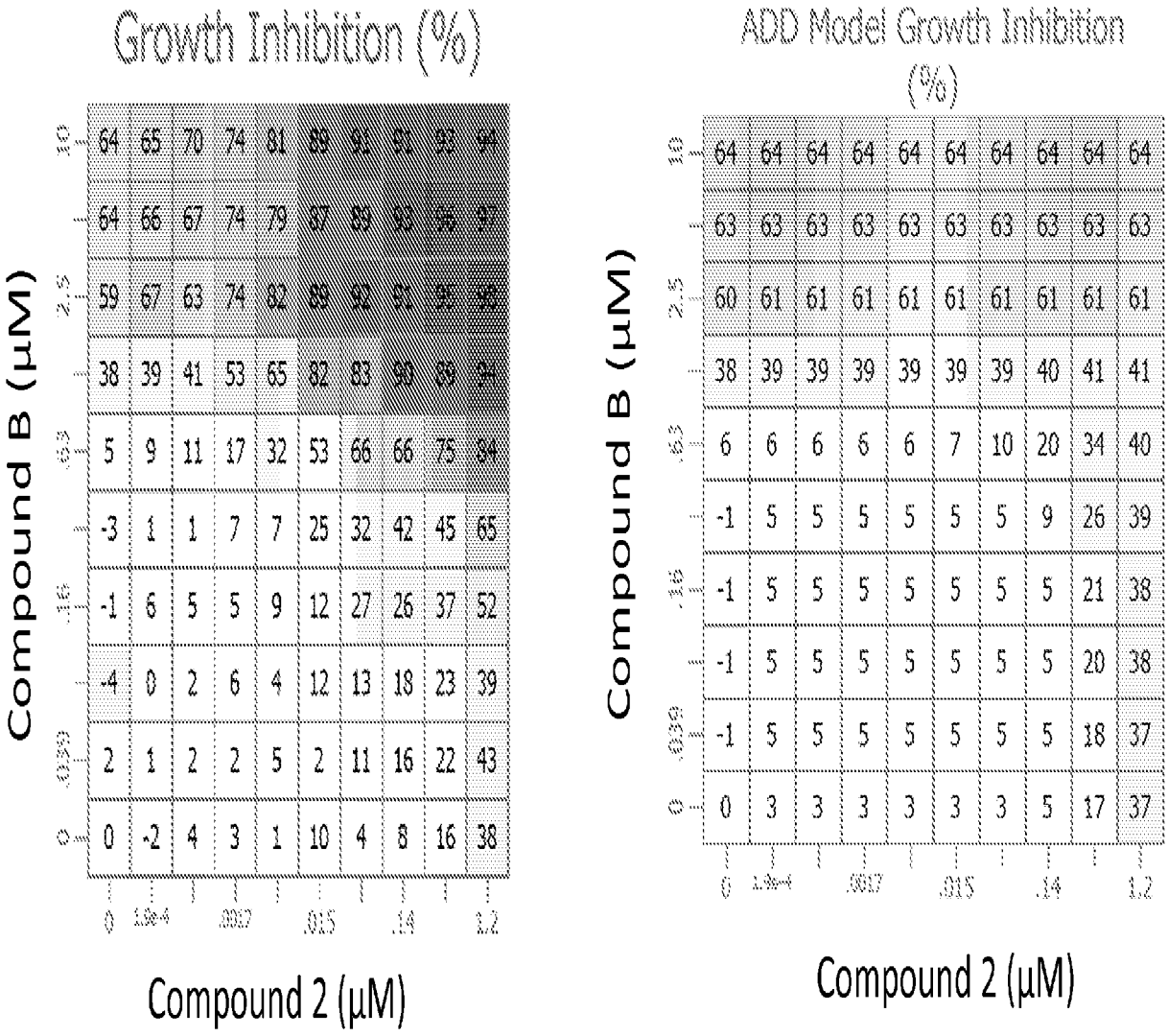


Figure 11a-Example 11; RKO cells

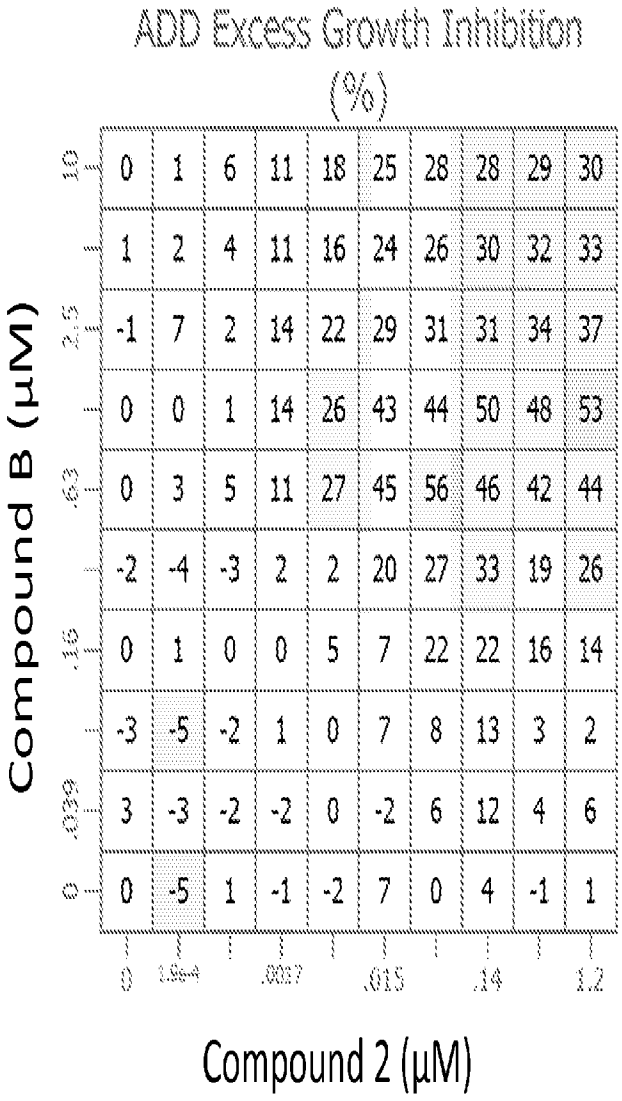


	Synergy Score
A x 1	8.21
A self-cross	0.235
1 self-cross	1.33

Figure 12-Example 12; RKO cells



Example 12a-Example 12; RKO cells



	Synergy Score
B x 2	7.6
B self-cross	0.154
2 self-cross	1.73

Figure 13-Example 13; RT4 cells

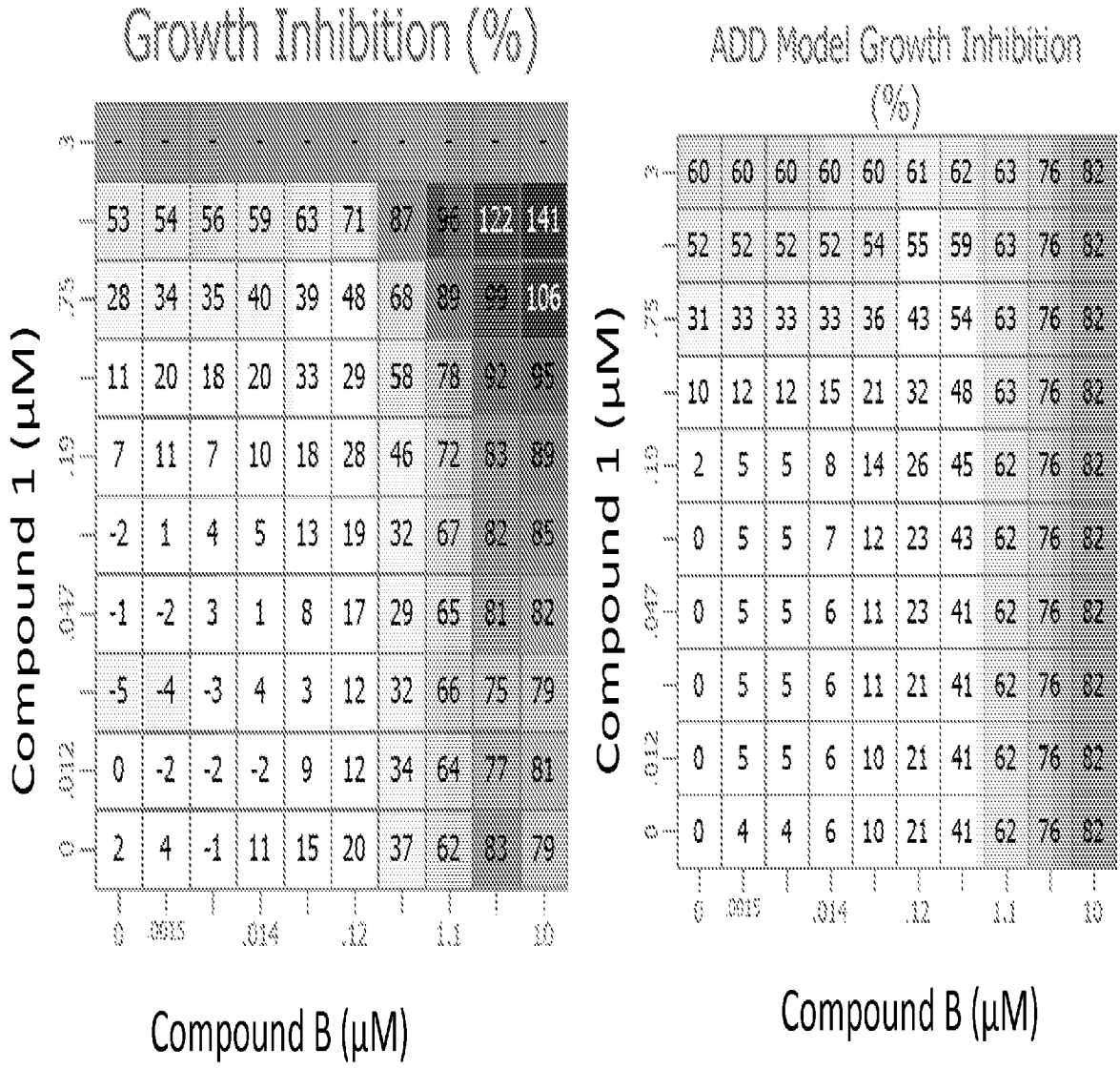
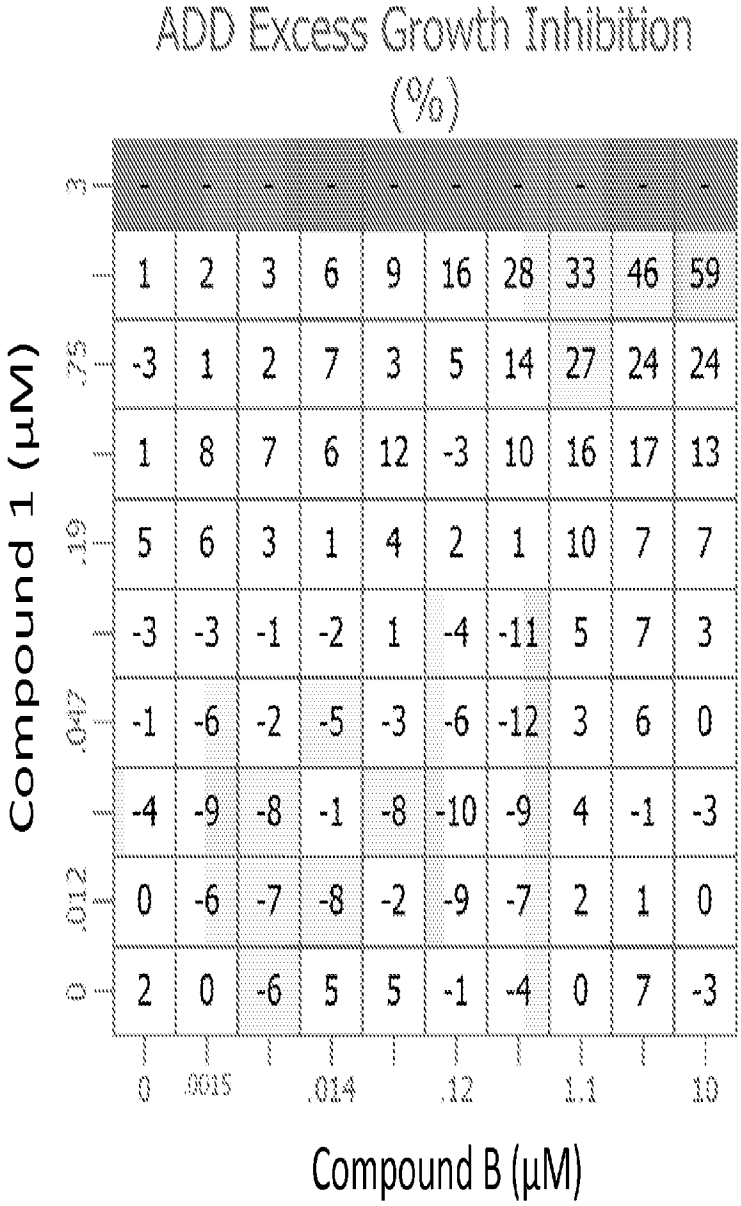


Figure 13a-Example 13; RT4 cells



	Synergy Score
B x 1	3.5
B self-cross	1.37
1 self-cross	0.835

Figure 14-Example 14; RT4 cells

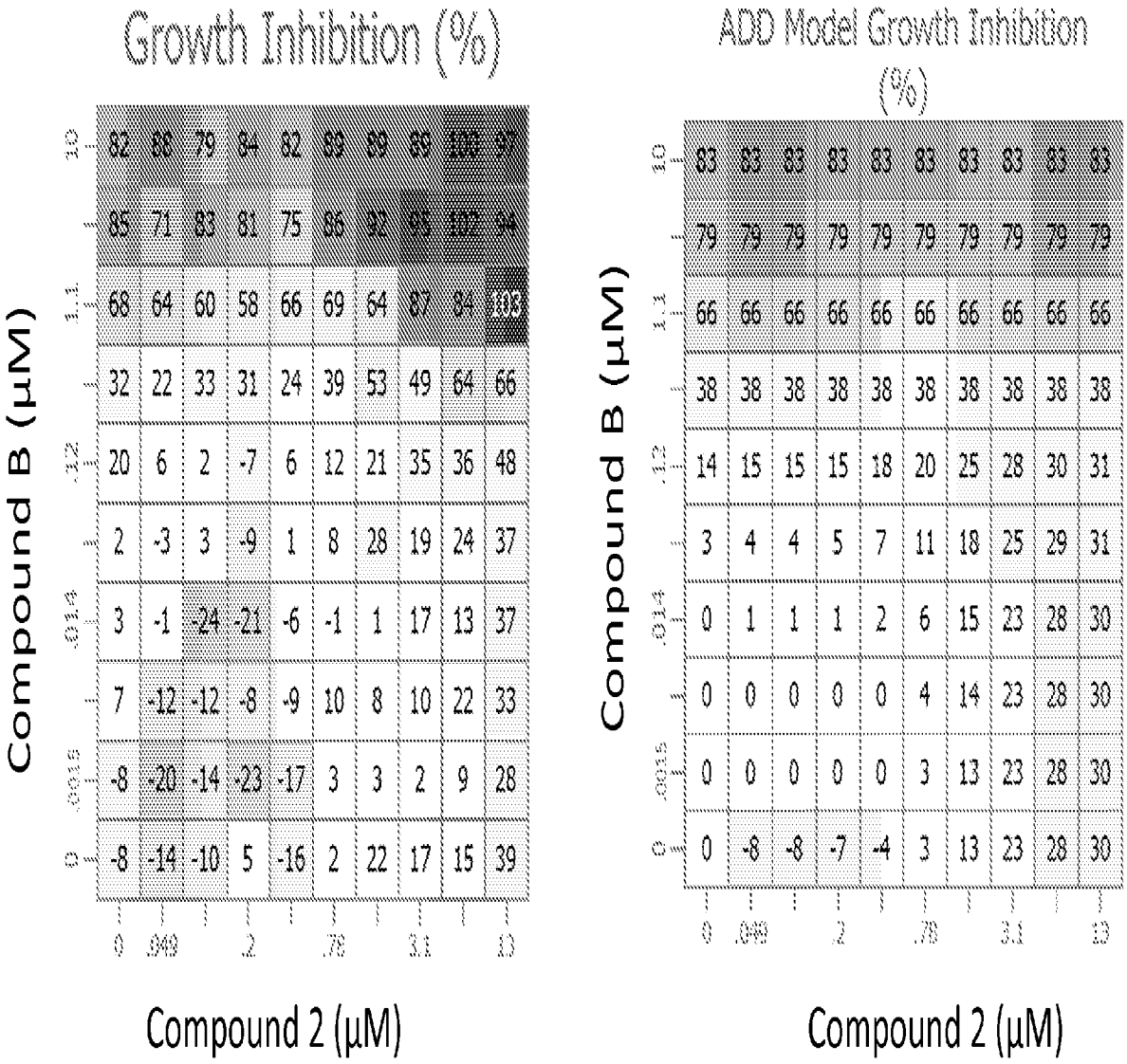
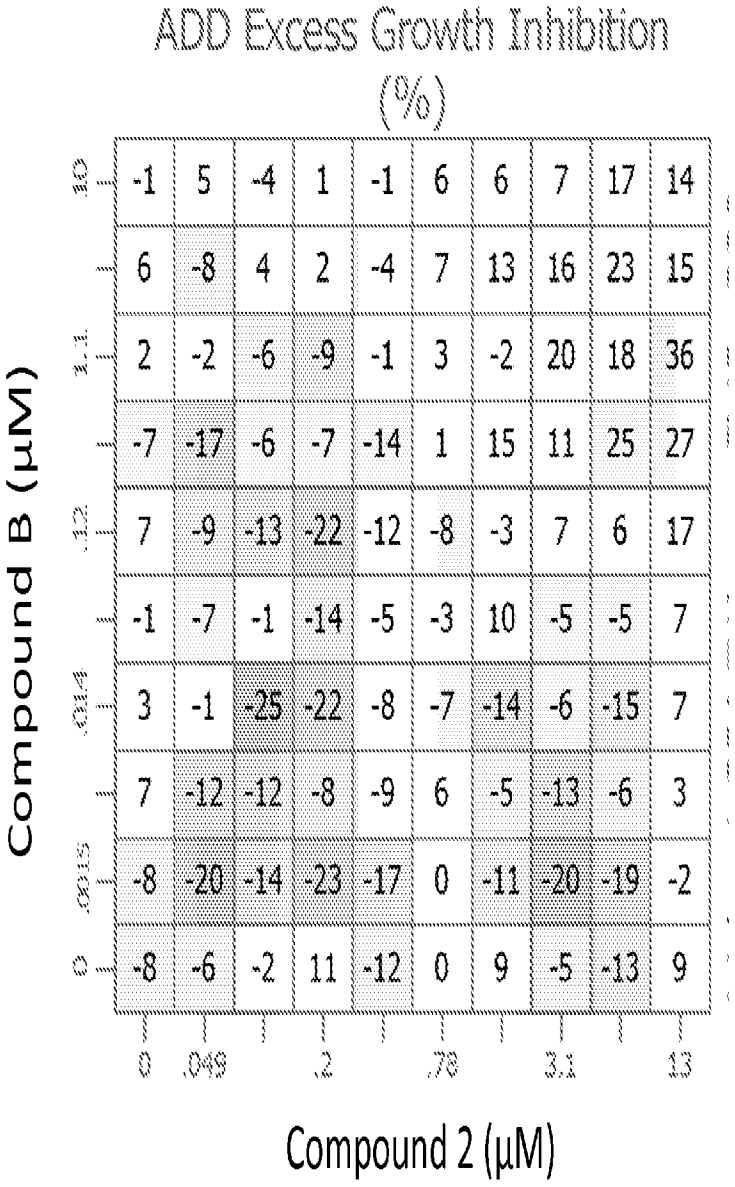


Figure 14a-Example 14; RT4 cells



	Synergy Score
B x 2	2.05
B self-cross	1.33
2 self-cross	0.405

Figure 15-Example 15; SH-4 cells

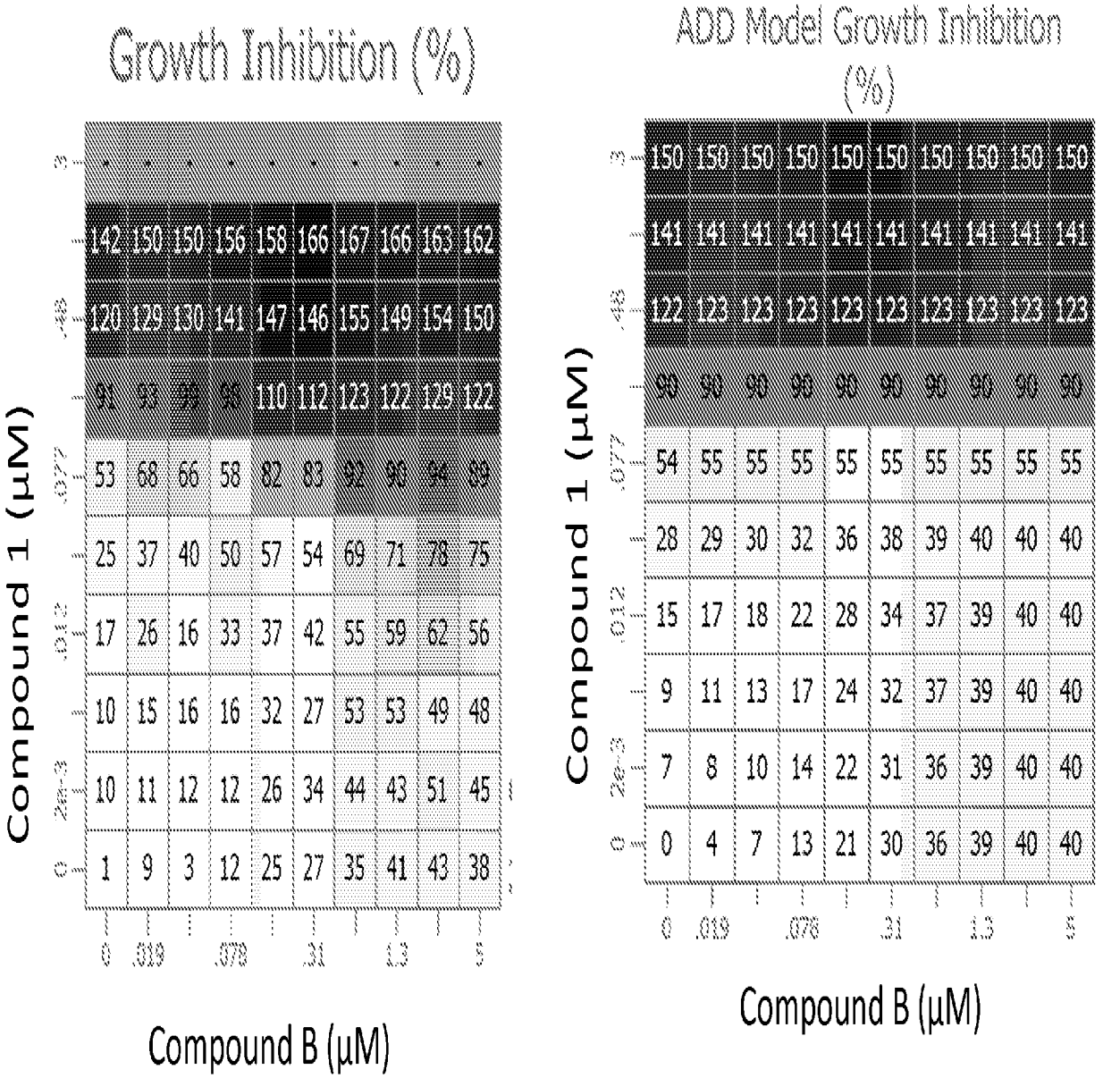
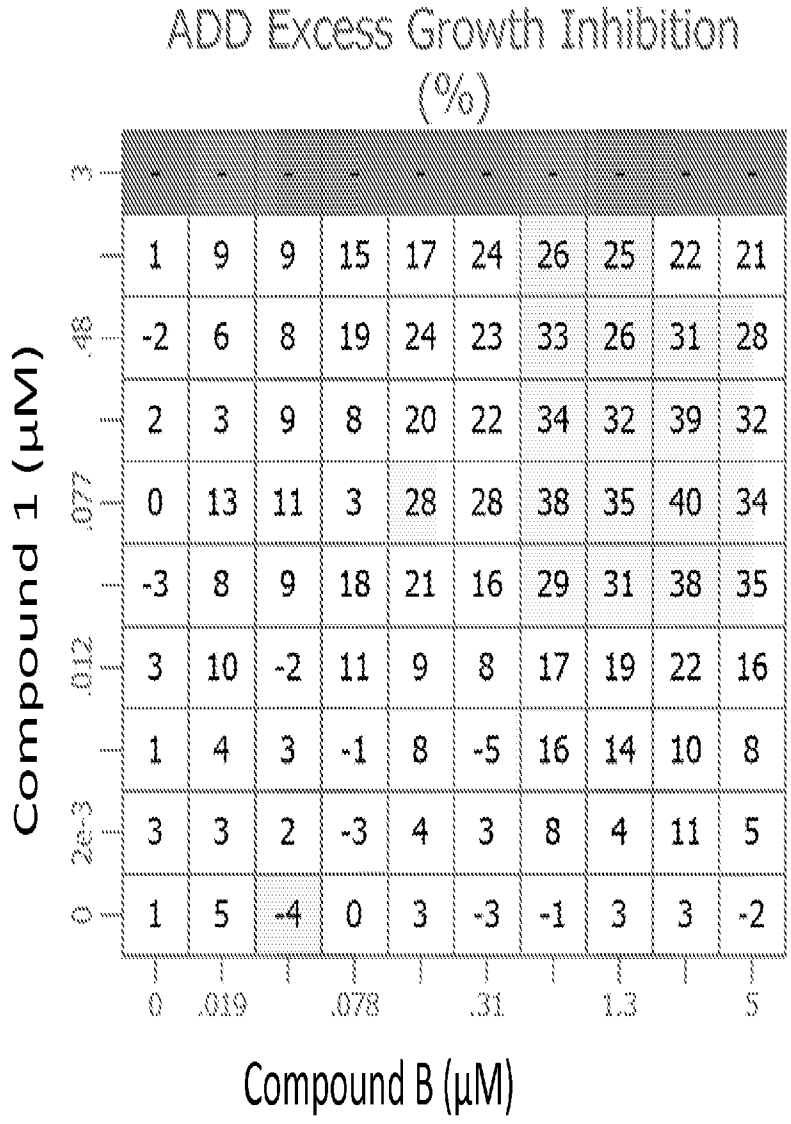


Figure 15a-Example 15; SH-4 cells



	Synergy Score
B x 1	8.84
B self-cross	0.259
1 self-cross	2.21

Figure 16-Example 16; SH-4 cells

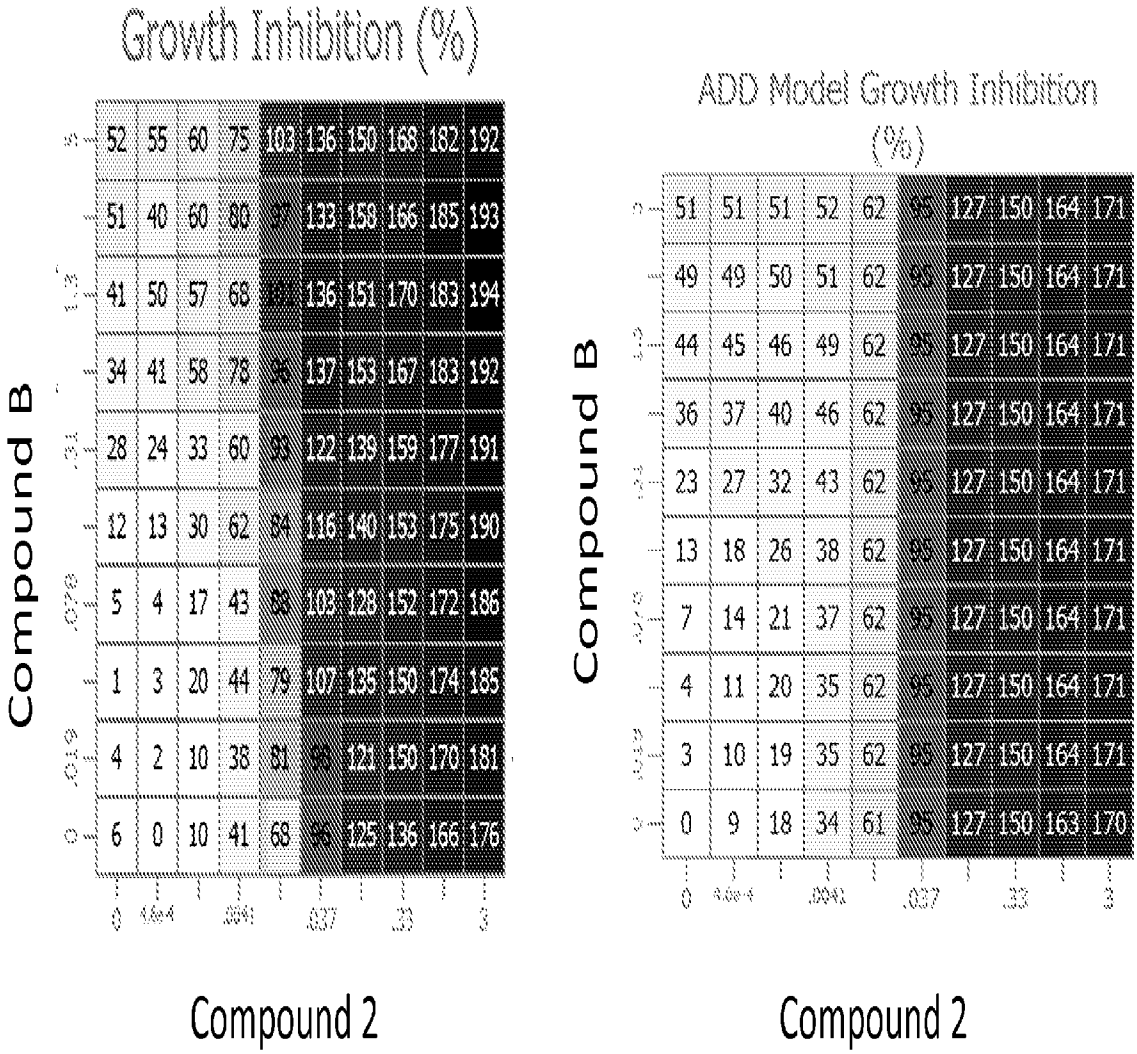
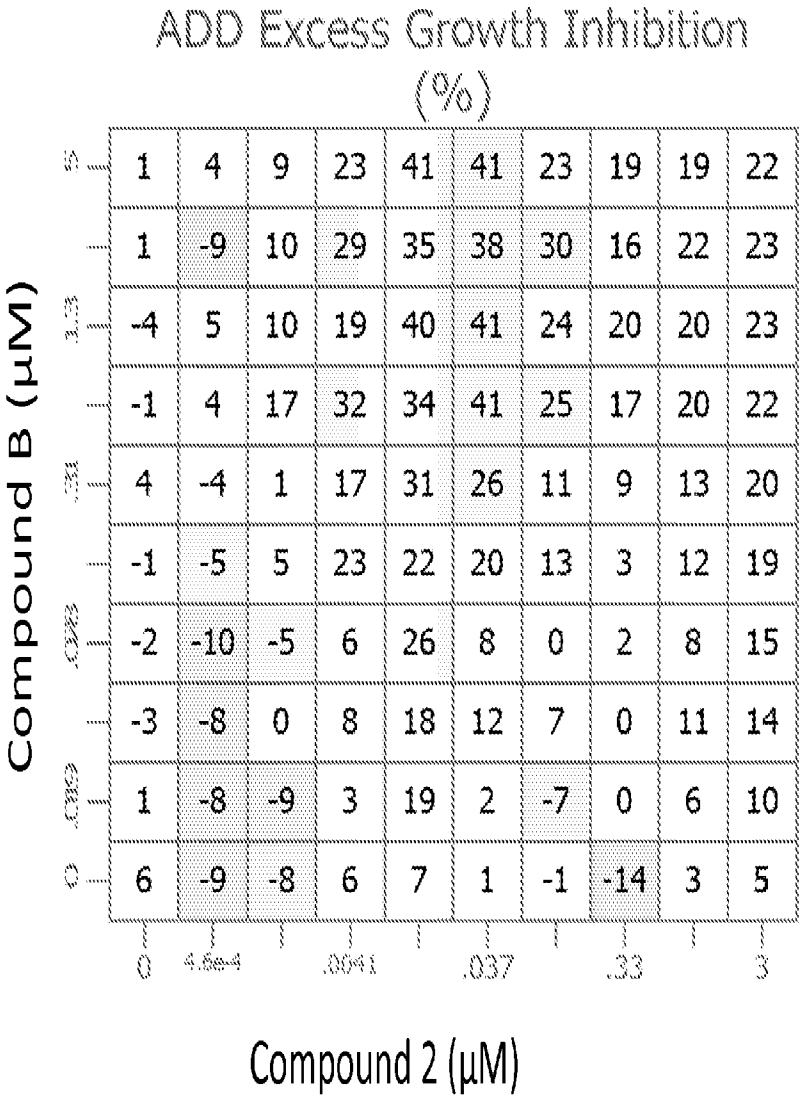


Figure 16a-Example 16; SH-4 cells



	Synergy Score
B x 2	12.1
B self-cross	0.29
2 self-cross	2.71

Figure 17-Example 17; SK-HEP-1

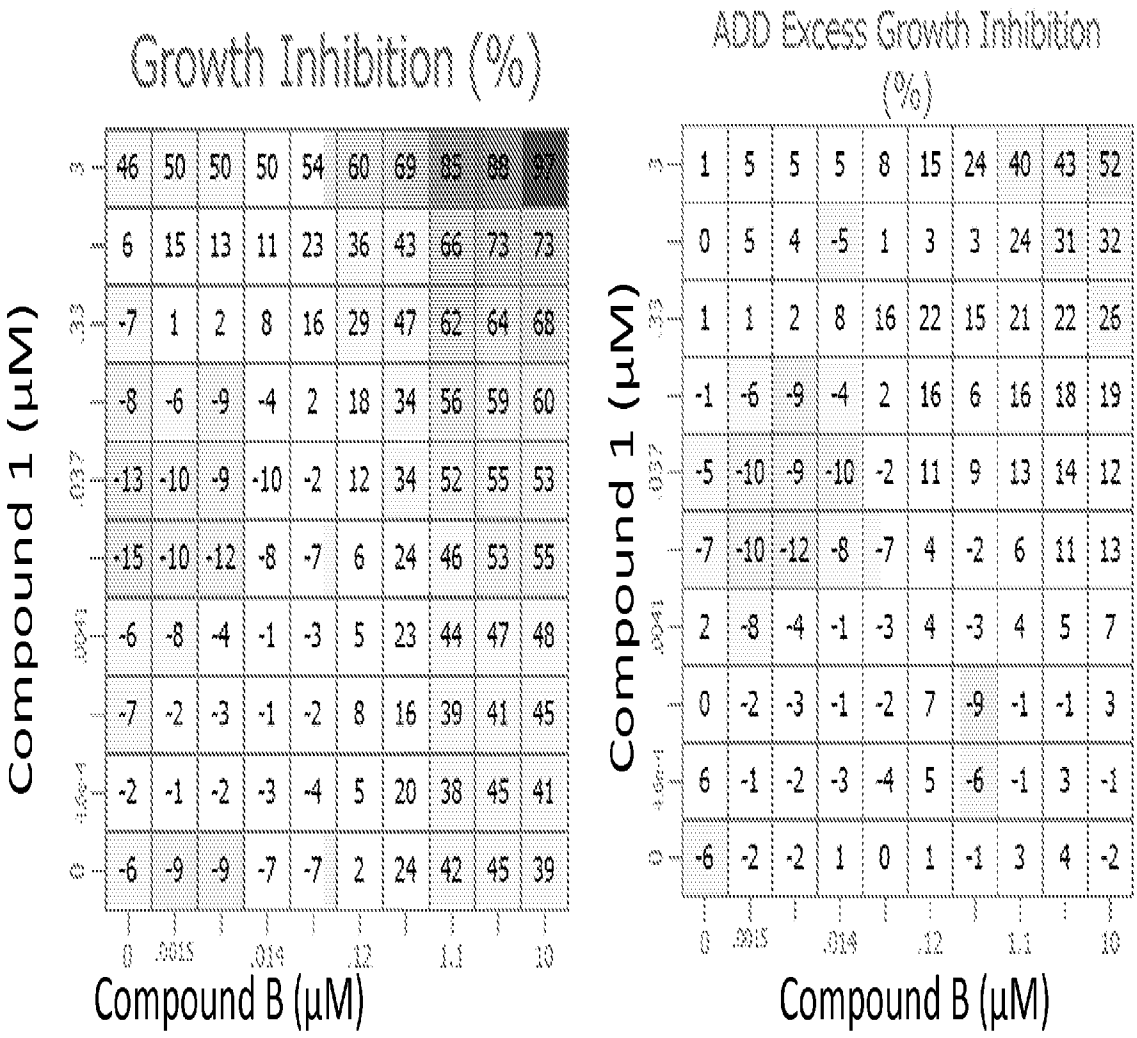
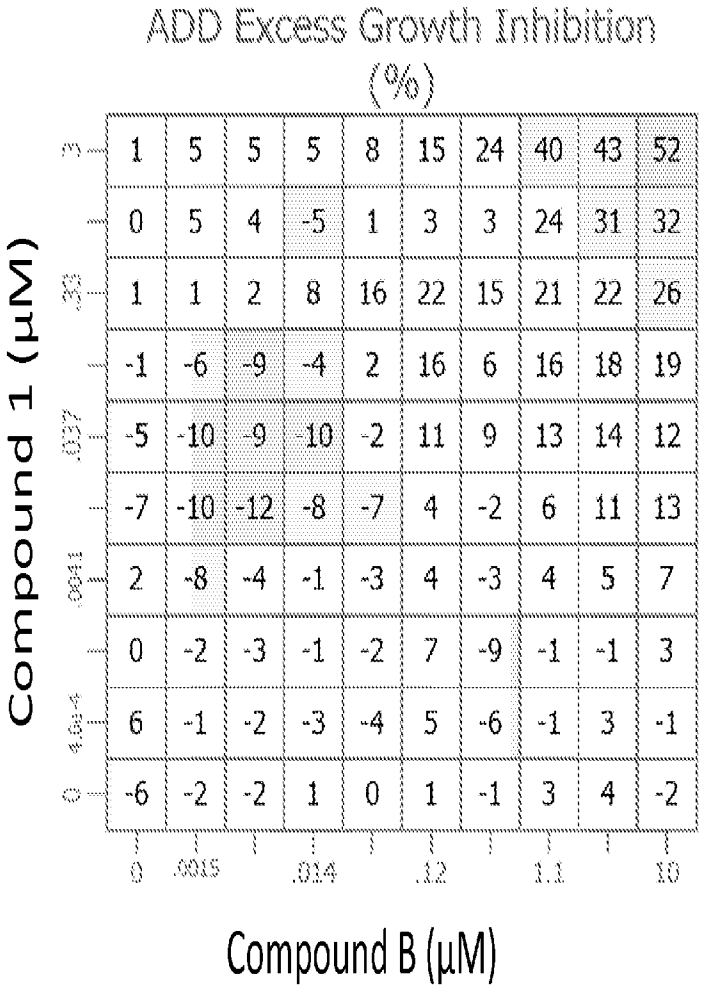


Figure 17a-Example 17; SK-HEP-1



	Synergy Score
B x 1	4.51
B self-cross	0.886
1 self-cross	0.923

Figure 18-Example 18; SK-HEP-1 cells

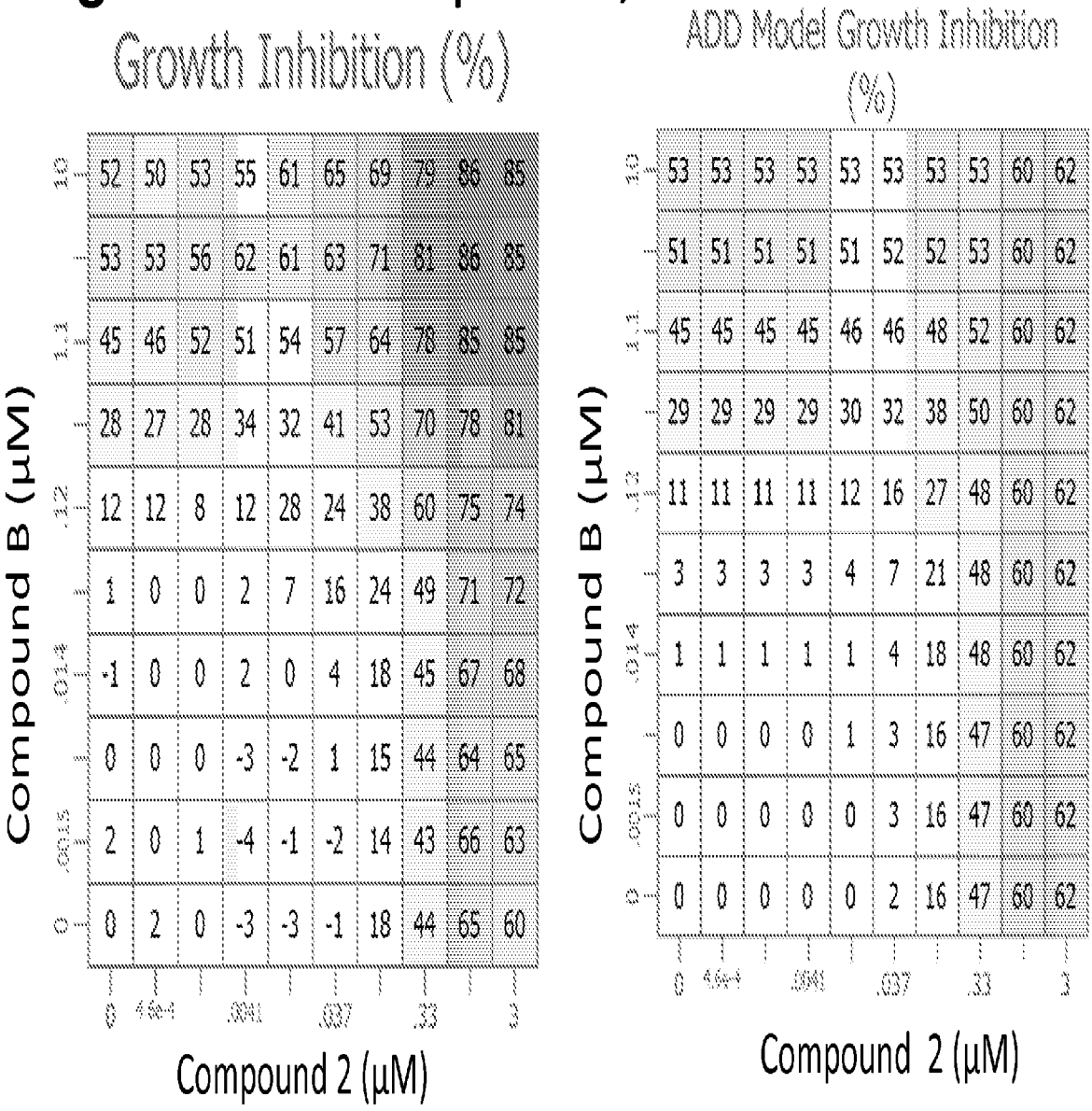
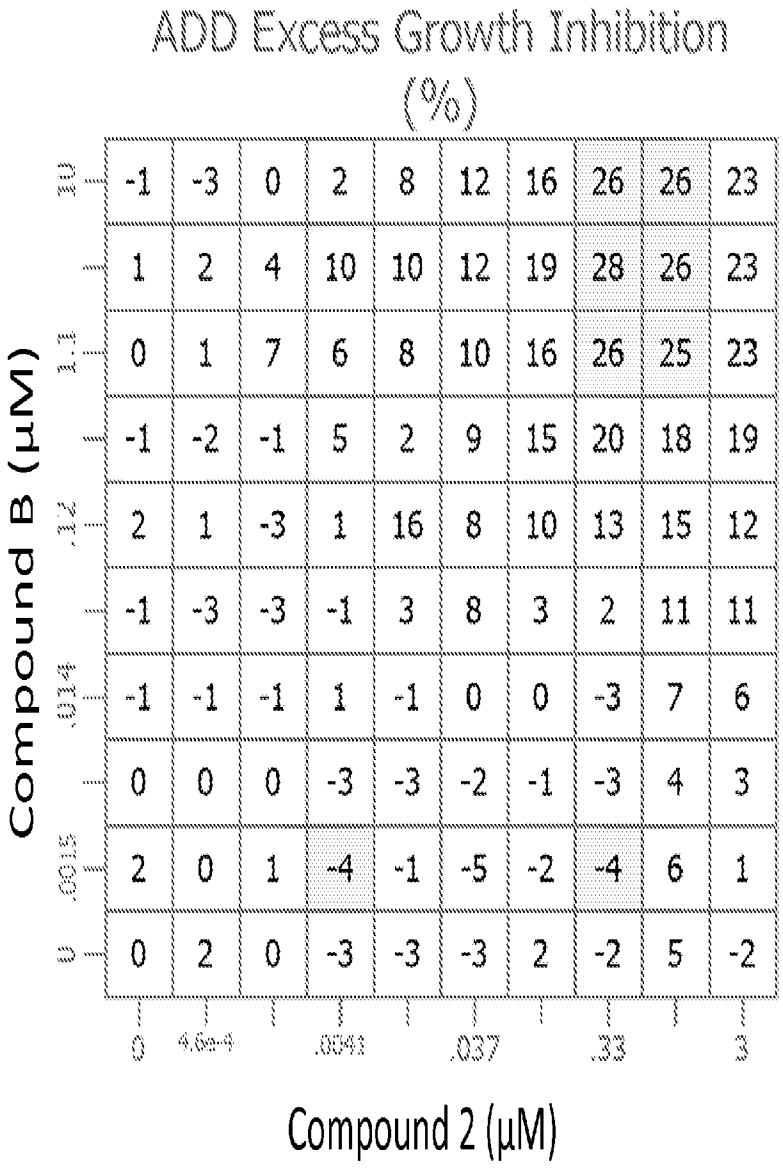


Figure 18a-Example 18; SK-HEP-1 cells



	Synergy Score
B x 2	4.95
B self-cross	0.827
2 self-cross	0.738

Figure 19-Example 19; A204 cells

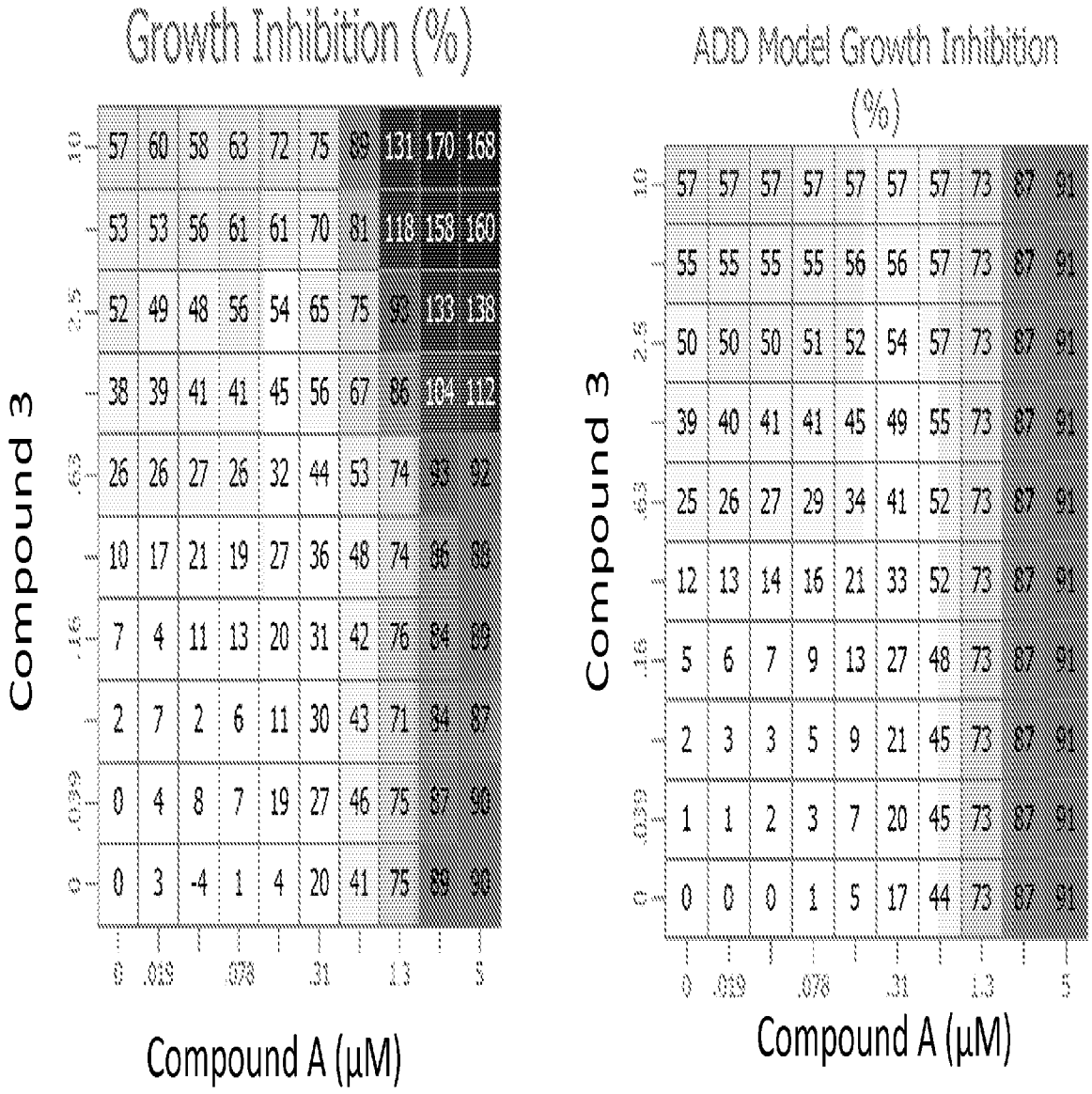
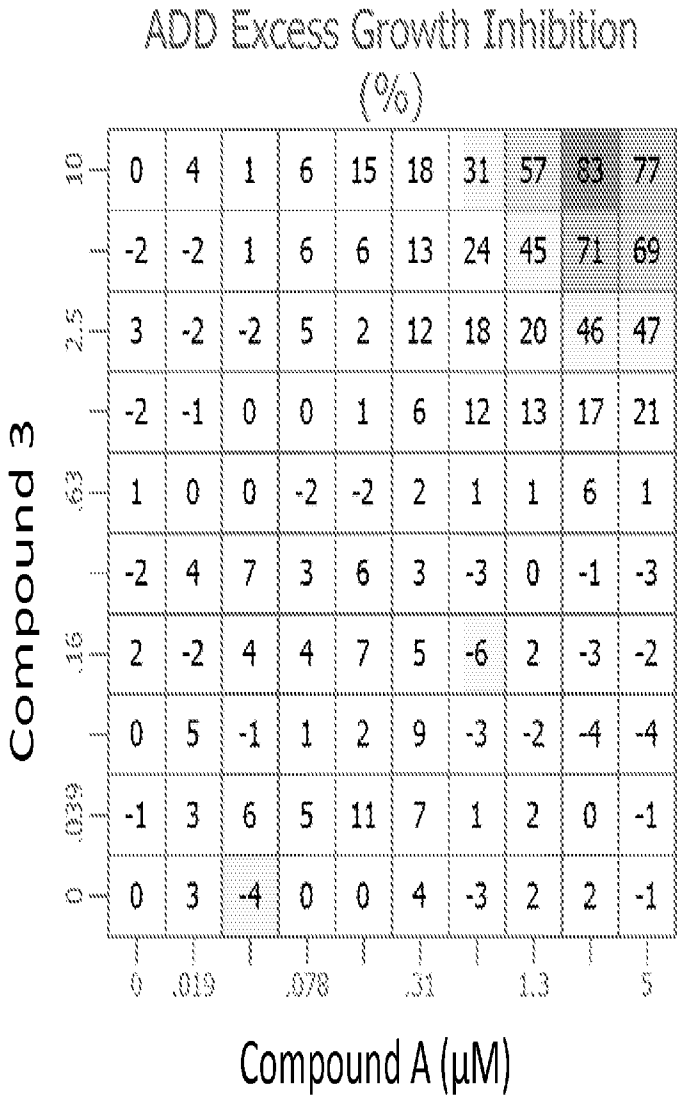


Figure 19a-Example 19; A204 cells



	Synergy Score
A x 3	4.71
A self-cross	0.621
3 self-cross	0.278

Figure 20-Example 20; A375sq2 cells

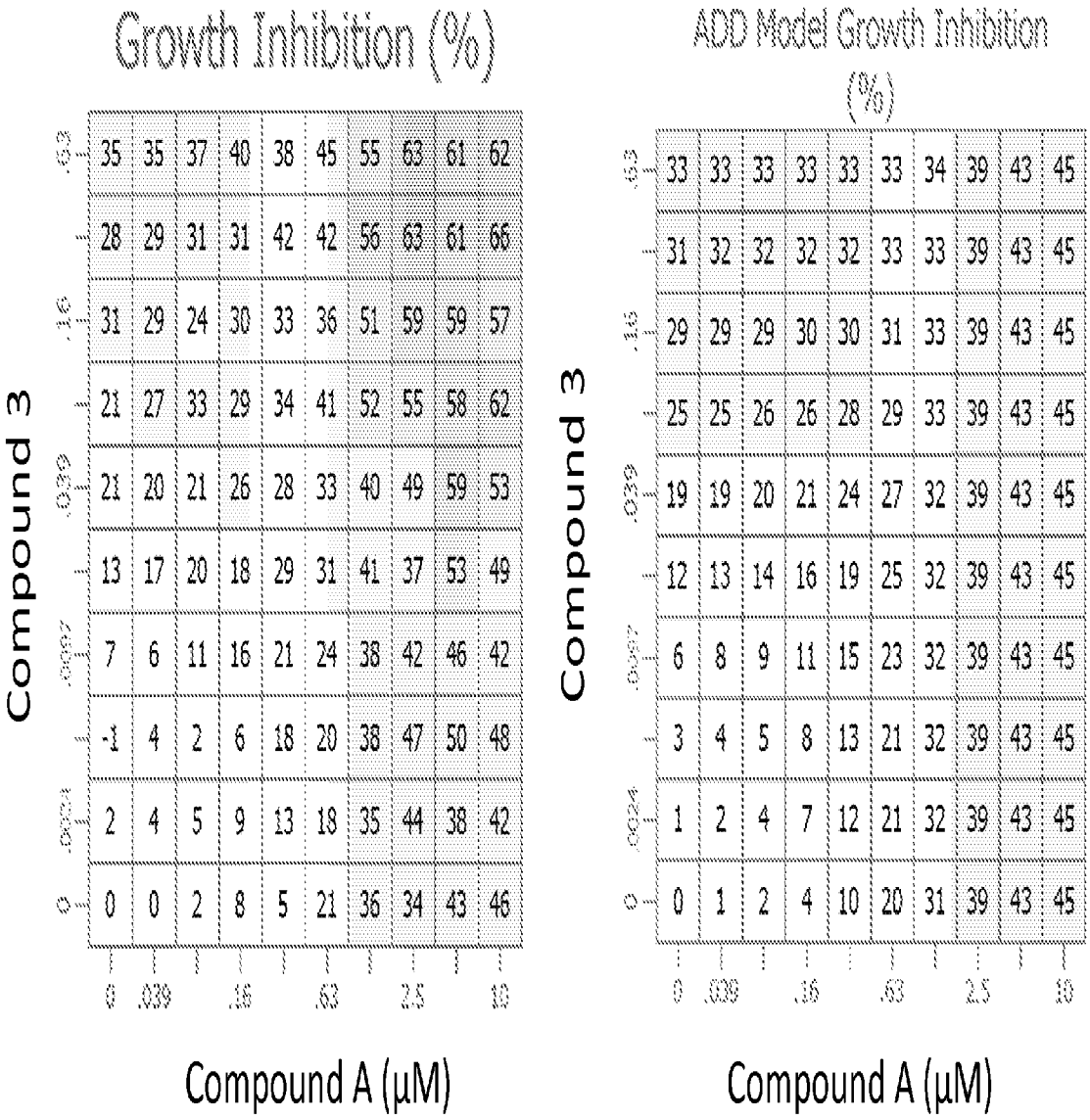
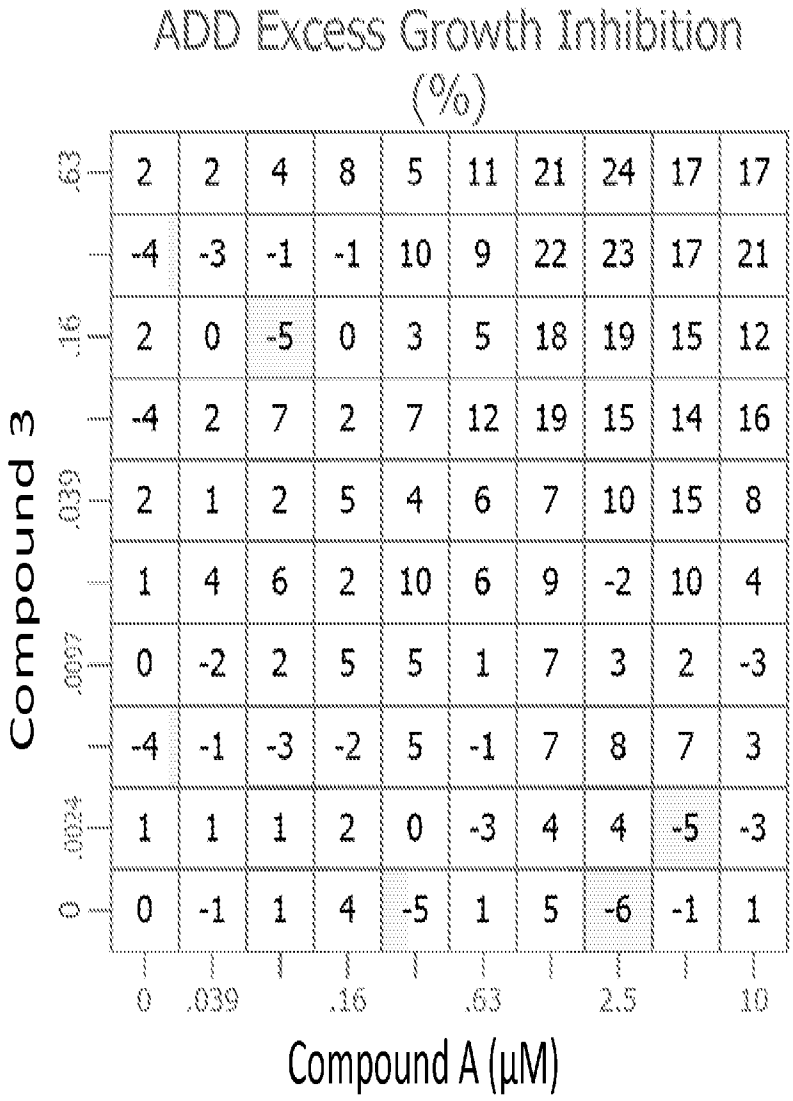


Figure 20a-Example 20; A375sq2 cells



	Synergy Score
A x 3	1.3
A self-cross	0.333
3 self-cross	0.101

Figure 21-Example 21; A-427 cells

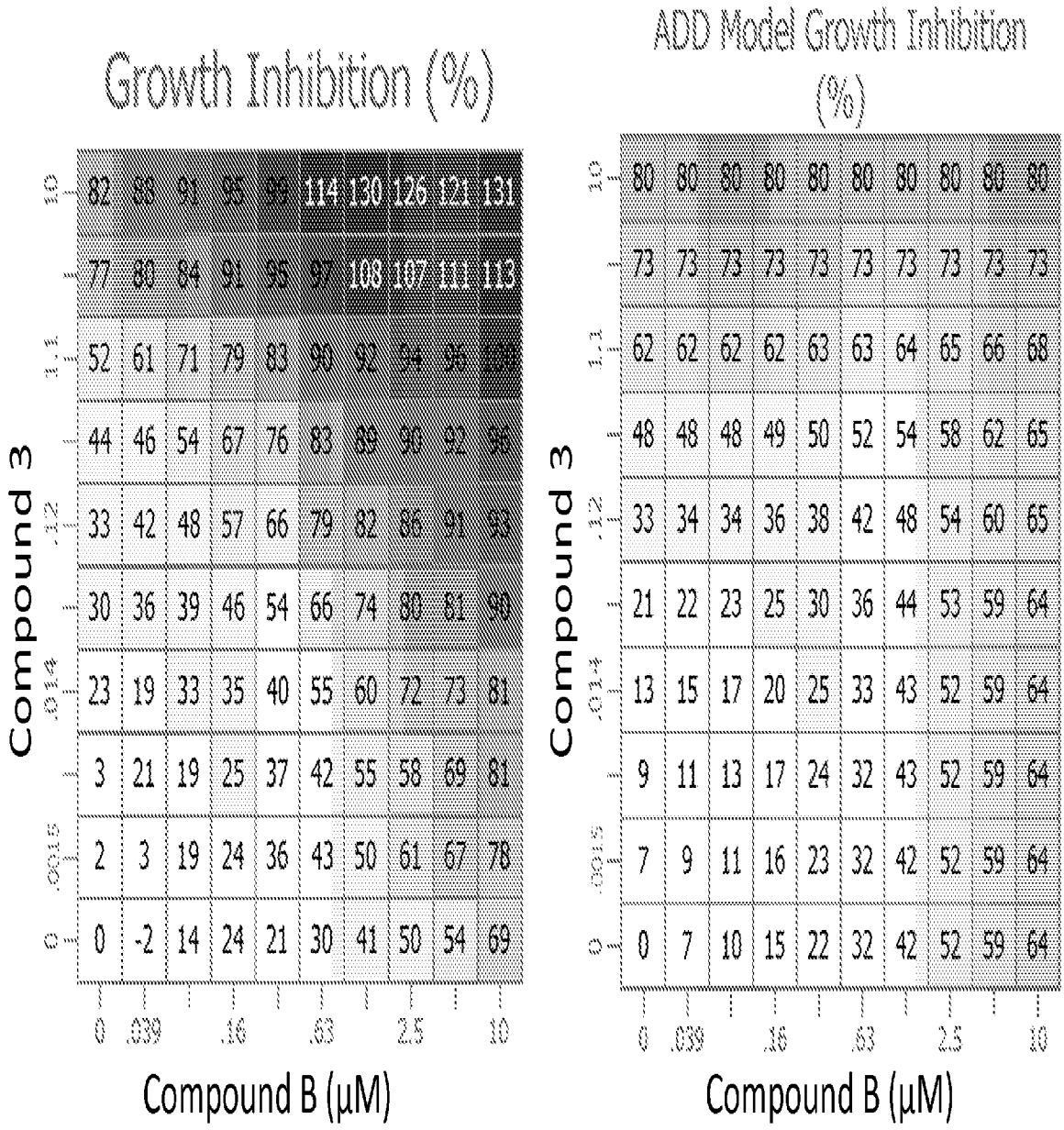
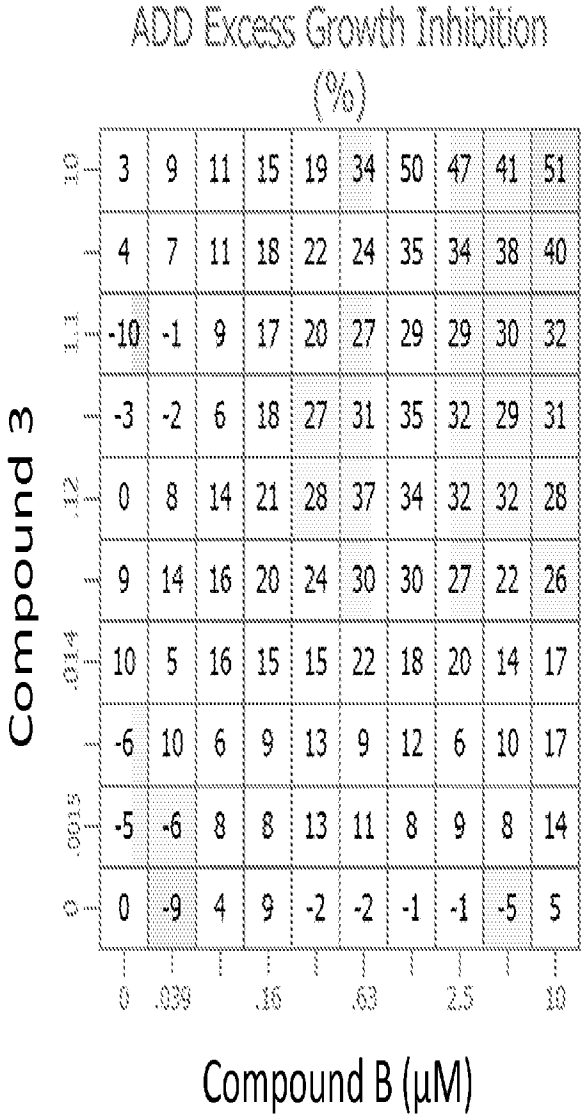


Figure 21a-Example 21; A-427 cells



	Synergy Score
B x 3	10.7
B self-cross	0.712
3 self-cross	1.34

Figure 22-Example 22; A-427 cells

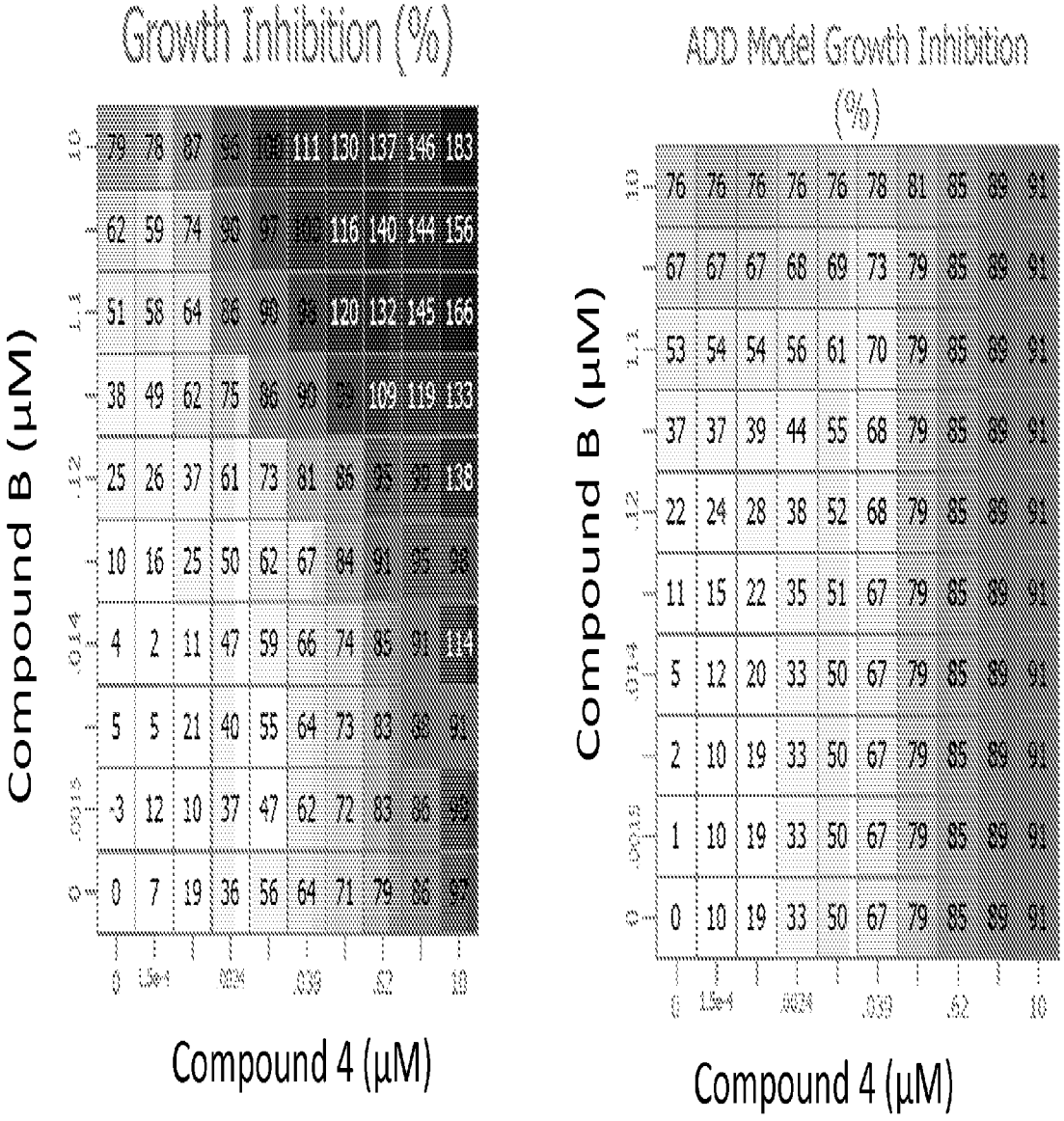
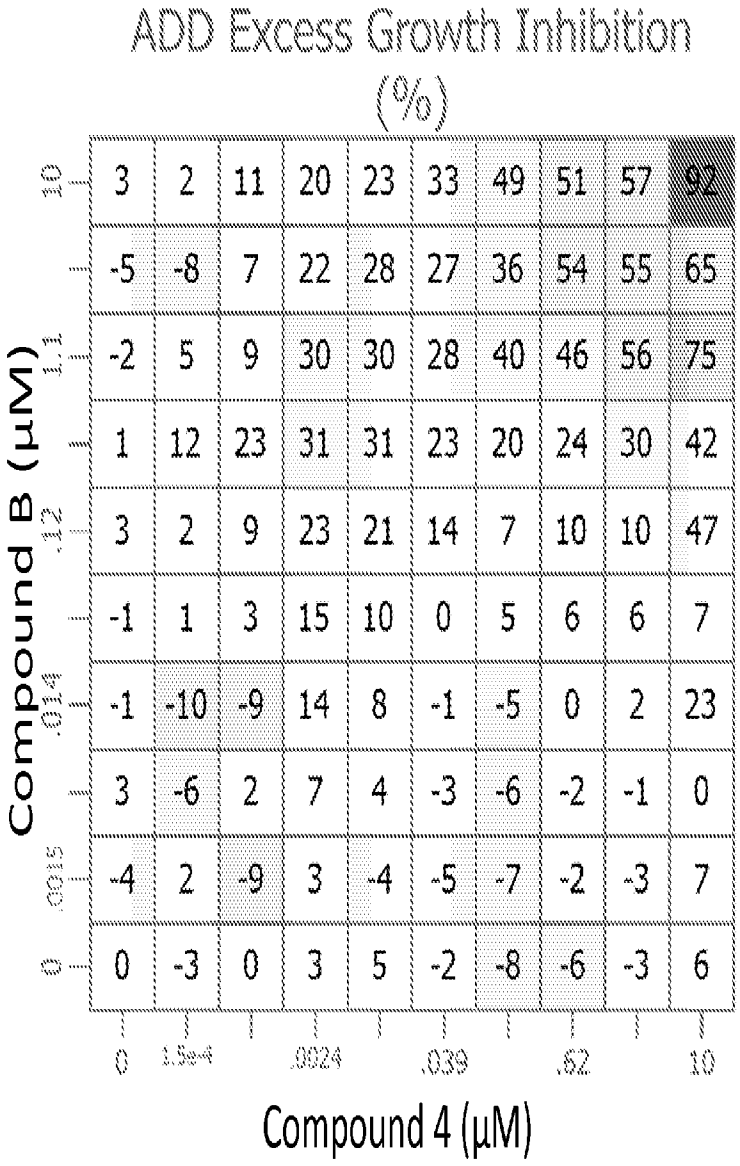


Figure 22a-Example 22; A-427 cells



	Synergy Score
B x4	26
B self-cross	1.67
4 self-cross	3.27

Figure 23-Example 23; C32 cells

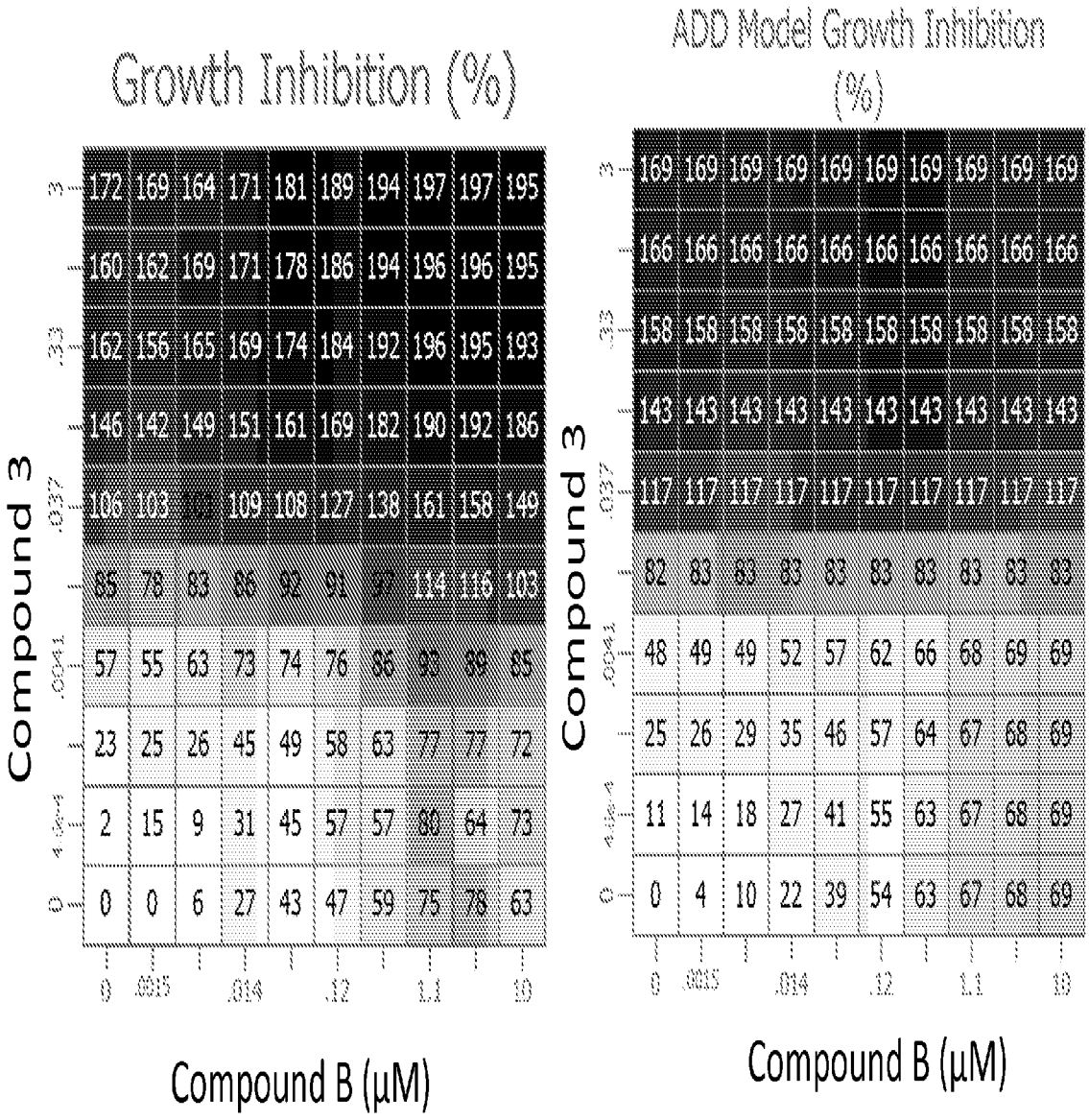
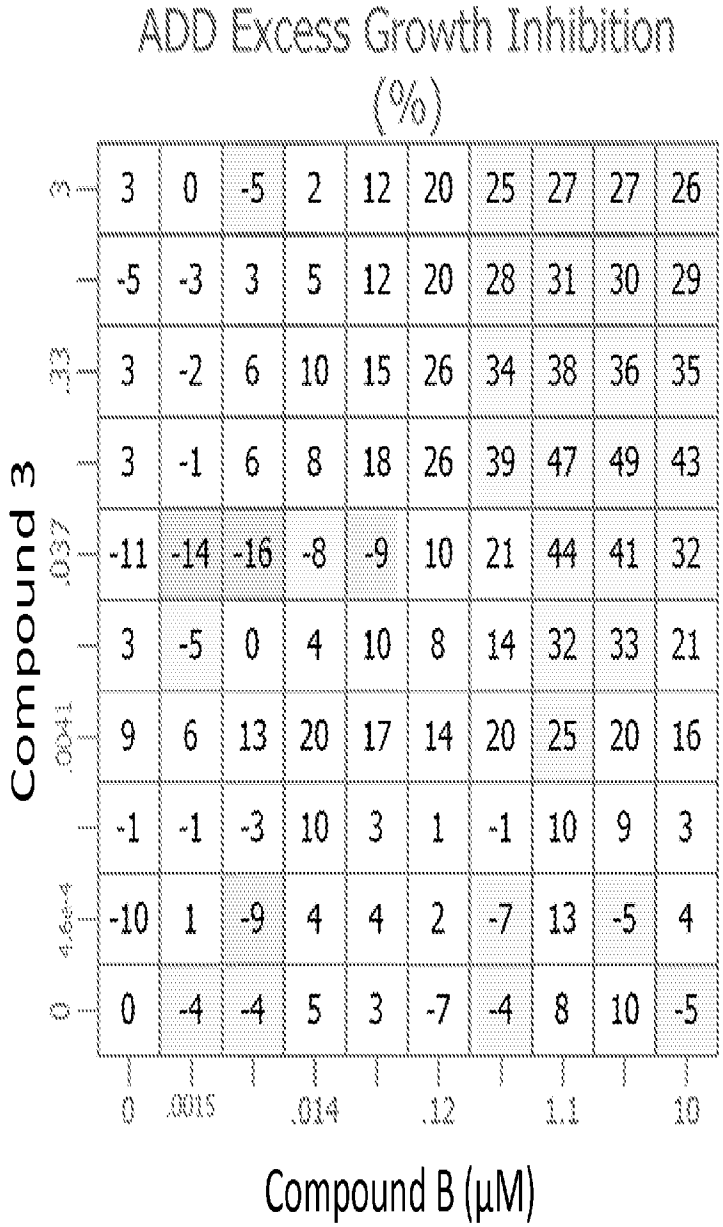


Figure 23a-Example 23; C32 cells



	Synergy Score
B x 3	22.9
B self-cross	0.886
3 self-cross	4.69

Figure 24-Example 24; C32 cells

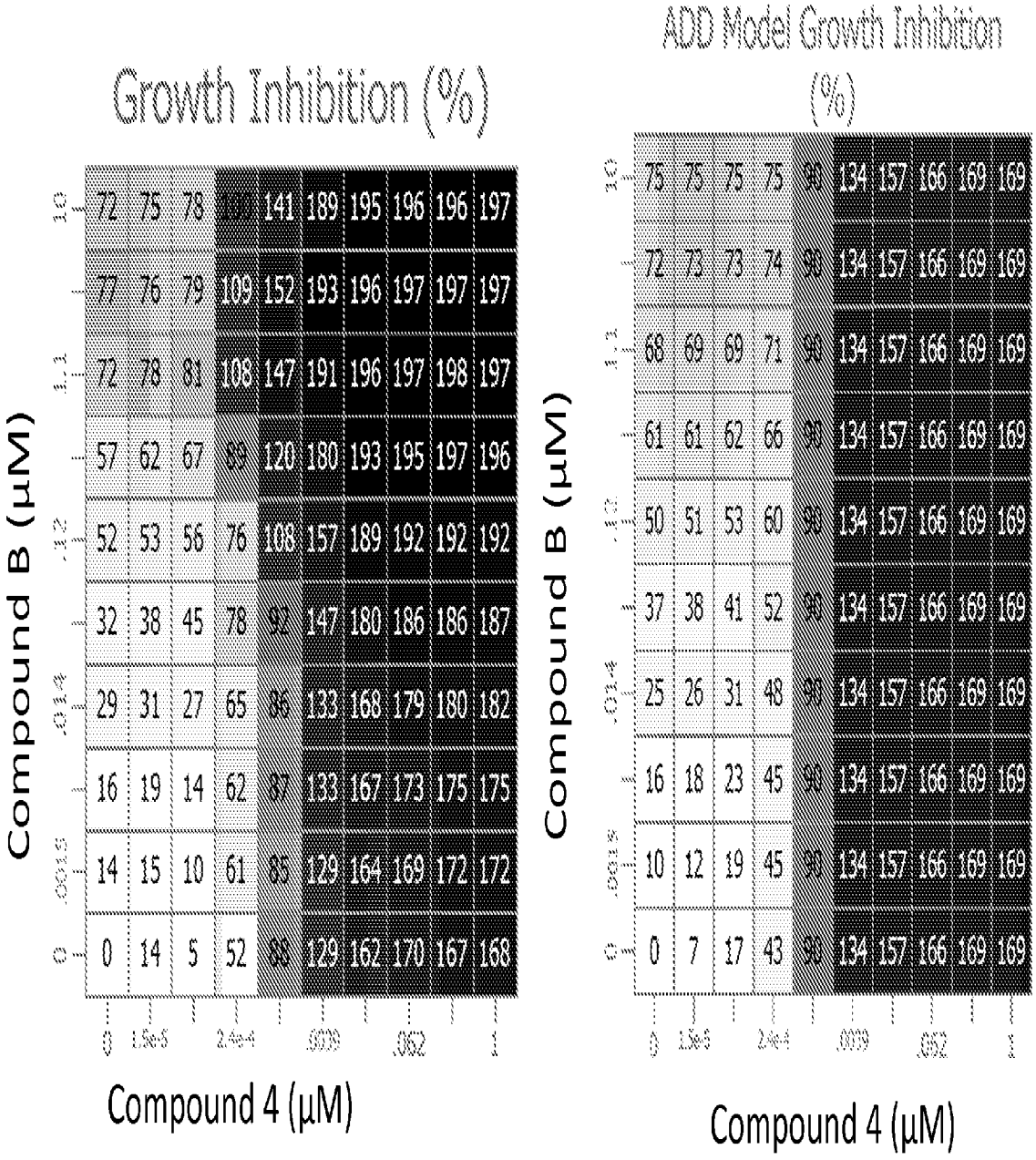
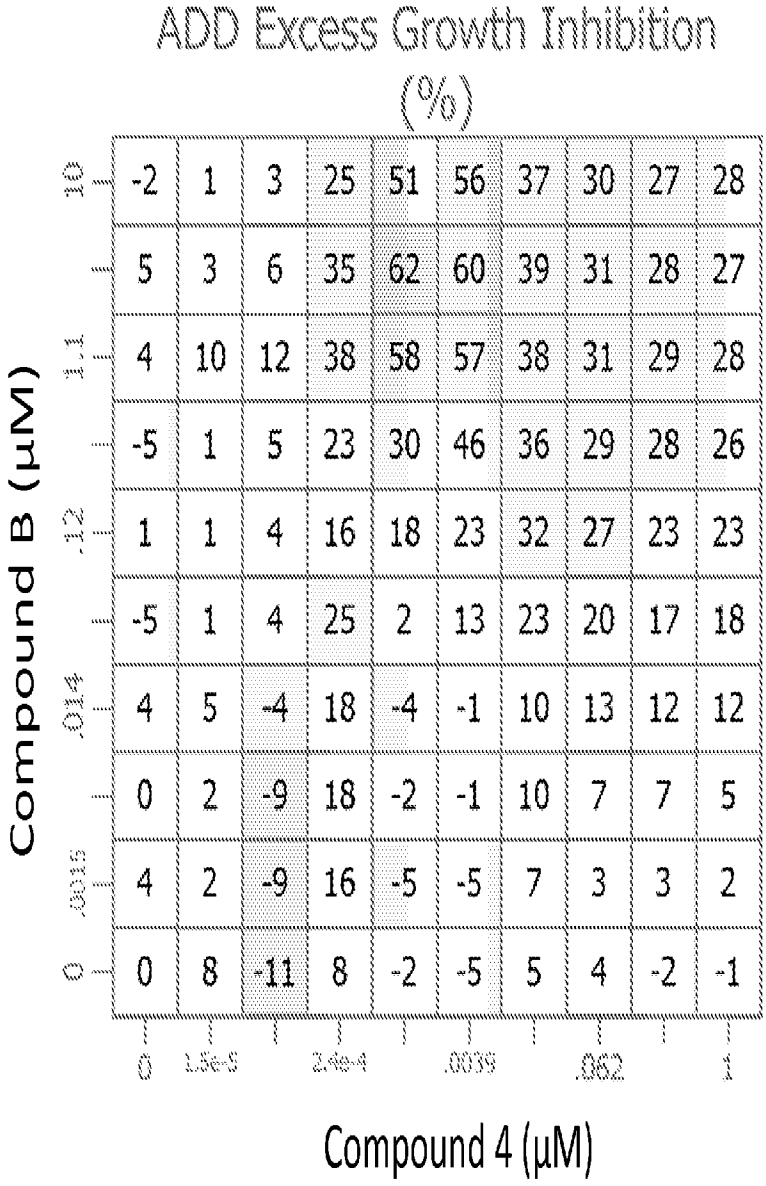


Figure 24a-Example 24; c32 cells



	Synergy Score
B x 4	37.7
B self-cross	0.73
4 self-cross	4.59

Figure 25-Example 25; G-361 cells

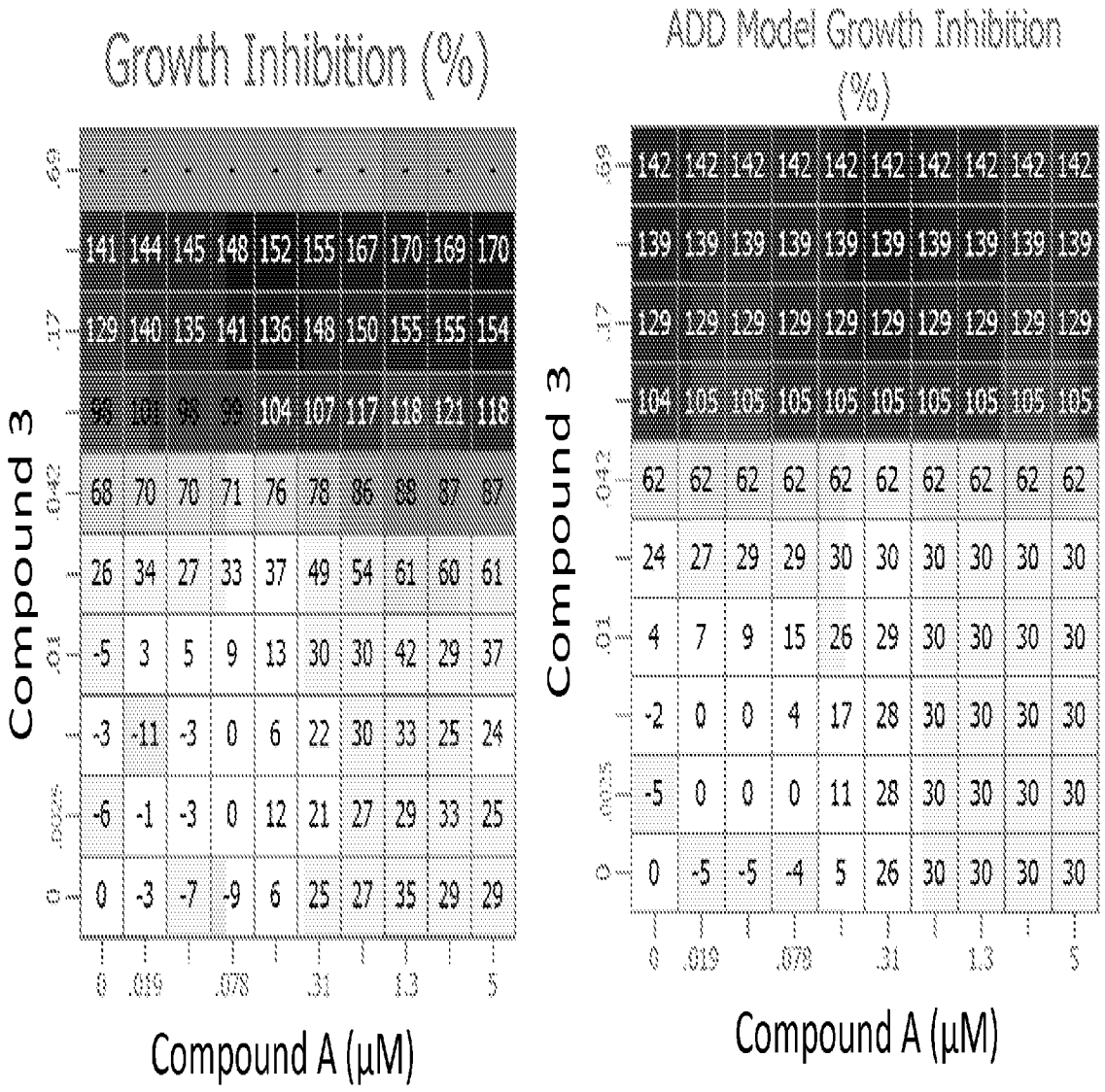
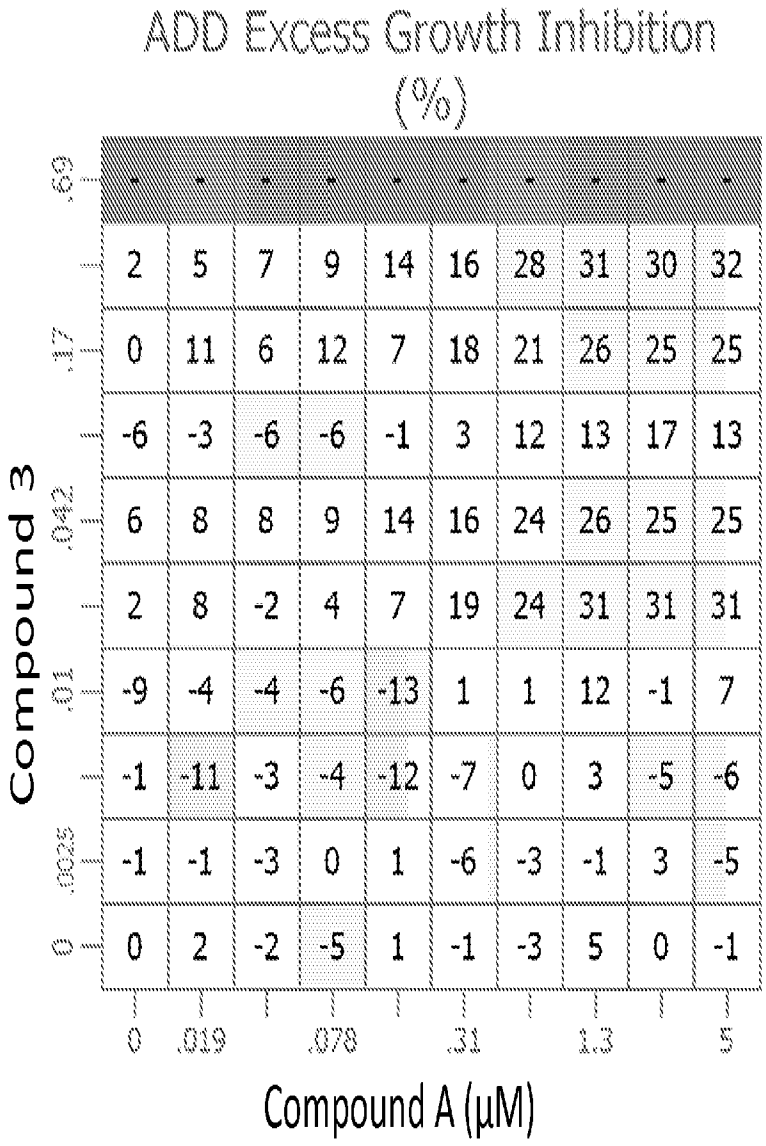


Figure 25a-Example 25; G-361 cells



	Synergy Score
A x 3	4.36
A self-cross	0.144
3 self-cross	0.697

Figure 27-Example 27; LS 174T cells

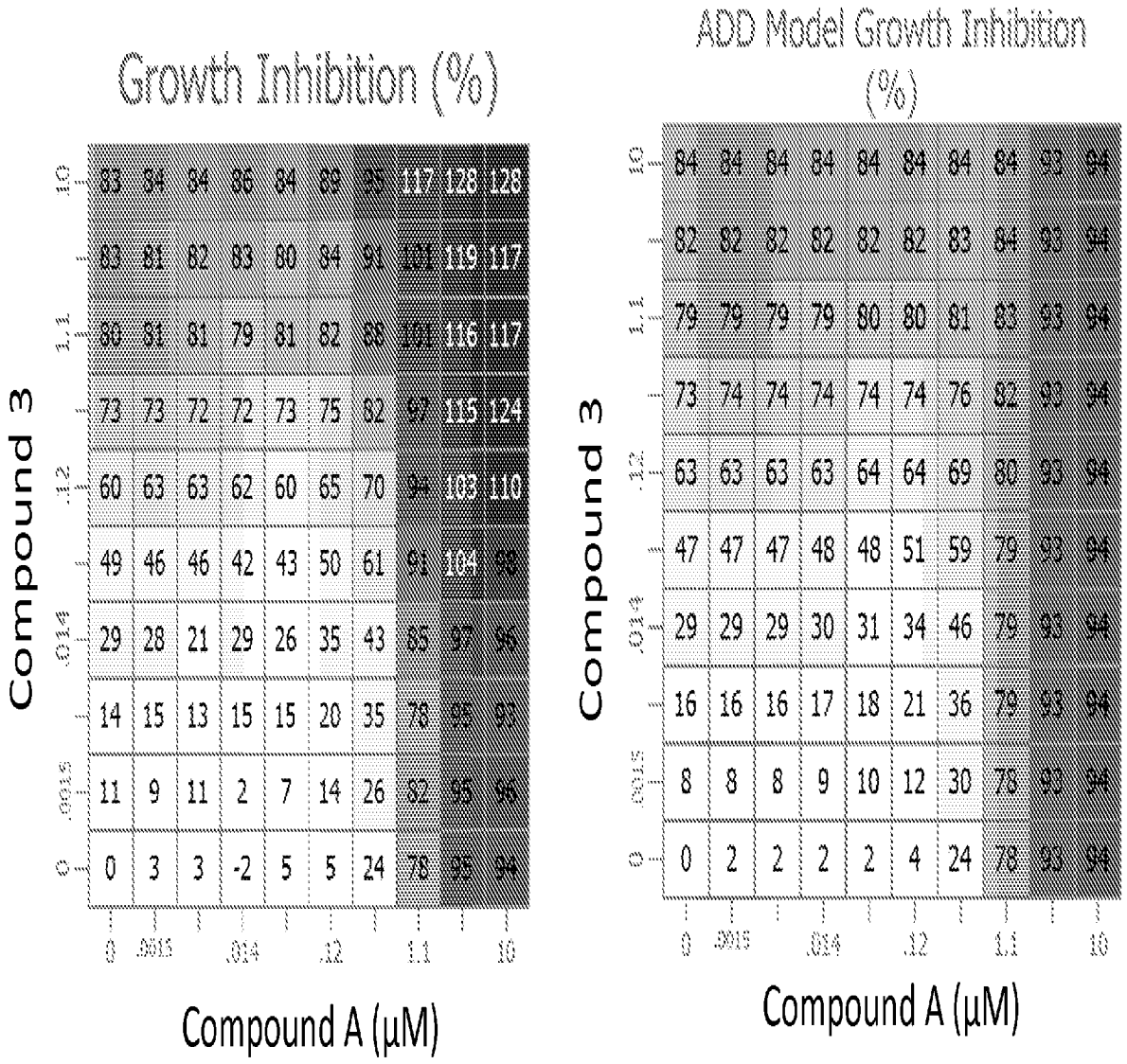
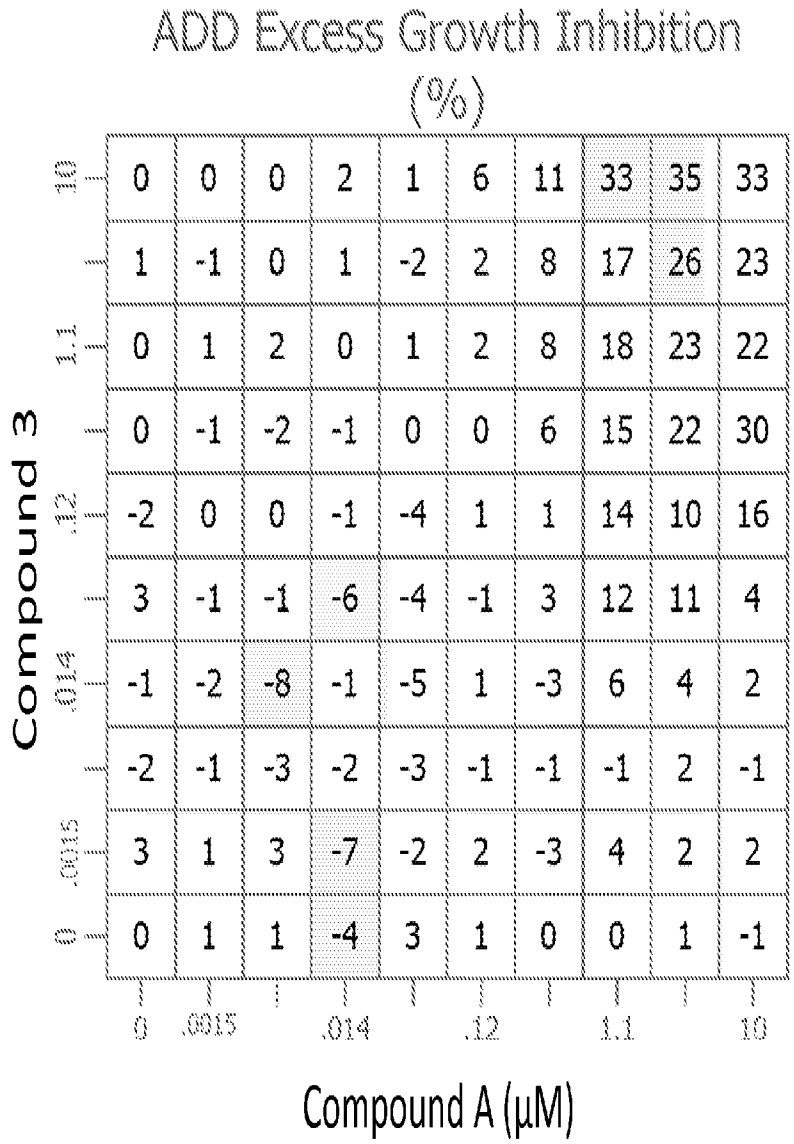


Figure 27a-Example 27; LS 174T cells



	Synergy Score
A x 3	5.85
A self-cross	0.578
3 self-cross	0.257

Figure 28-Example 28; MCF7 cells

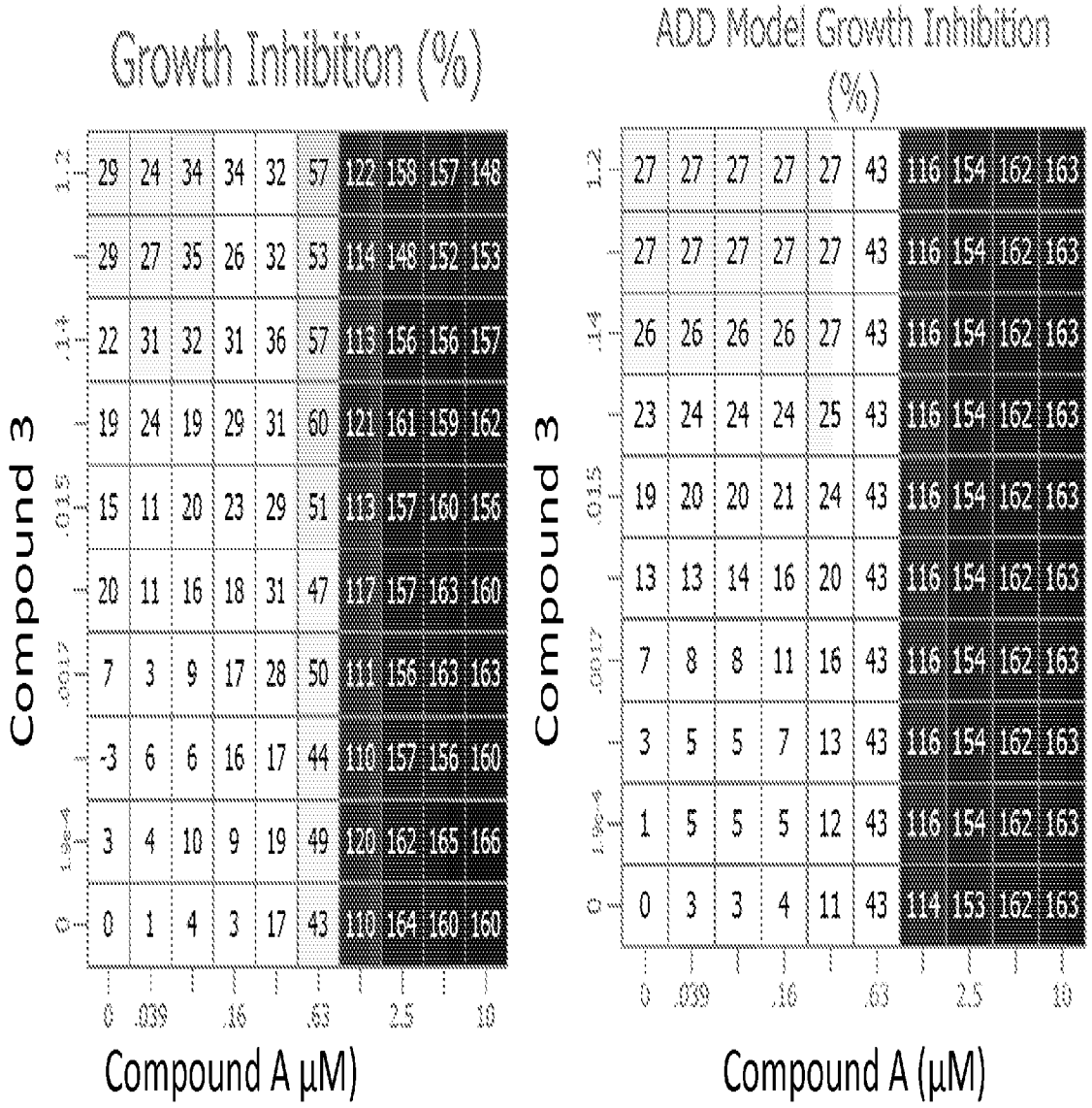
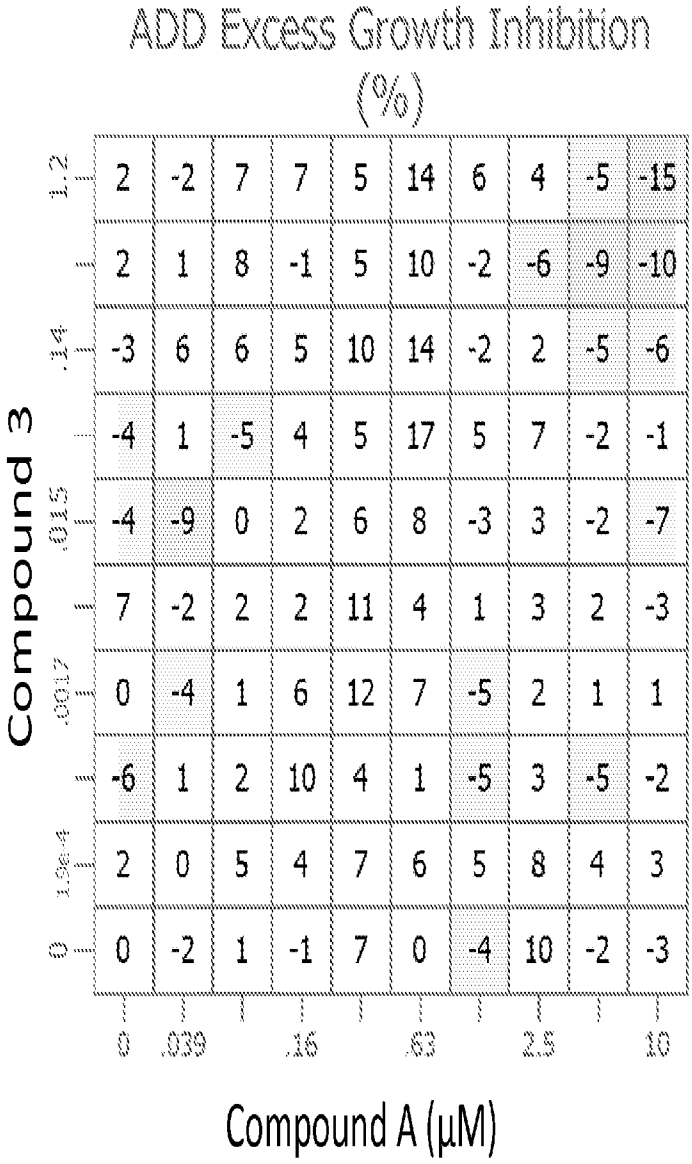


Figure 28a-Example 28; MCF7 cells



	Synergy Score
A x 3	1.31
A self-cross	0.753
3 self-cross	0.805

Figure 29-Example 29; NCI-H1666 cells

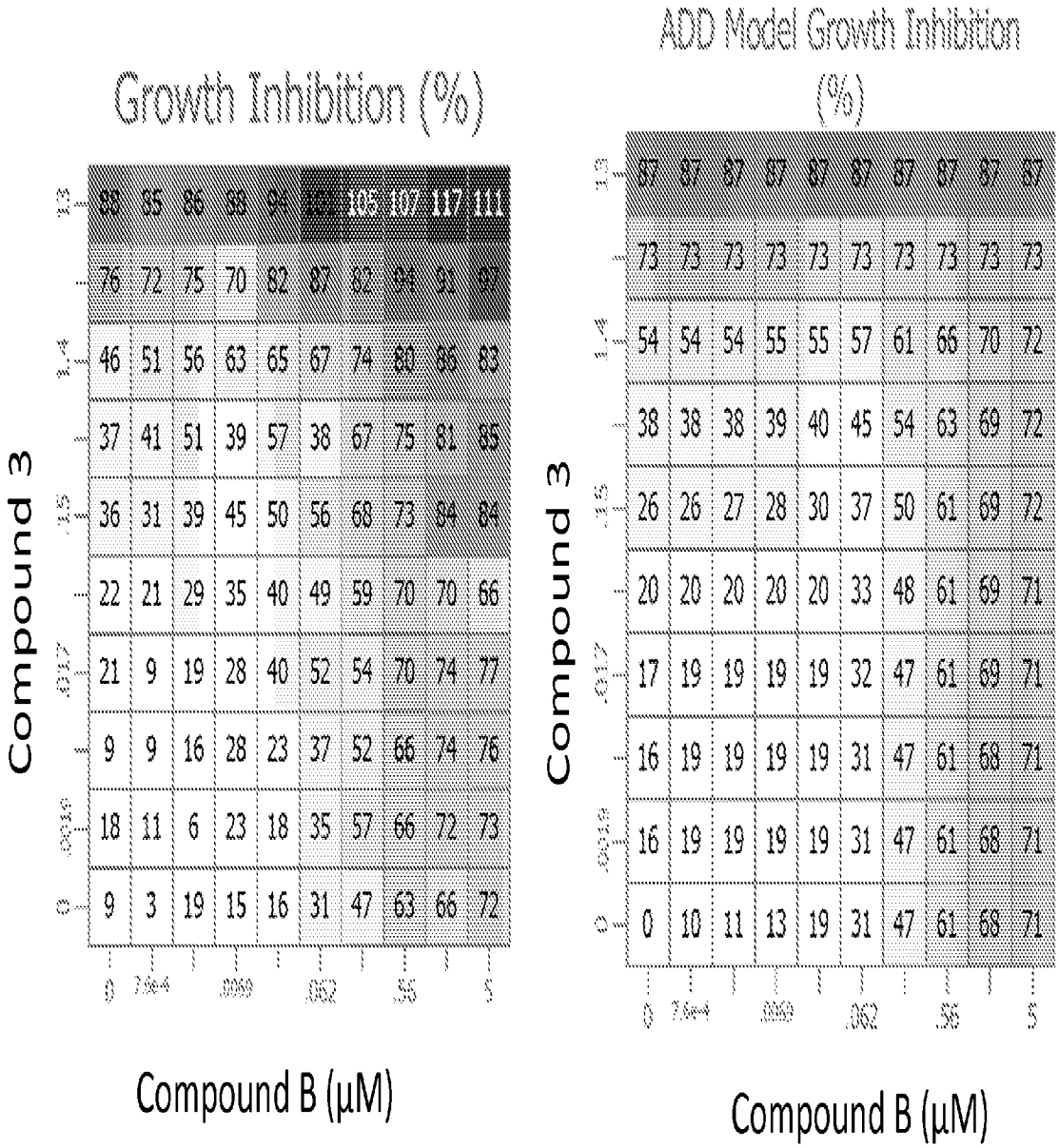
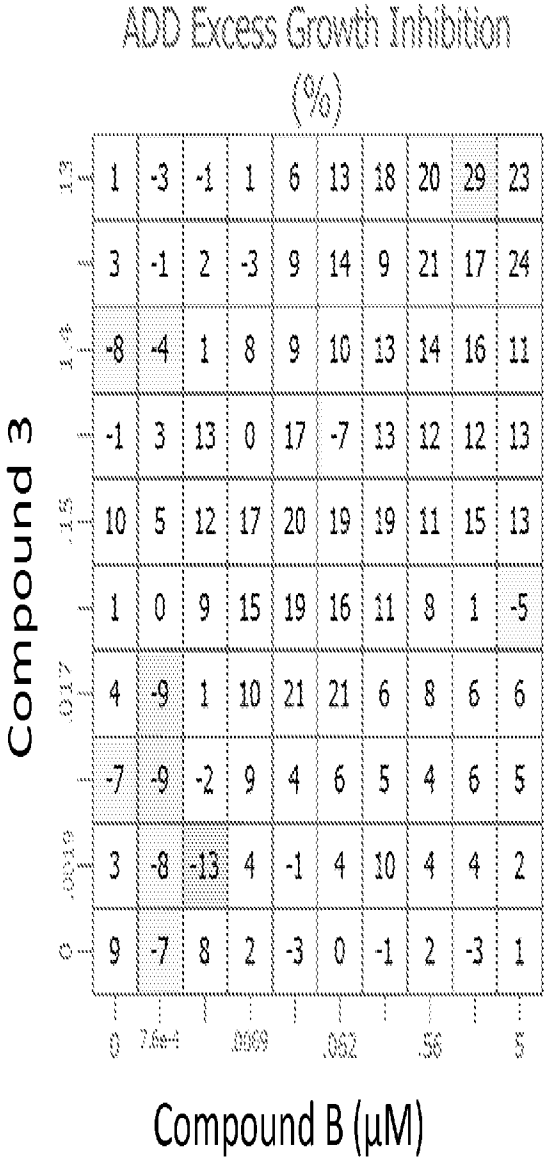


Figure 29a-Example 29; NCI-H1666 cells



	Synergy Score
B x 3	6.2
B self-cross	0.117
3 self-cross	2.22

Figure 30-Example 30; NCI-H1666 cells

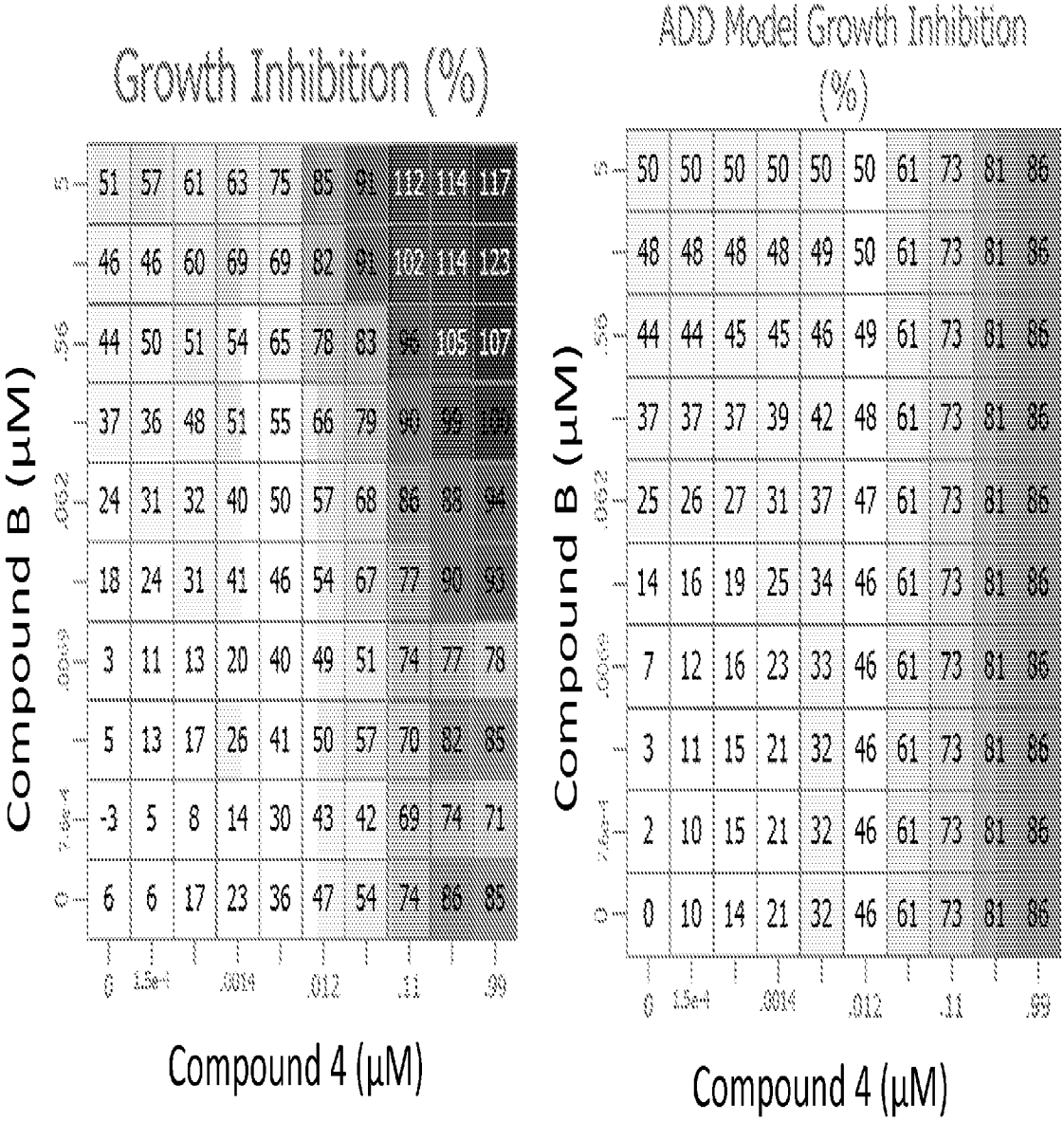
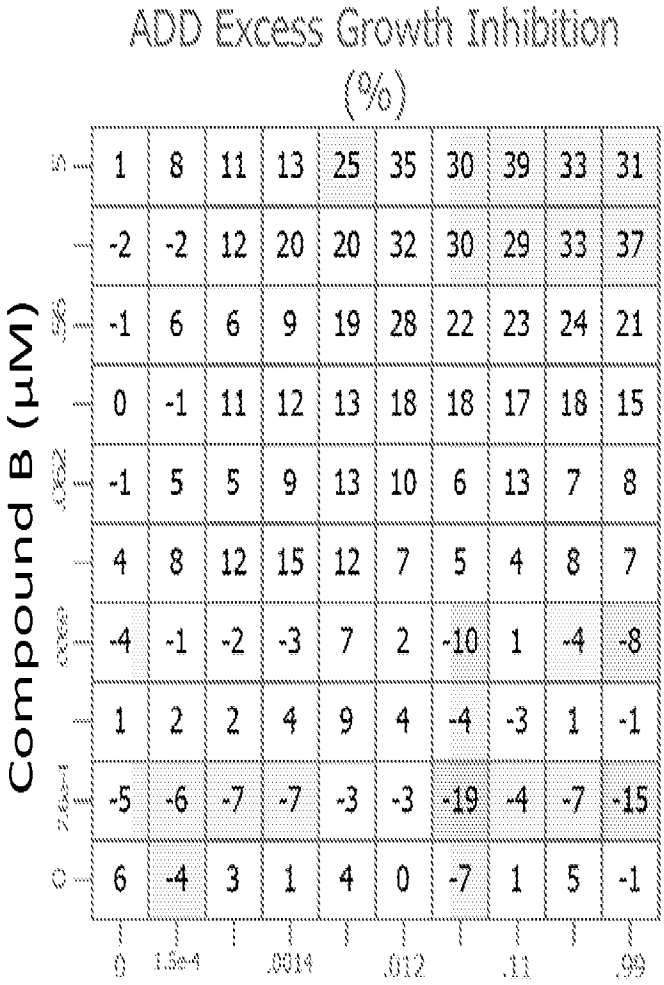


Figure 30a-Example 30; NCI-H1666 cells



	Synergy Score
B x 4	8.97
B self-cross	0.117
4 self-cross	0.602

Figure 31-Example 31; RKO cells

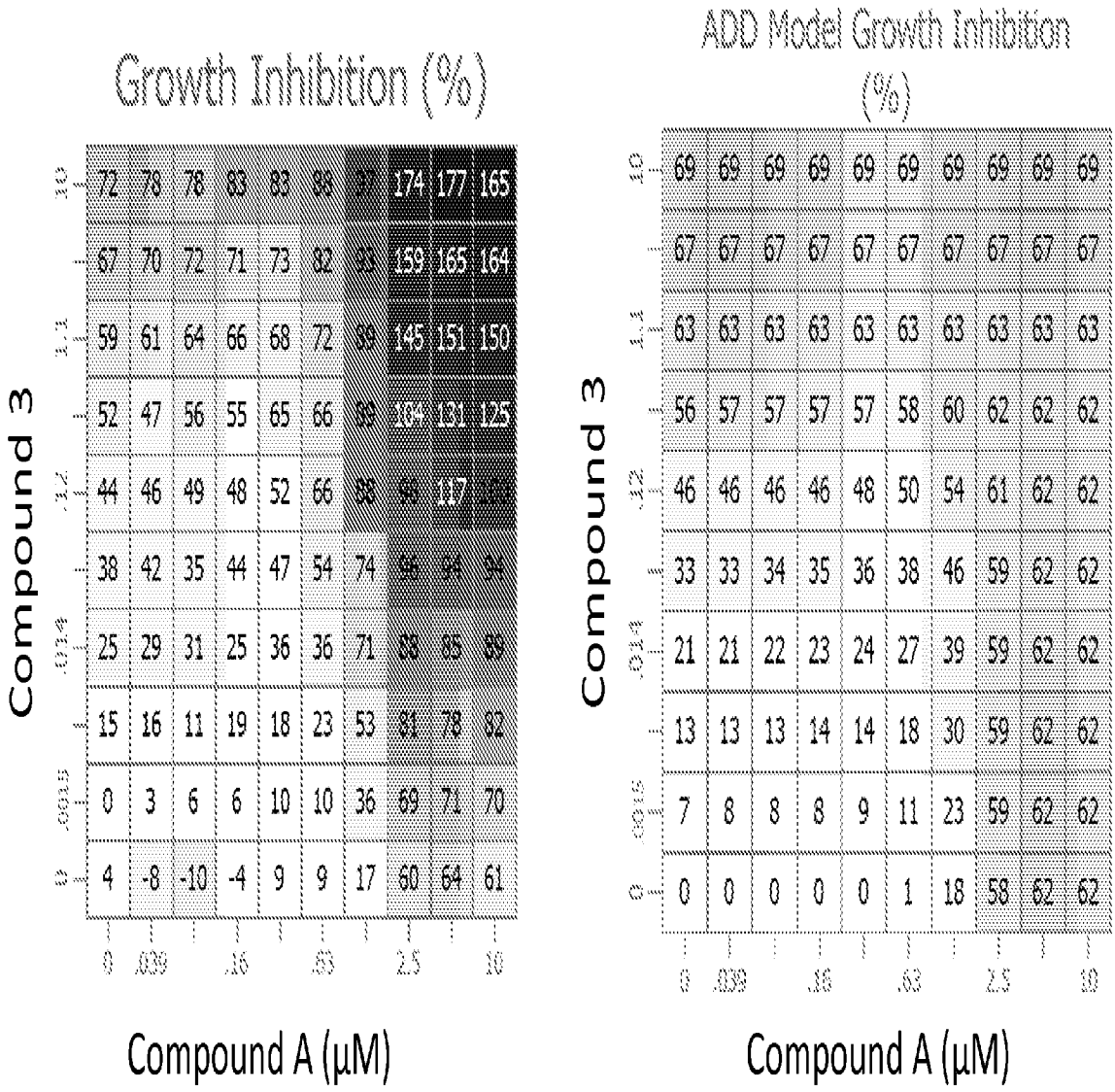
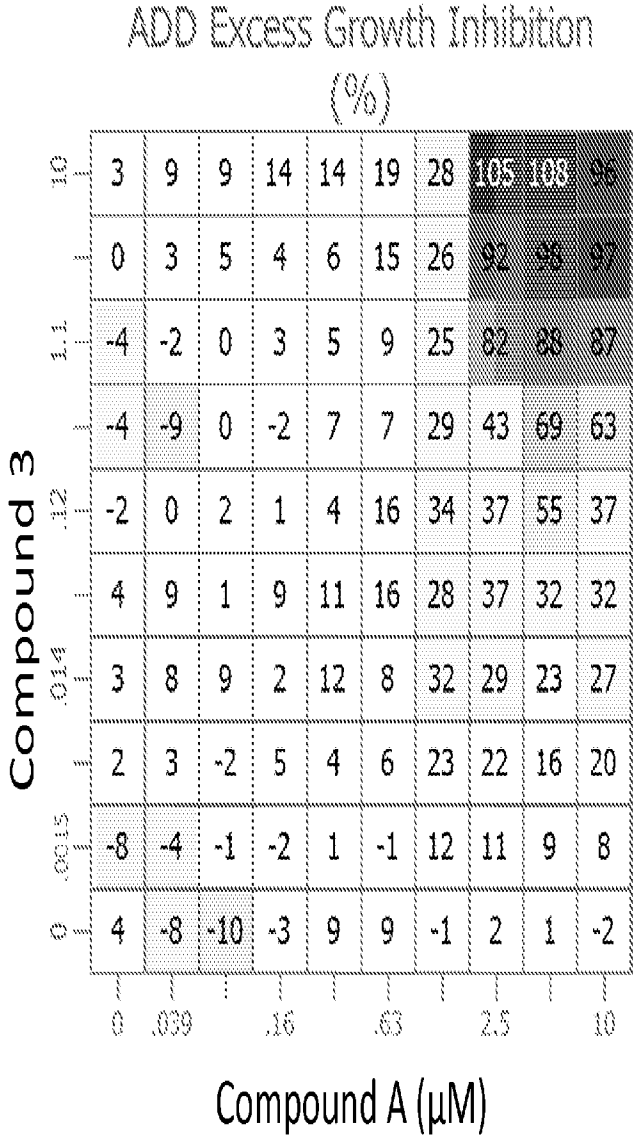


Figure 31a-Example 31; RKO cells



	Synergy Score
A x 3	17.6
A self-cross	0.235
3 self-cross	0.368

Figure 32-Example 32; RKO cells

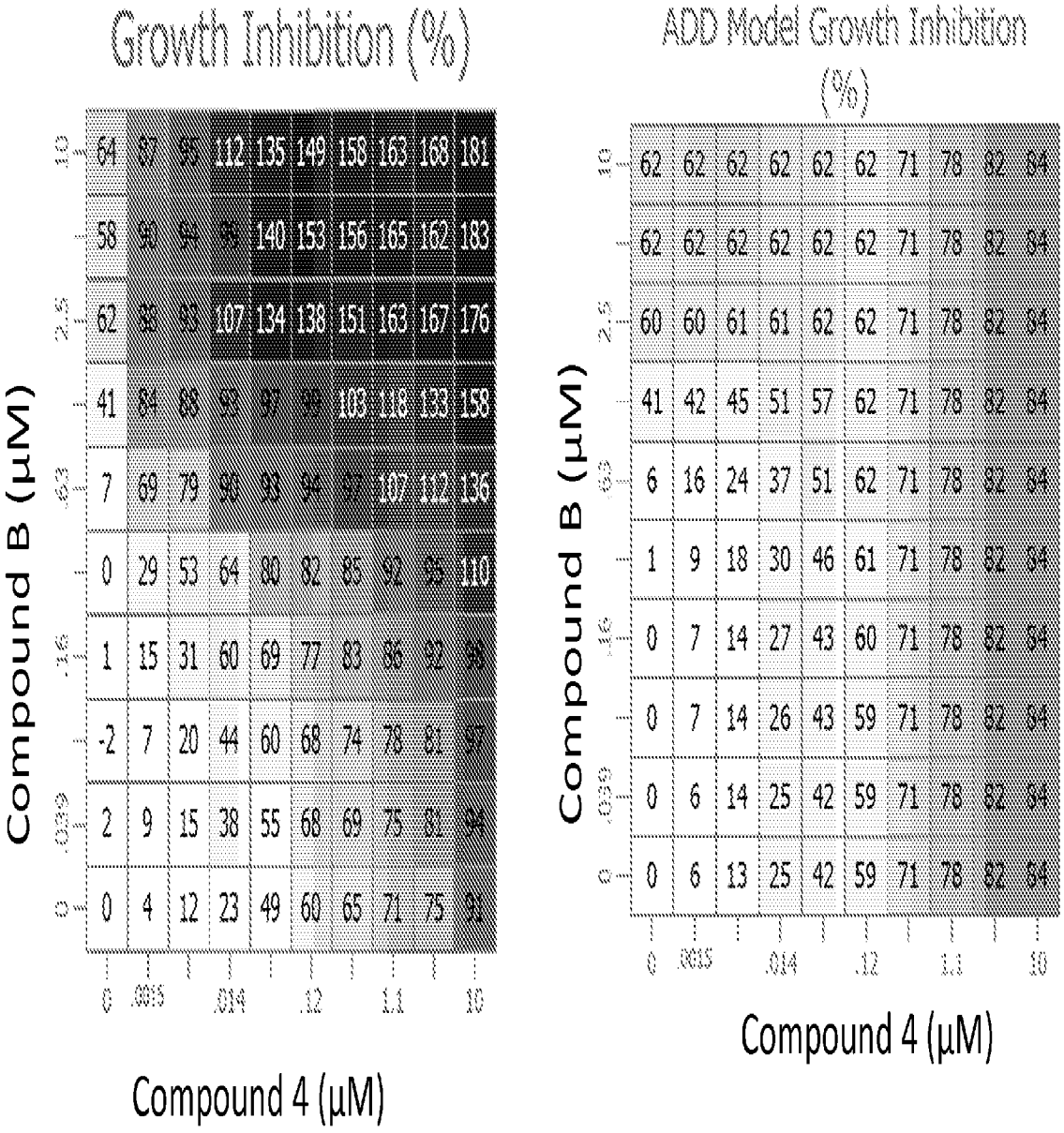
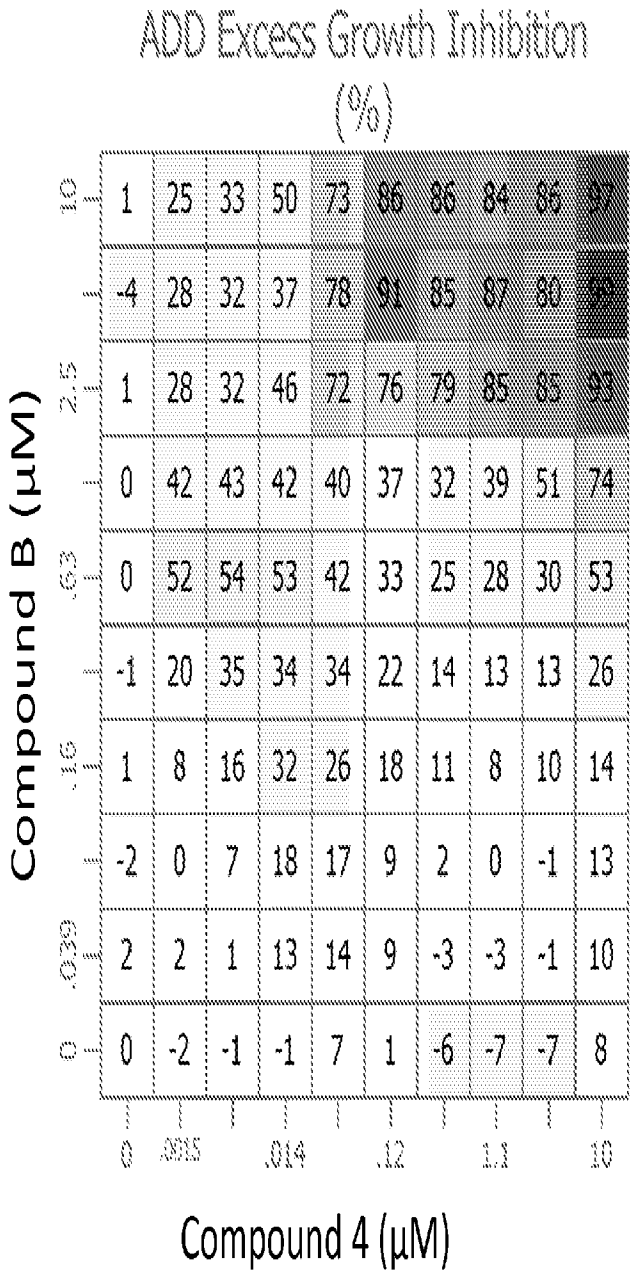


Figure 32a-Example 32; RKO cells



	Synergy Score
A x 4	29.3
B self-cross	0.154
4 self-cross	2.47

Figure 33-Example 33; RT4 cells

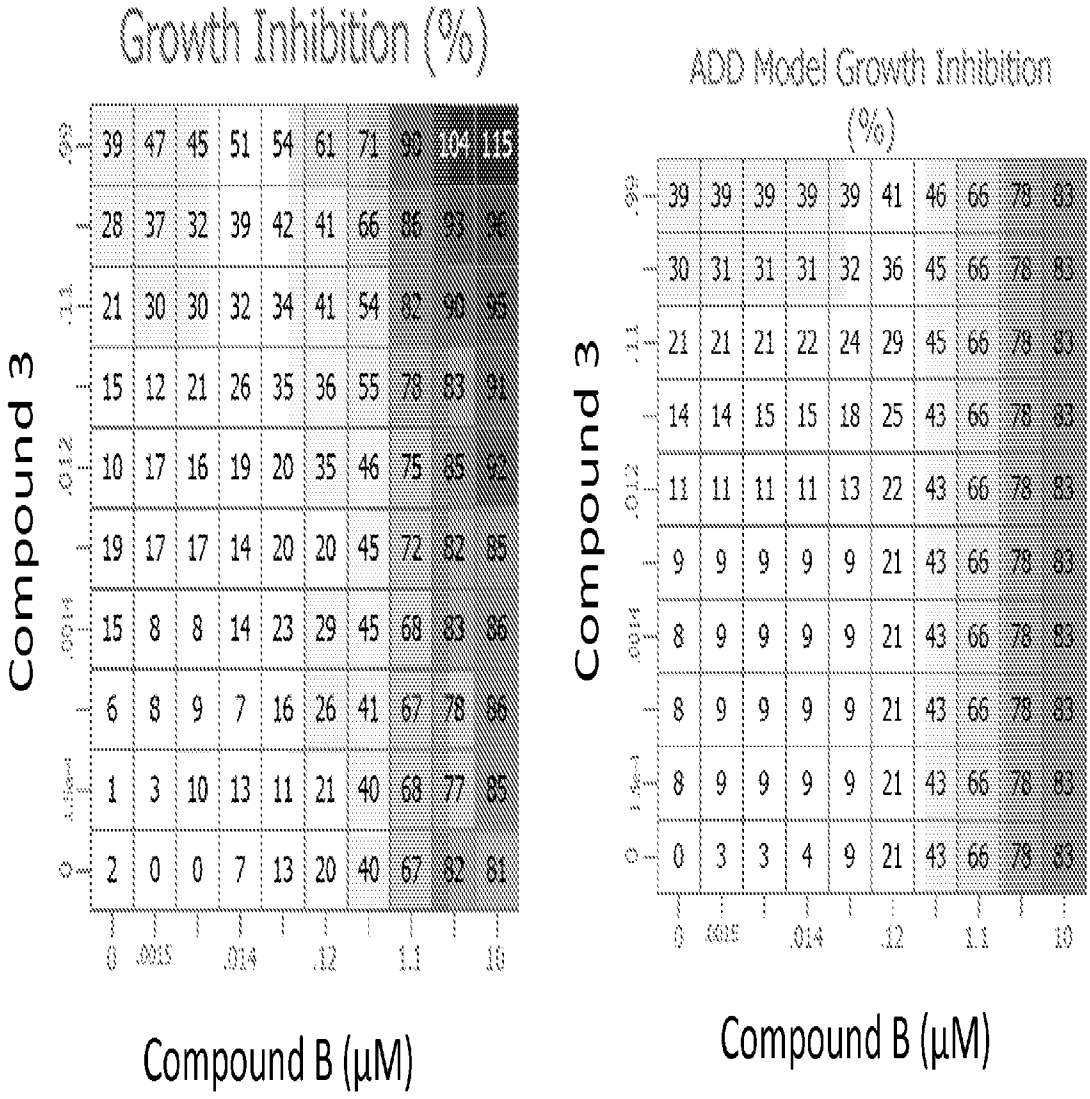
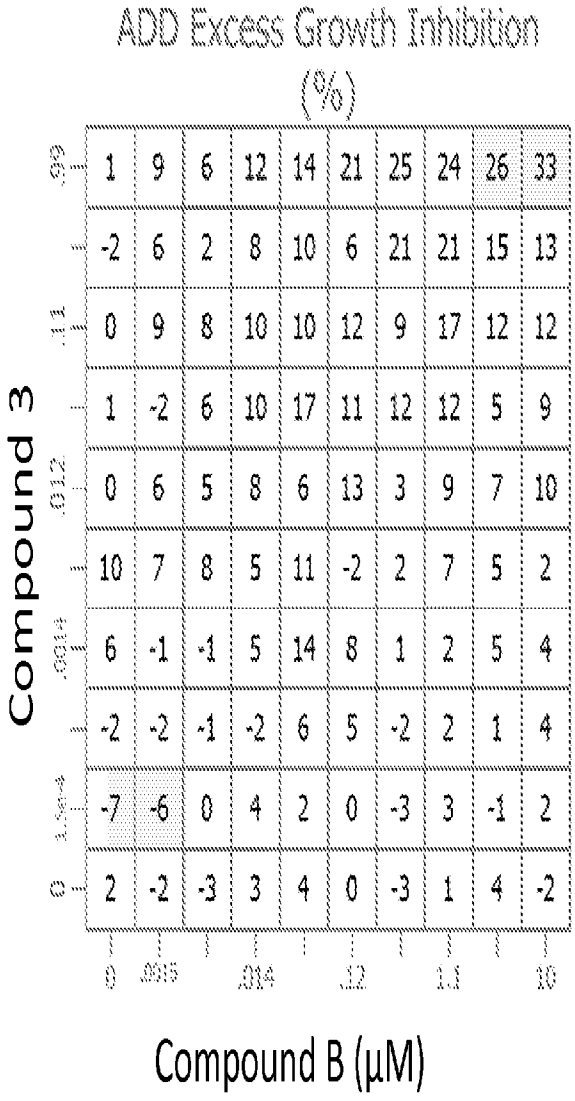


Figure 33a-Example 33; RT4 cells



	Synergy Score
B x 3	4.67
B self-cross	1.37
3 self-cross	0.666

Figure 34-Example 34; RT4 cells

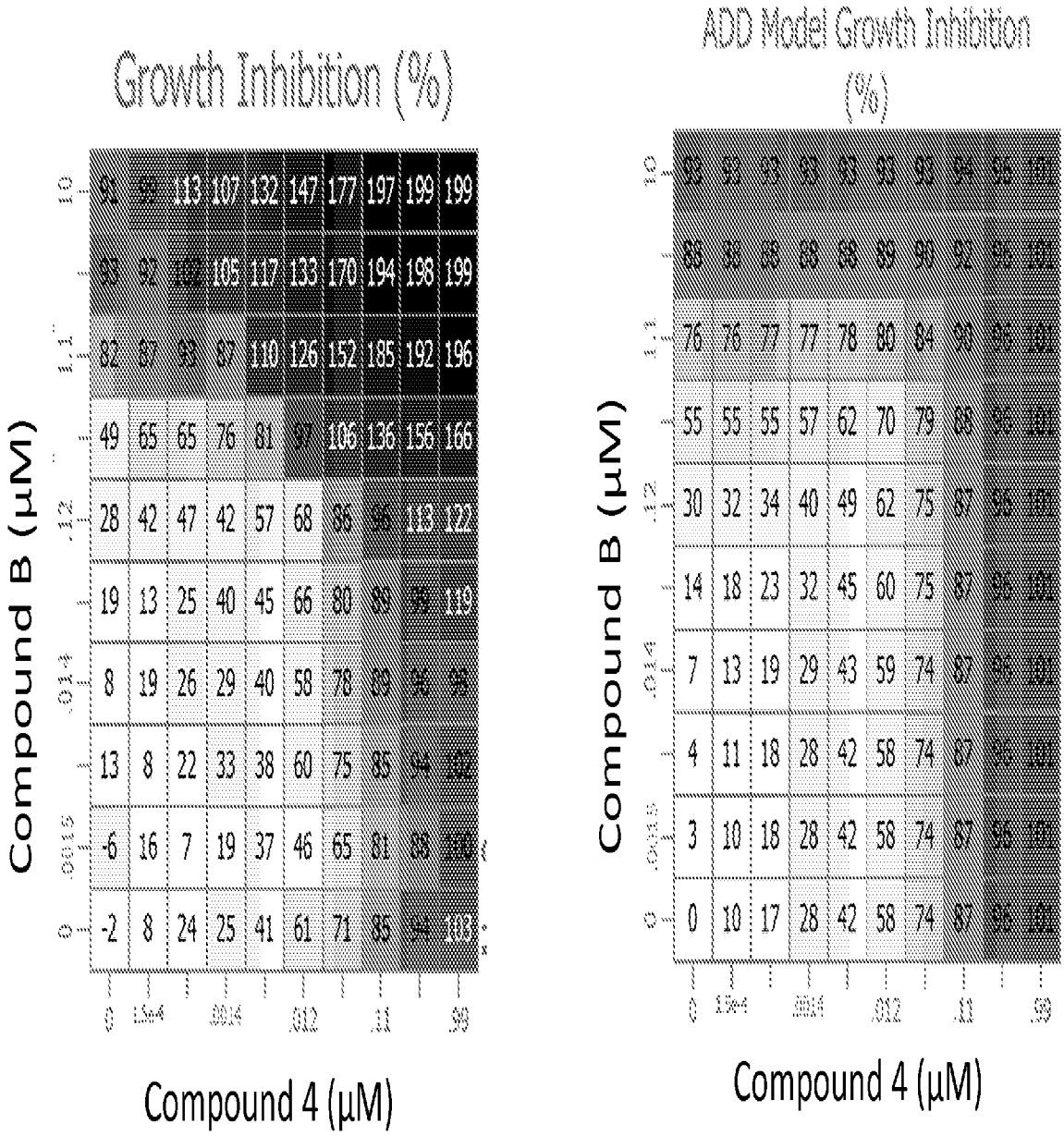
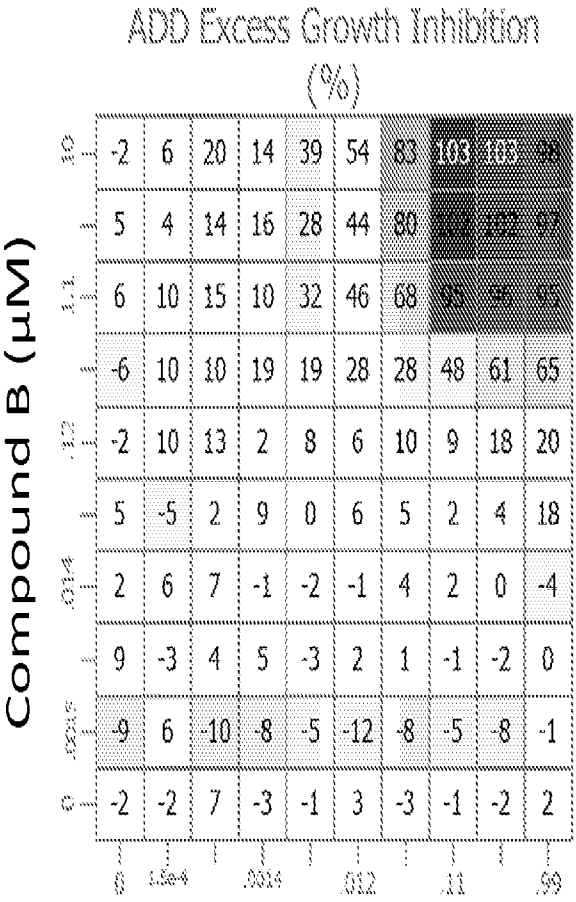


Figure 34a-Figure 34; RT4 cells



	Synergy Score
B x 4	36.8
B self-cross	1.33
4 self-cross	1.23

Figure 35-Example 35; SH-4 cells

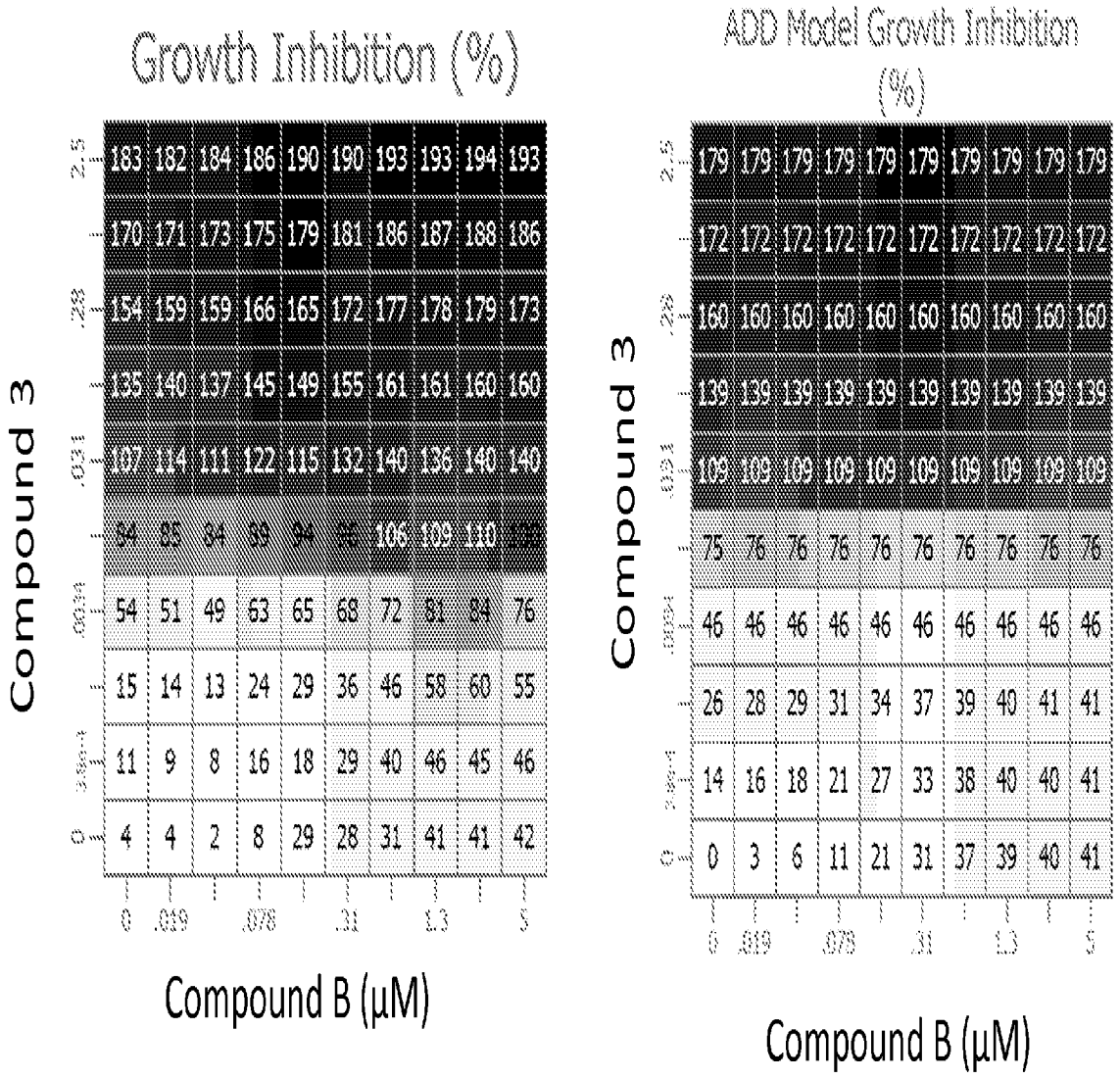
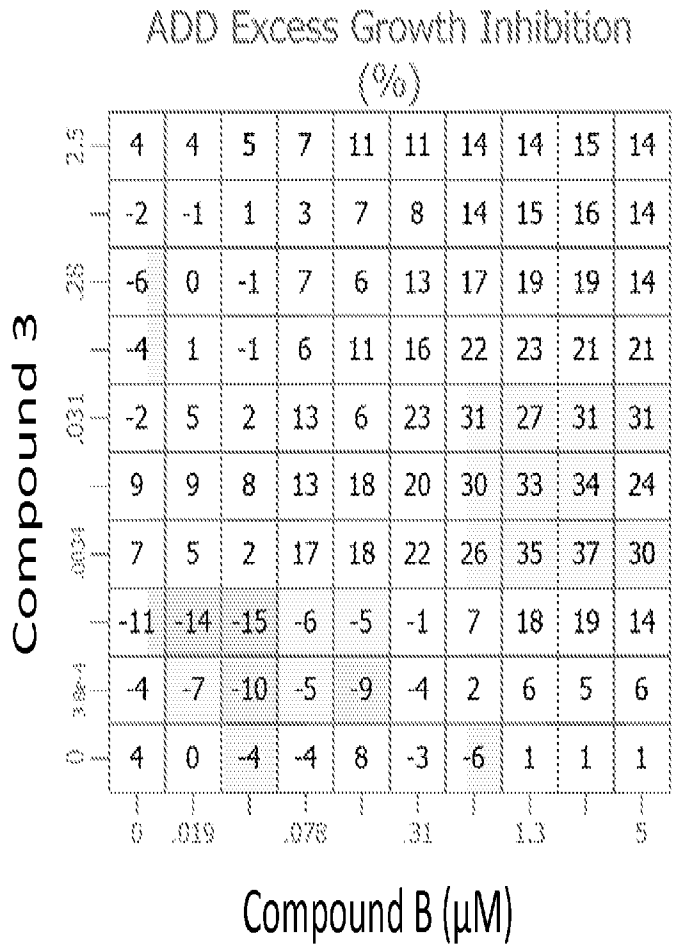


Figure 35a-Example 35; SH-4 cells



	Synergy Score
B x 3	9.82
B self-cross	0.259
3 self-cross	3.29

Figure 36-Example 36; SH-4 cells

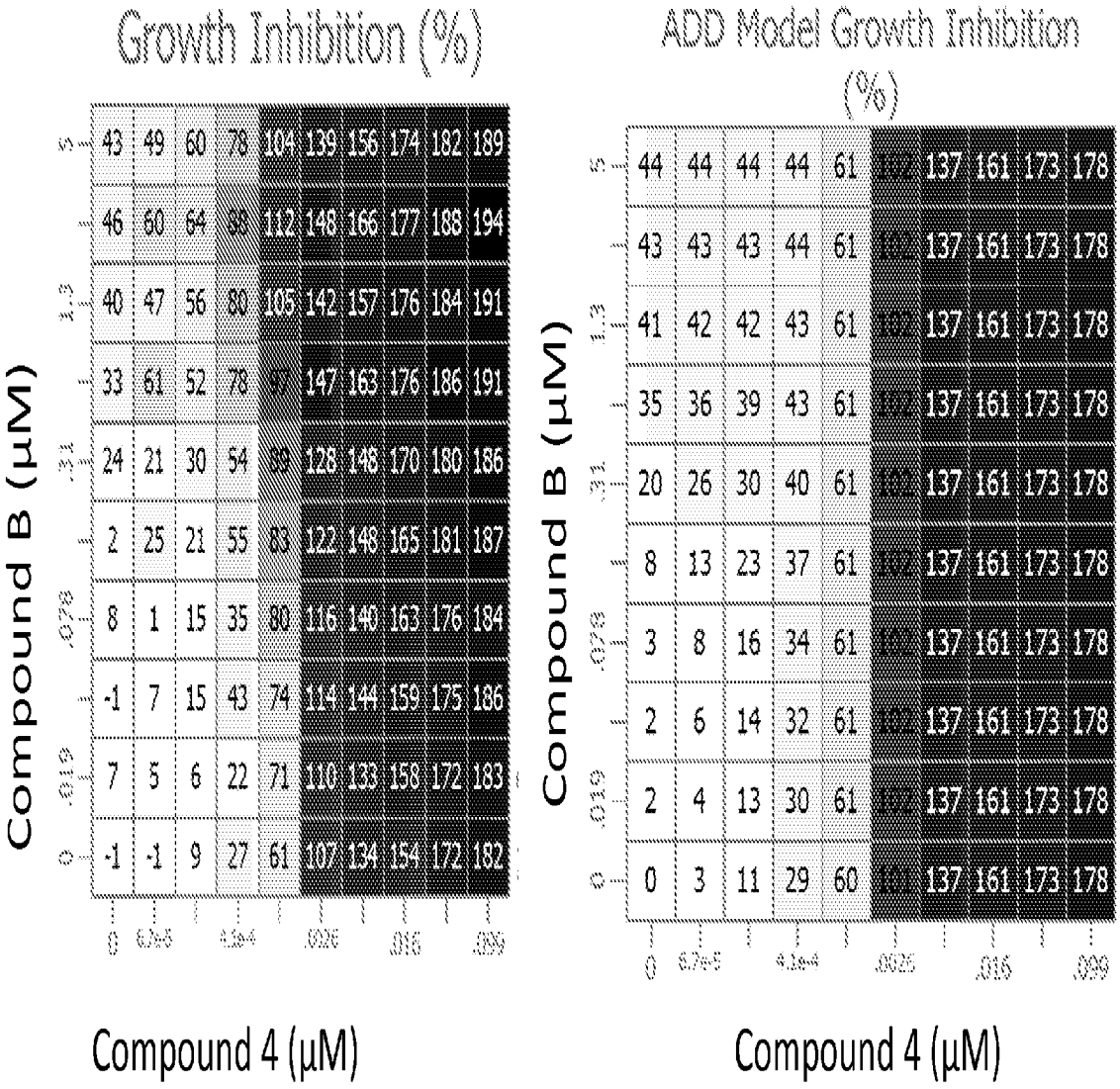
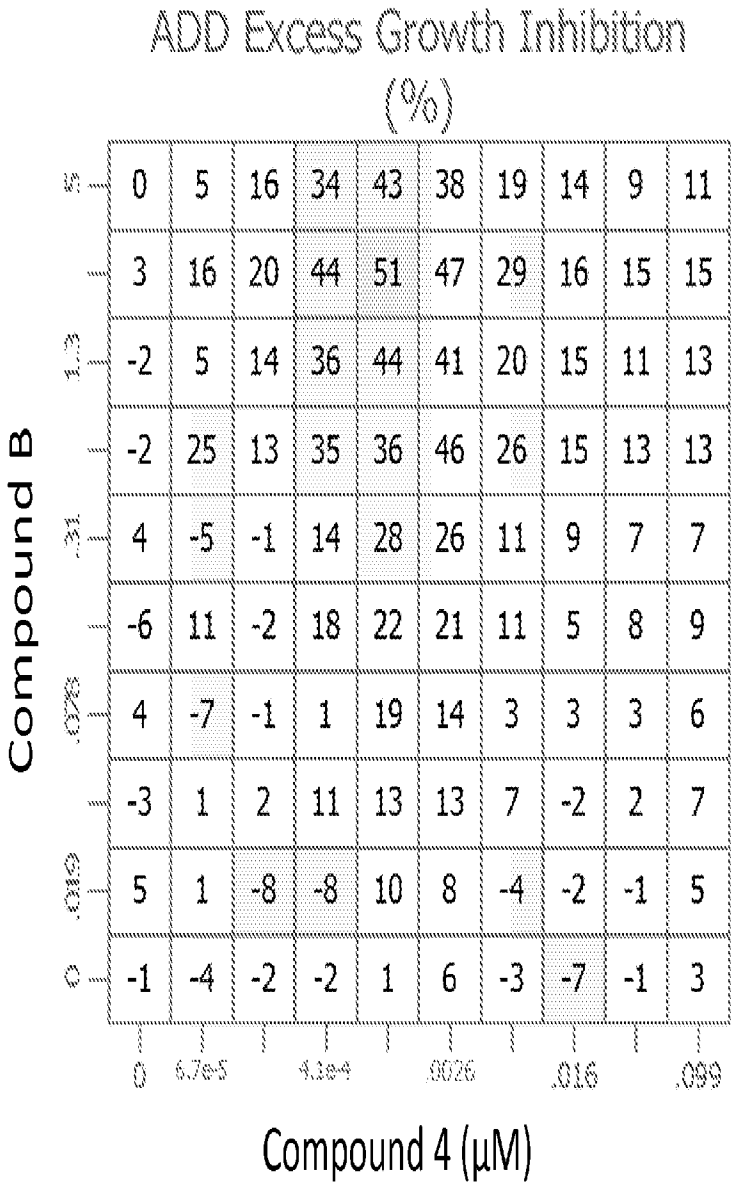


Figure 36a-Example 36; SH-4 cells



	Synergy Score
B x 4	9.13
B self-cross	0.29
4 self-cross	1.93

Figure 37-Example 37; SK-HEP-1 cells

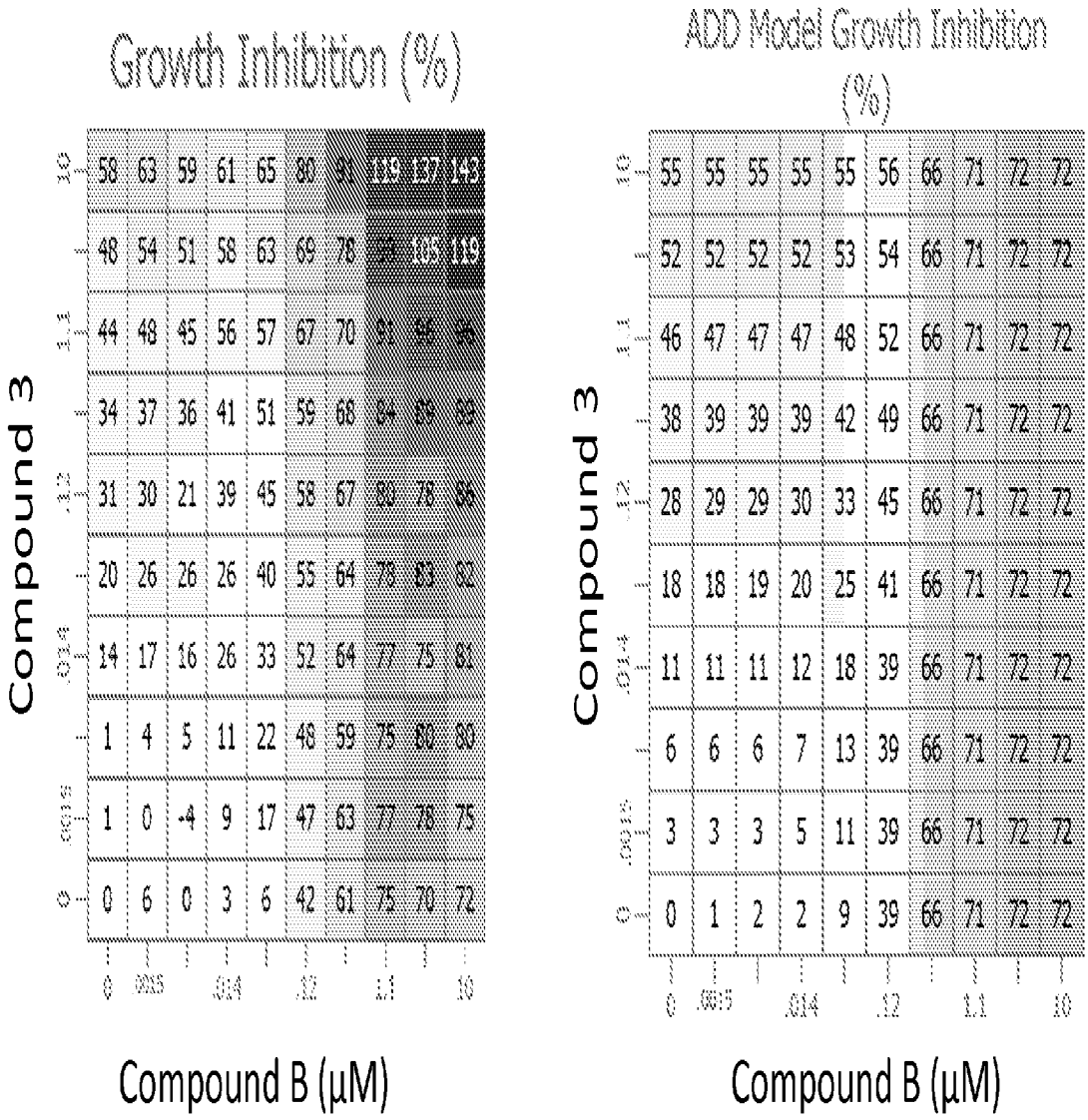
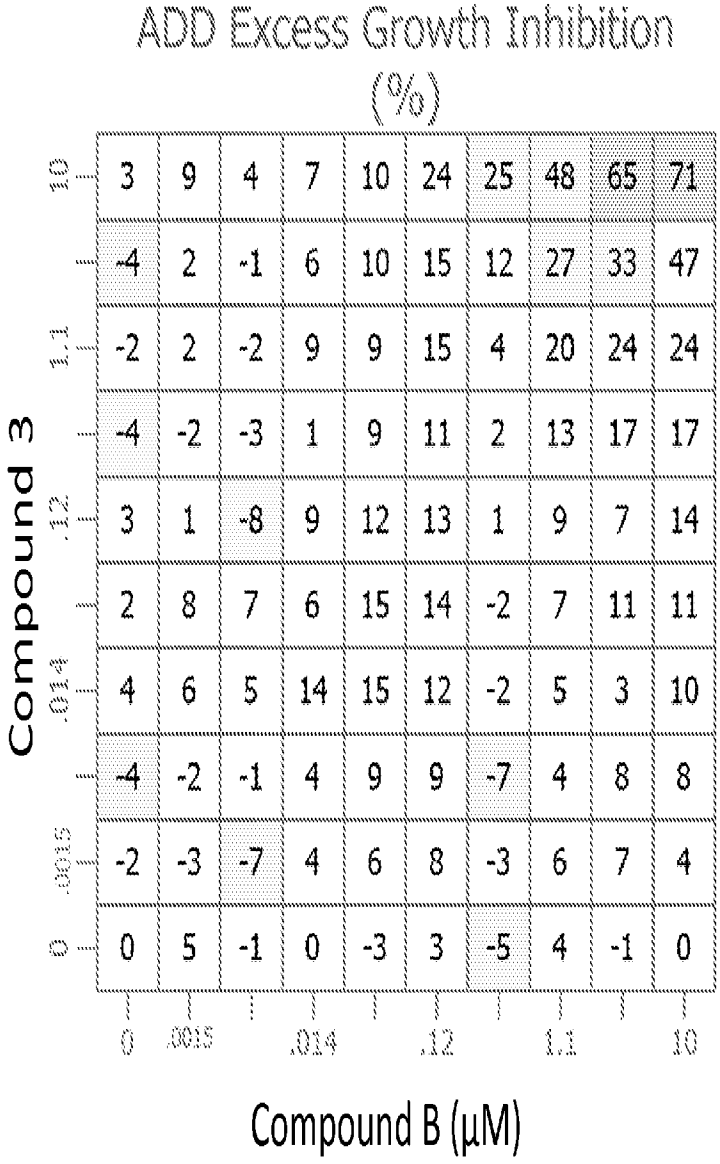


Figure 37a-Example 37; SK-HEP-1 cells



	Synergy Score
B x 3	9.09
B self-cross	0.886
3 self-cross	0.538

Figure 38-Example 38; SK-HEP-1 cells

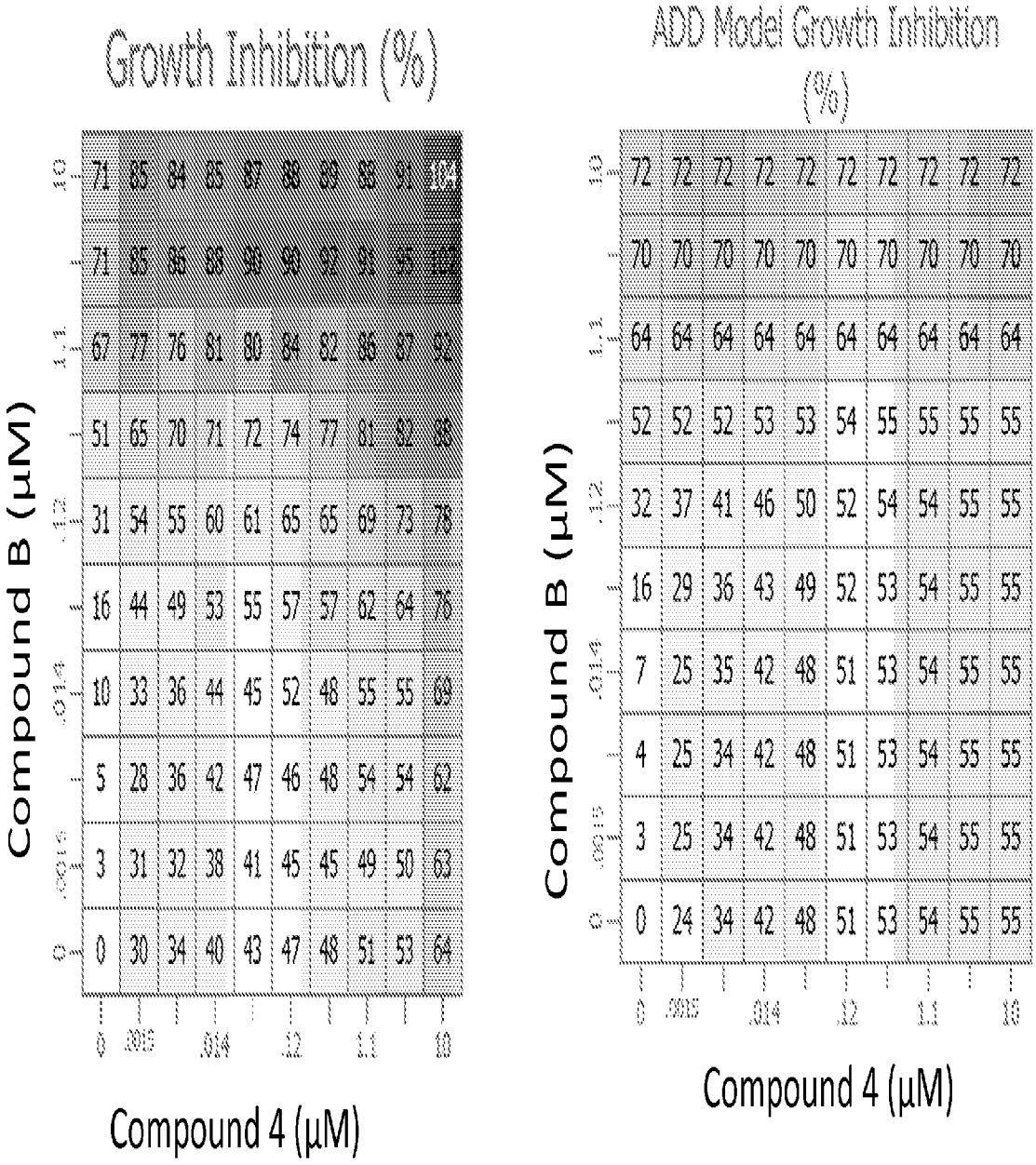
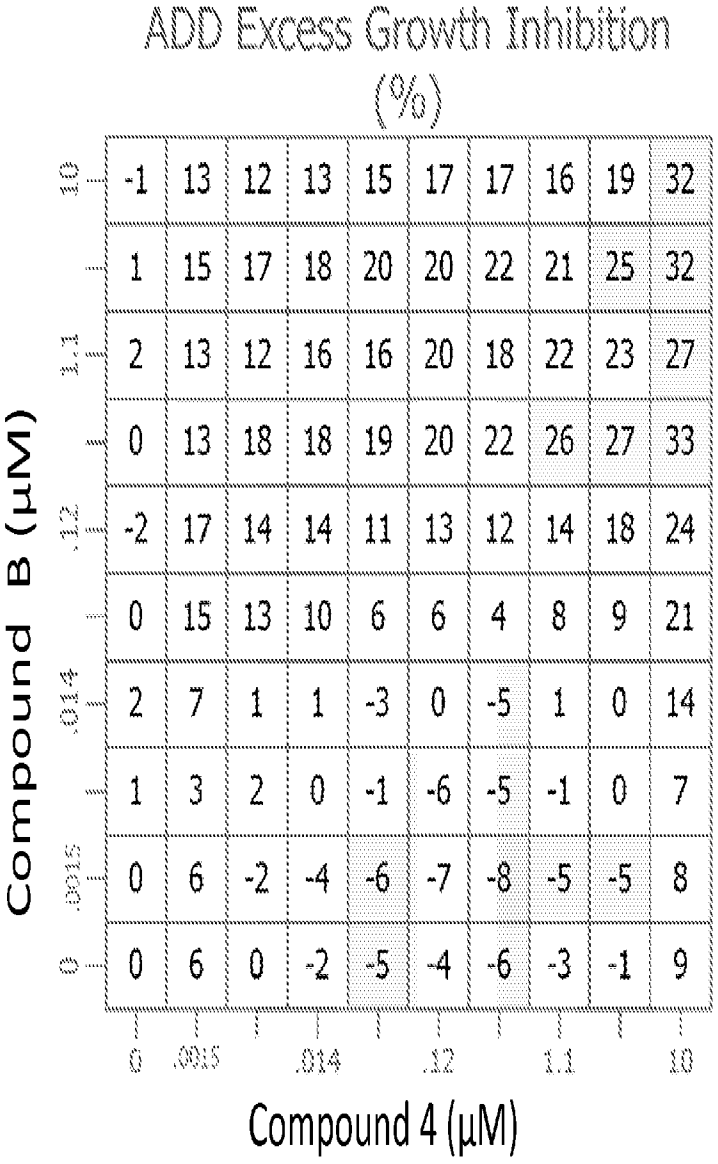


Figure 38a-Example 38; SK-HEP-1 cells



	Synergy Score
B x 4	9.38
B self-cross	0.118
4 self-cross	0.901

Figure 39-Example 39; A204 cells

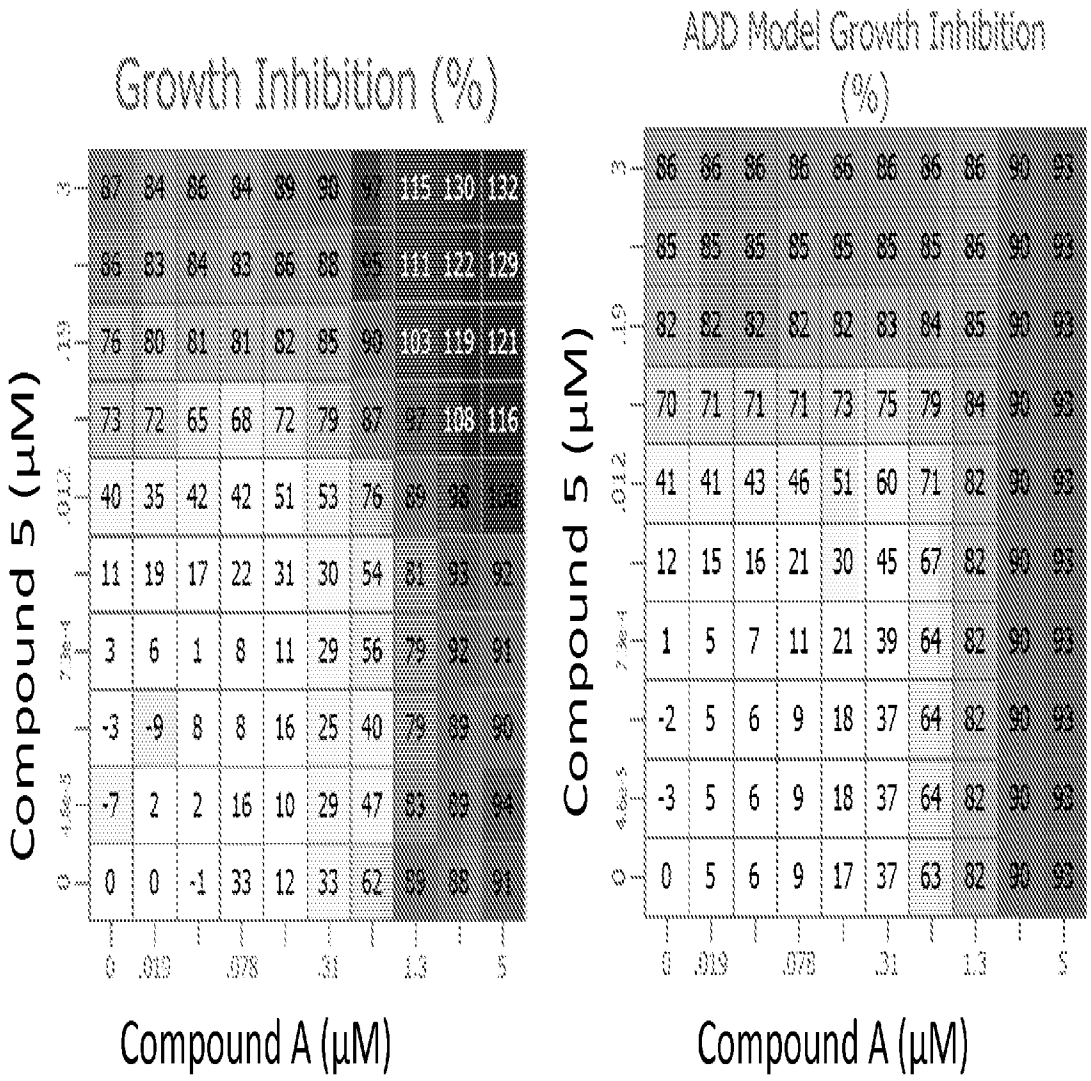
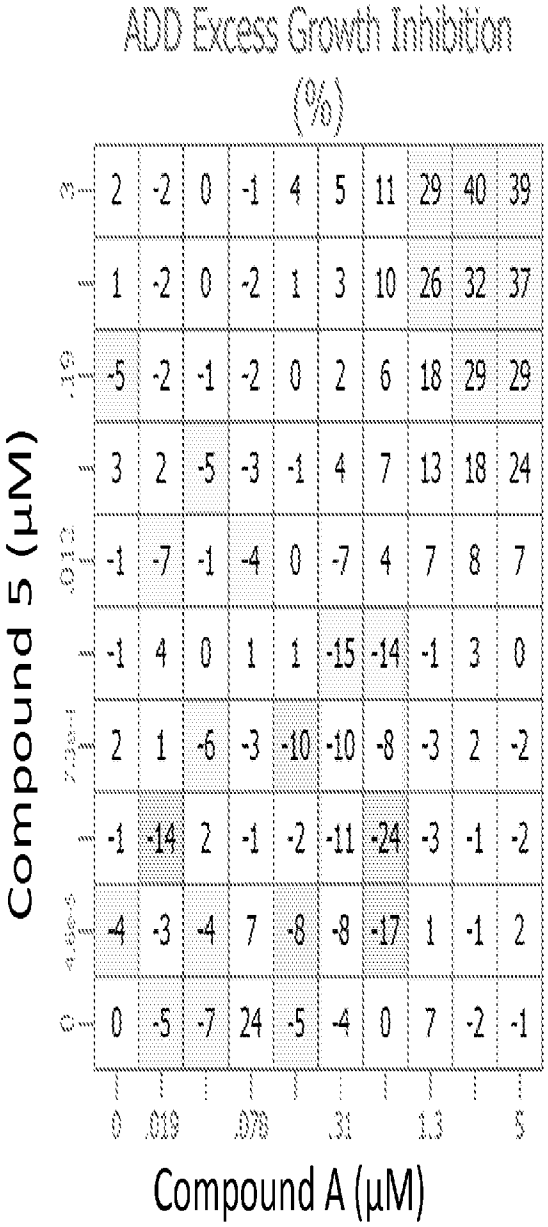


Figure 39a-Example 39; A204 cells



	Synergy Score
A x 5	4.62
A self-cross	0.621
5 self-cross	1.57

Figure 40-Example 40; A375sq2 cells

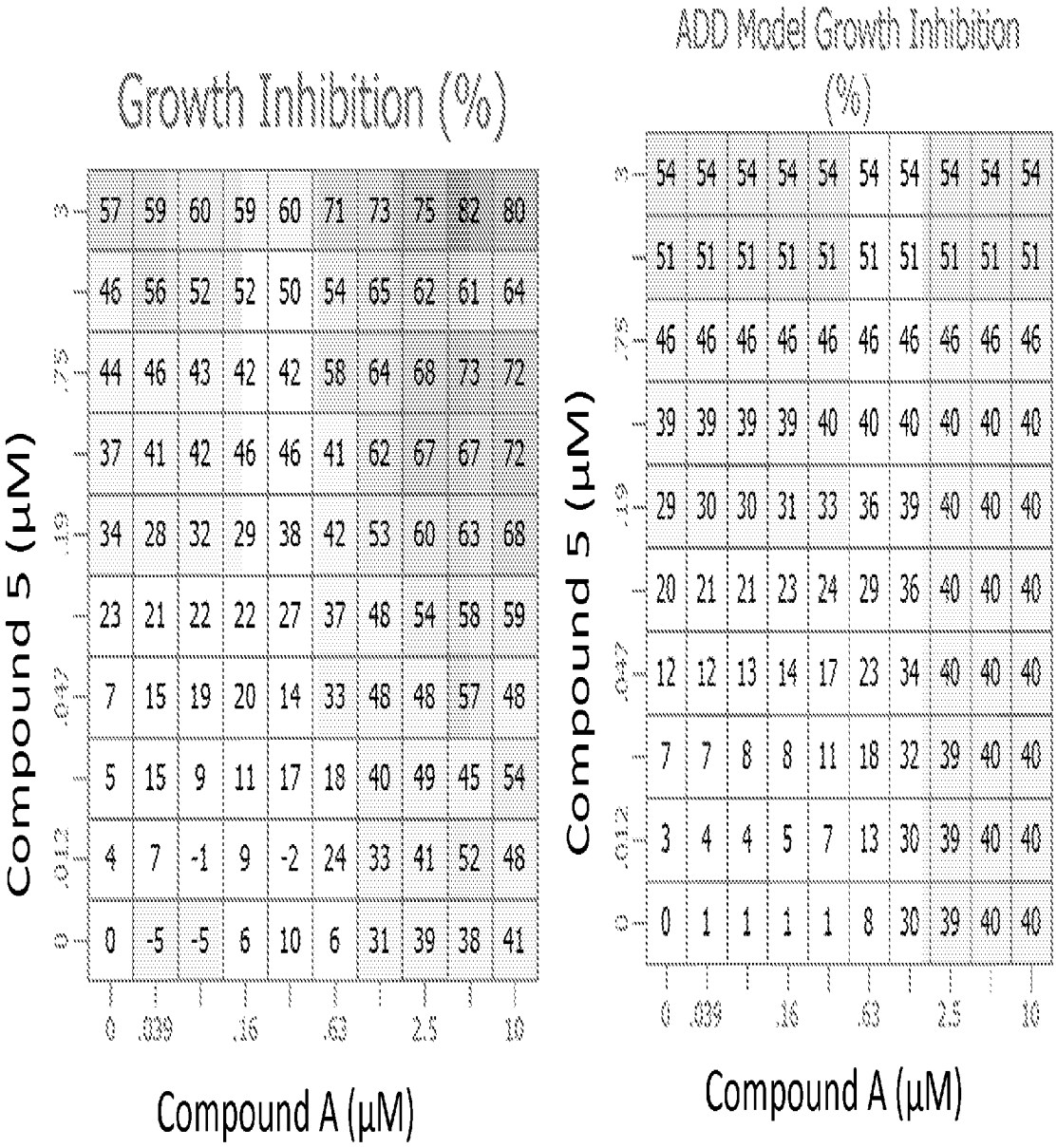
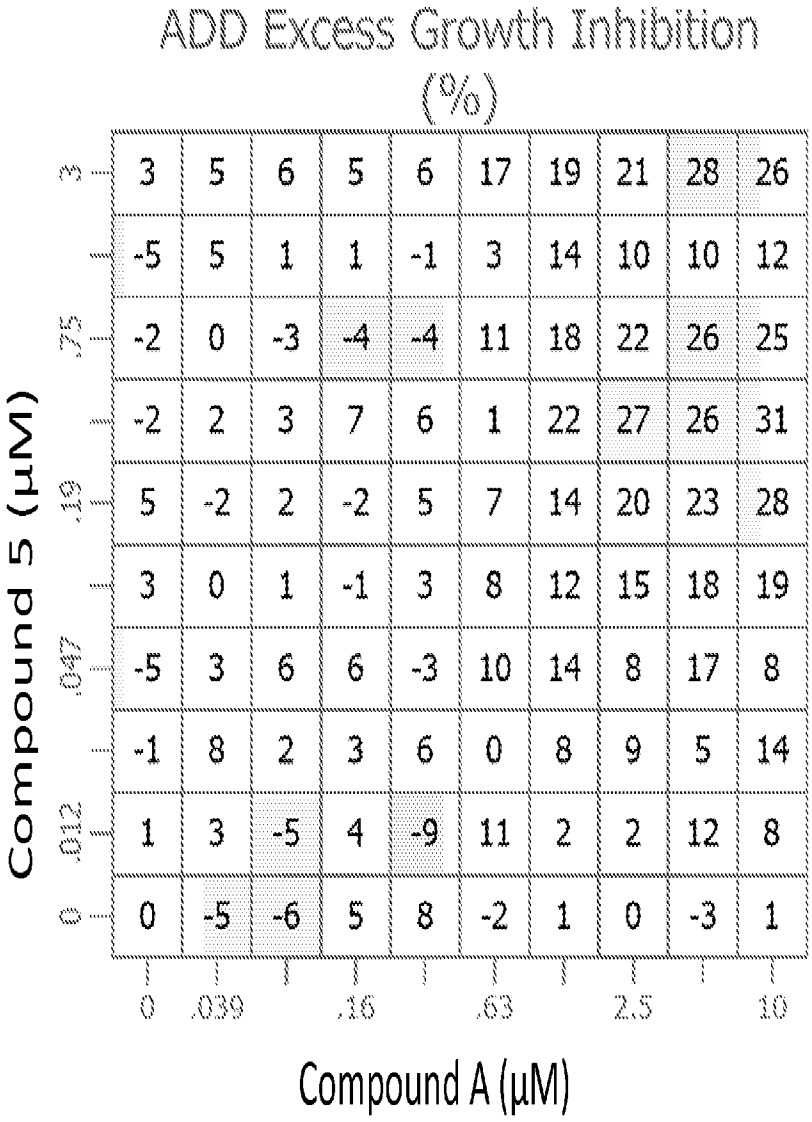


Figure 40a-Example 40; A375sq2 cells



	Synergy Score
A x 5	2.14
A self-cross	0.333
5 self-cross	0.294

Figure 41-Example 41; CAL-51 cells

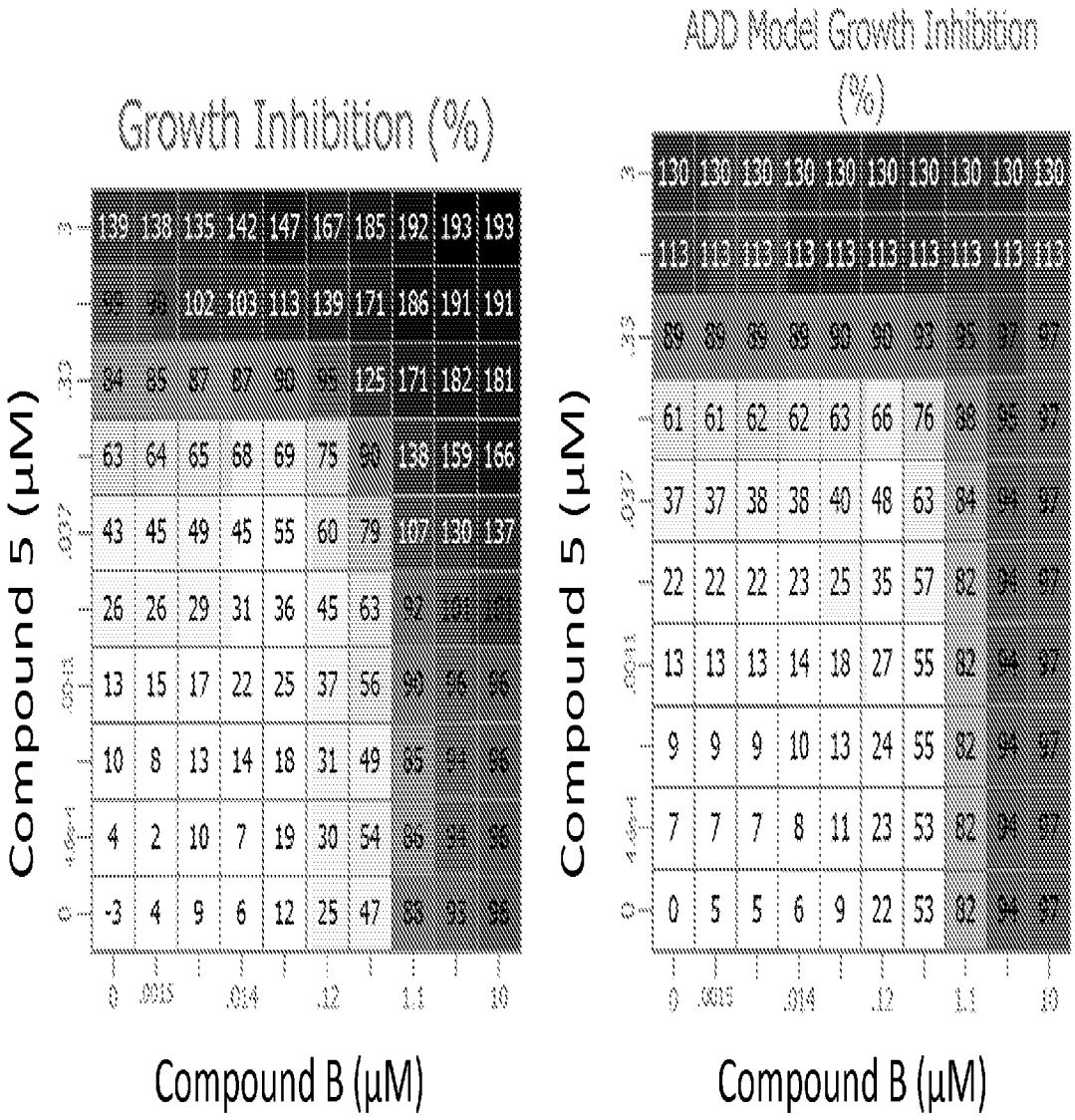
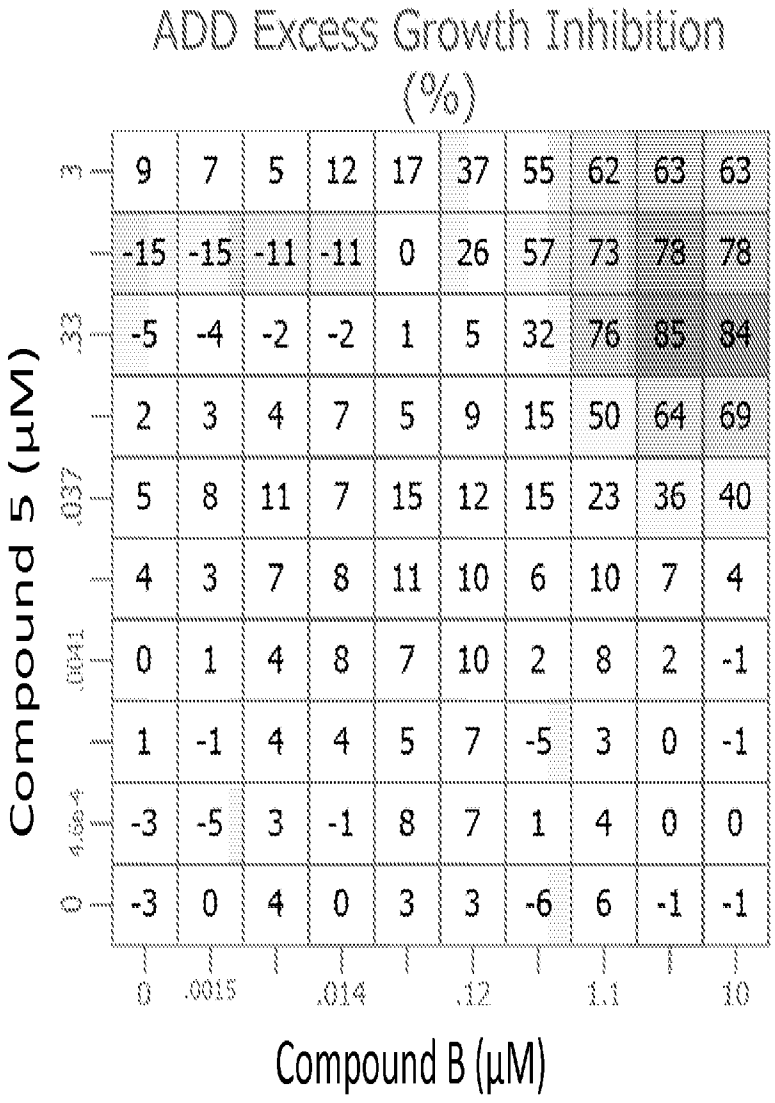


Figure 41a-Example 41; CAL-51 cells



	Synergy Score
B x 5	26.4
B self-cross	0.386
5 self-cross	3.85

Figure 42-Example 42; G-361 cells

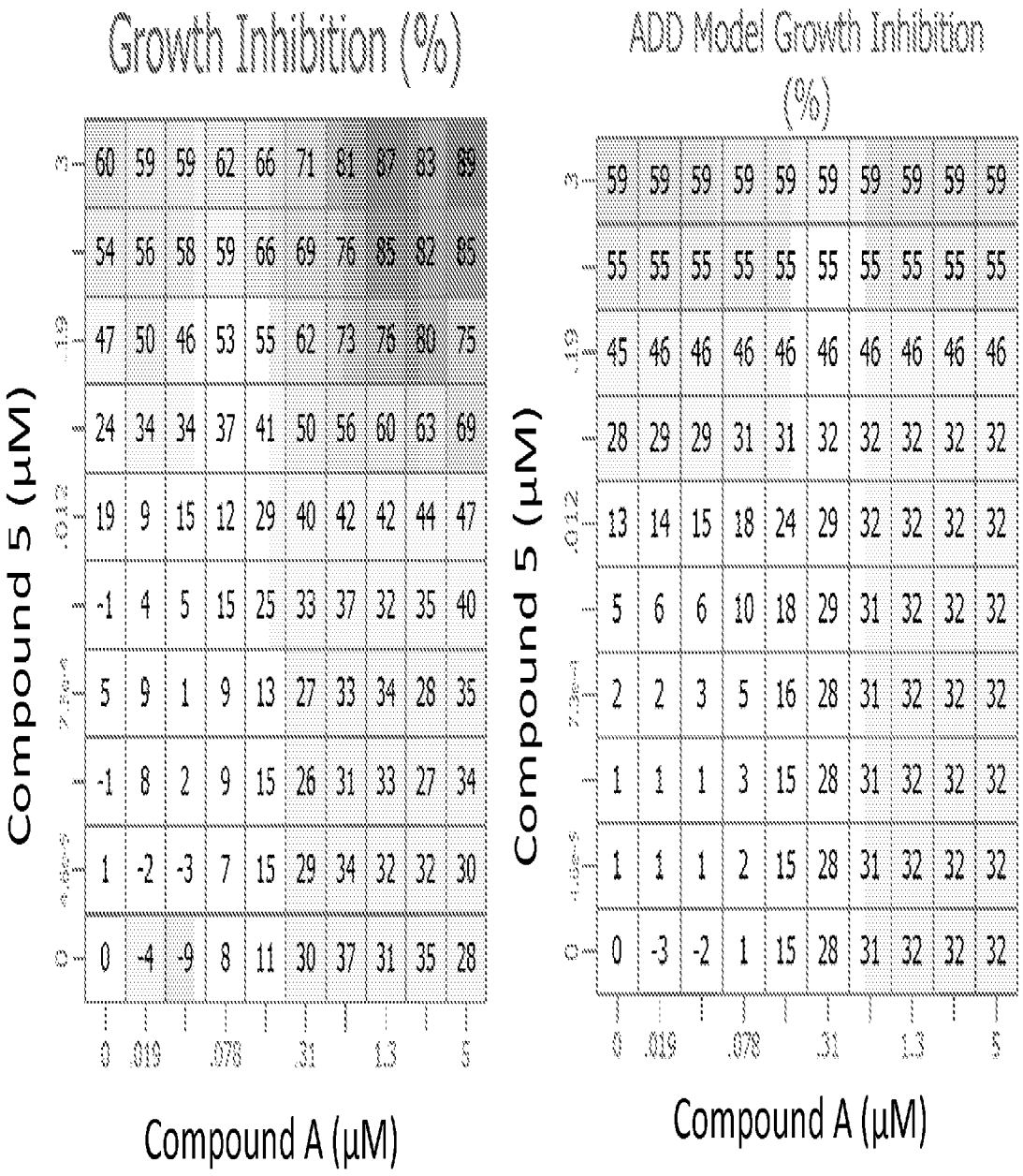
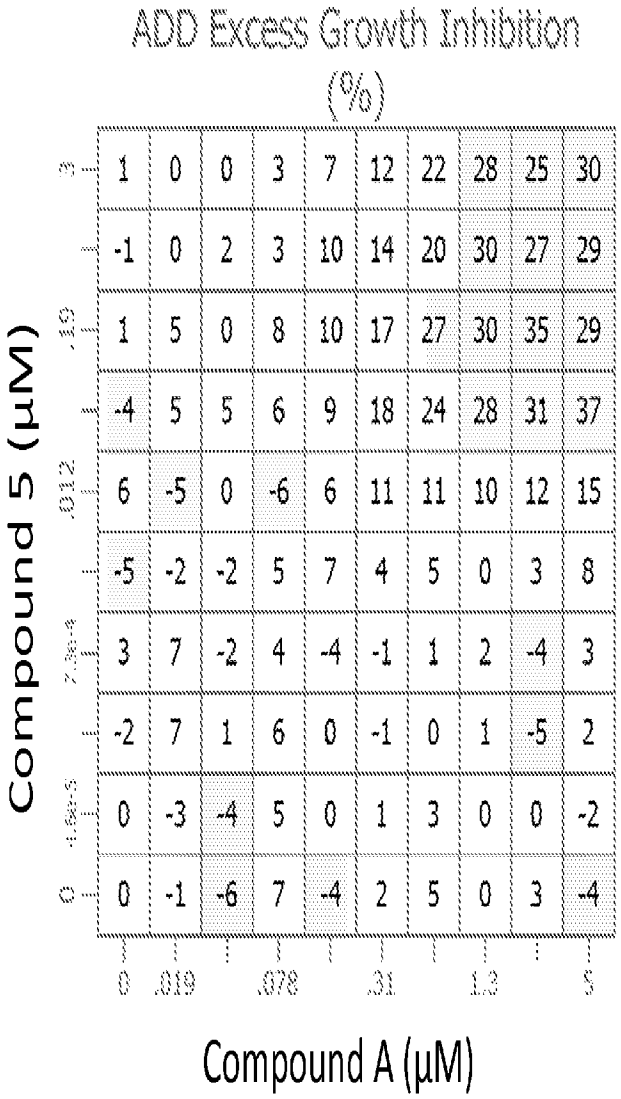


Figure 42a-Example 42; G-361 cells



	Synergy Score
A x 5	4.48
A self-cross	0.144
5 self-cross	1.93

Figure 43-Example 43; HT-1197 cells

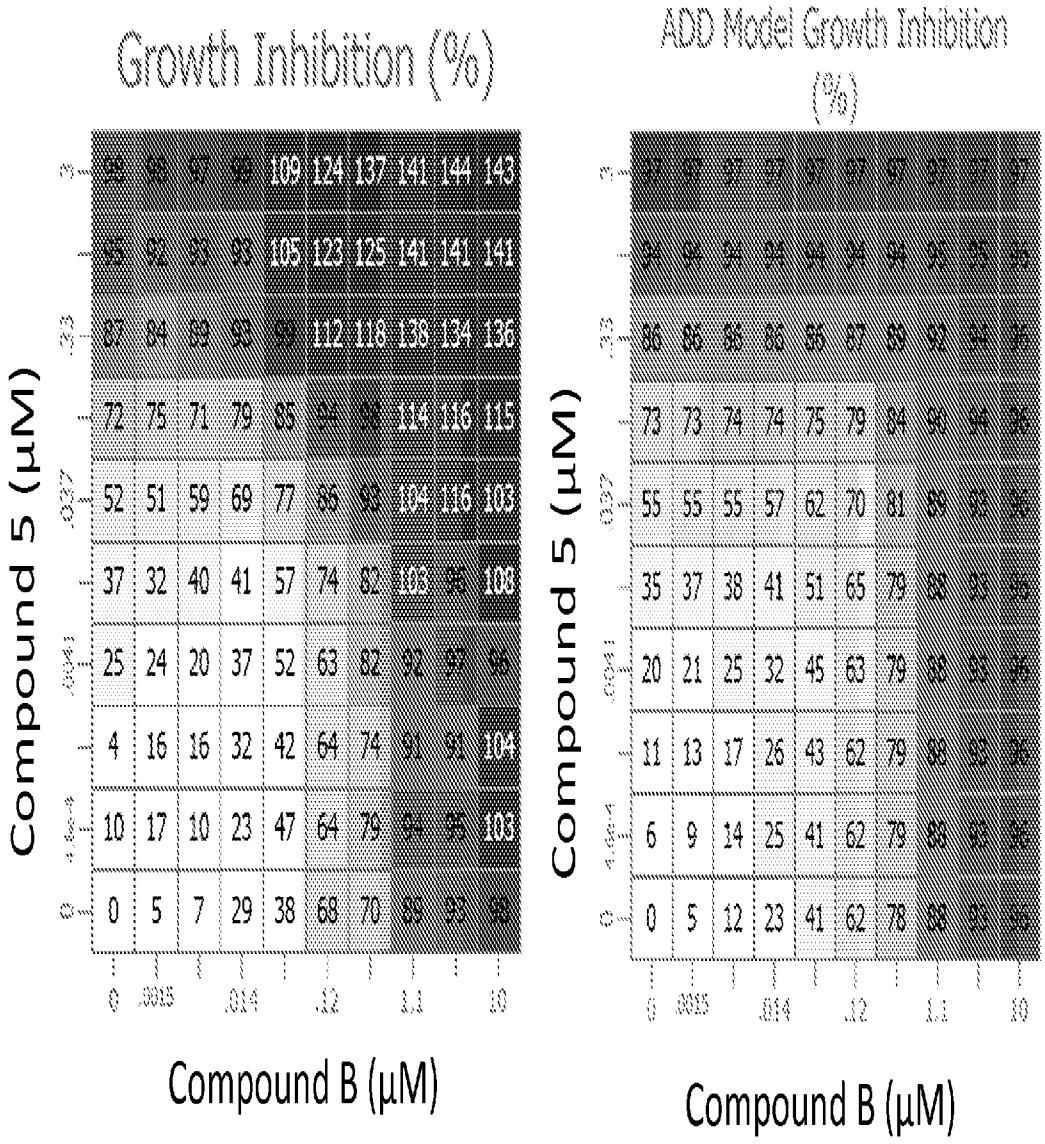
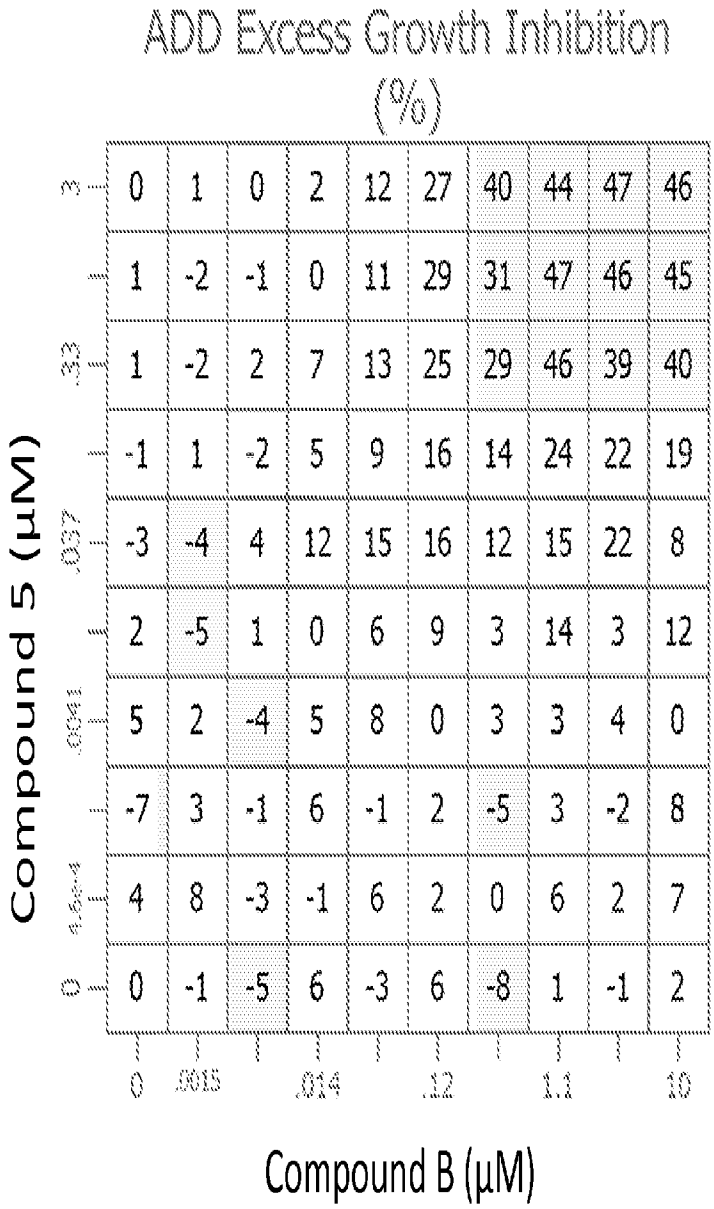


Figure 43a-Example 43; HT1197 cells



	Synergy Score
B x 5	13.8
B self-cross	0.901
5 self-cross	0.799

Figure 44-Example 44; LS 174T cells

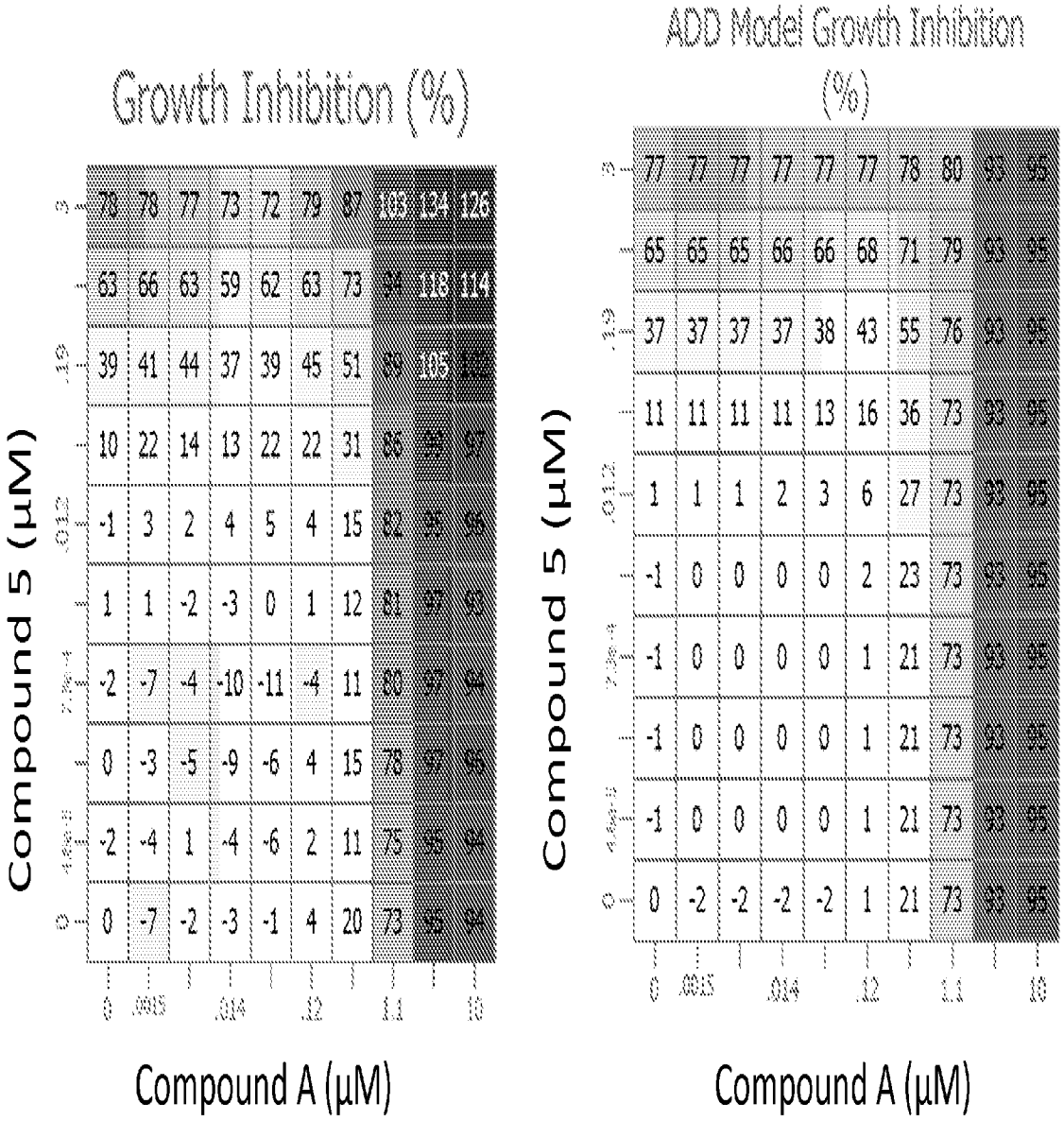
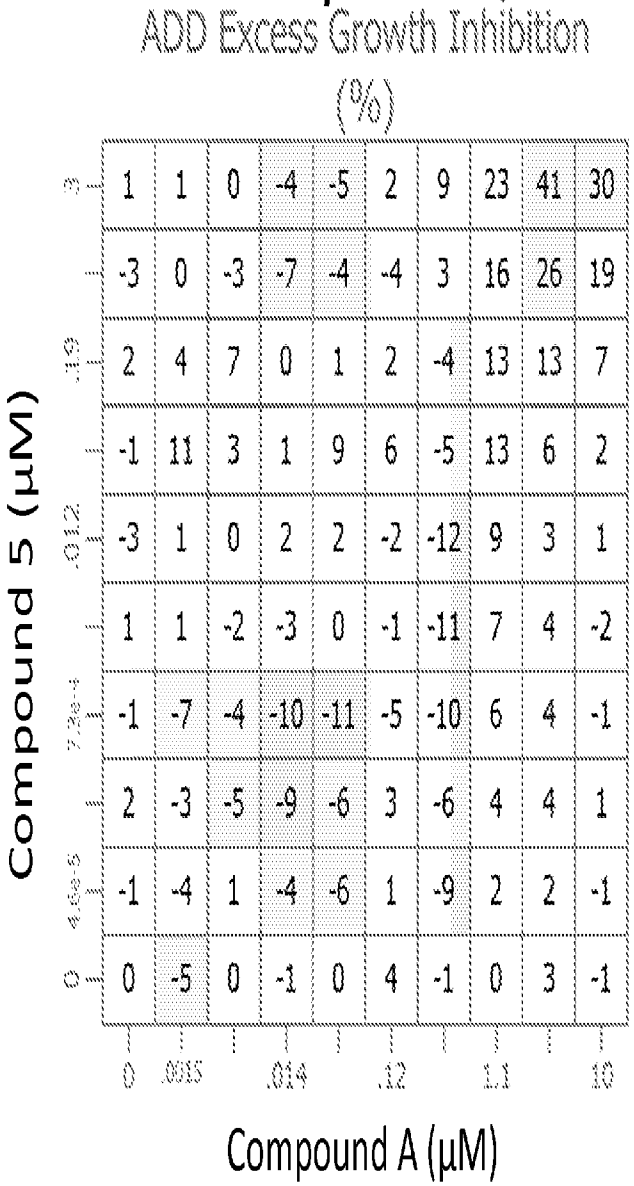


Figure 44a-Example 44; LS 174T cells



	Synergy Score
A x 5	4.56
A self-cross	0.578
5 self-cross	0.312

Figure 45-Example 45; MCF7 cells

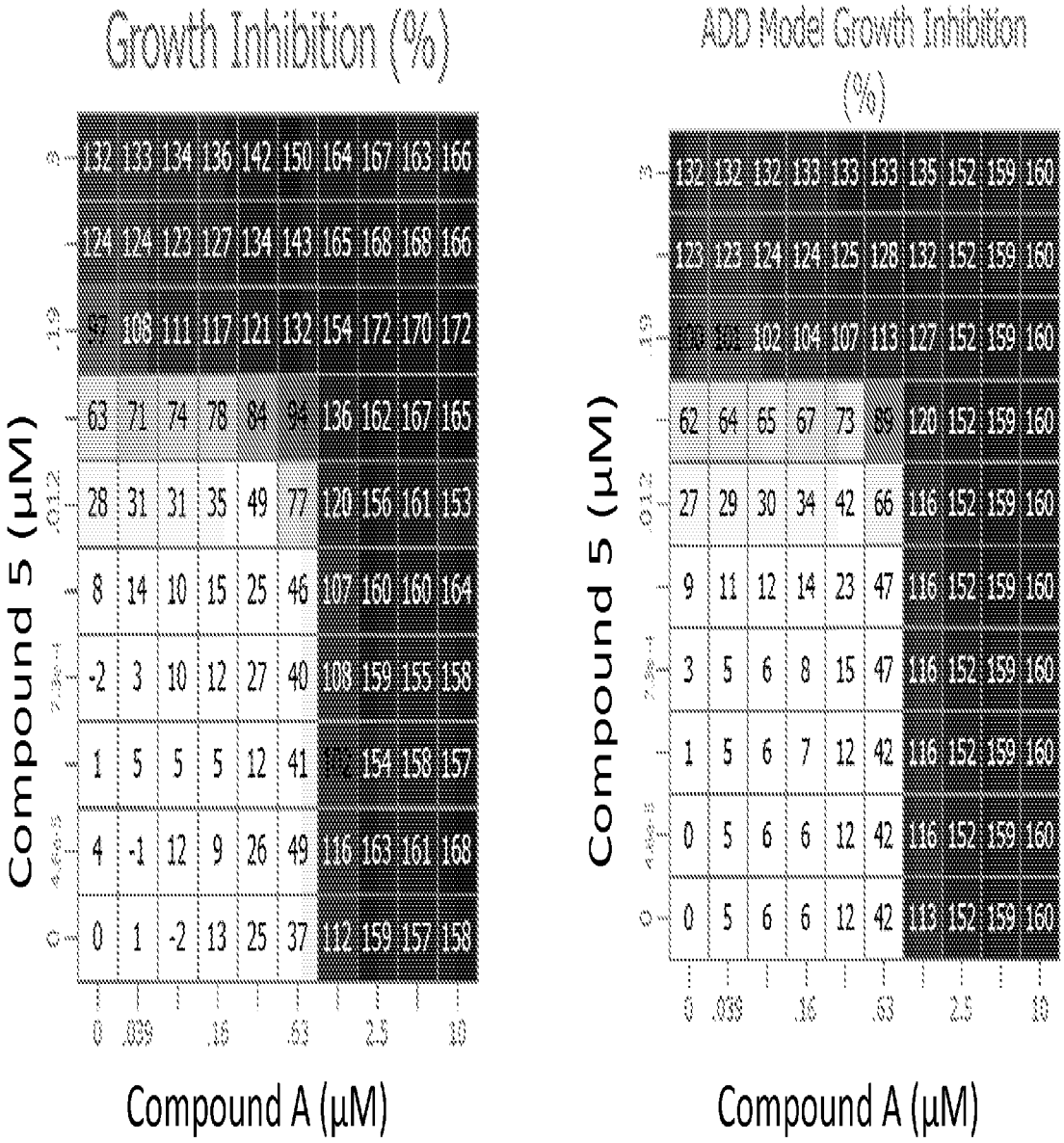
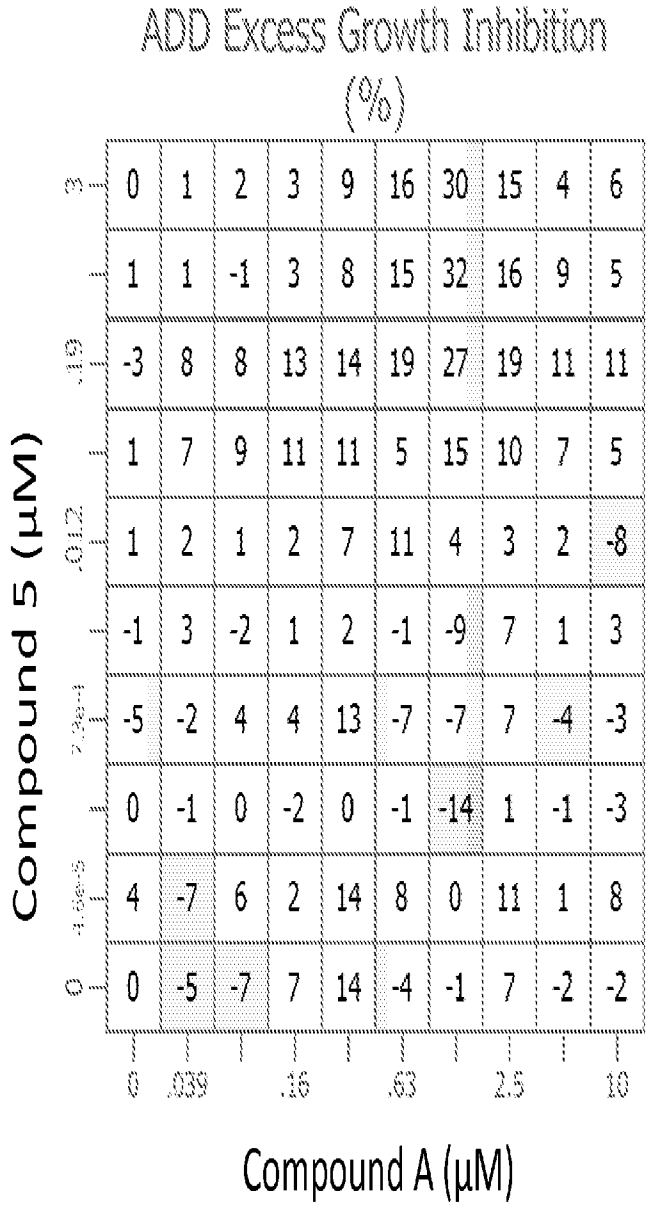


Figure 45a-Example 45; MCF7 cells



	Synergy Score
A x 5	6.32
A self-cross	0.753
5 self-cross	2.48

Figure 46-Example 46; NCI-H460 cells

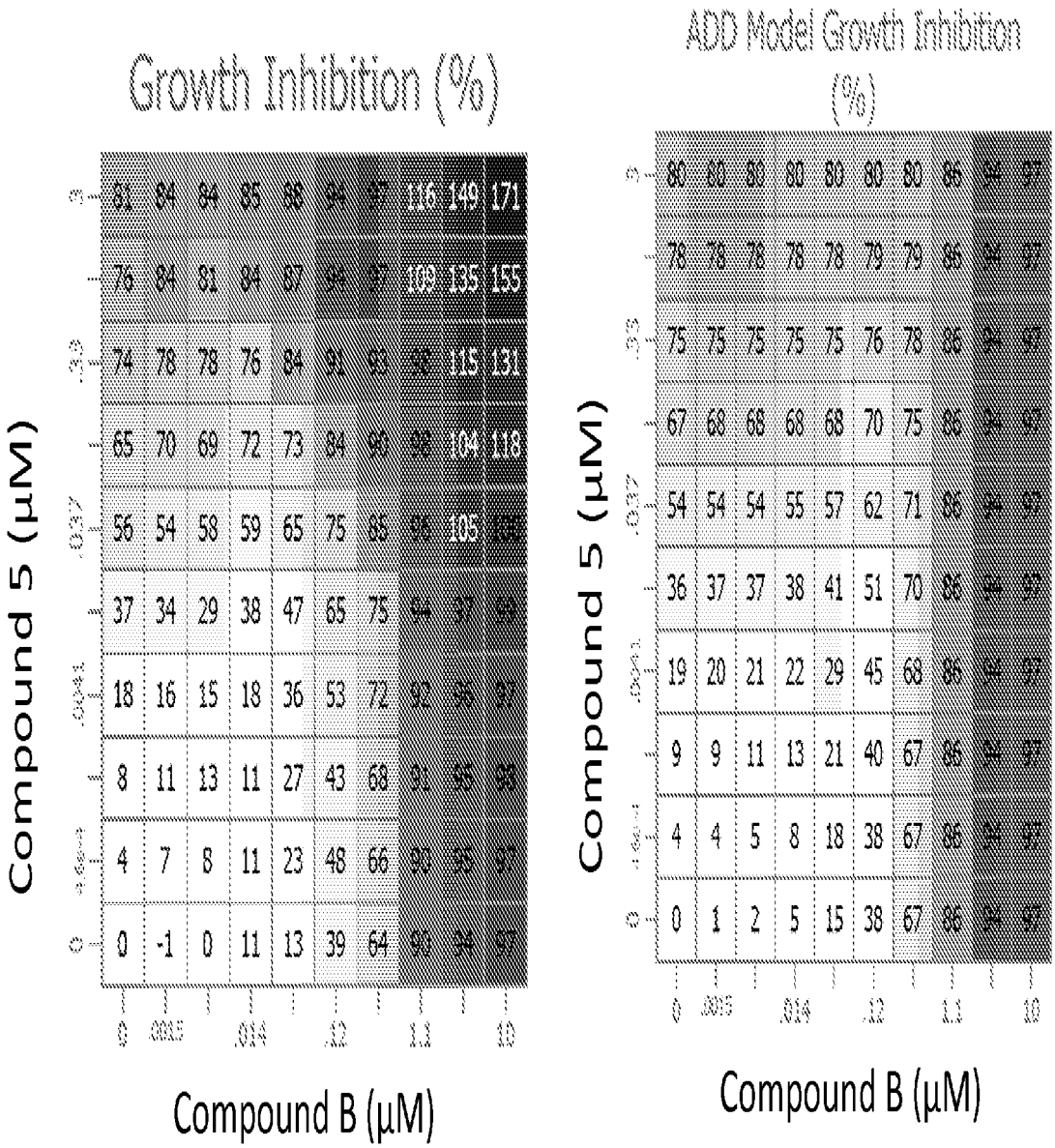
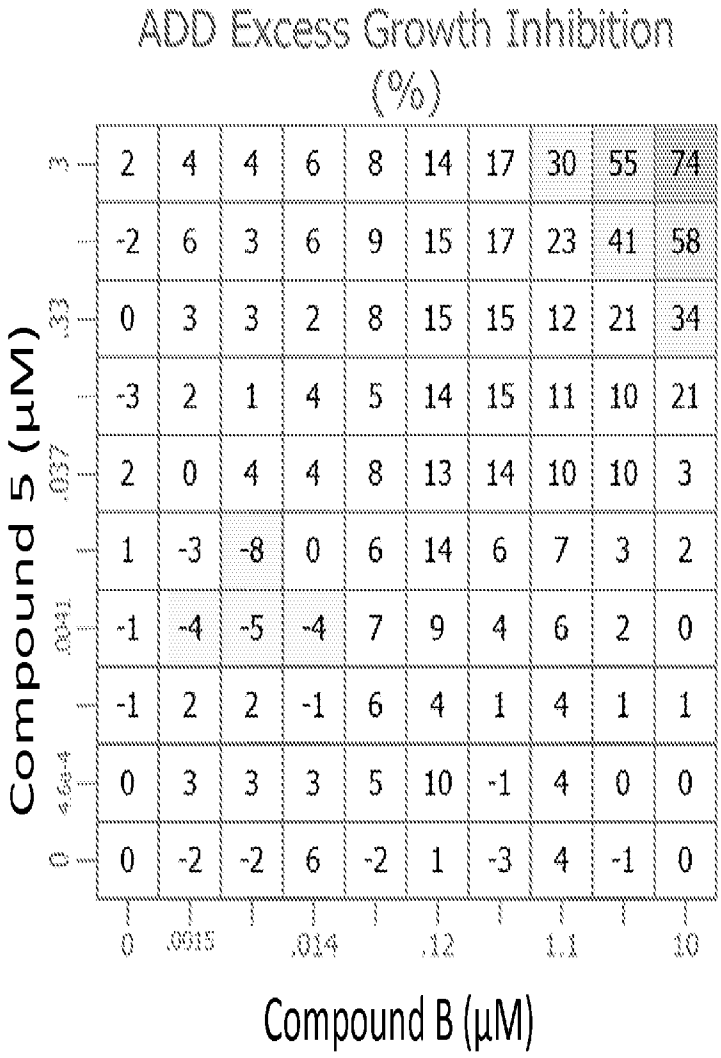


Figure 46a-Example 46; NCI-H460 cells



	Synergy Score
B x 5	10.1
B self-cross	0.496
5 self-cross	0.683

Figure 47-Example 47; RKO cells

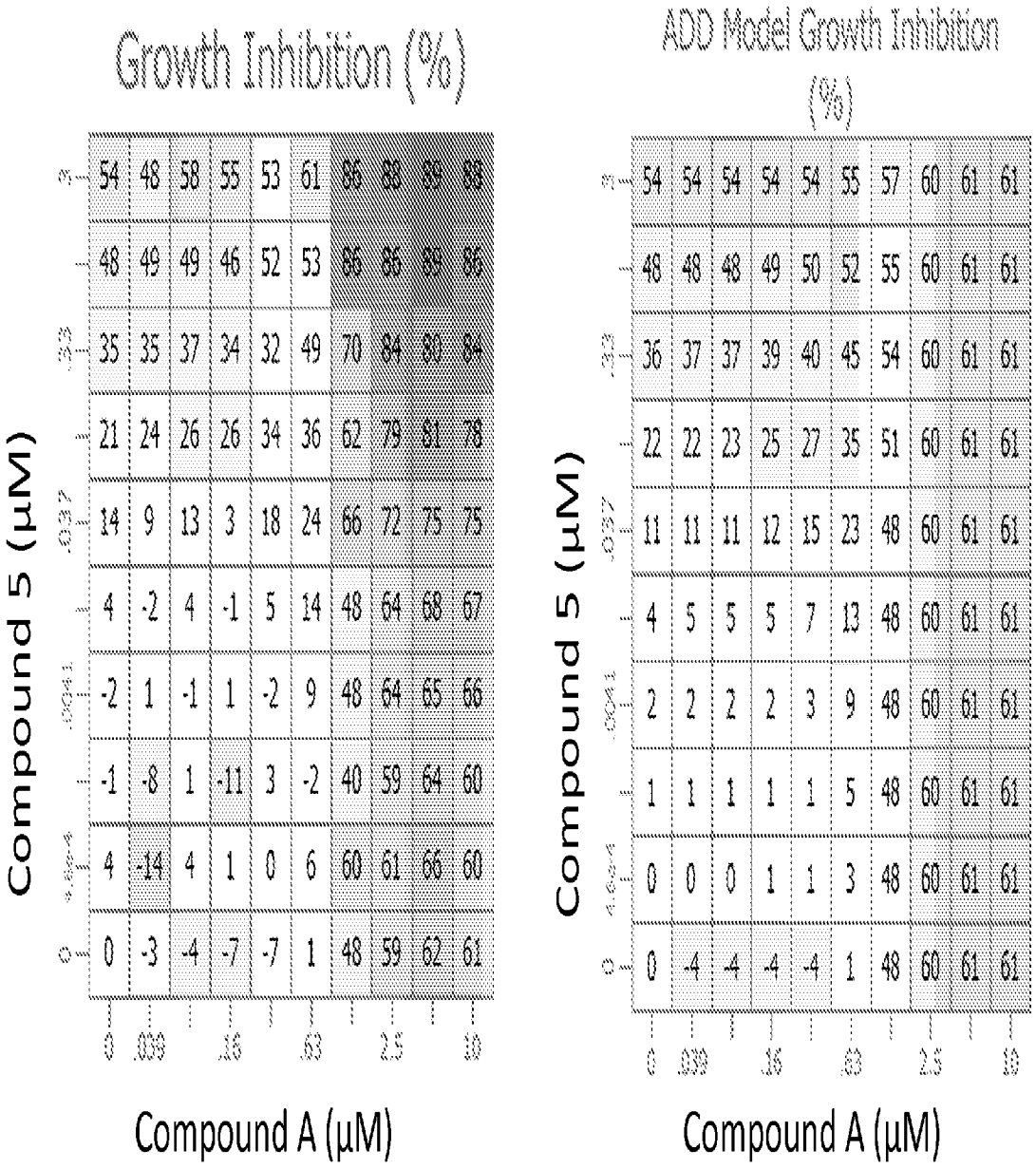
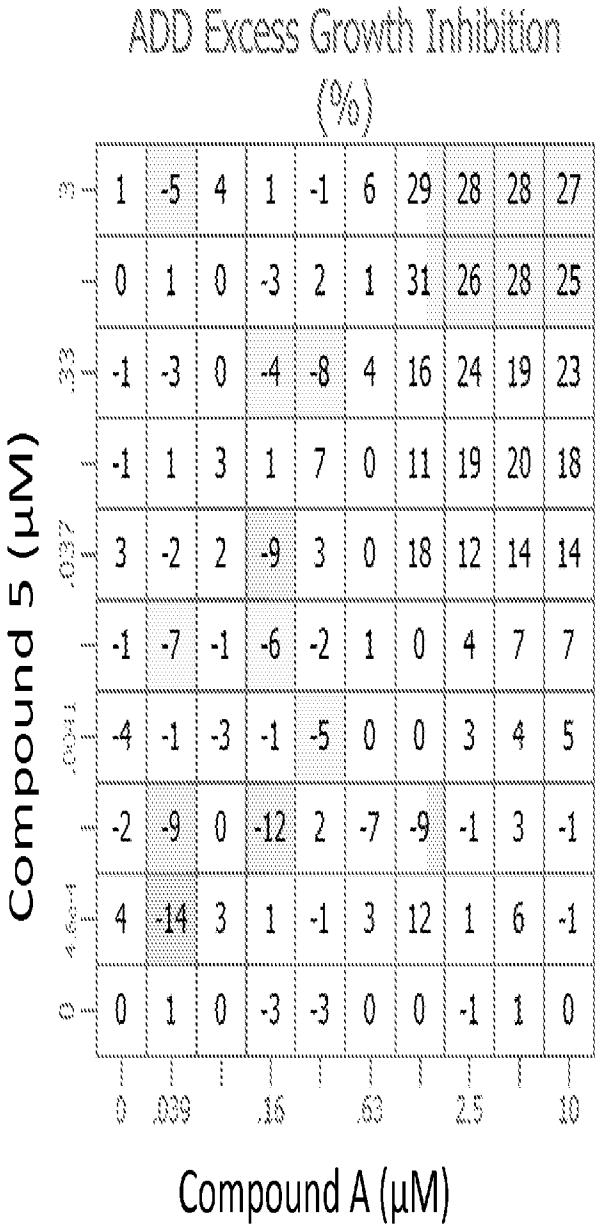


Figure 47a-Example 47; RKO cells



	Synergy Score
A x 5	3.06
A self-cross	0.235
5 self-cross	0.485

Figure 48-Example 48; A204 cells

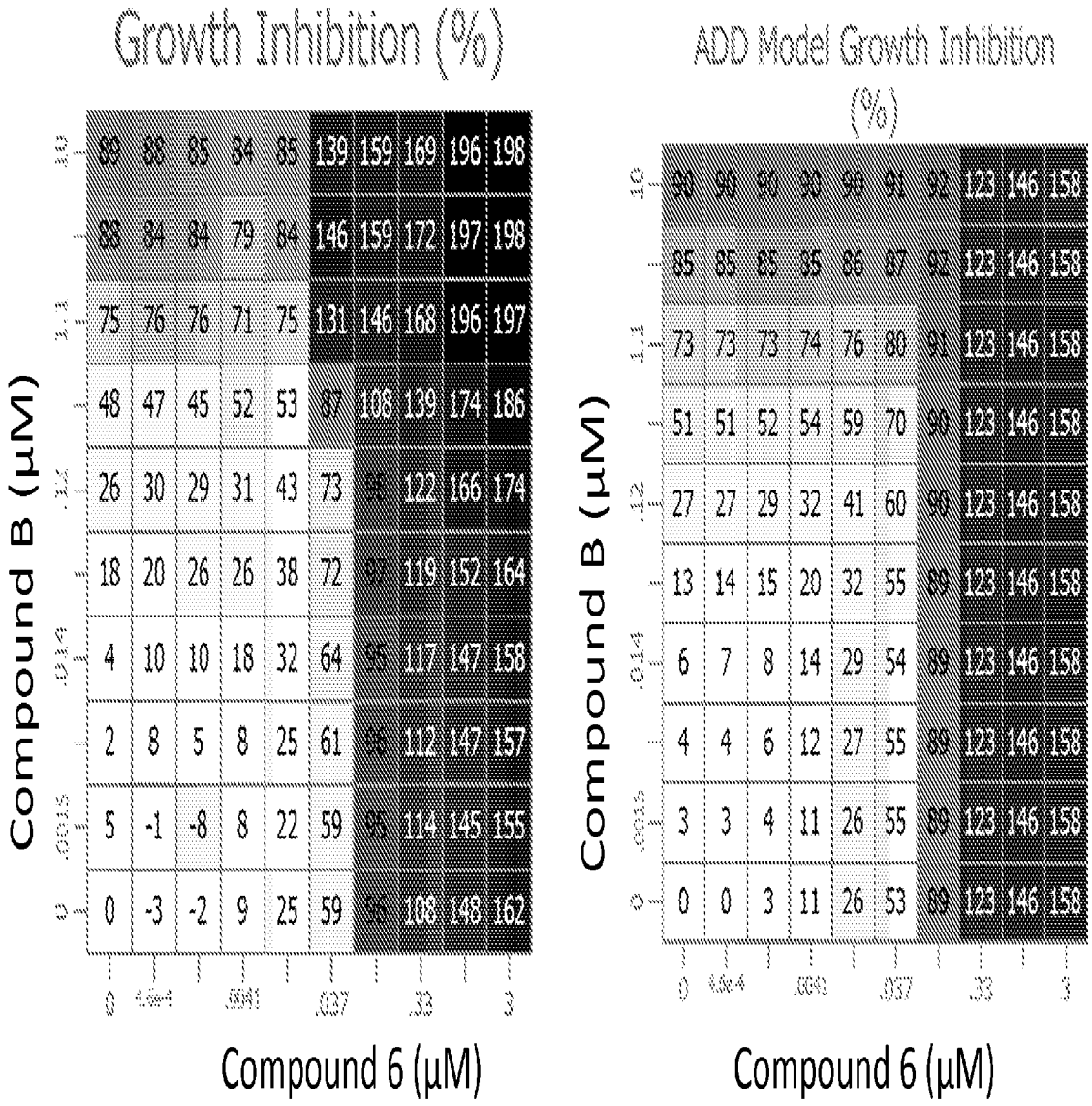
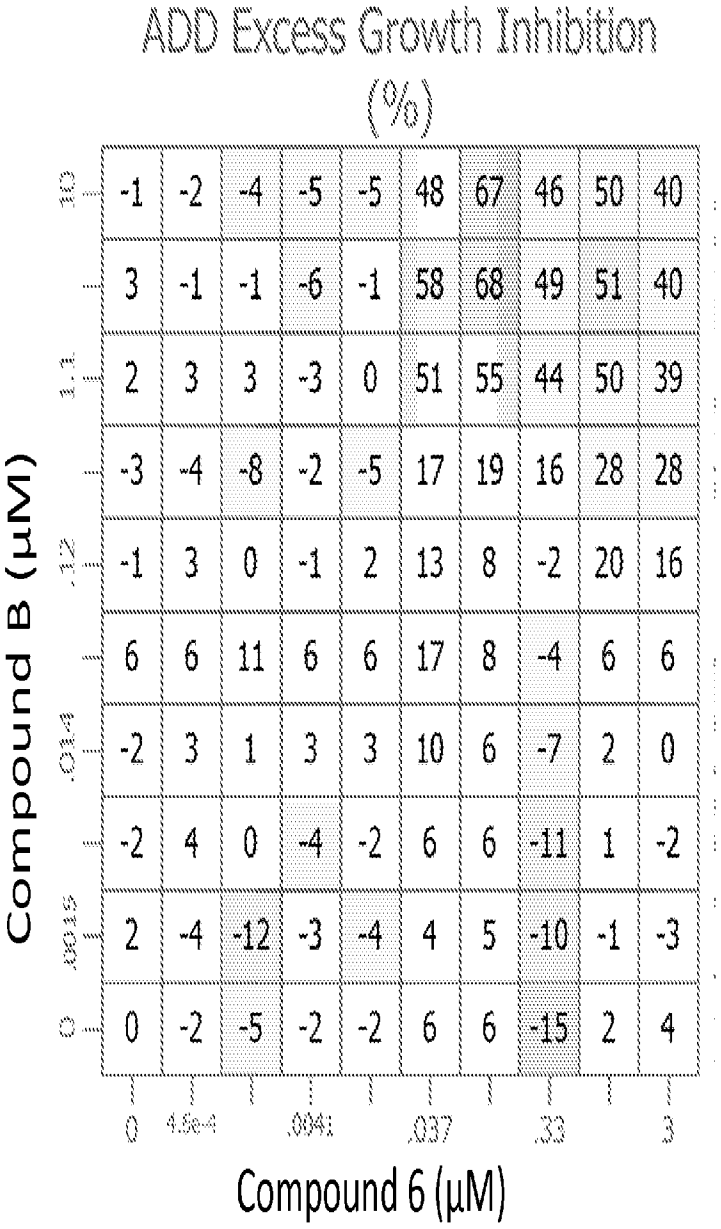


Figure 48a-Example 48; A204 cells



	Synergy Score
B x 6	19.4
B self-cross	0.792
6 self-cross	3.52

Figure 49-Example 49; A2780 cells

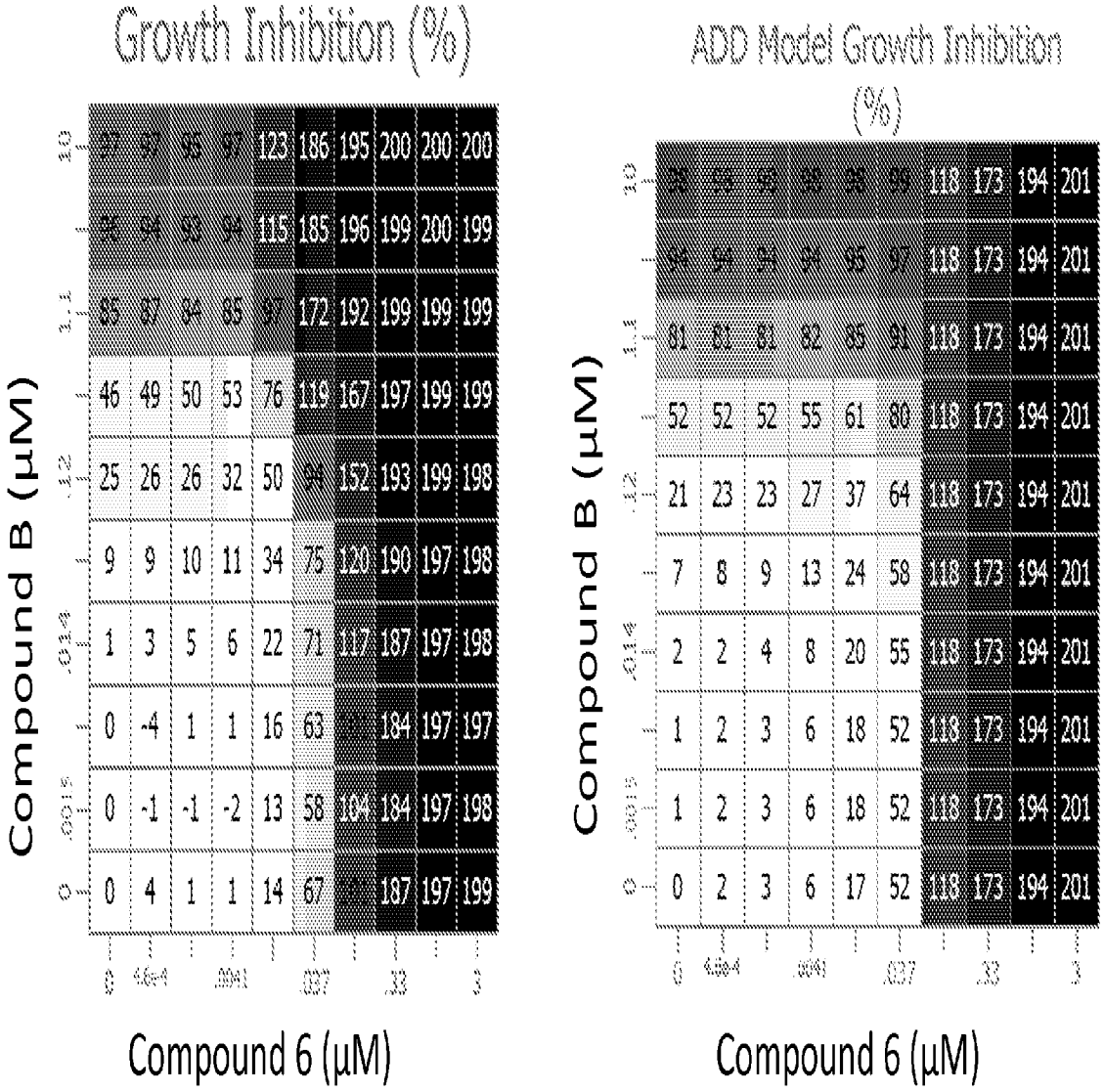
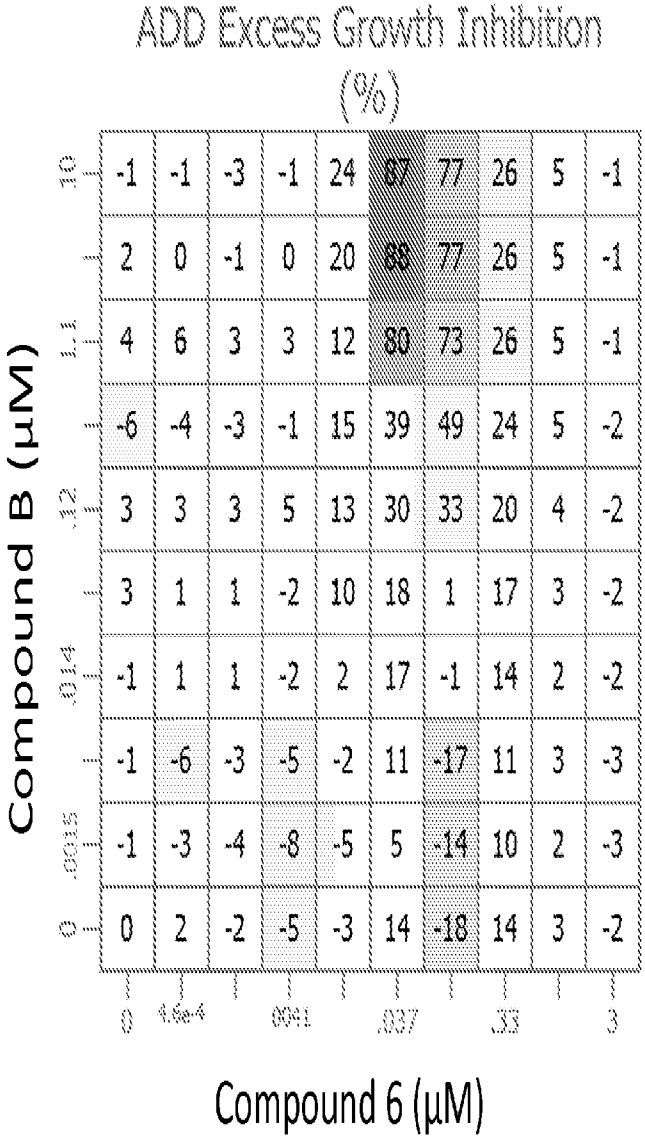


Figure 49a-Example 49; A2780 cells



	Synergy Score
B x 6	20
B cross-self	0.561
6 cross-self	4.38

Figure 50-Example 50; C32 cells

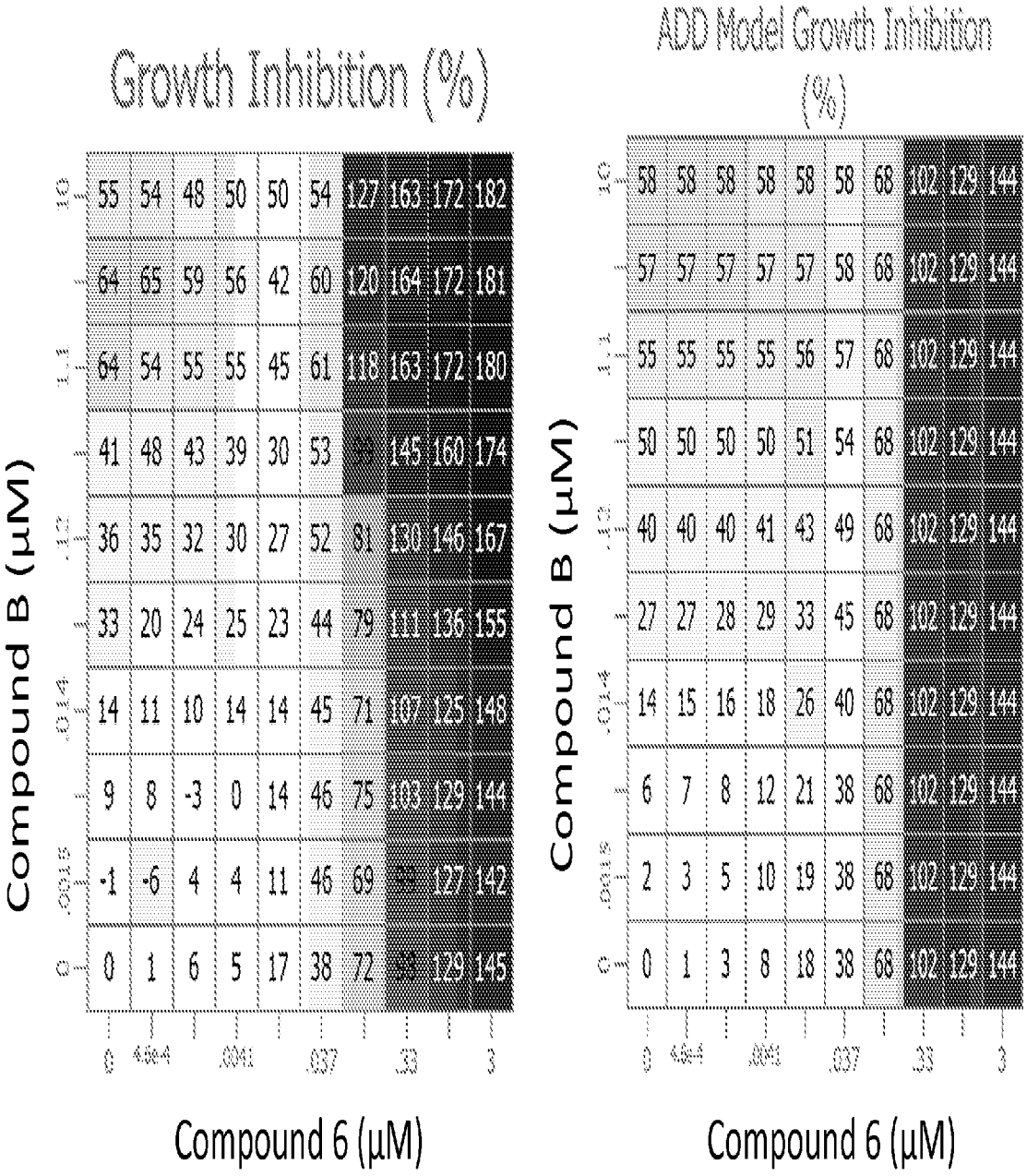
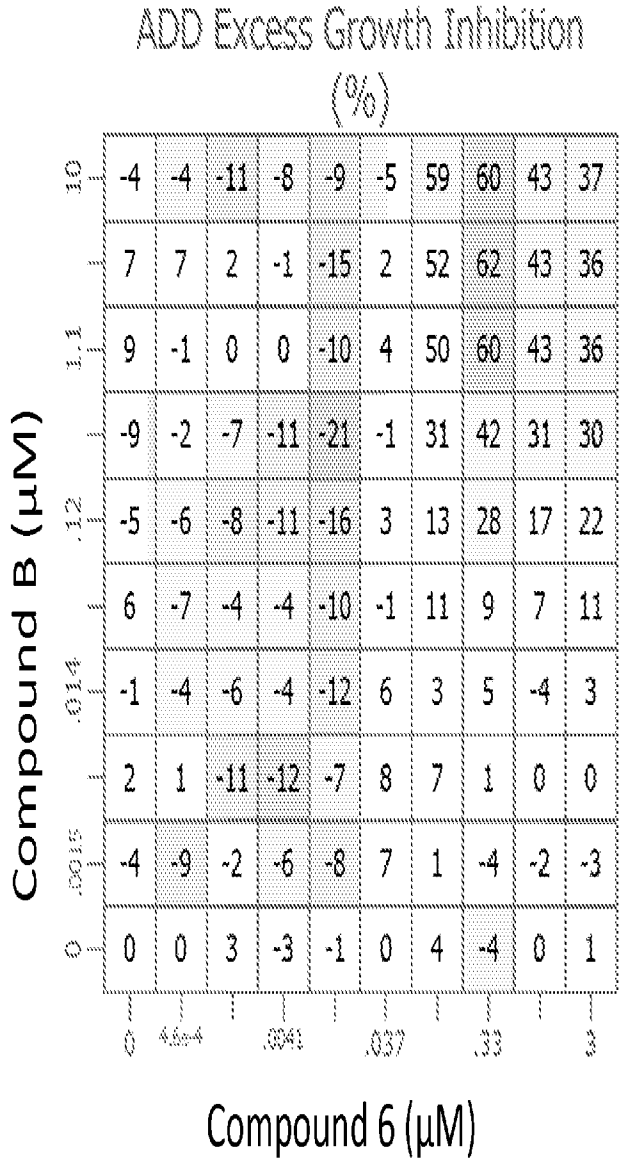


Figure 50a- Example 50; C32 cells



	Synergy Score
B x 6	15.7
B self-cross	1.09
6 self-cross	1.75

Figure 51-Example 51; G-401 cells

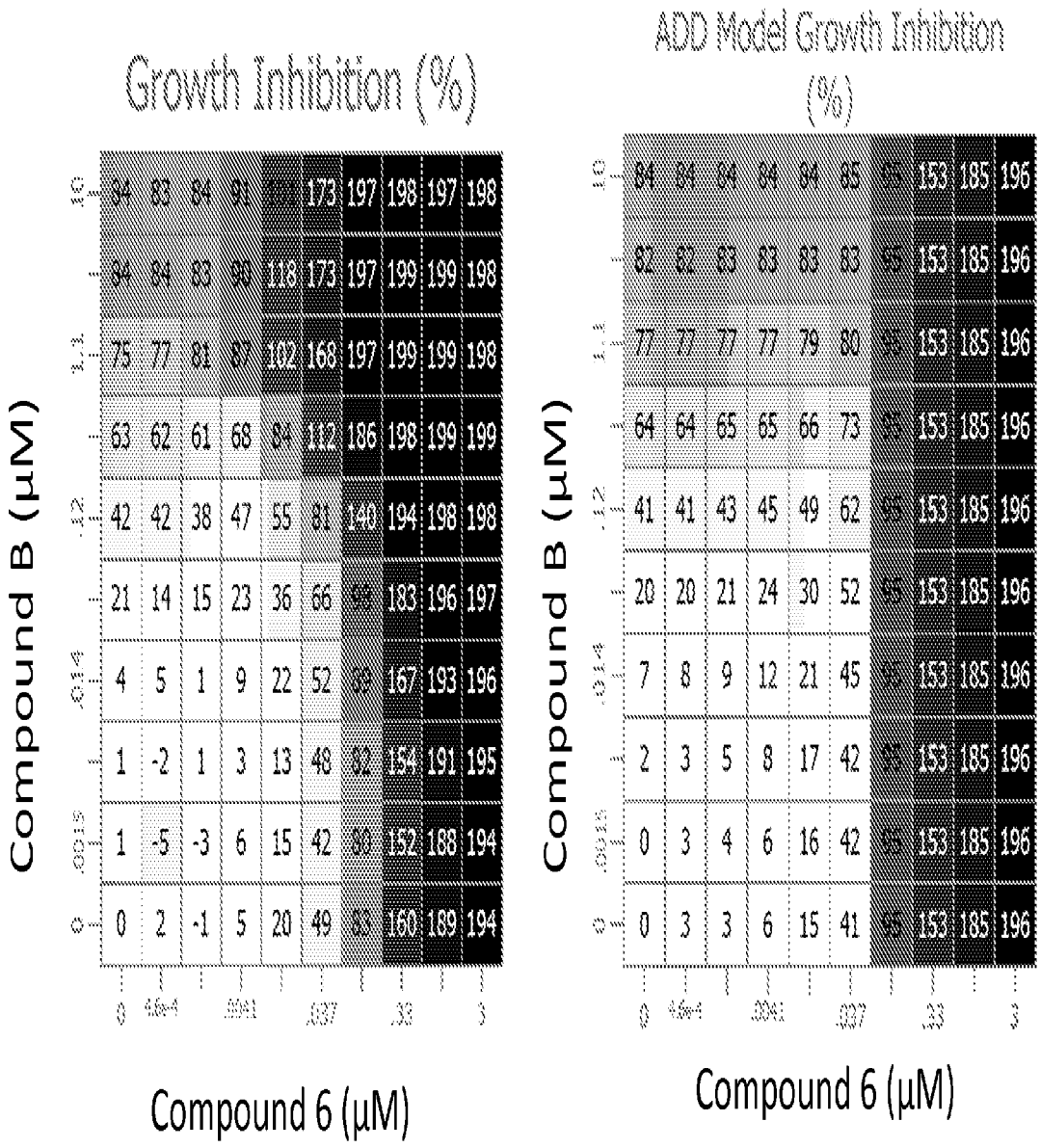
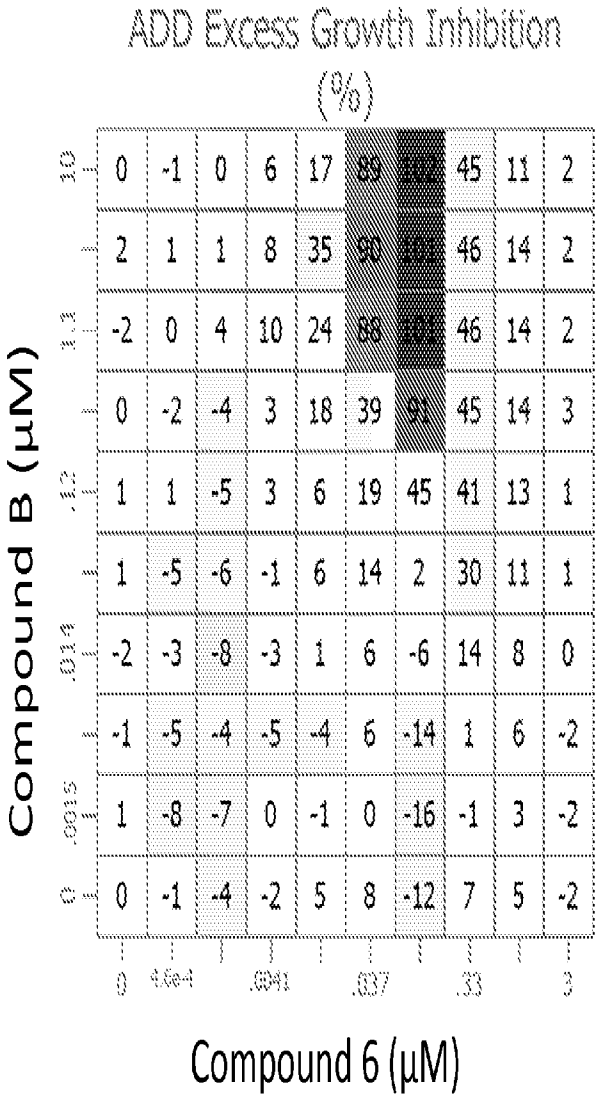


Figure 51a-Example 51; G-401 cells



	Synergy Score
B x 6	26.8
B self-cross	0.548
6 self-cross	4.14

Figure 52-Example 52; SK-HEP-1 cells

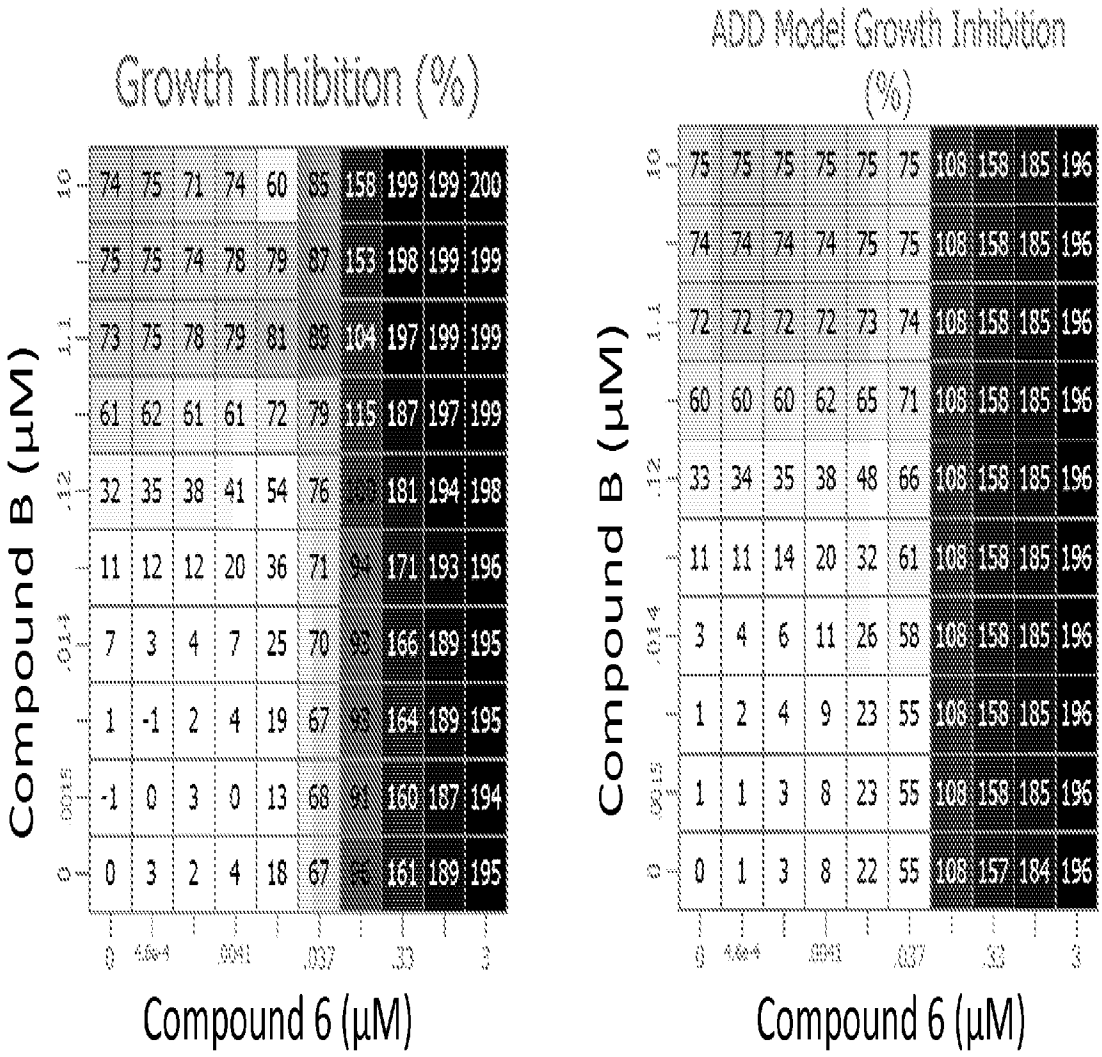
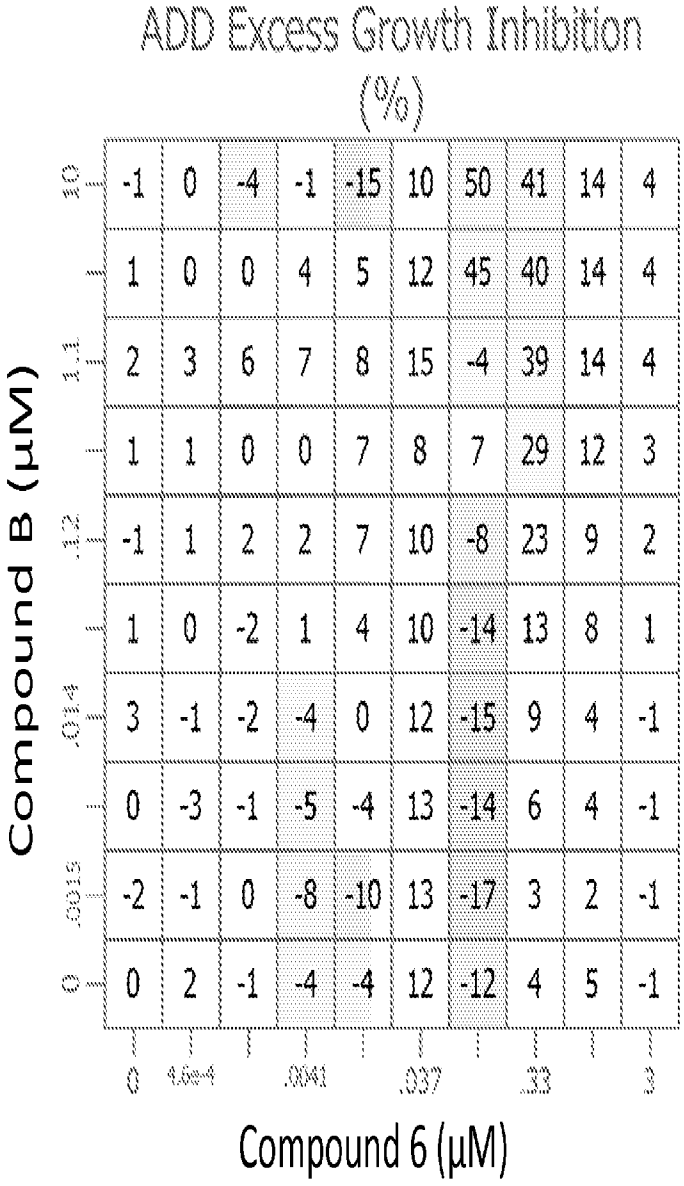


Figure 52a-Example 52; SK-HEP-1 cells



	Synergy Score
B x 6	10.3
B self-cross	0.827
6 self-cross	0.98

Figure 57-Example 57; BV-173 cells

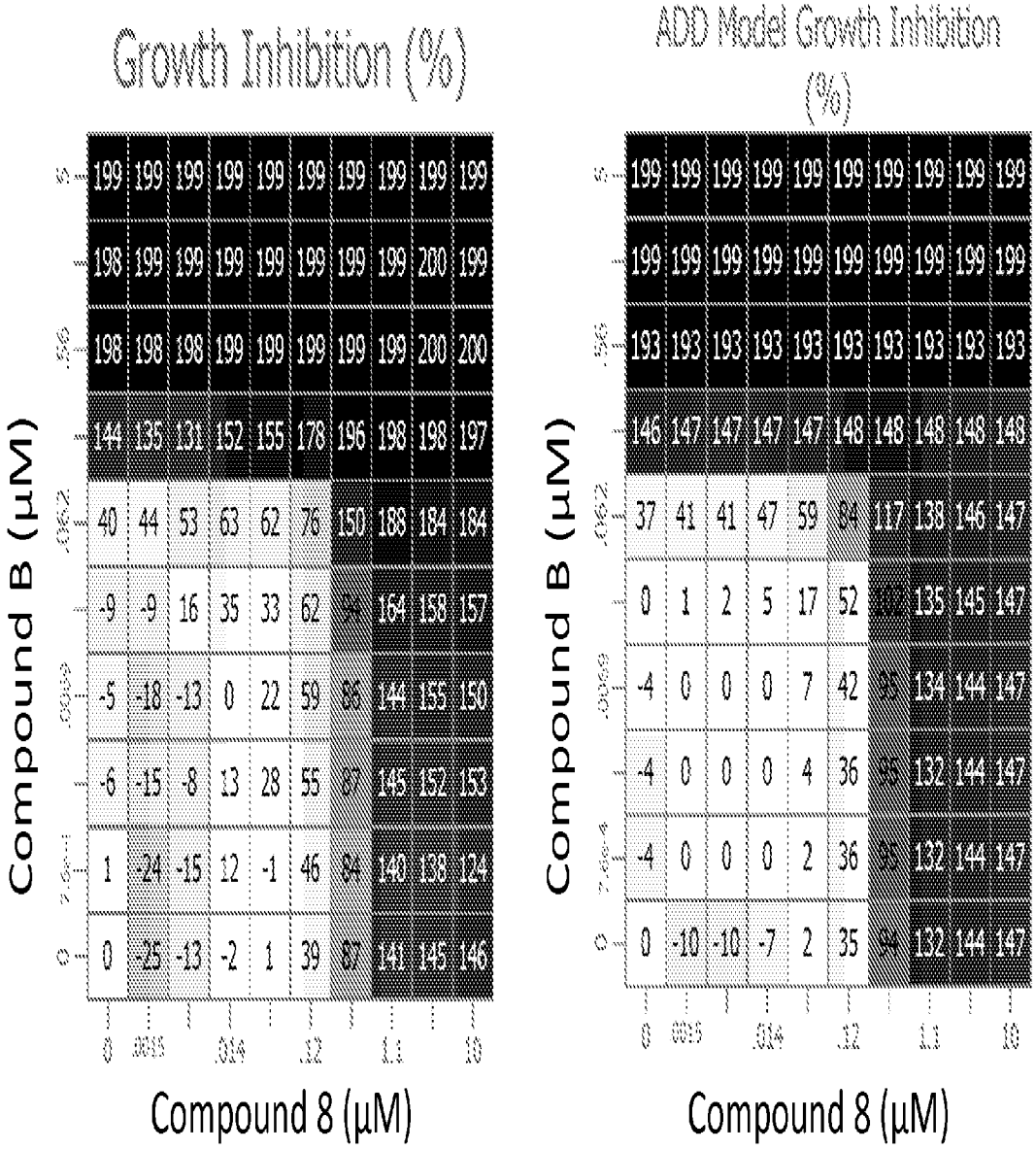
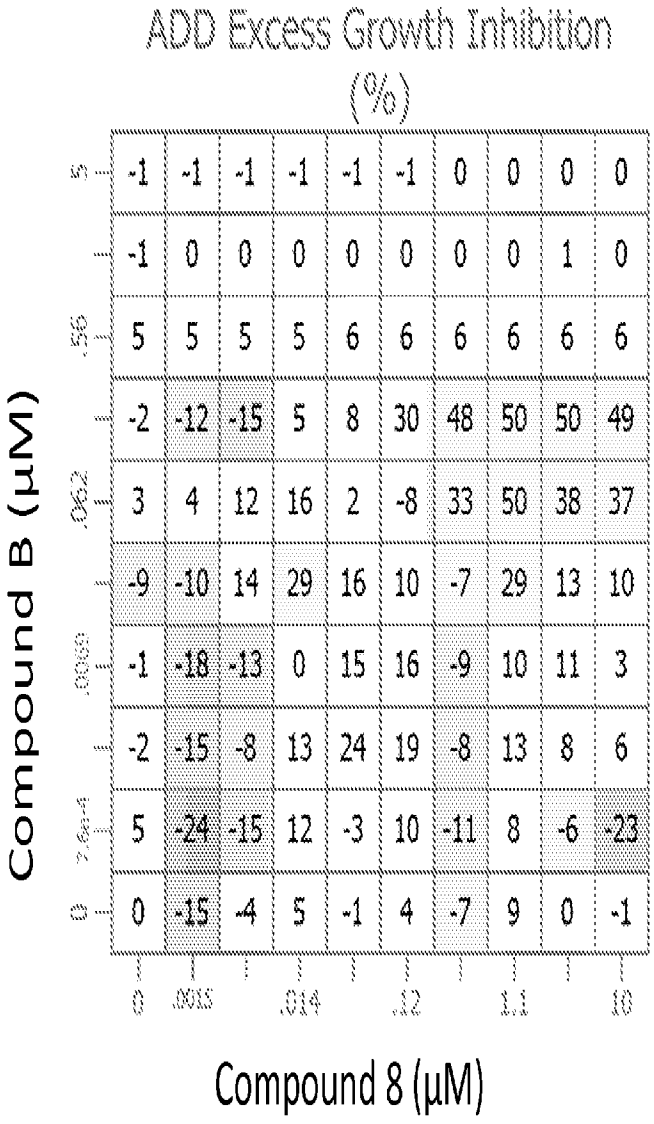


Figure 57a-Example 57; BV-173 cells



	Synergy Score
B x 8	13.3
B self-cross	2.68
8 self-cross	4.72

Figure 58-Example 58; CML-T1 cells

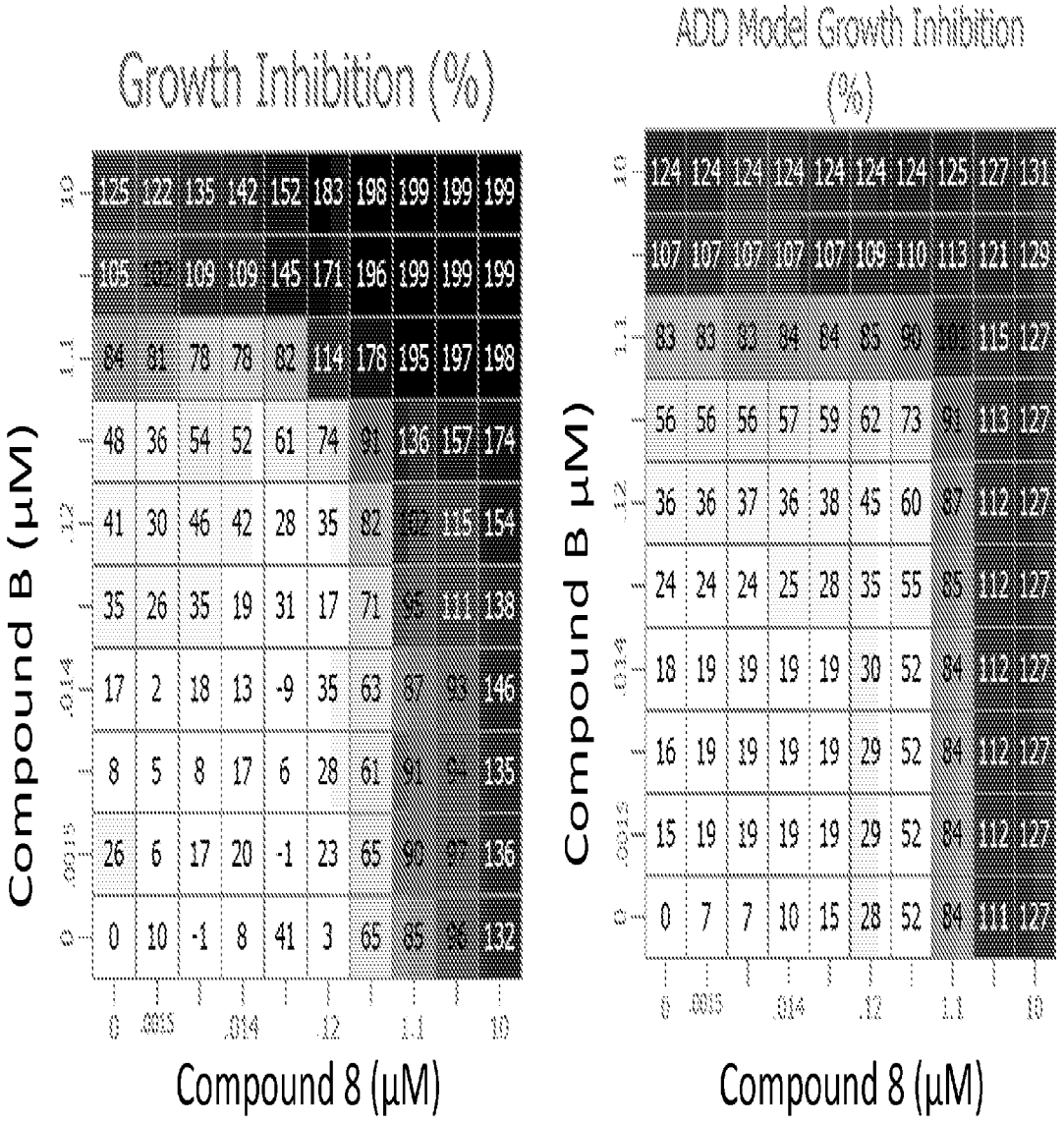
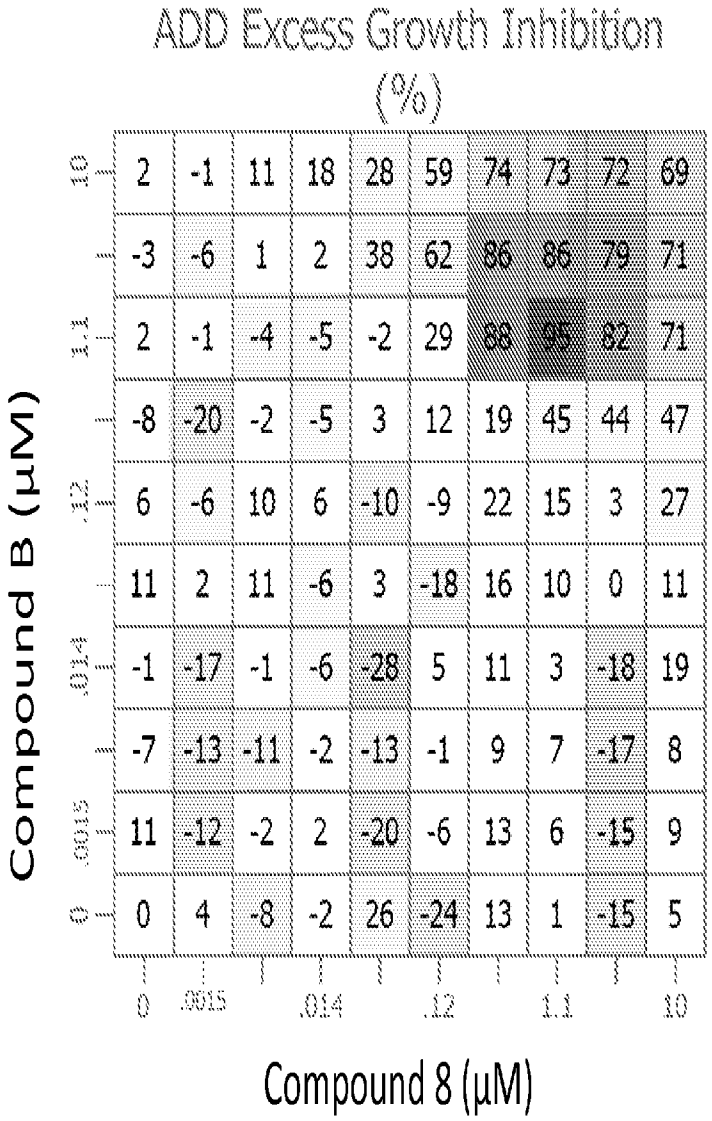


Figure 58a-Example 58; CML-T1 cells



	Synergy Score
B x 8	32.6
B self-cross	3.43
8 self-cross	6.61

Figure 59-Example 59; KNS-81-FD cells

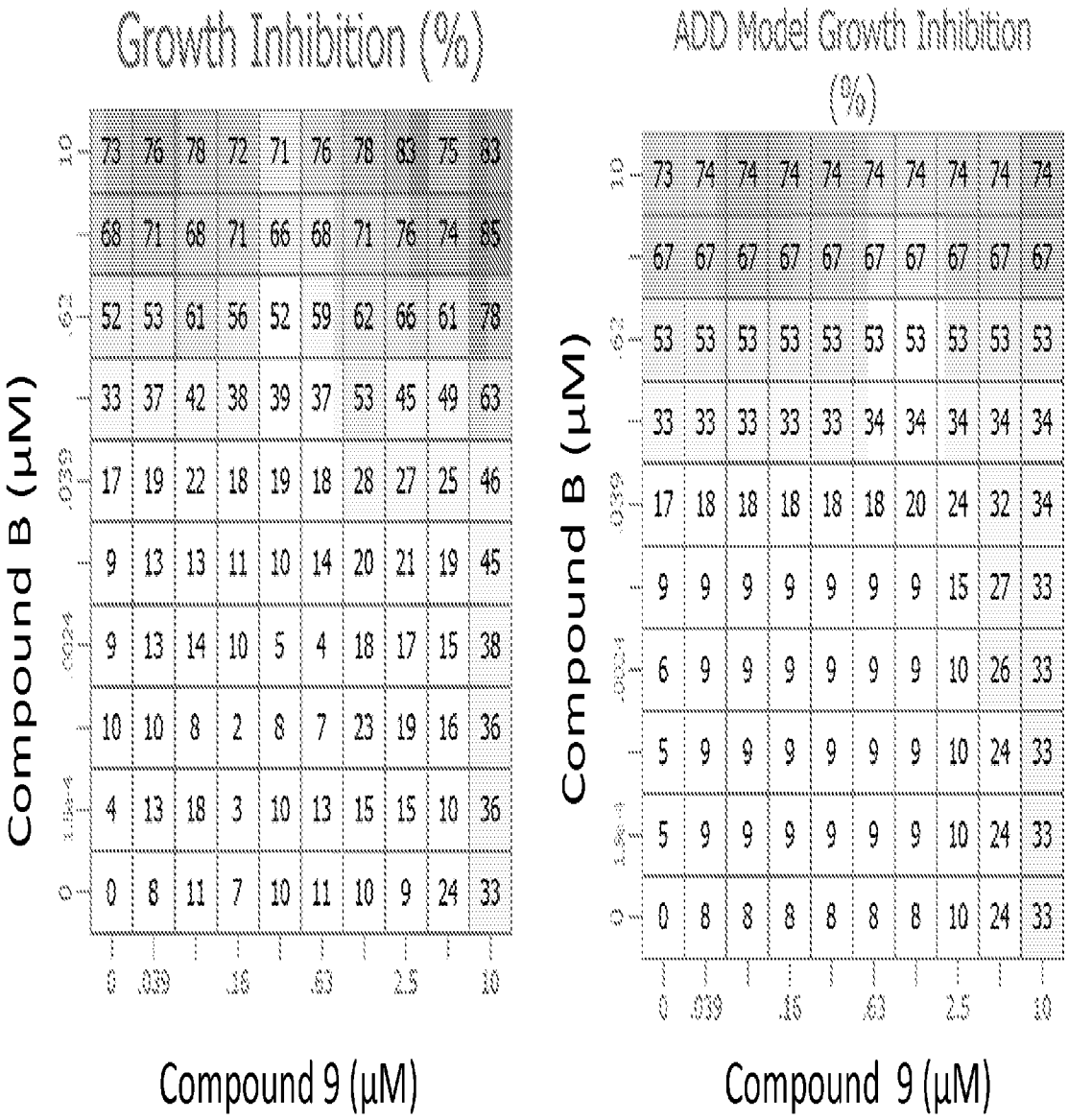
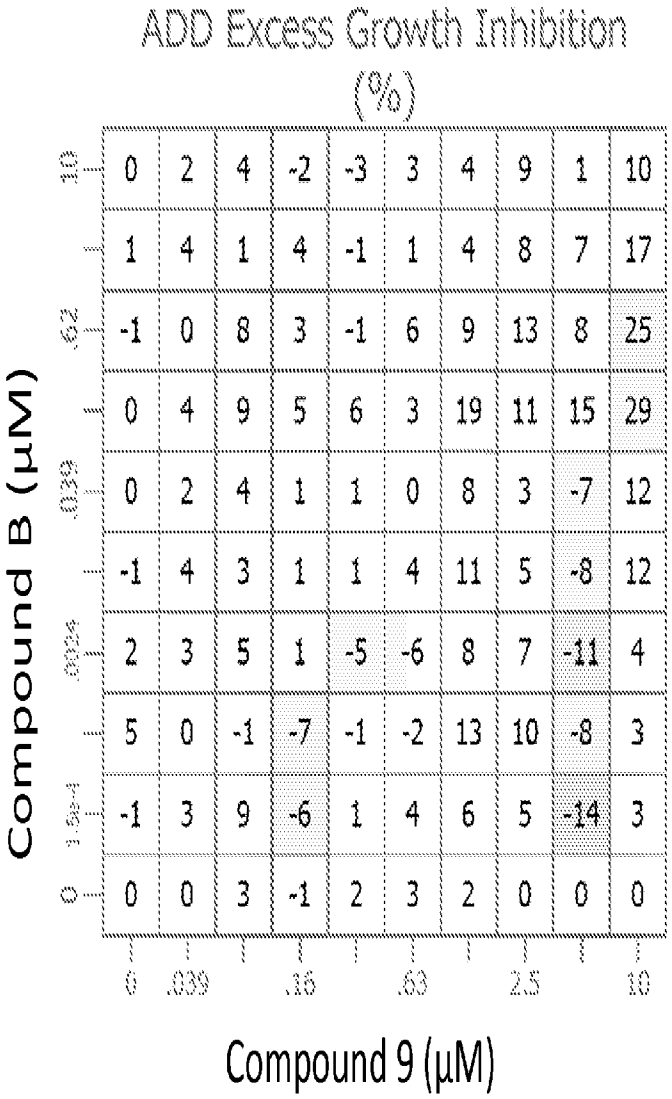


Figure 59a-Example 59; KNS-81-FD cells



	Synergy Score
B x 9	1.92
B self-cross	1.34
9 self-cross	0.103

Figure 60-Example 60; SW48 cells

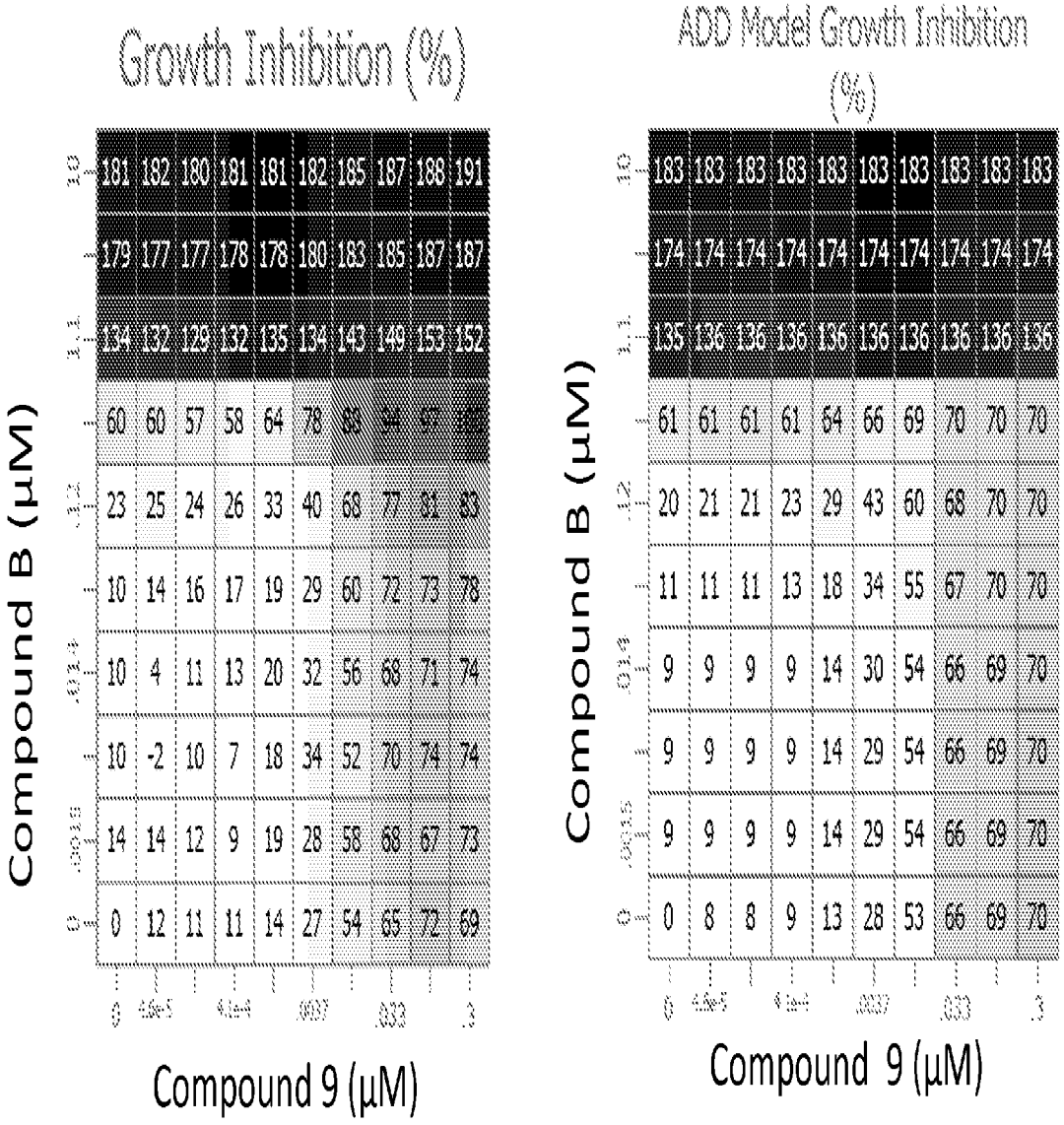
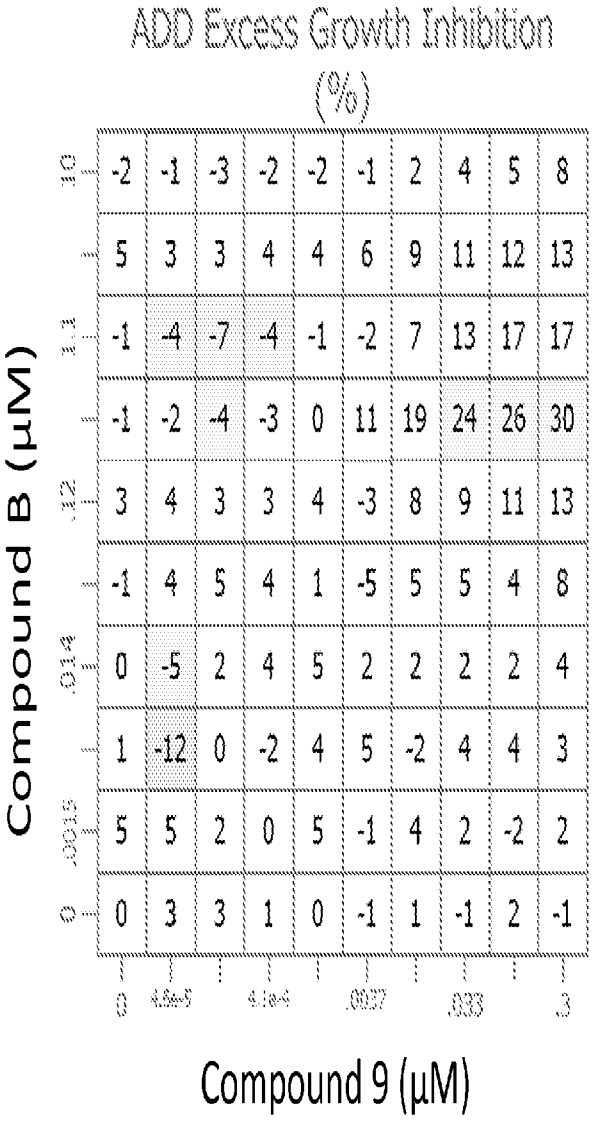


Figure 60a-Example 60; SW48 cells



	Synergy Score
B x 9	5.06
B self-cross	2.23
9 self-cross	0.59

Figure 61-Example 61; MDA-MB-175-VII cells

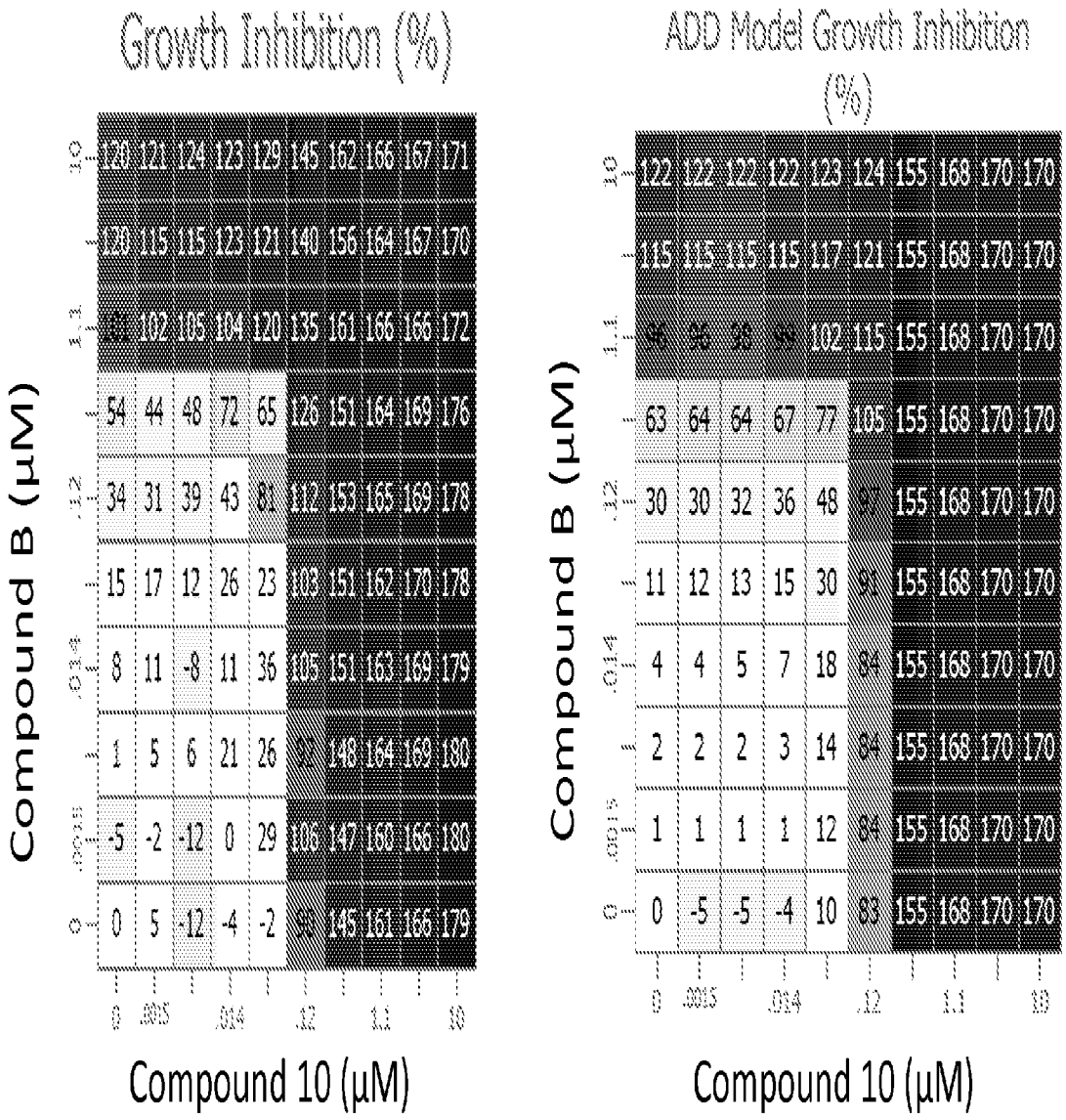
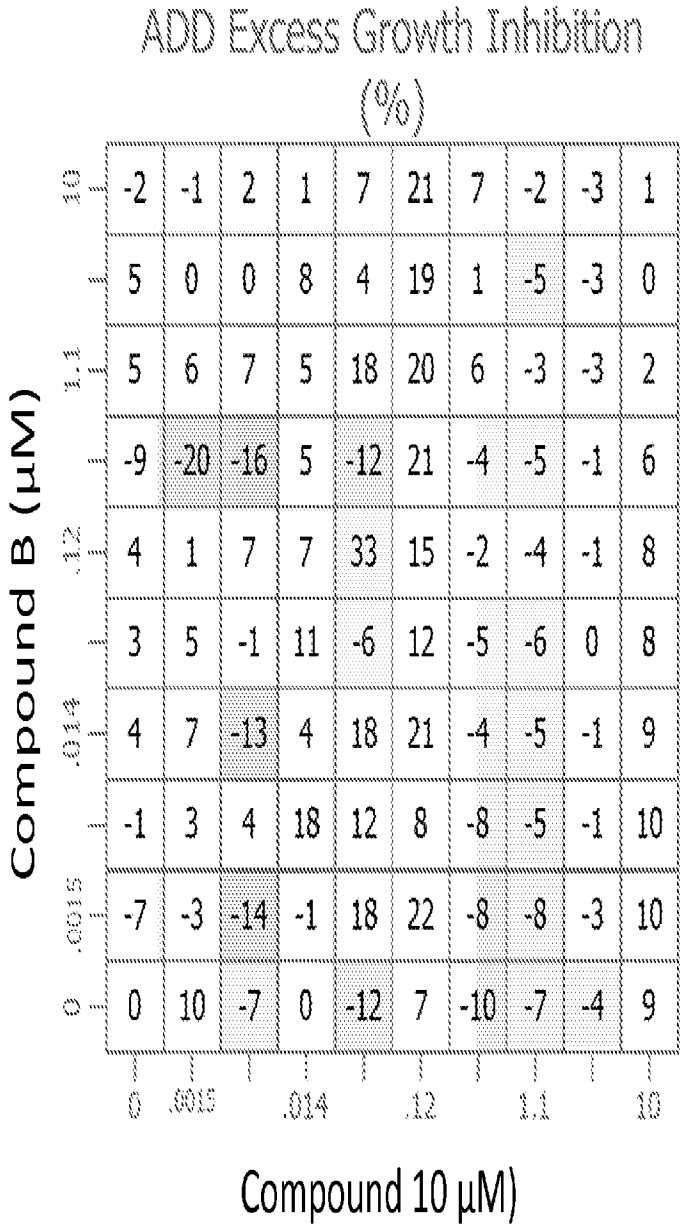


Figure 61a-Example 61; MDA-MB-175-VII cells



	Synergy Score
B x 10	5.29
B self-cross	1.53
10 self-cross	3.11

Figure 62-Example 62; UACC-812 cells

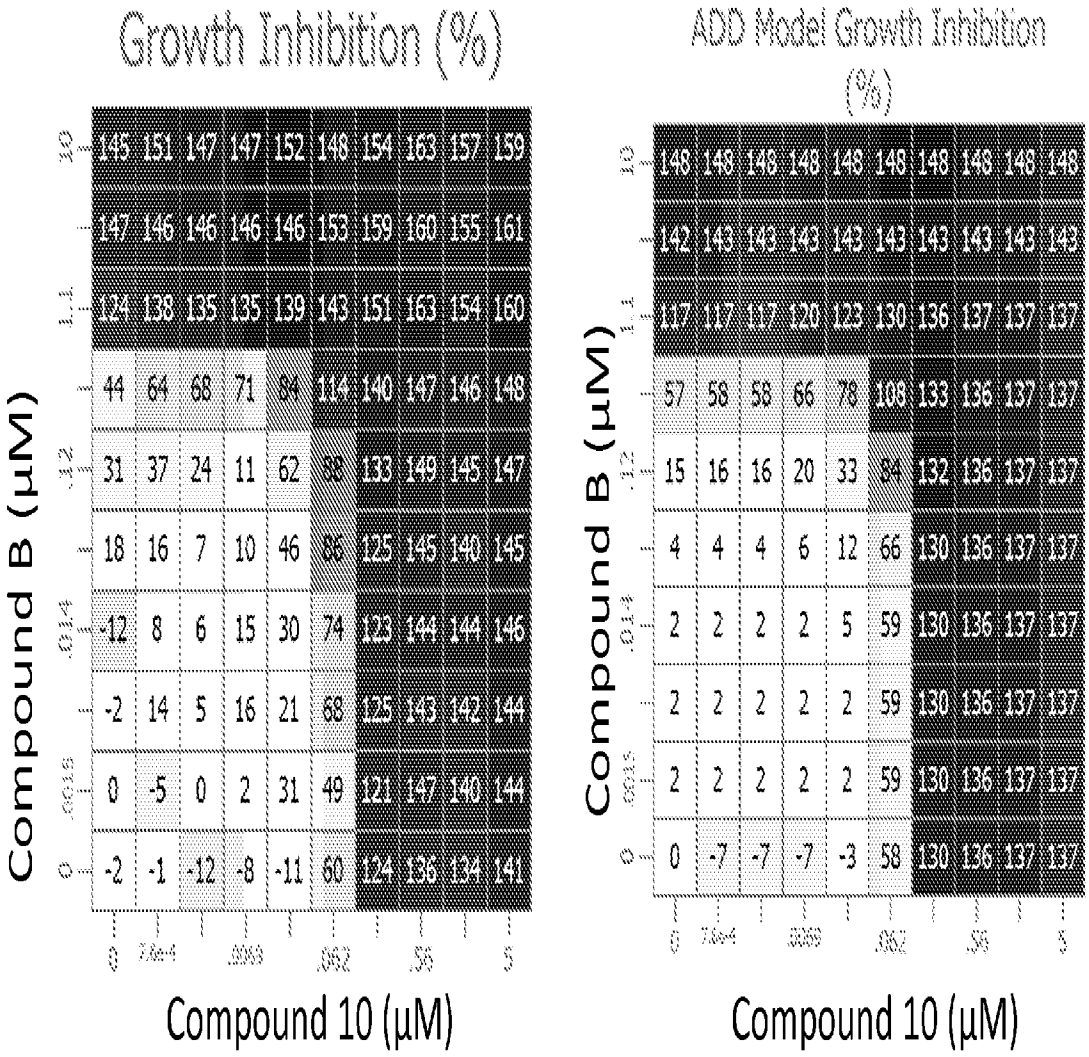
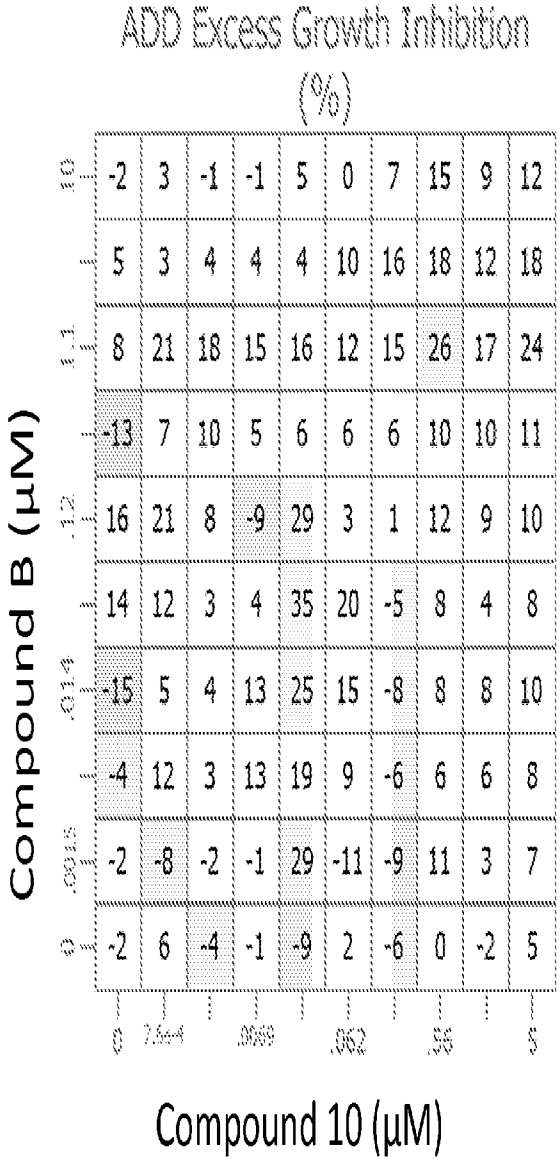


Figure 62a-Example 62; UACC-812 cells



	Synergy Score
B x 10	9.93
B self-cross	2.74
10 self-cross	2.06

Figure 63-Example 63; HCT 116 cells

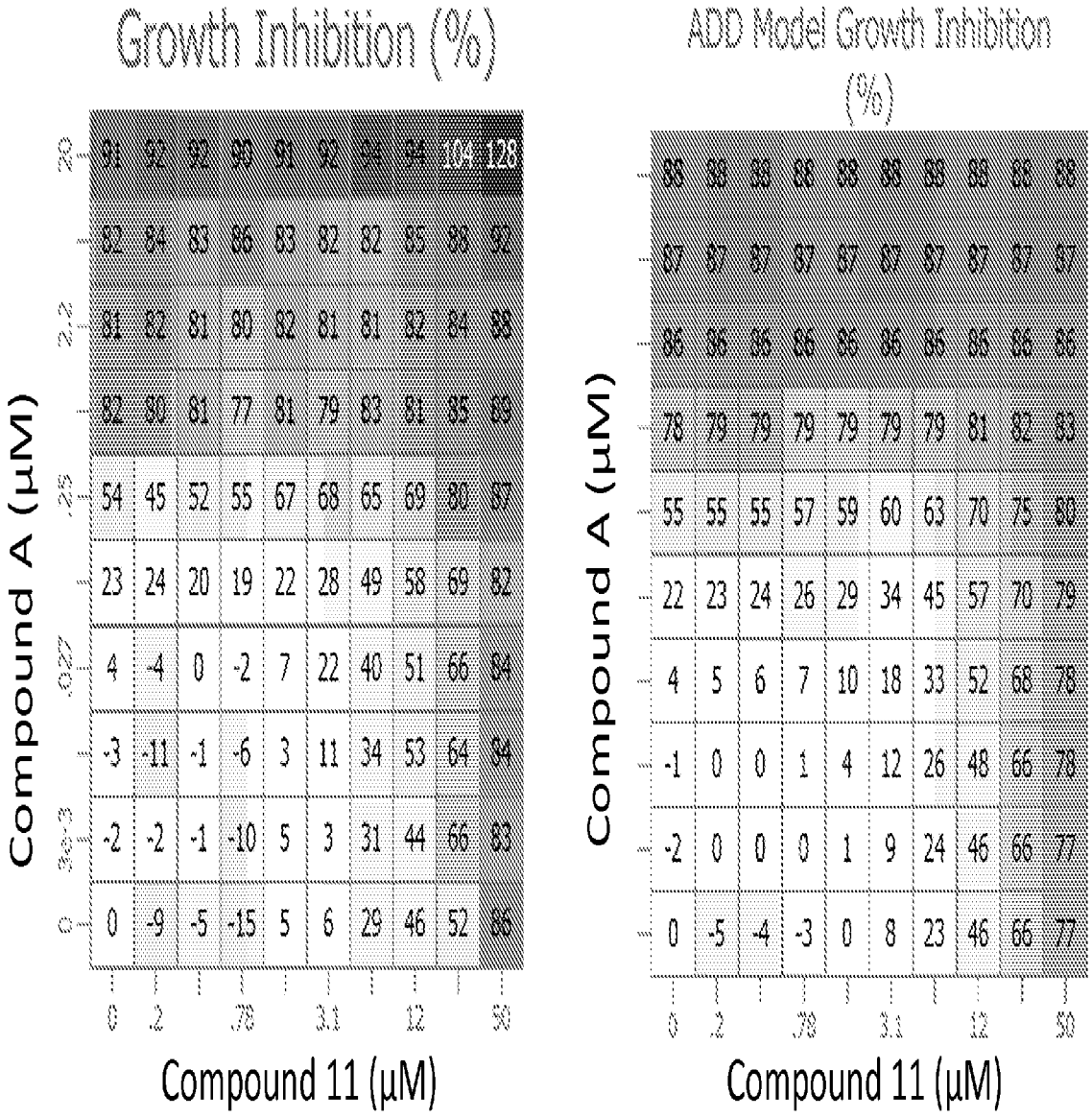
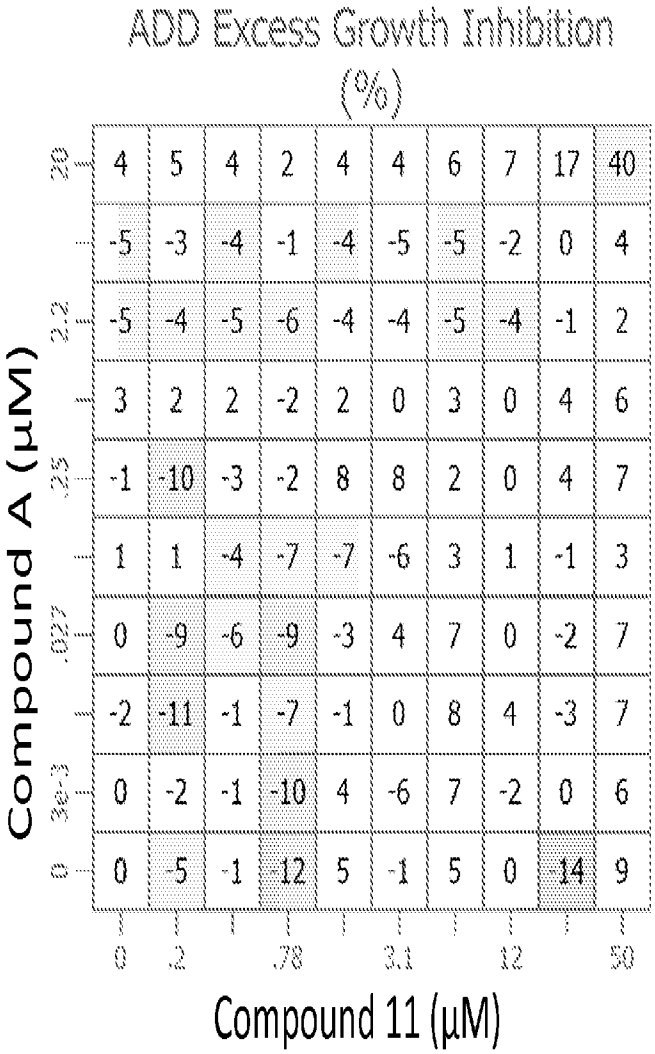


Figure 63a-Example 63; HCT 116 cells



	Synergy Score
A x 11	1.32
A self-cross	1.27
11 self-cross	0.244

Figure 64-Example 64; GDM-1 cells

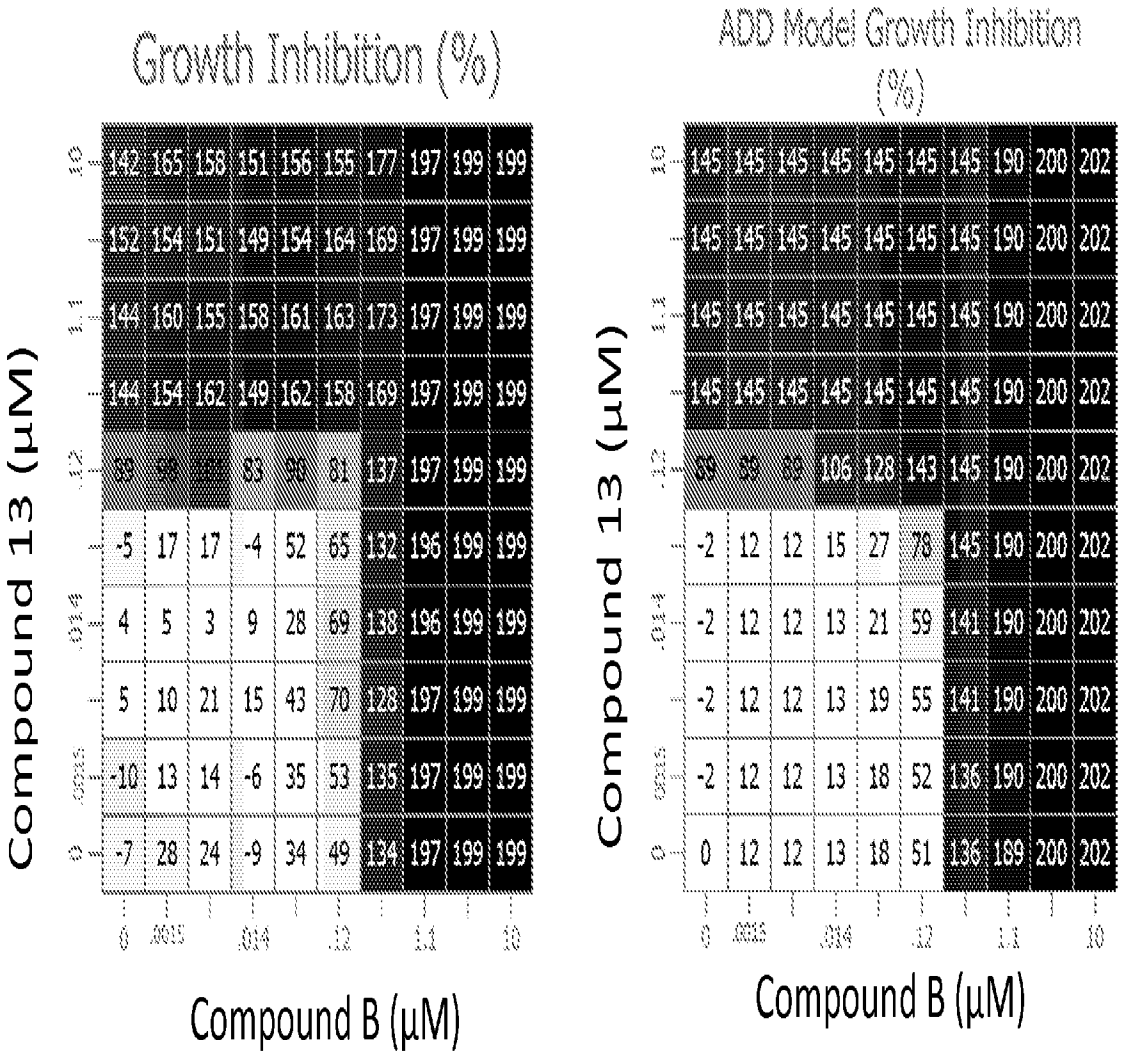
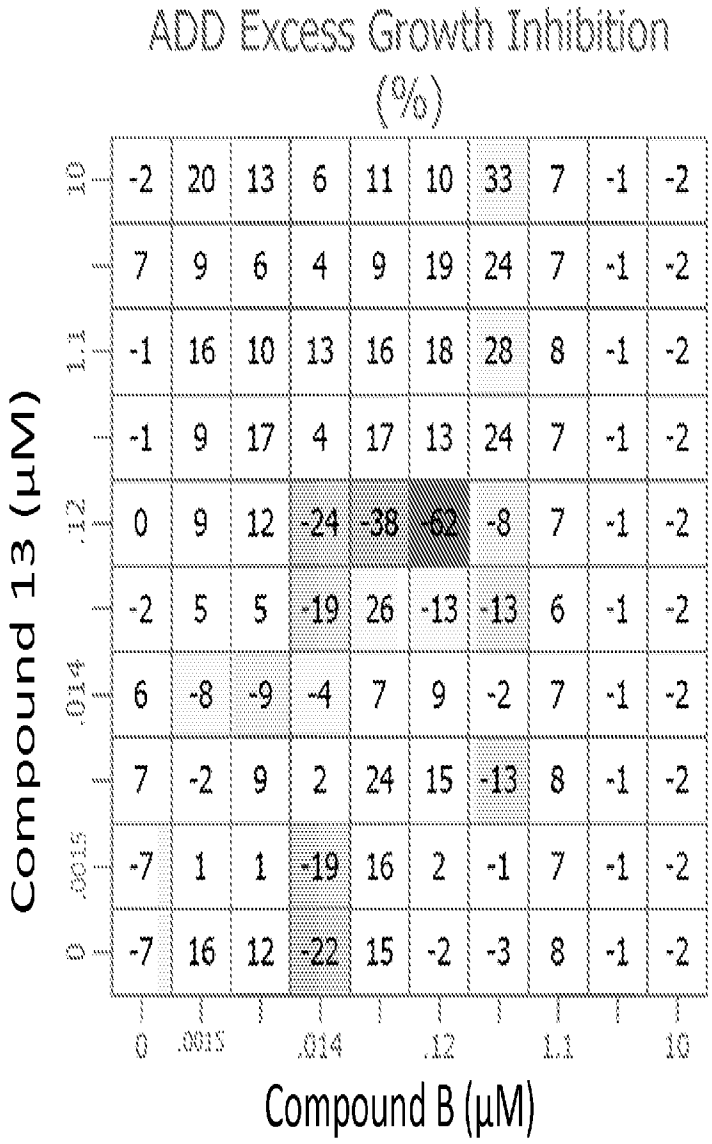


Figure 64a-Example 64; GDM-1 cells



	Synergy Score
B x 13	9.25
B self-cross	9.93
13 self-cross	2.71

Figure 65-Example 65; ML-2 cells

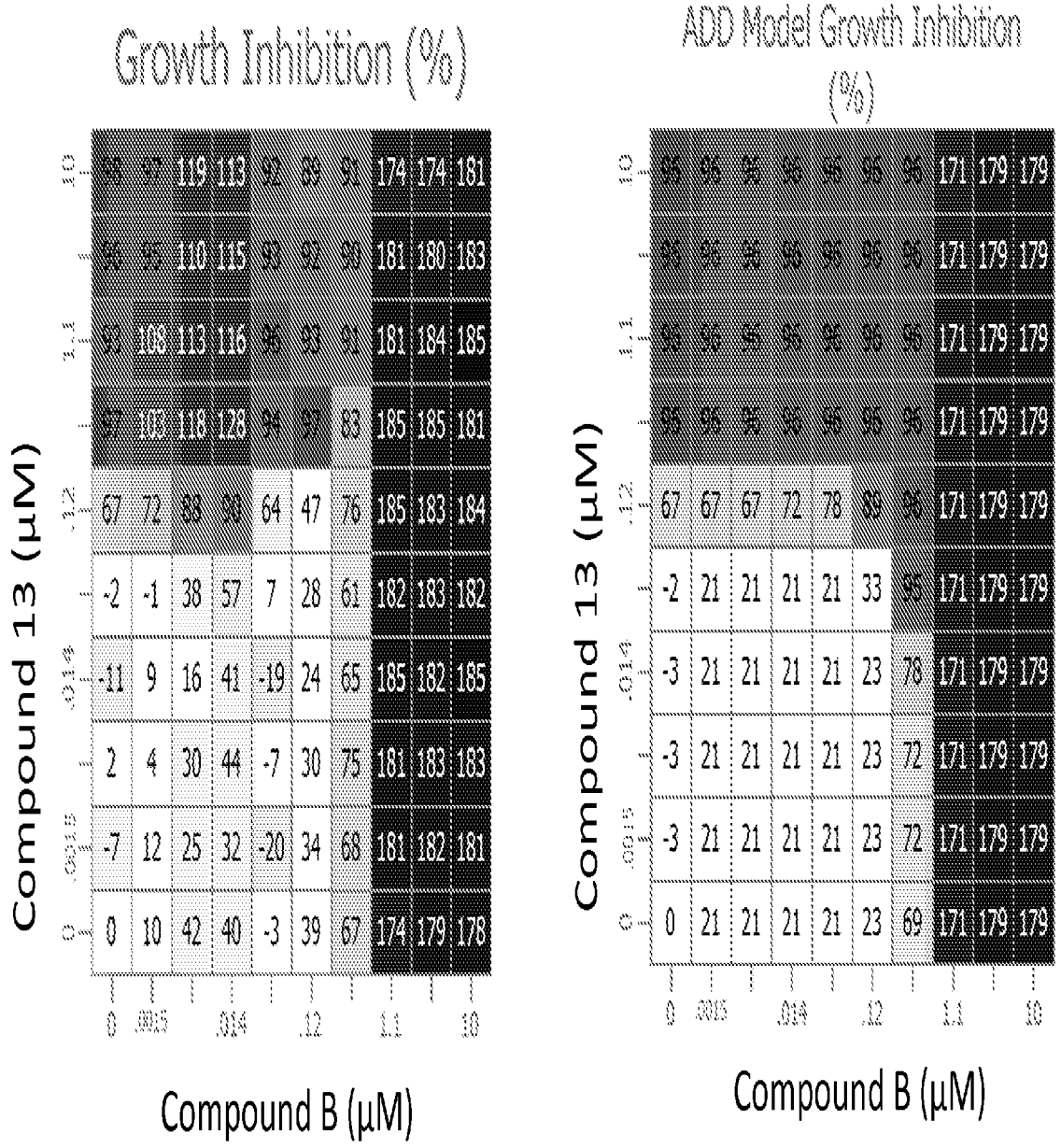
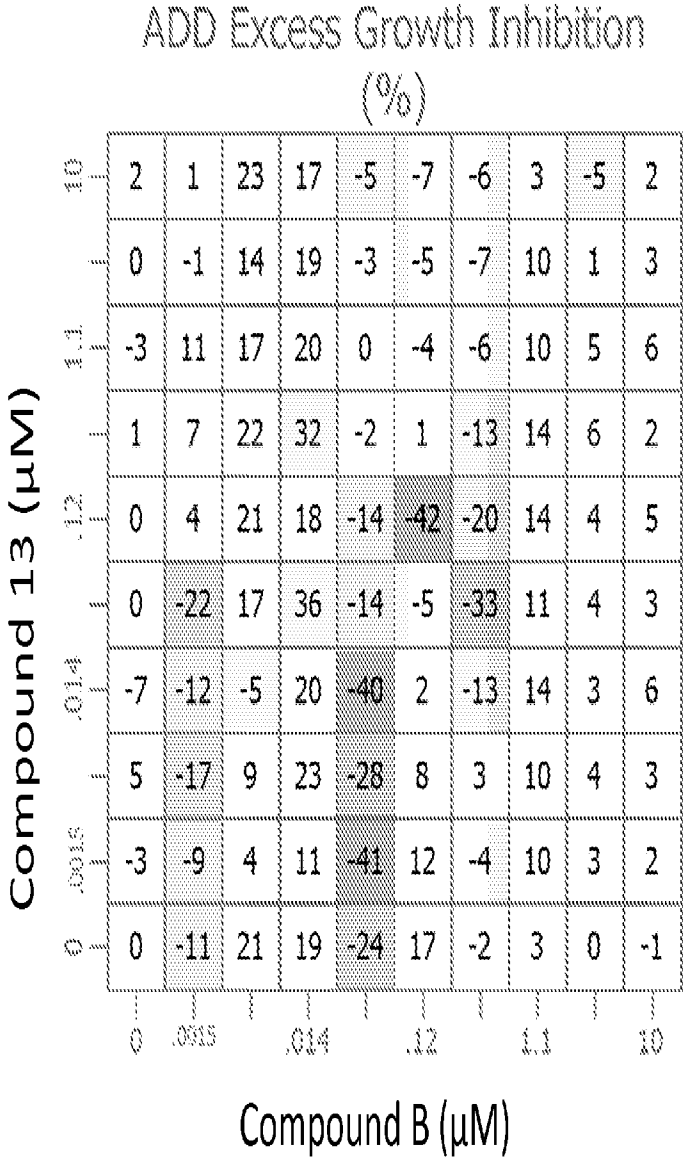


Figure 65a-Example 65; ML-2 cells



	Synergy Score
B x 13	7.24
B self-cross	14.9
13 self-cross	1.06

Figure 66-Example 66; MOLM-13 cells

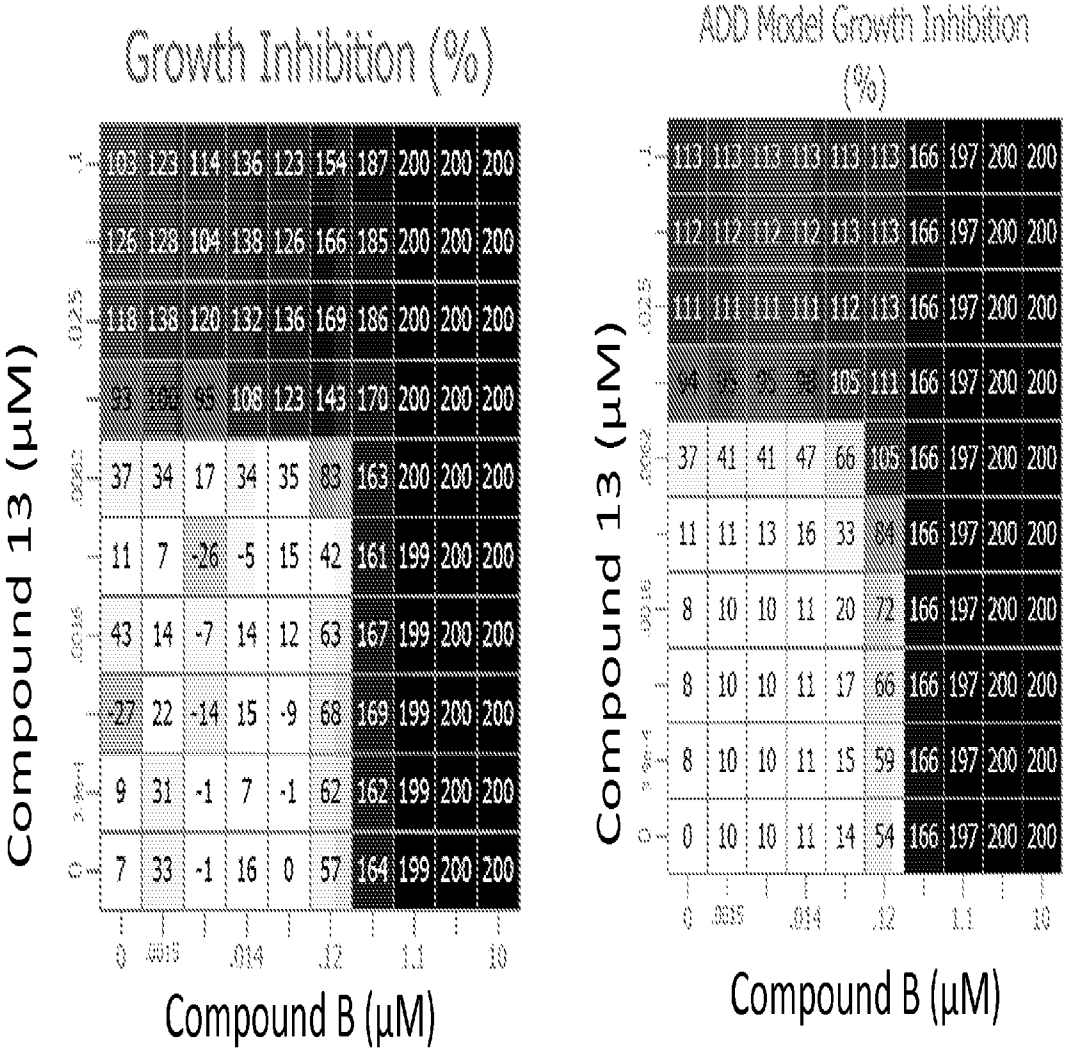
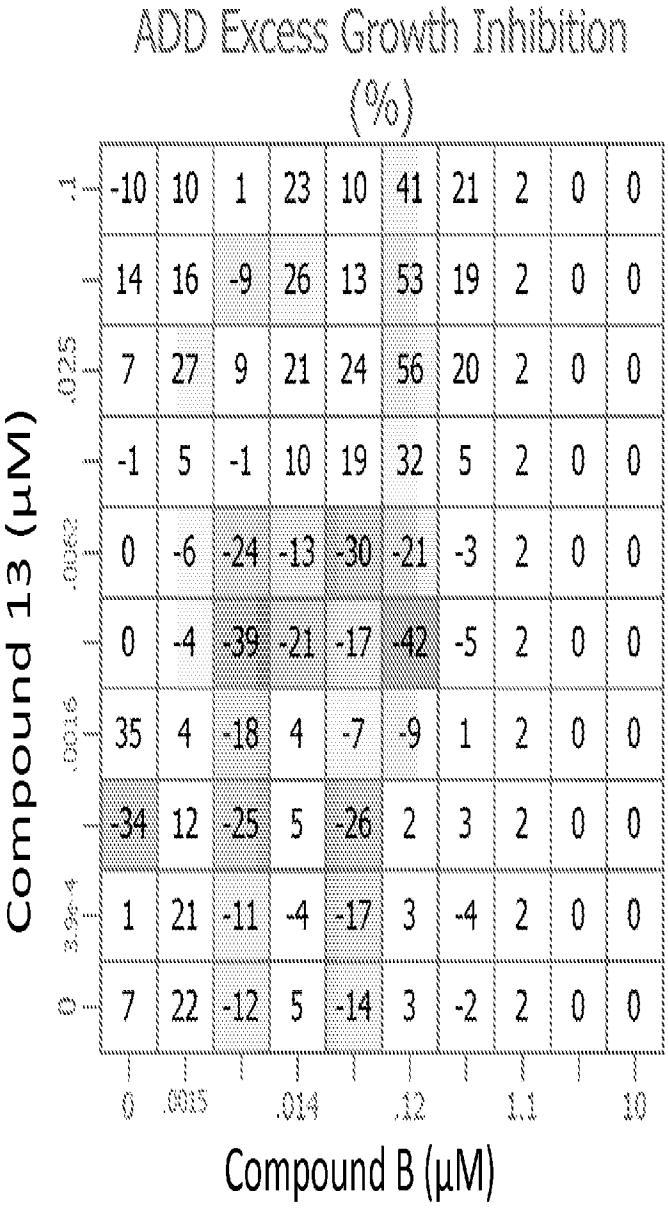


Figure 66a-Example 66; MOLM-13 cells



	Synergy Score
B x 13	5.66
B self-cross	.428
13 self-cross	.146

Figure 67-Example 67; OCI-AML3 cells

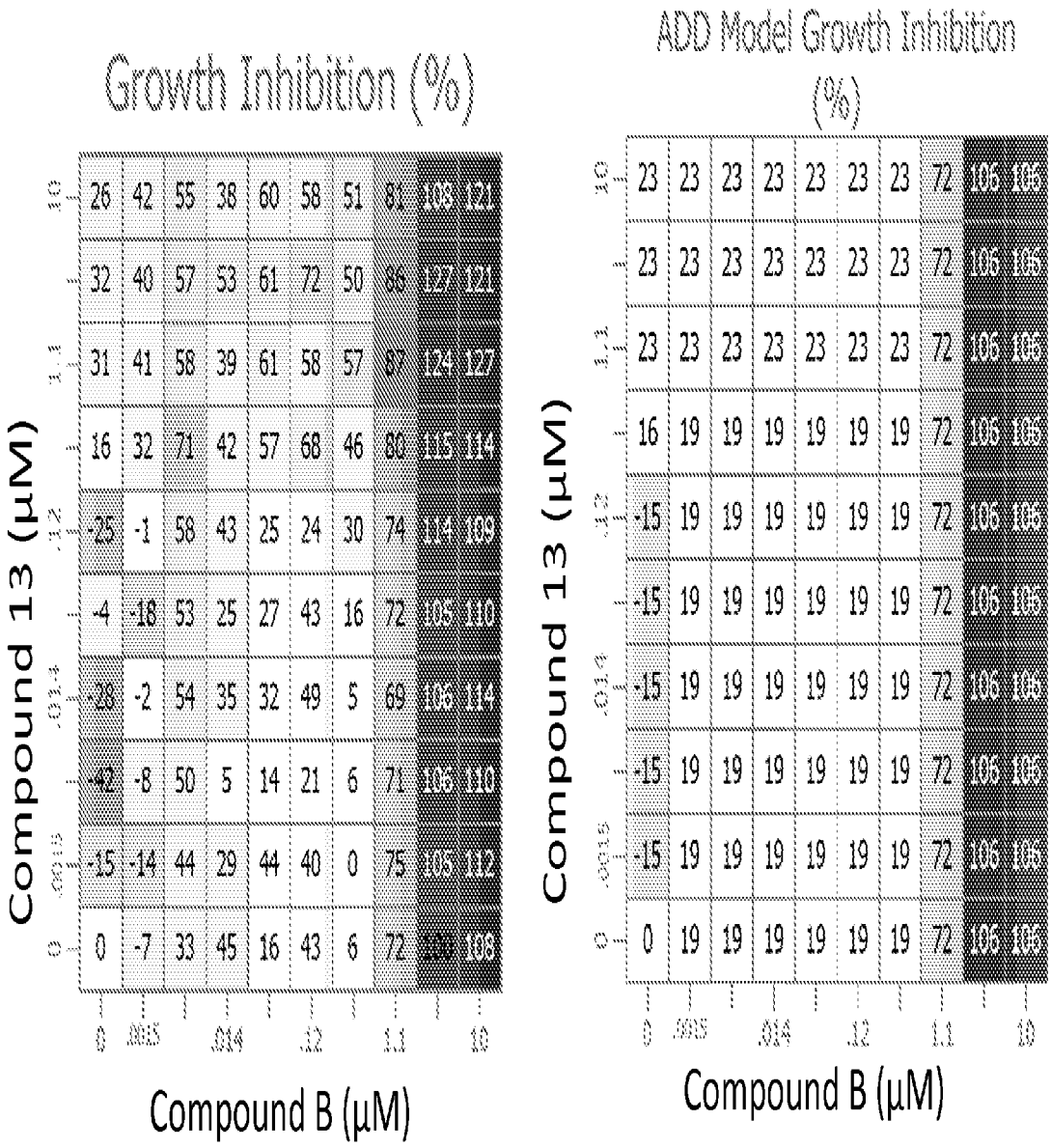
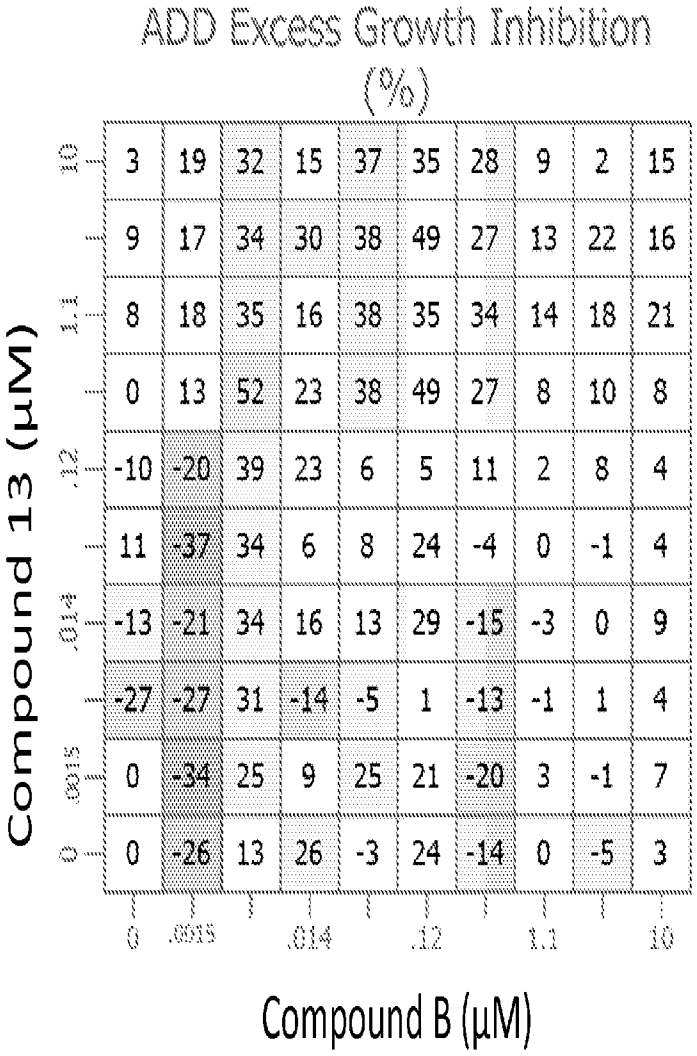
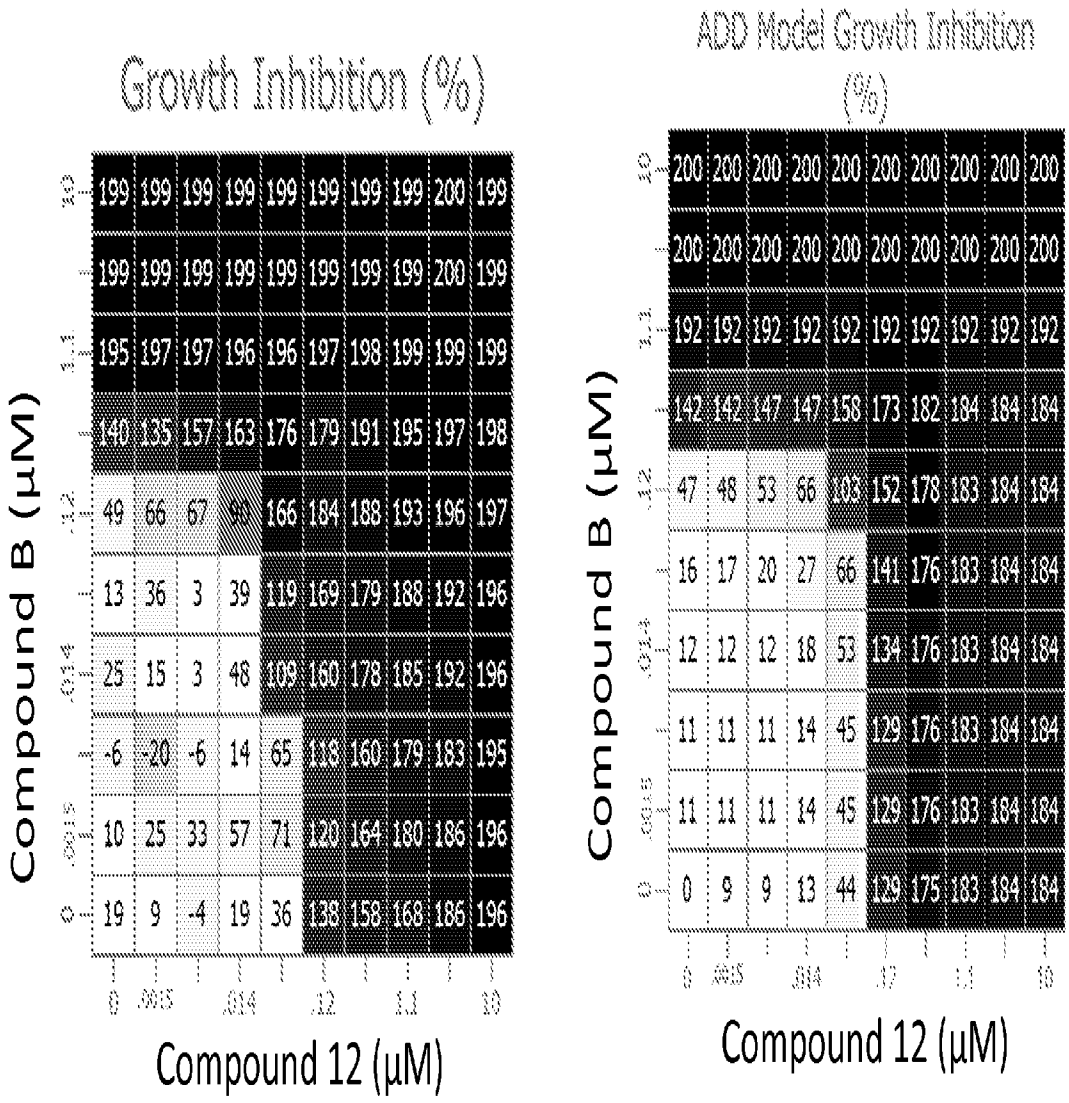


Figure 67a-Example 67; OCI-AML3 cells

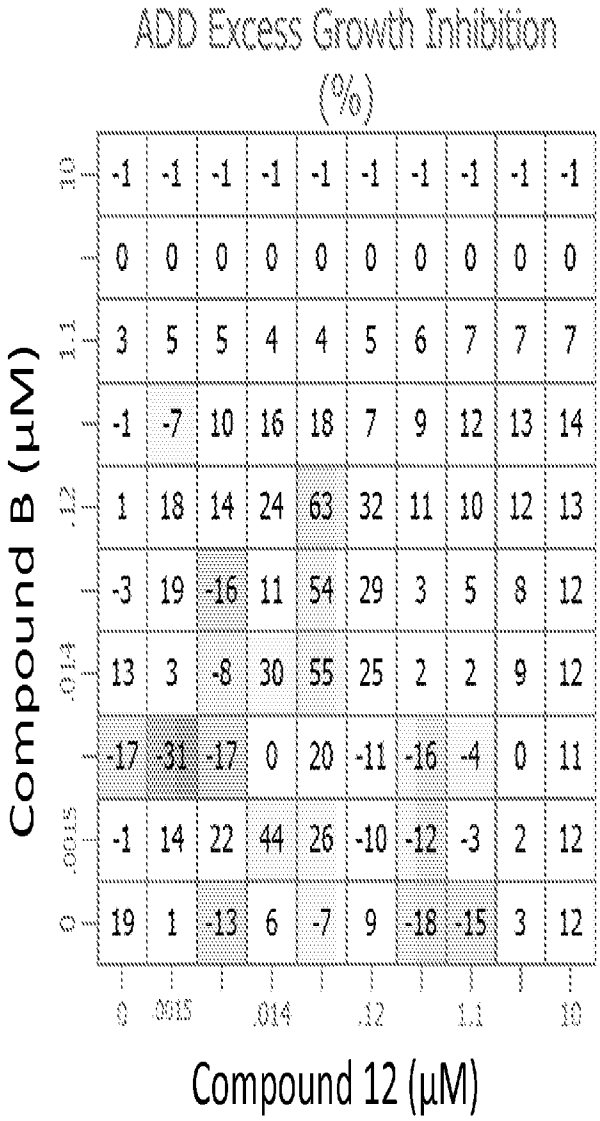


	Synergy Score
B x 13	9.62
B self-cross	3.91
13 self-cross	1.75

Figure 68-Example 68; GDM-1 cells



Example 68a-Figure 68; GDM-1 cells



	Synergy Score
B x 12	12.5
B self-cross	9.93
12 self-cross	7.87

Figure 69-Example 69; ML-2 cells

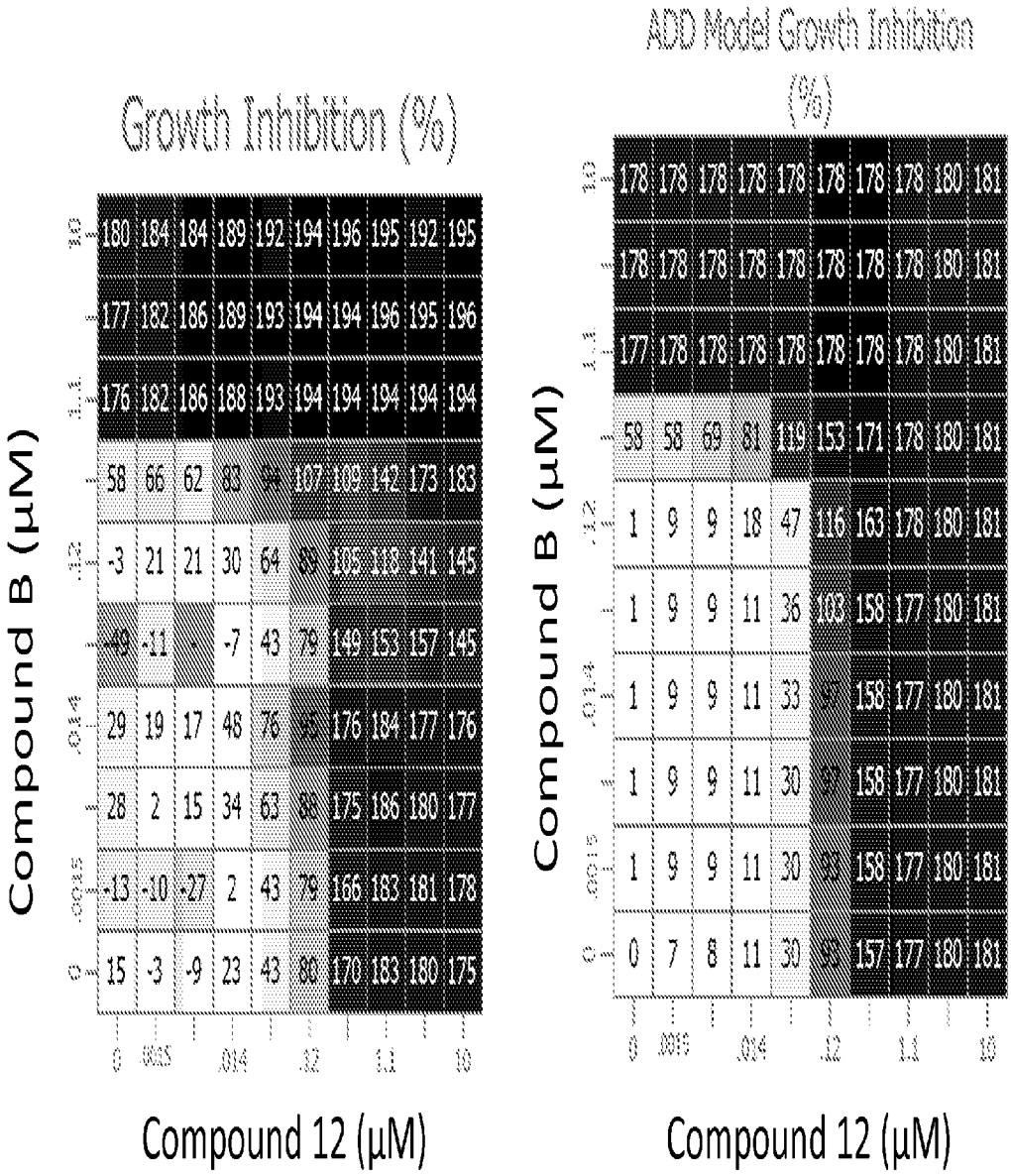
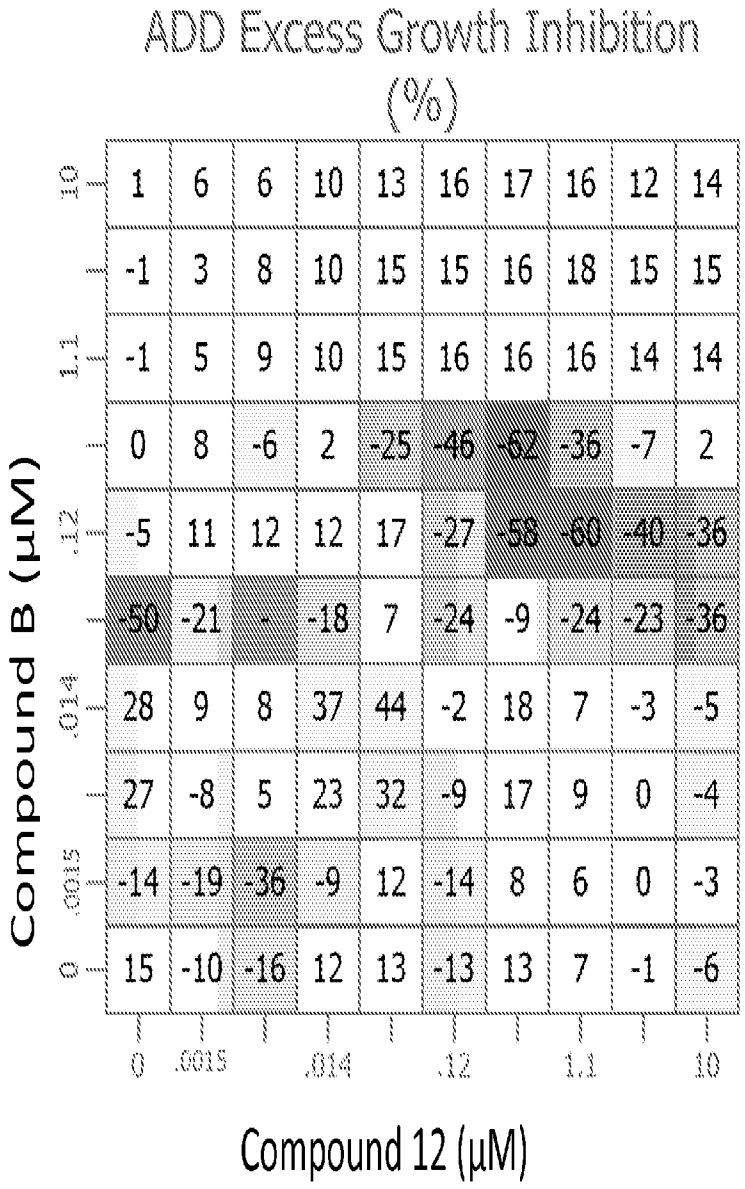


Figure 69a-example 69; ML-2 cells



	Synergy Score
B x 12	11
B self-cross	14.9
12 self-cross	8.62

Figure 70-Example 70; MOLM-13 cells

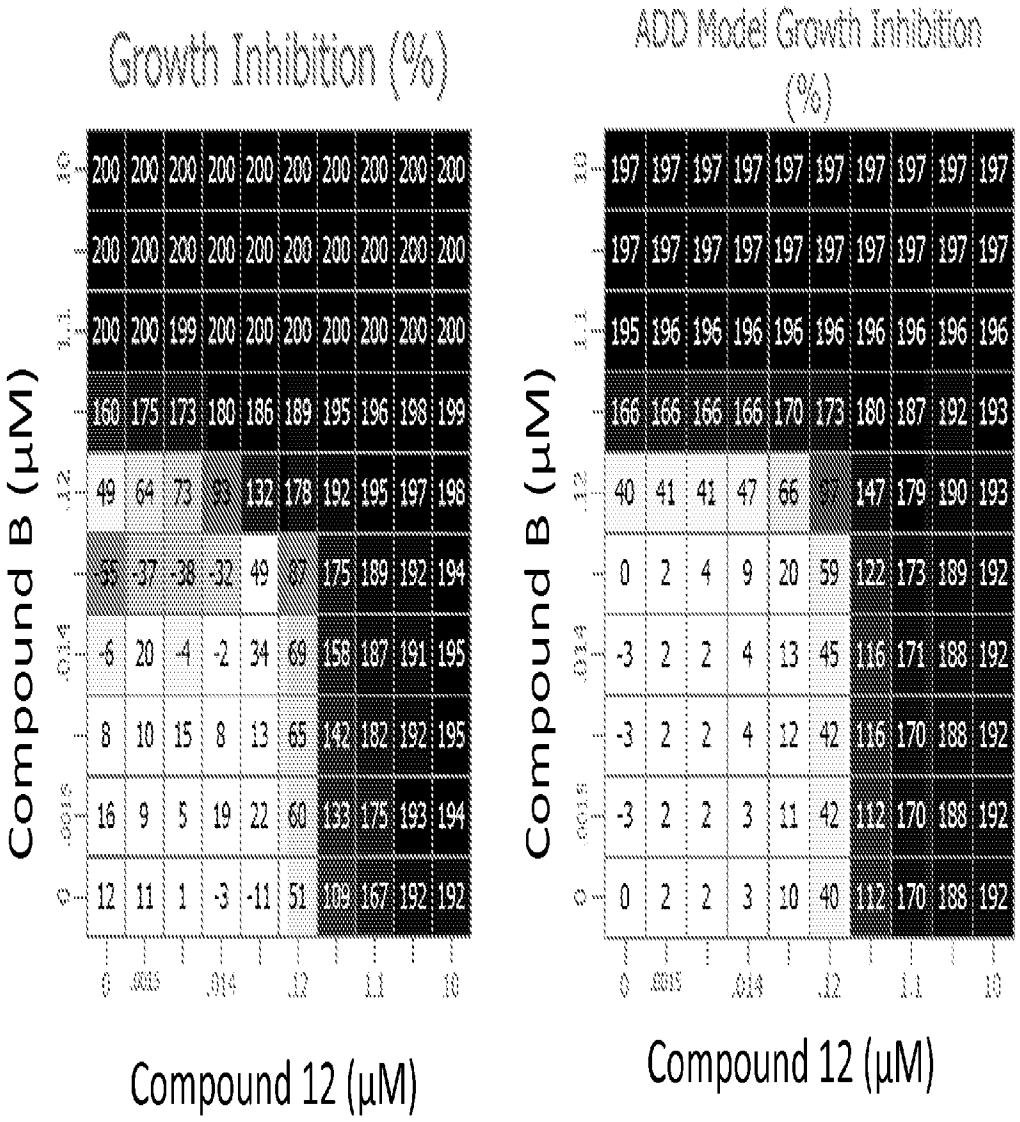
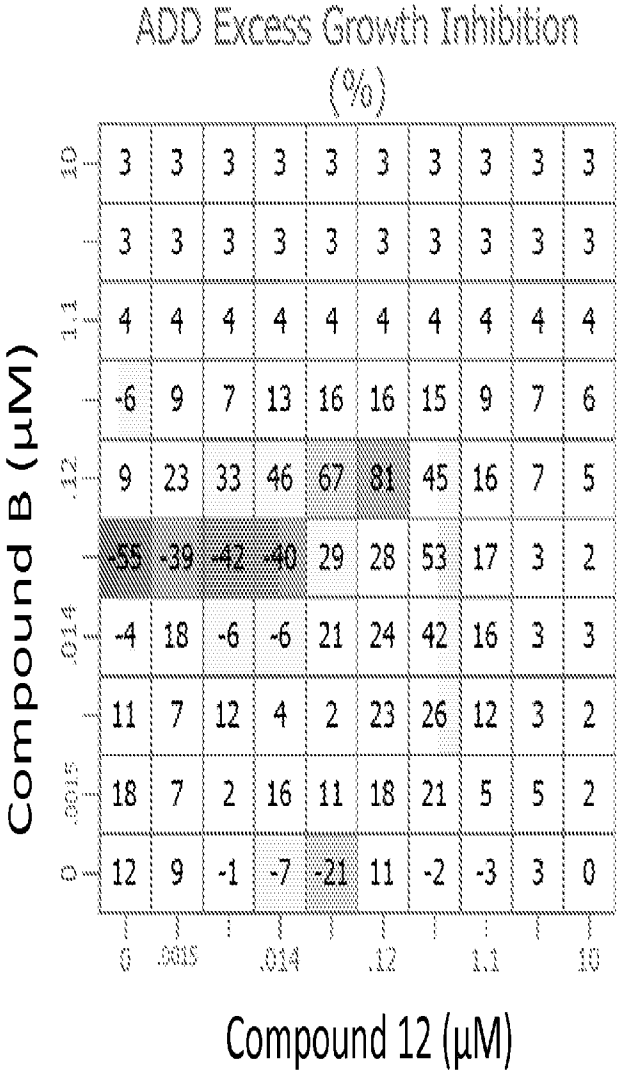


Figure 70a-Example70; MOLM-13 cells



	Synergy Score
B x 12	15.4
B self-cross	0.428
12 self-cross	1.7

Figure 71-Example 71; OCI-AML3 cells

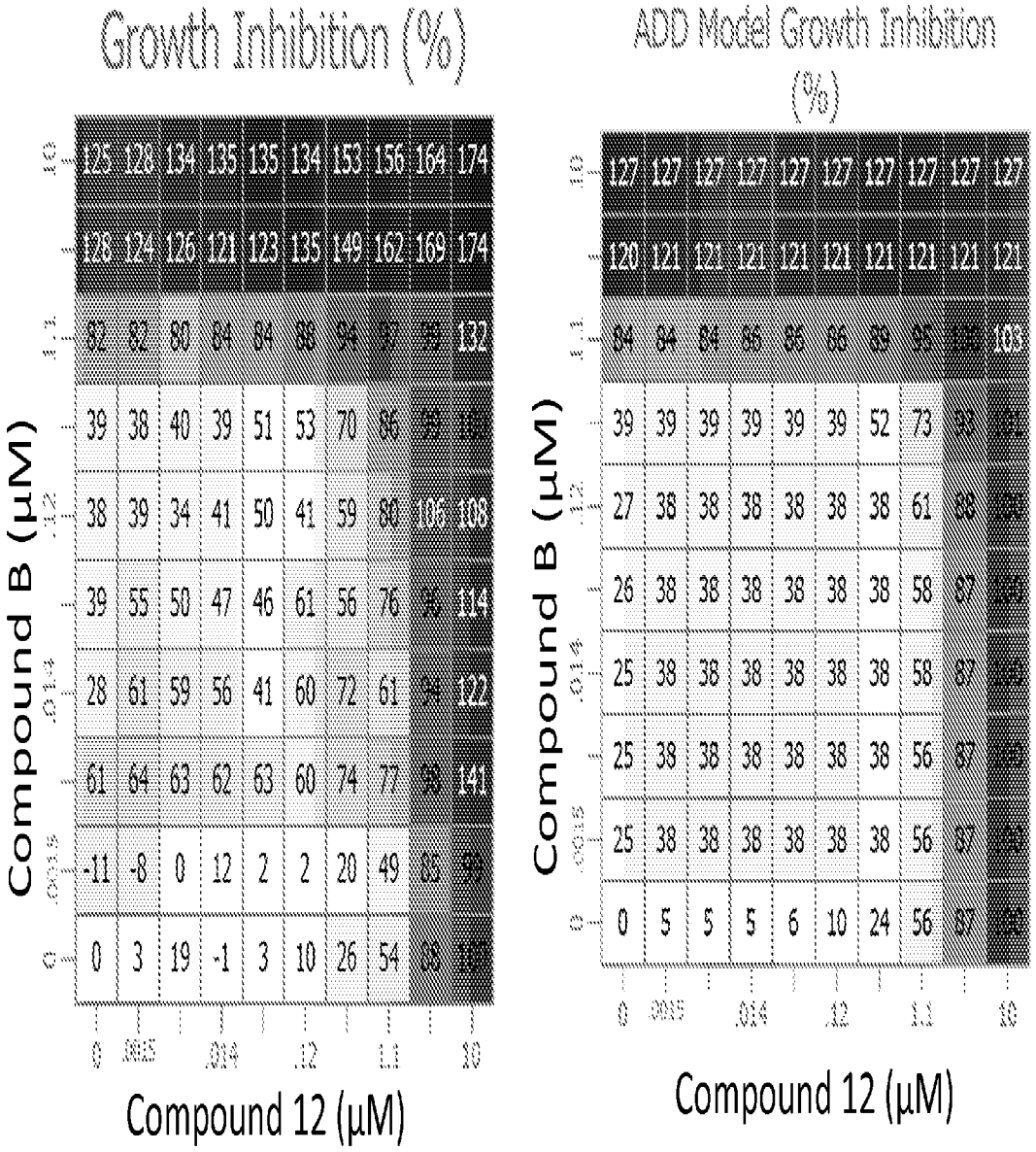
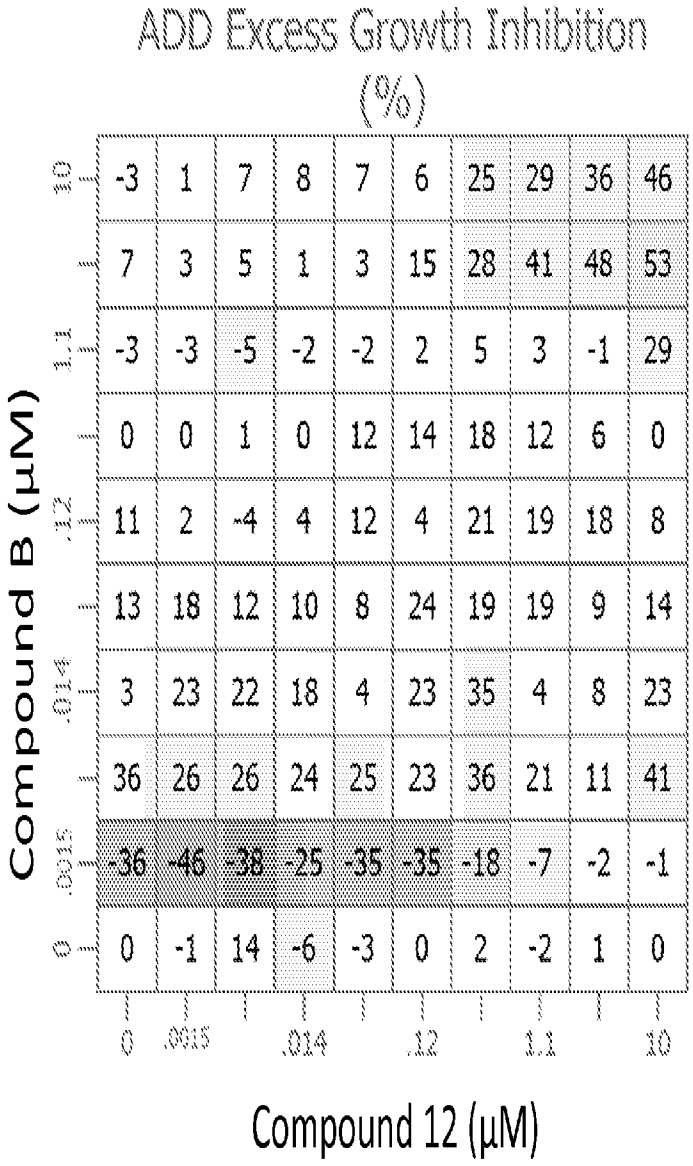


Figure 71a-Example 71; OCI-AML3 cells



	Synergy Score
B x 12	13.6
B self-cross	3.91
12 self-cross	5.81

Figure 72
AMG 232 – MAPKi Combinations

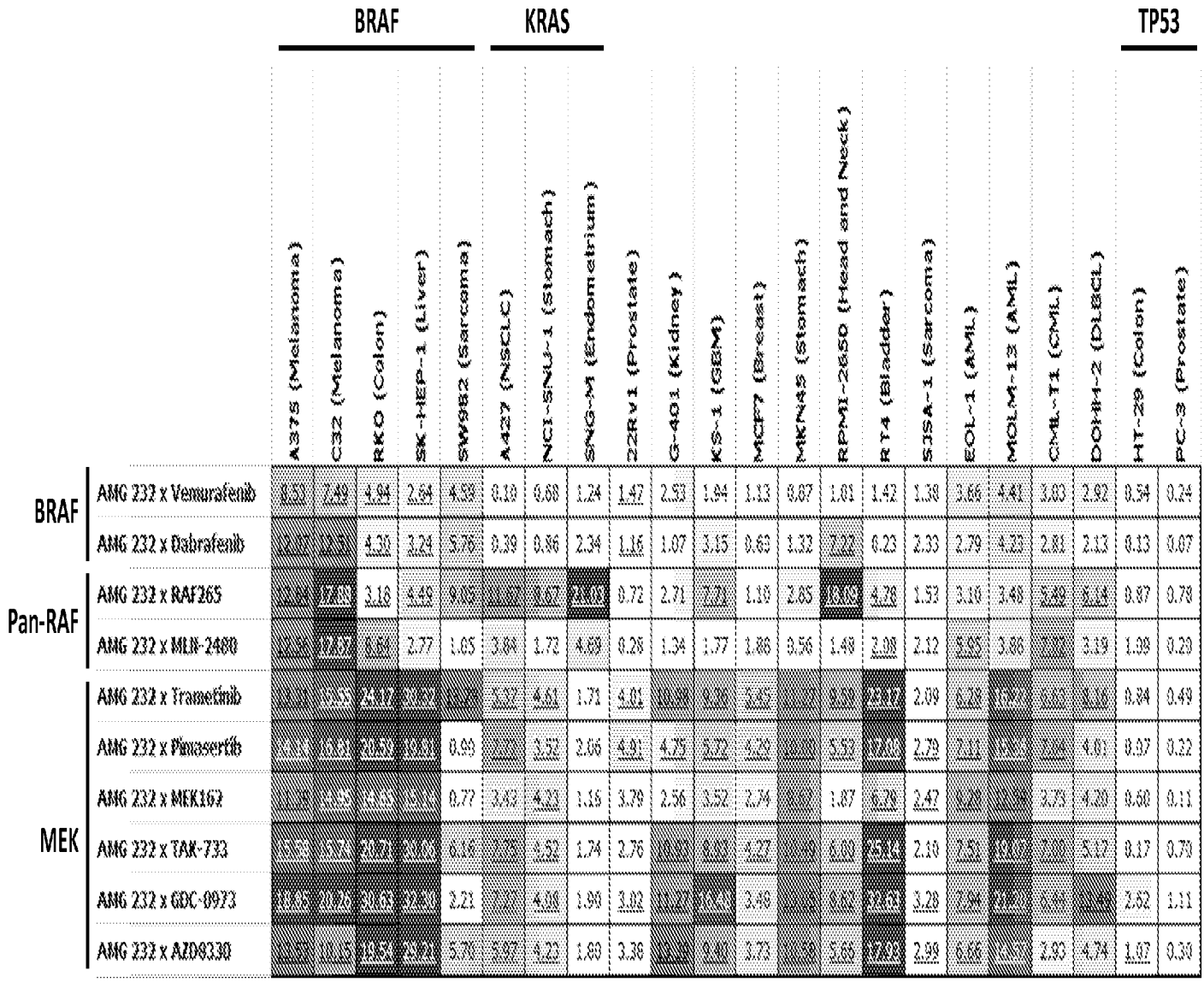


Figure 73
AM-7209 – MAPKi Combinations

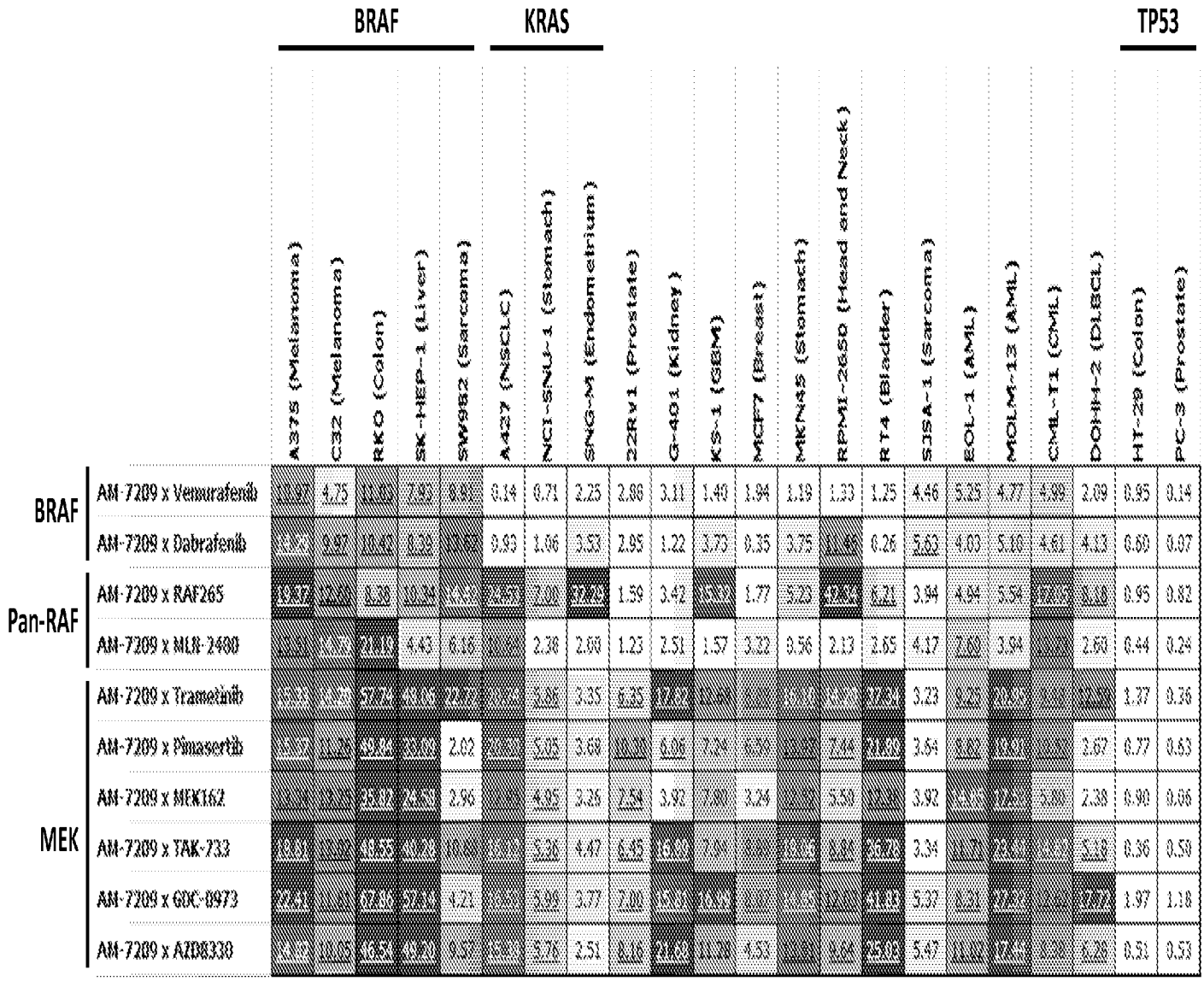


Figure 74
RG7112 – MAPKi Combinations

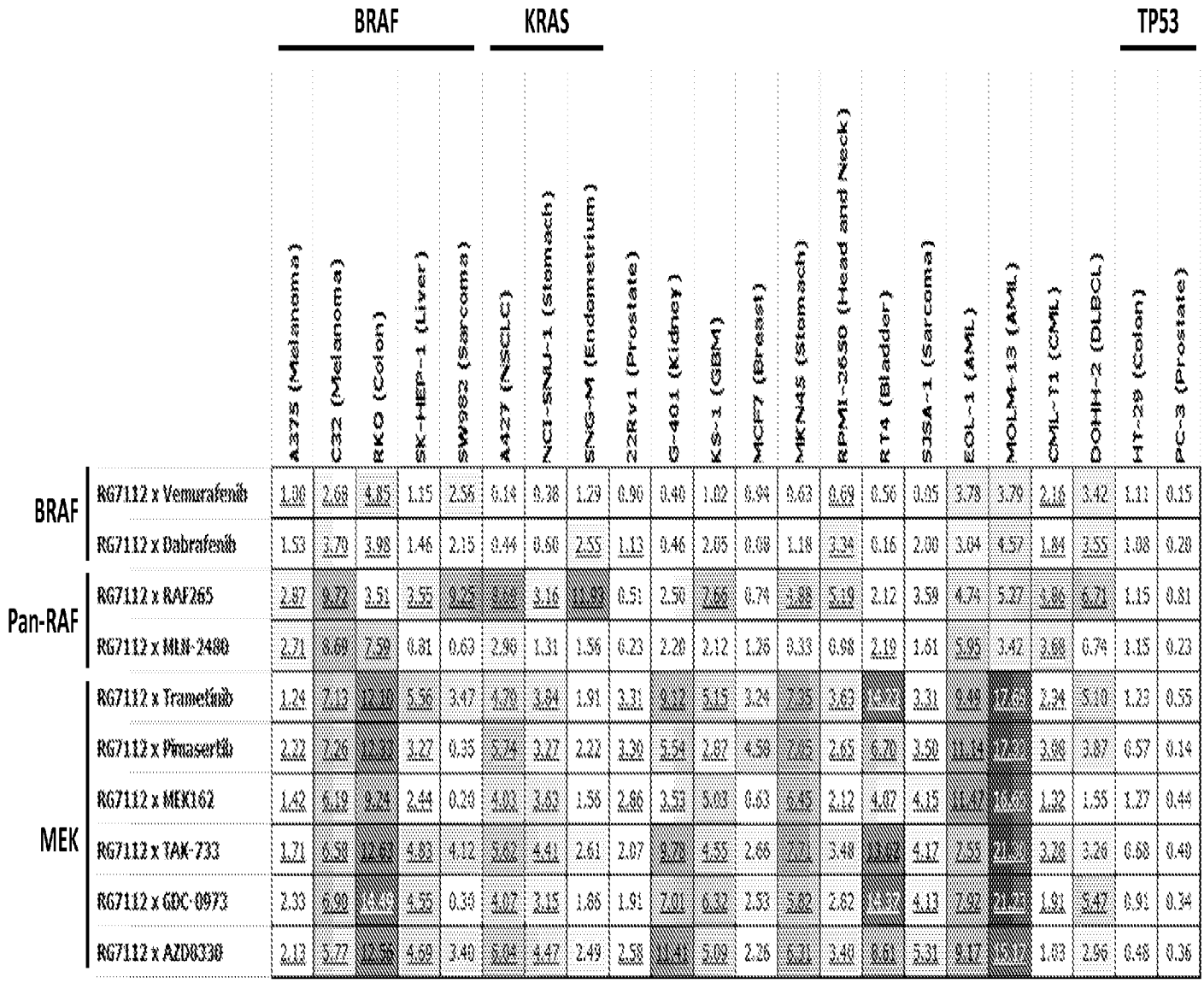


Figure 75
AMG 232 – PI3Ki Combinations

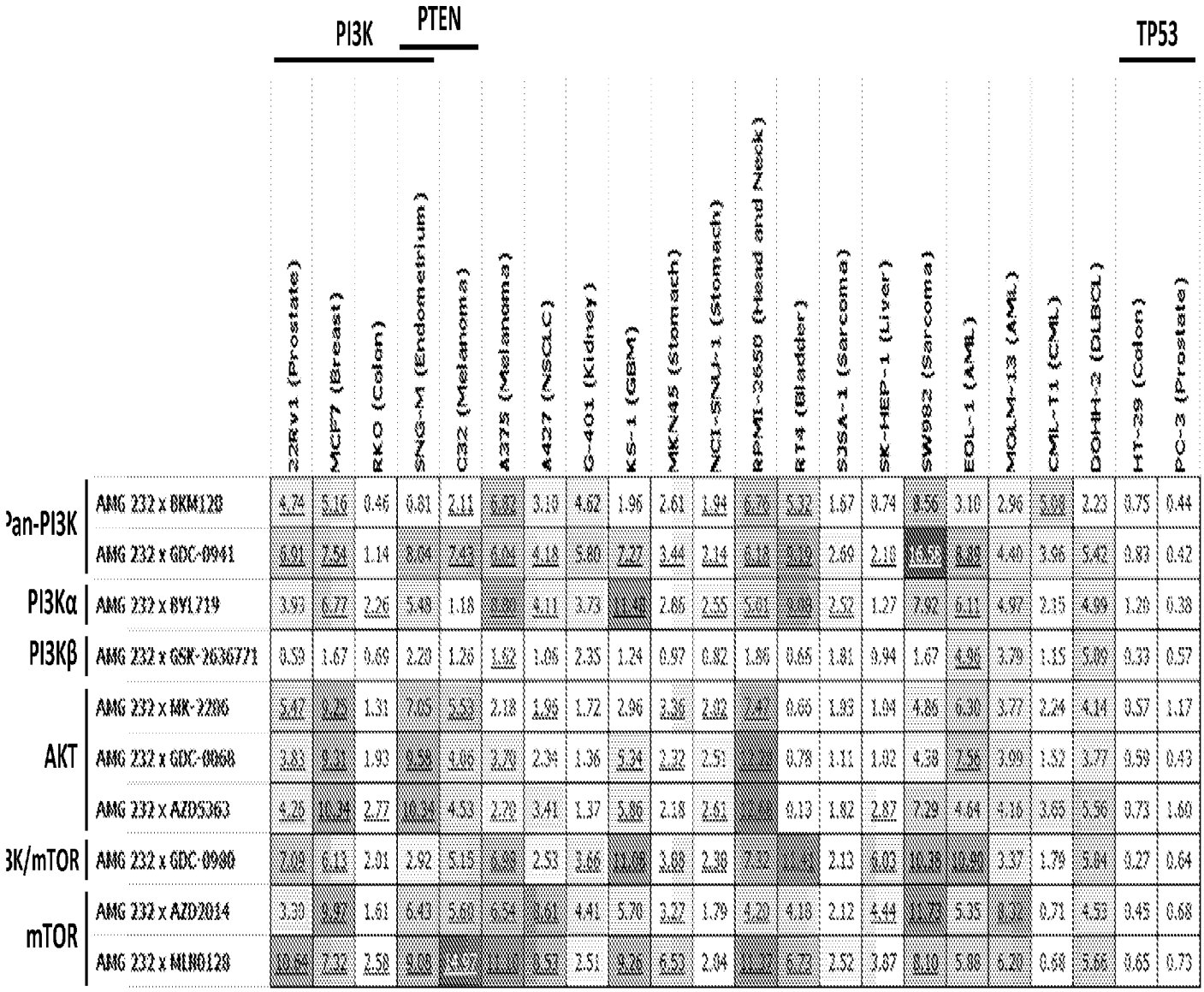


Figure 76
AM-7209 – PI3Ki Combinations

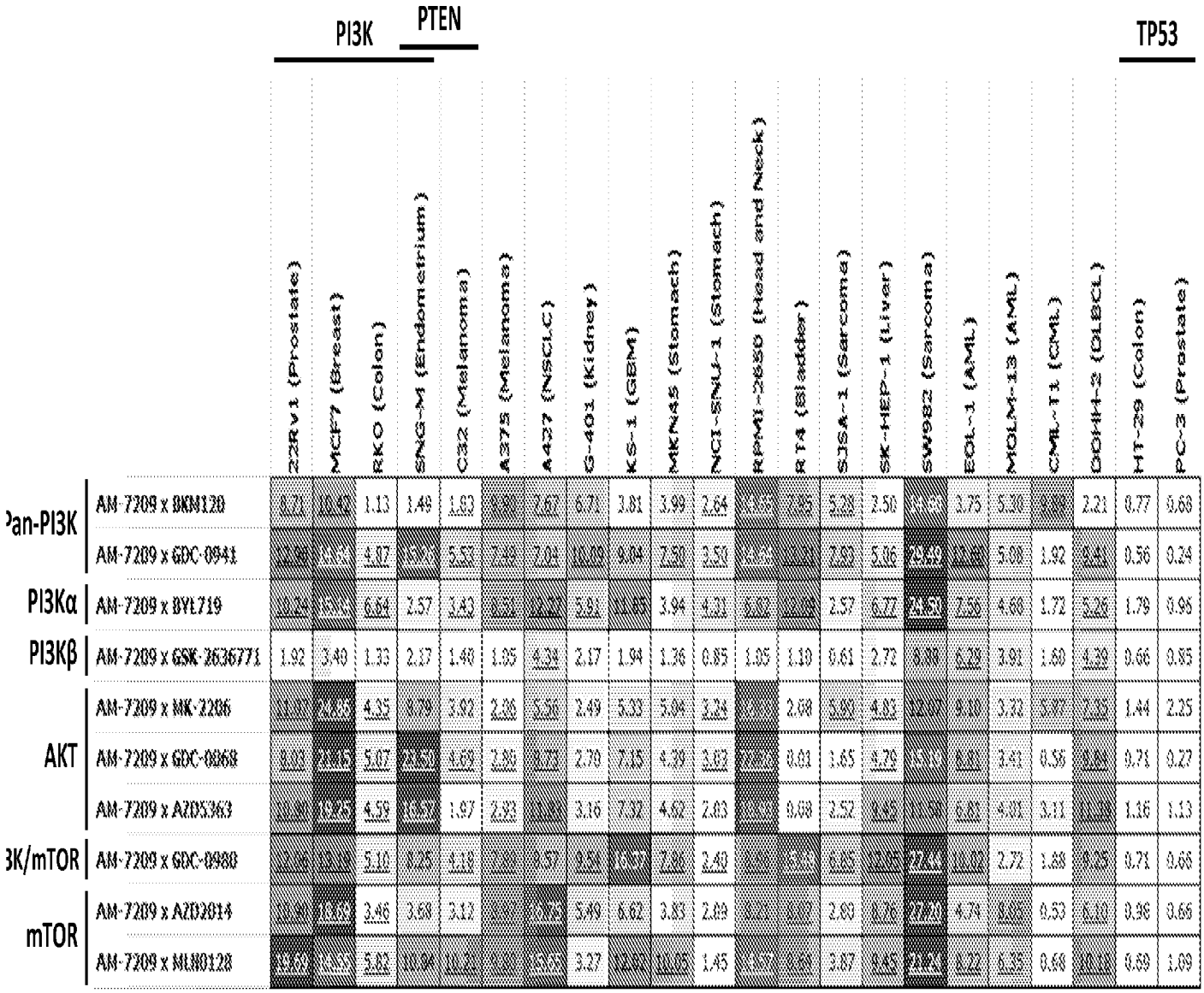


Figure 77

RG7112 – PI3Ki Combinations

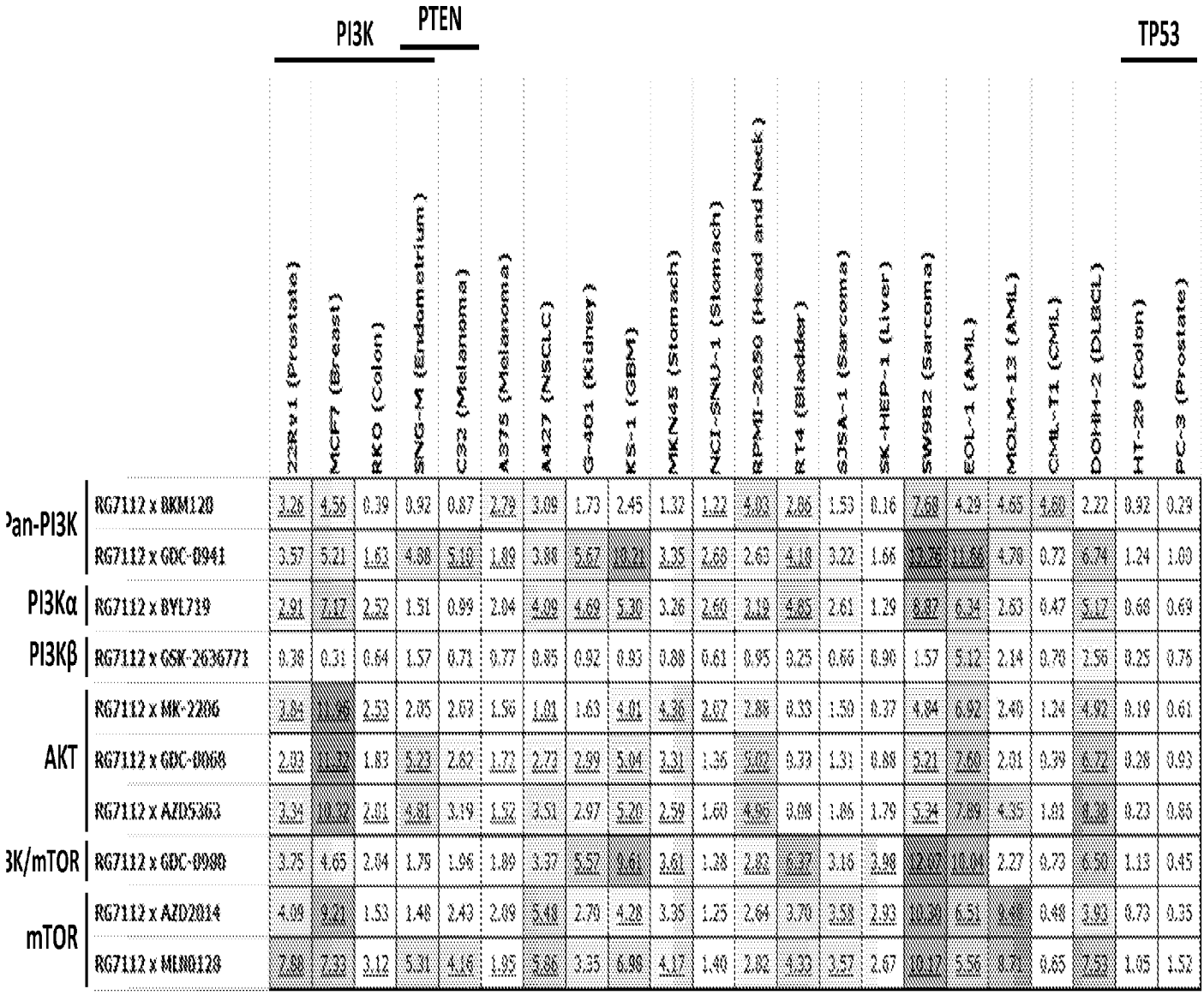


Figure 78

AMG 232 – Intrinsic Apoptosis Combinations

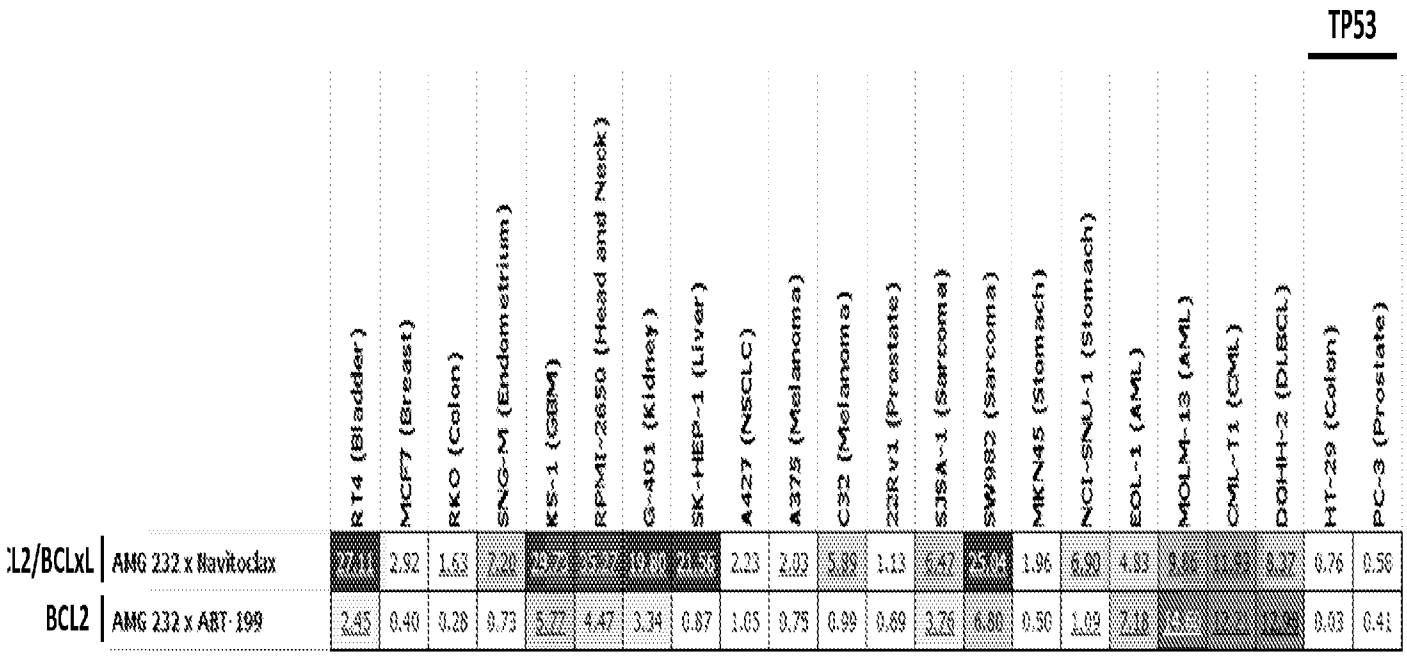


Figure 79

AM-7209 – Intrinsic Apoptosis Combinations

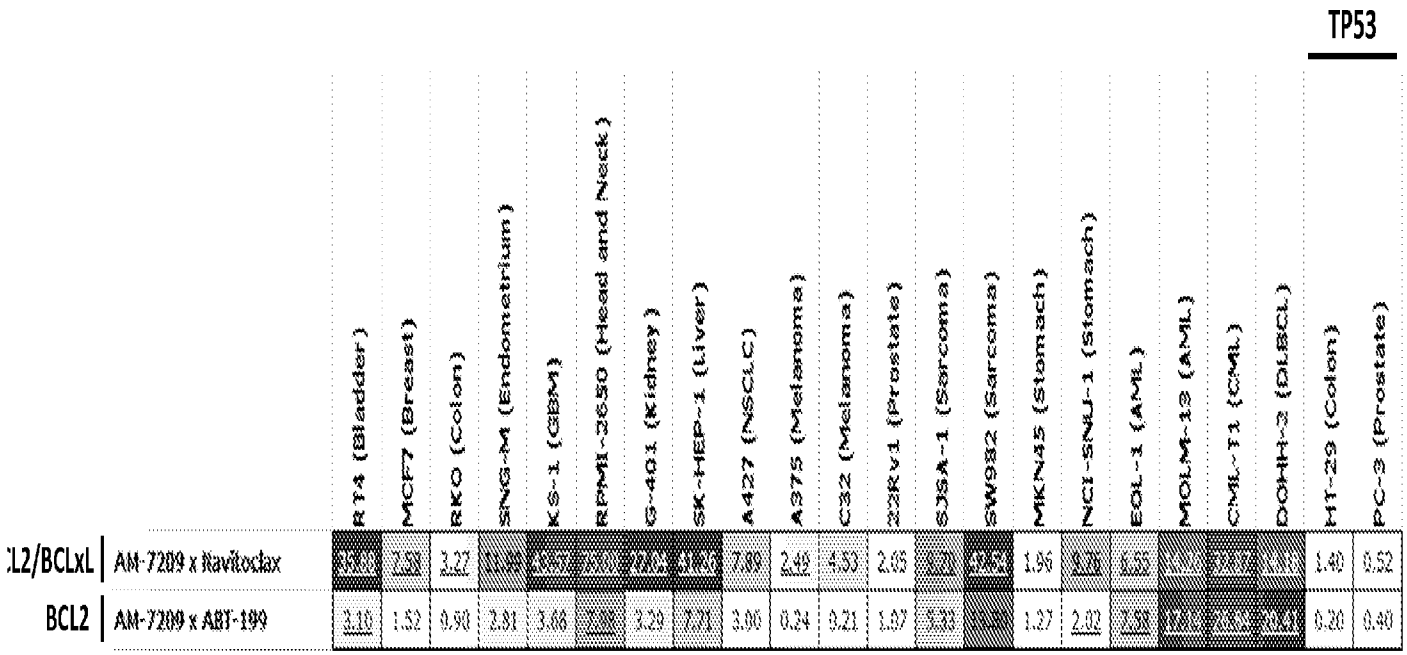


Figure 80
RG7112 – Intrinsic Apoptosis Combinations

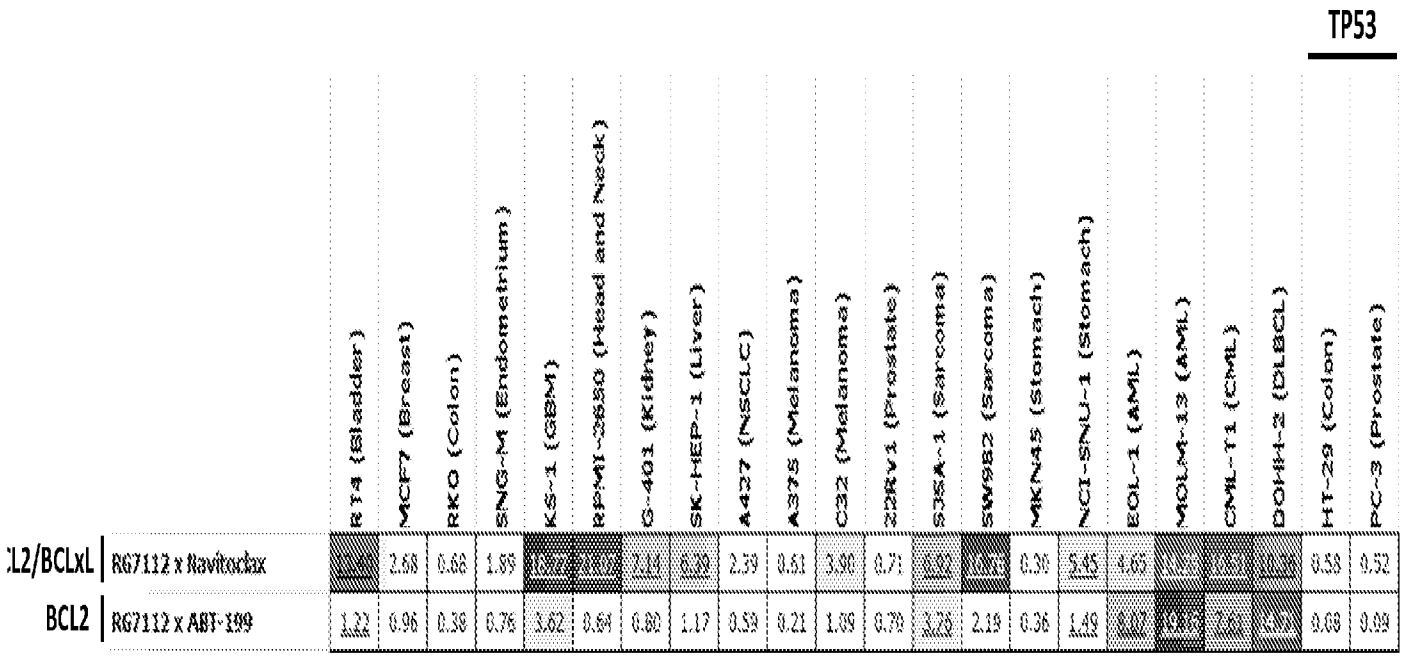


Figure 81
AMG 232 – Miscellaneous Combinations

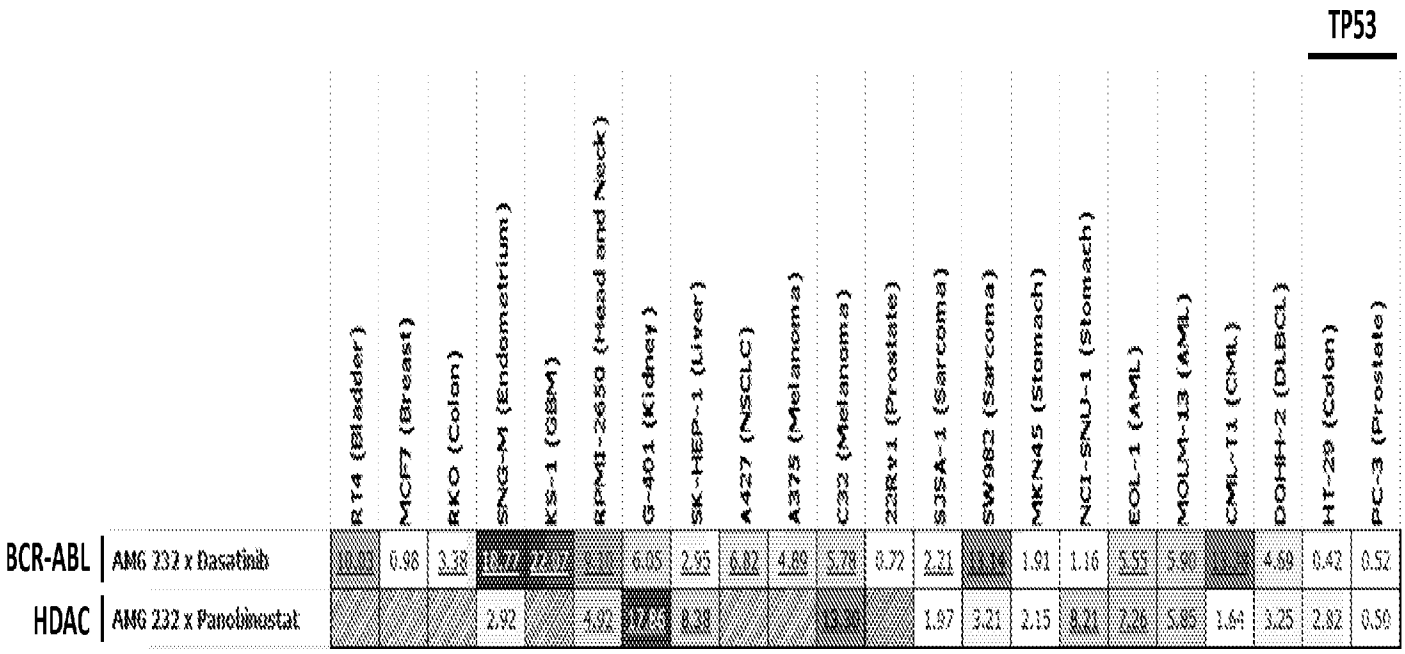


Figure 82
AM-7209 – Miscellaneous Combinations

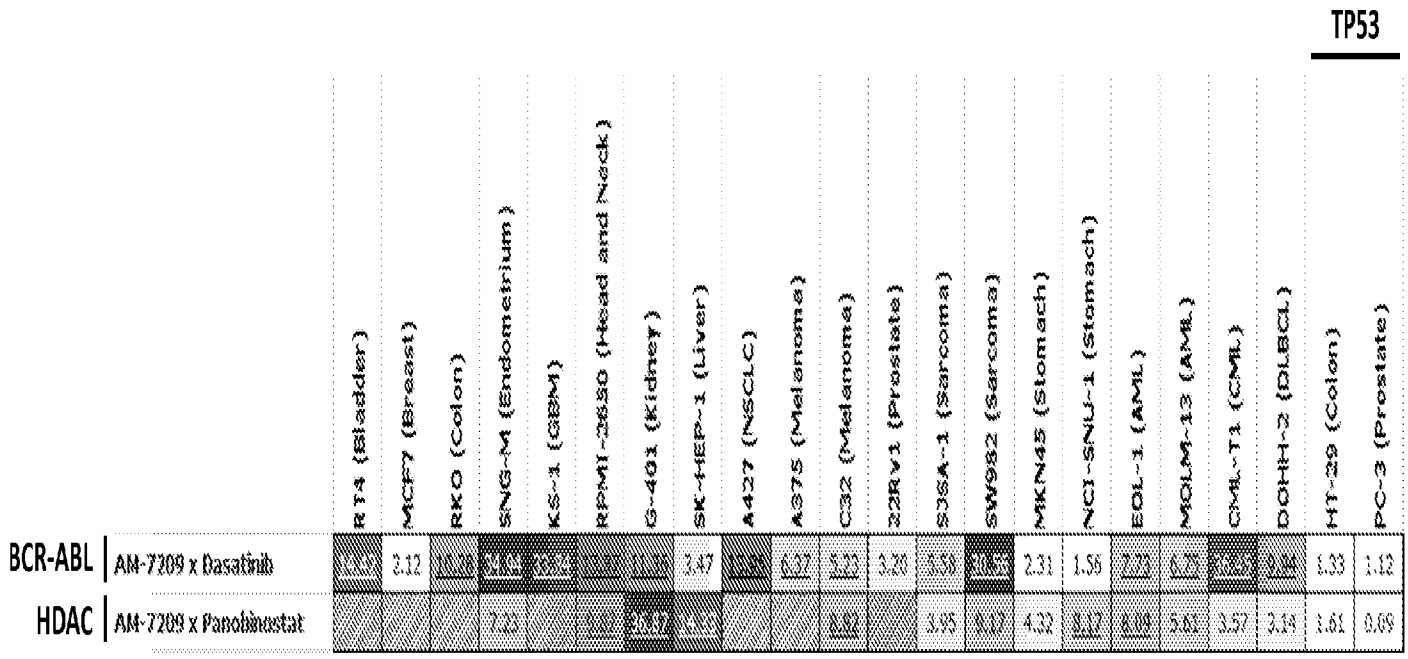


Figure 83
RG7112 – Miscellaneous Combinations

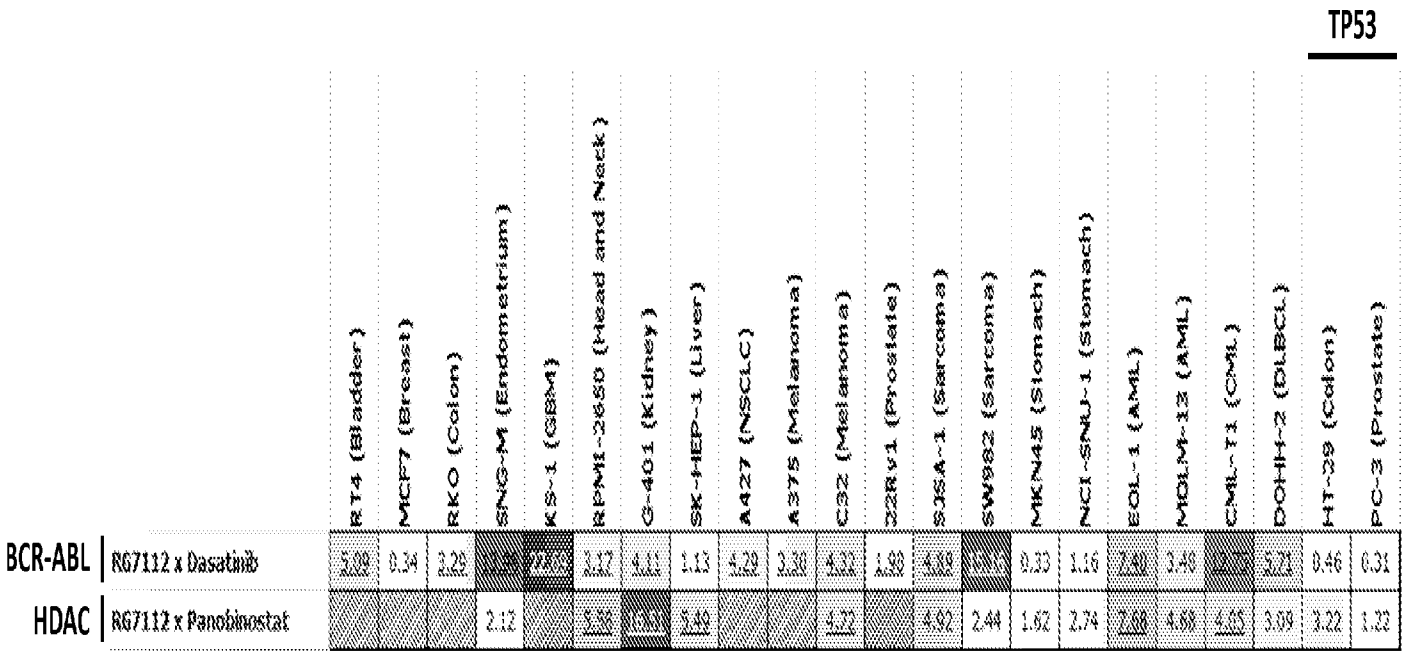


Figure 84

AMG 232 – Chemotherapeutic Combinations

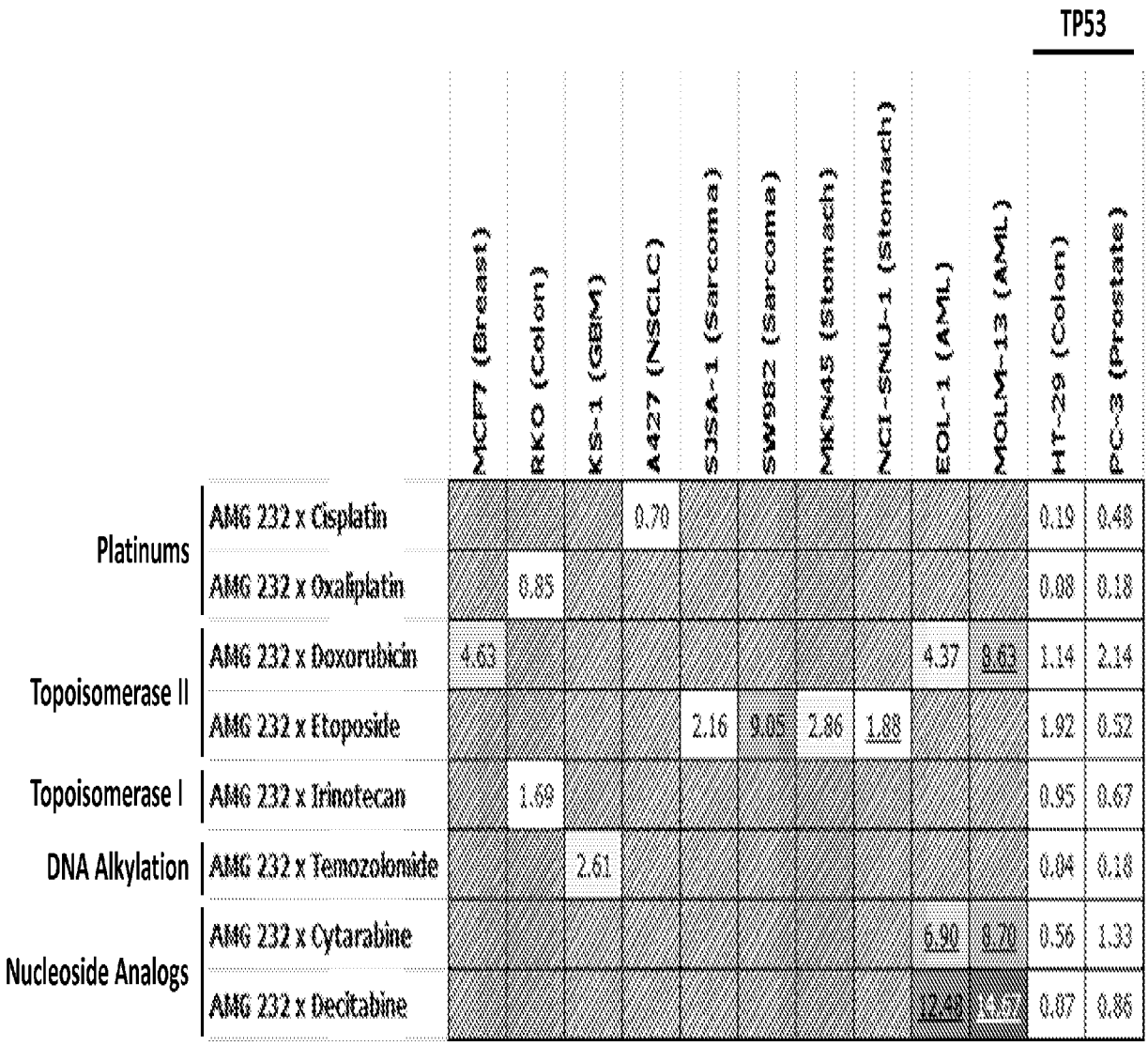


Figure 85

AM-7209 – Chemotherapeutic Combinations

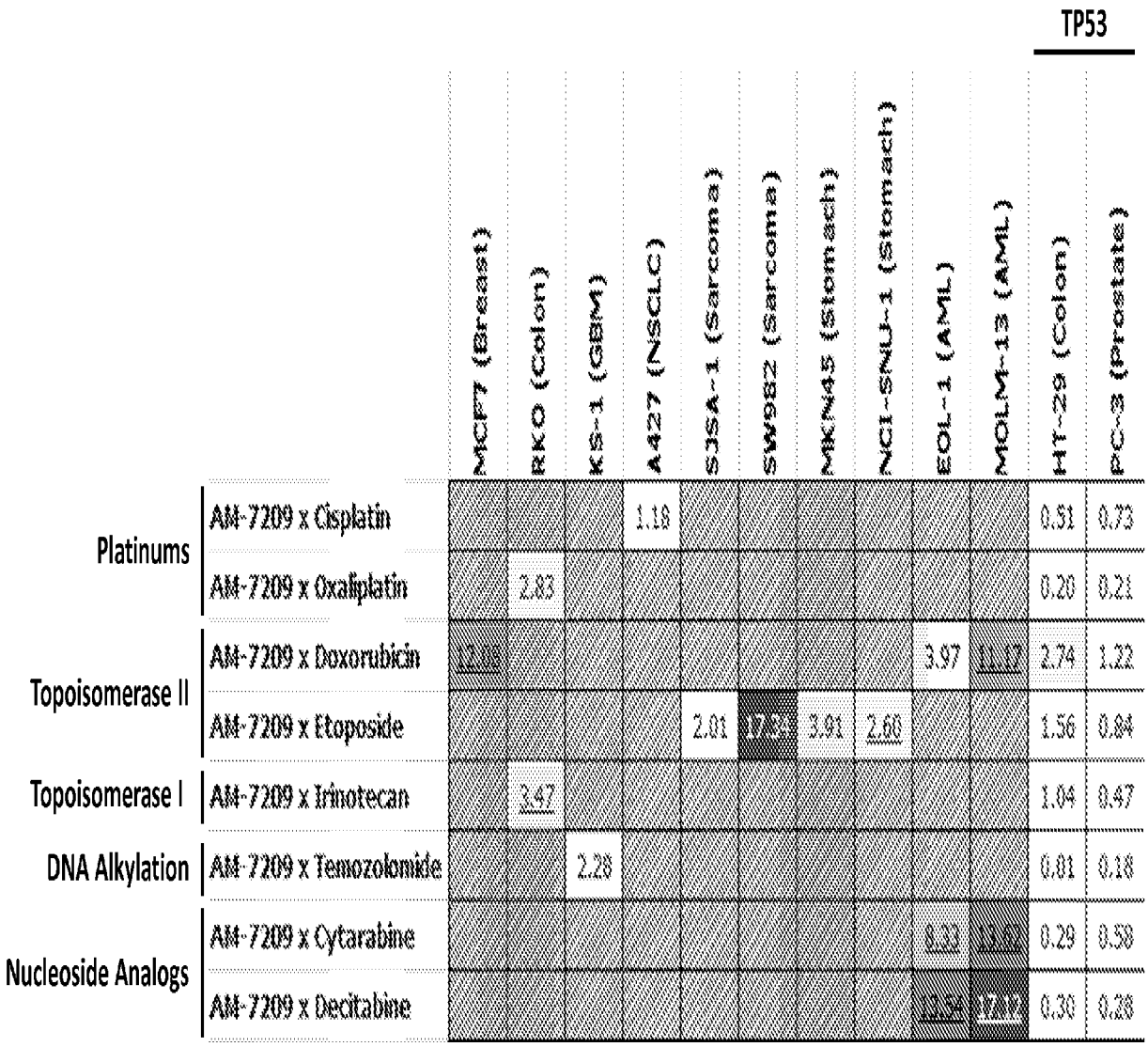


Figure 86
RG7112 – Chemotherapeutic Combinations

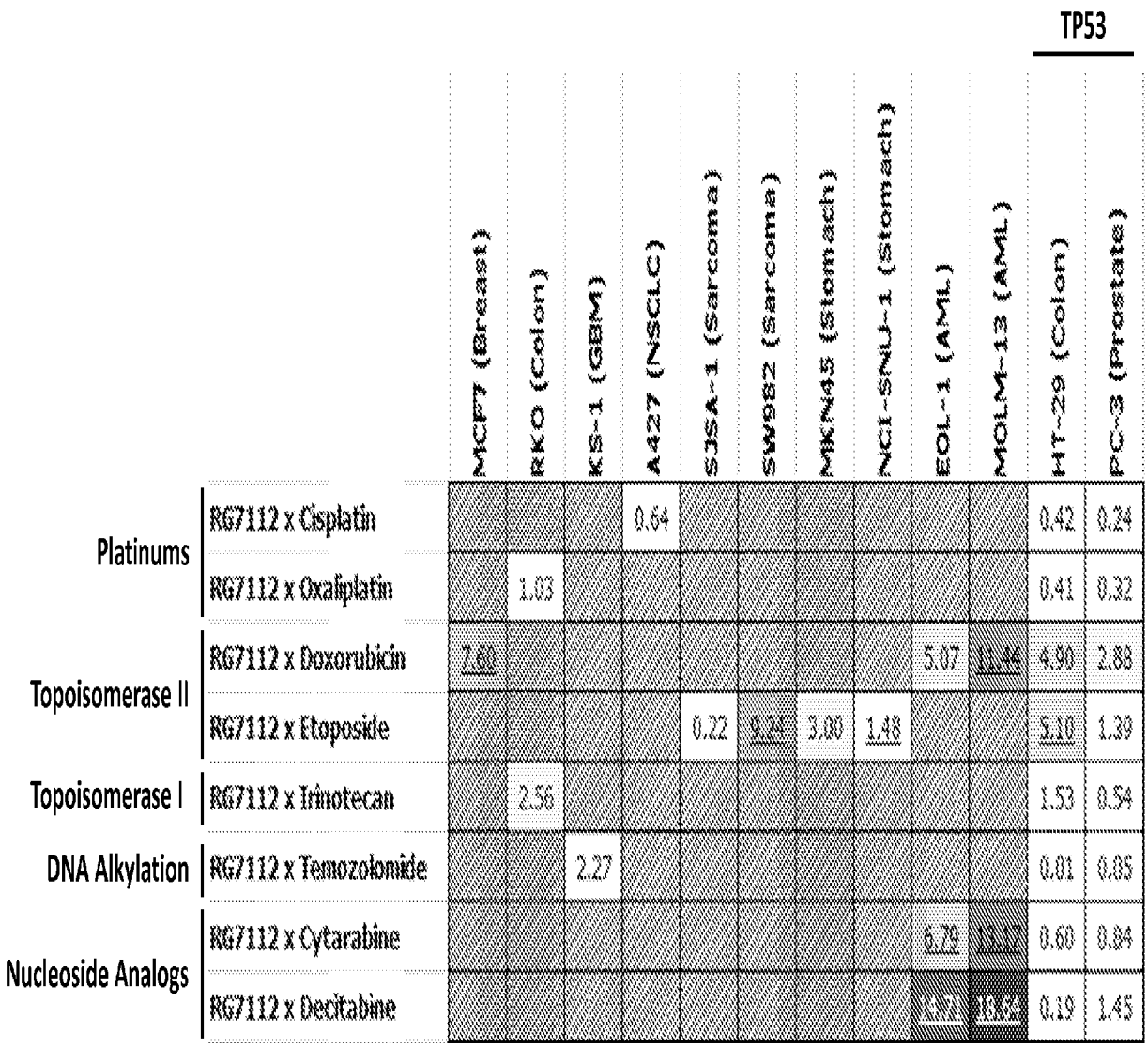


Figure 87

AMG 232 – Haematopoietic Lines

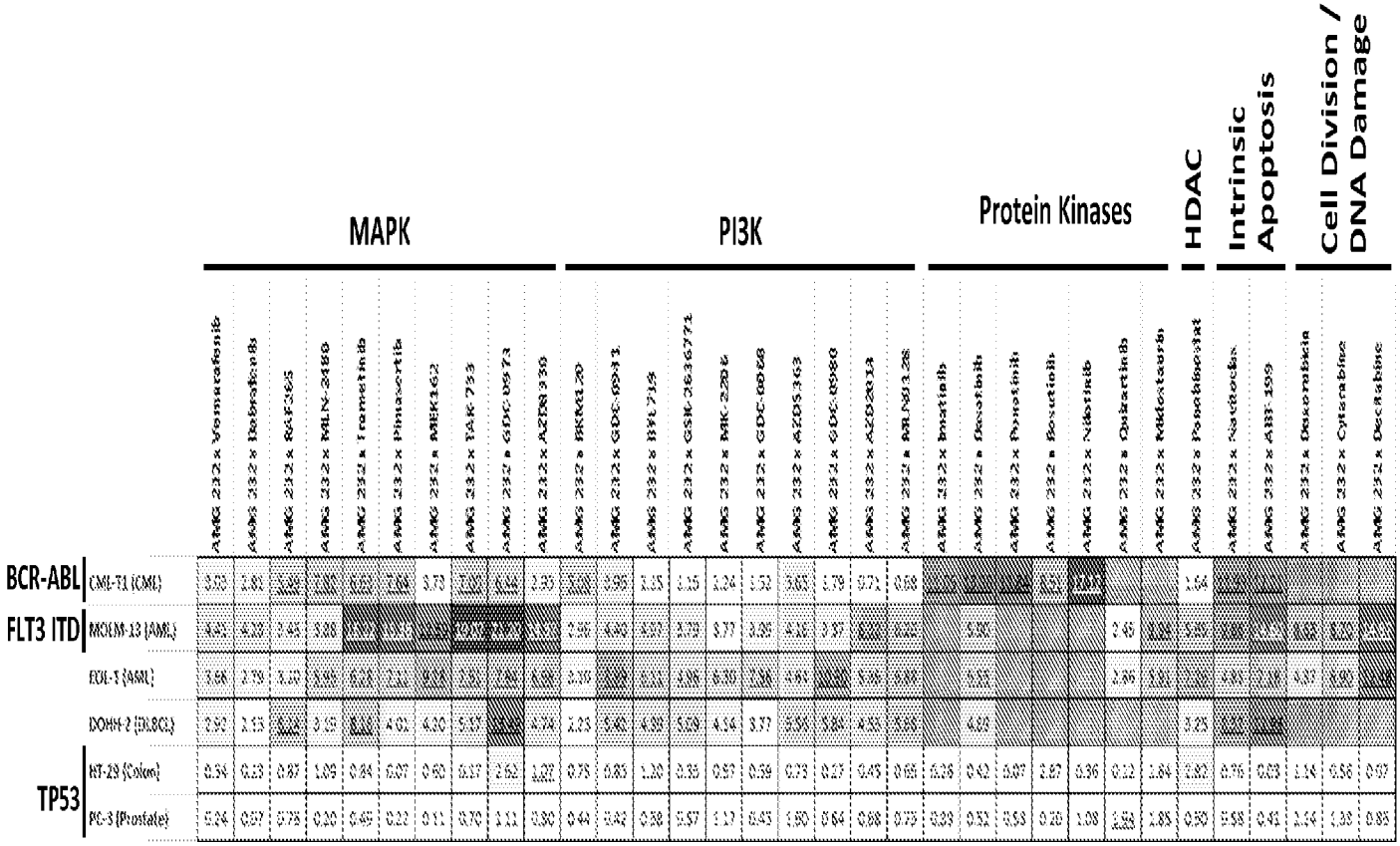


Figure 88

AM-7209 – Haematopoietic Lines

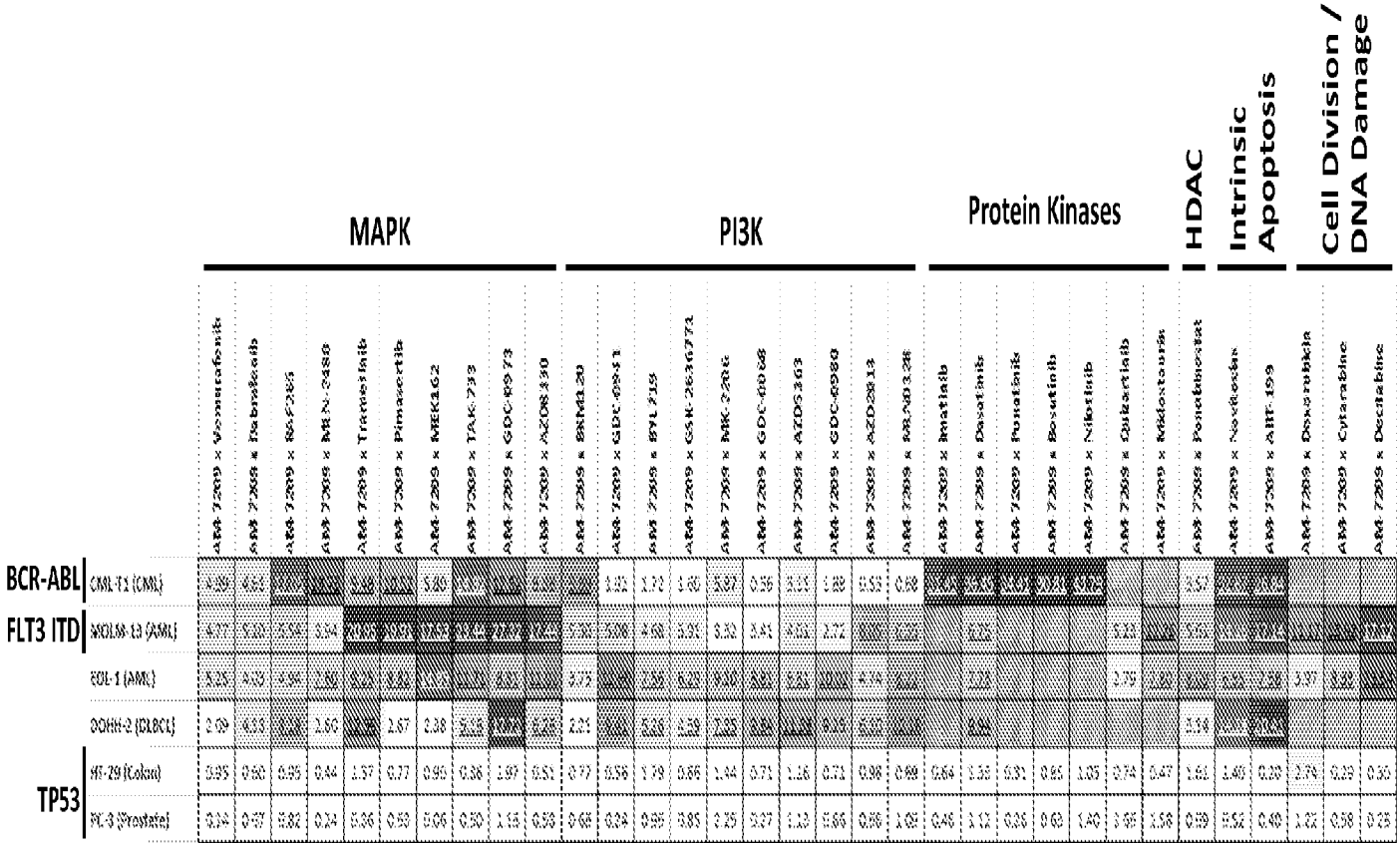


Figure 89

RG7112 – Haematopoietic Lines

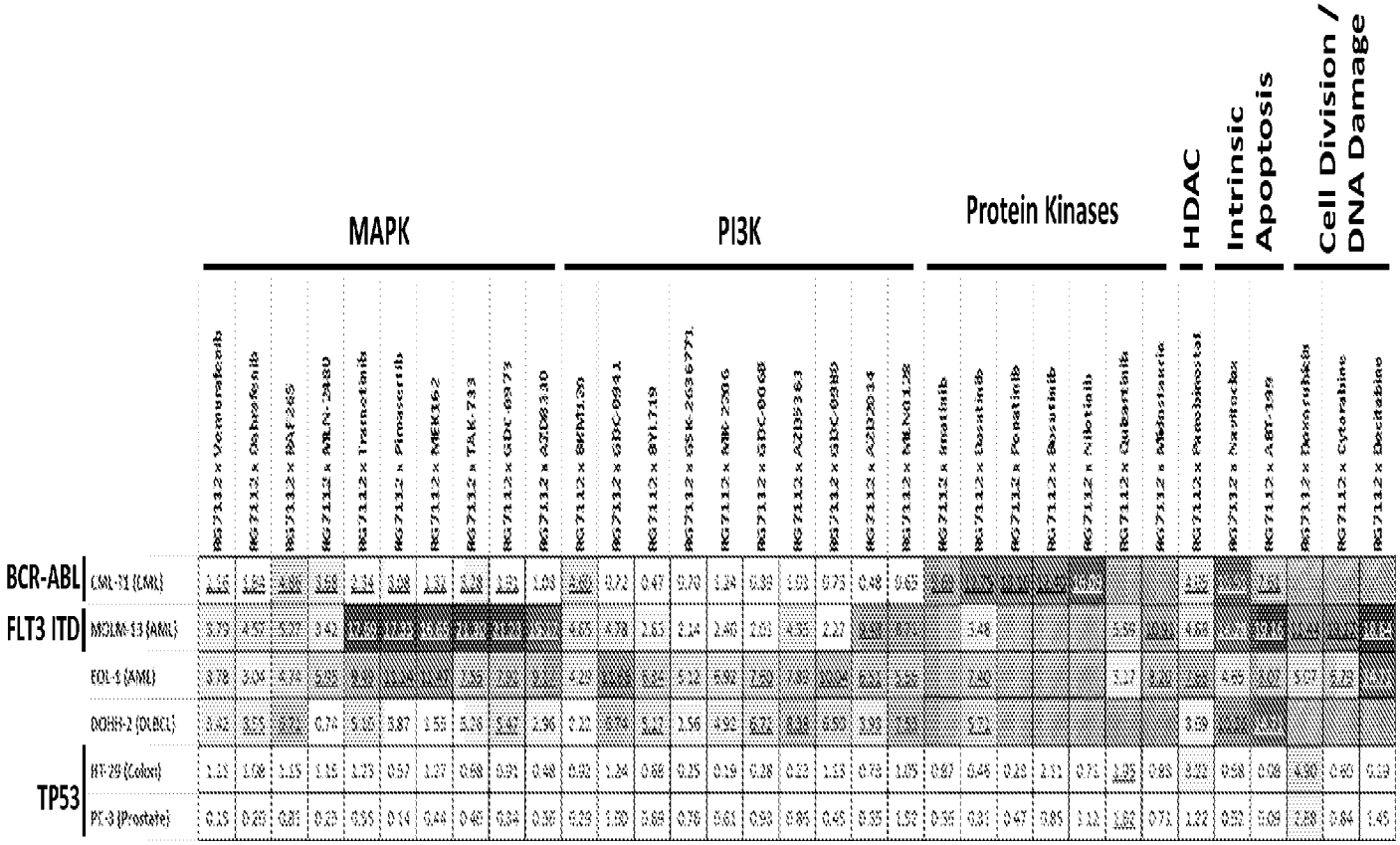


Figure A
MDM2 Inhibitor and Cisplatin in H460 Tumor

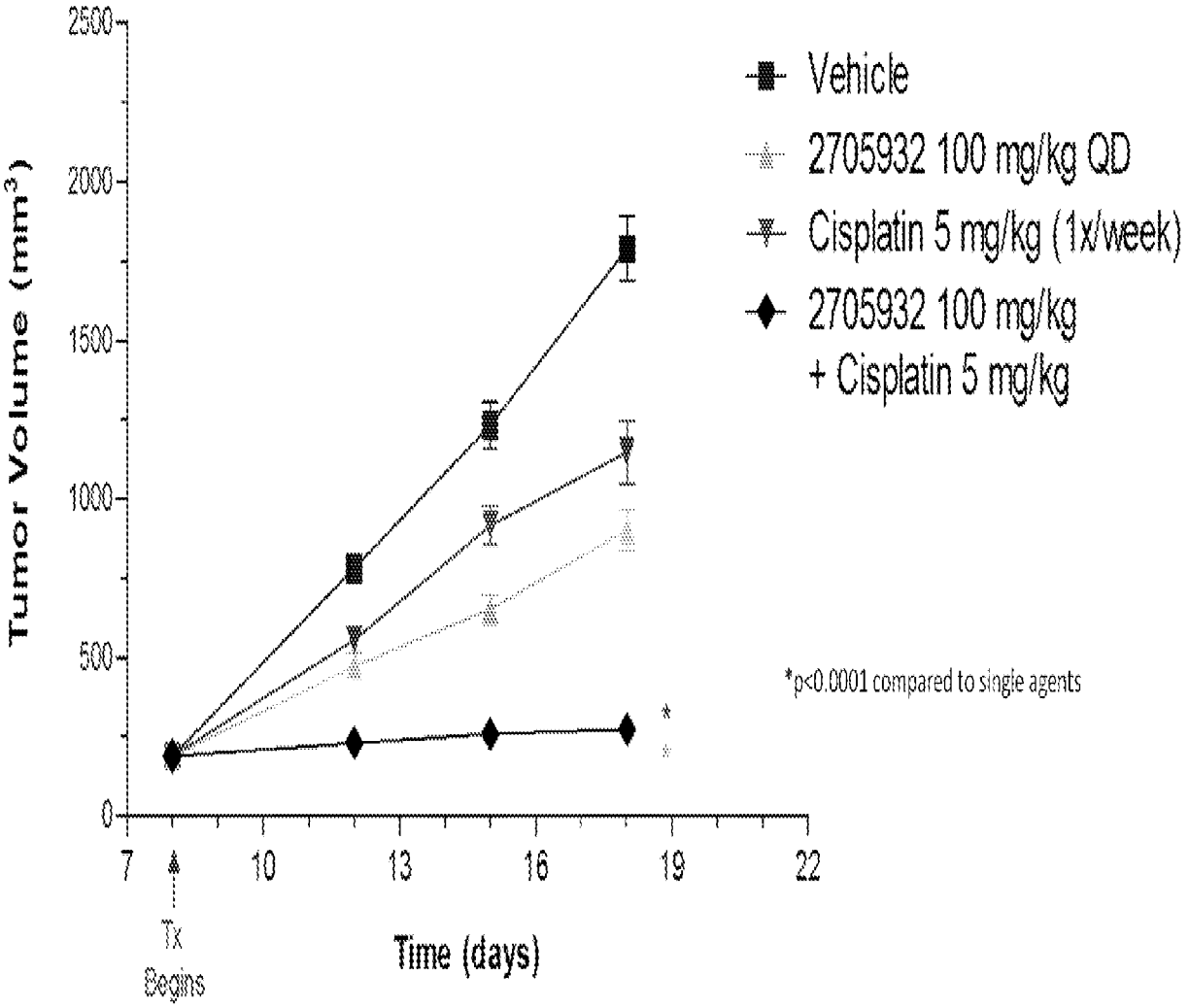


Figure B

MDM2 Inhibitor and Cisplatin in HCT116 Tumor

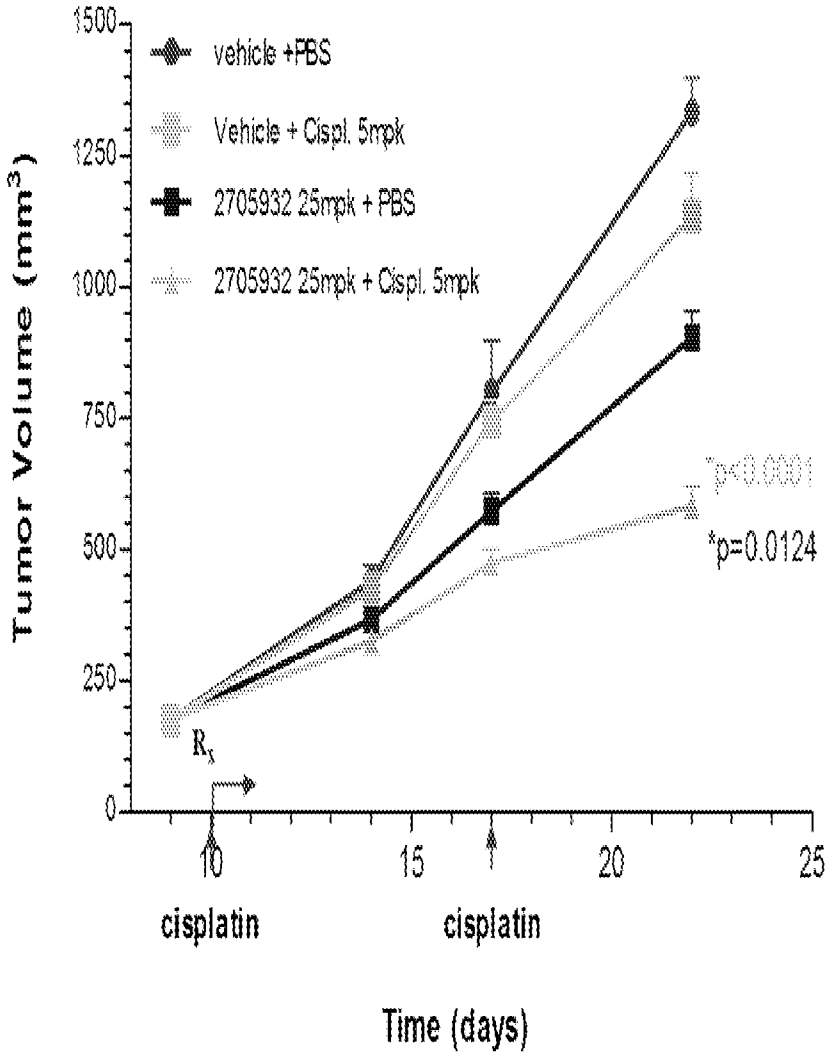
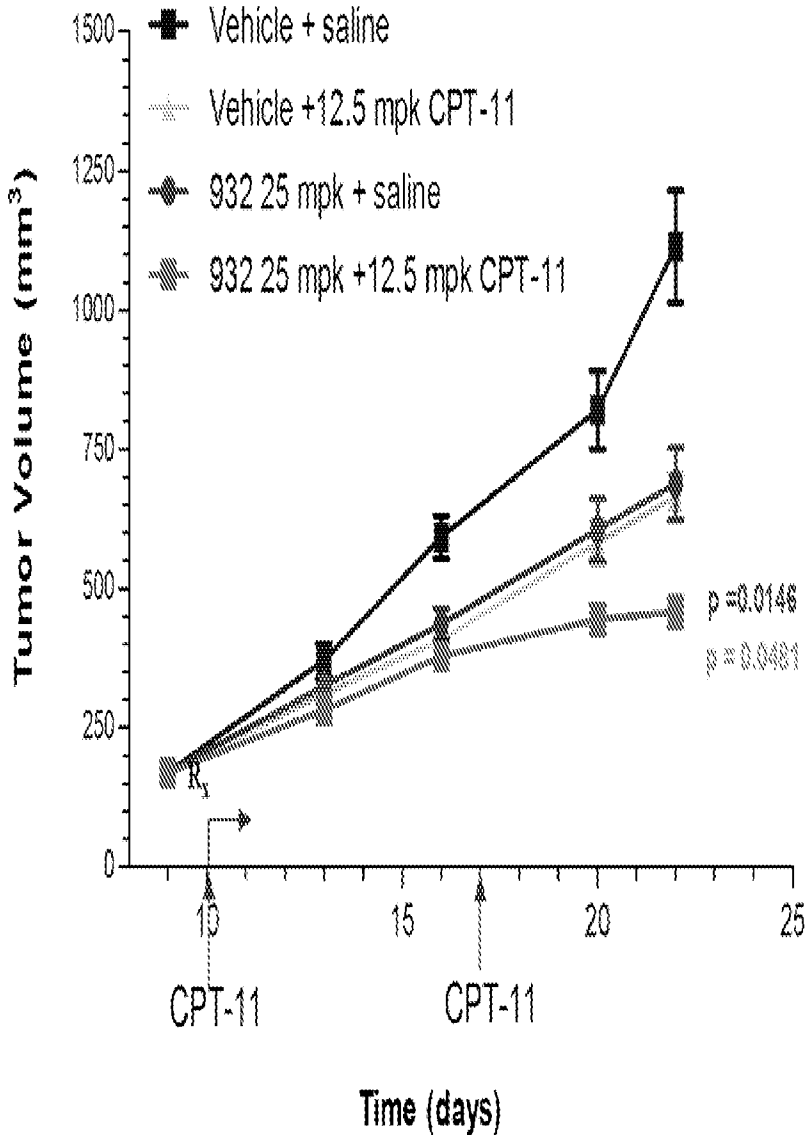


Figure C
MDM2 Inhibitor and CPT-11 in HCT116 Tumor

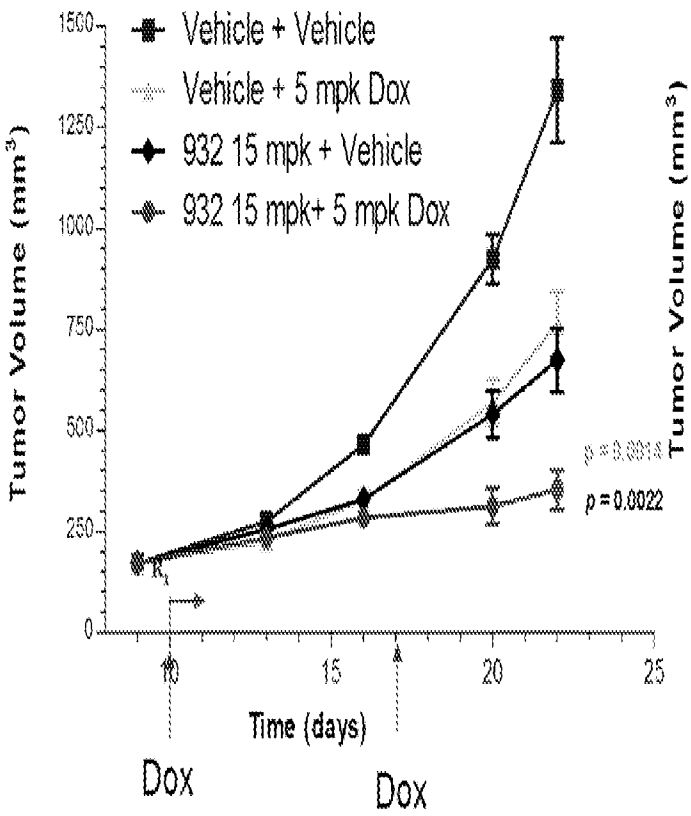


Vehicle (2705932): 15% HPßCD, 1% Pluronic F68, pH 8

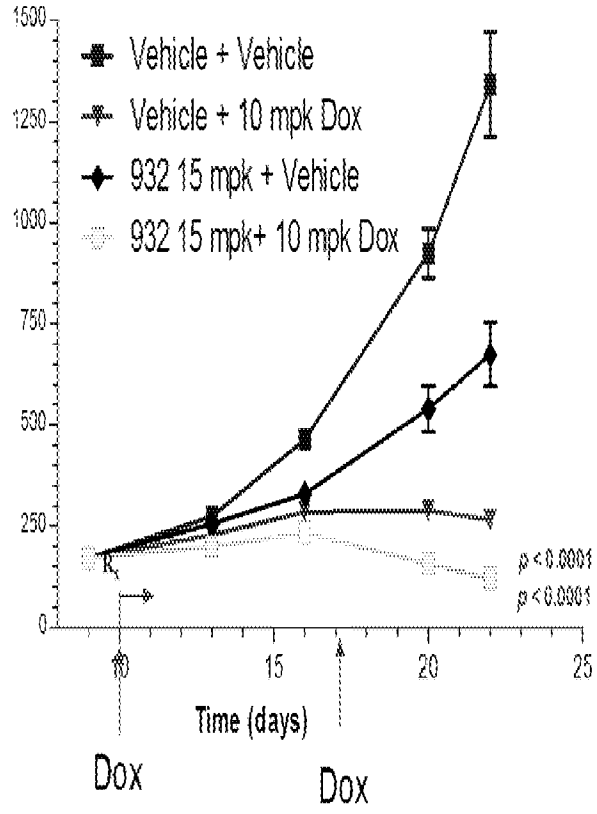
Figure D

MDM2 inhibitor and Doxorubicin in SJSA-1 Tumors

MDM2 Inhibition + Doxorubicin (5mpk)



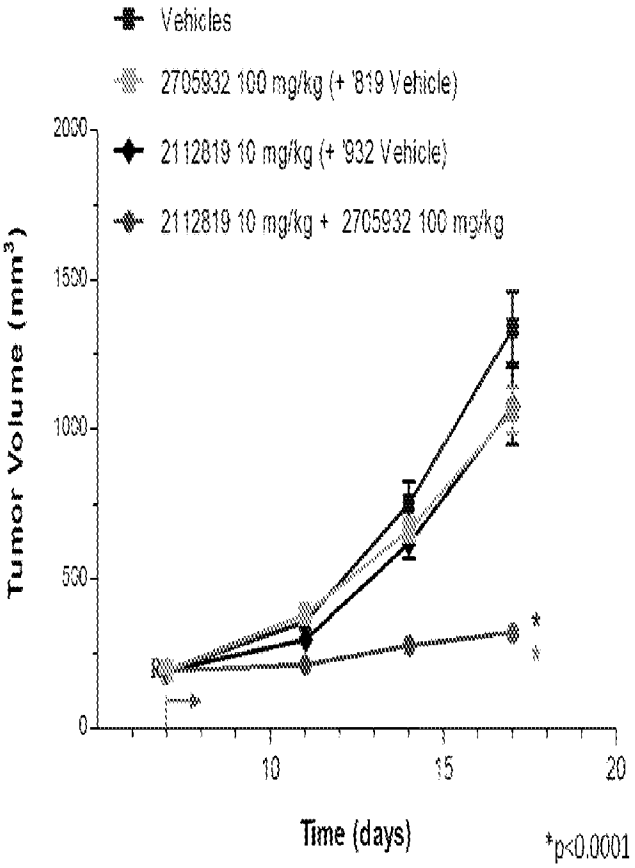
MDM2 Inhibition + Doxorubicin (10mpk)



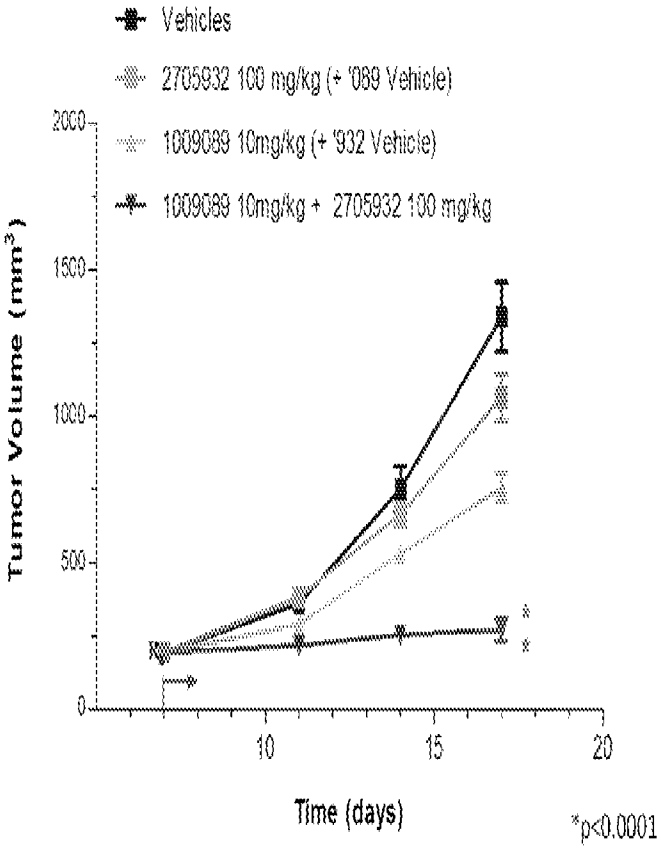
Vehicle (2705932): 15% HPßCD, 1% Pluronic F68, pH 9.4

Figure E
MDM2 Inhibitor and BRAF or MEK Inhibition in RKO Tumors

MDM2 Inhibition + BRAF Inhibition



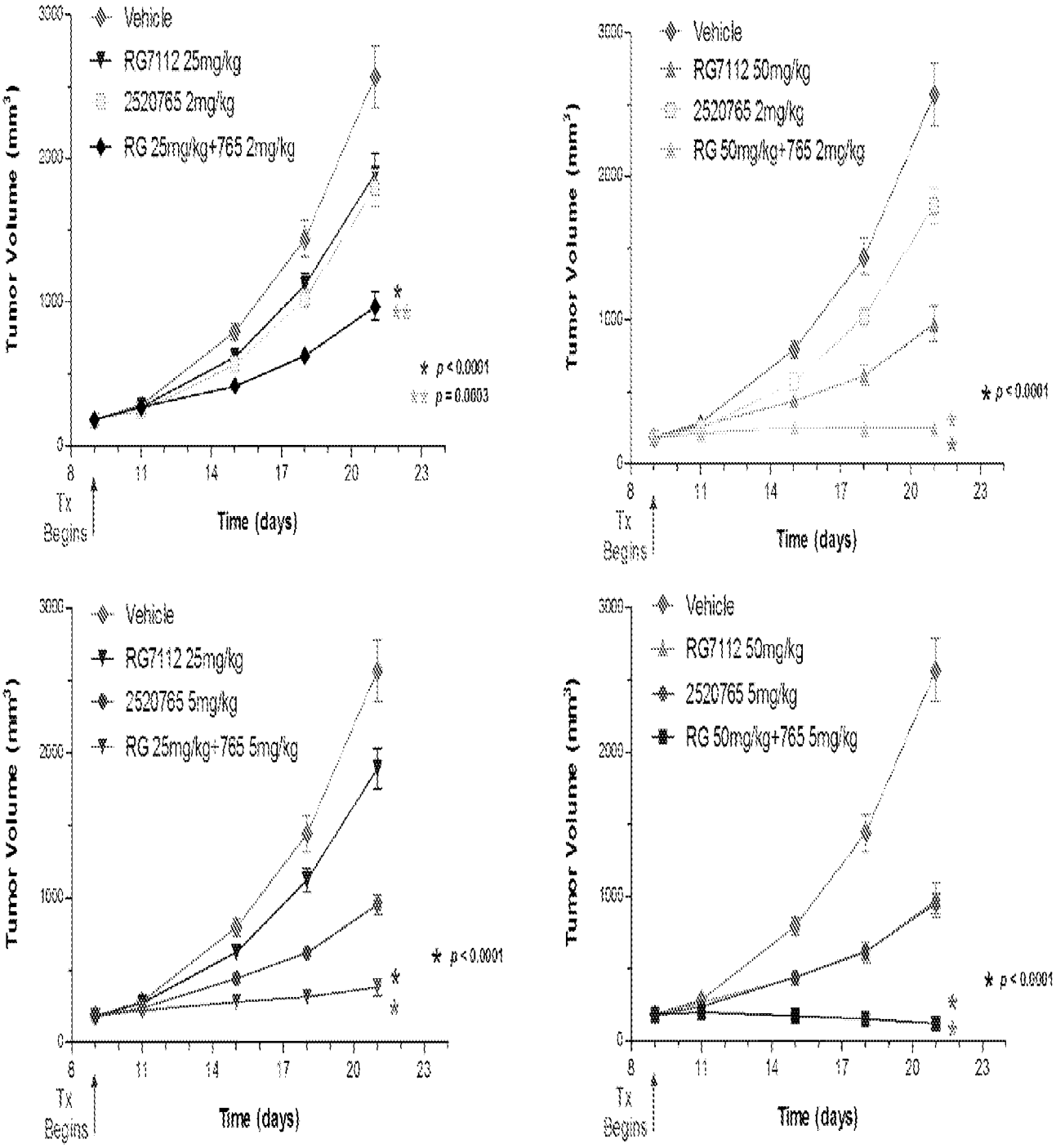
MDM2 Inhibition + MEK Inhibition



1 DIC in 1009089 group on day 11 (N=9)
1 DIC in '819/'932 combination group on day 17 (N=9)
Vehicle (2112819/1009089): 2% HPMC, 1% Tween 80, pH 2.2
Vehicle (2705932): 15% HPßCD, 1% Pluronic F68, pH 8

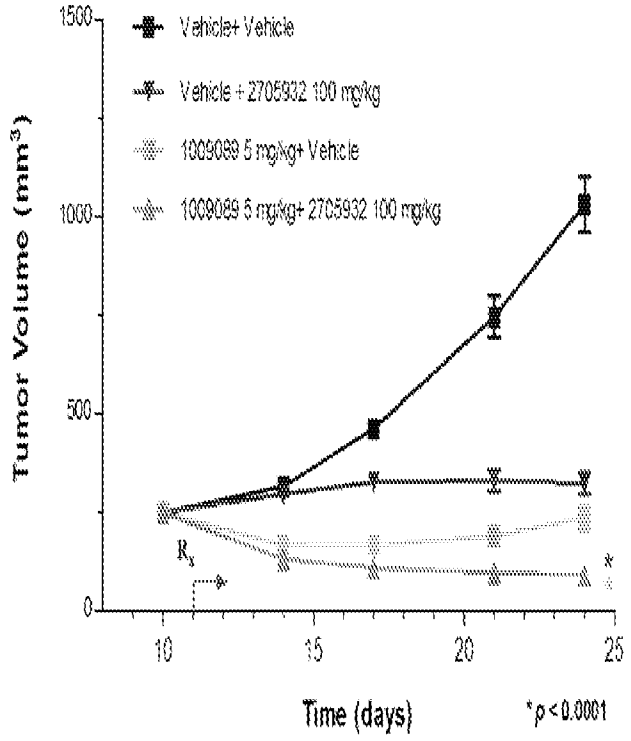
Blinded study (daily oral dosing)

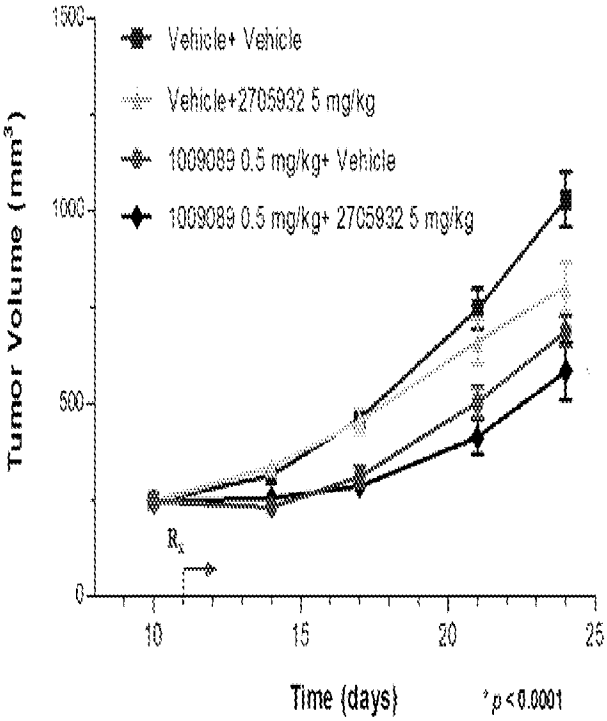
Figure F
MDM2 Inhibitor and PI3K Inhibitor in U87 Tumor



All curves are derived from a single blinded study (dai)ly oral dosing

Figure G
MDM2 Inhibitor and MEK Inhibitor in A375 Tumors





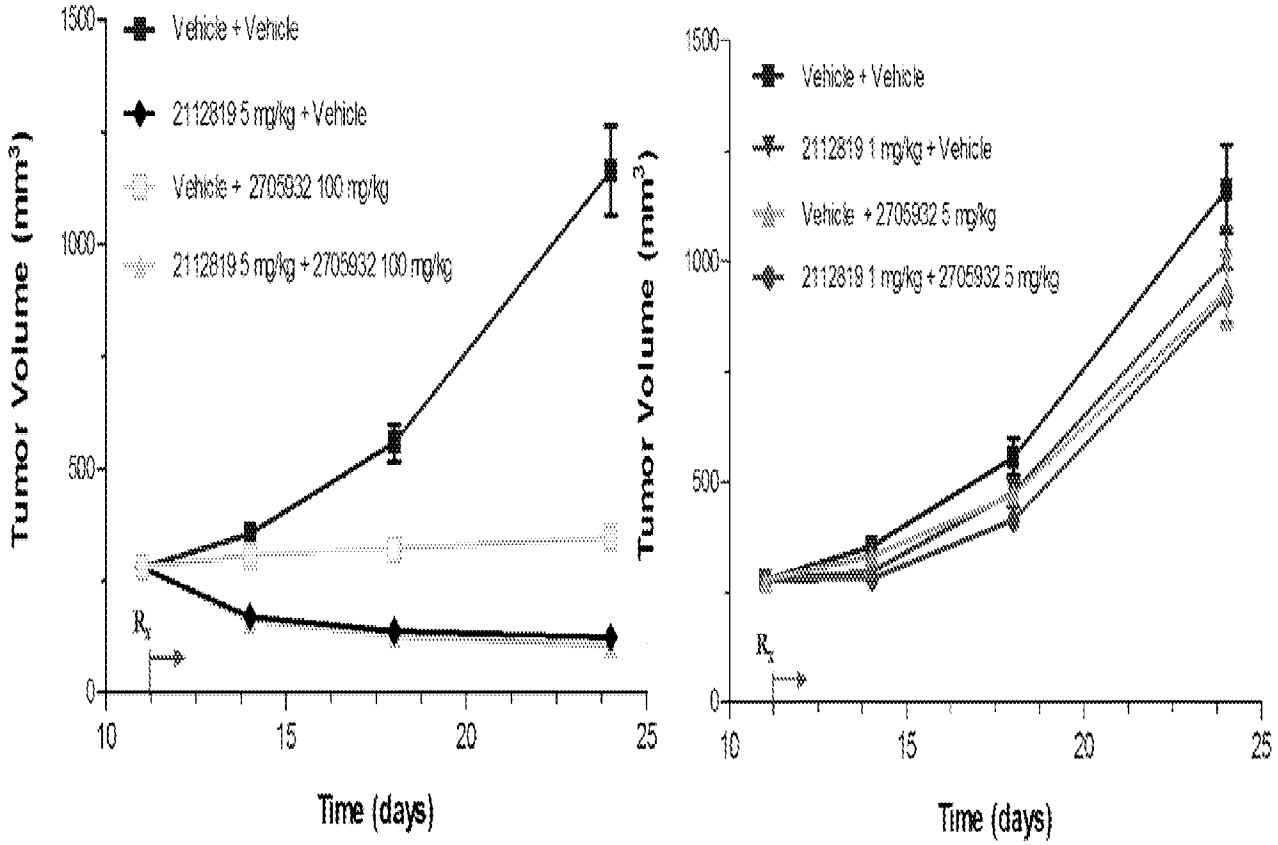
Group	% TGI
Vehicle+ Vehicle	0.0
Vehicle + 2705932 100 mg/kg	90.5
1009089 5 mg/kg+ Vehicle	101.6
1009089 5 mg/kg+ 2705932 100 mg/kg	120.1

Group	% TGI
Vehicle+ Vehicle	0.0
Vehicle+2705932 5 mg/kg	29.1
1009089 0.5 mg/kg+ Vehicle	43.7
1009089 0.5 mg/kg+ 2705932 5 mg/kg	57.0

Vehicle (1009089): 2% HPMC, 1% Tween 80, pH 2.2

Vehicle (2705932): 15% HPßCD, 1% Pluronic F68, pH 8

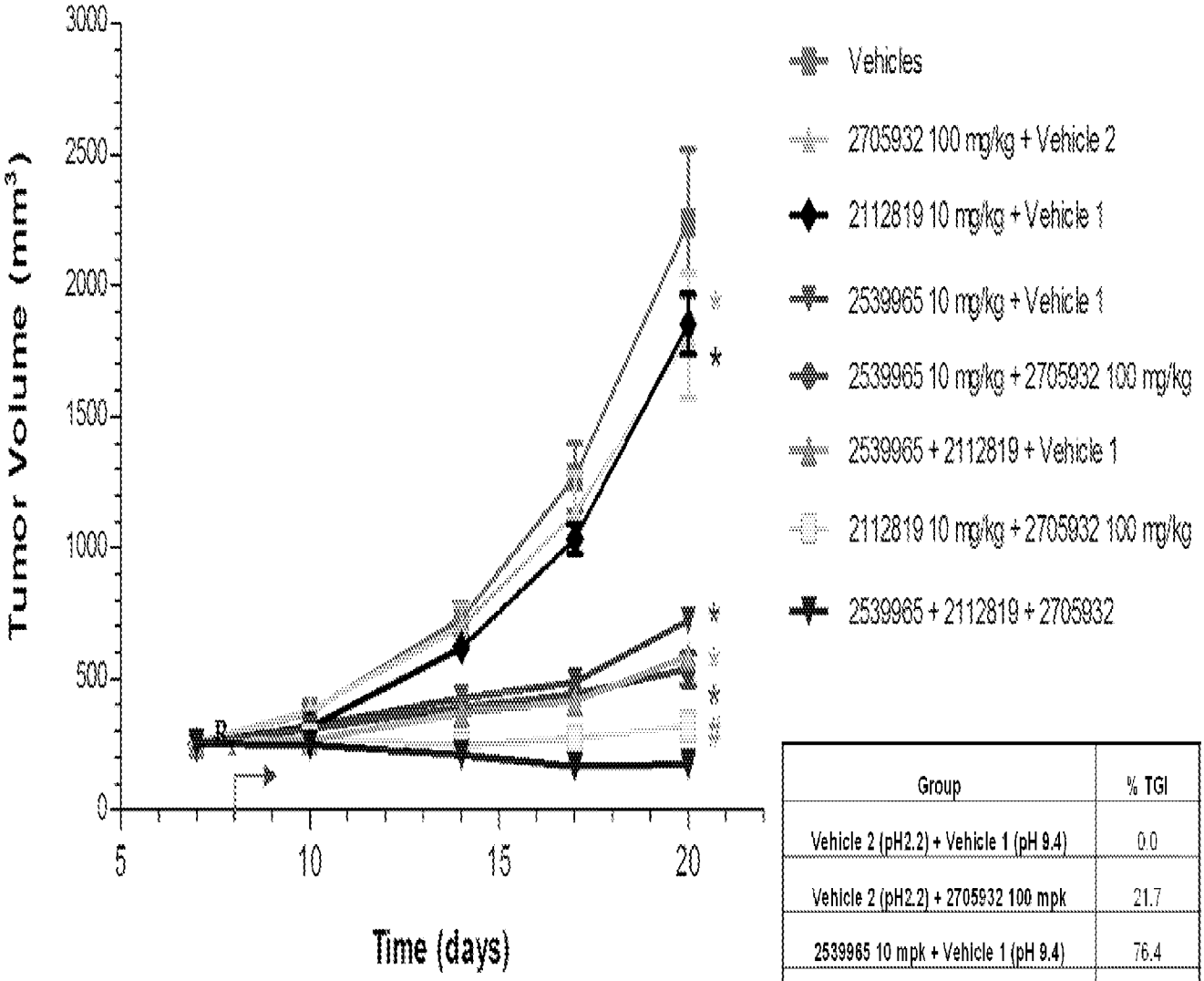
Figure H
MDM2 Inhibitor and BRAF Inhibitor in A375sq2 Tumors



* p<0.0001 compare to 2705932 100mg/kg

Vehicle (2112819): 2% HPMC, 1% Tween 80, pH 2.2
Vehicle (2705932): 15% HPßCD, 1% Pluronic F68, pH 8

Figure I
Combination of MDM2, PI3K and BRAF Inhibition in RKO Tumors



Group	% TGI
Vehicle 2 (pH2.2) + Vehicle 1 (pH 9.4)	0.0
Vehicle 2 (pH2.2) + 2705932 100 mpk	21.7
2539965 10 mpk + Vehicle 1 (pH 9.4)	76.4
2112819 10 mpk + Vehicle 1 (pH 9.4)	19.5
2539965 10 mpk + 2705932 100 mpk	85.7
2112819 10 mpk + 2705932 100 mpk	96.6
2539965 +2112819+ Vehicle 1 (pH 9.4)	83.2
2539965 +2112819+2705932 100 mg/kg	R= 30.7

Blinded Study

RMANOVA: p values are comparisons with the triple combination group

* $p < 0.0001$

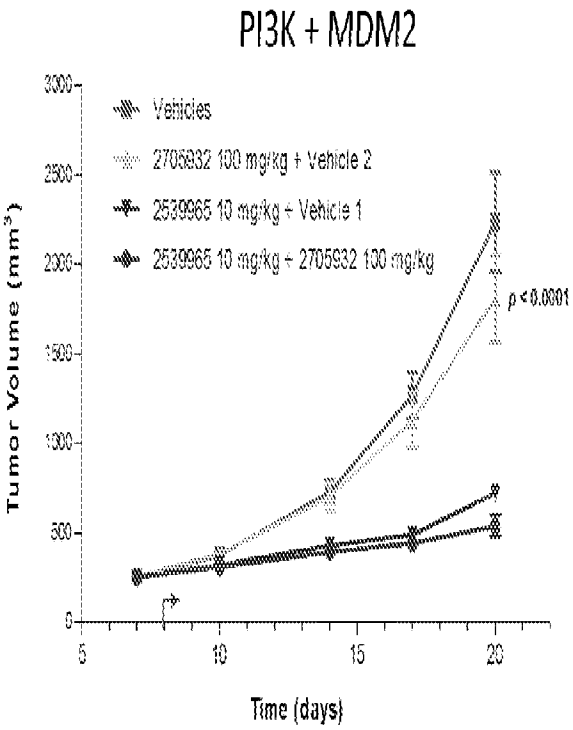
$p = 0.0090$

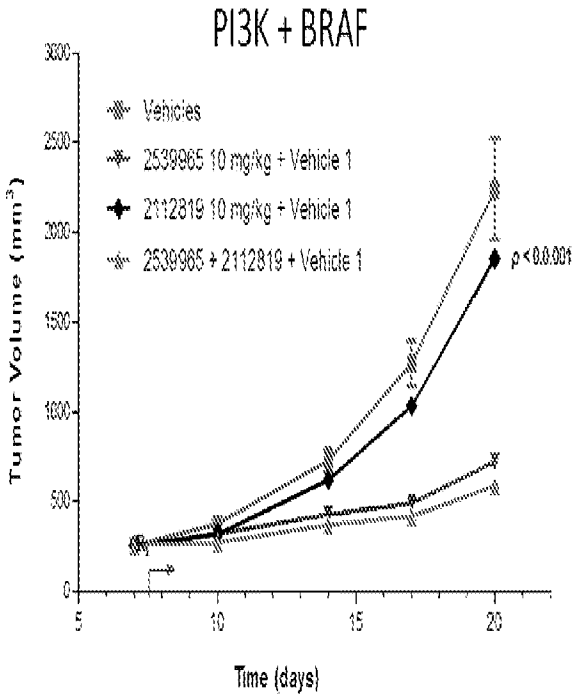
Vehicle 1 (2705932): 15% HPßCD, 1% Pluronic F68, pH 9.4

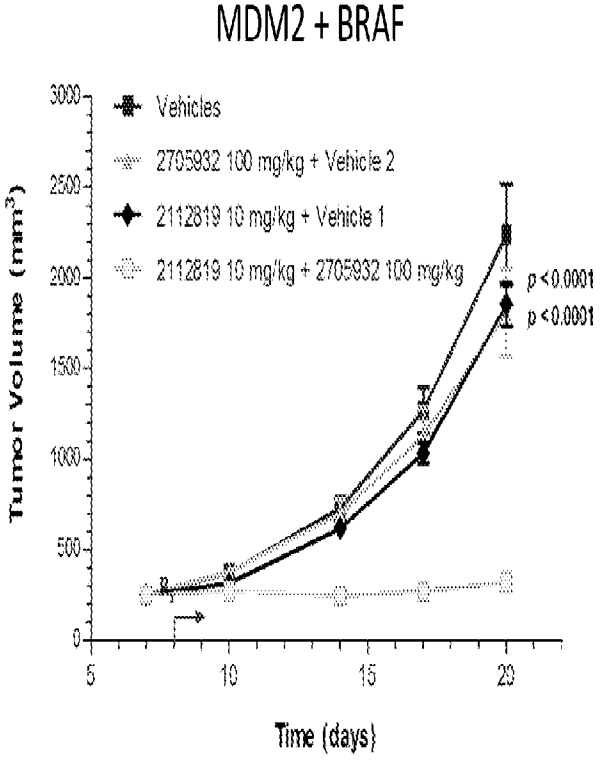
Vehicle 2 (2112819/2539965): 15% HPßCD, 1% Pluronic F68, pH 2.2

Figure J

Combination of MDM2, PI3K and BRAF Inhibition in the RKO Tumor Model (single agents vs. double combinations)







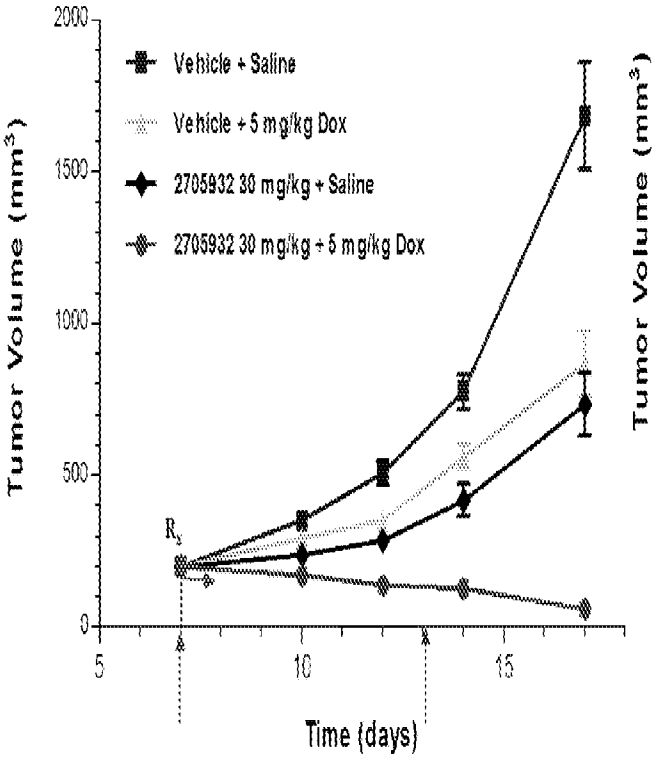
Blinded study:
RMANOVA p values are comparisons to the double combination groups

Vehicle 1 (2705932): 15% HPßCD, 1% Pluronic F68, pH 9.4
Vehicle 2 (2112819/2539965): 15% HPßCD, 1% Pluronic F68, pH 2.2

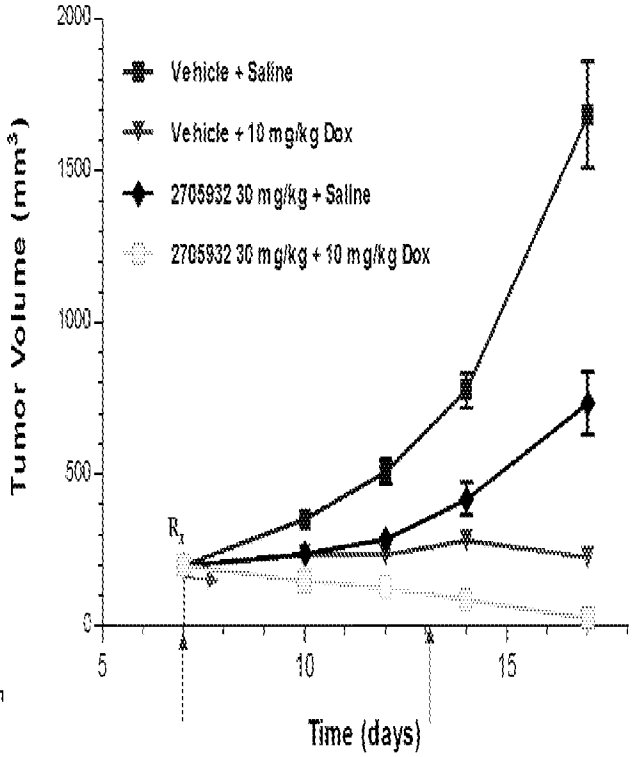
Figure K

MDM2 Inhibitor and Doxorubicin in Molm13 Tumors

MDM2 Inhibition + Doxorubicin (5mpk)



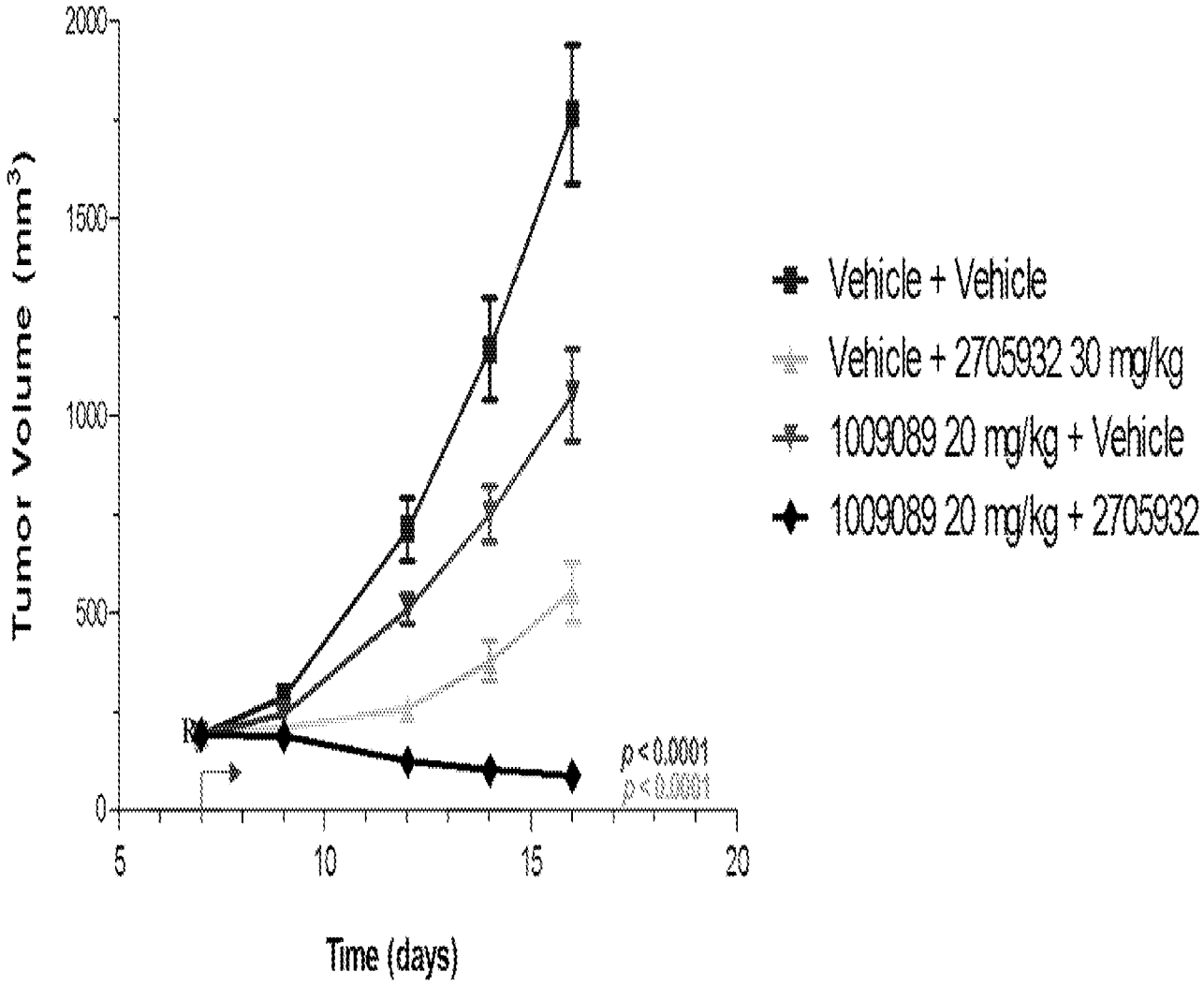
MDM2 Inhibition + Doxorubicin (10mpk)



Vehicle (2705932): 15% HPßCD, 1% Pluronic F68, pH 9.4

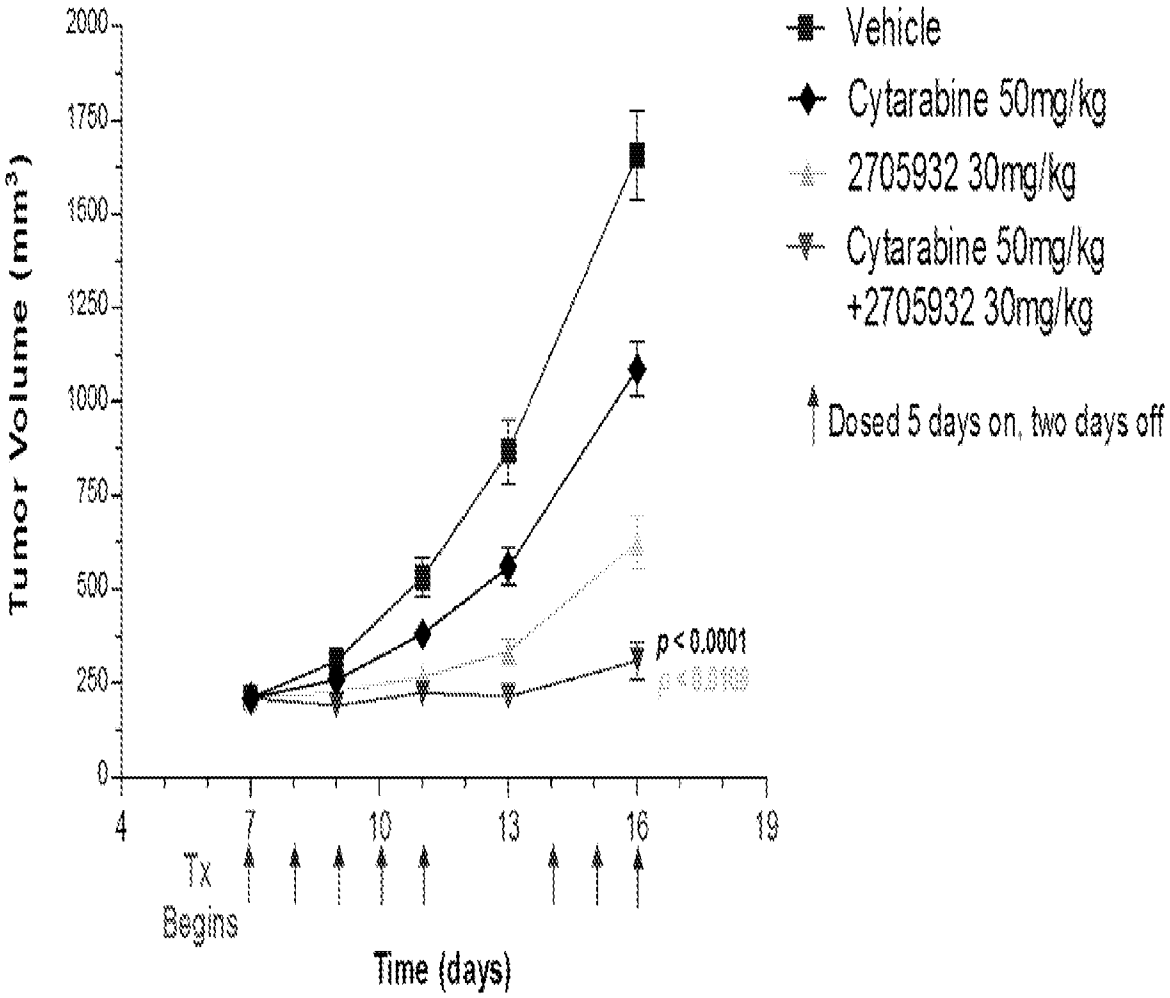
Figure L

MDM2 Inhibitor and MEK inhibitor in Molm13 Tumors



Vehicle (2705932): 15% HPßCD, 1% Pluronic F68, pH 9.4
Vehicle (1009089): 2% HPMC, 1% Tween 80, pH 2.2

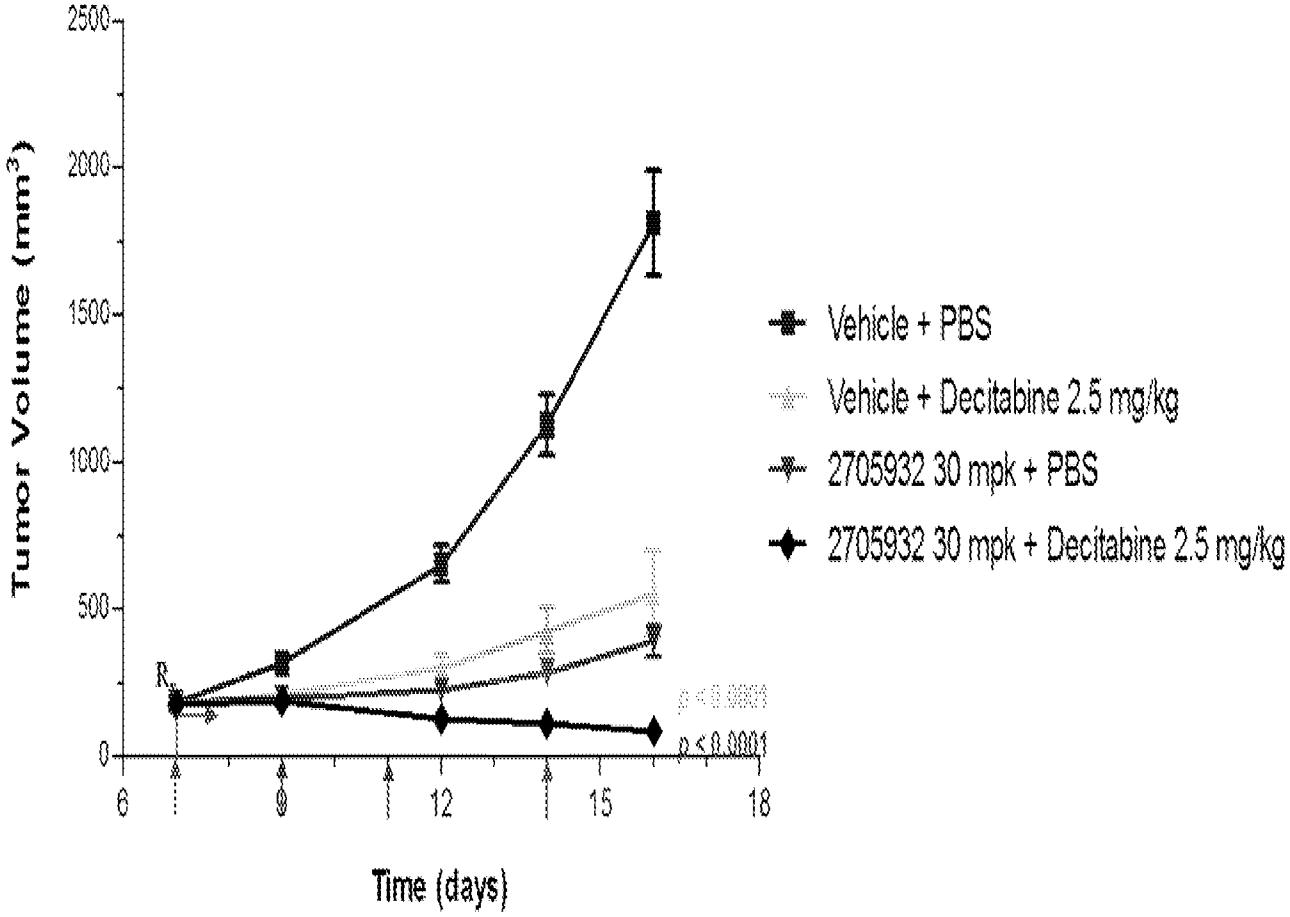
Figure M
MDM2 Inhibitor and Cytarabine in Molm13 Tumors



Vehicle: 15% HPβCD, 1% Pluronic F68, pH 9.4 and Saline

Figure N

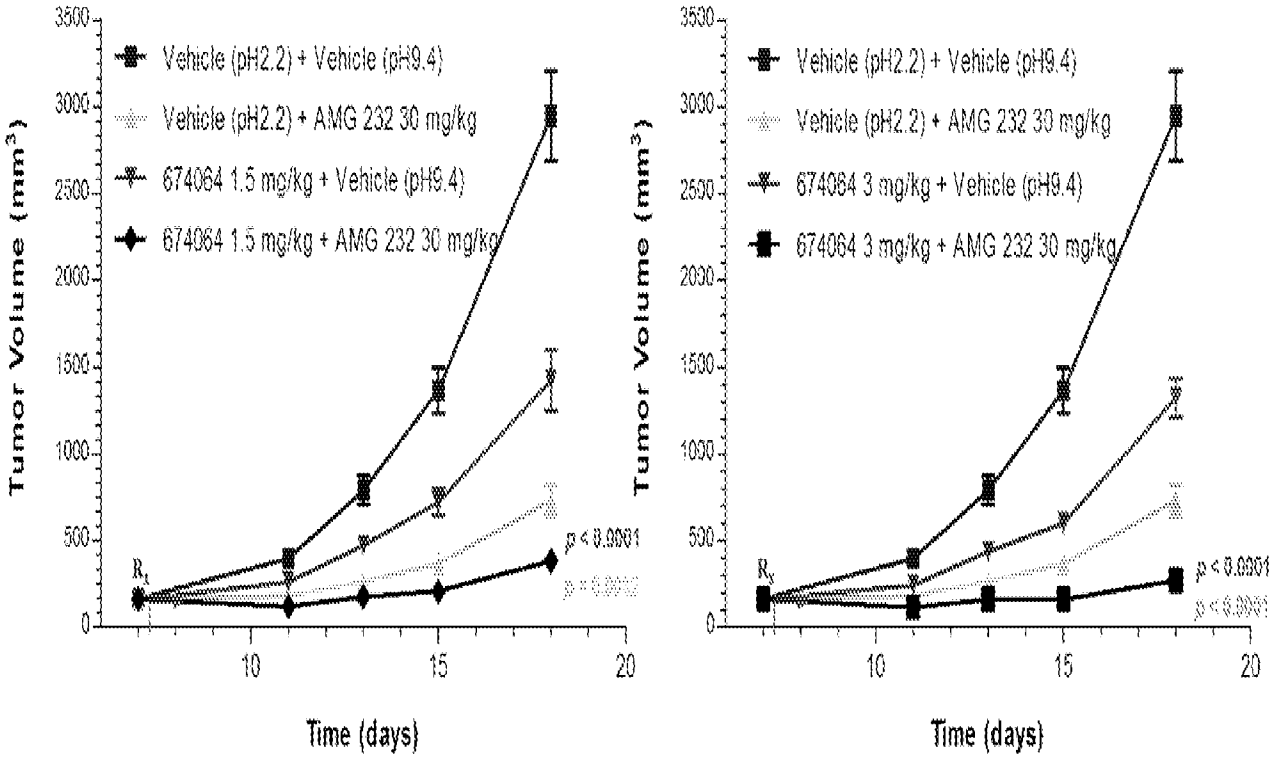
MDM2 Inhibitor and Decitabine in Molm13 Tumors



Vehicle (2705932): 15% HPßCD, 1% Pluronic F68, pH 9.4

Figure O

MDM2 Inhibition and Sorafenib inMolm13 Tumors



Vehicle (674064): 2% HPMC, 1% Tween 80, pH 2.2

Vehicle (2705932): 15% HPßCD, 1% Pluronic F68, pH 9.4