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Saha et al.

(54) **METHODS AND COMPOSITIONS FOR TREATING NON-ERK MAPK PATHWAY INHIBITOR-RESISTANT CANCERS**

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(52) **U.S. Cl.**

CPC ***A61K 31/4439*** (2013.01); ***A61K 45/06*** (2013.01); ***A61K 31/506*** (2013.01); ***A61K 31/519*** (2013.01); ***C12Q 1/6886*** (2013.01); *C12Q 2600/106* (2013.01); *C12Q 2600/156* (2013.01)

(57) **ABSTRACT**

The present invention provides, inter alia, methods, pharmaceutical compositions, and kits for treating or ameliorating the effects of a cancer in a subject, which cancer is refractory or resistant to non-ERK MAPK pathway inhibitor therapy. Also provided are methods for identifying a subject having cancer who would benefit from therapy with an ERK inhibitor and methods for inhibiting phosphorylation of RSK in a cancer cell that is refractory or resistant to a non-ERK MAPK pathway inhibitor.

FIG. 1A

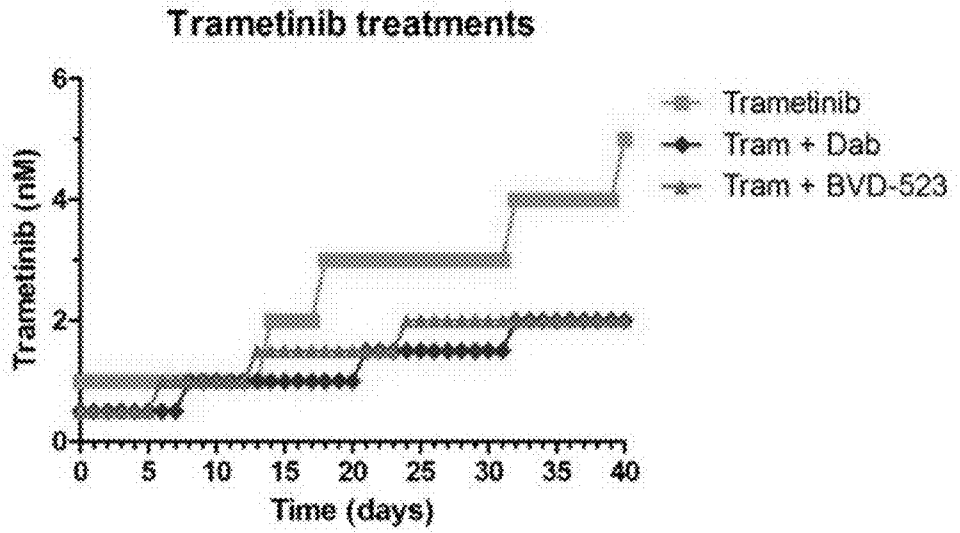

Trametinib treatments
Trametinib (nM)
0
2
4
6
0 5 10 15 20 25 30 35 40
Time (days)
Trametinib
Tram + Dab
Tram + BVD-523

FIG. 1B

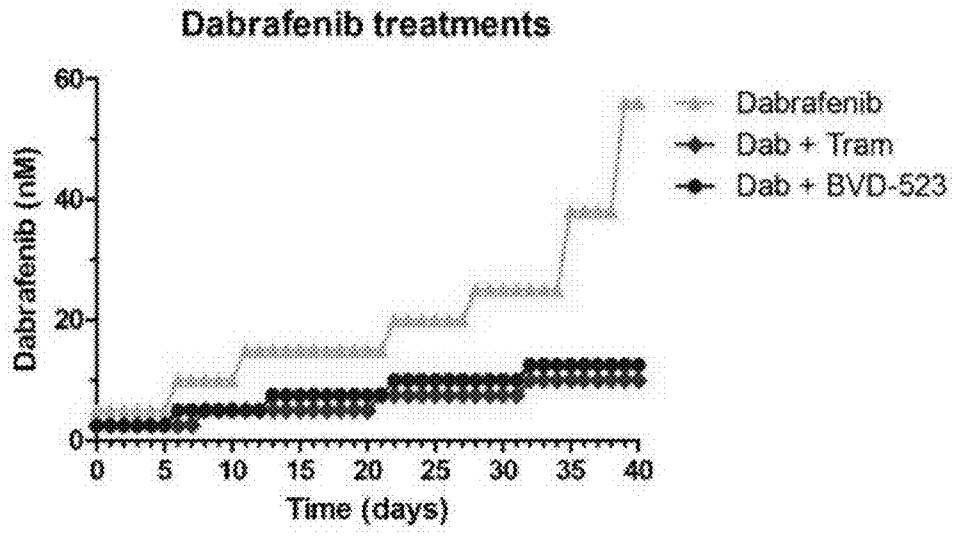

Dabrafenib treatments
Dabrafenib (nM)
0
20
40
60
0 5 10 15 20 25 30 35 40
Time (days)
Dabrafenib
Dab + Tram
Dab + BVD-523

FIG. 1C

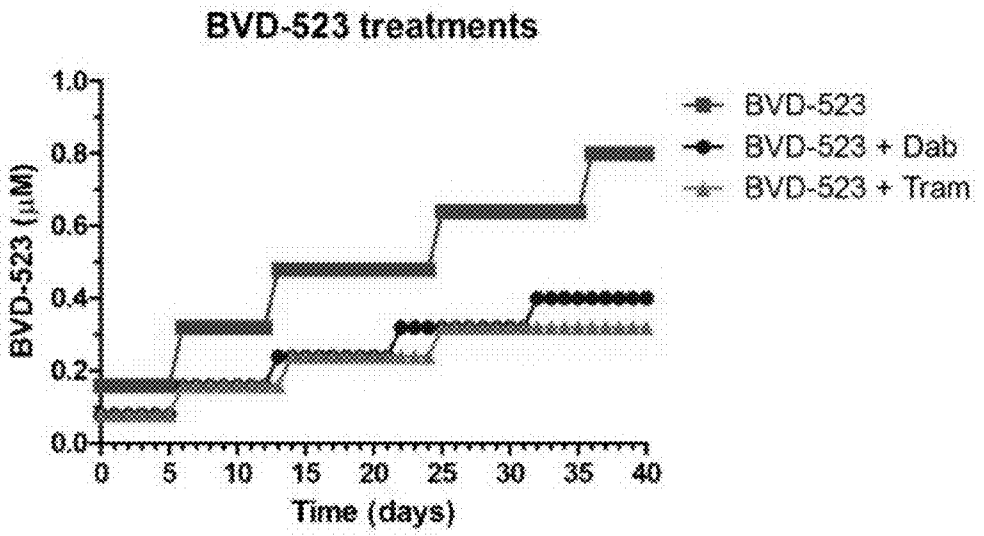

BVD-523 treatments
BVD-523 (μM)
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
30
35
40
Time (days)
BVD-523
BVD-523 + Dab
BVD-523 + Tram

FIG. 2A

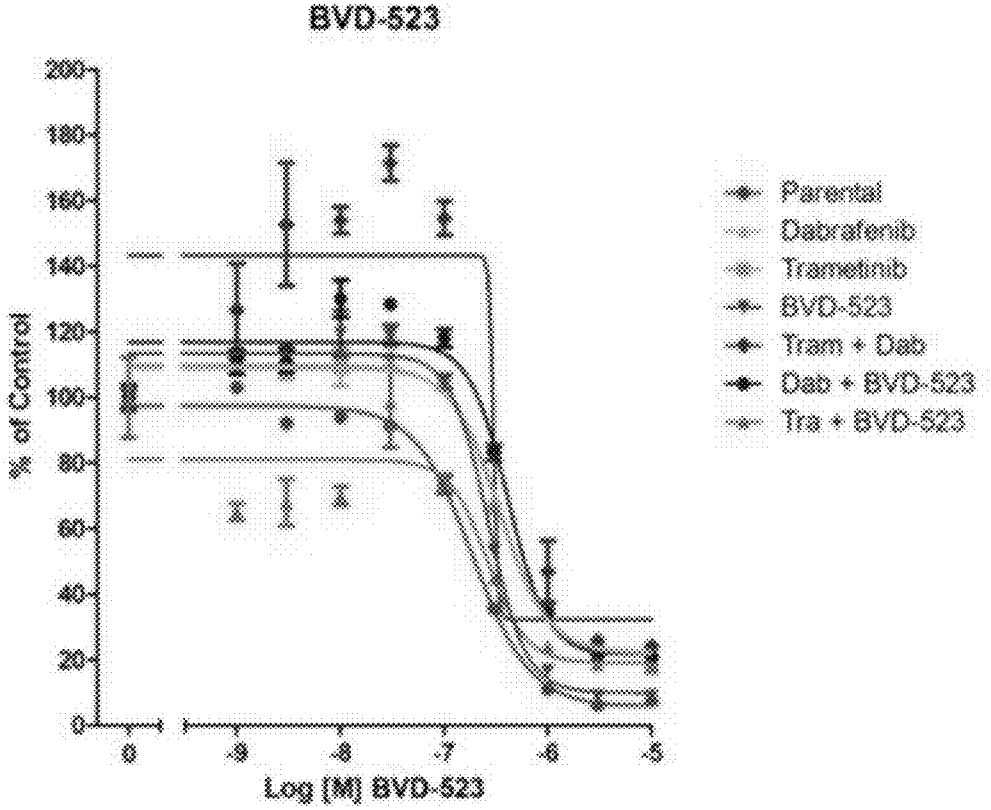

BVD-523
% of Control
200
180
160
140
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] BVD-523
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 2B

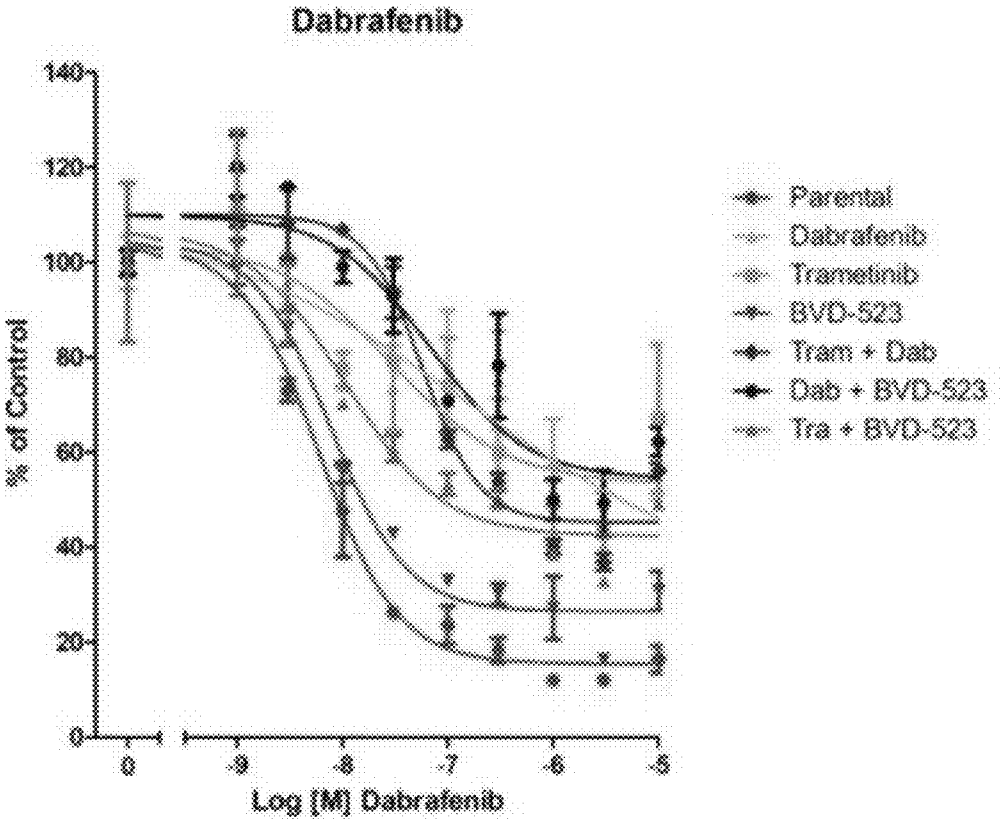

Dabrafenib
% of Control
140
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] Dabrafenib
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 2C

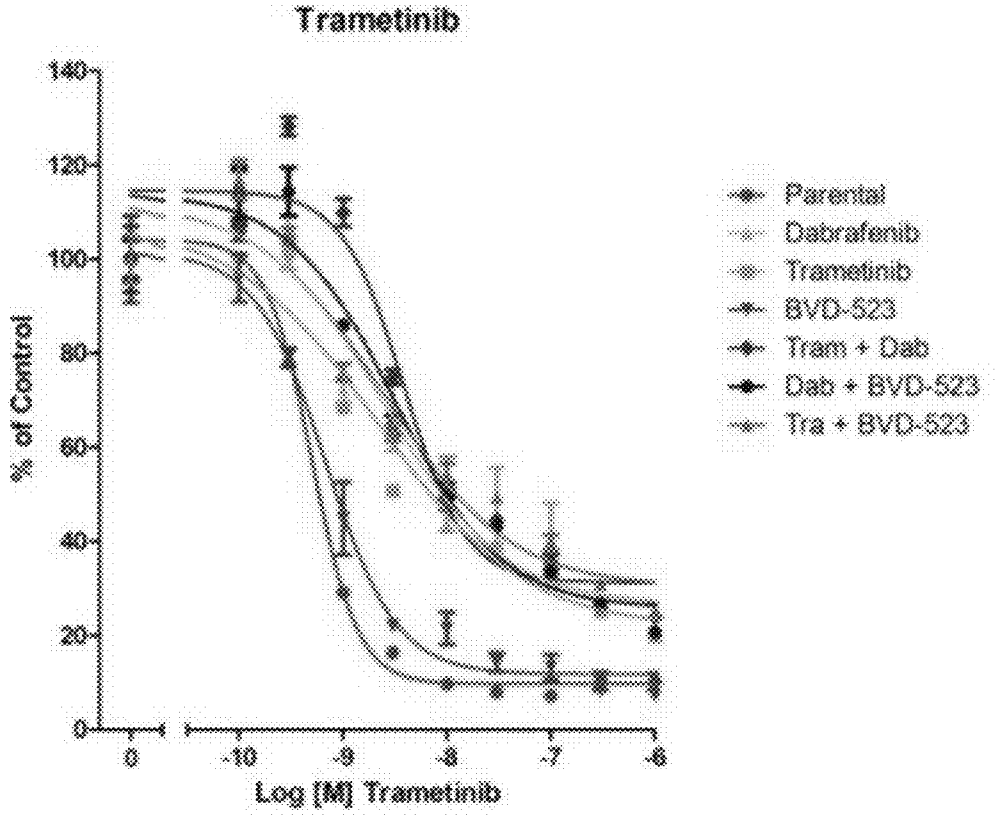

Trametinib
% of Control
140
120
100
80
60
40
20
0
0
-10
-9
-8
-7
-6
Log [M] Trametinib
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 2D

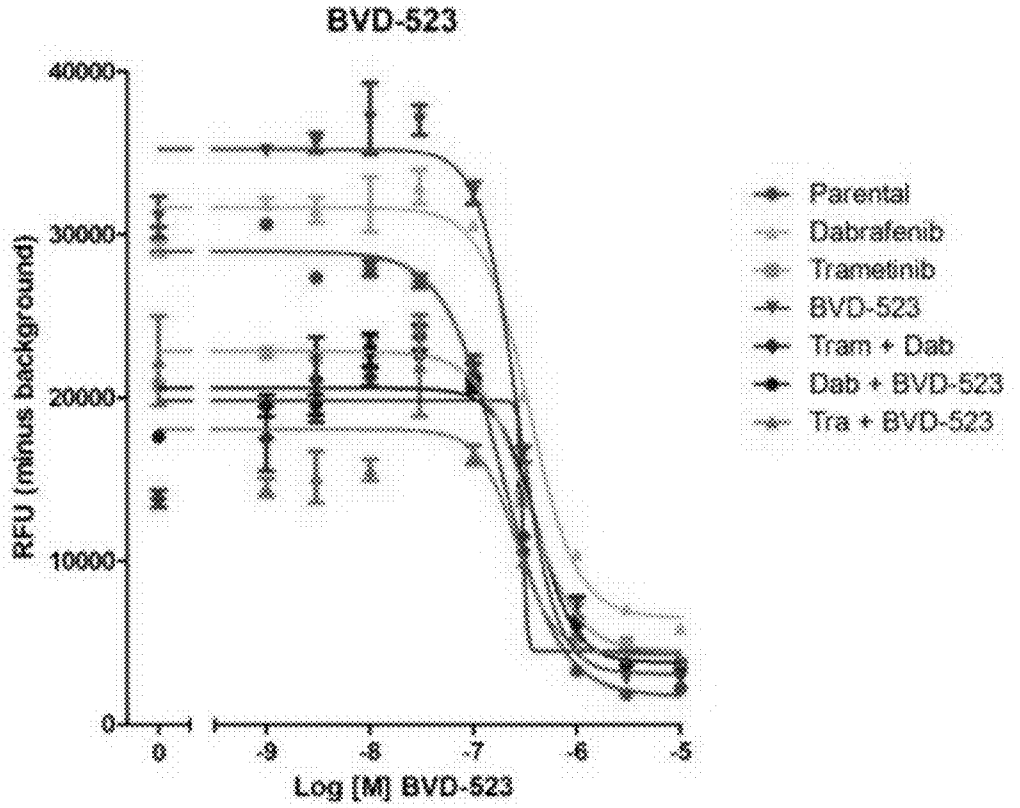

BVD-523
40000
30000
20000
10000
0
RFU (minus background)
0
-9
-8
-7
-6
-5
Log [M] BVD-523
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 2E

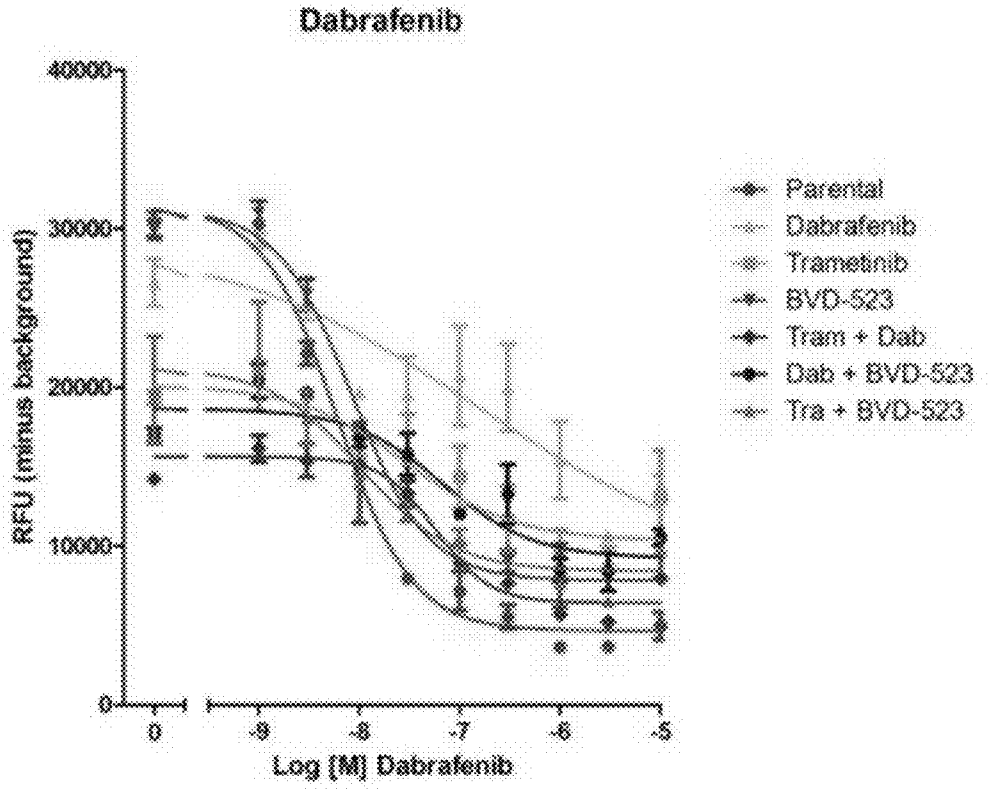

Dabrafenib
40000
30000
20000
10000
0
RFU (minus background)
0
-9
-8
-7
-6
-5
Log [M] Dabrafenib
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 2F

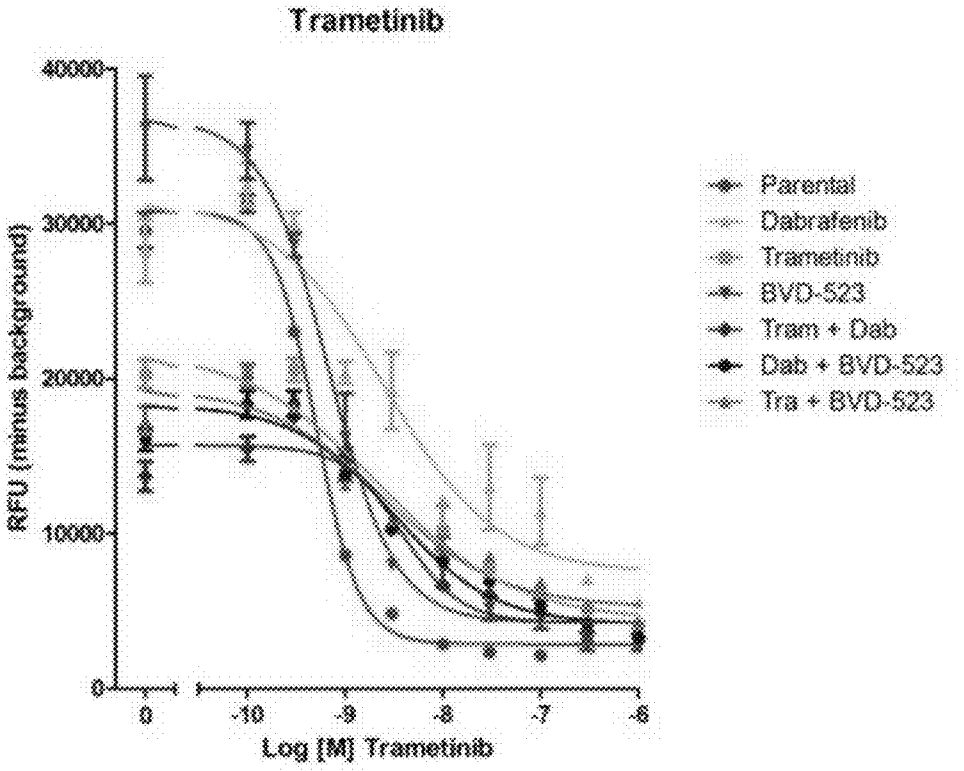

Trametinib
RFU (minus background)
40000
30000
20000
10000
0
0
-10
-9
-8
-7
-6
Log [M] Trametinib
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 2G

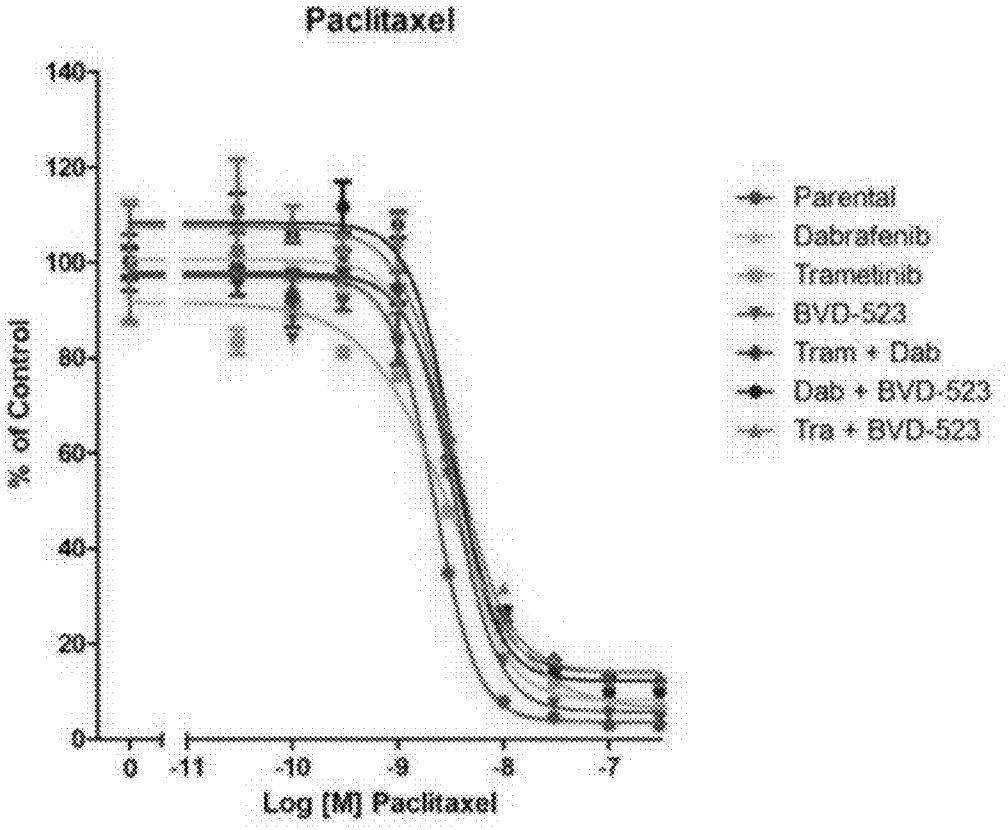

Paclitaxel
% of Control
140
120
100
80
60
40
20
0
0
-11
-10
-9
-8
-7
Log [M] Paclitaxel
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 2H

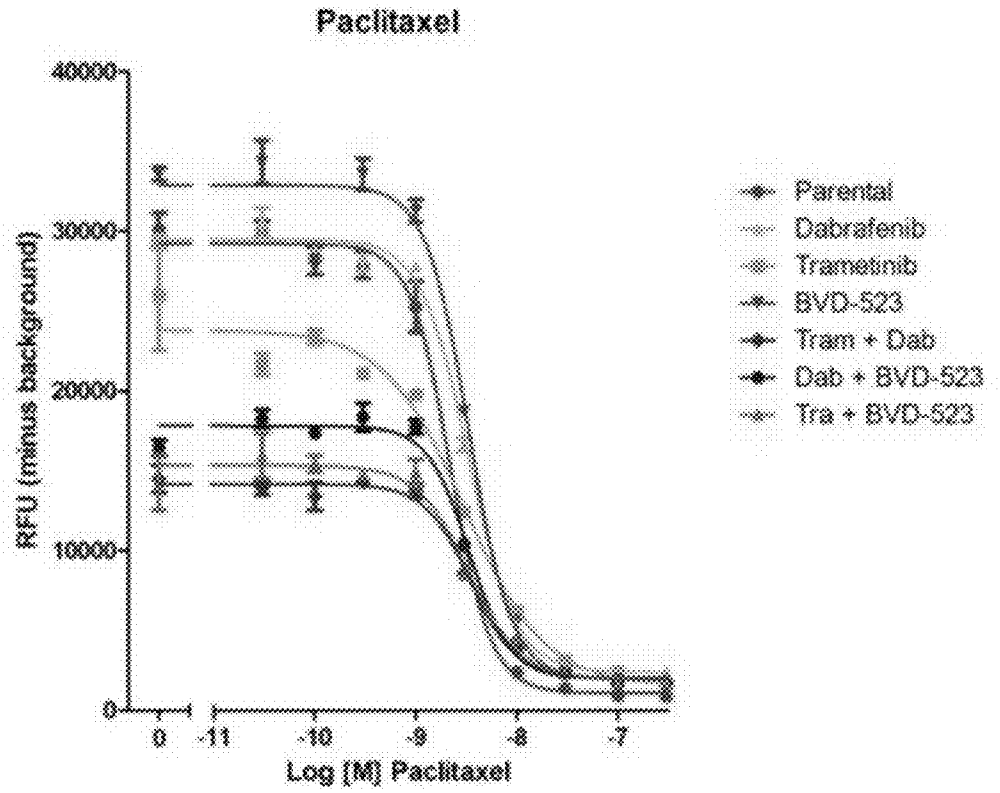

Paclitaxel
RFU (minus background)
40000
30000
20000
10000
0
0
-11
-10
-9
-8
-7
Log [M] Paclitaxel
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 3A

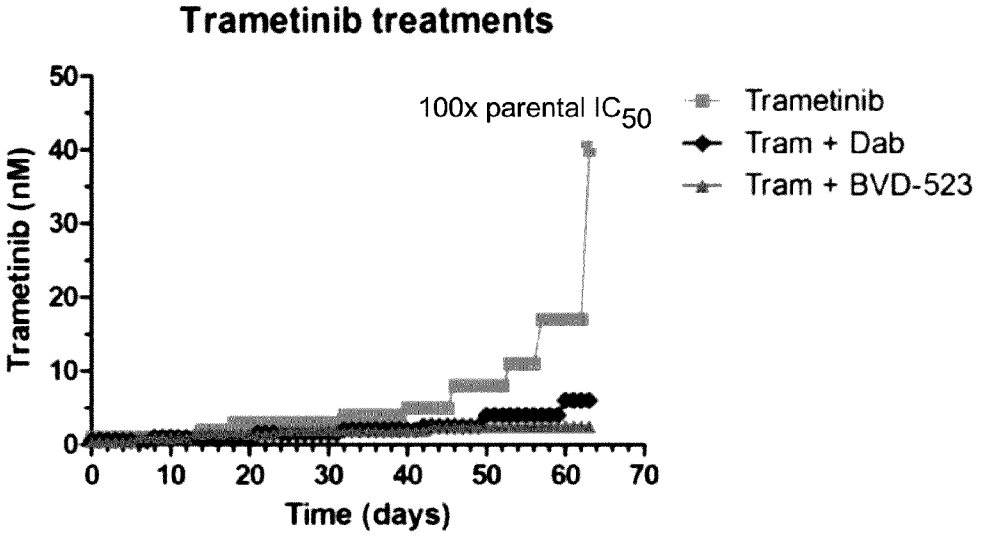

Trametinib treatments
100x parental IC50
Trametinib
Tram + Dab
Tram + BVD-523
Trametinib (nM)
Time (days)
0
10
20
30
40
50
60
70

FIG. 3B

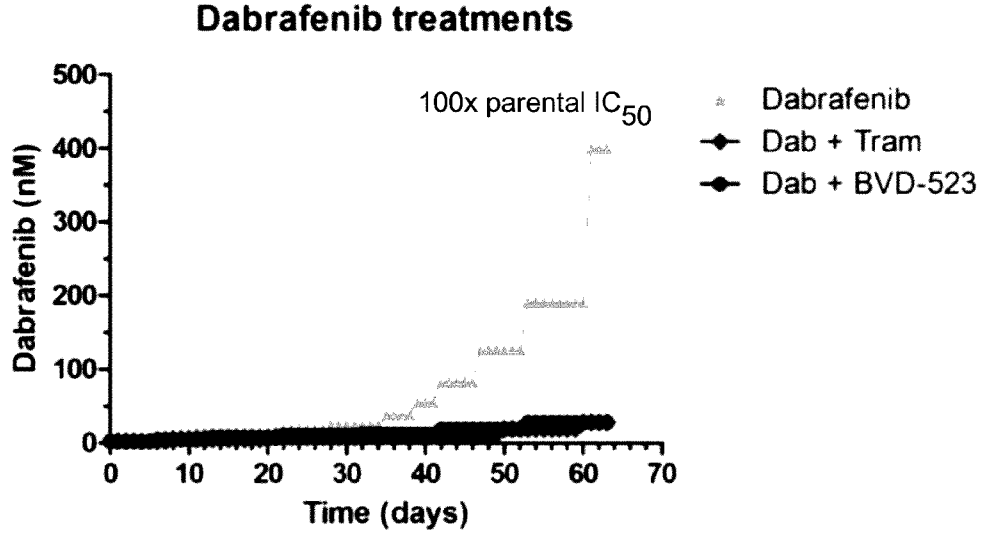

Dabrafenib treatments
100x parental IC50
Dabrafenib
Dab + Tram
Dab + BVD-523
Dabrafenib (nM)
Time (days)
0
100
200
300
400
500
10
20
30
40
50
60
70

FIG. 3C

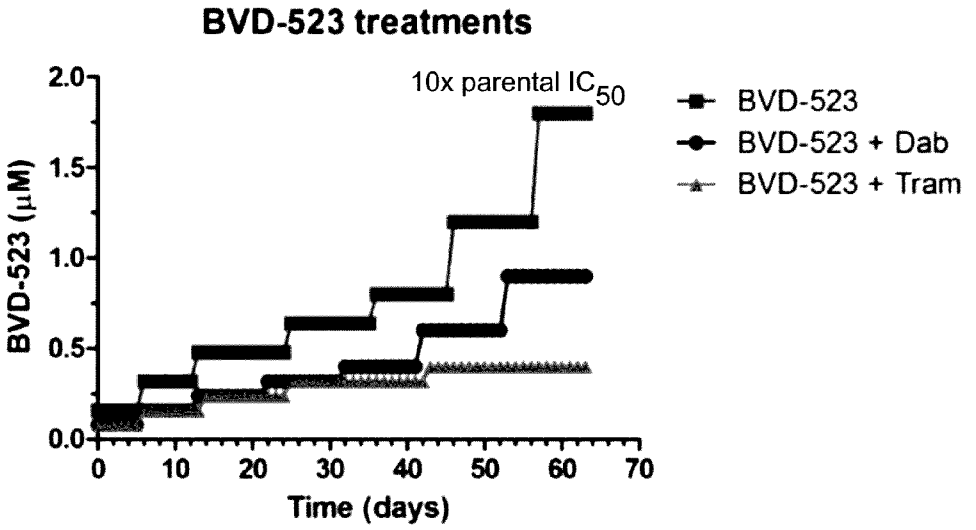

BVD-523 treatments
10x parental IC50
BVD-523
BVD-523 + Dab
BVD-523 + Tram
BVD-523 (μM)
2.0
1.5
1.0
0.5
0.0
0
10
20
30
40
50
60
70
Time (days)

FIG. 3D

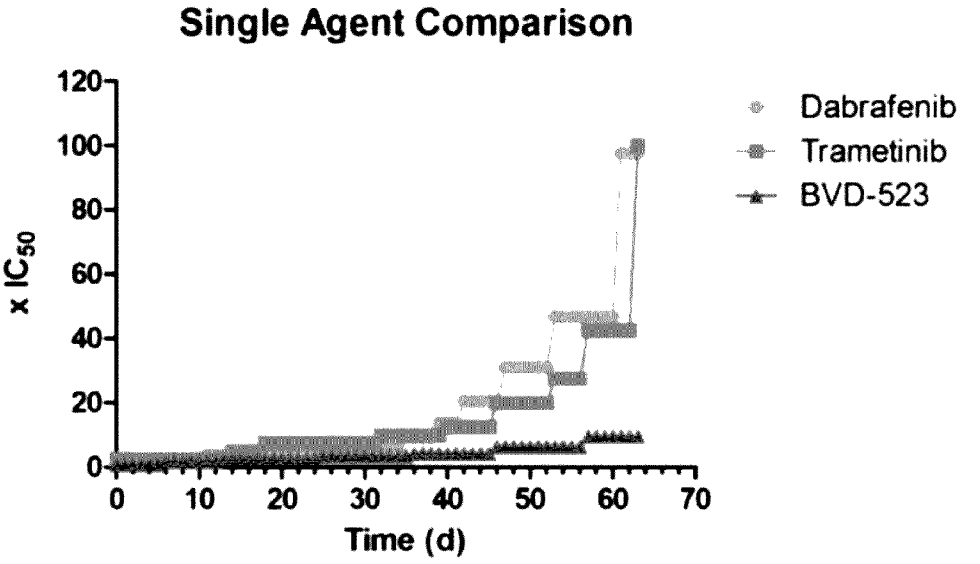

Single Agent Comparison
Dabrafenib
Trametinib
BVD-523
x IC50
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
Time (d)

FIG. 4A

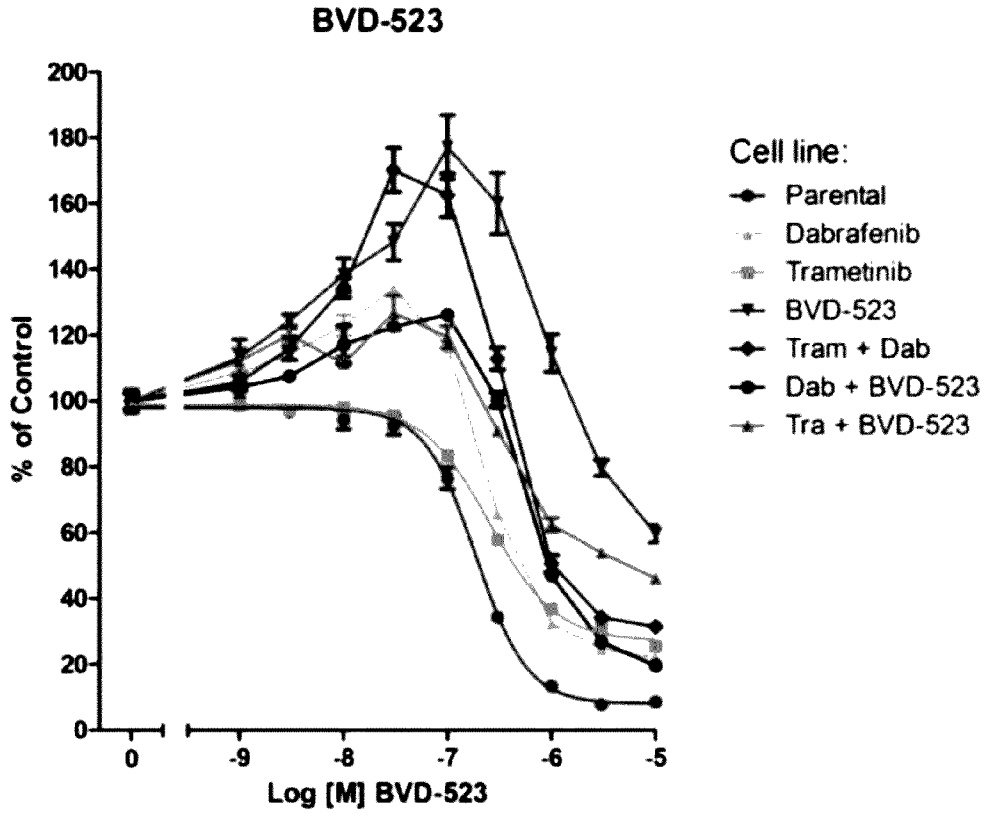

BVD-523
% of Control
200
180
160
140
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] BVD-523
Cell line:
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 4B

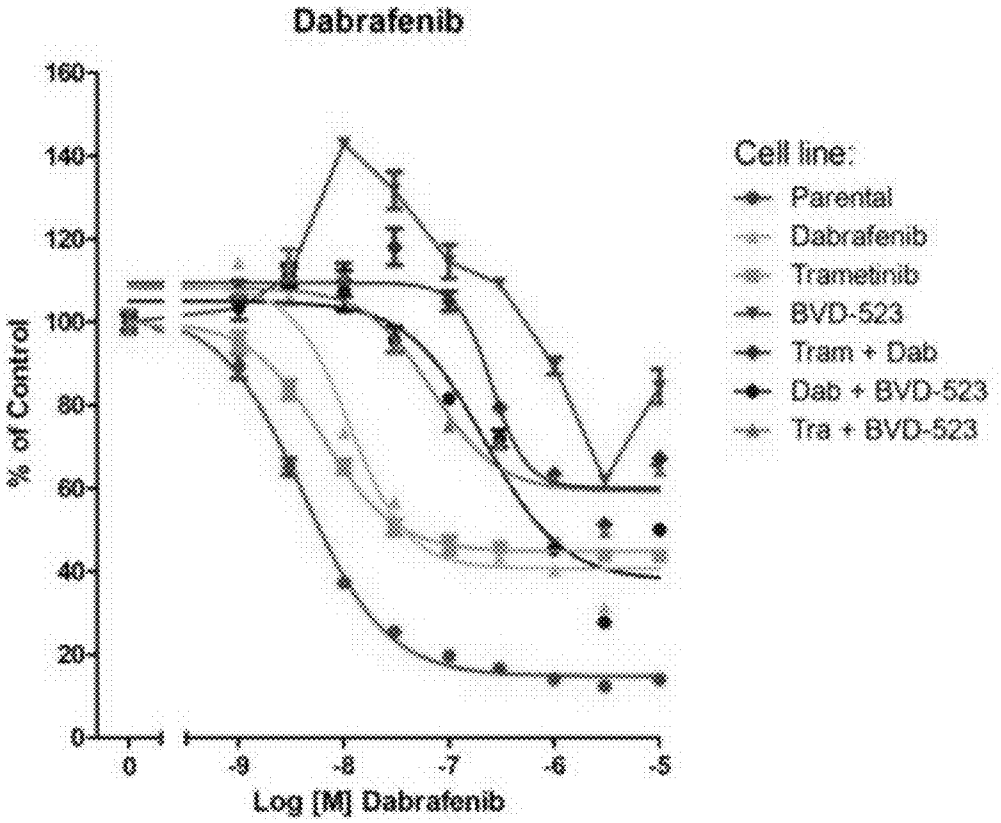

Dabrafenib
% of Control
160
140
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] Dabrafenib
Cell line:
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 4C

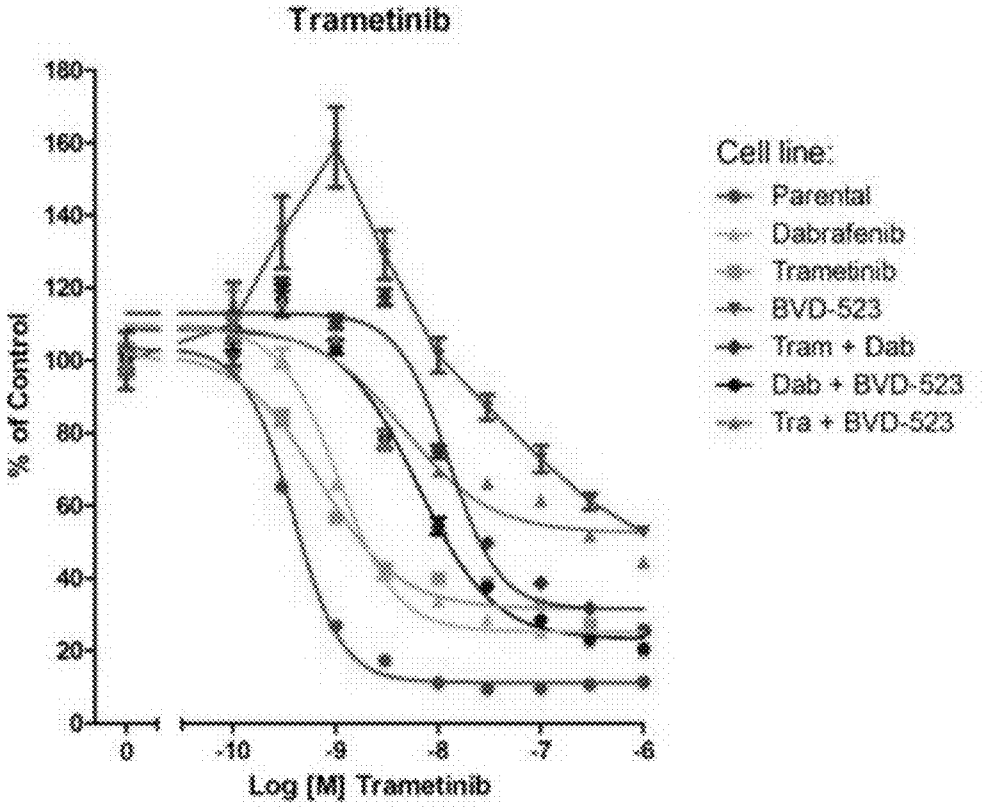

Trametinib
% of Control
180
160
140
120
100
80
60
40
20
0
0
-10
-9
-8
-7
-6
Log [M] Trametinib
Cell line:
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 4D

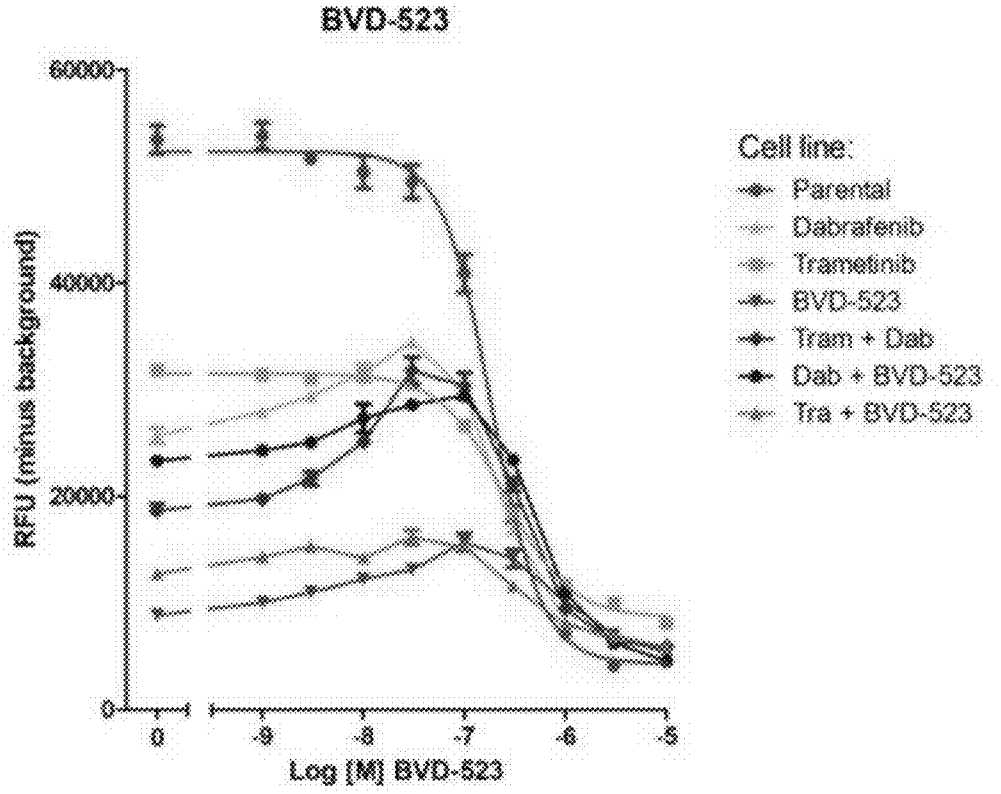

BVD-523
60000
40000
20000
0
RFU (minus background)
0
-9
-8
-7
-6
-5
Log [M] BVD-523
Cell line:
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 4E

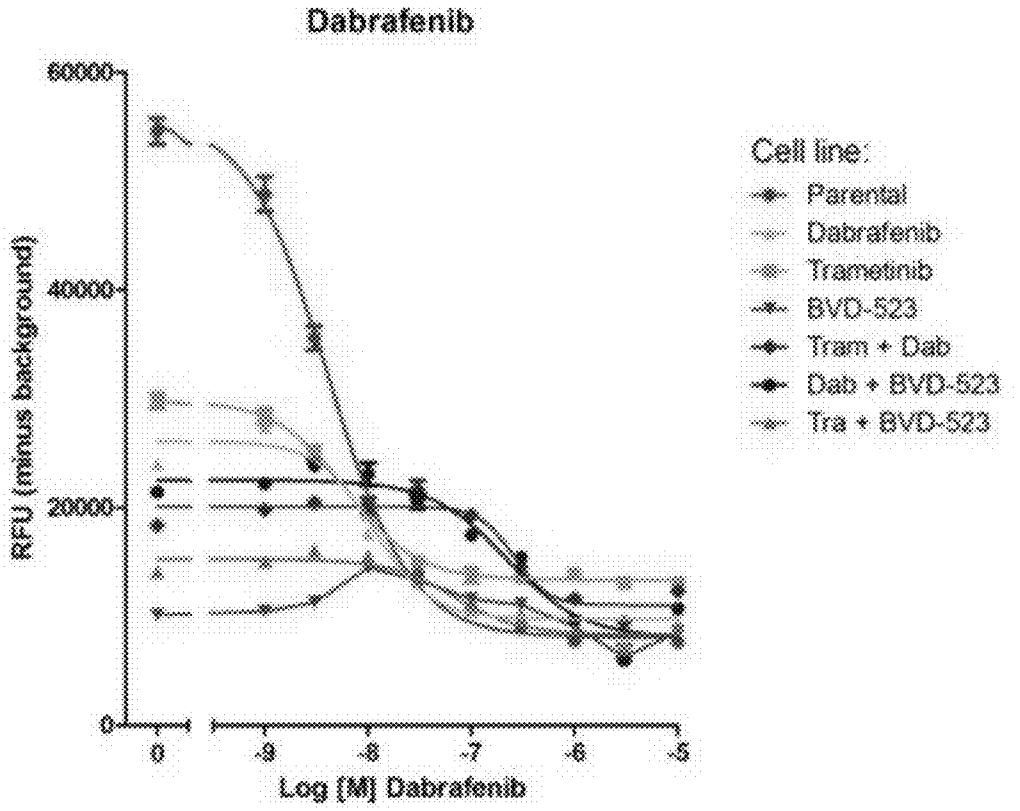

Dabrafenib
60000
40000
20000
0
RFU (minus background)
0
-9
-8
-7
-6
-5
Log [M] Dabrafenib
Cell line:
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 4F

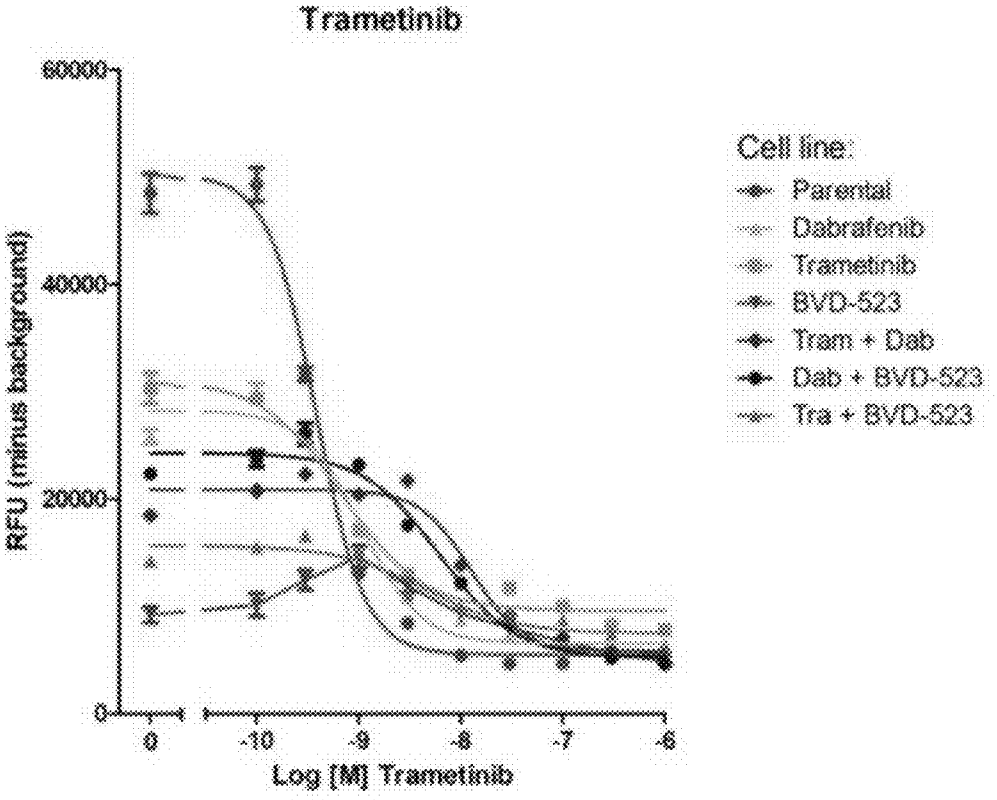

Trametinib
60000
40000
20000
0
RFU (minus background)
0
-10
-9
-8
-7
-6
Log [M] Trametinib
Cell line:
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 4G

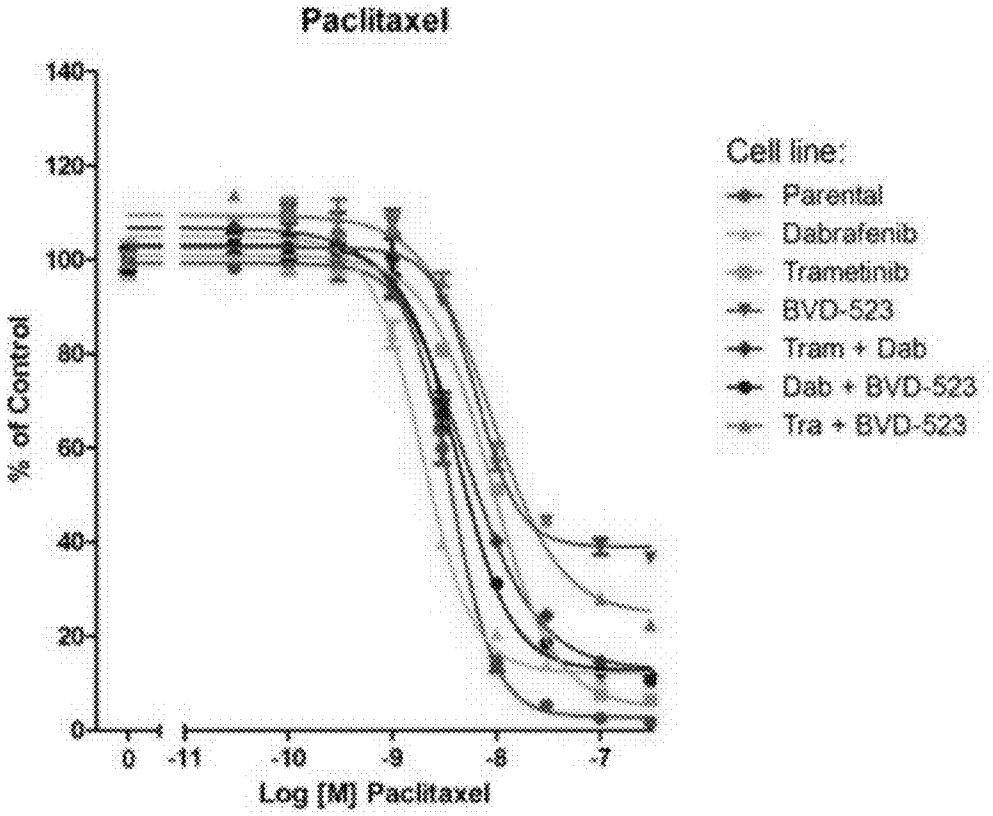

Paclitaxel
% of Control
140
120
100
80
60
40
20
0
0
-11
-10
-9
-8
-7
Log [M] Paclitaxel
Cell line:
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 4H

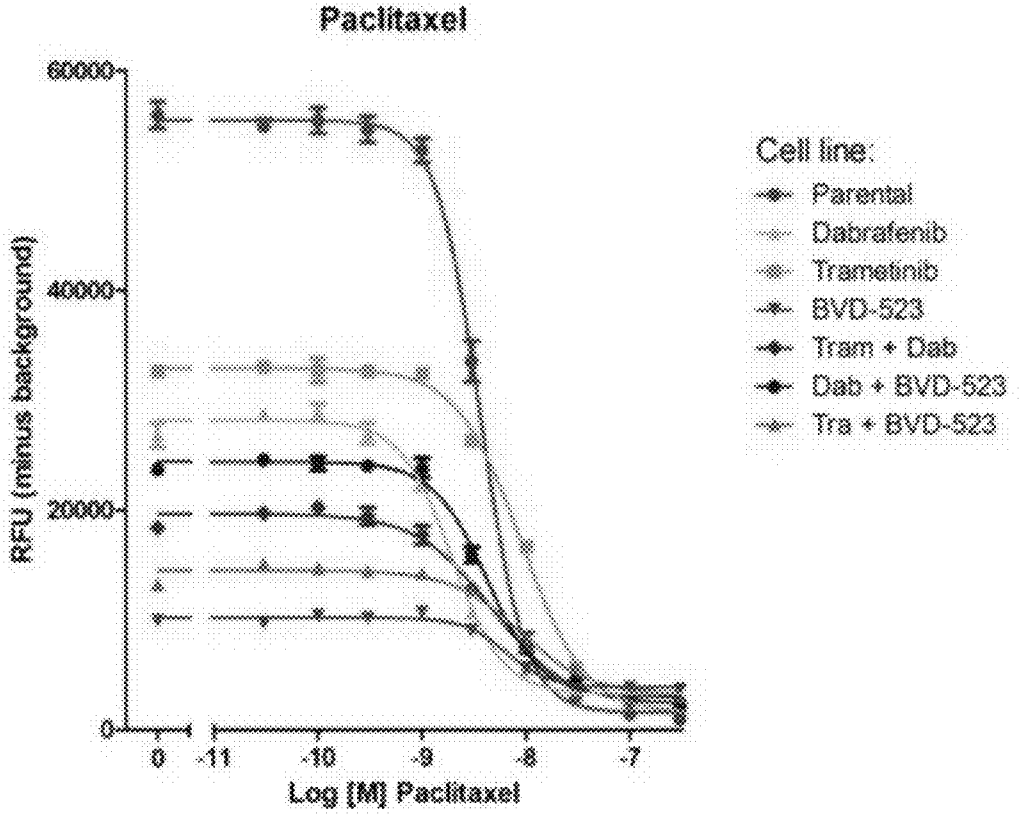

Paclitaxel
60000
40000
20000
0
RFU (minus background)
0
-11
-10
-9
-8
-7
Log [M] Paclitaxel
Cell line:
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 5A

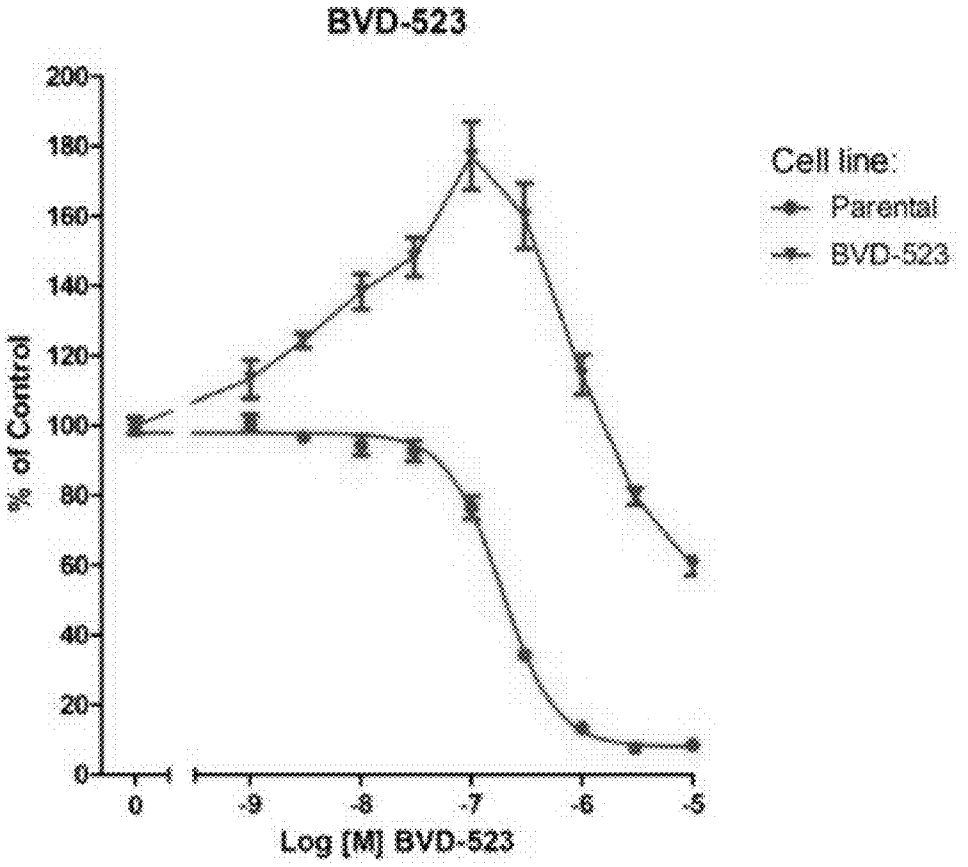

BVD-523
% of Control
200
180
160
140
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] BVD-523
Cell line:
Parental
BVD-523

FIG. 5B

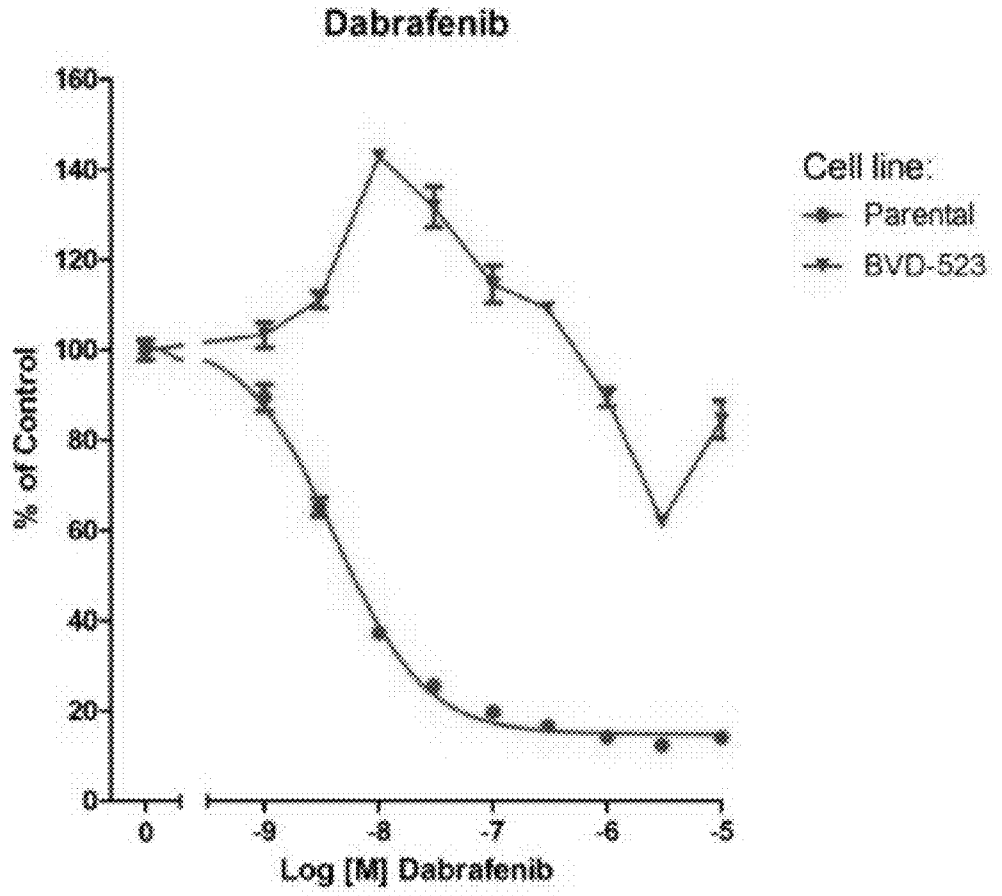

Dabrafenib
% of Control
160
140
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] Dabrafenib
Cell line:
Parental
BVD-523

FIG. 5C

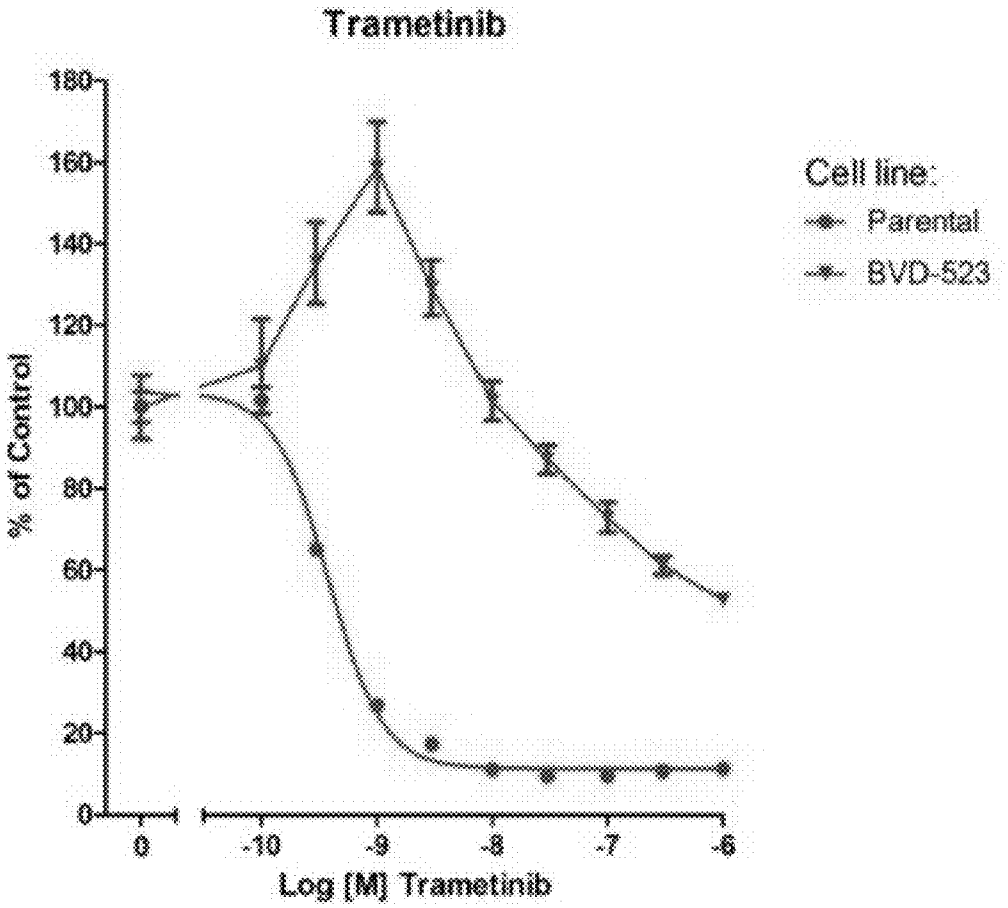

Trametinib
% of Control
180
160
140
120
100
80
60
40
20
0
0
-10
-9
-8
-7
-6
Log [M] Trametinib
Cell line:
Parental
BVD-523

FIG. 5D

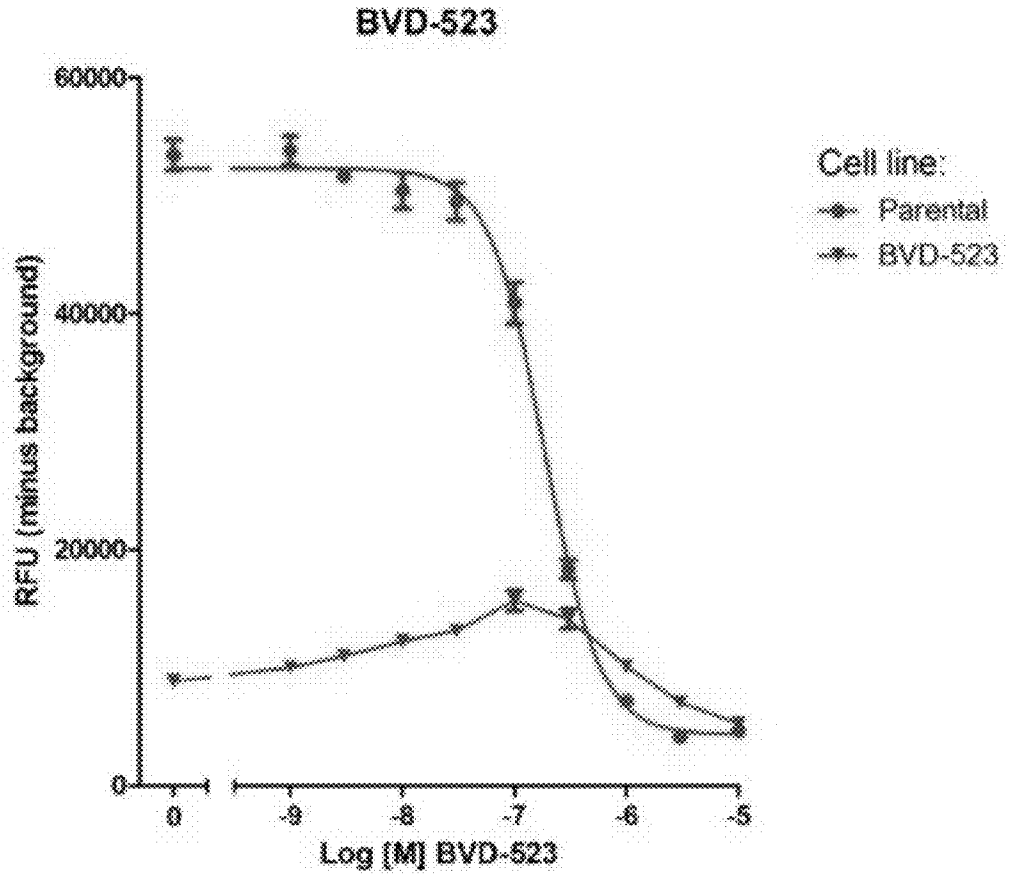

BVD-523
60000
40000
20000
0
RFU (minus background)
0
-9
-8
-7
-6
-5
Log [M] BVD-523
Cell line:
Parental
BVD-523

FIG. 5E

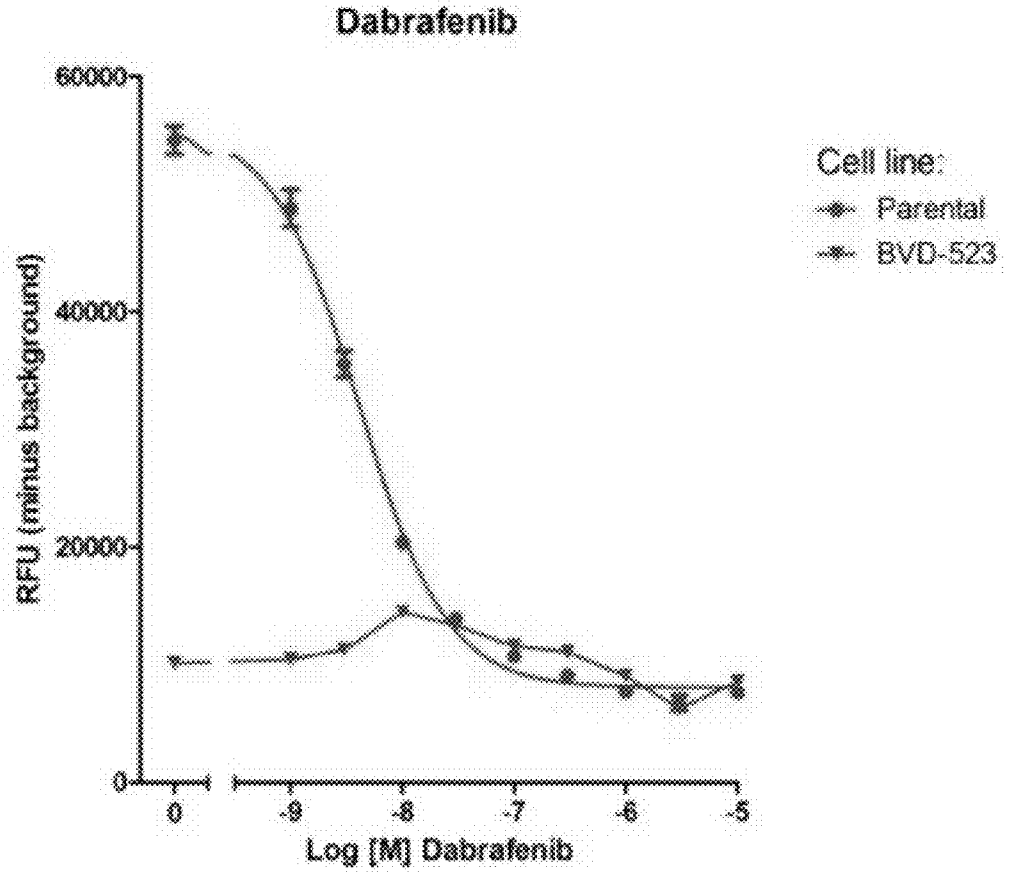

Dabrafenib
60000
40000
20000
0
RFU (minus background)
0
-9
-8
-7
-6
-5
Log [M] Dabrafenib
Cell line:
Parental
BVD-523

FIG. 5F

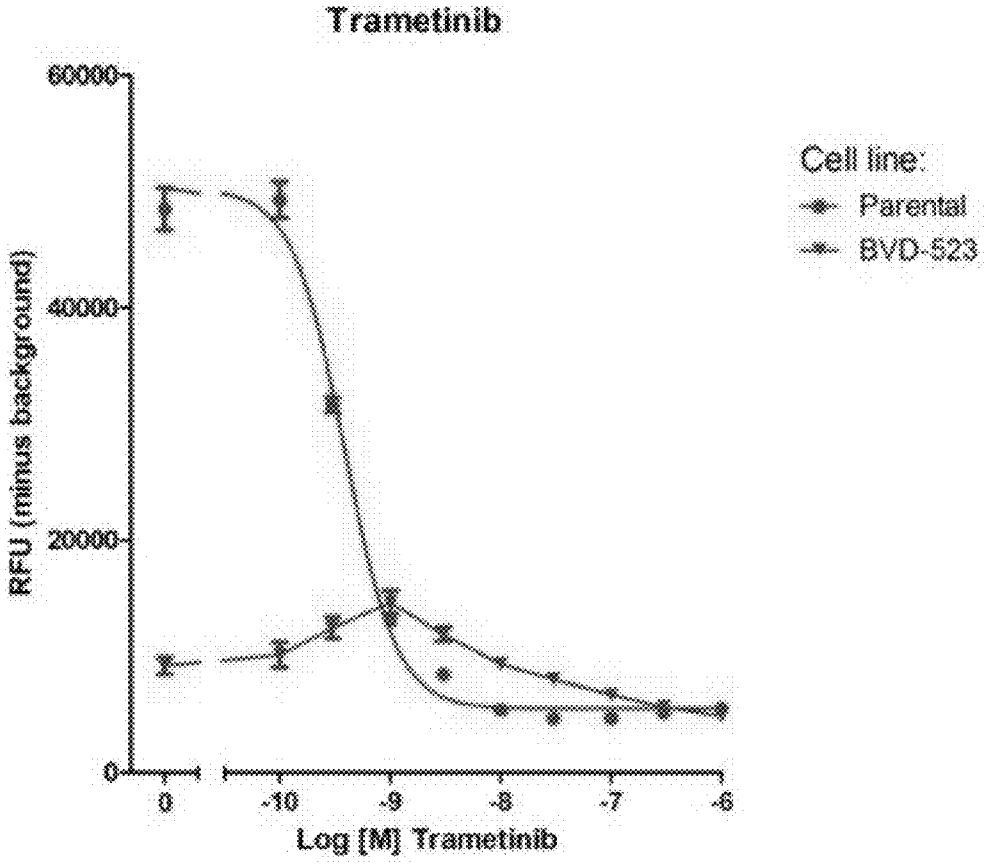

Trametinib
60000
40000
20000
0
RFU (minus background)
0
-10
-9
-8
-7
-6
Log [M] Trametinib
Cell line:
Parental
BVD-523

FIG. 5G

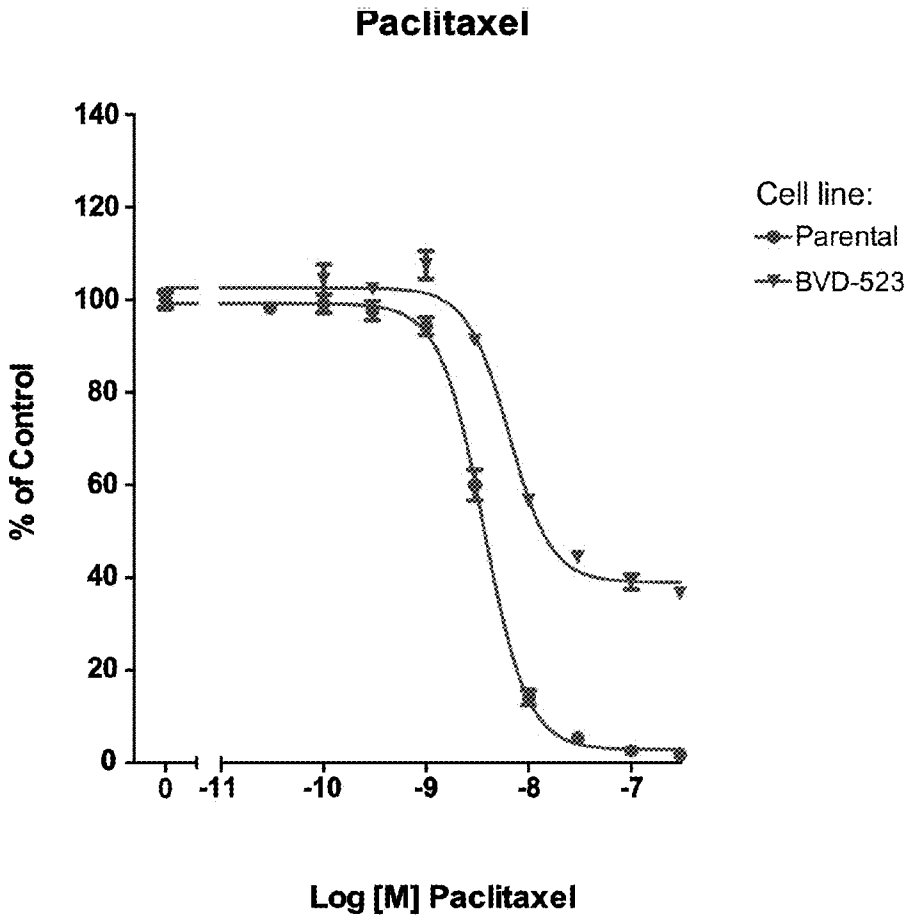

Paclitaxel
140
120
100
80
60
40
20
0
% of Control
0
-11
-10
-9
-8
-7
Log [M] Paclitaxel
Cell line:
Parental
BVD-523

FIG. 5H

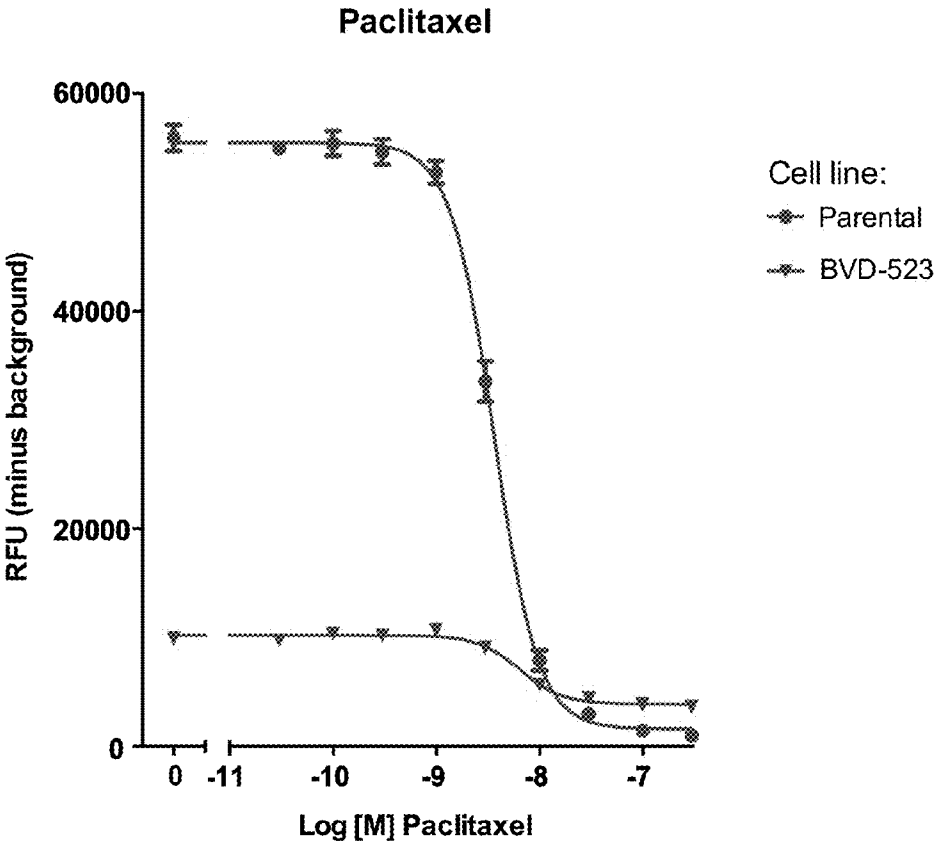

Paclitaxel
60000
40000
20000
0
RFU (minus background)
0
-11
-10
-9
-8
-7
Log [M] Paclitaxel
Cell line:
Parental
BVD-523

FIG. 6A

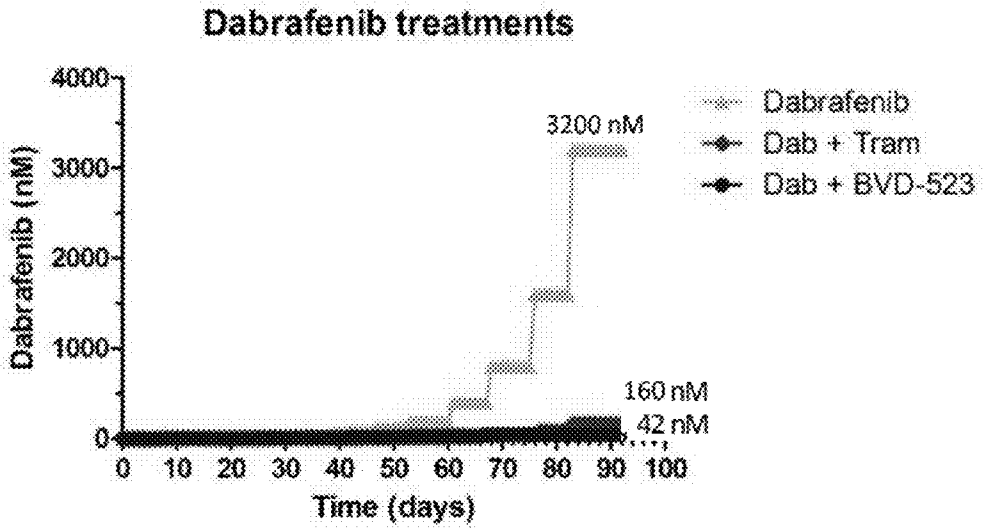

Dabrafenib treatments
Dabrafenib (nM)
4000
3000
2000
1000
0
3200 nM
160 nM
42 nM
0 10 20 30 40 50 60 70 80 90 100
Time (days)
Dabrafenib
Dab + Tram
Dab + BVD-523

FIG. 6B

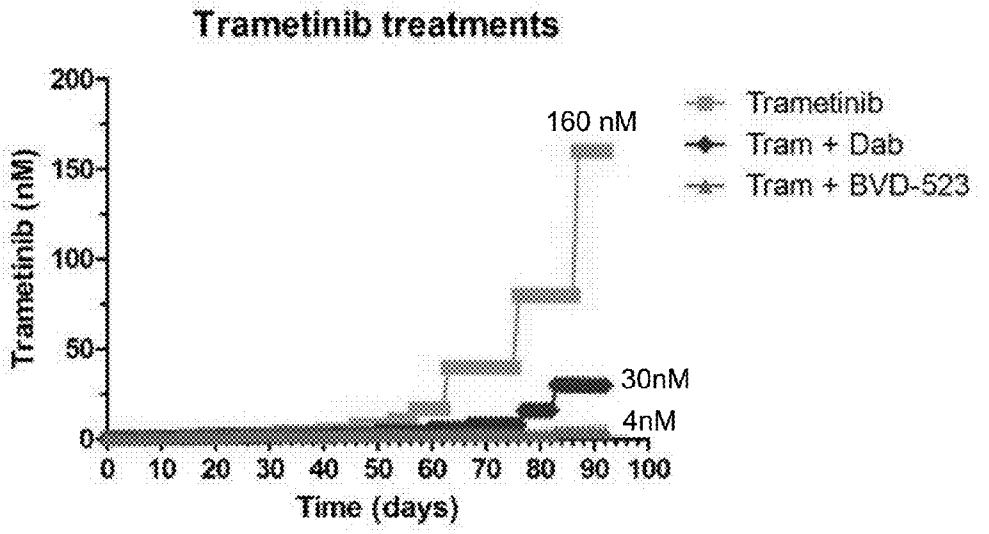

Trametinib treatments
Trametinib (nM)
200
150
100
50
0
160 nM
30nM
4nM
0 10 20 30 40 50 60 70 80 90 100
Time (days)
Trametinib
Tram + Dab
Tram + BVD-523

FIG. 6C

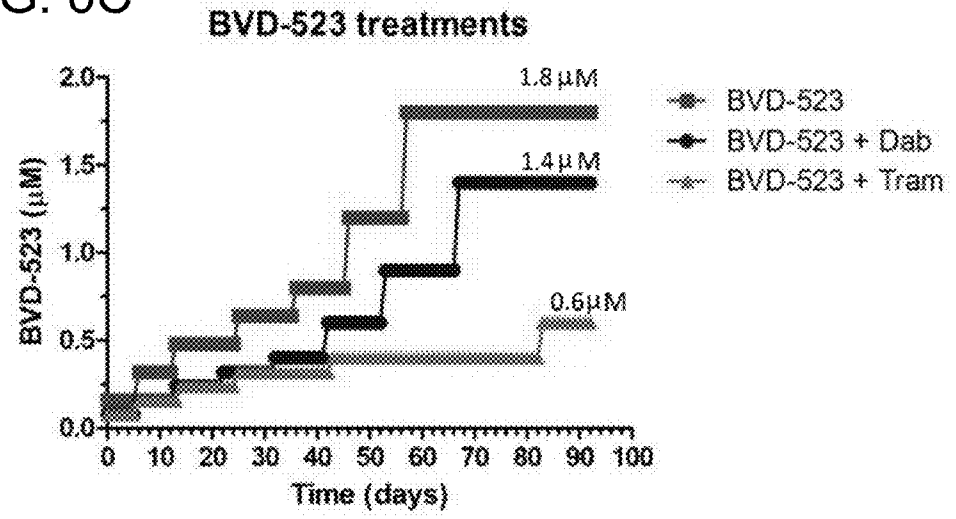

BVD-523 treatments
BVD-523 (μM)
2.0
1.5
1.0
0.5
0.0
1.8 μM
1.4 μM
0.6μM
0 10 20 30 40 50 60 70 80 90 100
Time (days)
BVD-523
BVD-523 + Dab
BVD-523 + Tram

FIG. 6D

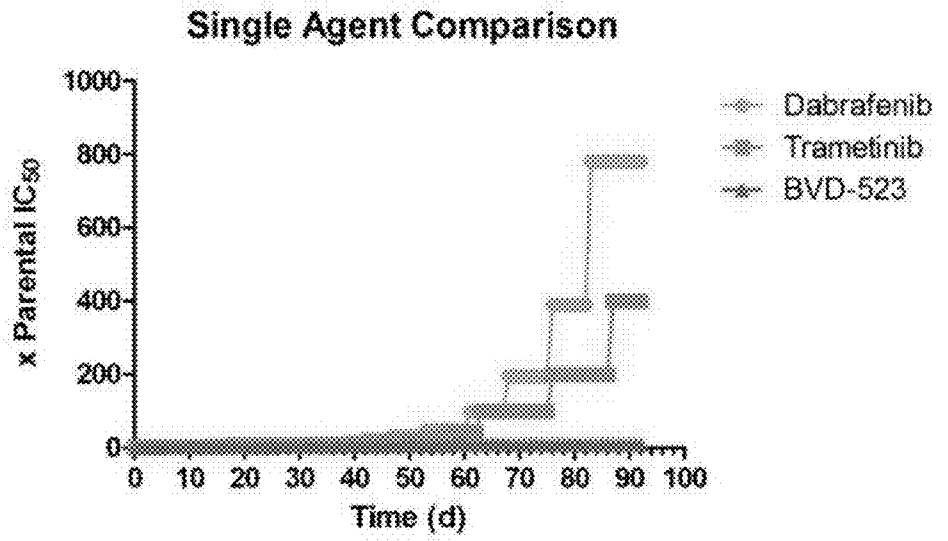

Single Agent Comparison
x Parental IC50
1000
800
600
400
200
0
0 10 20 30 40 50 60 70 80 90 100
Time (d)
Dabrafenib
Trametinib
BVD-523

FIG. 7

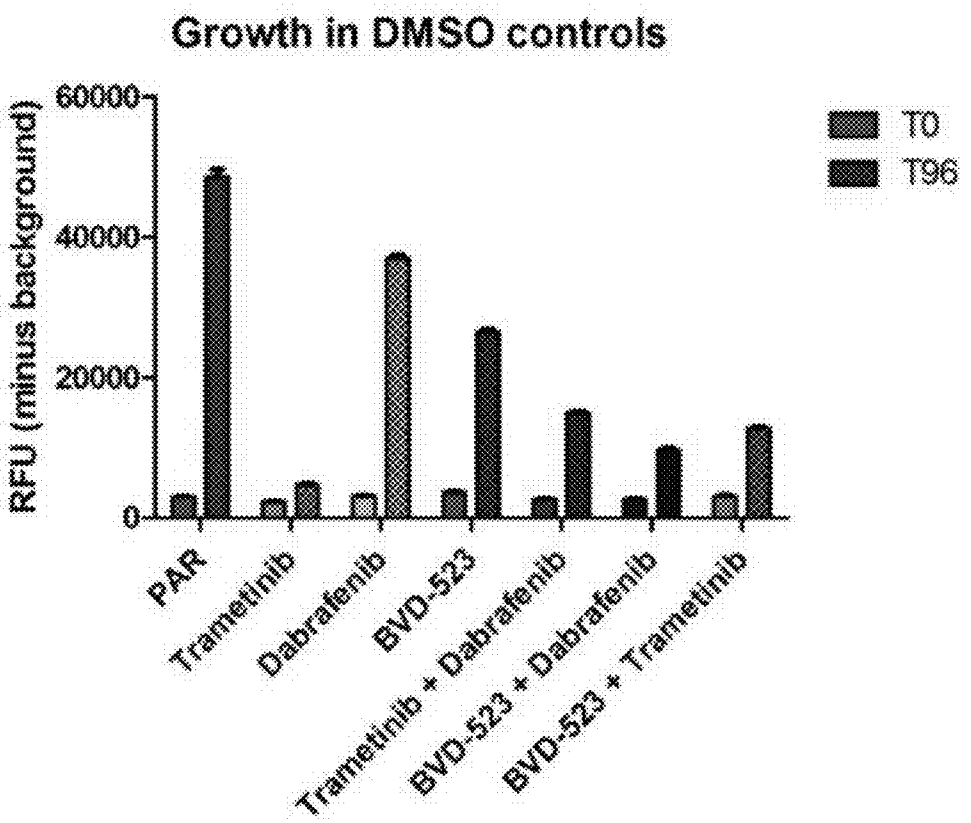

Growth in DMSO controls
RFU (minus background)
60000
40000
20000
0
T0
T96
PAR
Trametinib
Dabrafenib
BVD-523
Trametinib + Dabrafenib
BVD-523 + Dabrafenib
BVD-523 + Trametinib

FIG. 8A

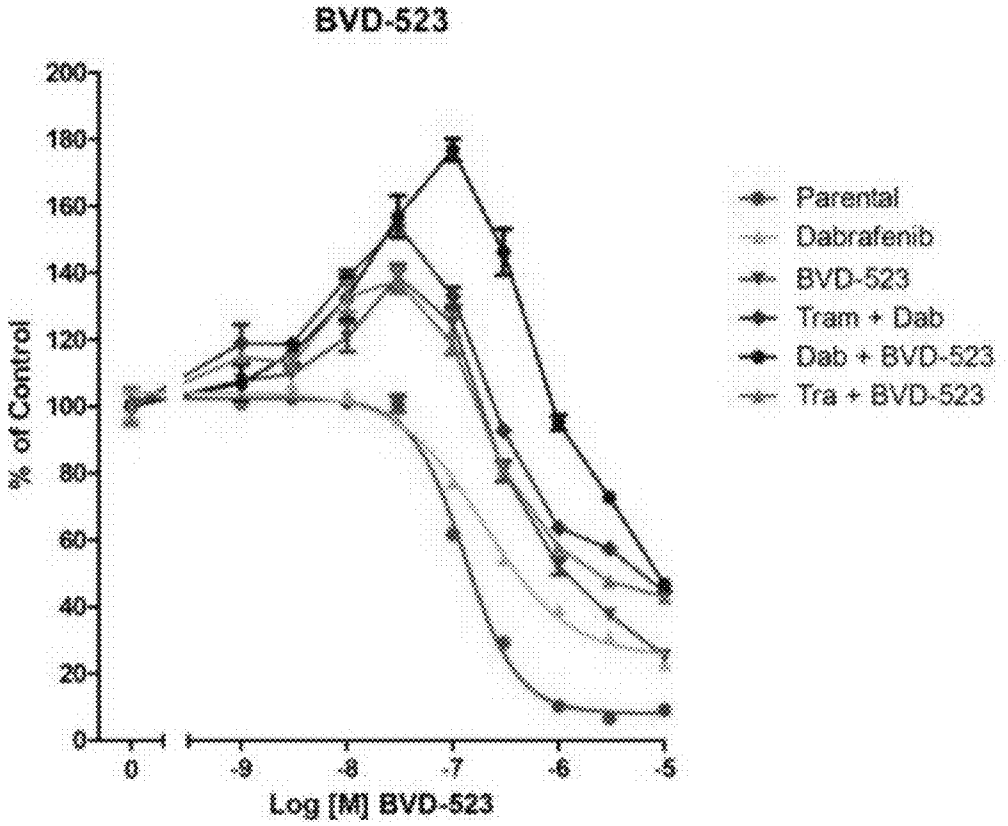

BVD-523
% of Control
200
180
160
140
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] BVD-523
Parental
Dabrafenib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 8B

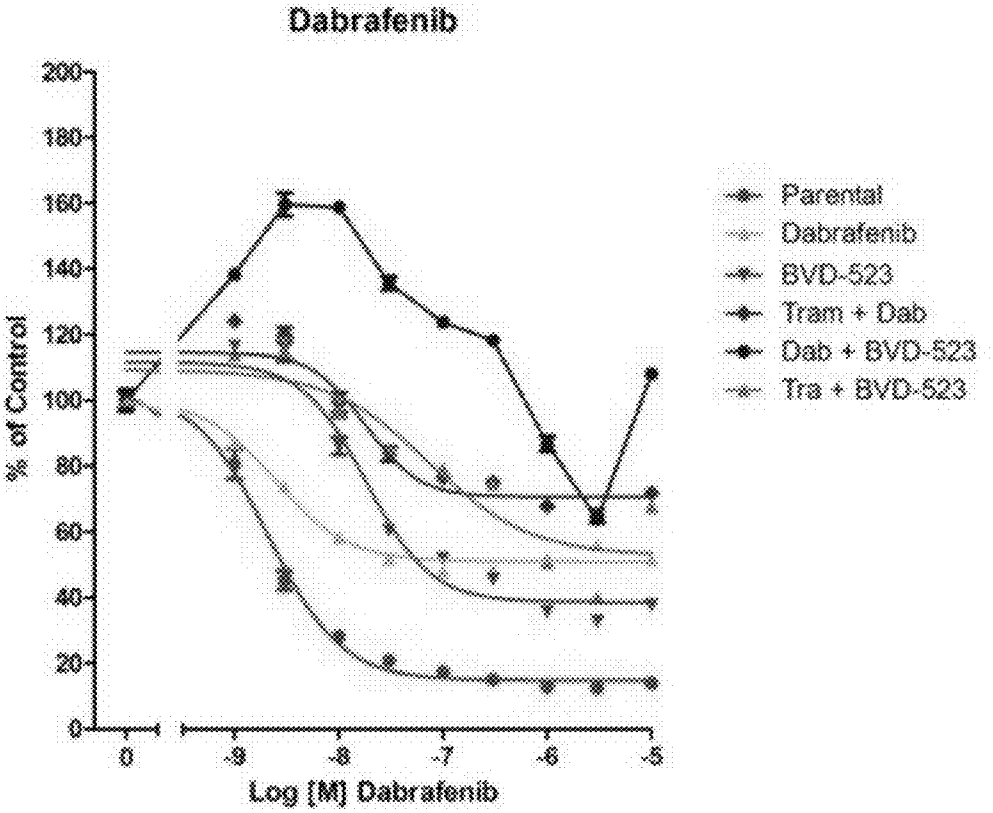

Dabrafenib
% of Control
200
180
160
140
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] Dabrafenib
Parental
Dabrafenib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 8C

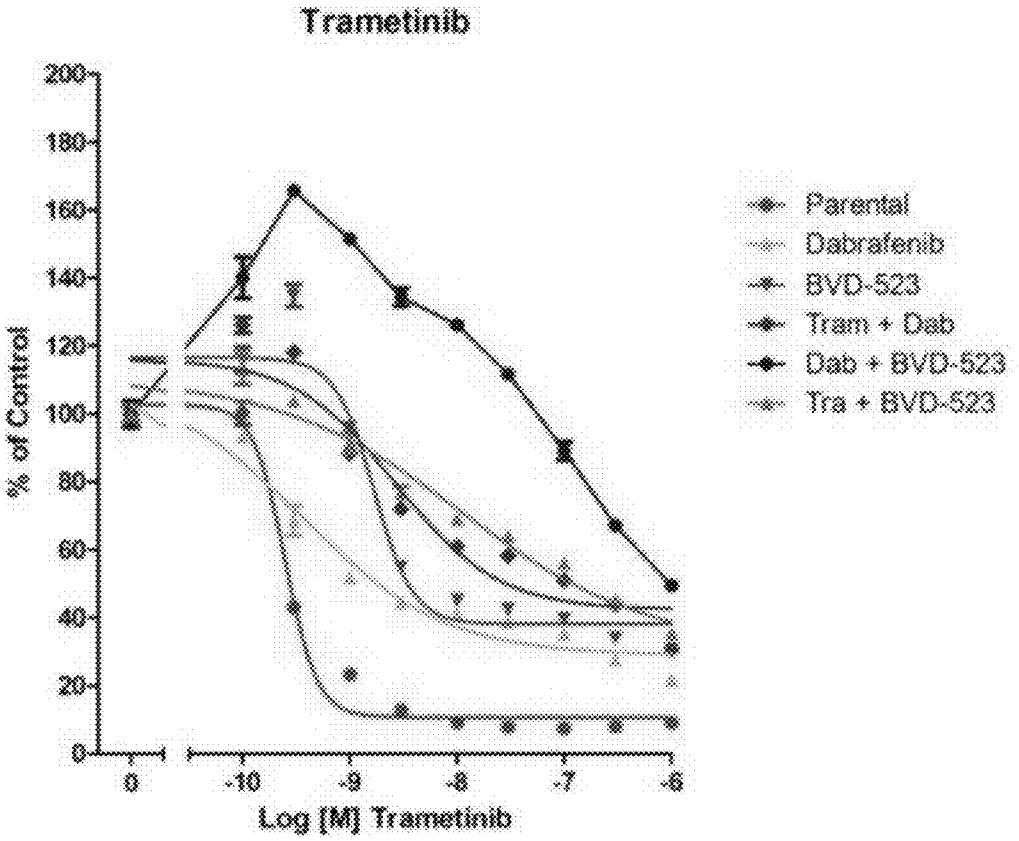

Trametinib
% of Control
200
180
160
140
120
100
80
60
40
20
0
0
-10
-9
-8
-7
-6
Log [M] Trametinib
Parental
Dabrafenib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 8D

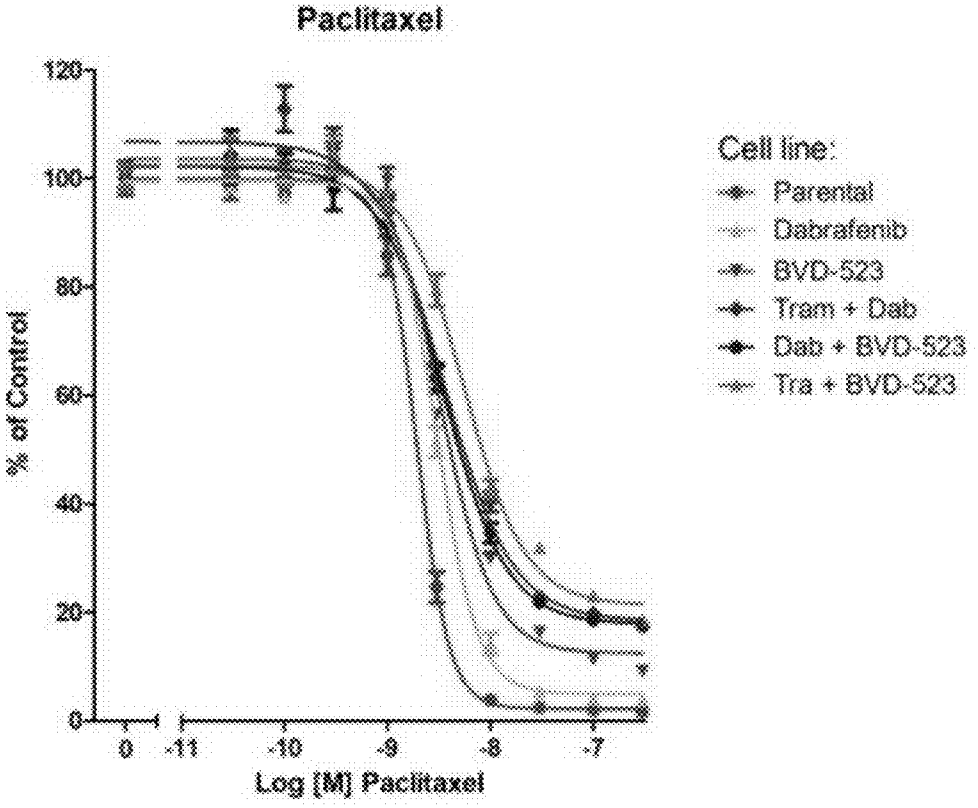

Paclitaxel
% of Control
120
100
80
60
40
20
0
0
-11
-10
-9
-8
-7
Log [M] Paclitaxel
Cell line:
Parental
Dabrafenib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 9A

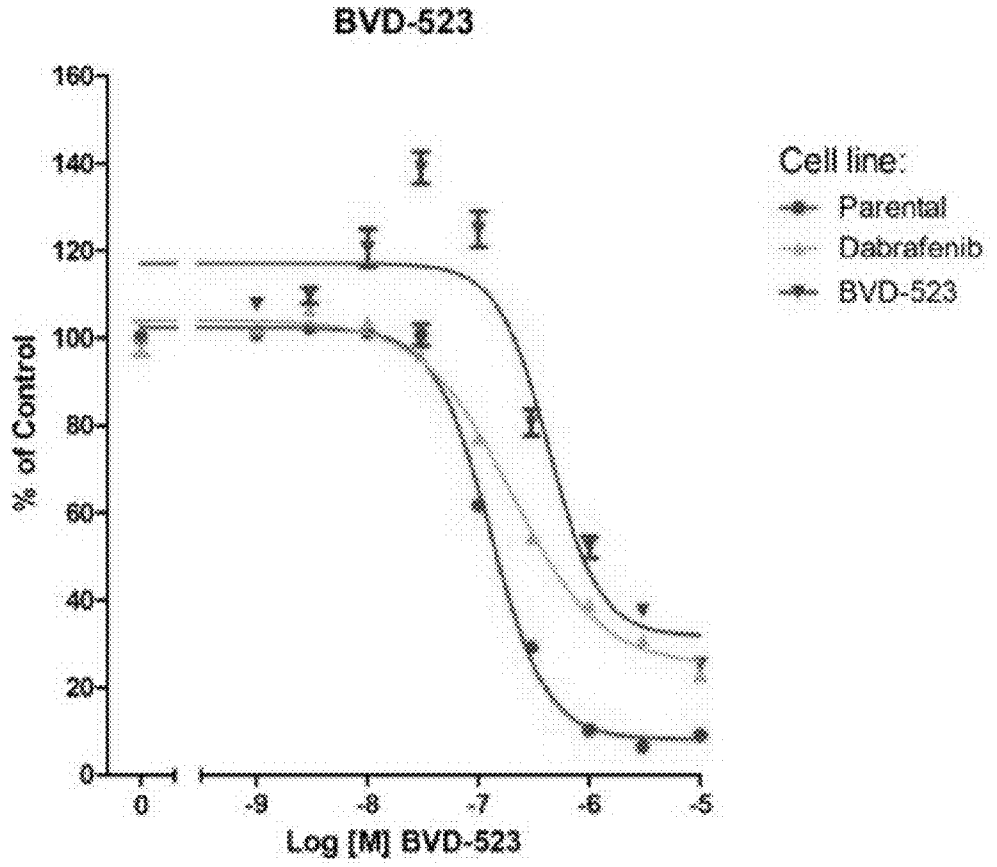

BVD-523
% of Control
160
140
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] BVD-523
Cell line:
Parental
Dabrafenib
BVD-523

FIG. 9B

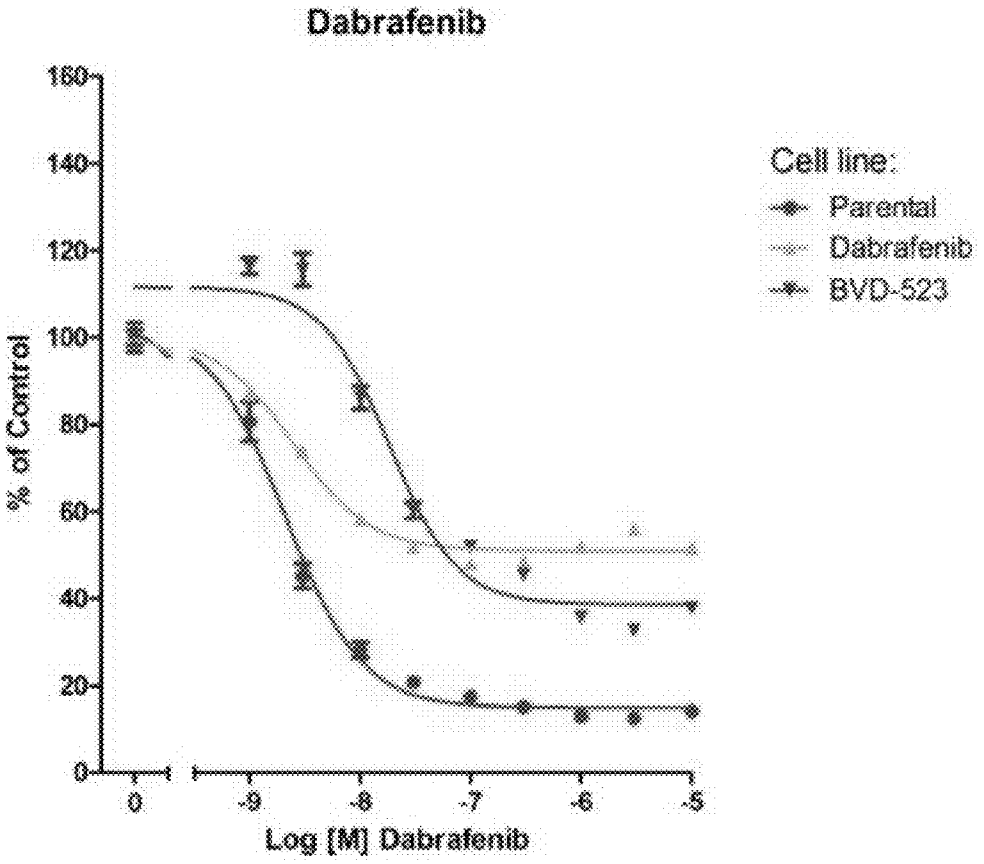

Dabrafenib
% of Control
160
140
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] Dabrafenib
Cell line:
Parental
Dabrafenib
BVD-523

FIG. 9C

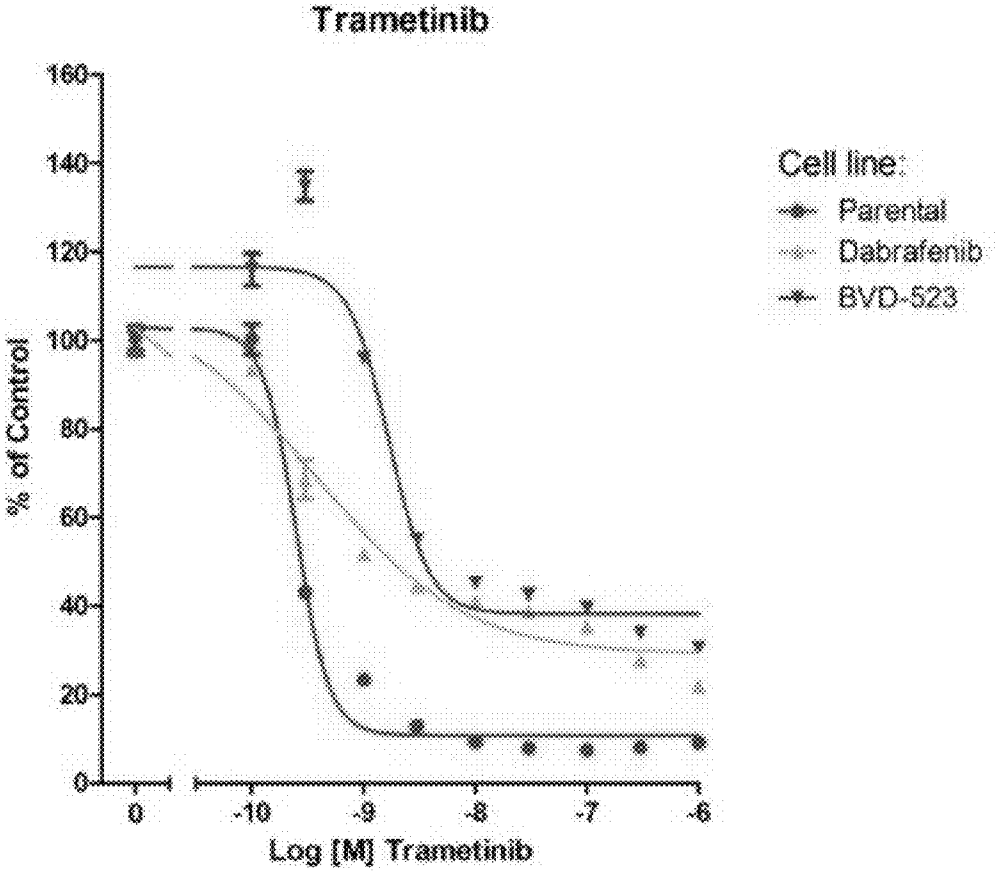

Trametinib
% of Control
160
140
120
100
80
60
40
20
0
0
-10
-9
-8
-7
-6
Log [M] Trametinib
Cell line:
Parental
Dabrafenib
BVD-523

FIG. 9D

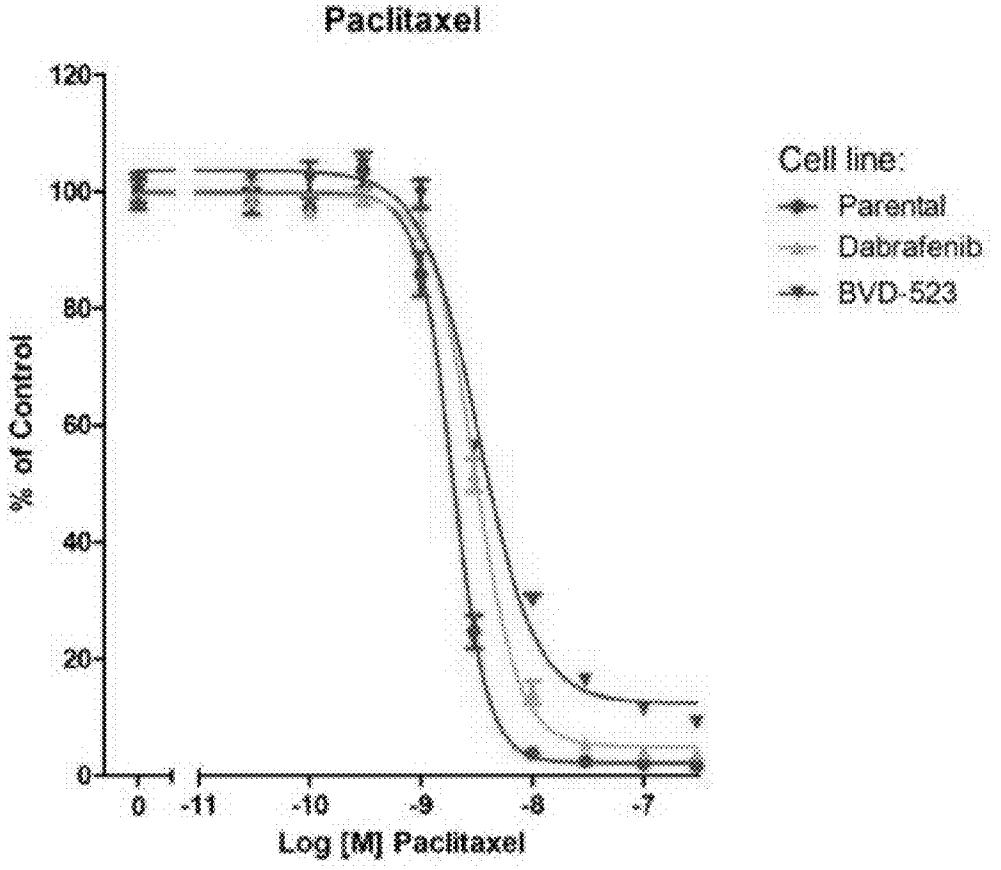

Paclitaxel
120
100
80
60
40
20
0
% of Control
0
-11
-10
-9
-8
-7
Log [M] Paclitaxel
Cell line:
Parental
Dabrafenib
BVD-523

FIG. 10A

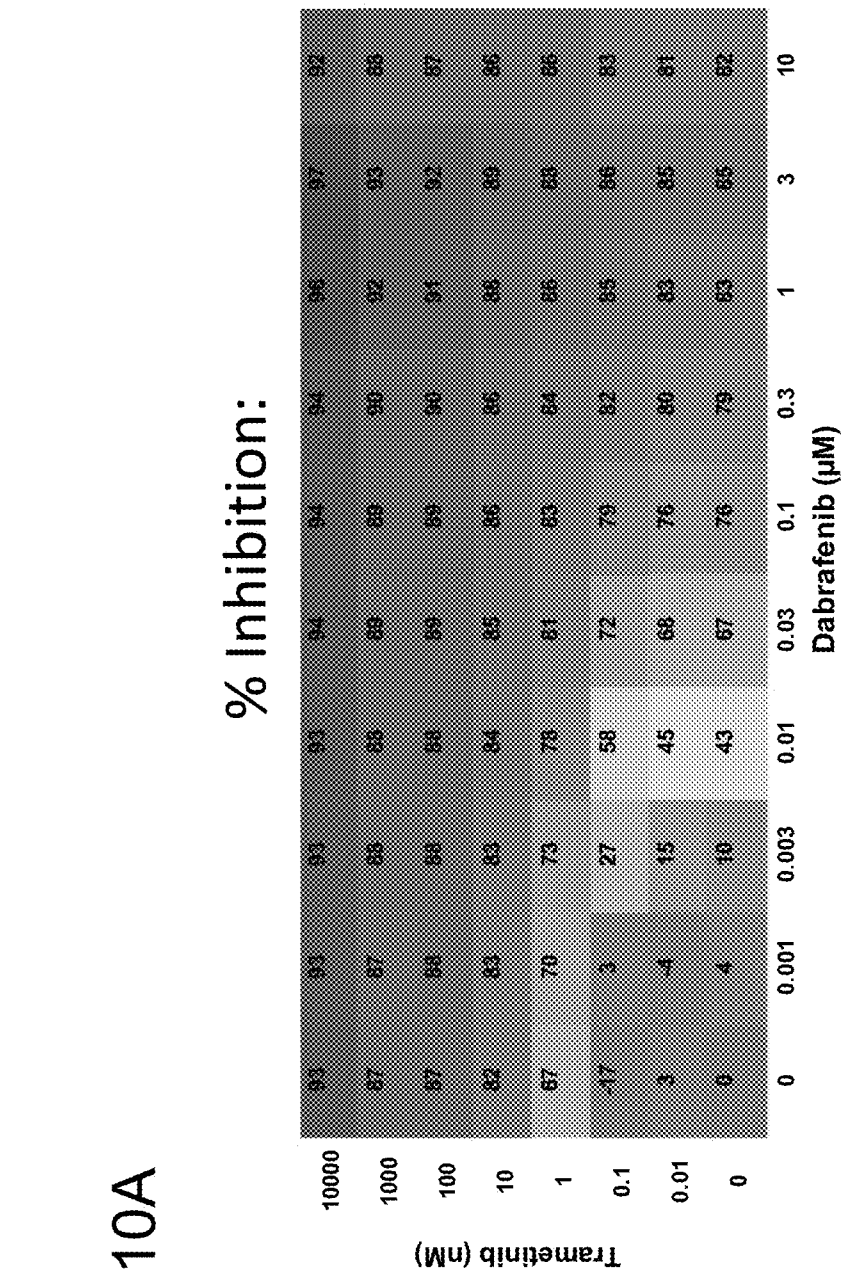

% Inhibition:
Trametinib (nM)
10000
1000
100
10
1
0.1
0.01
0
Dabrafenib (μM)
0
0.001
0.003
0.01
0.03
0.1
0.3
1
3
10

FIG. 10B

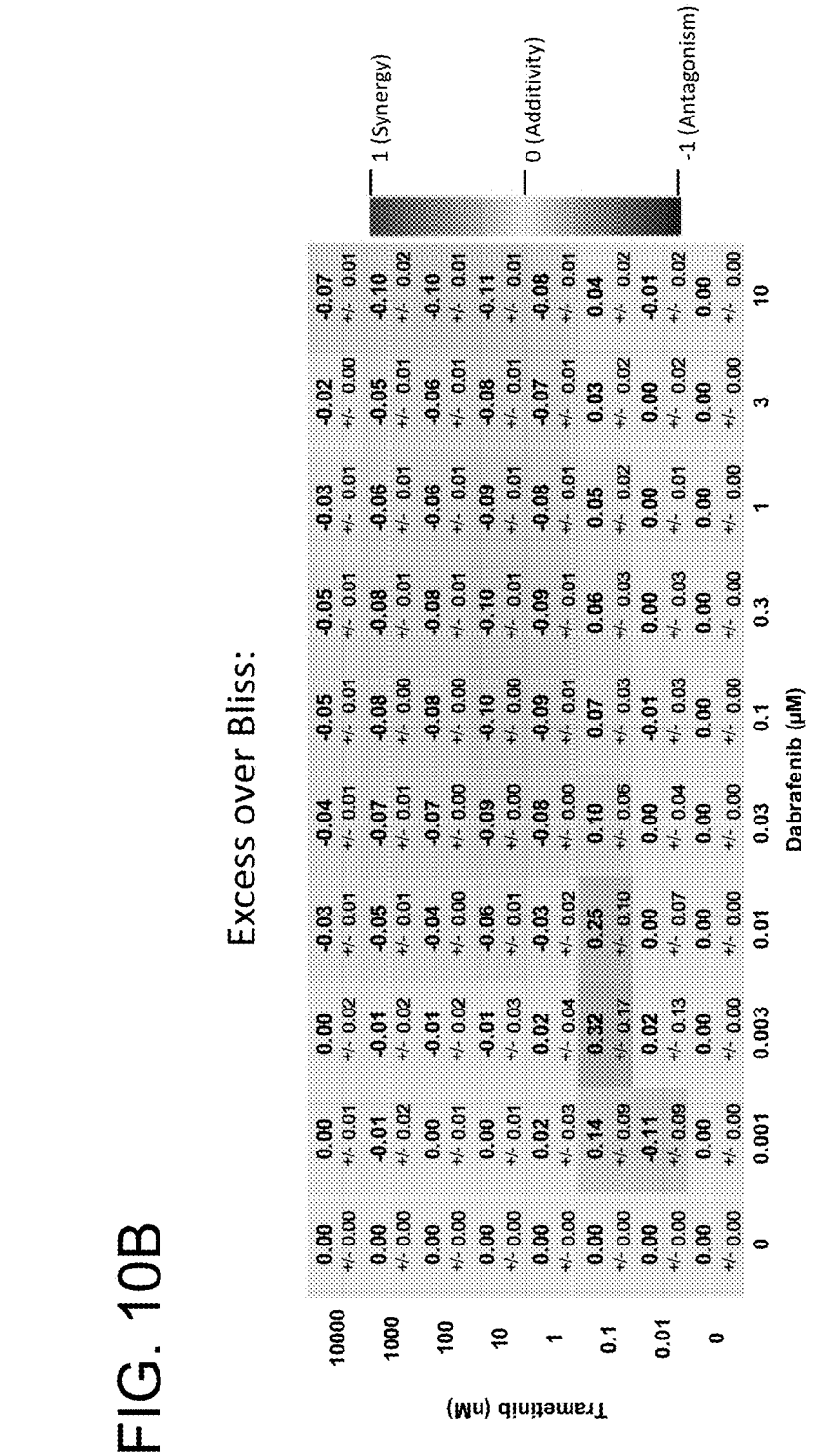

Excess over Bliss:
1 (Synergy)
0 (Additivity)
-1 (Antagonism)
Trametinib (nM)
Dabrafenib (μM)
10000
1000
100
10
1
0.1
0.01
0
0
0.001
0.003
0.01
0.03
0.1
0.3
1
3
10

FIG. 10C

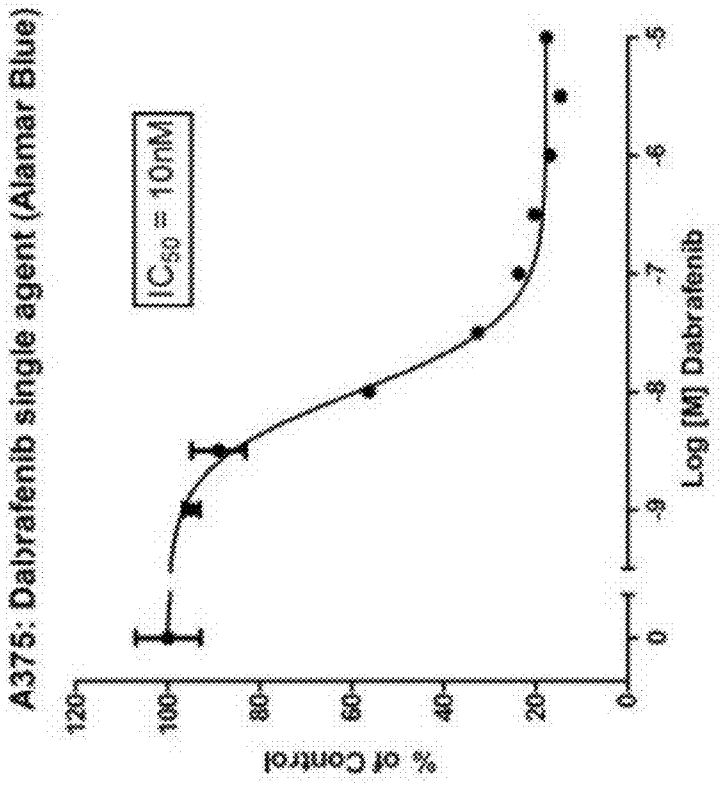


FIG. 10D

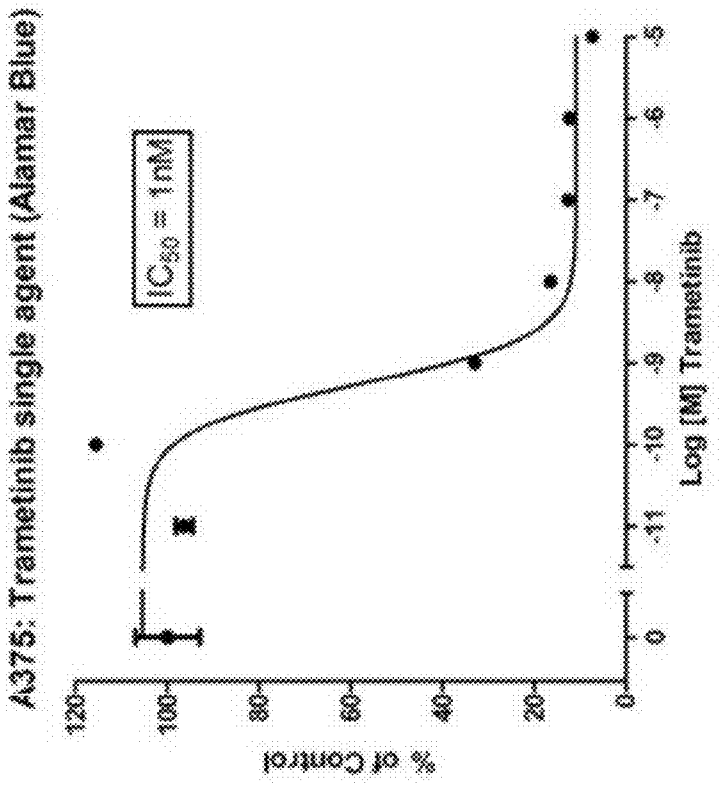


FIG. 10E

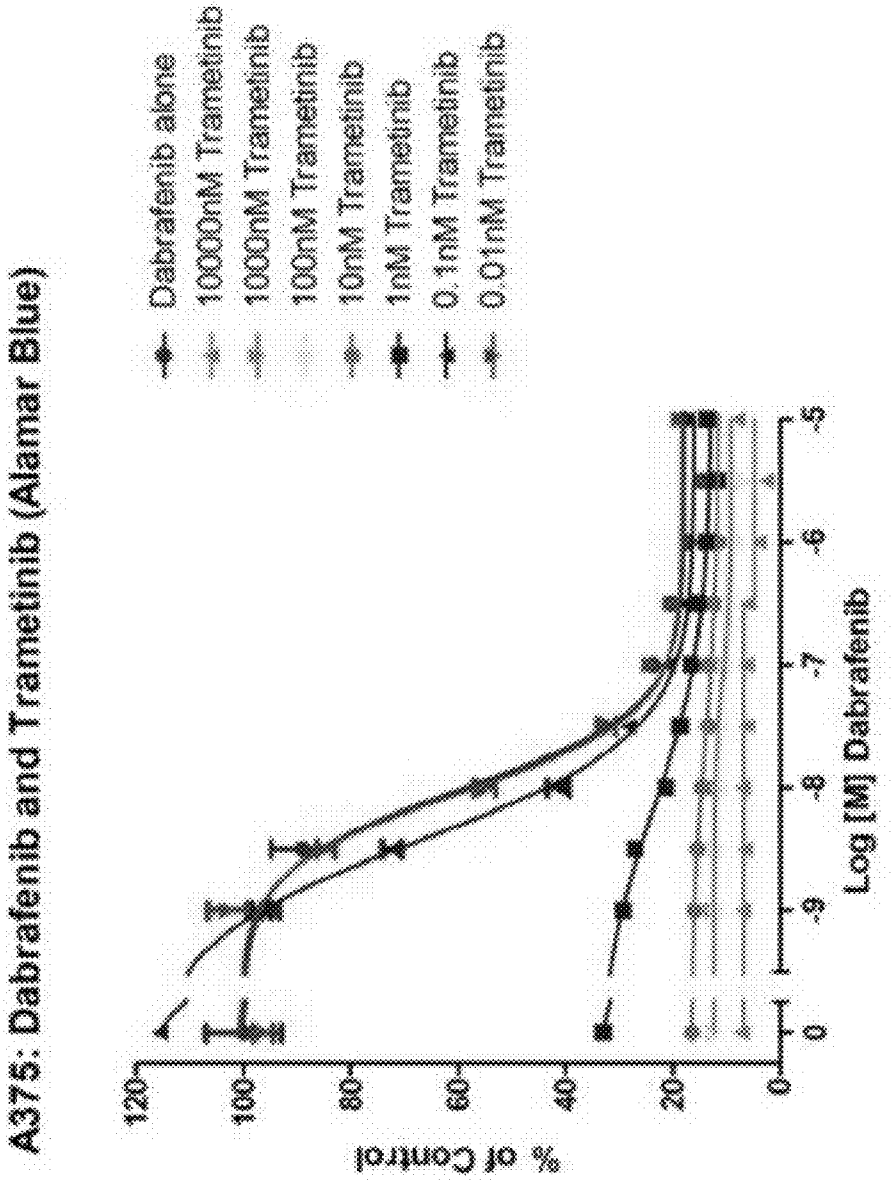

A375: Dabrafenib and Trametinib (Alamar Blue)
Dabrafenib alone
10000nM Trametinib
1000nM Trametinib
100nM Trametinib
10nM Trametinib
1nM Trametinib
0.1nM Trametinib
0.01nM Trametinib
% of Control
120
100
80
60
40
20
0
0
-5
-6
-7
-8
-9
Log [M] Dabrafenib

FIG. 11A

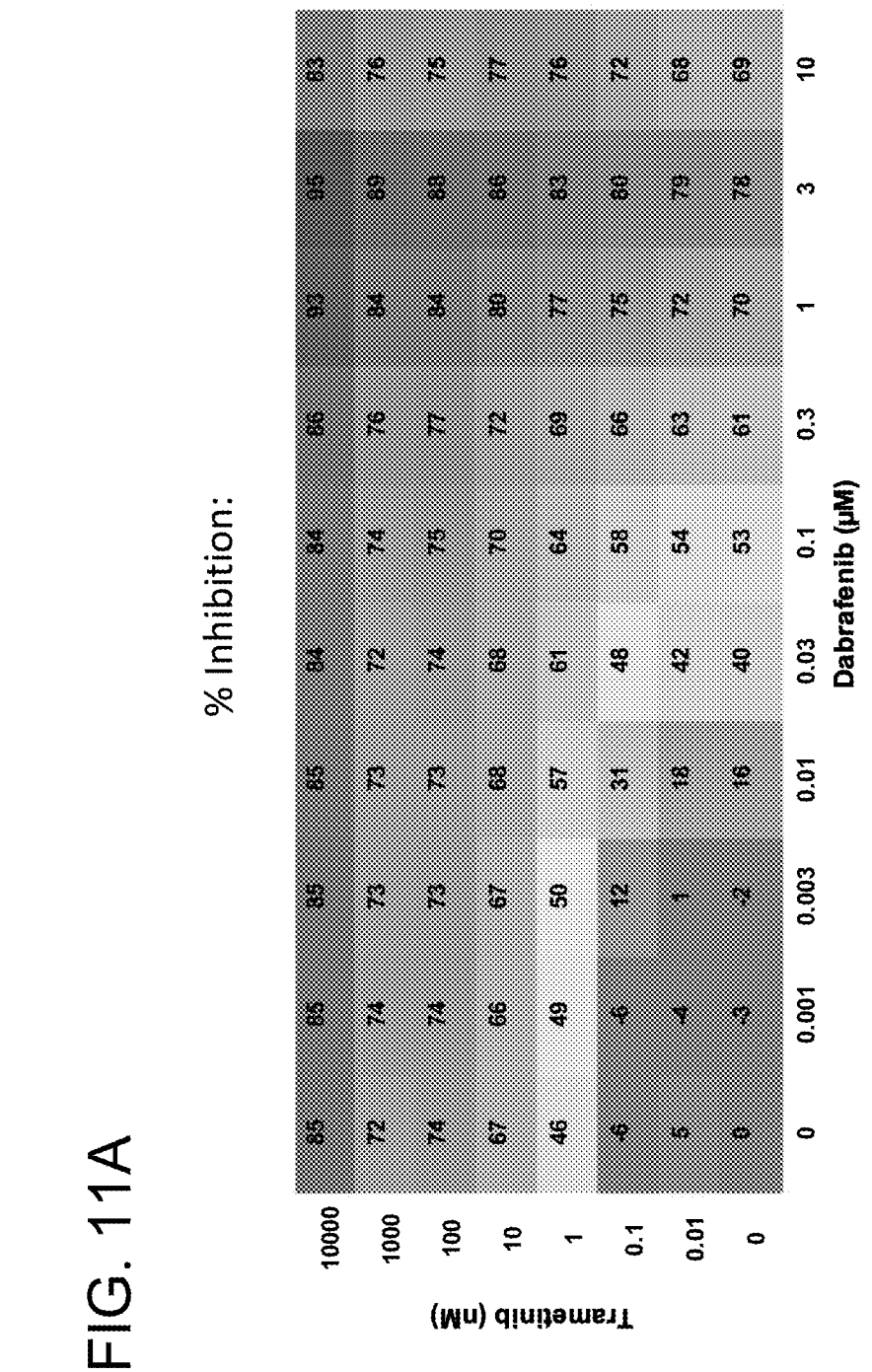

% Inhibition:
Trametinib (nM)
10000
1000
100
10
1
0.1
0.01
0
Dabrafenib (μM)
0
0.001
0.003
0.01
0.03
0.1
0.3
1
3
10
85 85 85 85 84 84 86 83 85 83
72 74 73 73 72 74 76 84 89 76
74 74 73 73 74 75 77 84 88 75
67 66 67 68 68 70 72 80 86 77
46 49 50 57 61 64 69 77 83 76
-6 -4 12 31 48 58 66 75 80 72
5 -4 1 18 42 54 63 72 79 68
0 -3 -2 16 40 53 61 70 78 69

FIG. 11B

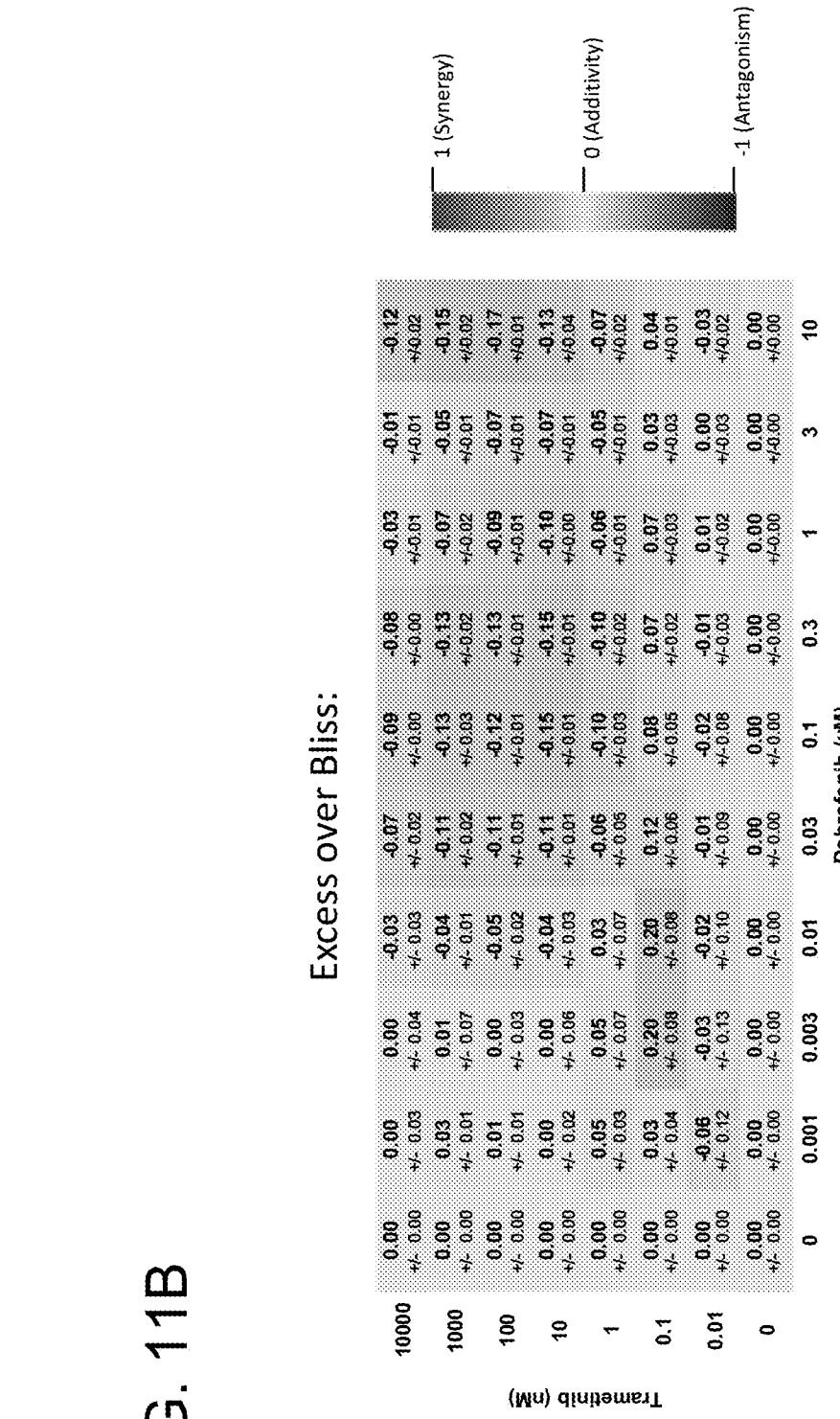

Excess over Bliss:
1 (Synergy)
0 (Additivity)
-1 (Antagonism)
Trametinib (nM)
Dabrafenib (μM)
10000
1000
100
10
1
0.1
0.01
0
0
0.001
0.003
0.01
0.03
0.1
0.3
1
3
10
0.00 +/- 0.00
0.00 +/- 0.03
0.00 +/- 0.04
-0.03 +/- 0.03
-0.07 +/- 0.02
-0.09 +/- 0.00
-0.08 +/- 0.00
-0.03 +/- 0.01
-0.01 +/- 0.01
-0.12 +/- 0.02
0.00 +/- 0.00
0.03 +/- 0.01
0.01 +/- 0.07
-0.04 +/- 0.01
-0.11 +/- 0.02
-0.13 +/- 0.03
-0.13 +/- 0.02
-0.07 +/- 0.02
-0.05 +/- 0.01
-0.15 +/- 0.02
0.00 +/- 0.00
0.01 +/- 0.01
0.00 +/- 0.03
-0.05 +/- 0.02
-0.11 +/- 0.01
-0.12 +/- 0.01
-0.13 +/- 0.01
-0.09 +/- 0.01
-0.07 +/- 0.01
-0.17 +/- 0.01
0.00 +/- 0.00
0.00 +/- 0.02
0.00 +/- 0.06
-0.04 +/- 0.03
-0.11 +/- 0.01
-0.15 +/- 0.01
-0.15 +/- 0.01
-0.10 +/- 0.00
-0.07 +/- 0.01
-0.13 +/- 0.04
0.00 +/- 0.00
0.05 +/- 0.03
0.05 +/- 0.07
0.03 +/- 0.07
-0.06 +/- 0.05
-0.10 +/- 0.03
-0.10 +/- 0.02
-0.06 +/- 0.01
-0.05 +/- 0.01
-0.07 +/- 0.02
0.00 +/- 0.00
0.03 +/- 0.04
0.20 +/- 0.08
0.20 +/- 0.08
0.12 +/- 0.06
0.08 +/- 0.05
0.07 +/- 0.02
0.07 +/- 0.03
0.03 +/- 0.03
0.04 +/- 0.01
0.00 +/- 0.00
-0.06 +/- 0.12
-0.03 +/- 0.13
-0.02 +/- 0.10
-0.01 +/- 0.09
-0.02 +/- 0.08
-0.01 +/- 0.03
0.01 +/- 0.02
0.00 +/- 0.03
-0.03 +/- 0.02
0.00 +/- 0.00
0.00 +/- 0.00
0.00 +/- 0.00
0.00 +/- 0.00
0.00 +/- 0.00
0.00 +/- 0.00
0.00 +/- 0.00
0.00 +/- 0.00
0.00 +/- 0.00

FIG. 11C

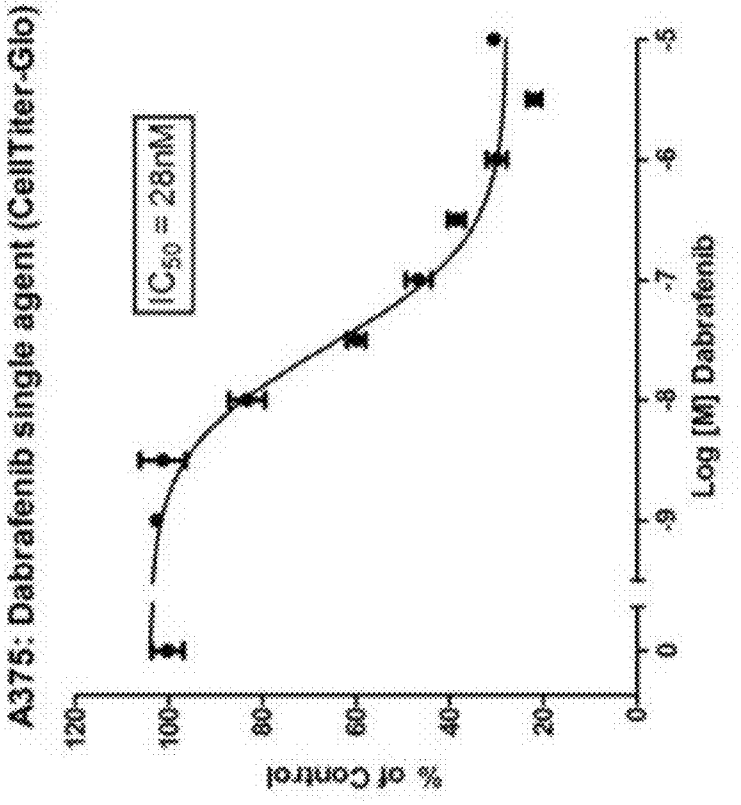


FIG. 11D

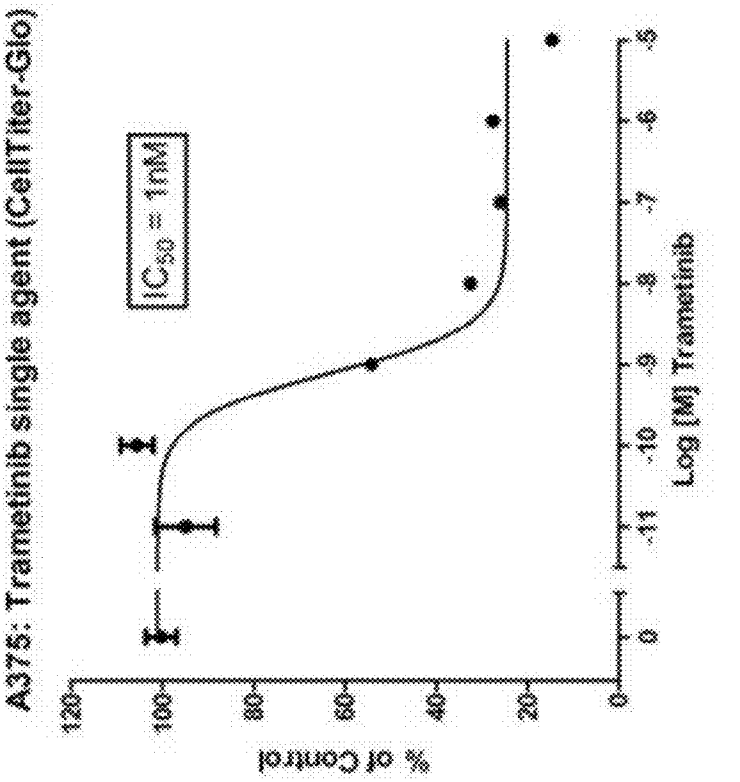


FIG. 11E

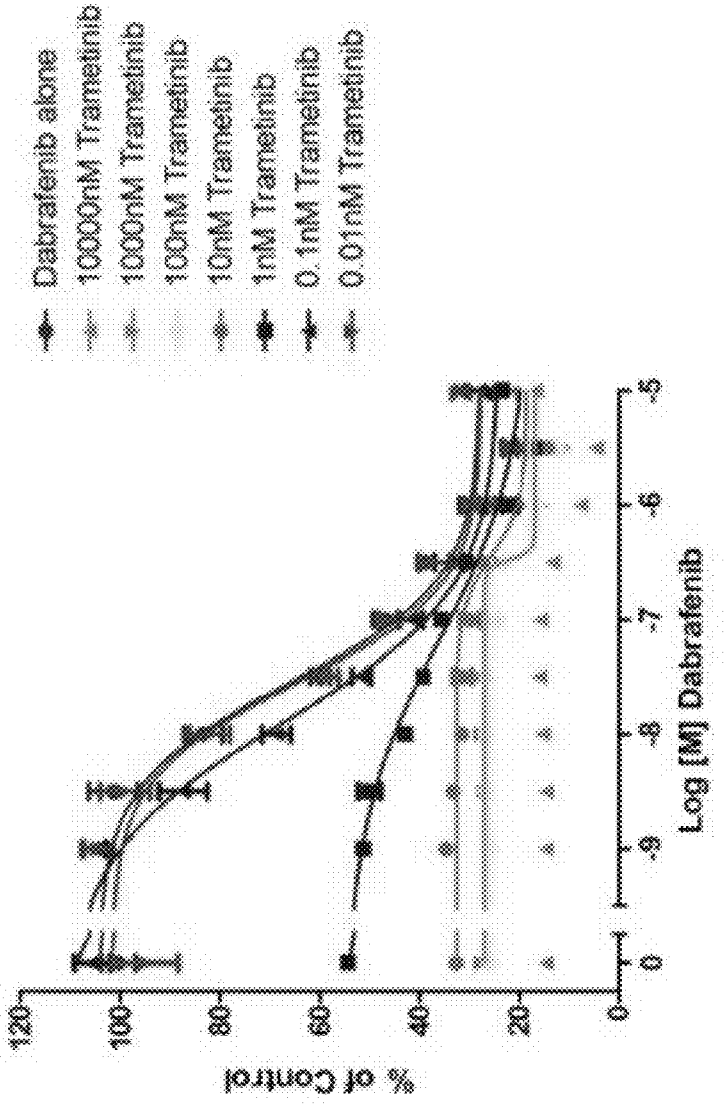

A375: Dabrafenib and Trametinib (CellTiter-Glo)
Dabrafenib alone
1000nM Trametinib
100nM Trametinib
10nM Trametinib
1nM Trametinib
0.1nM Trametinib
0.01nM Trametinib
% of Control
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] Dabrafenib

FIG. 12A

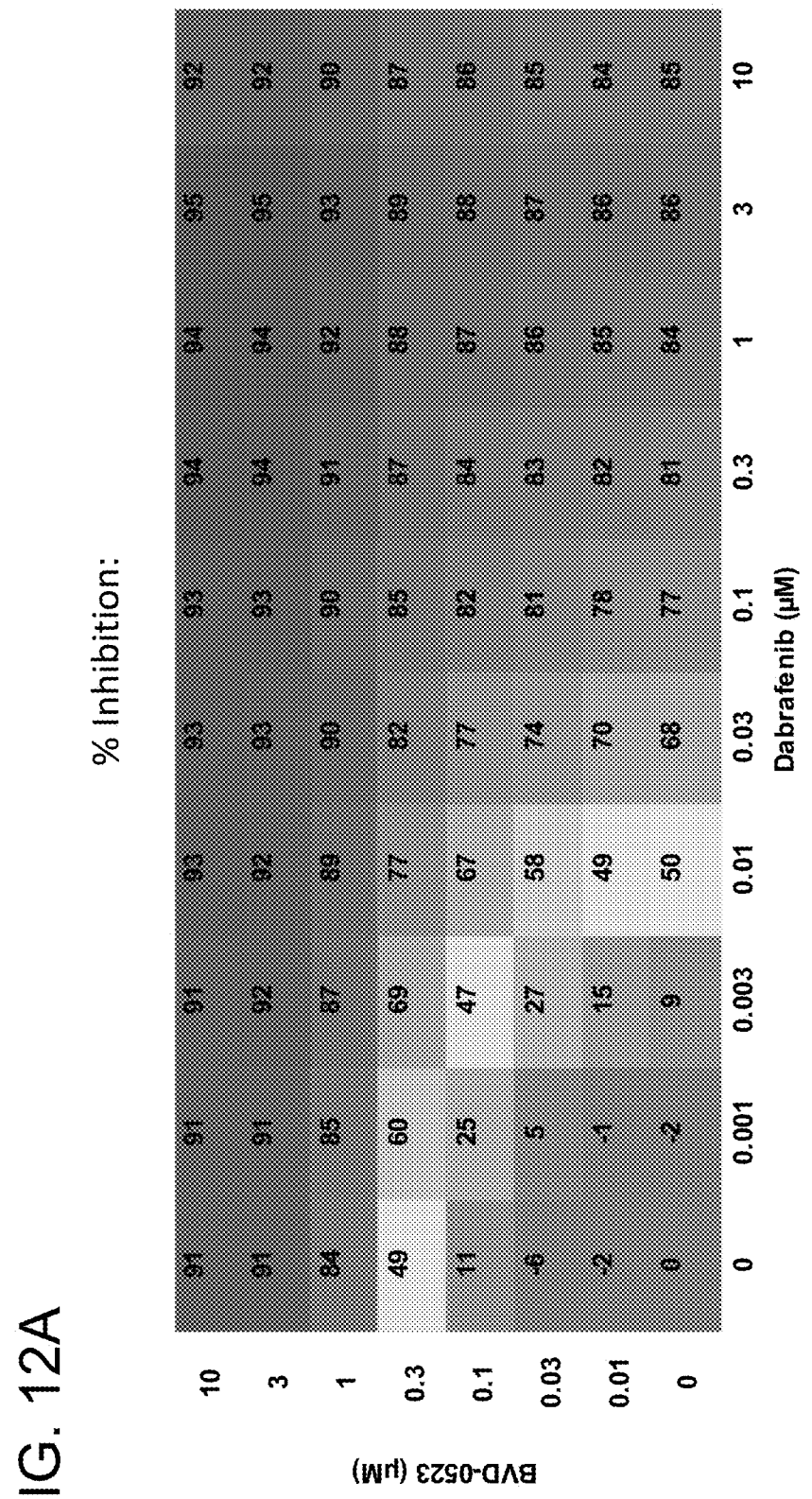

% Inhibition:
BVD-0523 (μM)
10 94 91 91 91 93 93 93 94 94 92
3 91 91 92 92 93 93 93 94 94 95 92
1 84 85 87 89 90 90 90 91 92 93 90
0.3 49 60 69 77 82 85 85 87 88 89 87
0.1 11 25 47 67 77 82 82 84 87 88 86
0.03 -6 5 27 58 74 81 81 83 86 87 85
0.01 -2 -1 15 49 70 78 78 82 85 86 84
0 0 -2 9 50 68 77 77 81 84 86 83
0 0.001 0.003 0.01 0.03 0.1 0.3 1 3 10
Dabrafenib (μM)

FIG. 12B

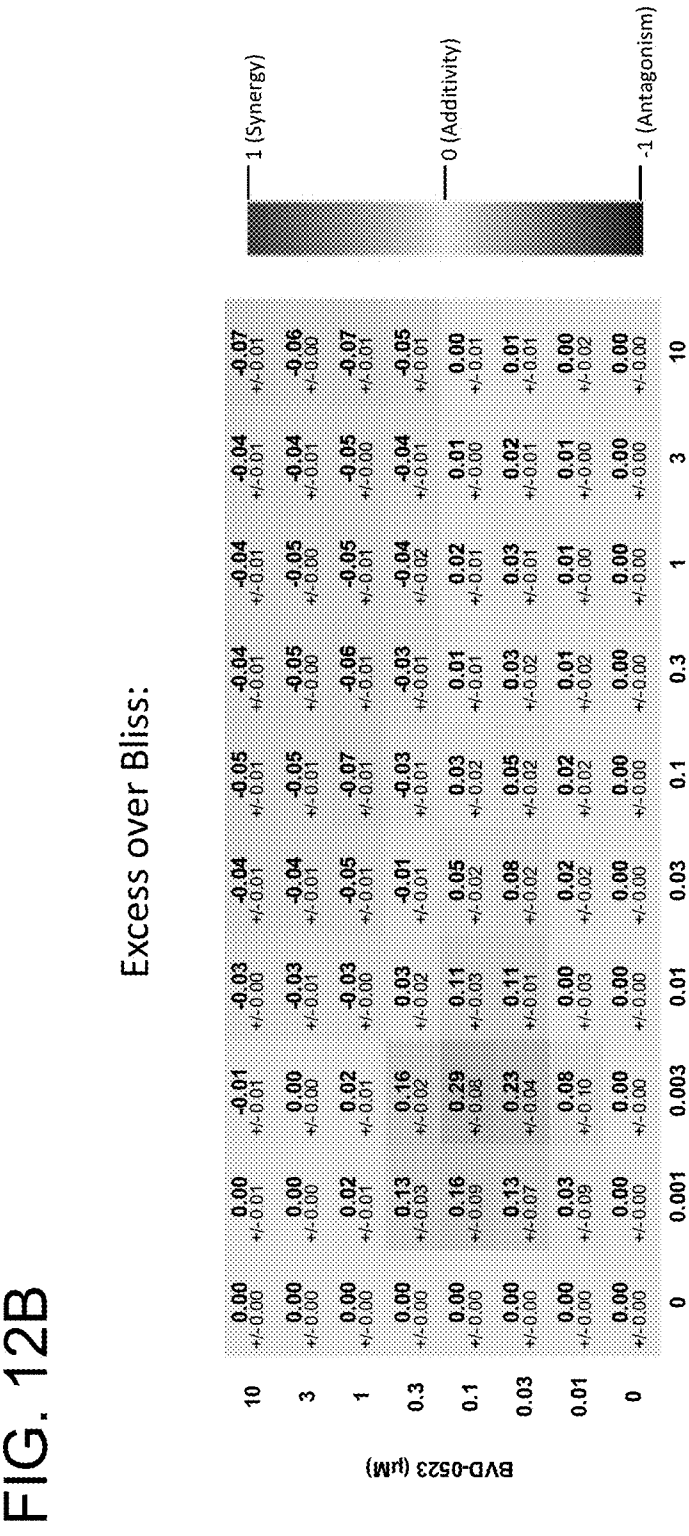

Excess over Bliss:
1 (Synergy)
0 (Additivity)
-1 (Antagonism)
BVD-0523 (μM)
Dabrafenib (μM)
10
3
1
0.3
0.1
0.03
0.01
0
0
0.001
0.003
0.01
0.03
0.1
0.3
1
3
10

FIG. 12C

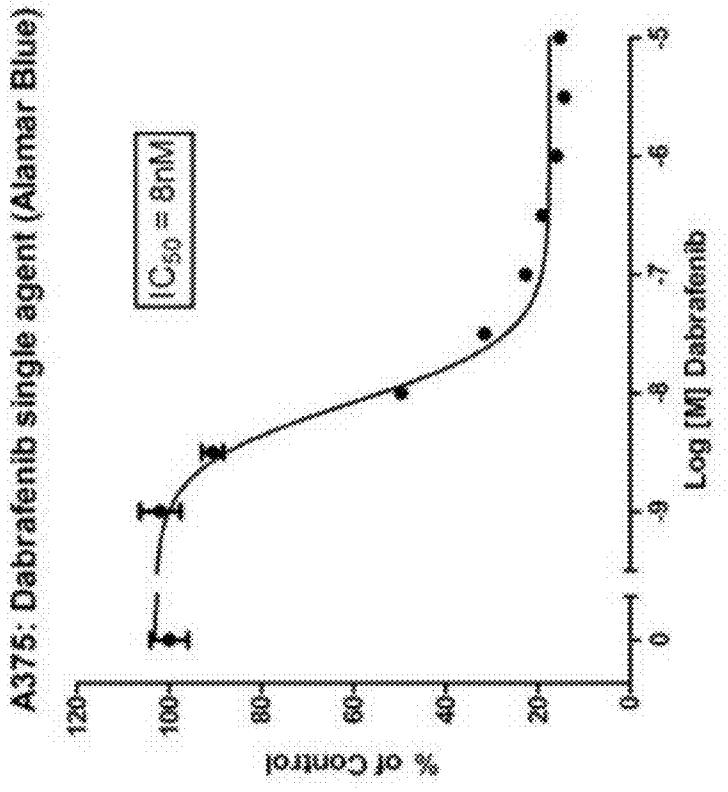


FIG. 12D

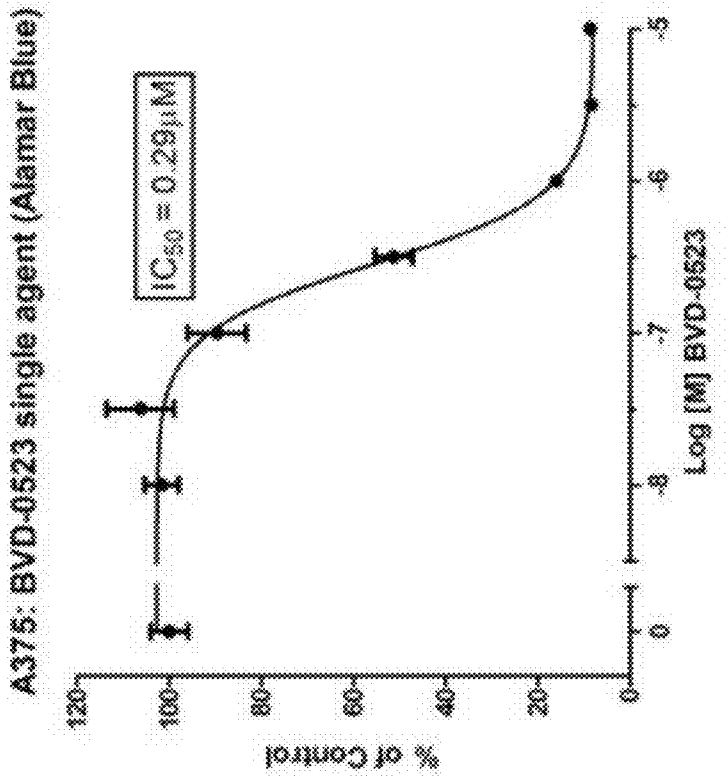


FIG. 12E

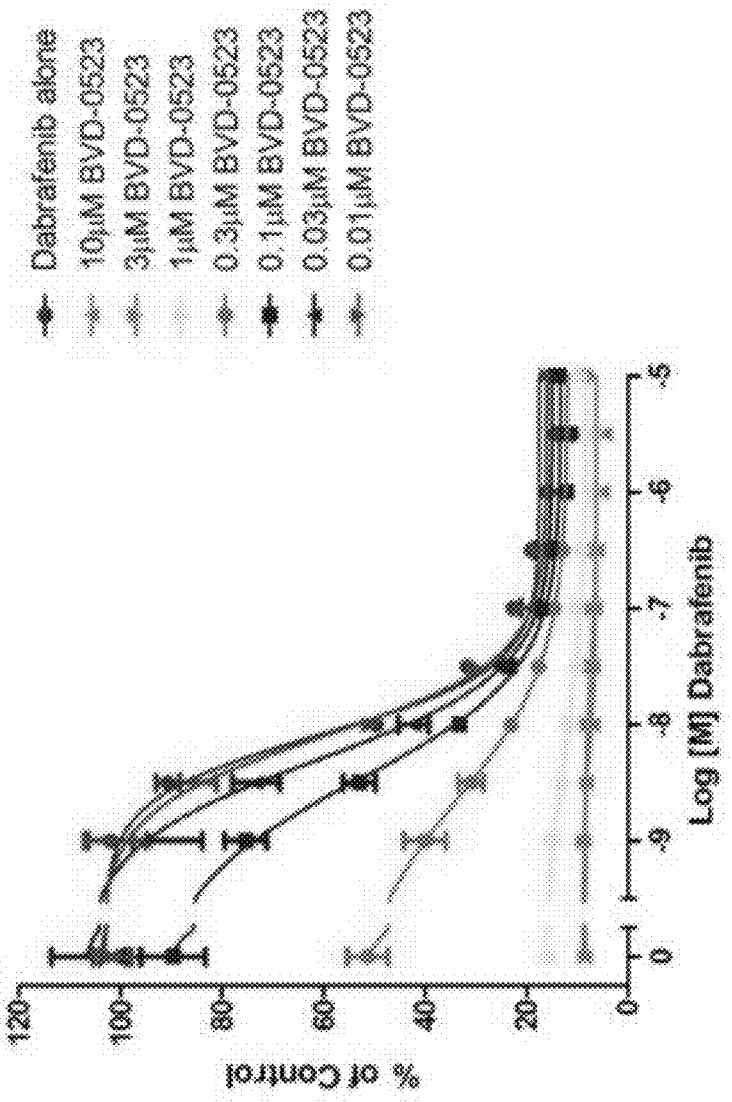

A375: Dabrafenib and BVD-0523 (Alamar Blue)
Dabrafenib alone
10μM BVD-0523
3μM BVD-0523
1μM BVD-0523
0.3μM BVD-0523
0.1μM BVD-0523
0.03μM BVD-0523
0.01μM BVD-0523
% of Control
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] Dabrafenib

FIG. 13A

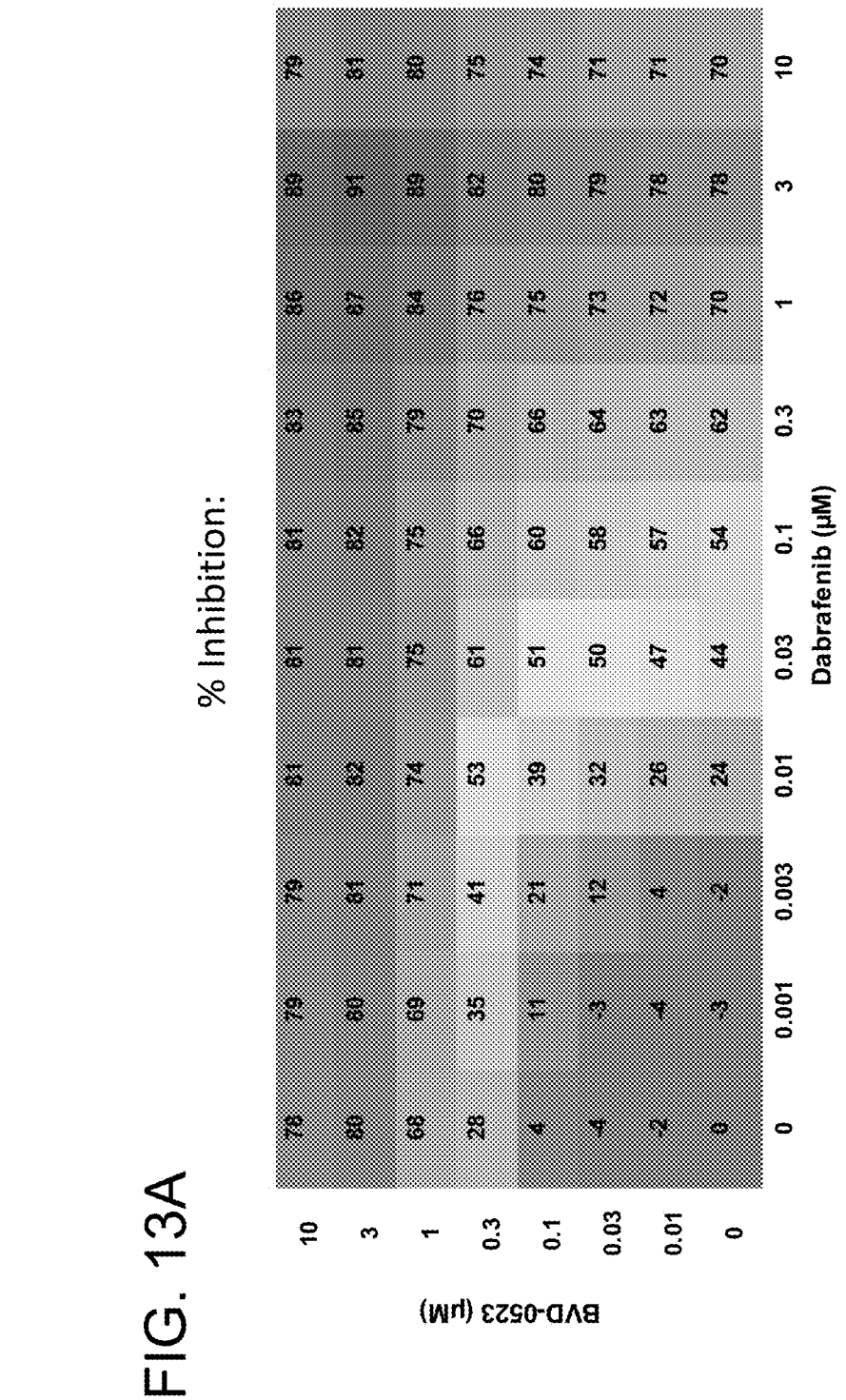

% Inhibition:
BVD-0523 (μM)
10 3 1 0.3 0.1 0.03 0.01 0
78 79 79 81 81 81 82 79
89 80 81 82 82 81 85 91
68 69 71 74 75 75 79 84
28 35 41 53 61 61 70 76
4 11 21 39 51 51 66 75
-4 -3 12 32 50 47 64 73
-2 -4 4 26 47 57 63 72
0 -3 -2 24 44 54 62 70
Dabrafenib (μM)
0 0.001 0.003 0.01 0.03 0.1 0.3 1 3 10
79 81 88 75 74 71 71 70
89 91 89 82 80 79 78 78
86 87 84 76 75 73 72 70
83 85 79 70 66 64 63 62
81 82 75 66 60 58 57 54
81 81 75 61 51 50 47 44
81 82 74 53 39 32 26 24
79 81 71 41 21 12 4 -2
79 80 69 35 11 -3 -4 -3
78 80 68 28 4 -4 -2 0

FIG. 13B

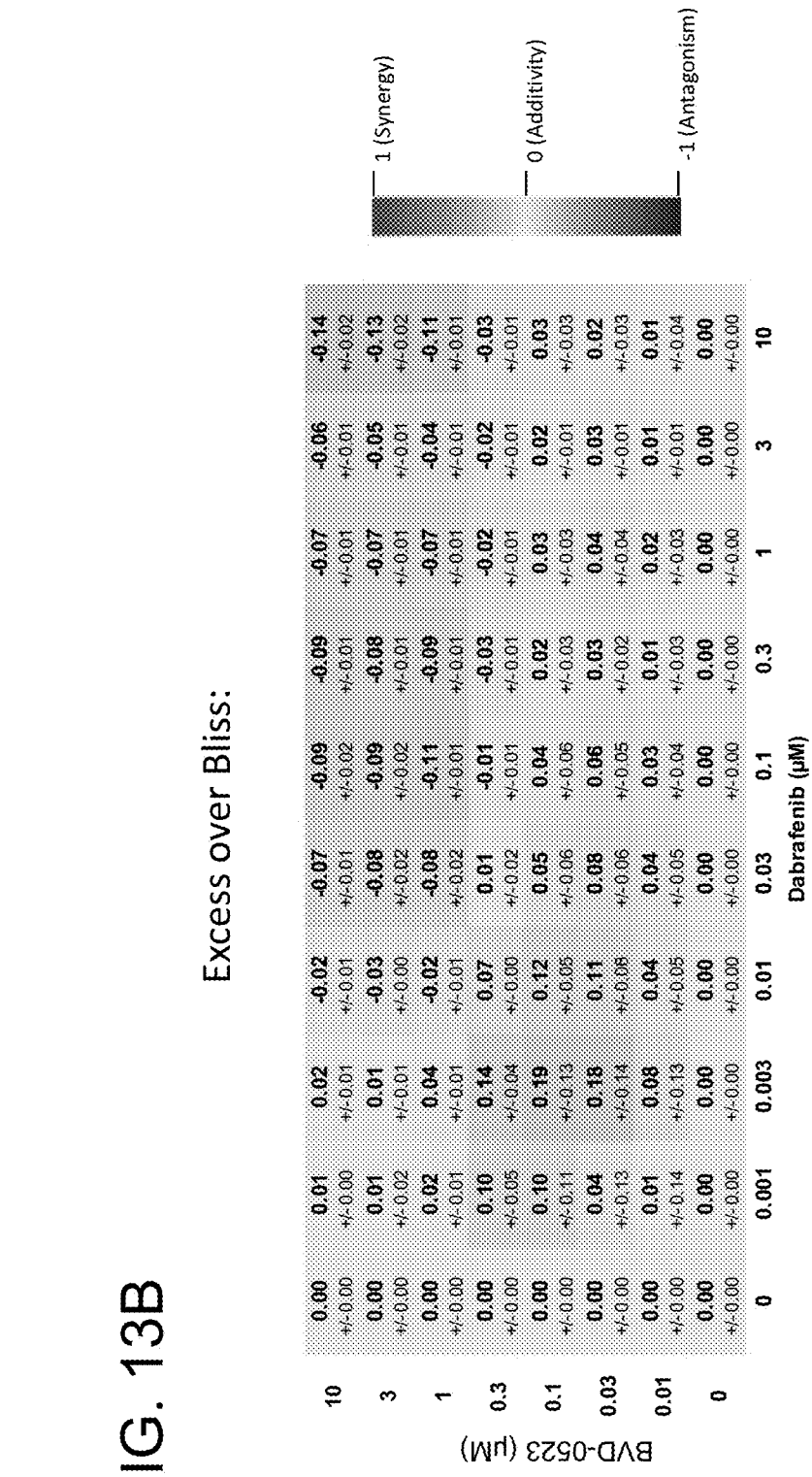

Excess over Bliss:
1 (Synergy)
0 (Additivity)
-1 (Antagonism)
BVD-523 (μM)
Dabrafenib (μM)
10
3
1
0.3
0.1
0.03
0.01
0
0
0.001
0.003
0.01
0.03
0.1
0.3
1
3
10
0.00 +/-0.00 | 0.01 +/-0.00 | 0.02 +/-0.01 | -0.02 +/-0.01 | -0.07 +/-0.01 | -0.09 +/-0.02 | -0.09 +/-0.01 | -0.07 +/-0.01 | -0.06 +/-0.01 | -0.14 +/-0.02
0.00 +/-0.00 | 0.01 +/-0.02 | 0.01 +/-0.01 | -0.03 +/-0.00 | -0.08 +/-0.02 | -0.09 +/-0.02 | -0.08 +/-0.01 | -0.07 +/-0.01 | -0.05 +/-0.01 | -0.13 +/-0.02
0.00 +/-0.00 | 0.02 +/-0.01 | 0.04 +/-0.01 | -0.02 +/-0.01 | -0.08 +/-0.02 | -0.11 +/-0.01 | -0.09 +/-0.01 | -0.07 +/-0.01 | -0.04 +/-0.01 | -0.11 +/-0.01
0.00 +/-0.00 | 0.10 +/-0.05 | 0.14 +/-0.04 | 0.07 +/-0.00 | 0.01 +/-0.02 | -0.01 +/-0.01 | -0.03 +/-0.01 | -0.02 +/-0.01 | -0.02 +/-0.01 | -0.03 +/-0.01
0.00 +/-0.00 | 0.10 +/-0.11 | 0.19 +/-0.13 | 0.12 +/-0.05 | 0.05 +/-0.06 | 0.04 +/-0.06 | 0.02 +/-0.03 | 0.03 +/-0.03 | 0.02 +/-0.01 | 0.03 +/-0.03
0.00 +/-0.00 | 0.04 +/-0.13 | 0.18 +/-0.14 | 0.11 +/-0.06 | 0.08 +/-0.06 | 0.06 +/-0.05 | 0.03 +/-0.02 | 0.04 +/-0.04 | 0.03 +/-0.01 | 0.02 +/-0.03
0.00 +/-0.00 | 0.01 +/-0.14 | 0.08 +/-0.13 | 0.04 +/-0.05 | 0.04 +/-0.05 | 0.03 +/-0.04 | 0.01 +/-0.03 | 0.02 +/-0.03 | 0.01 +/-0.01 | 0.01 +/-0.04
0.00 +/-0.00 | 0.00 +/-0.00 | 0.00 +/-0.00 | 0.00 +/-0.00 | 0.00 +/-0.00 | 0.00 +/-0.00 | 0.00 +/-0.00 | 0.00 +/-0.00 | 0.00 +/-0.00 | 0.00 +/-0.00

FIG. 13C

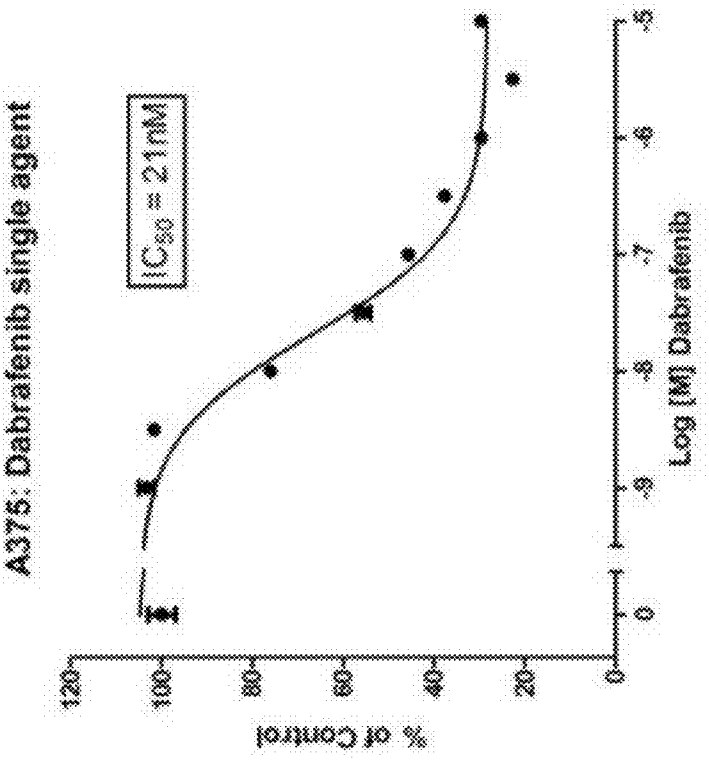


FIG. 13D

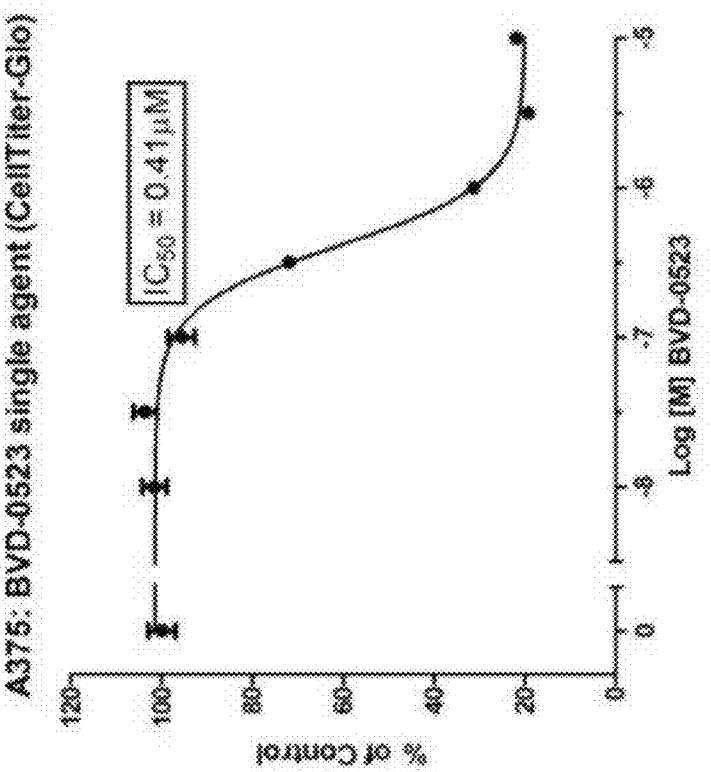


FIG. 13E

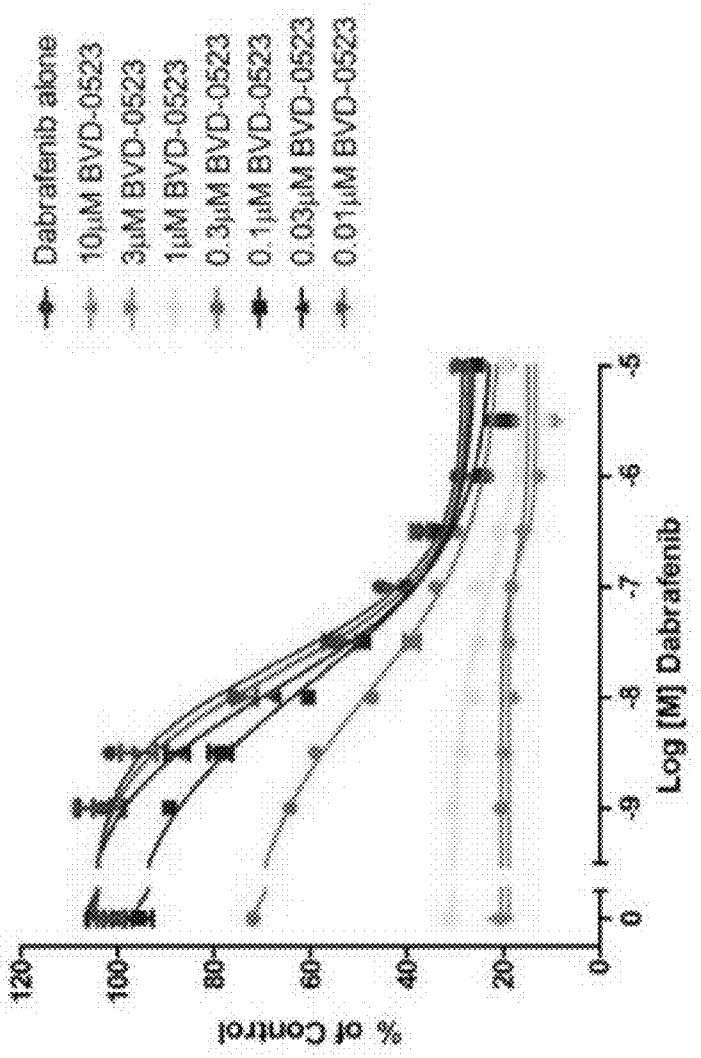

A375: Dabrafenib and BVD-0523 (CellTiter-Glo)
Dabrafenib alone
10μM BVD-0523
3μM BVD-0523
1μM BVD-0523
0.3μM BVD-0523
0.1μM BVD-0523
0.03μM BVD-0523
0.01μM BVD-0523
% of Control
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] Dabrafenib

FIG. 14A

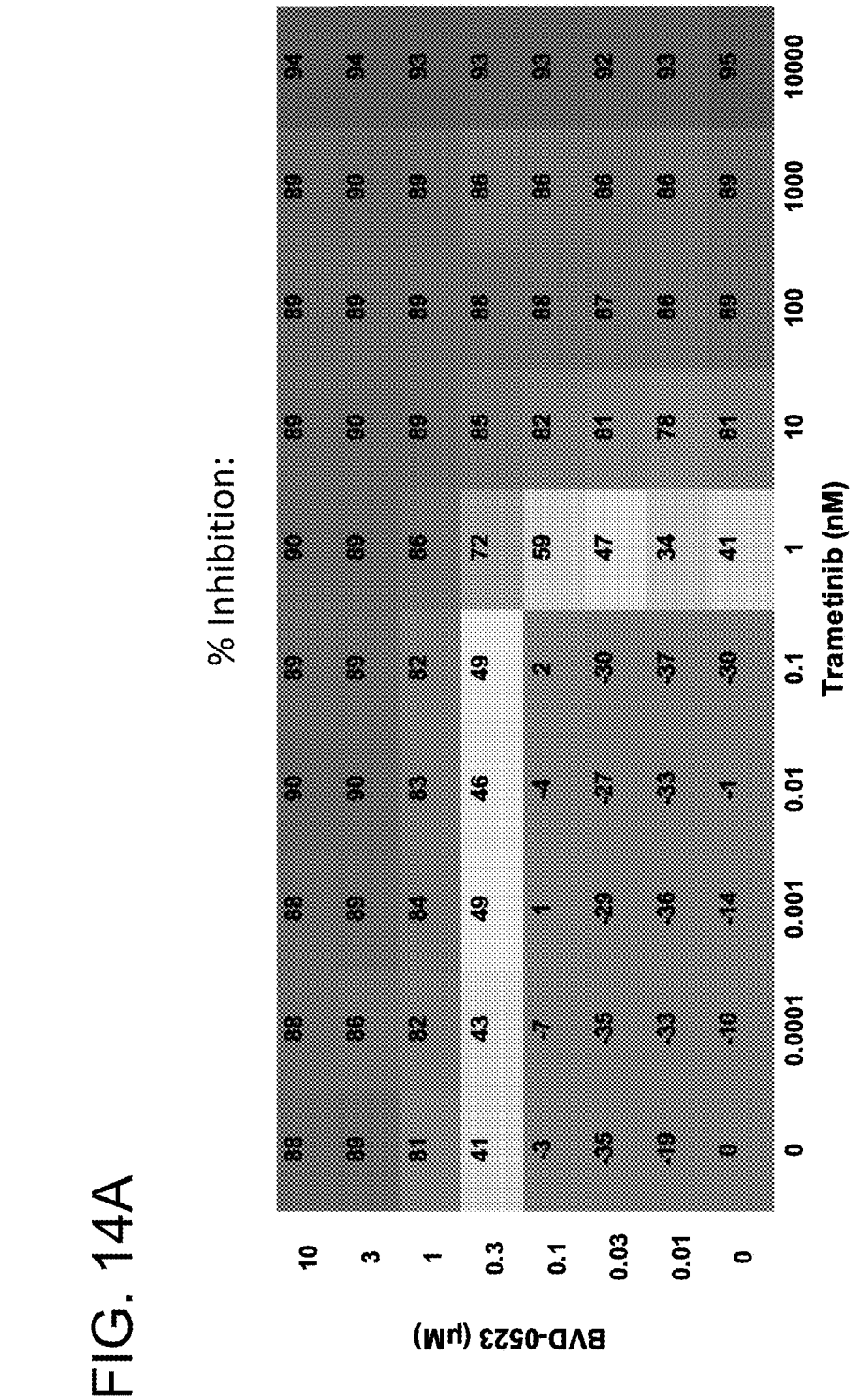

% Inhibition:
BVD-523 (μM)
10
3
1
0.3
0.1
0.03
0.01
0
Trametinib (nM)
0
0.0001
0.001
0.01
0.1
1
10
100
1000
10000

FIG. 14B

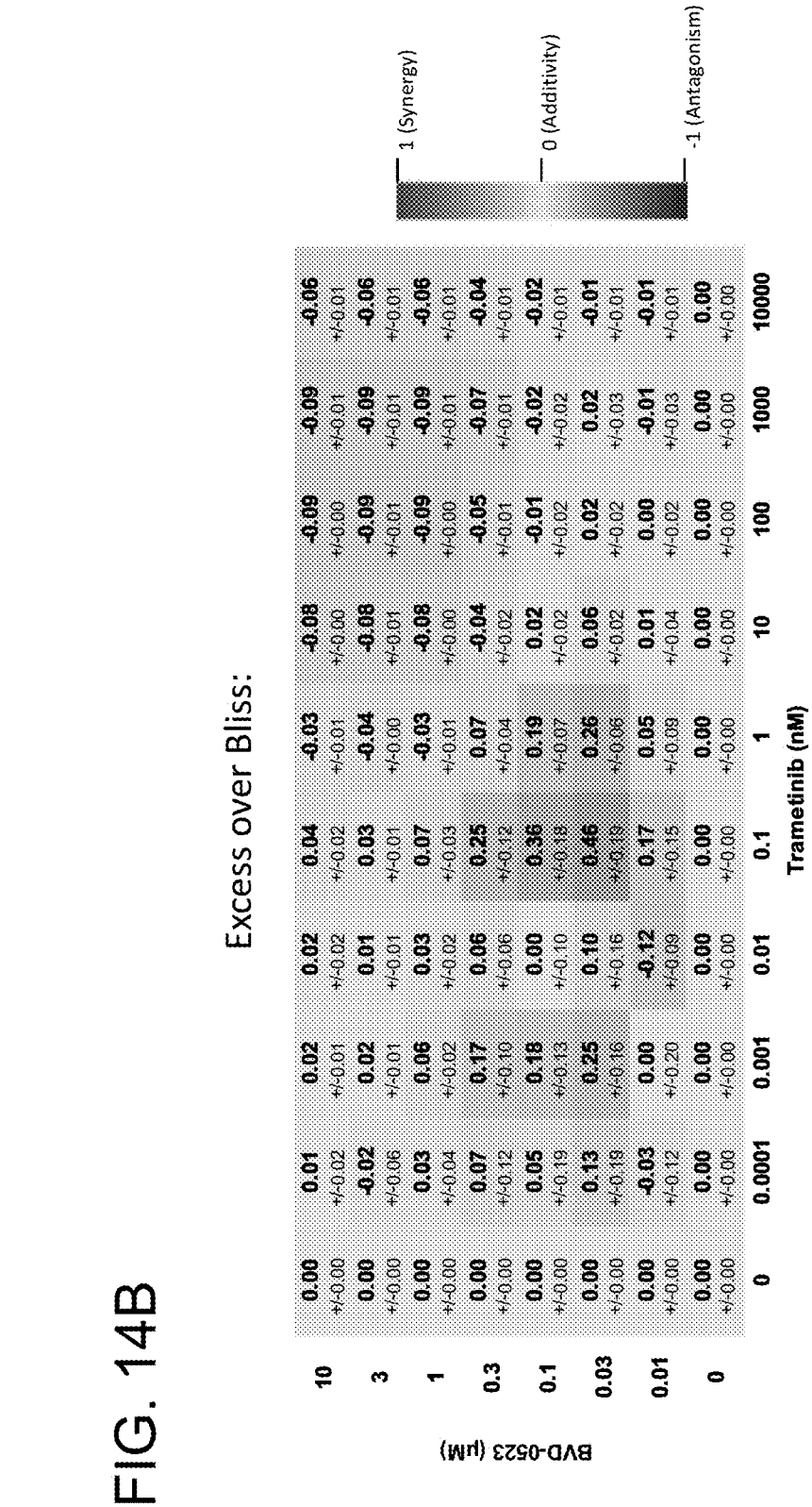

Excess over Bliss:
1 (Synergy)
0 (Additivity)
-1 (Antagonism)
BVD-523 (μM)
Trametinib (nM)
10
3
1
0.3
0.1
0.03
0.01
0
0
0.0001
0.001
0.01
0.1
1
10
100
1000
10000
0.00 +/-0.00 | 0.01 +/-0.02 | 0.02 +/-0.01 | 0.02 +/-0.02 | 0.04 +/-0.02 | -0.03 +/-0.01 | -0.08 +/-0.00 | -0.09 +/-0.00 | -0.09 +/-0.01 | -0.06 +/-0.01
0.00 +/-0.00 | -0.02 +/-0.06 | 0.02 +/-0.01 | 0.01 +/-0.01 | 0.03 +/-0.01 | -0.04 +/-0.00 | -0.08 +/-0.01 | -0.09 +/-0.01 | -0.09 +/-0.01 | -0.06 +/-0.01
0.00 +/-0.00 | 0.03 +/-0.04 | 0.06 +/-0.02 | 0.03 +/-0.02 | 0.07 +/-0.03 | -0.03 +/-0.01 | -0.08 +/-0.00 | -0.09 +/-0.00 | -0.09 +/-0.01 | -0.06 +/-0.01
0.00 +/-0.00 | 0.07 +/-0.12 | 0.17 +/-0.10 | 0.06 +/-0.06 | 0.25 +/-0.12 | 0.07 +/-0.04 | -0.04 +/-0.02 | -0.05 +/-0.01 | -0.07 +/-0.01 | -0.04 +/-0.01
0.00 +/-0.00 | 0.05 +/-0.19 | 0.18 +/-0.13 | 0.00 +/-0.10 | 0.36 +/-0.18 | 0.19 +/-0.07 | 0.02 +/-0.02 | -0.01 +/-0.02 | -0.02 +/-0.02 | -0.02 +/-0.01
0.00 +/-0.00 | 0.13 +/-0.19 | 0.25 +/-0.16 | 0.10 +/-0.16 | 0.46 +/-0.18 | 0.26 +/-0.06 | 0.06 +/-0.02 | 0.02 +/-0.02 | 0.02 +/-0.03 | -0.01 +/-0.01
0.00 +/-0.00 | -0.03 +/-0.12 | 0.00 +/-0.09 | -0.12 +/-0.09 | 0.17 +/-0.15 | 0.05 +/-0.09 | 0.01 +/-0.04 | 0.00 +/-0.02 | -0.01 +/-0.03 | -0.01 +/-0.01
0.00 +/-0.00 | 0.00 +/-0.00 | 0.00 +/-0.00 | 0.00 +/-0.00 | 0.00 +/-0.00 | 0.00 +/-0.00 | 0.00 +/-0.00 | 0.00 +/-0.00 | 0.00 +/-0.00 | 0.00 +/-0.00

FIG. 14C

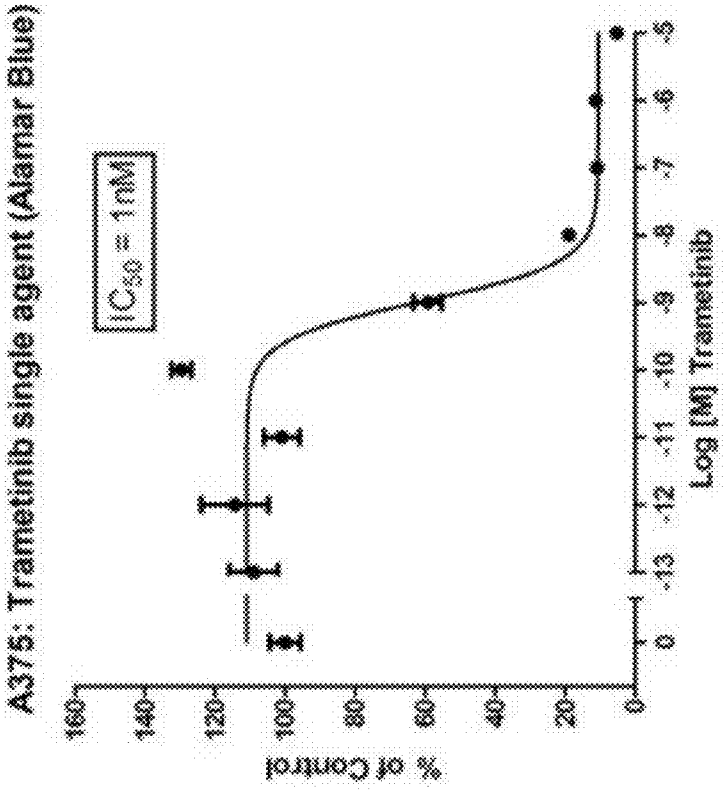


FIG. 14D

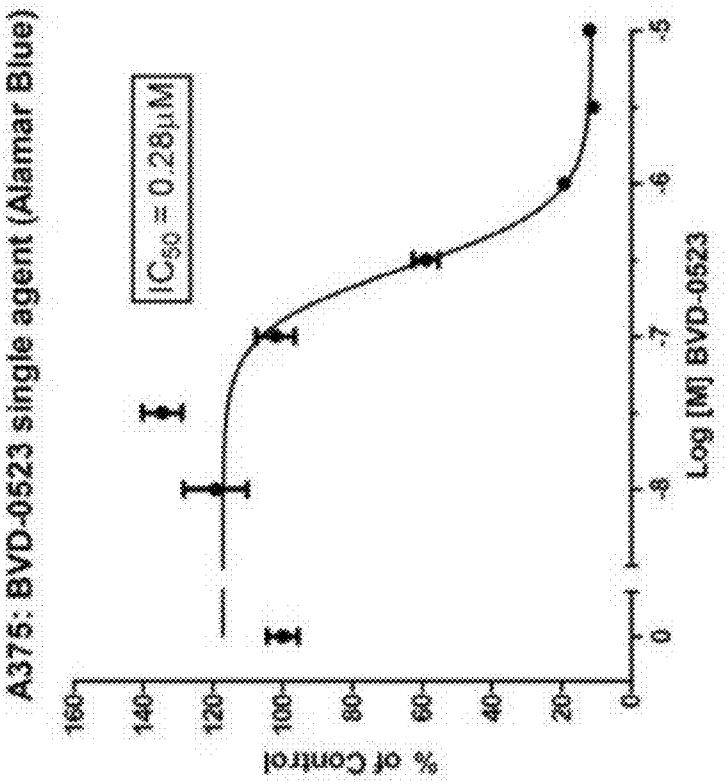


FIG. 14E

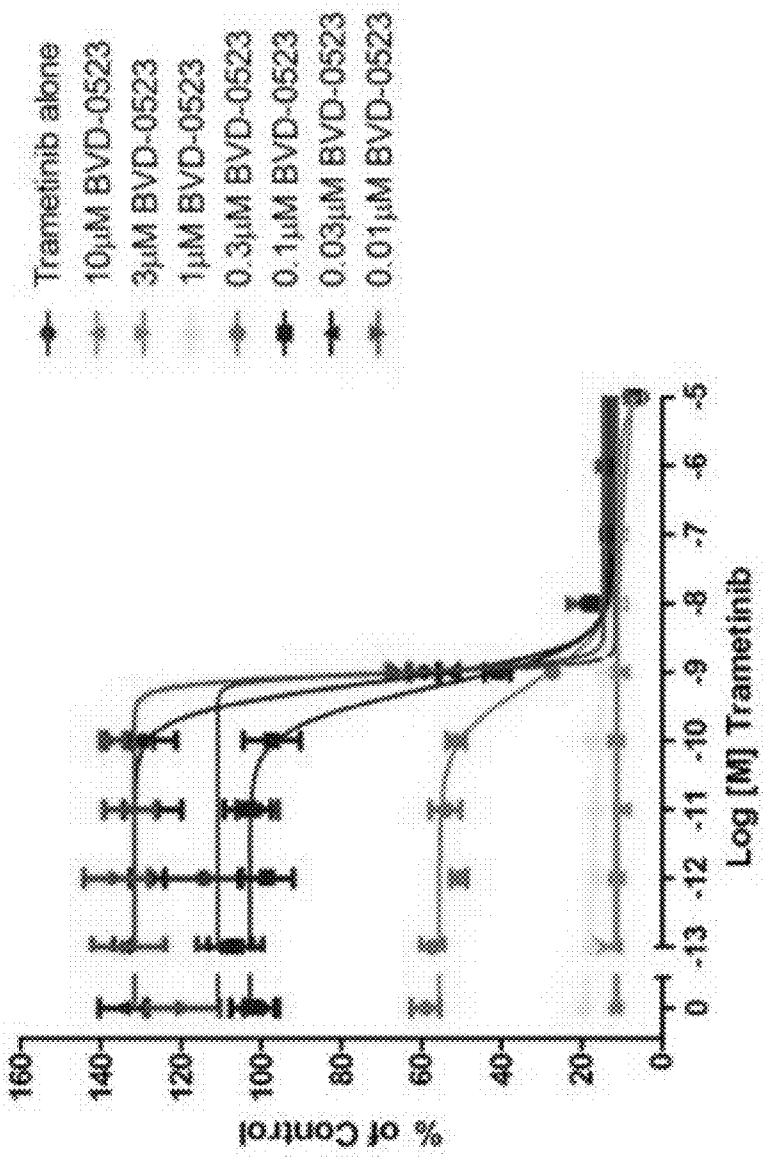

A375: Trametinib and BVD-0523 (Alamar Blue)
Trametinib alone
10μM BVD-0523
3μM BVD-0523
1μM BVD-0523
0.3μM BVD-0523
0.1μM BVD-0523
0.03μM BVD-0523
0.01μM BVD-0523
% of Control
160
140
120
100
80
60
40
20
0
0 -13 -12 -11 -10 -9 -8 -7 -6 -5
Log [M] Trametinib

FIG. 15A

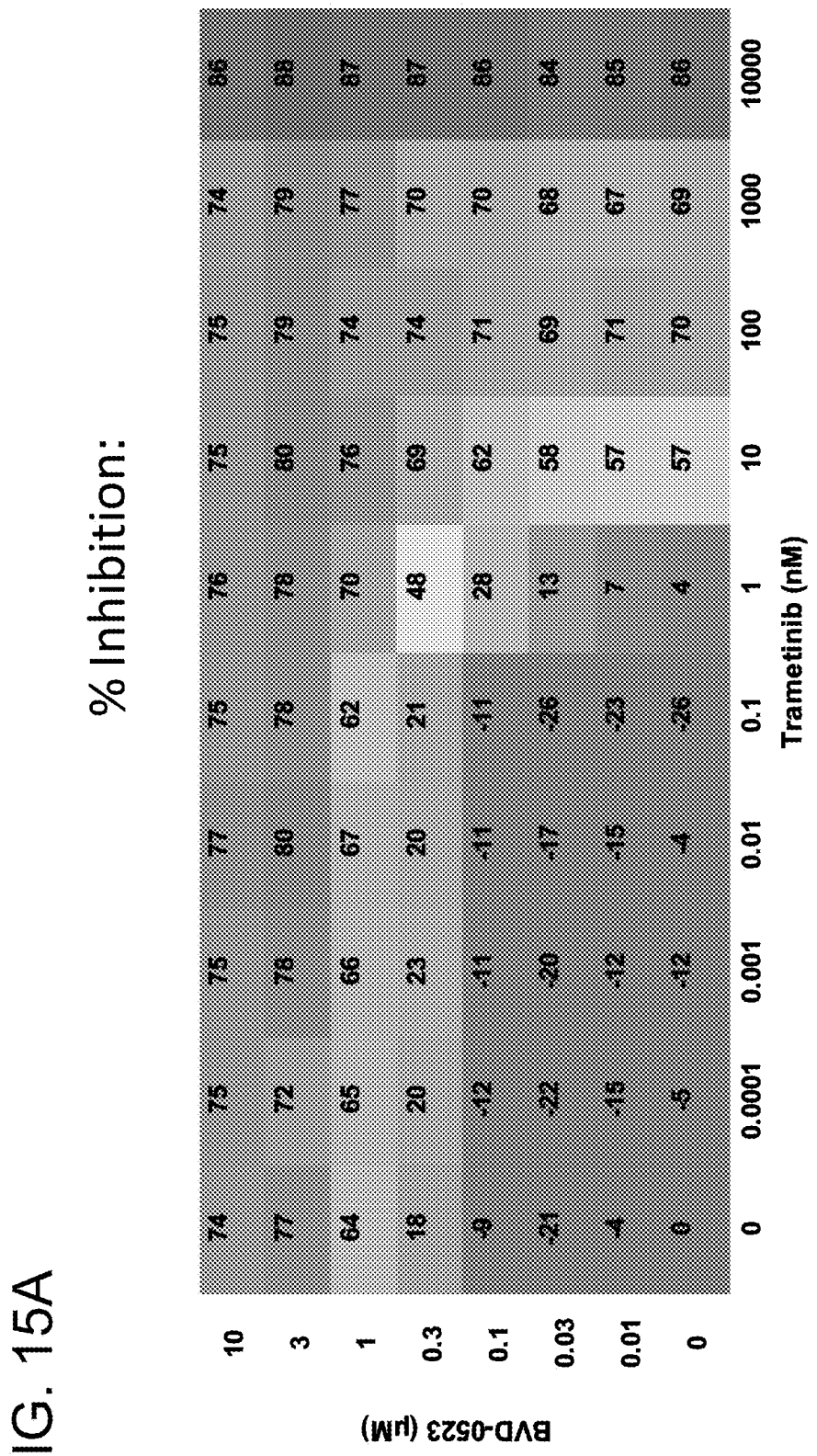

% Inhibition:
BVD-0523 (μM)
10
3
1
0.3
0.1
0.03
0.01
0
74 75 75 77 75 76 75 75 74 86
77 72 78 80 78 78 80 79 79 88
64 65 66 67 62 70 76 74 77 87
18 20 23 20 21 48 69 74 70 87
-9 -12 -11 -11 -11 28 62 71 70 86
-21 -22 -20 -17 -26 13 58 69 68 84
-4 -15 -12 -15 -23 7 57 71 67 85
0 -5 -12 -4 -26 4 57 70 69 86
0 0.0001 0.001 0.01 0.1 1 10 100 1000 10000
Trametinib (nM)

FIG. 15B

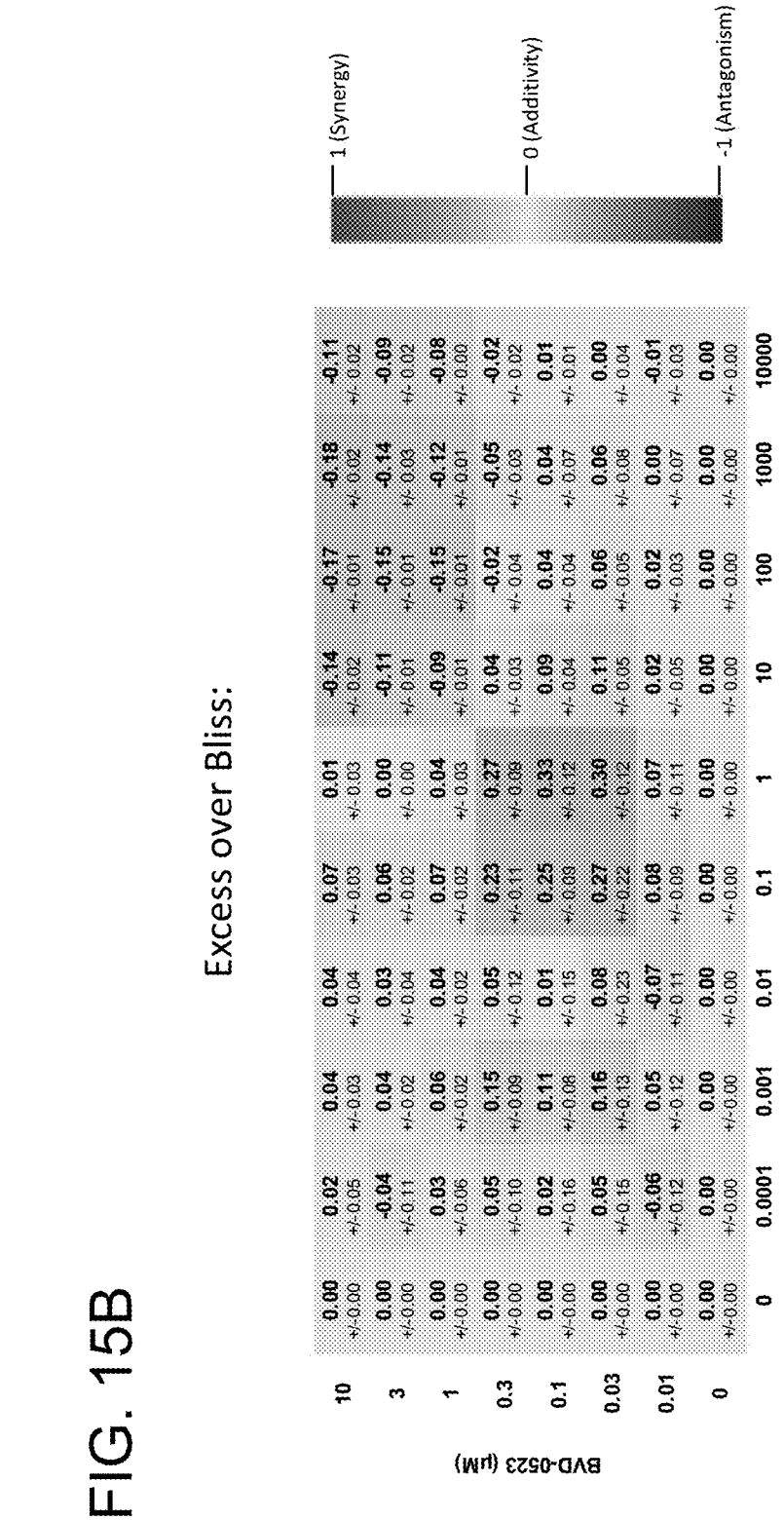

Excess over Bliss:
1 (Synergy)
0 (Additivity)
-1 (Antagonism)
BVD-523 (μM)
10
3
1
0.3
0.1
0.03
0.01
0
0 0.0001 0.001 0.01 0.1 1 10 100 1000 10000
Trametinib (nM)
0.00 +/-0.00 0.02 +/-0.05 0.04 +/-0.03 0.04 +/-0.04 0.07 +/-0.03 0.01 +/-0.03 -0.14 +/-0.02 -0.17 +/-0.01 -0.18 +/-0.02 -0.11 +/-0.02
0.00 +/-0.00 -0.04 +/-0.11 0.04 +/-0.02 0.03 +/-0.04 0.06 +/-0.02 0.00 +/-0.00 -0.11 +/-0.01 -0.15 +/-0.01 -0.14 +/-0.03 -0.09 +/-0.02
0.00 +/-0.00 0.03 +/-0.06 0.06 +/-0.02 0.04 +/-0.02 0.07 +/-0.02 0.04 +/-0.03 -0.09 +/-0.01 -0.15 +/-0.01 -0.12 +/-0.01 -0.08 +/-0.00
0.00 +/-0.00 0.05 +/-0.10 0.15 +/-0.09 0.05 +/-0.12 0.23 +/-0.11 0.27 +/-0.08 0.04 +/-0.03 -0.02 +/-0.04 -0.05 +/-0.03 -0.02 +/-0.02
0.00 +/-0.00 0.02 +/-0.16 0.11 +/-0.08 0.01 +/-0.15 0.25 +/-0.08 0.33 +/-0.12 0.09 +/-0.04 0.04 +/-0.04 0.04 +/-0.07 0.01 +/-0.01
0.00 +/-0.00 0.05 +/-0.15 0.16 +/-0.13 0.08 +/-0.23 0.27 +/-0.22 0.30 +/-0.12 0.11 +/-0.05 0.06 +/-0.05 0.06 +/-0.08 0.00 +/-0.04
0.00 +/-0.00 -0.06 +/-0.12 0.05 +/-0.12 -0.07 +/-0.11 0.08 +/-0.09 0.07 +/-0.11 0.02 +/-0.05 0.02 +/-0.03 0.00 +/-0.07 -0.01 +/-0.03
0.00 +/-0.00 0.00 +/-0.00 0.00 +/-0.00 0.00 +/-0.00 0.00 +/-0.00 0.00 +/-0.00 0.00 +/-0.00 0.00 +/-0.00 0.00 +/-0.00

FIG. 15C

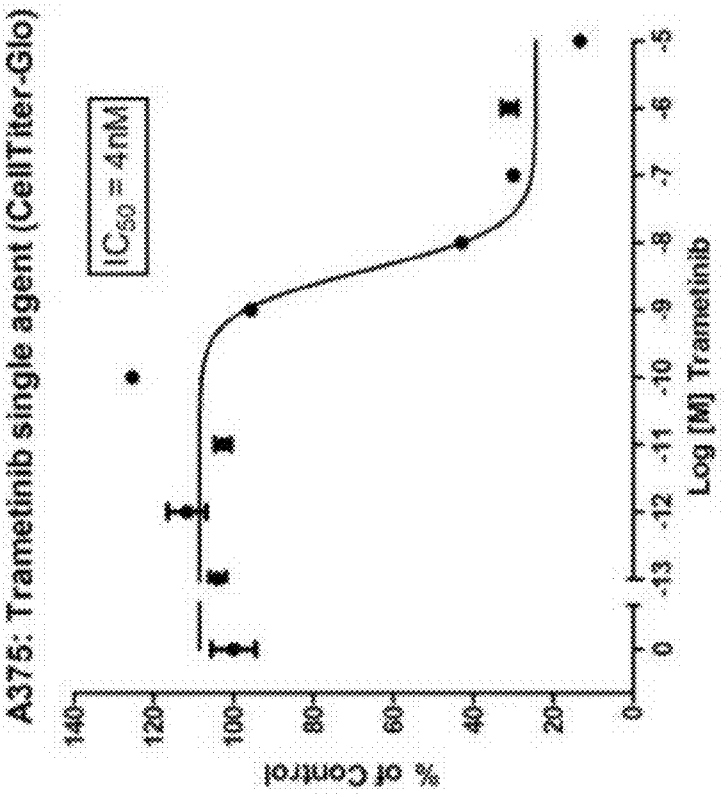


FIG. 15D

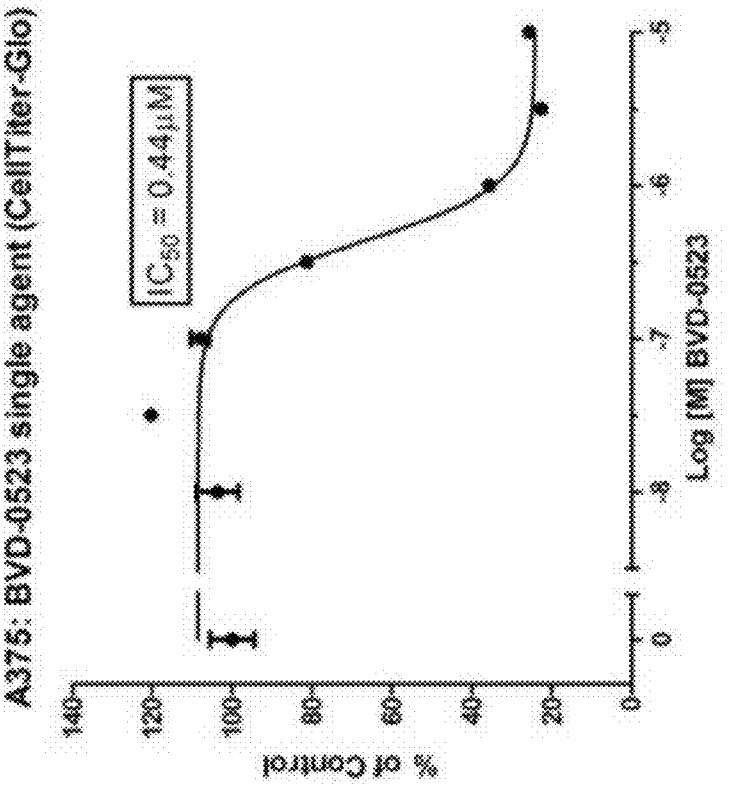


FIG. 15E

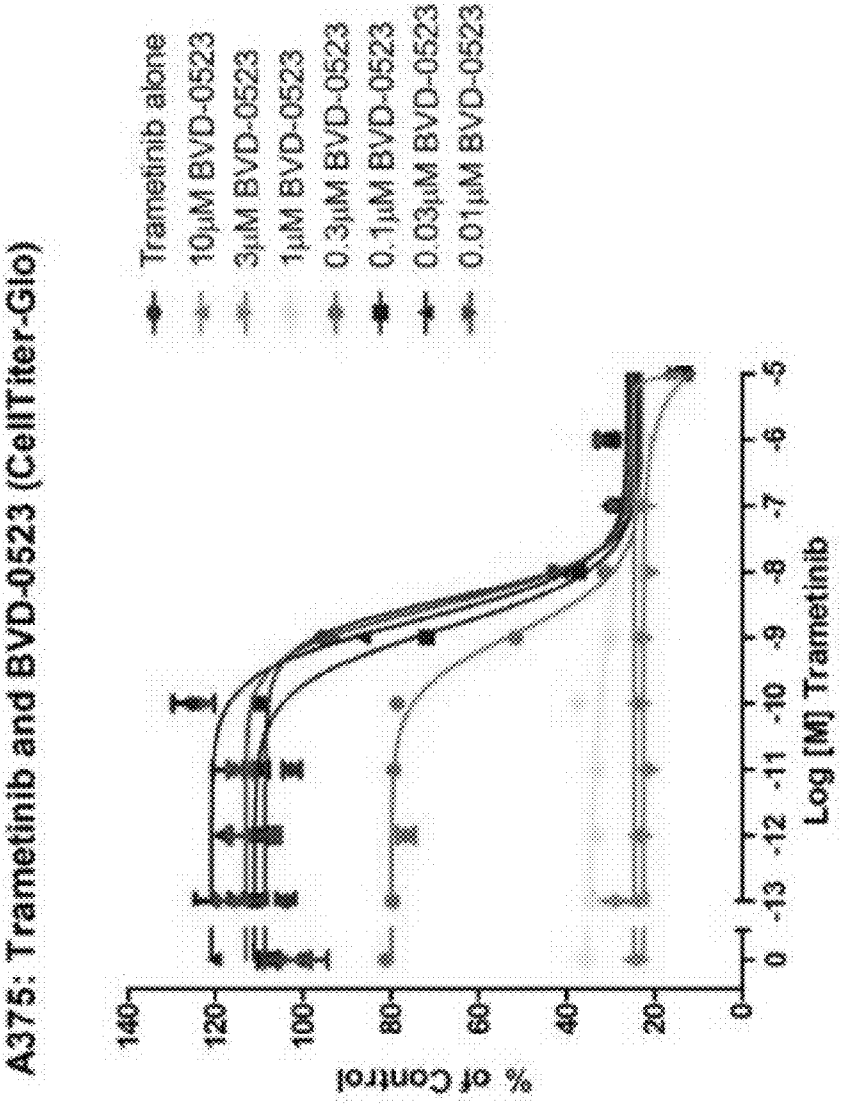

A375: Trametinib and BVD-0523 (CellTiter-Glo)
Trametinib alone
10μM BVD-0523
3μM BVD-0523
1μM BVD-0523
0.3μM BVD-0523
0.1μM BVD-0523
0.03μM BVD-0523
0.01μM BVD-0523
% of Control
140
120
100
80
60
40
20
0
0
-13
-12
-11
-10
-9
-8
-7
-6
-5
Log [M] Trametinib

FIG. 16A

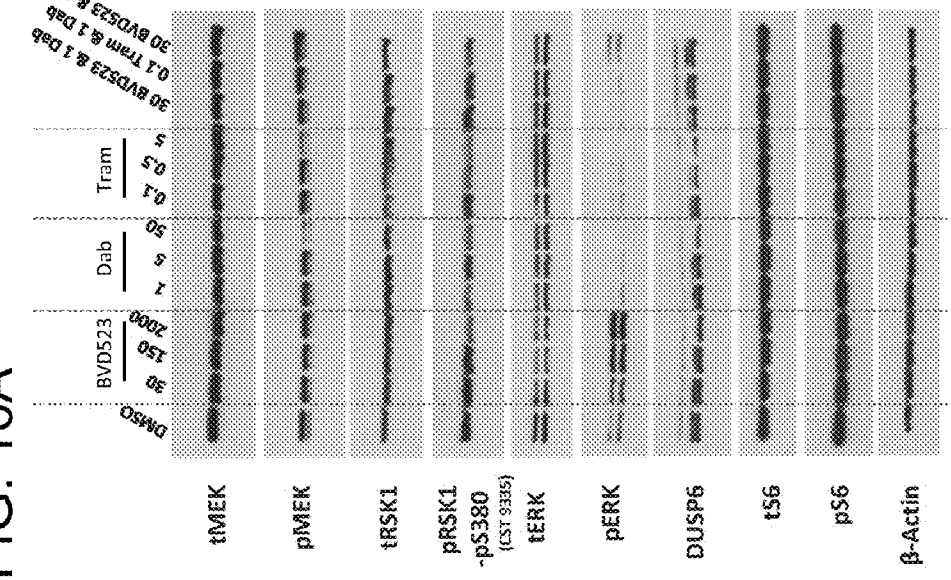


FIG. 16B

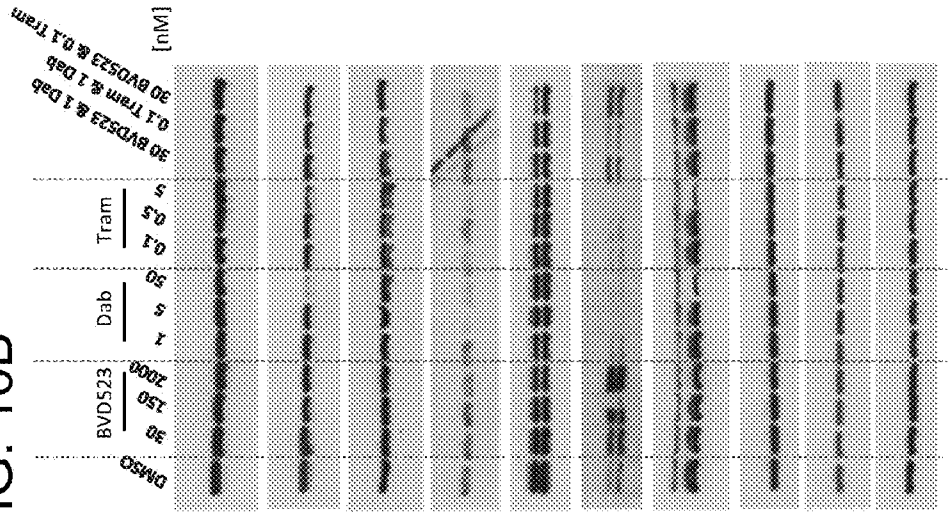


FIG. 16C

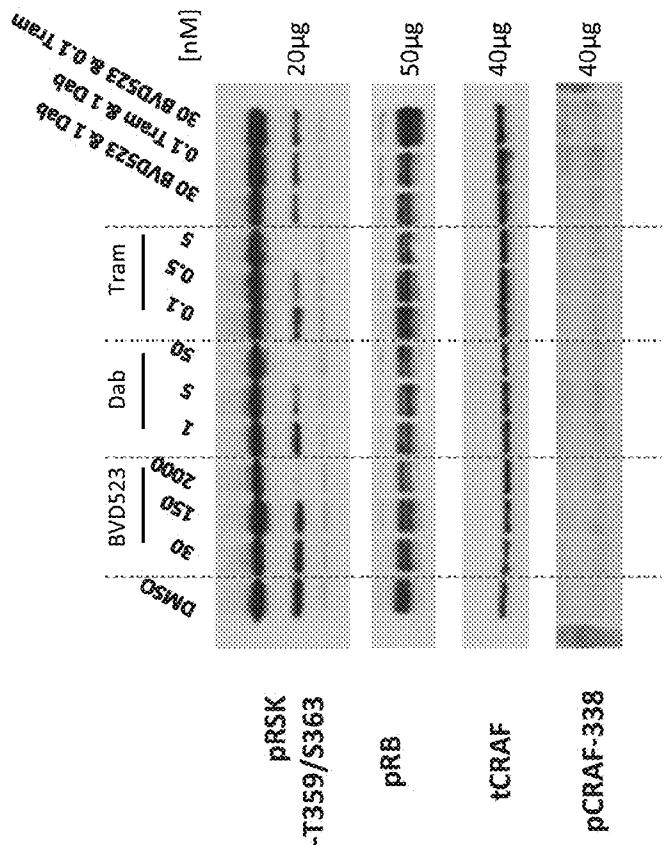


FIG. 16D

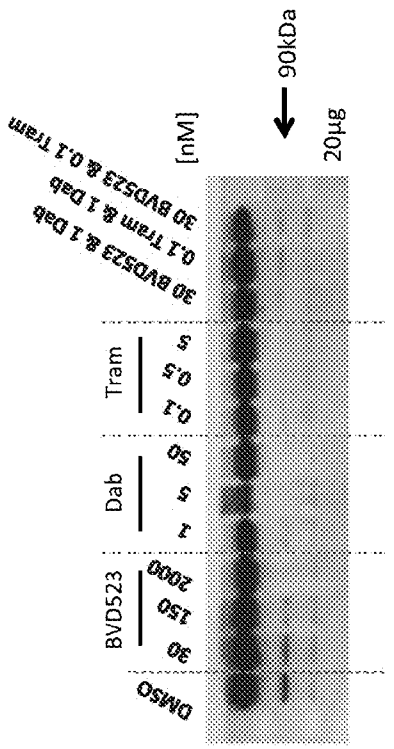


FIG. 17A

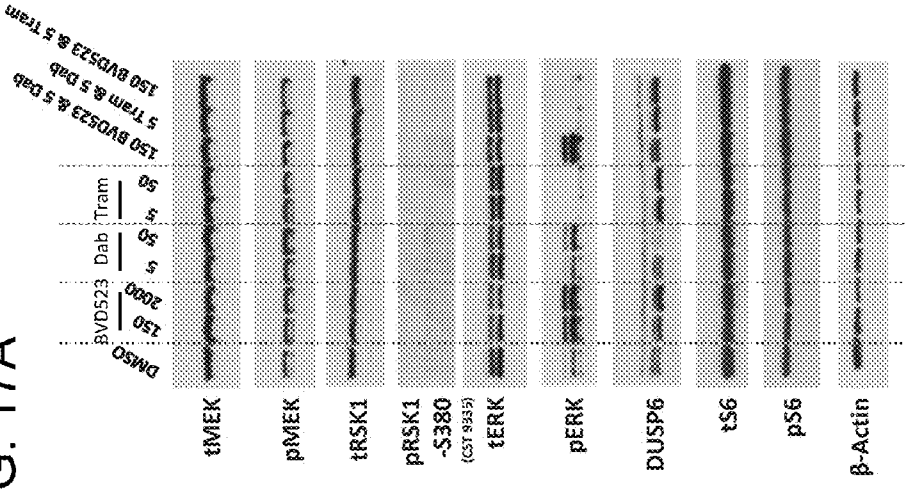


FIG. 17B

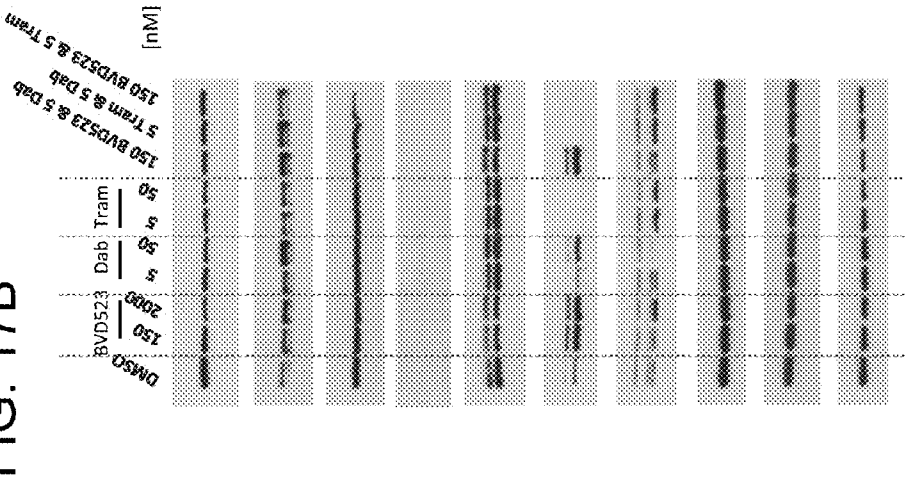


FIG. 17C

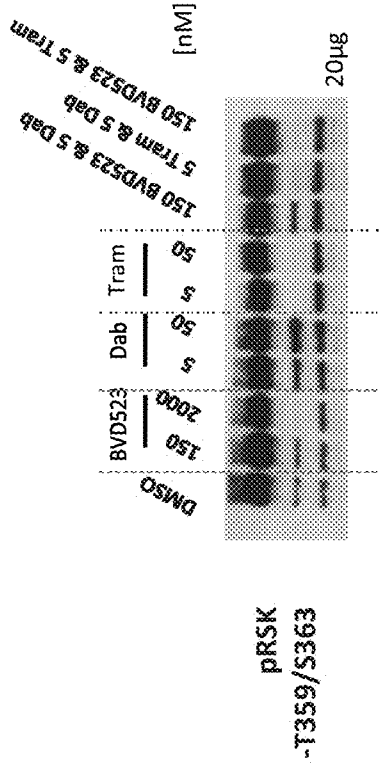


FIG. 17D

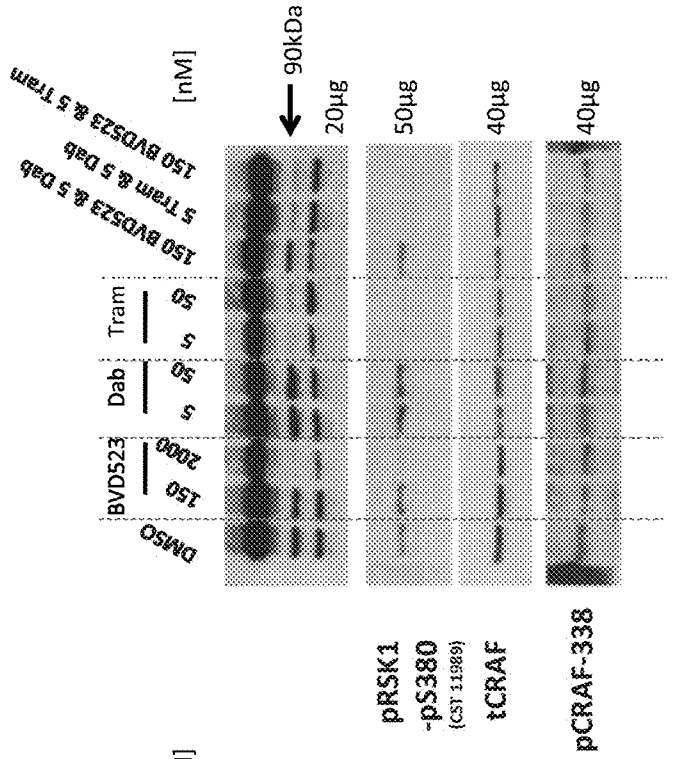


FIG. 18A

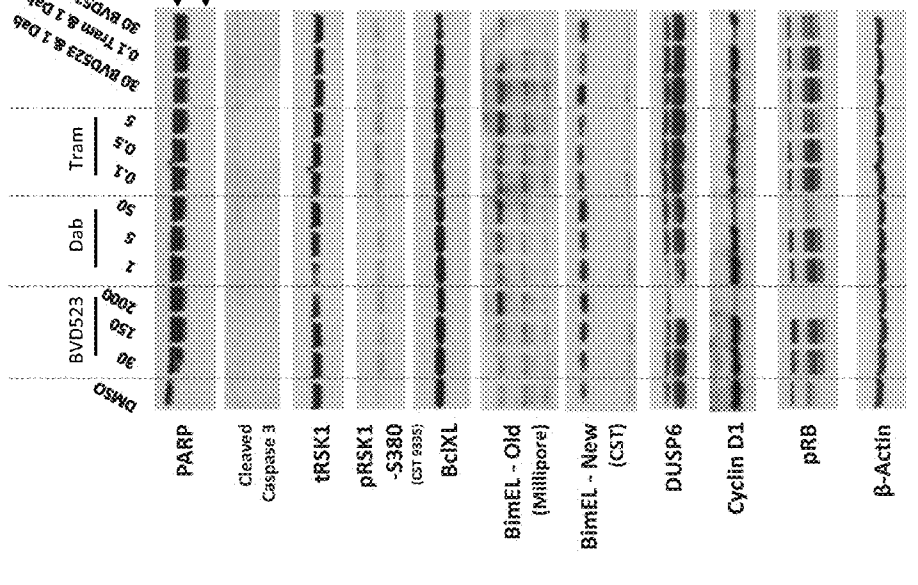


FIG. 18B

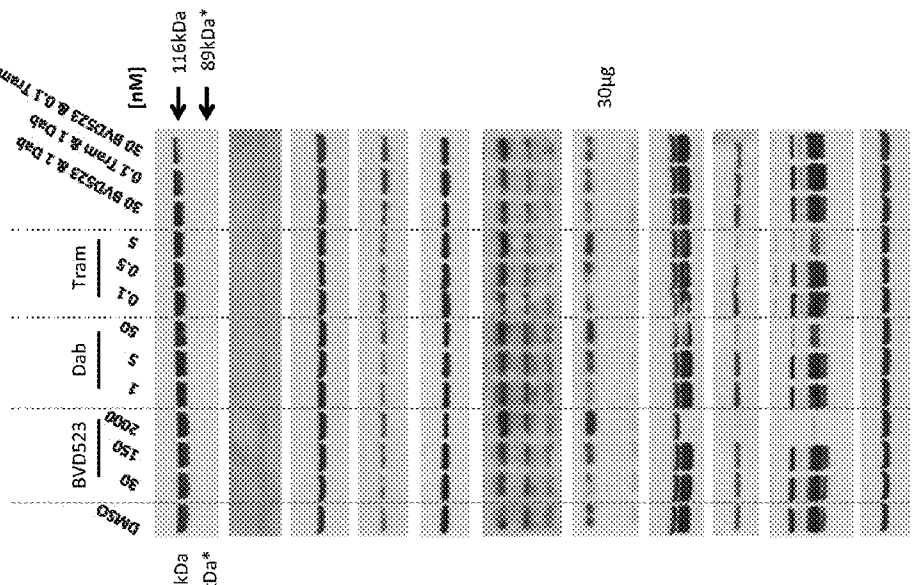


FIG. 18C

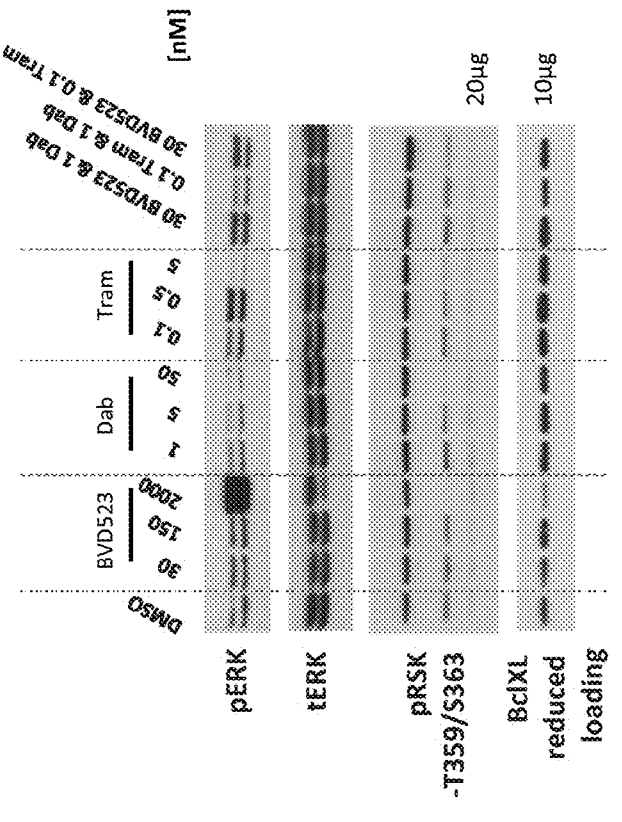


FIG. 18D

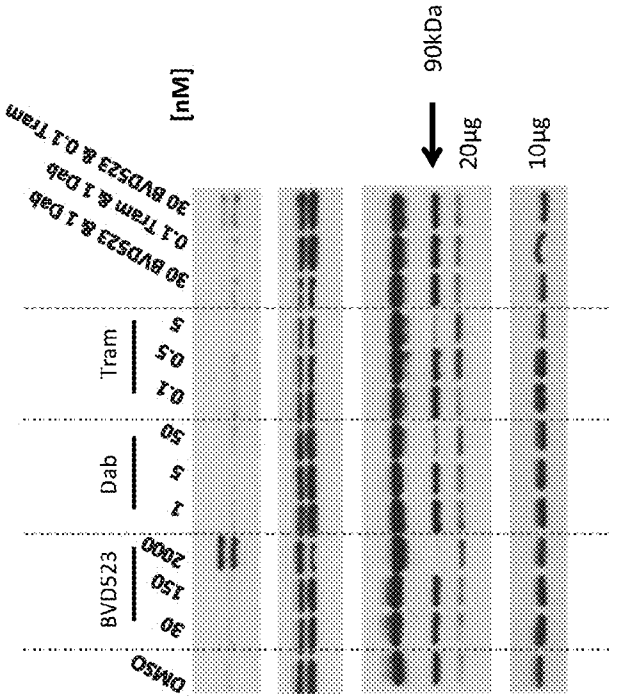


FIG. 19

Resistance Condition	Starting Concentration (nM)	Maintenance Concentration (nM)		
		Month 1	Month 2	Month 3
Dabrafenib_R	5	25	400	3200
Trametinib_R	1	3	40	160
BVD-523_R	160	640	1800	1200
Dabrafenib/Trametinib_R	2.5/0.5	7.5/1.5	28/6	160/30
Dabrafenib/BVD-523_R	2.5/80	10/320	28/900	42/1500
Trametinib/BVD-523_R	0.5/80	2/320	2.5/400	4/600

Resistance Condition	Multiple Above Starting Concentration		
	Month 1	Month 2	Month 3
Dabrafenib_R	5X	80X	640X
Trametinib_R	3X	40X	160X
BVD-523_R	4X	11.25X	7.5X
Dabrafenib/Trametinib_R	3X	11.2X	64X
Dabrafenib/BVD-523_R	4X	11.2X	16.8X
Trametinib/BVD-523_R	4X	5X	8X

Resistance Condition	IC50 Fold Change			
	Dabrafenib	Trametinib	BVD-523	Paclitaxel
Parental	1.00	1.00	1.00	1.00
Trametinib_R	2.51	2.60	1.76	2.53
Dabrafenib_R	3.79	3.28	1.84	6.62
BVD-523_R	748.11	105.20	16.84	2.97
Trametinib + Dabrafenib_R	103.17	38.60	4.22	1.66
Dabrafenib + BVD-523_R	71.87	18.04	4.32	1.35
Trametinib + BVD-523_R	27.51	26.69	3.81	3.96

Resistance Condition	Percent Growth at ~10X Parental IC50			
	Dabrafenib	Trametinib	BVD-523	Paclitaxel
Parental	13.30%	6.80%	0.00%	1.95%
Trametinib_R	33.53%	30.15%	20.02%	13.52%
Dabrafenib_R	36.45%	25.96%	8.21%	9.36%
BVD-523_R	230.03%	172.91%	57.49%	34.02%
Trametinib + Dabrafenib_R	131.10%	125.01%	12.65%	15.44%
Dabrafenib + BVD-523_R	93.55%	71.37%	8.70%	11.41%
Trametinib + BVD-523_R	86.71%	64.03%	27.70%	30.71%
IC50, Parental (nM)	4.11	0.38	186.21	3.65
~10X Parental concentration	30.20	3.00	3019.95	36.48

FIG. 20

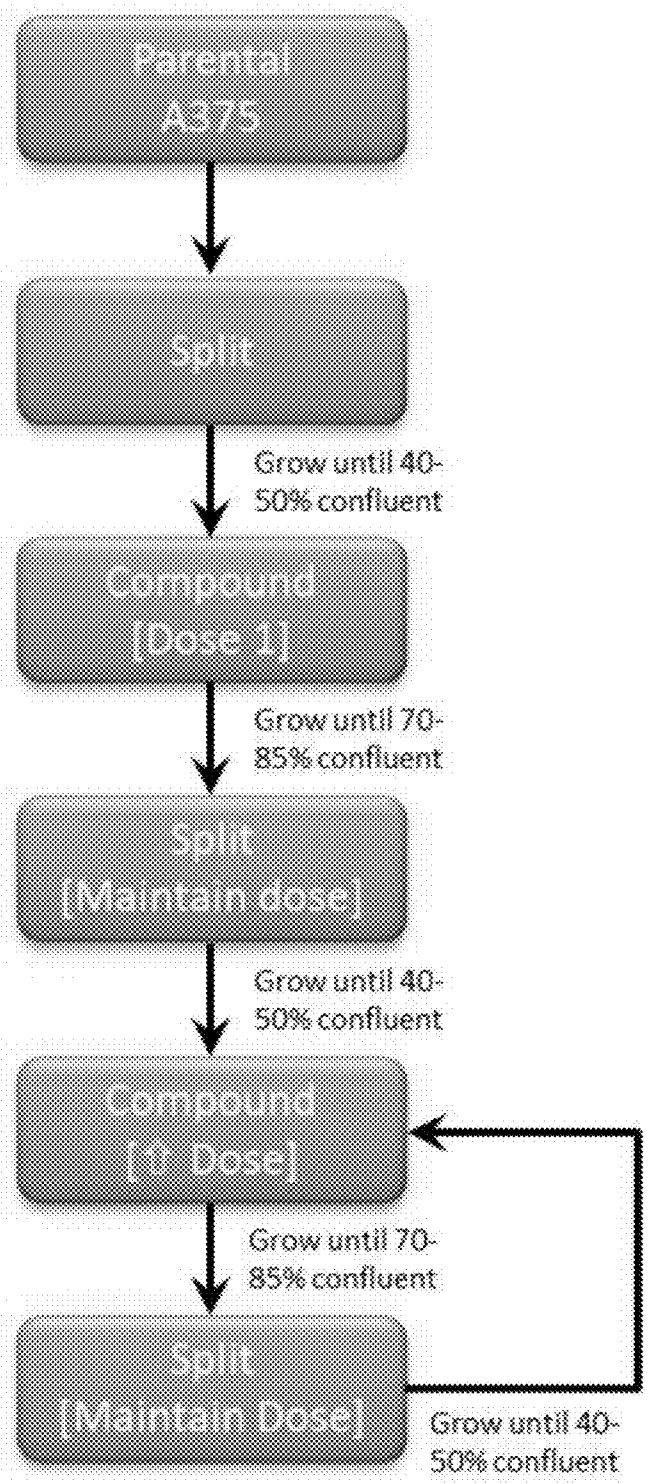

Parental A375
Split
Grow until 40-50% confluent
Compound [Dose 1]
Grow until 70-85% confluent
Split [Maintain dose]
Grow until 40-50% confluent
Compound [n Dose]
Grow until 70-85% confluent
Split [Maintain dose]
Grow until 40-50% confluent

FIG. 21

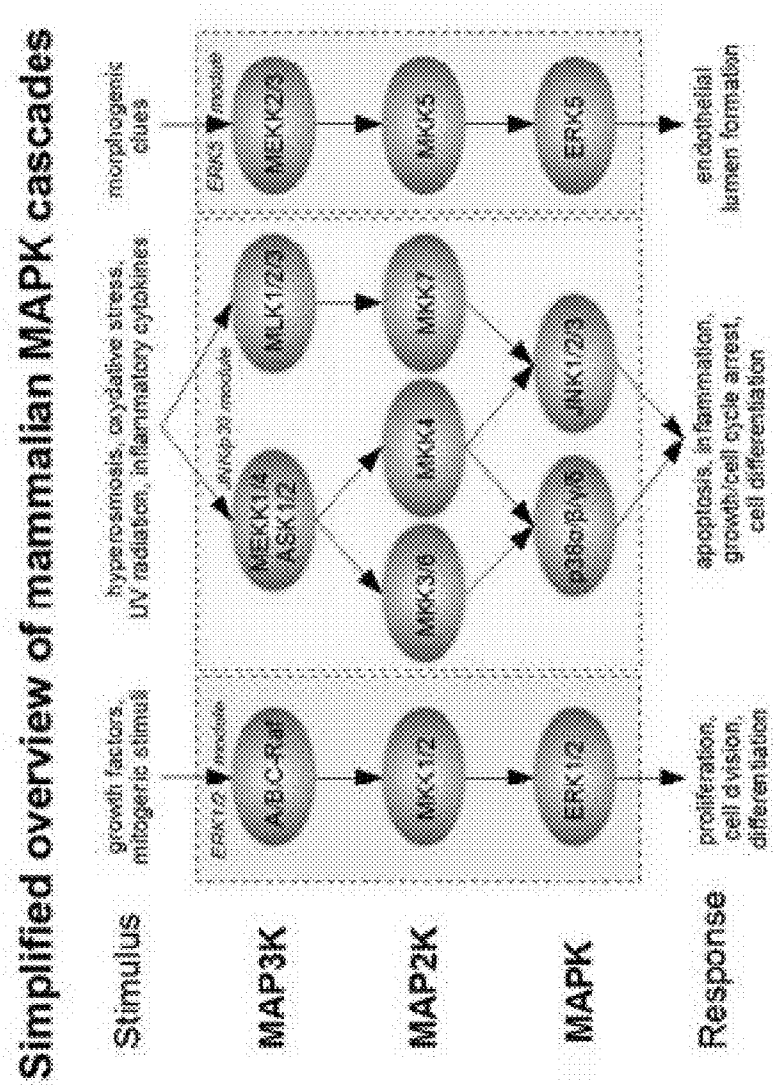

Simplified overview of mammalian MAPK cascades
Stimulus
MAP3K
MAP2K
MAPK
Response
growth factors, mitogenic stimuli
hyperosmosis, oxydative stress, UV radiation, inflammatory cytokines
morphogenic clues
ERK1/2 module
JNK/p38 module
ERK5 module
A-B-C-Raf
MEKK1/4 ASK1/2
MLK1/2/3
MEKK2/3
MKK3/6
MKK4
MKK7
MKK5
ERK1/2
p38α-β1/β2
JNK1/2/3
ERK5
proliferation, cell division, differentiation
apoptosis, inflammation, growth/cell cycle arrest, cell differentiation
endothelial lumen formation

FIG. 22A

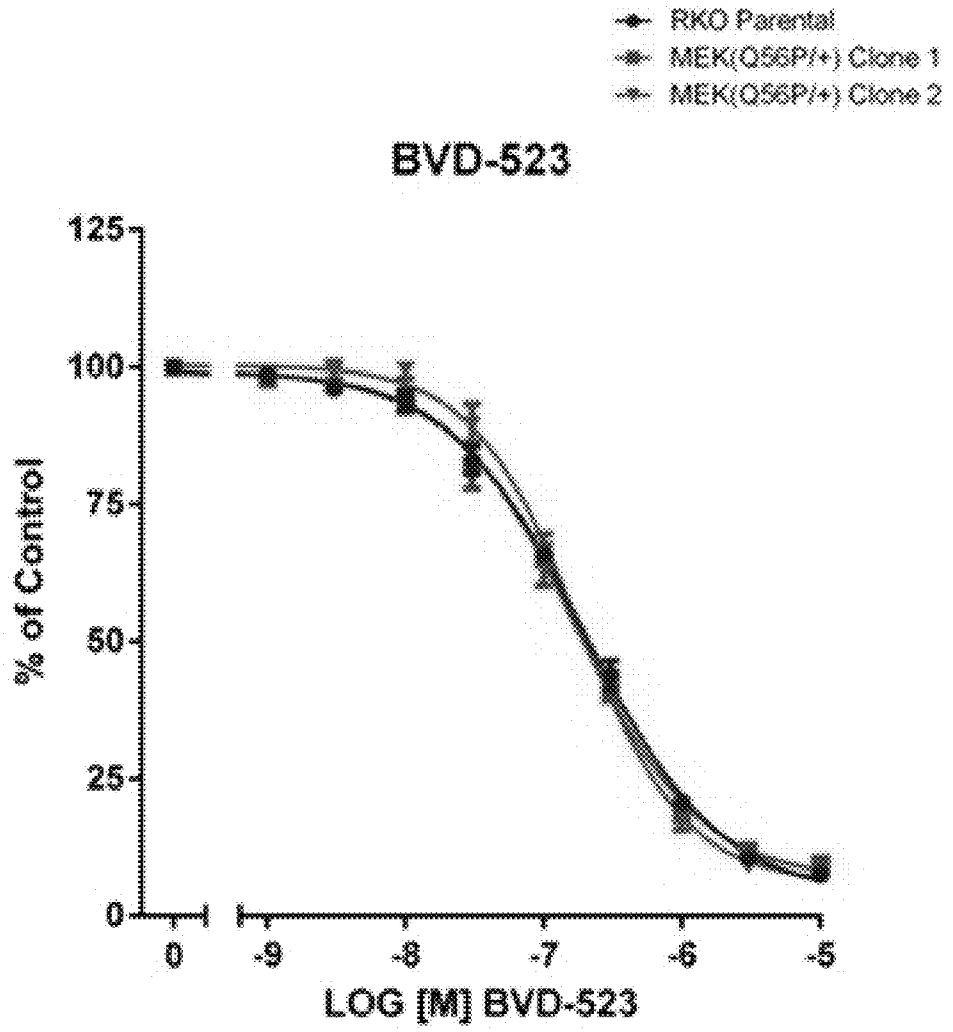

RKO Parental
MEK(Q56P/+) Clone 1
MEK(Q56P/+) Clone 2
BVD-523
125
100
75
50
25
0
% of Control
0
-9
-8
-7
-6
-5
LOG [M] BVD-523

FIG. 22B

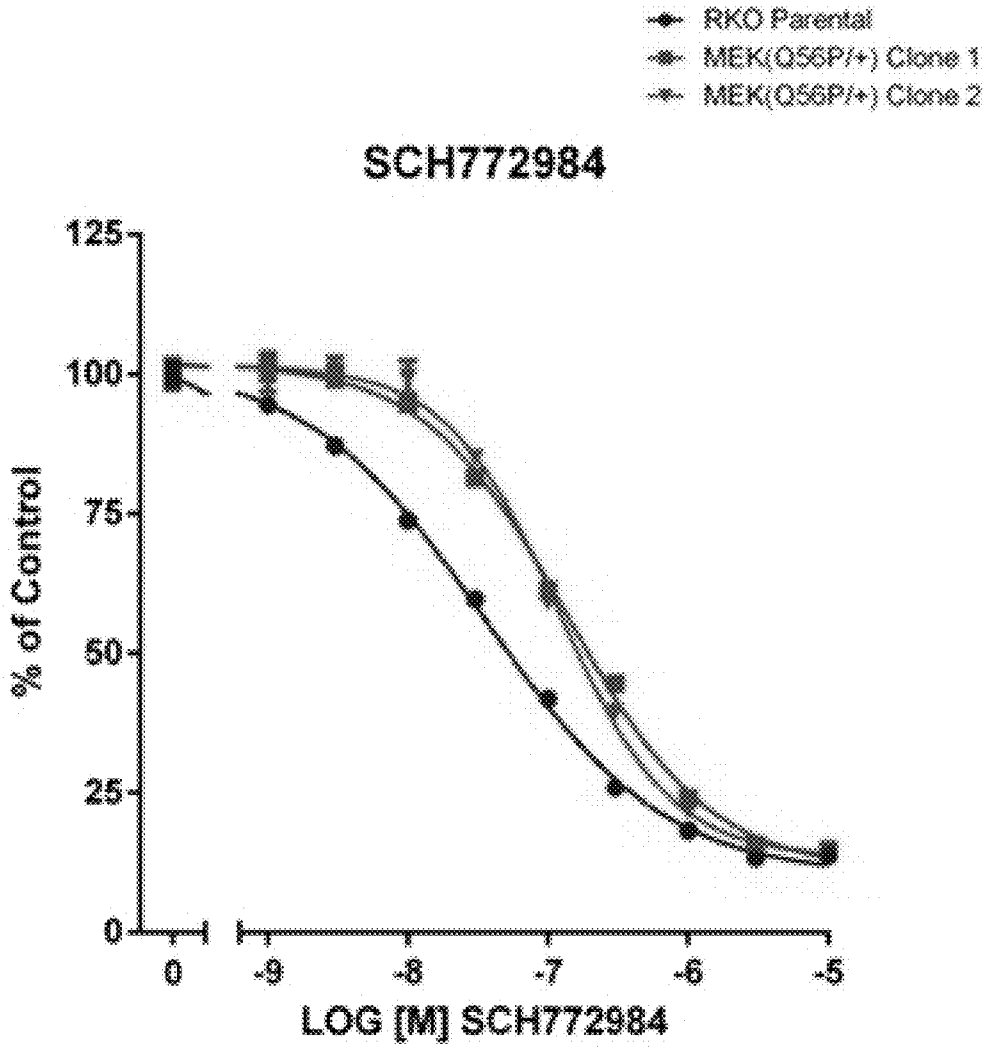

RKO Parental
MEK(Q56P/+) Clone 1
MEK(Q56P/+) Clone 2
SCH772984
125
100
75
50
25
0
% of Control
0
-9
-8
-7
-6
-5
LOG [M] SCH772984

FIG. 22C

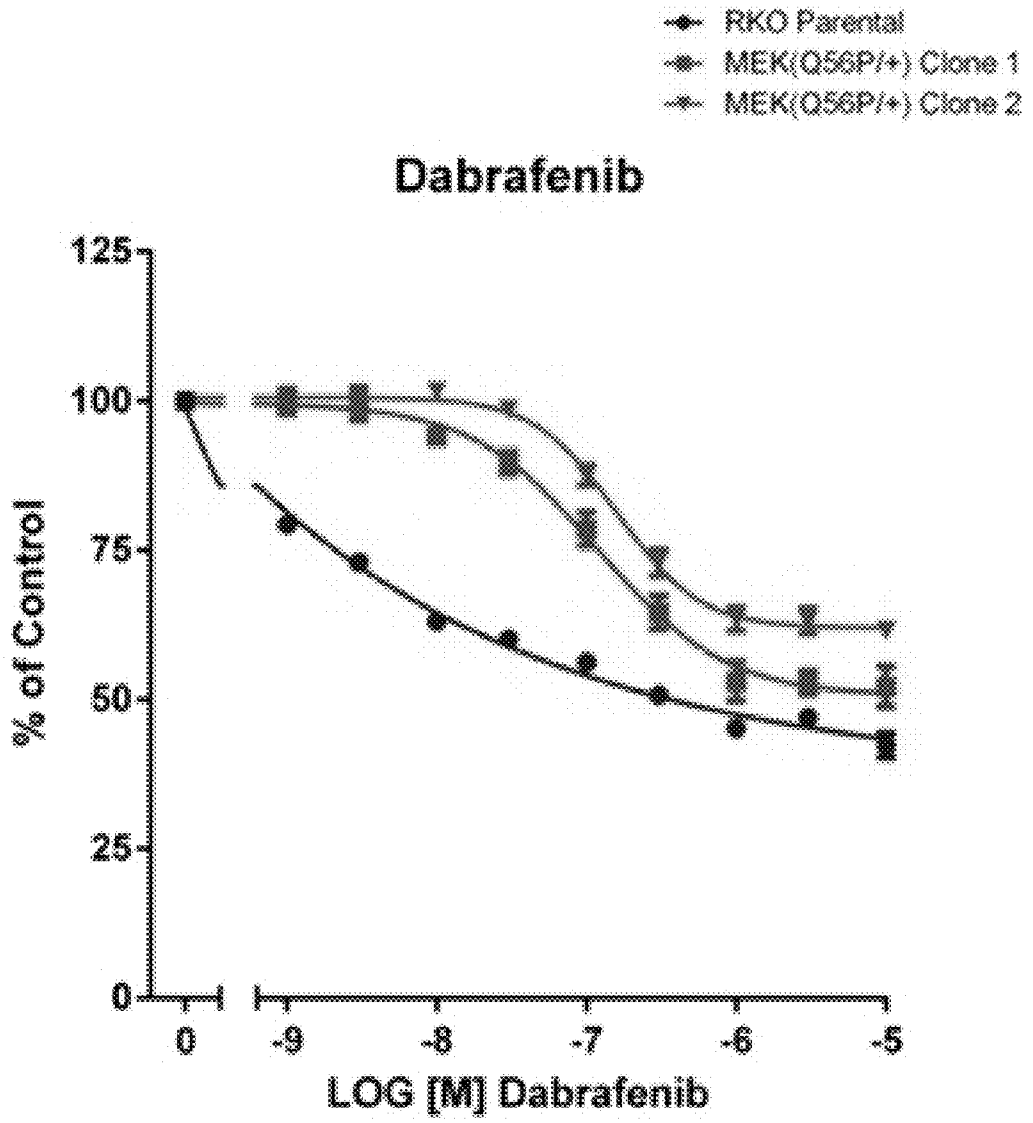

RKO Parental
MEK(Q56P/+) Clone 1
MEK(Q56P/+) Clone 2
Dabrafenib
125
100
75
50
25
0
% of Control
0
-9
-8
-7
-6
-5
LOG [M] Dabrafenib

FIG. 22D

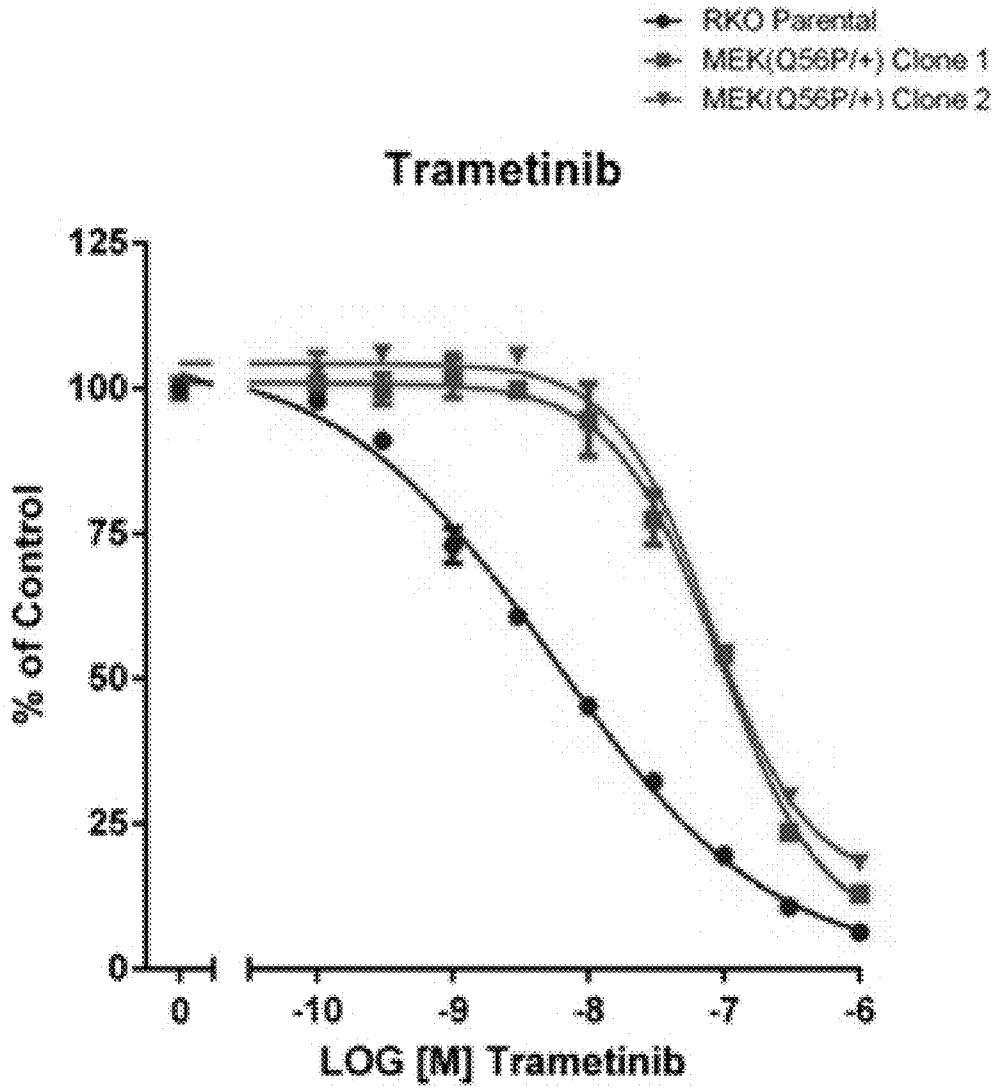

RKO Parental
MEK(Q56P/+) Clone 1
MEK(Q56P/+) Clone 2
Trametinib
125
100
75
50
25
0
% of Control
0
-10
-9
-8
-7
-6
LOG [M] Trametinib

FIG. 22E

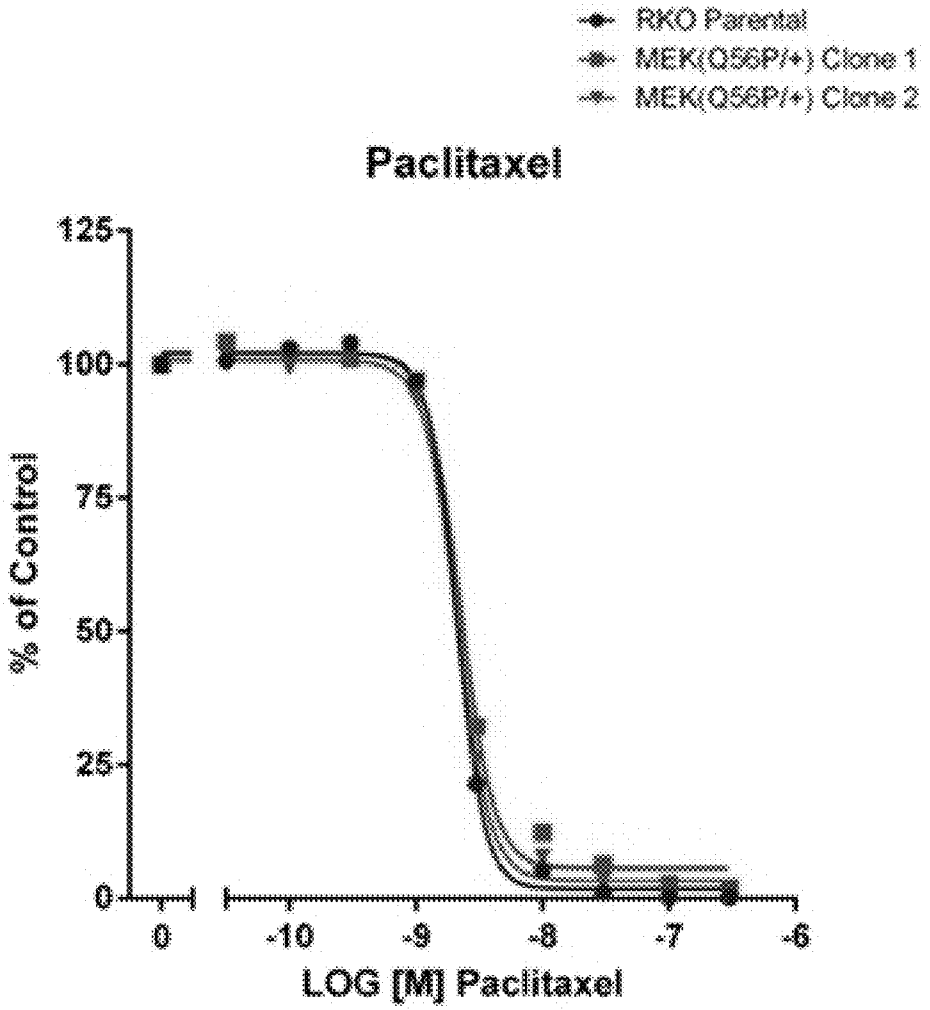

RKO Parental
MEK(Q56P/+) Clone 1
MEK(Q56P/+) Clone 2
Paclitaxel
125
100
75
50
25
0
% of Control
0
-10
-9
-8
-7
-6
LOG [M] Paclitaxel

FIG. 23A

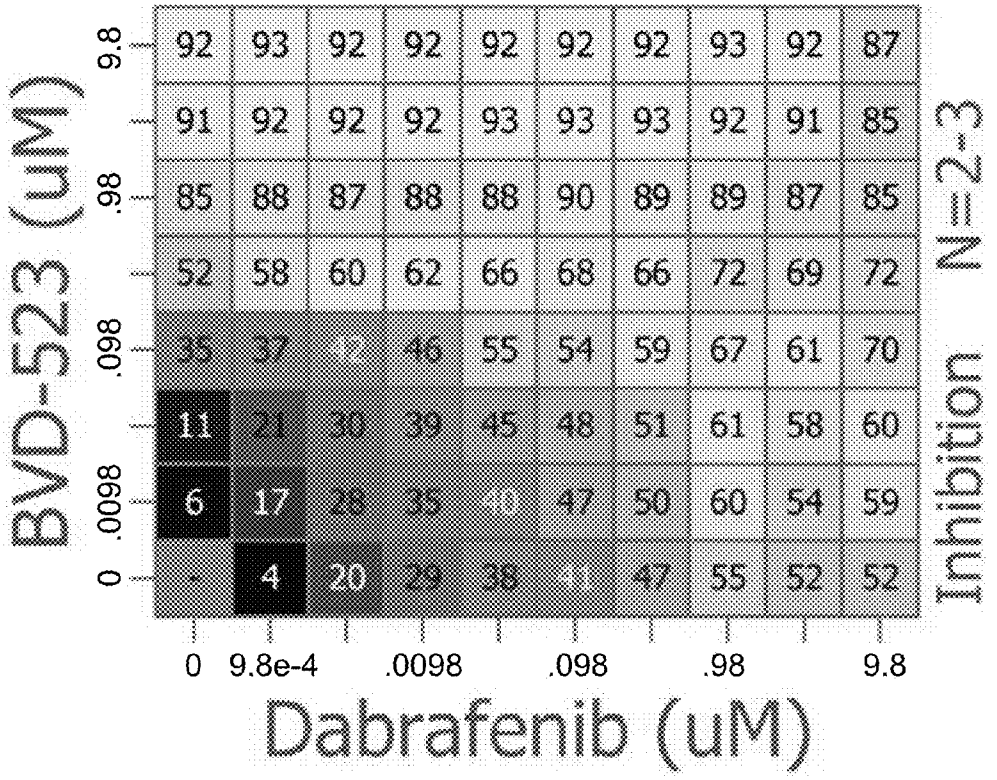

BVD-523 (uM)
9.8
.98
.098
.0098
0
92 93 92 92 92 92 92 93 92 87
91 92 92 92 93 93 93 92 91 85
85 88 87 88 88 90 89 89 87 85
52 58 60 62 66 68 66 72 69 72
35 37 46 55 54 59 67 61 70
11 21 30 39 45 48 51 61 58 60
6 17 28 35 47 50 60 54 59
4 20 29 38 47 55 52 52
Inhibition N=2-3
0
9.8e-4
.0098
.098
.98
9.8
Dabrafenib (uM)

FIG. 23B

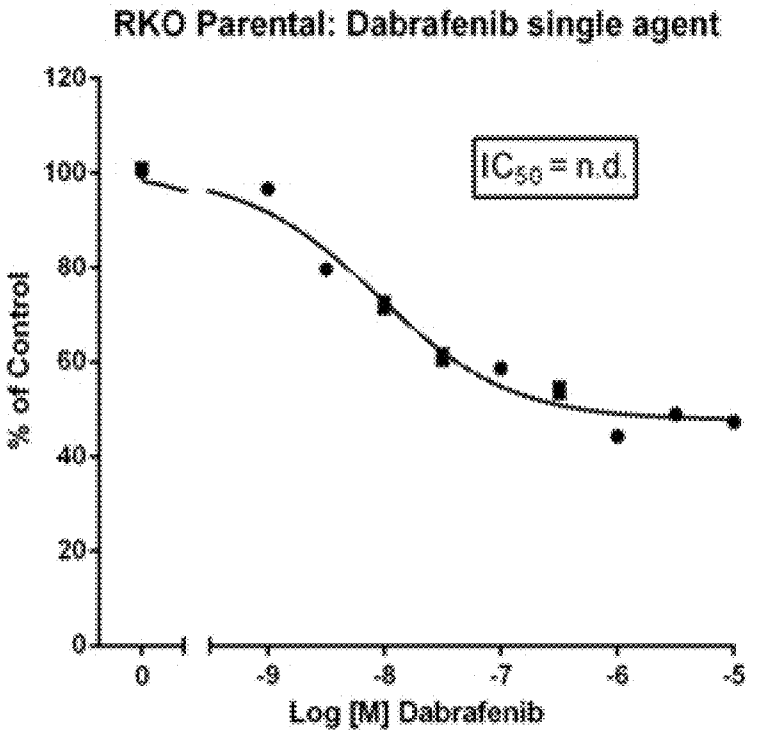


FIG. 23C

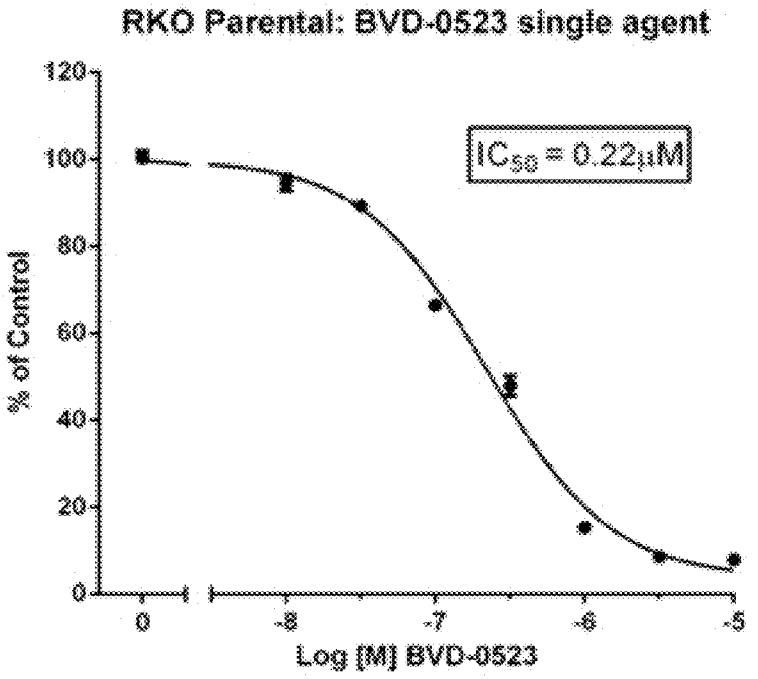


FIG. 23E

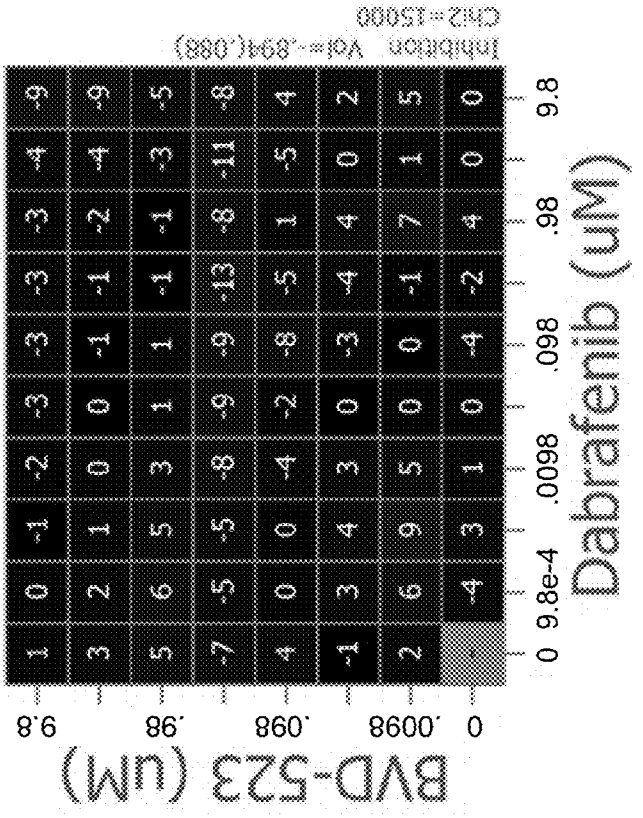


FIG. 23D

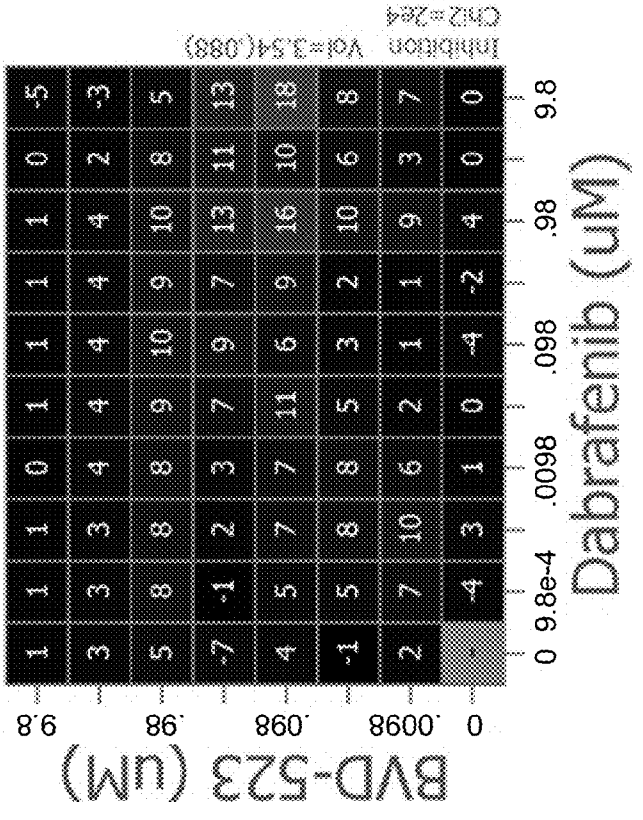


FIG. 23F

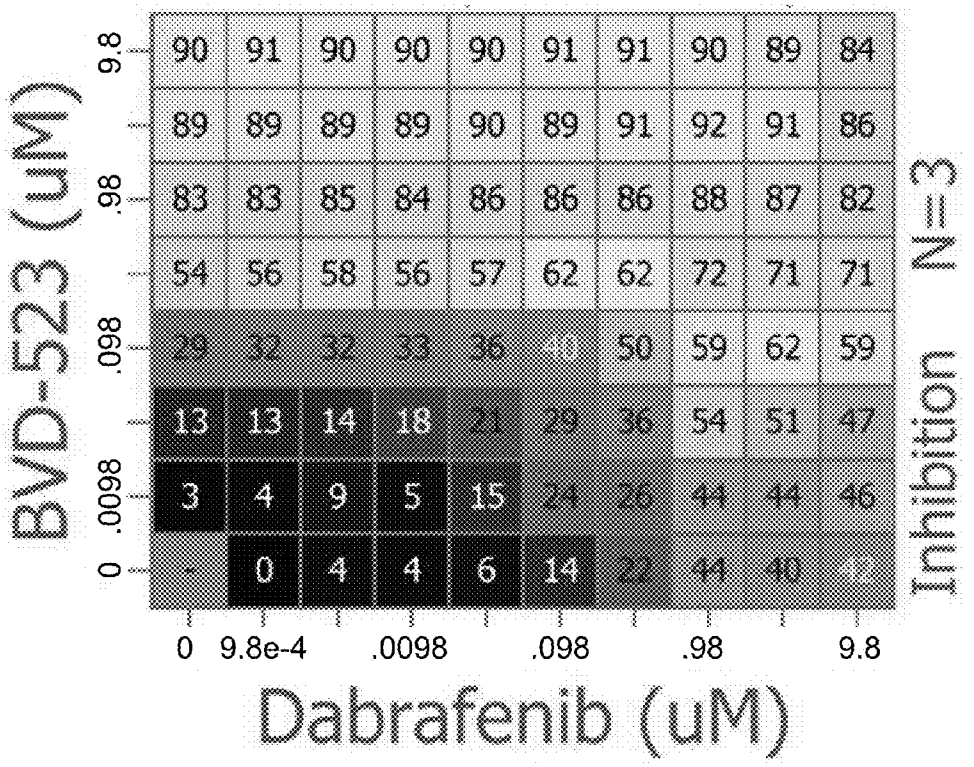

BVD-523 (uM)
9.8
.98
.098
.0098
0
90 91 90 90 90 91 91 90 89 84
89 89 89 89 90 89 91 92 91 86
83 83 85 84 86 86 86 88 87 82
54 56 58 56 57 62 62 72 71 71
29 32 32 33 36 40 50 59 62 59
13 13 14 18 21 29 36 54 51 47
3 4 9 5 15 24 26 44 44 46
- 0 4 4 6 14 22 44 40
0 9.8e-4 .0098 .098 .98 9.8
Dabrafenib (uM)
Inhibition N=3

FIG. 23G

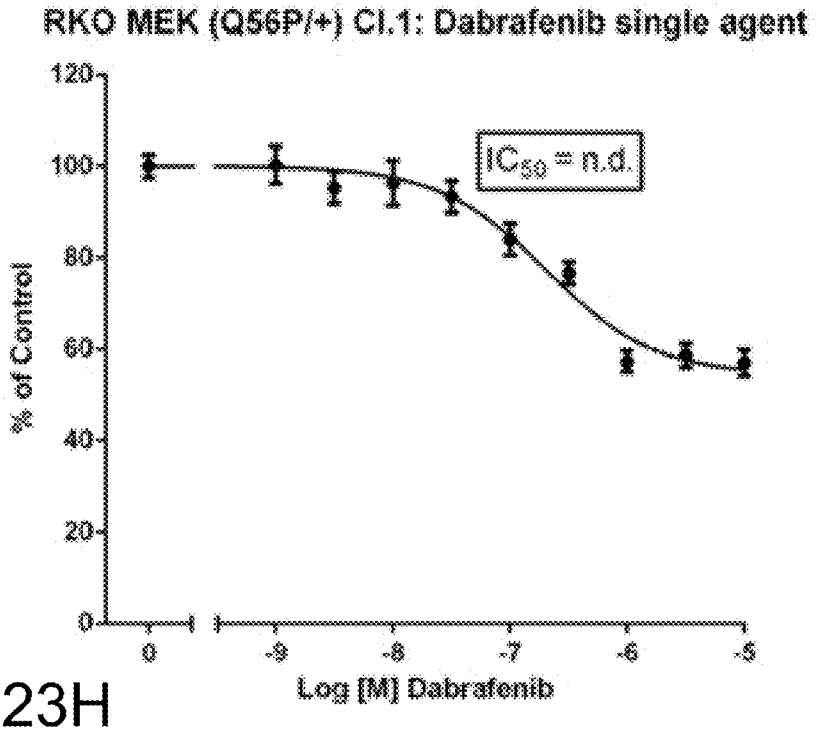


FIG. 23H

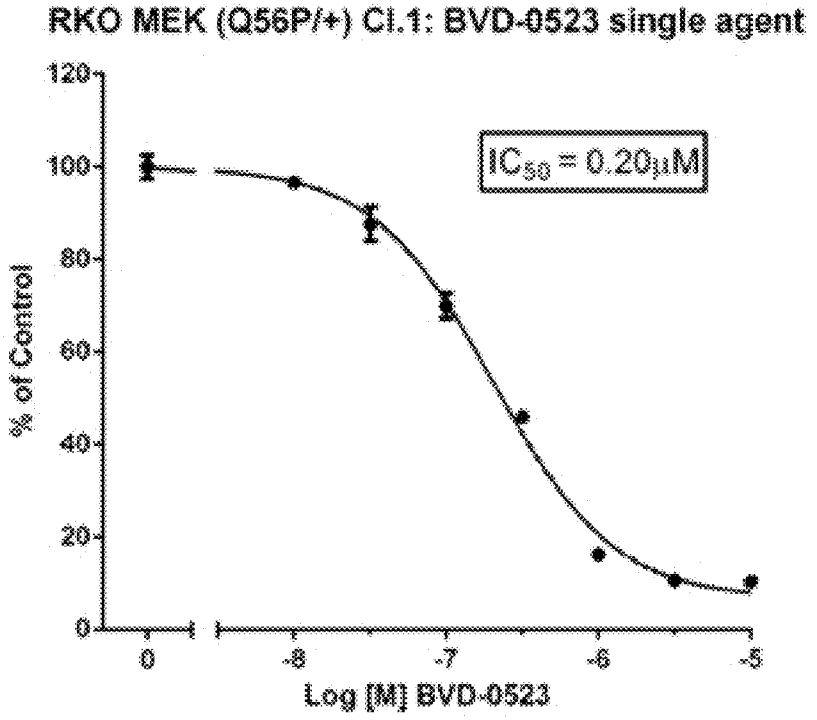


FIG. 23J

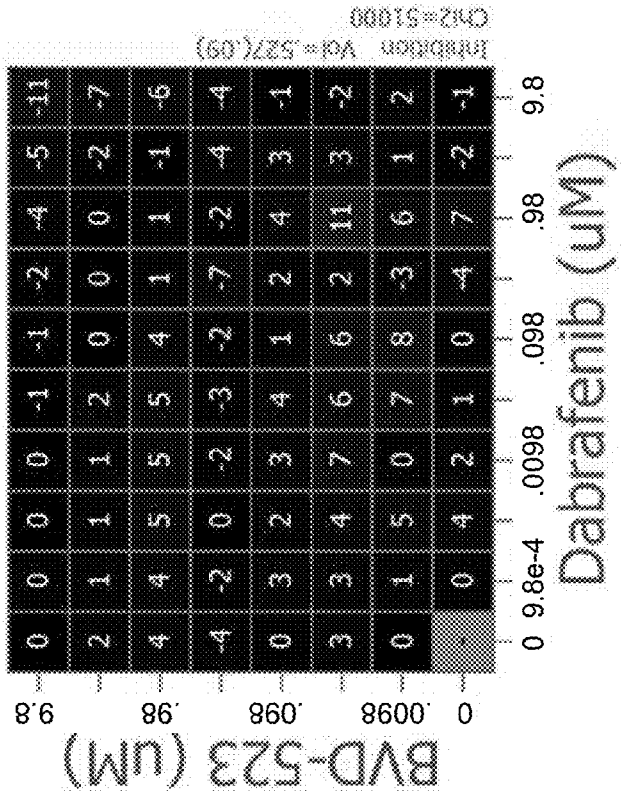


FIG. 23I

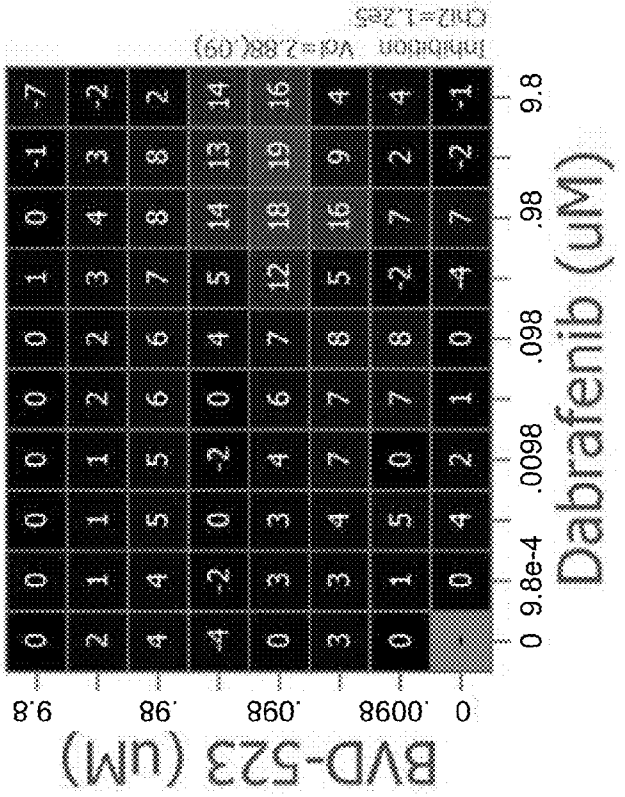


FIG. 23K

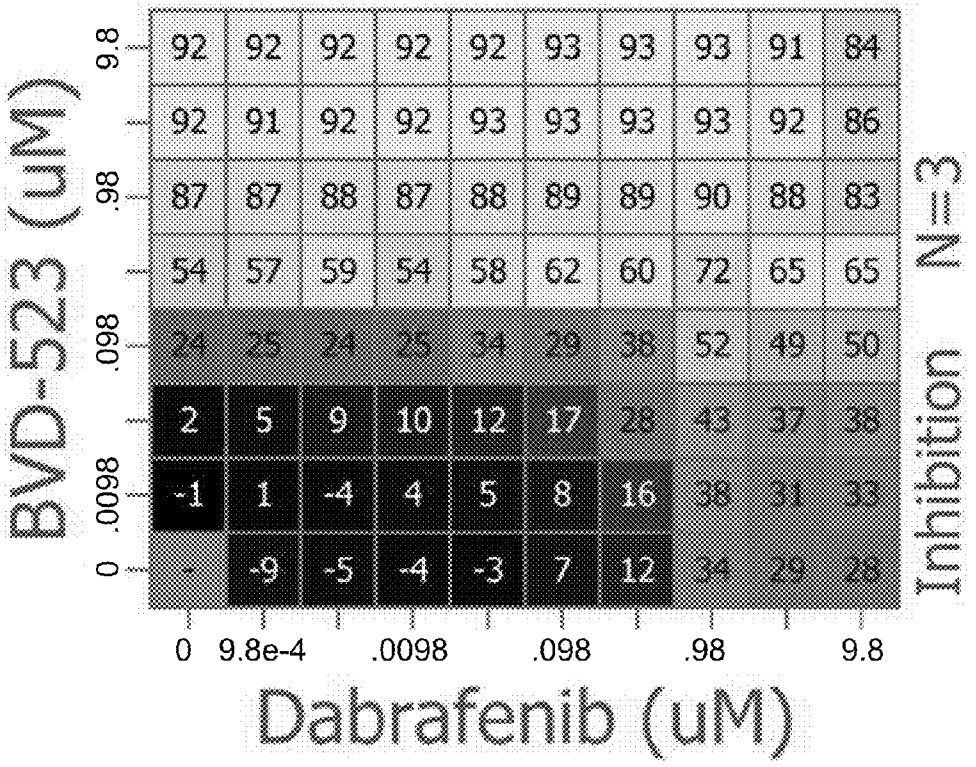

BVD-523 (uM)
9.8
.98
.098
.0098
0
92 92 92 92 92 93 93 93 91 84
92 91 92 92 93 93 93 93 92 86
87 87 88 87 88 89 89 90 88 83
54 57 59 54 58 62 60 72 65 65
24 25 24 25 34 29 38 52 49 50
2 5 9 10 12 17 28 43 37 38
-1 1 -4 4 5 8 16 38 31 33
- -9 -5 -4 -3 7 12 34 29 28
0
9.8e-4
.0098
.098
.98
9.8
Dabrafenib (uM)
Inhibition N=3

FIG. 23L

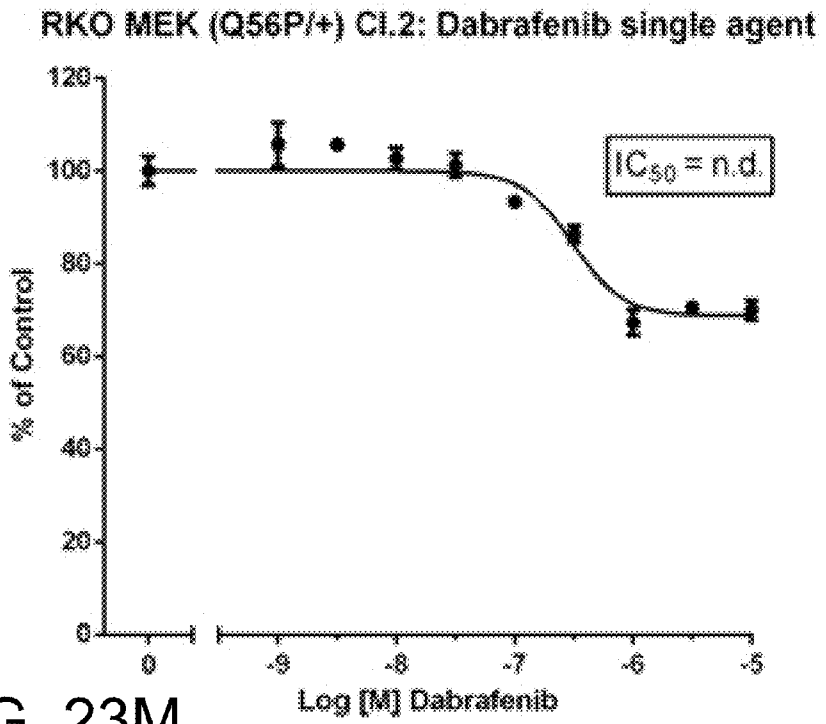


FIG. 23M

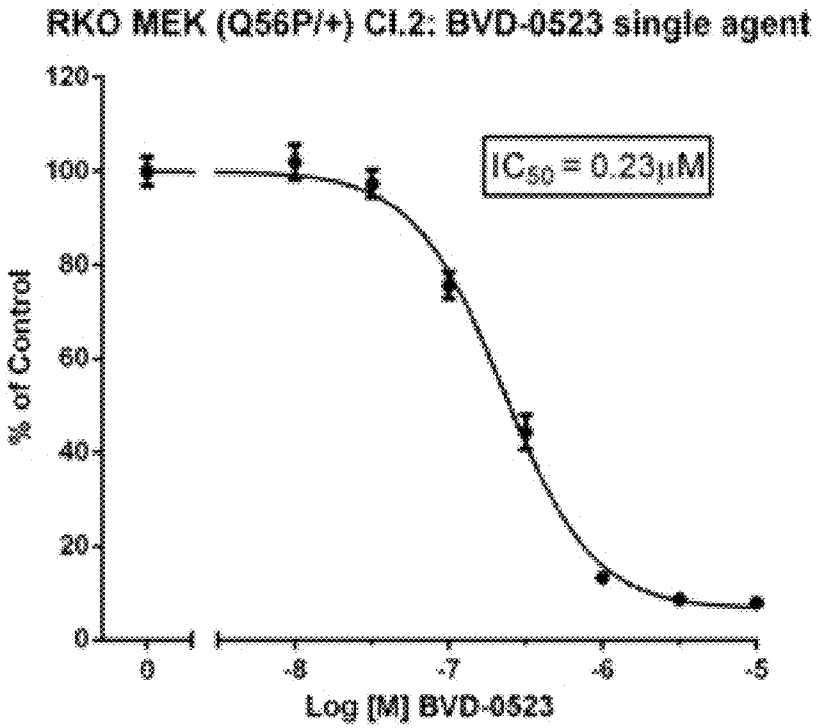


FIG. 23O

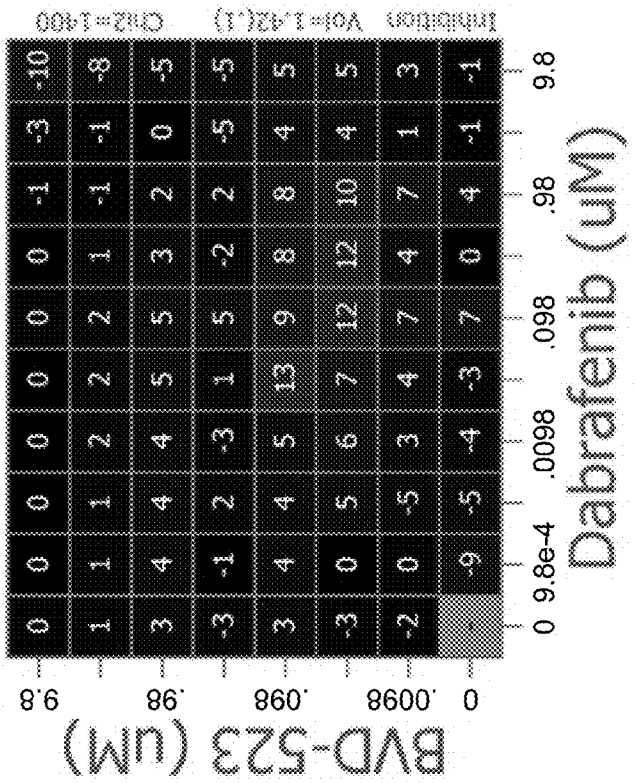


FIG. 23N

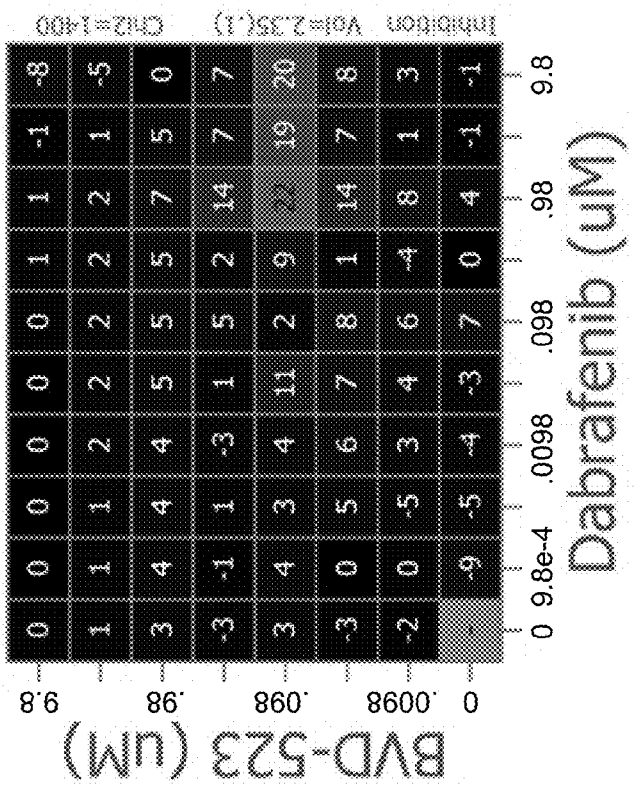


FIG. 24A

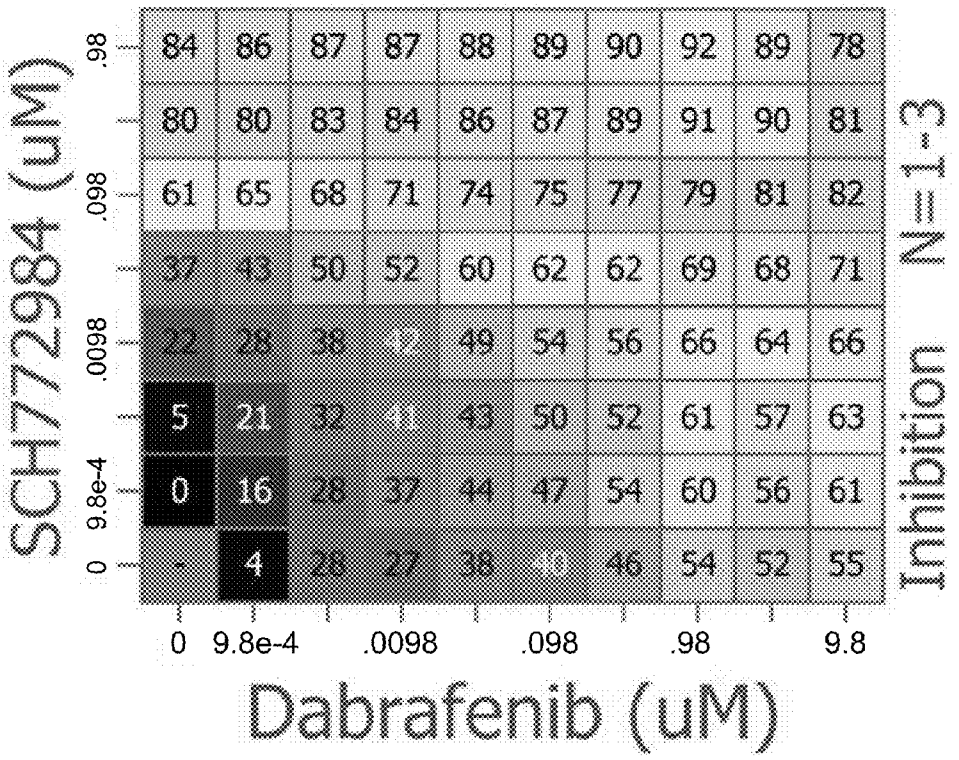

SCH772984 (uM)
.98
.098
.0098
9.8e-4
0
84 86 87 87 88 89 90 92 89 78
80 80 83 84 86 87 89 91 90 81
61 65 68 71 74 75 77 79 81 82
37 43 50 52 60 62 62 69 68 71
22 28 38 49 54 56 66 64 66
5 21 32 43 50 52 61 57 63
0 16 28 37 44 47 54 60 56 61
4 26 27 38 46 54 52 55
0 9.8e-4 .0098 .098 .98 9.8
Dabrafenib (uM)
Inhibition N=1-3

FIG. 24B

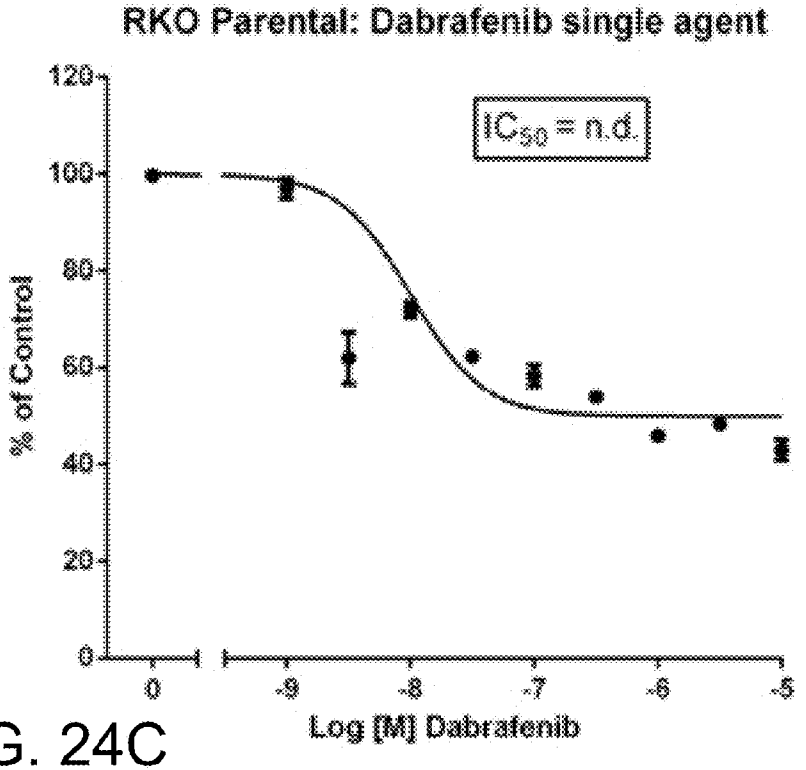


FIG. 24C

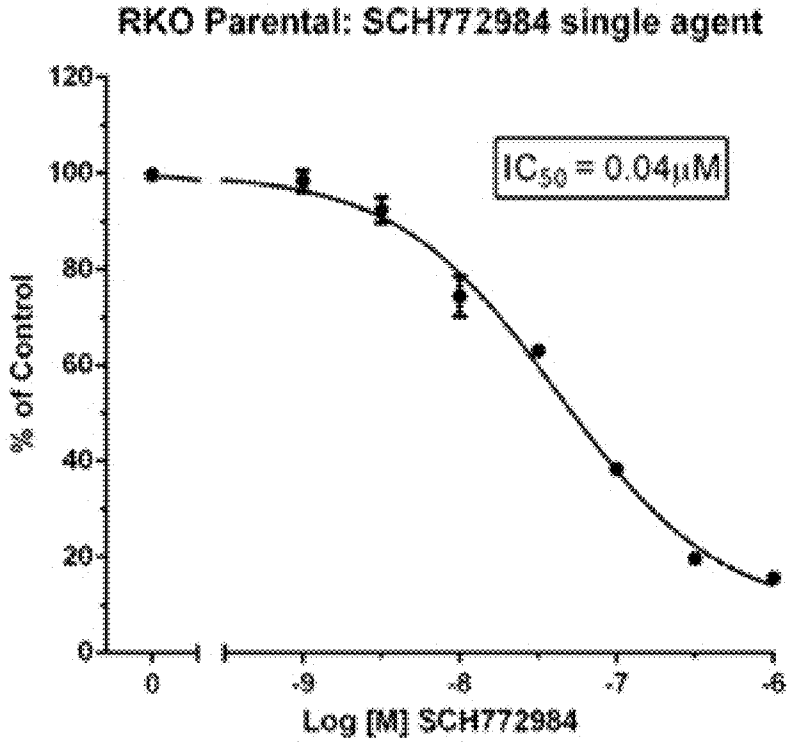


FIG. 24D

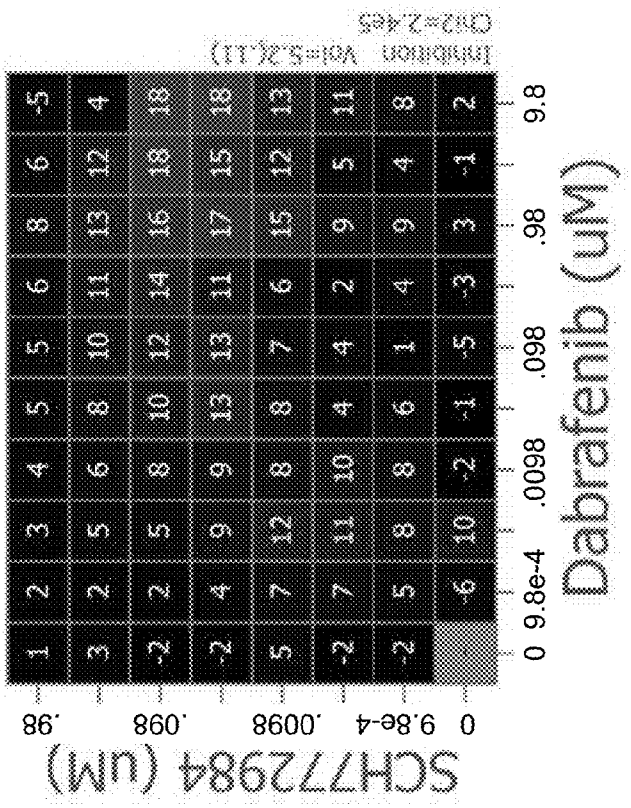


FIG. 24E

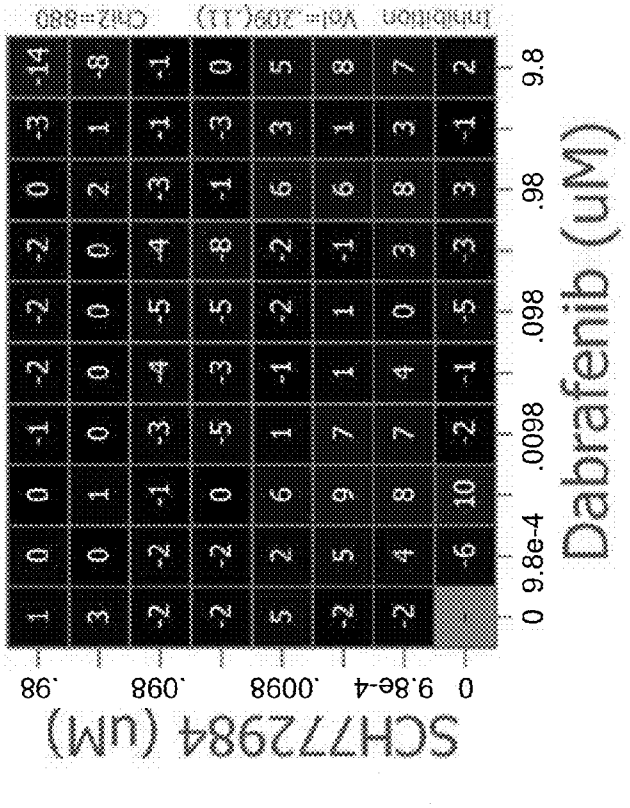


FIG. 24F

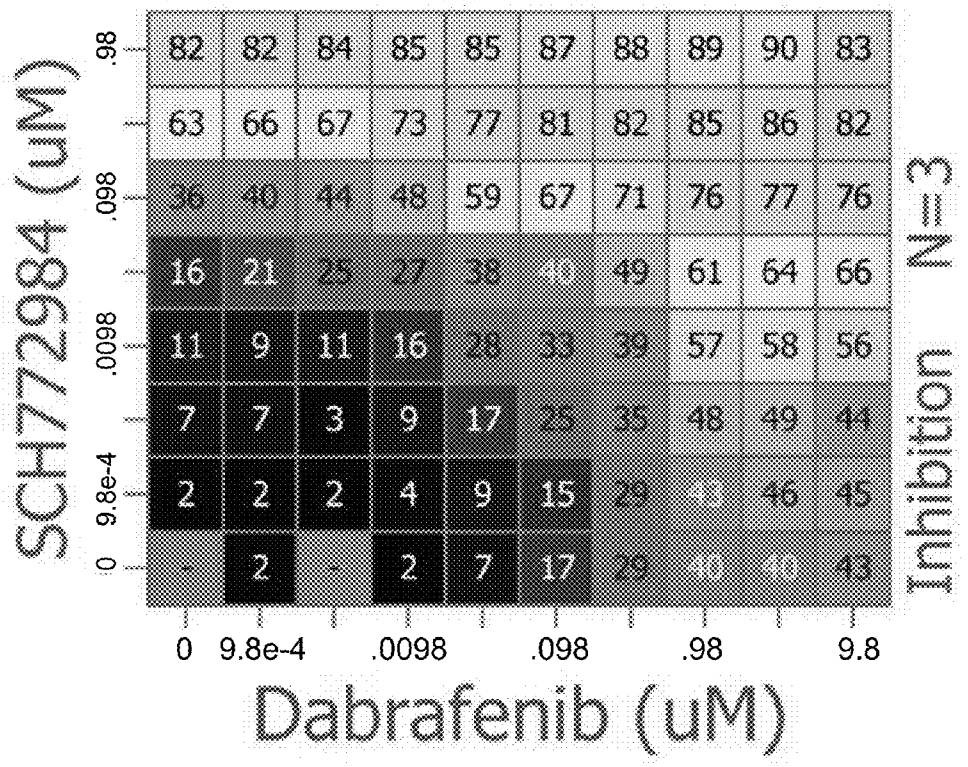

SCH772984 (uM)
.98
.098
.0098
9.8e-4
0
82 82 84 85 85 87 88 89 90 83
63 66 67 73 77 81 82 85 86 82
36 40 44 48 59 67 71 76 77 76
16 21 25 27 38 49 61 64 66
11 9 11 16 28 39 57 58 56
7 7 3 9 17 25 35 48 49 44
2 2 2 4 9 15 29 46 45
- 2 - 2 7 17 29 40 43
0 9.8e-4 .0098 .098 .98 9.8
Dabrafenib (uM)
Inhibition N=3

FIG. 24G

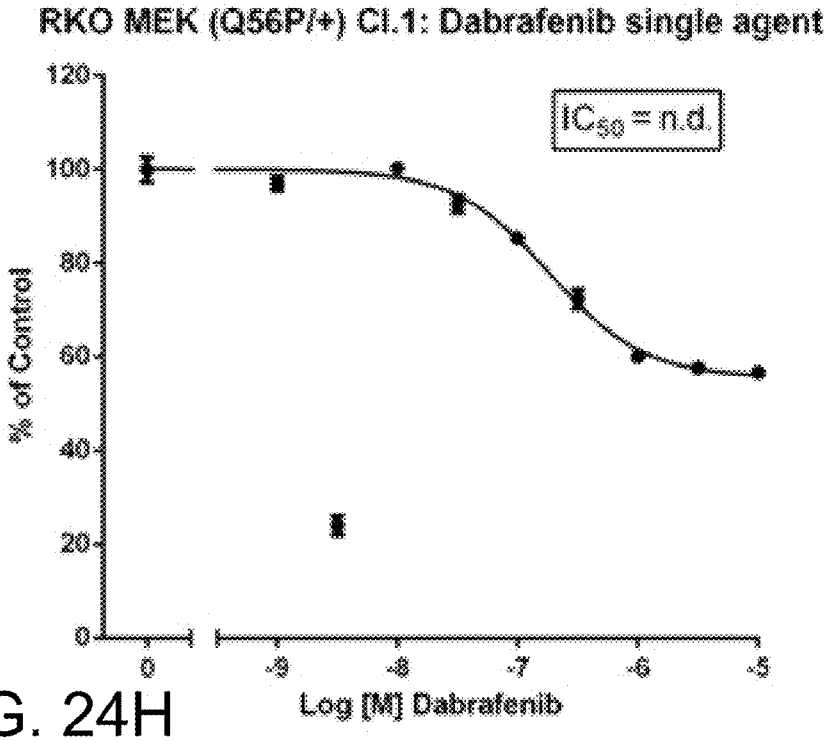


FIG. 24H

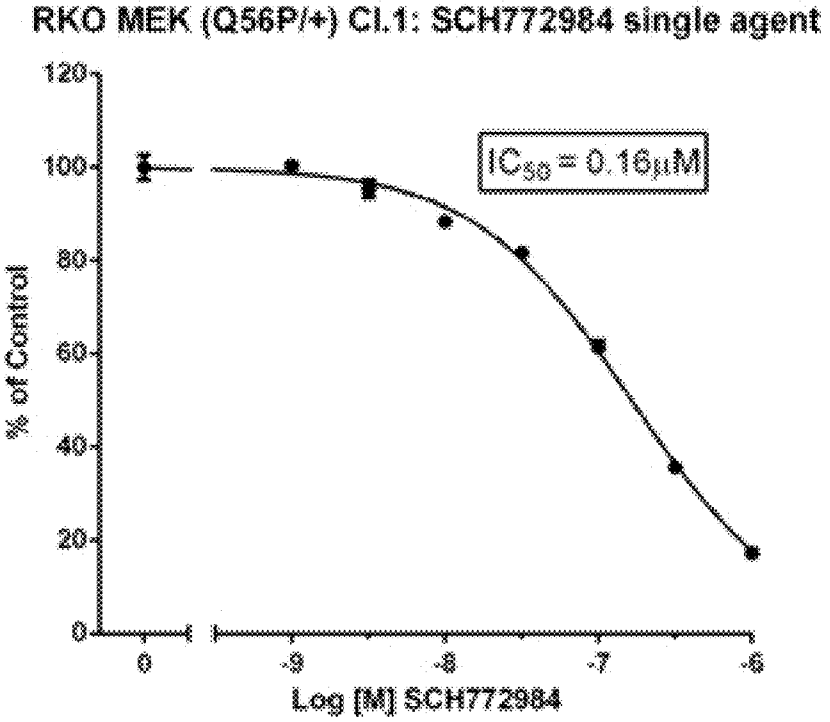


FIG. 24J

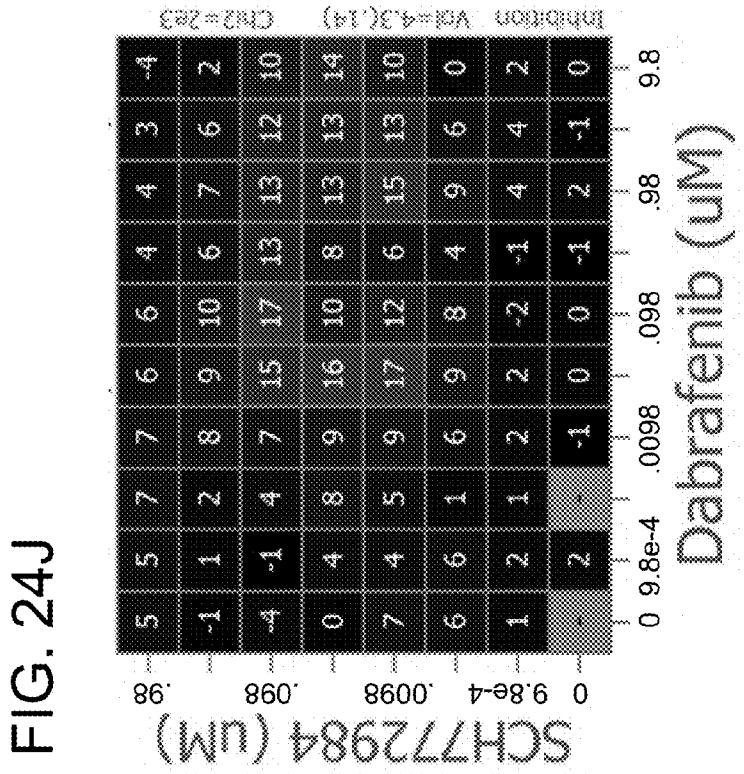


FIG. 24I

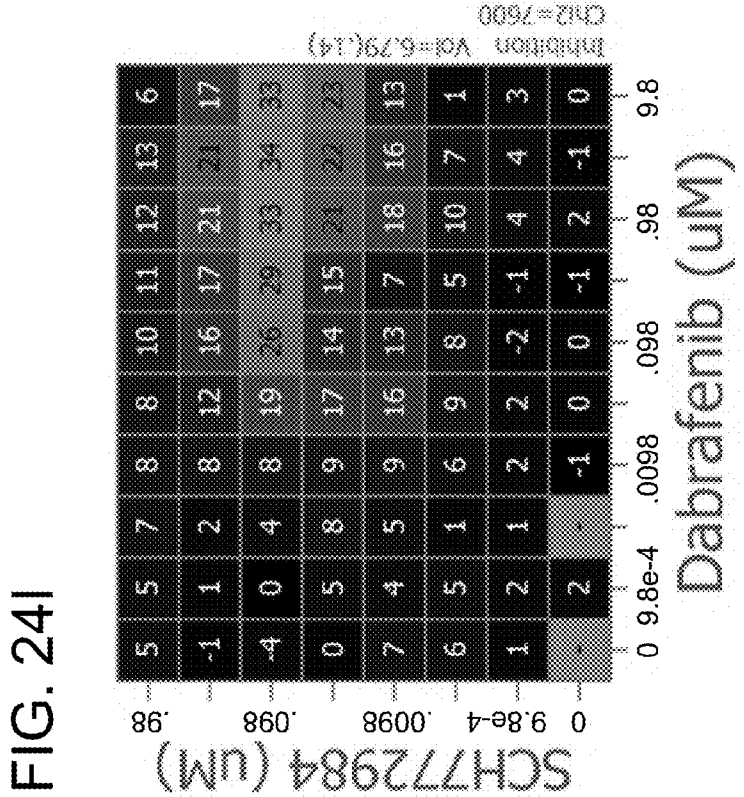


FIG. 24K

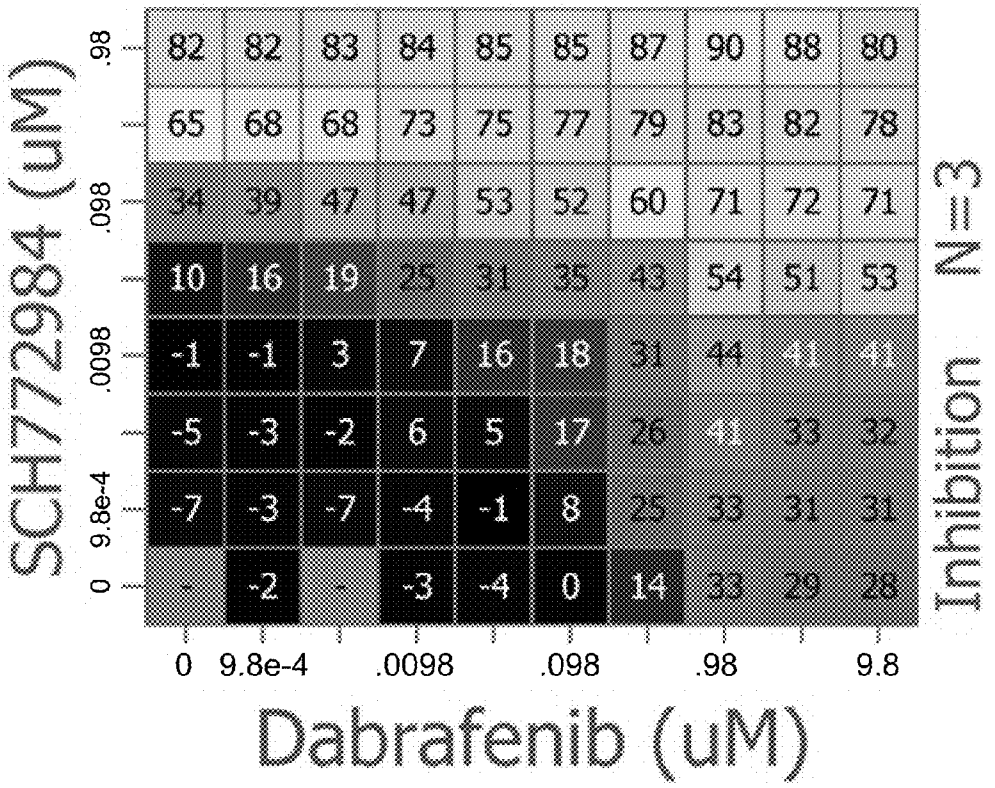

SCH772984 (uM)
.98
.098
.0098
9.8e-4
0
82 82 83 84 85 85 87 90 88 80
65 68 68 73 75 77 79 83 82 78
34 39 47 47 53 52 60 71 72 71
10 16 19 25 31 35 43 54 51 53
-1 -1 3 7 16 18 31 44 41 41
-5 -3 -2 6 5 17 26 41 33 32
-7 -3 -7 -4 -1 8 25 33 31 31
- -2 - -3 -4 0 14 33 29 28
Inhibition N=3
0 9.8e-4 .0098 .098 .98 9.8
Dabrafenib (uM)

FIG. 24L

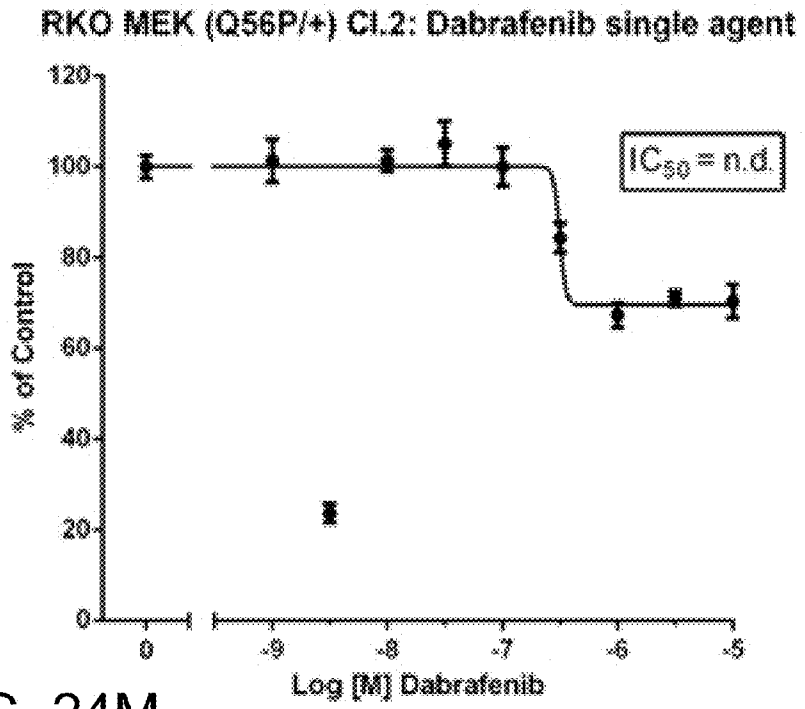


FIG. 24M

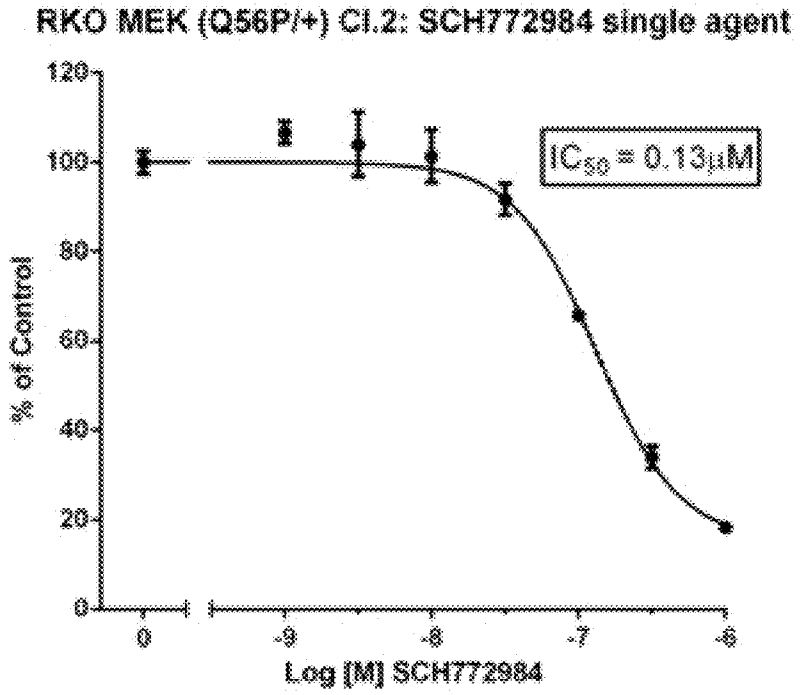


FIG. 24O

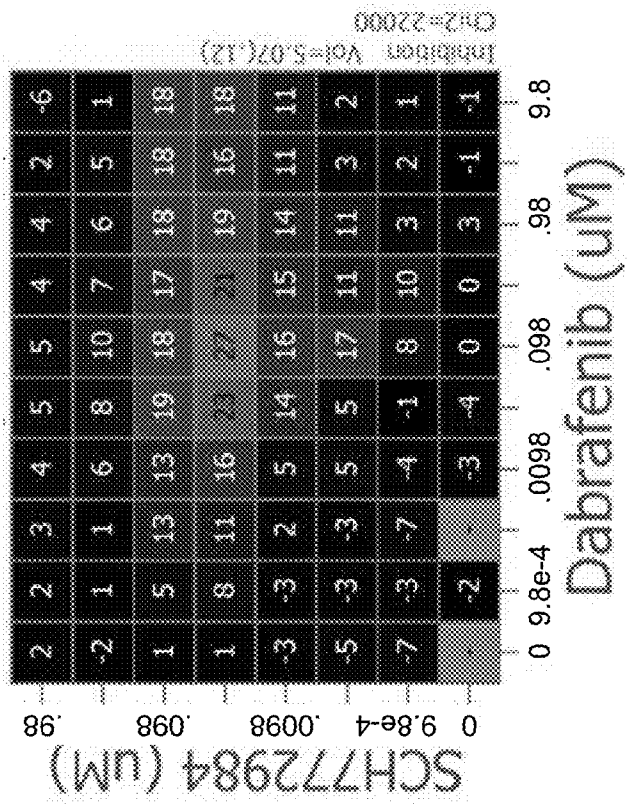


FIG. 24N

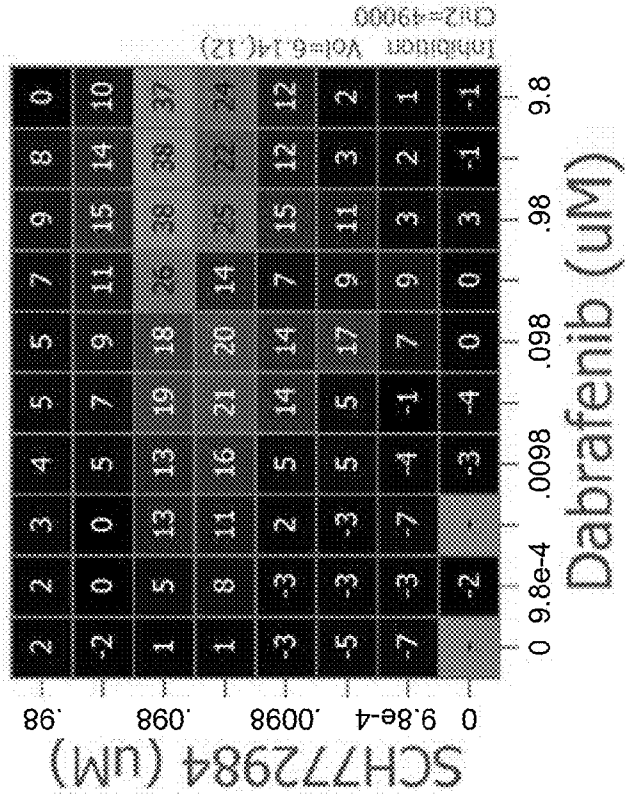


FIG. 25A

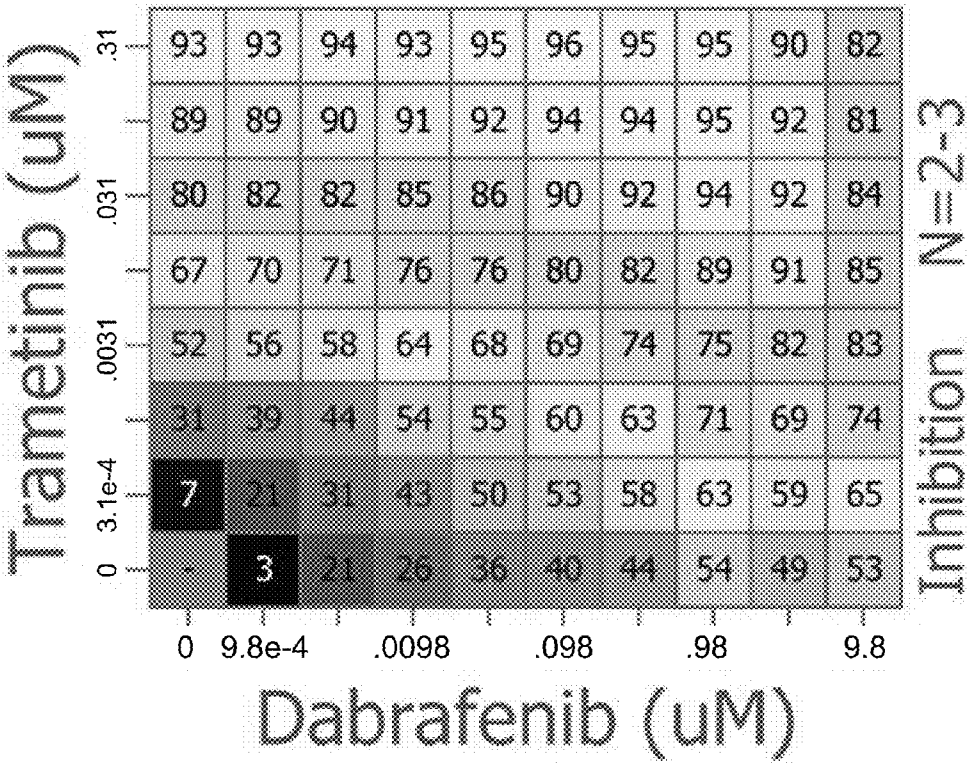

Trametinib (uM)
.31
.031
.0031
3.1e-4
0
93 93 94 93 95 96 95 95 90 82
89 89 90 91 92 94 94 95 92 81
80 82 82 85 86 90 92 94 92 84
67 70 71 76 76 80 82 89 91 85
52 56 58 64 68 69 74 75 82 83
31 39 44 54 55 60 63 71 69 74
7 21 31 43 50 53 58 63 59 65
- 3 21 26 36 40 44 54 49 53
0
9.8e-4
.0098
.098
.98
9.8
Dabrafenib (uM)
Inhibition N=2-3

FIG. 25B

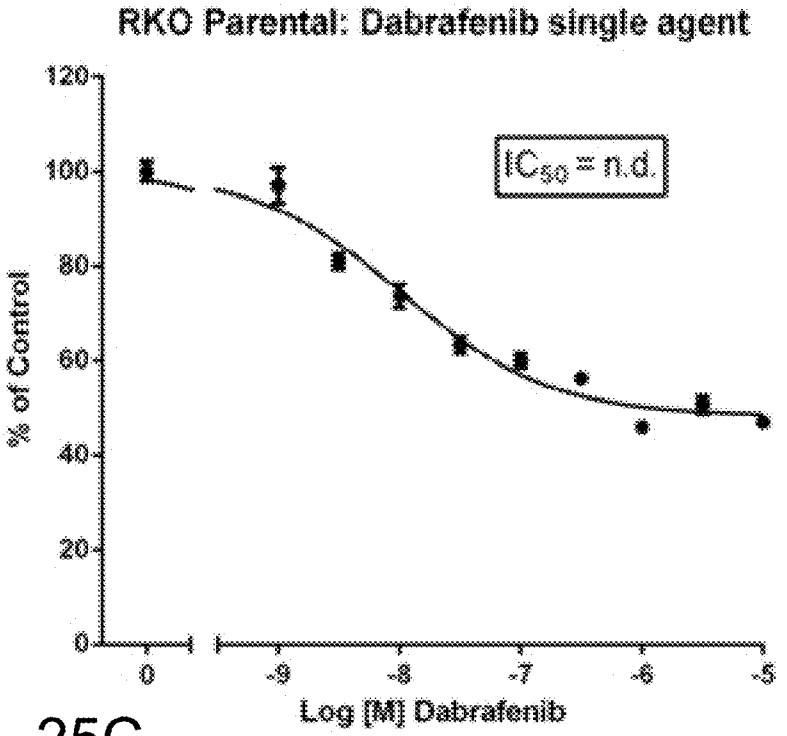


FIG. 25C

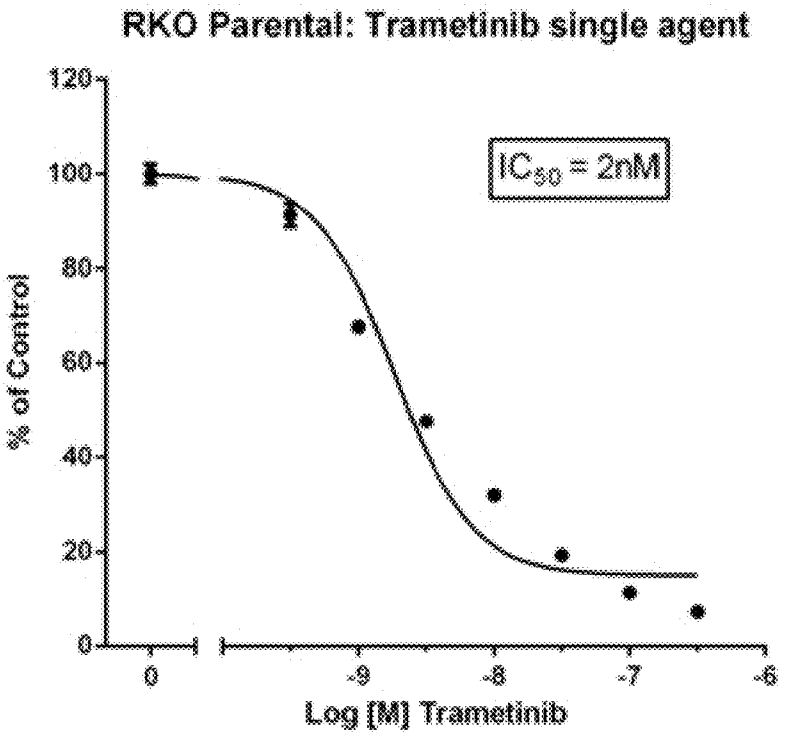


FIG. 25D

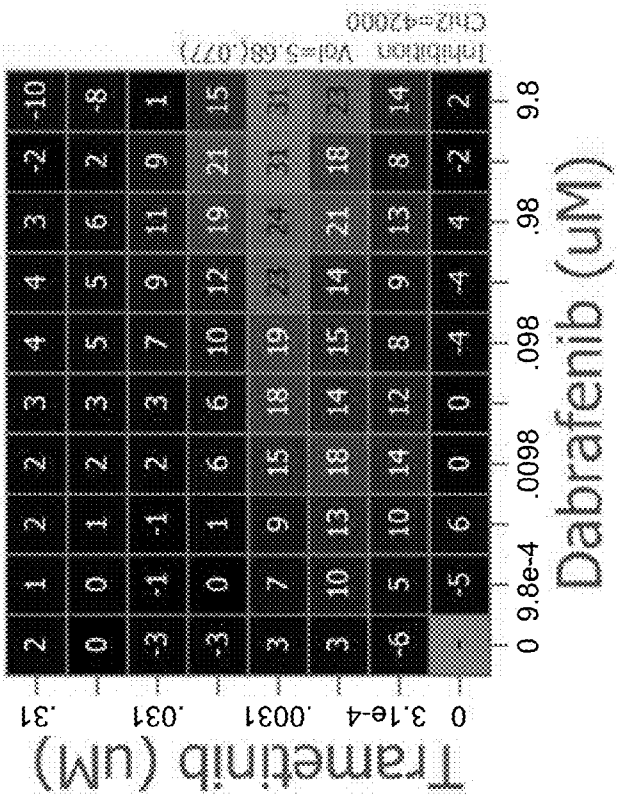


FIG. 25E

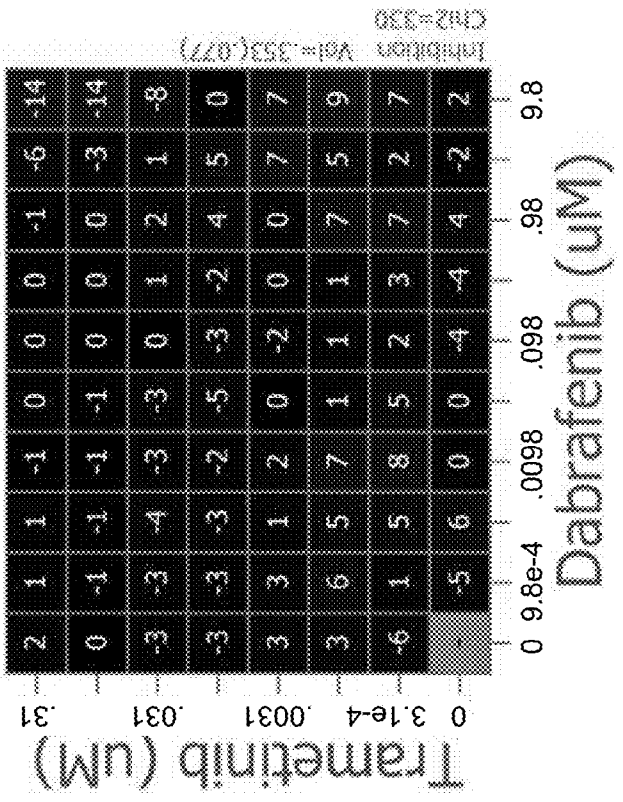


FIG. 25F

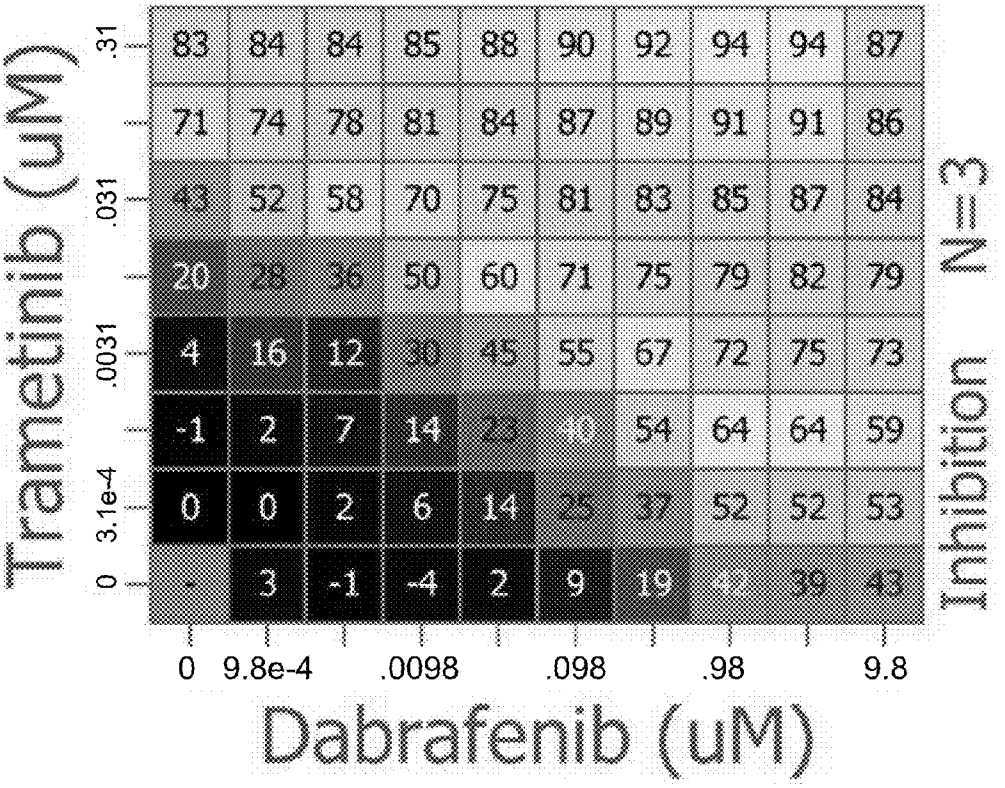

Trametinib (uM)
.31
.031
.0031
3.1e-4
0
83 84 84 85 88 90 92 94 94 87
71 74 78 81 84 87 89 91 91 86
43 52 58 70 75 81 83 85 87 84
20 28 36 50 60 71 75 79 82 79
4 16 12 30 45 55 67 72 75 73
-1 2 7 14 23 40 54 64 64 59
0 0 2 6 14 25 37 52 52 53
- 3 -1 -4 2 9 19 27 39 43
0 9.8e-4 .0098 .098 .98 9.8
Dabrafenib (uM)
Inhibition N=3

FIG. 25G

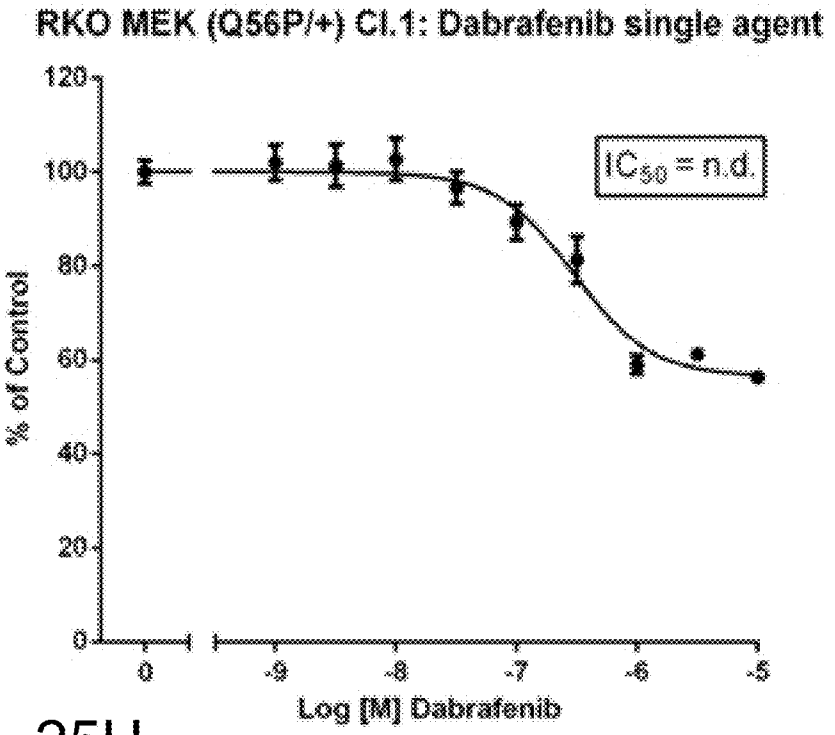


FIG. 25H

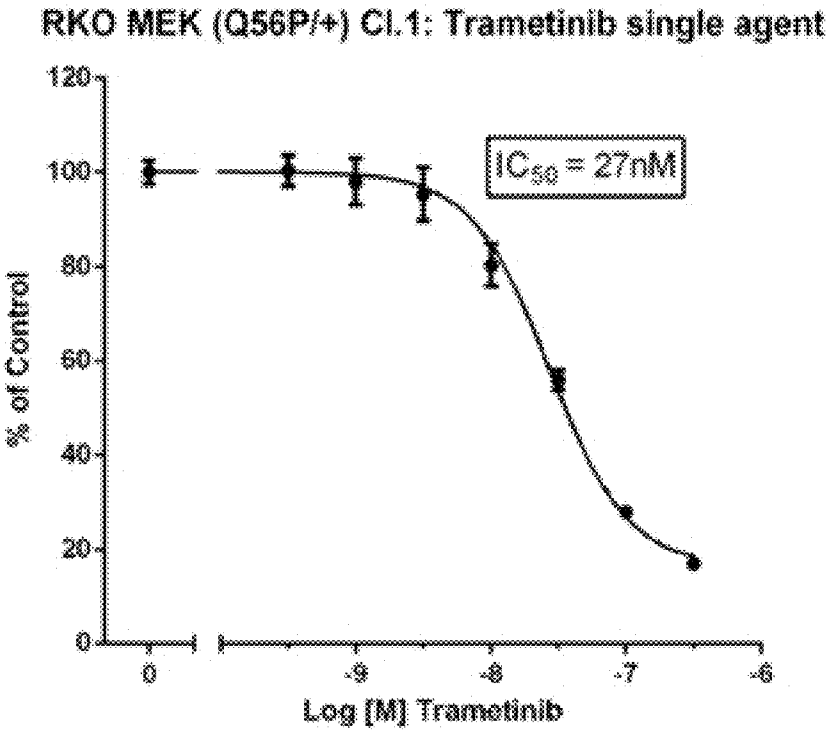


FIG. 25I

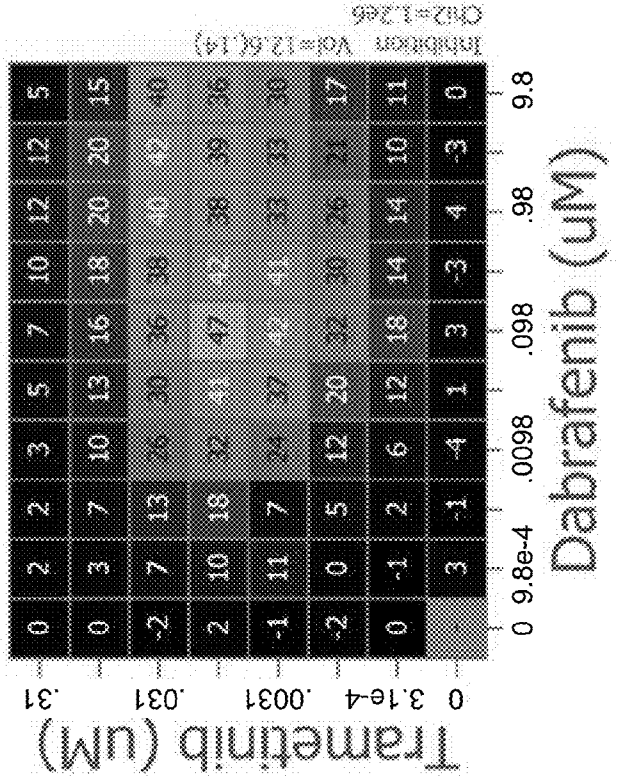


FIG. 25J

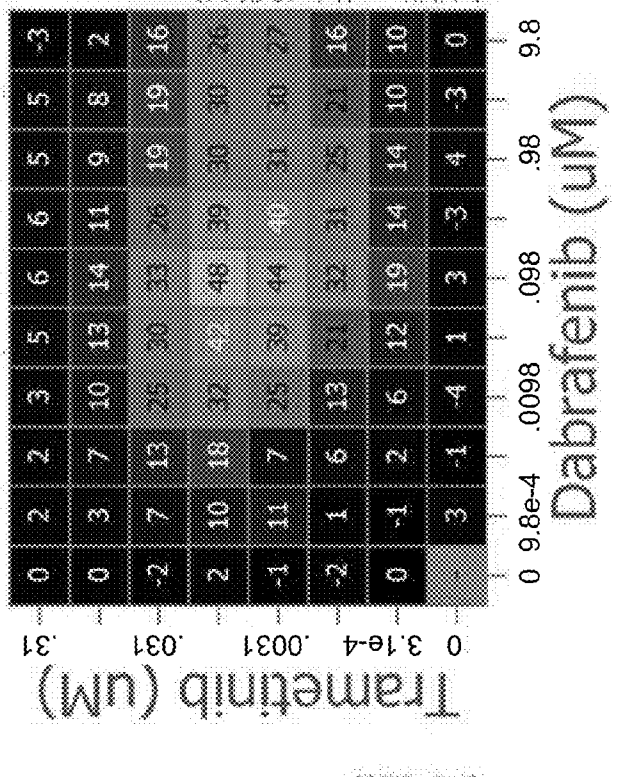


FIG. 25K

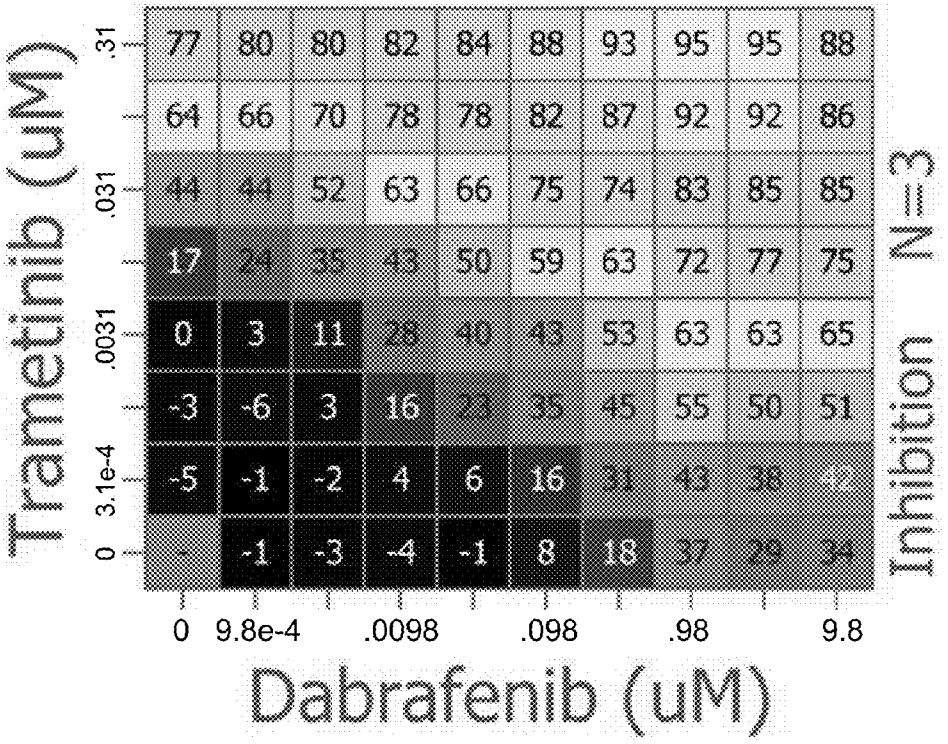

Trametinib (uM)
.31
.031
.0031
3.1e-4
0
77 80 80 82 84 88 93 95 95 88
64 66 70 78 78 82 87 92 92 86
44 44 52 63 66 75 74 83 85 85
17 24 35 43 50 59 63 72 77 75
0 3 11 28 40 43 53 63 63 65
-3 -6 3 16 23 35 45 55 50 51
-5 -1 -2 4 6 16 31 43 38 42
- -1 -3 -4 -1 8 18 37 29 34
Inhibition N=3
0 9.8e-4 .0098 .098 .98 9.8
Dabrafenib (uM)

FIG. 25L

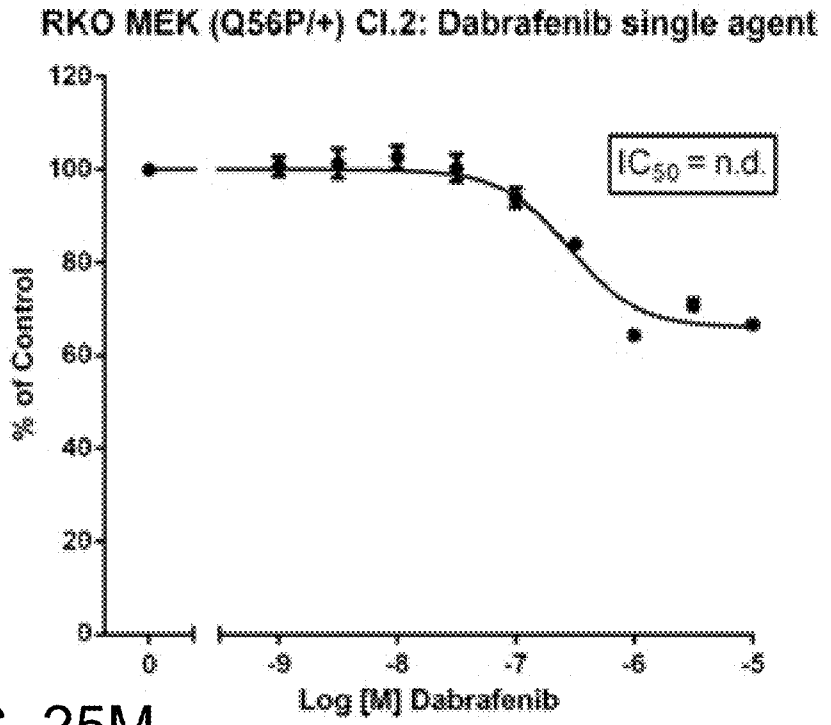


FIG. 25M

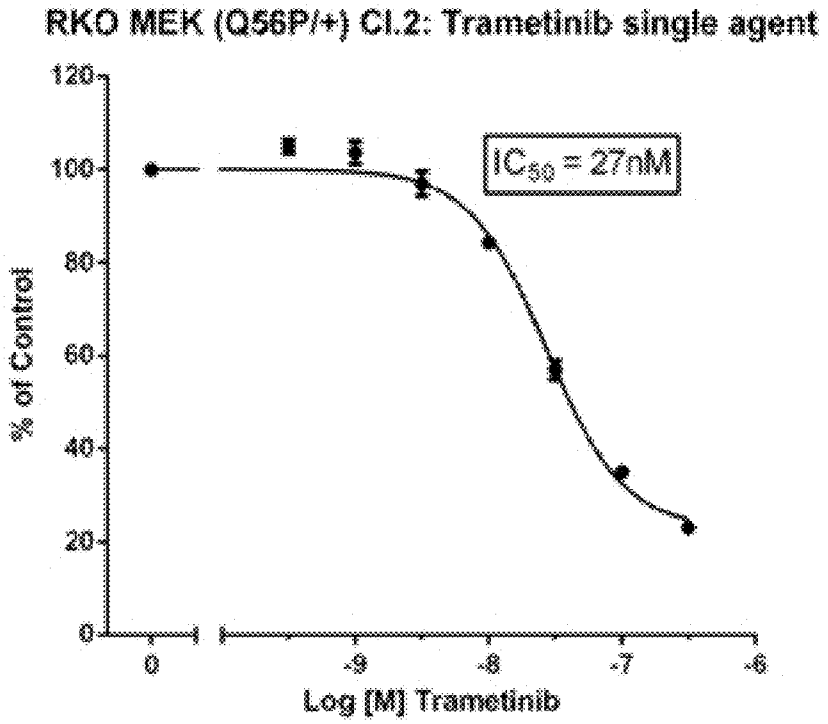


FIG. 25N

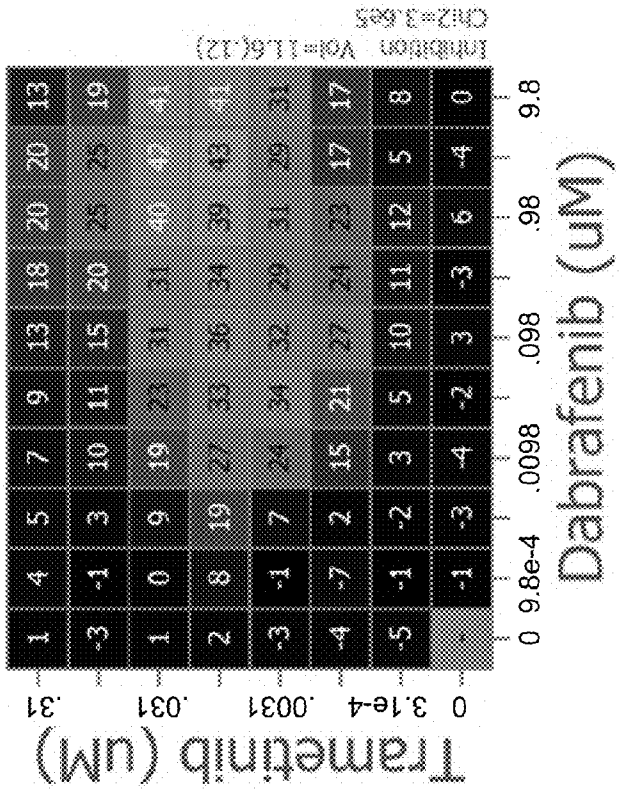


FIG. 25O

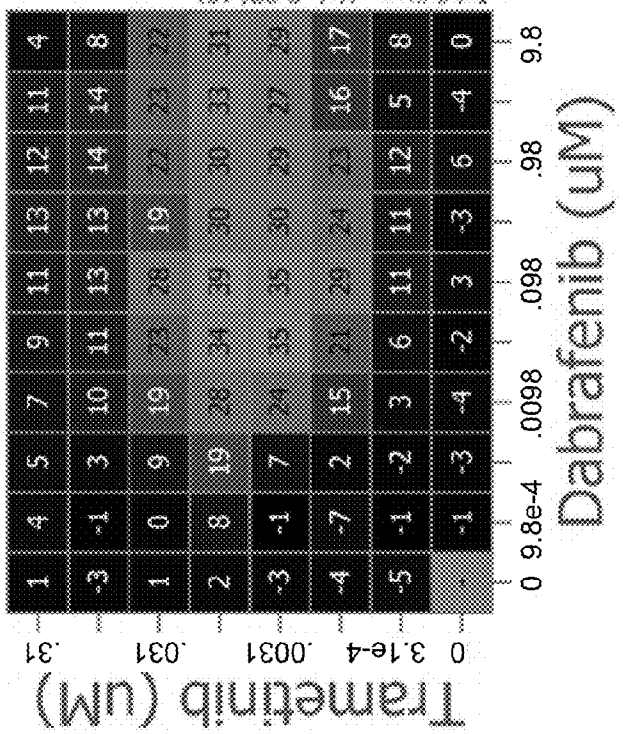


FIG. 26A

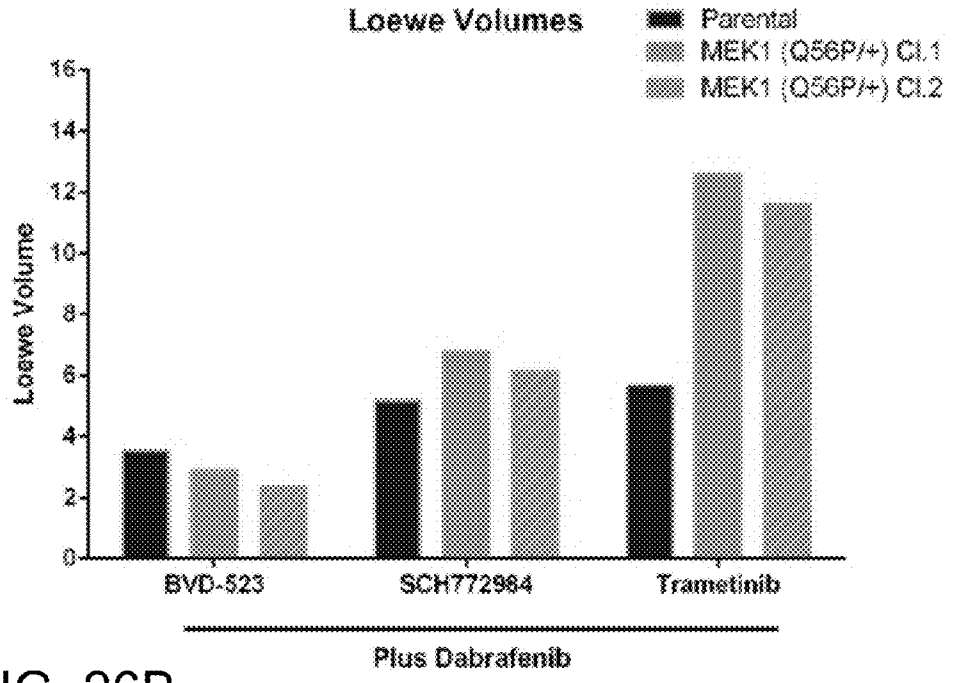


FIG. 26B

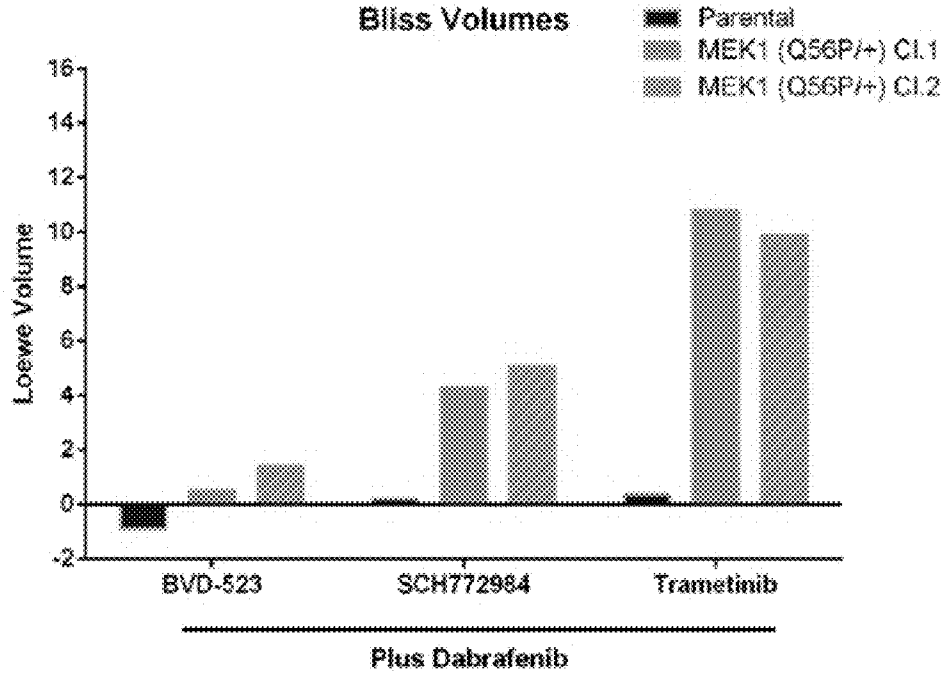


FIG. 26C

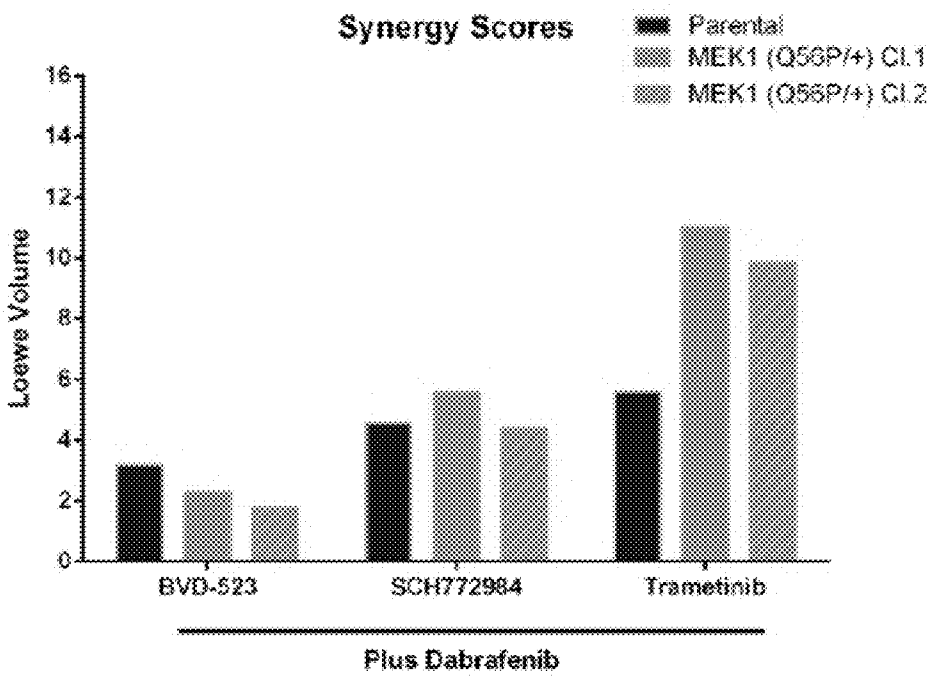

Synergy Scores
Parental
MEK1 (Q56P/+) Cl.1
MEK1 (Q56P/+) Cl.2
Loewe Volume
16
14
12
10
8
6
4
2
0
BVD-523
SCH772984
Trametinib
Plus Dabrafenib

FIG. 27A

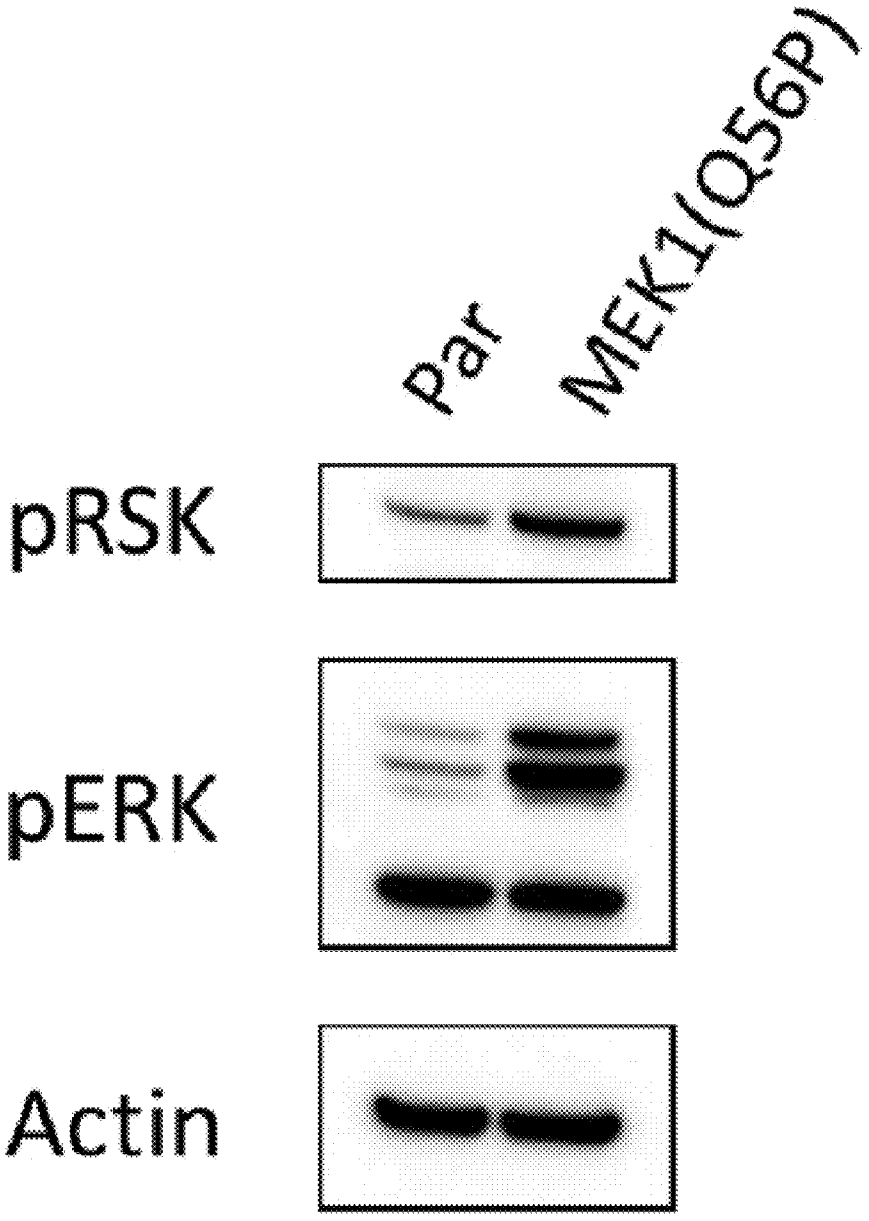


FIG. 27B

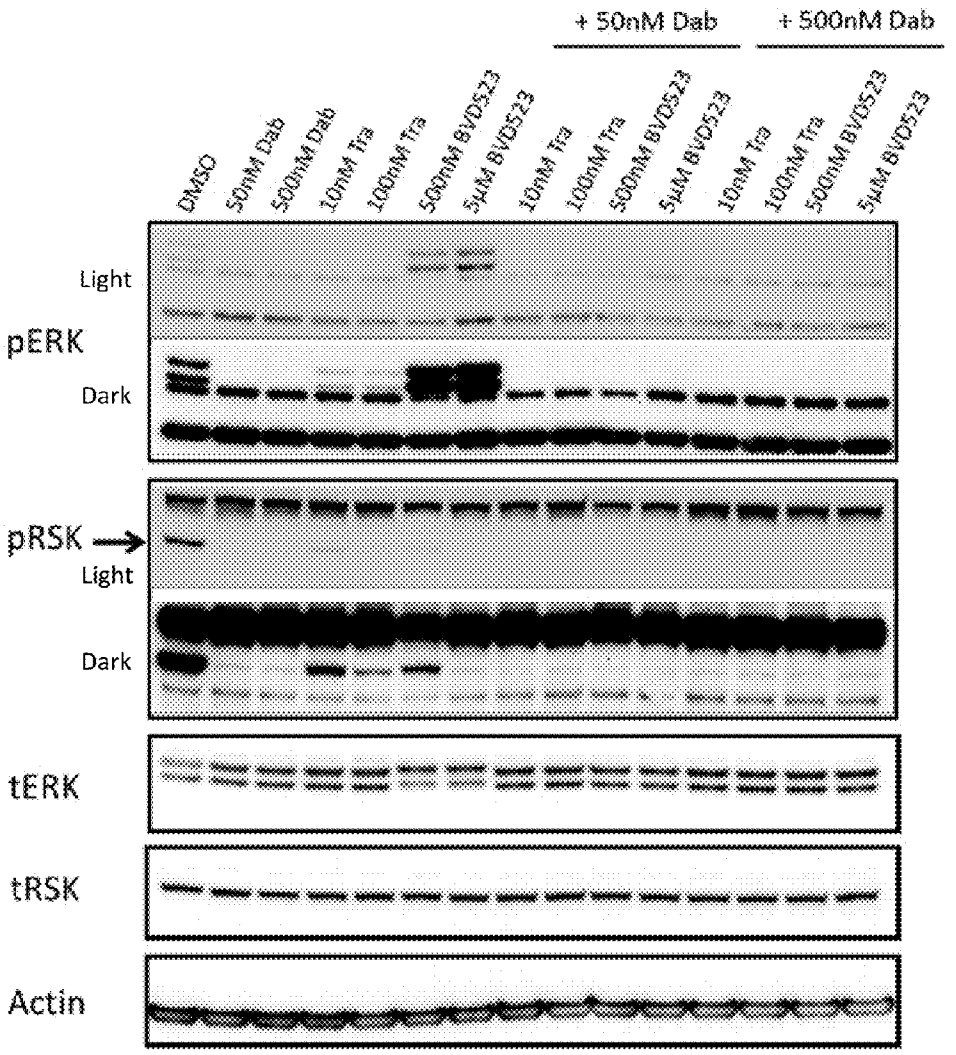

+ 50nM Dab
+ 500nM Dab
DMSO
50nM Dab
500nM Dab
10nM Tra
100nM Tra
500nM BVD523
5μM BVD523
10nM Tra
100nM Tra
500nM BVD523
5μM BVD523
10nM Tra
100nM Tra
500nM BVD523
5μM BVD523
Light
pERK
Dark
pRSK
Light
Dark
tERK
tRSK
Actin

FIG. 27C

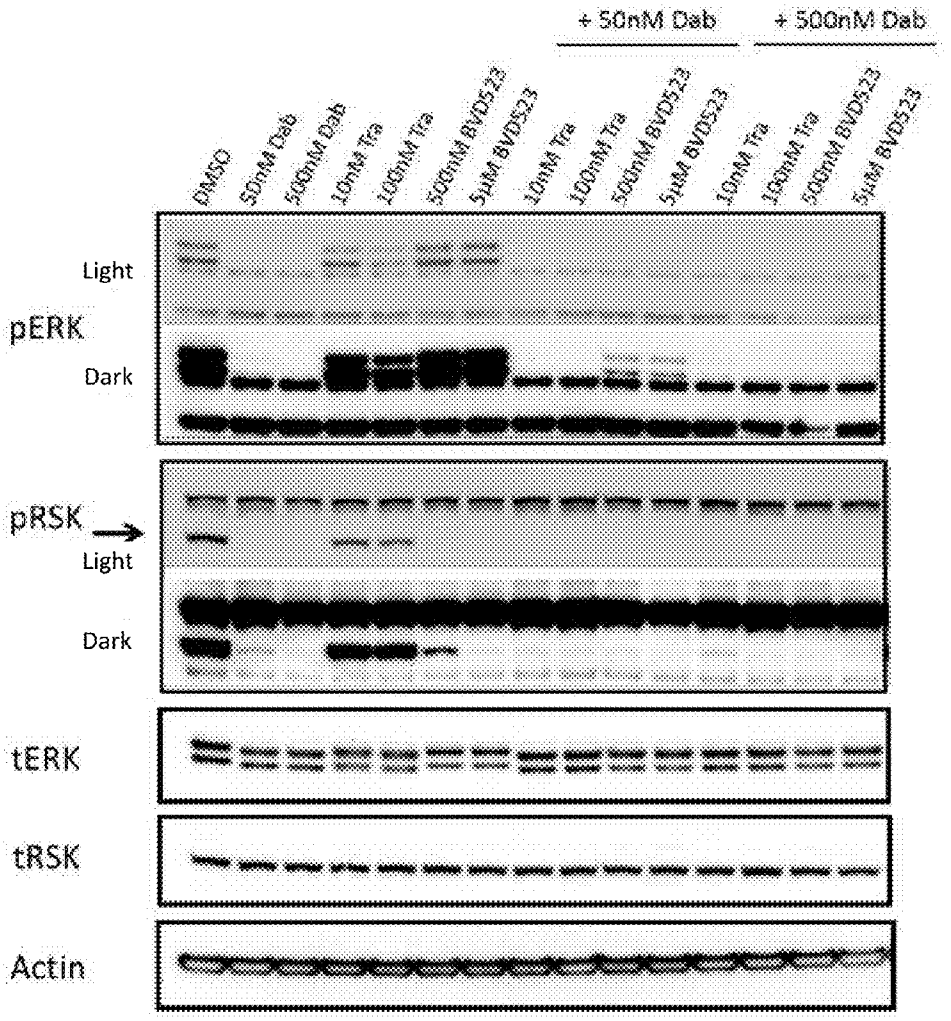

+ 50nM Dab
+ 500nM Dab
DMSO
50nM Dab
500nM Dab
10nM Tra
100nM Tra
500nM BVD523
5μM BVD523
10nM Tra
100nM Tra
500nM BVD523
5μM BVD523
10nM Tra
150nM Tra
500nM BVD523
5μM BVD523
Light
pERK
Dark
pRSK
Light
Dark
tERK
tRSK
Actin

FIG. 27D

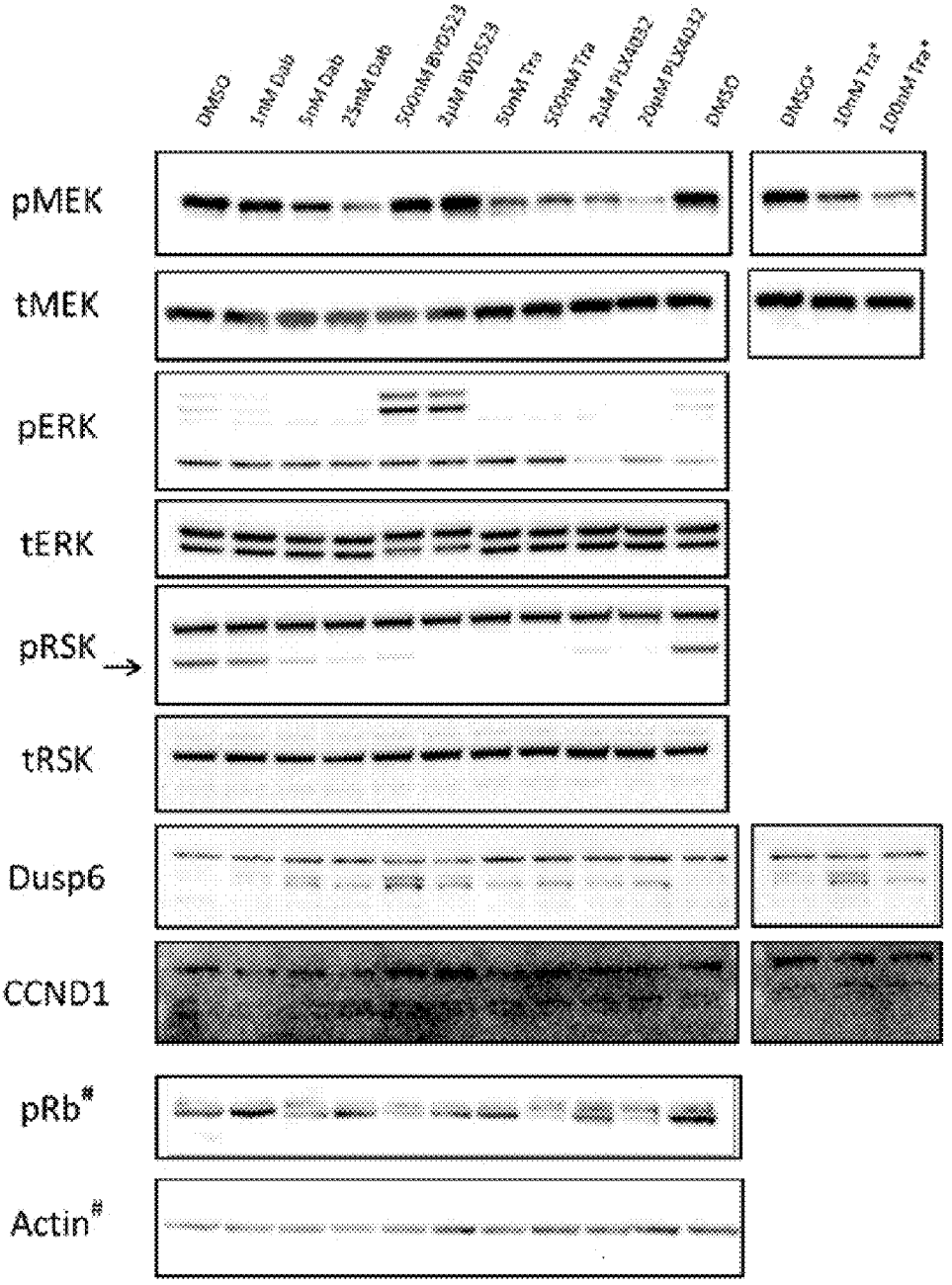

DMSO
1nM Dab
5nM Dab
25nM Dab
500nM BVD523
2μM BVD523
50nM Tra
500nM Tra
2μM PLX4032
20μM PLX4032
DMSO
DMSO*
10nM Tra*
100nM Tra*
pMEK
tMEK
pERK
tERK
pRSK
tRSK
Dusp6
CCND1
pRb#
Actin#

FIG. 27E

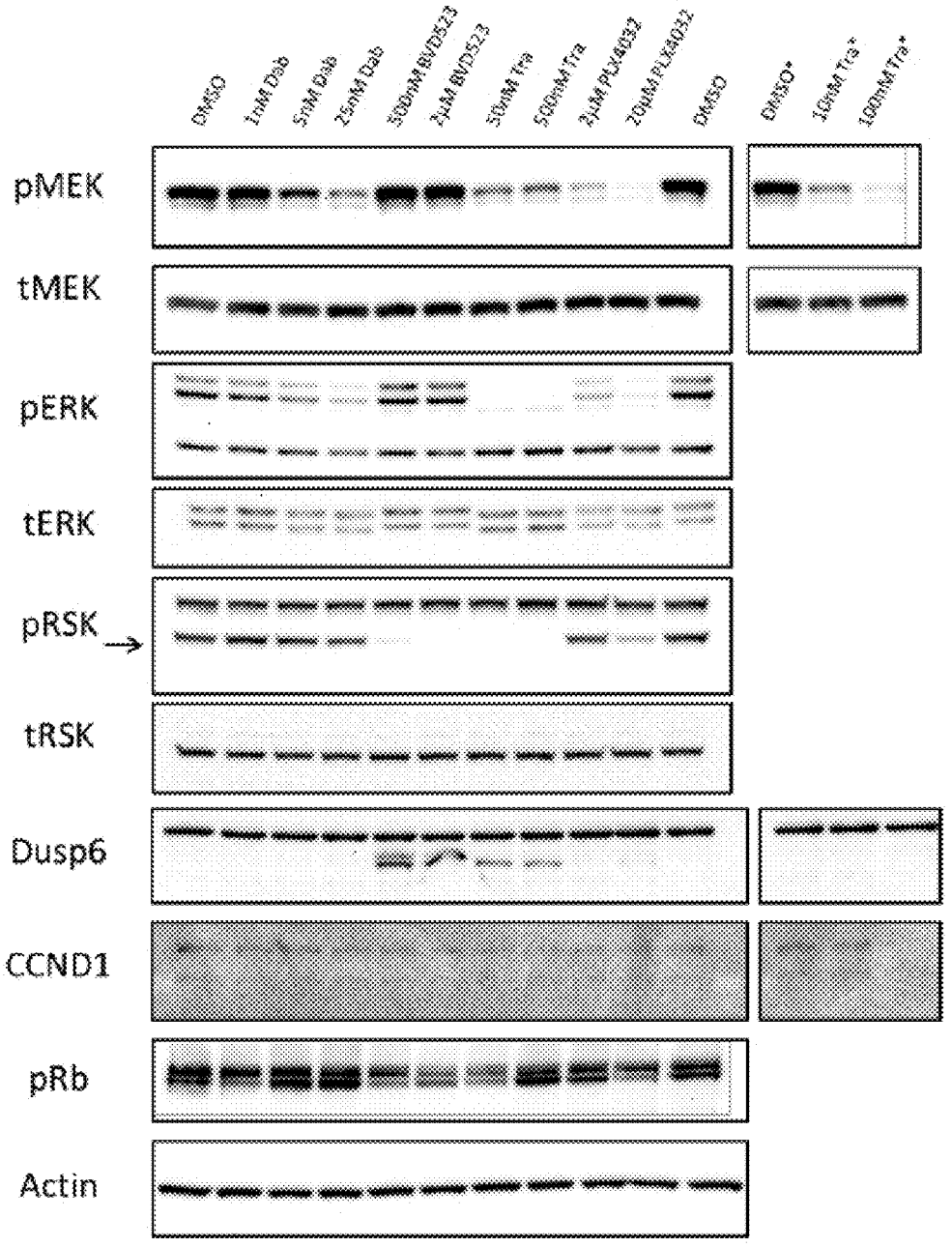

DMSO
1nM Dab
5nM Dab
25nM Dab
500nM BVD523
2μM BVD523
50nM Tra
500nM Tra
2μM PLX4032
20μM PLX4032
DMSO
DMSO*
15nM Tra*
100nM Tra*
pMEK
tMEK
pERK
tERK
pRSK
tRSK
Dusp6
CCND1
pRb
Actin

FIG. 27F

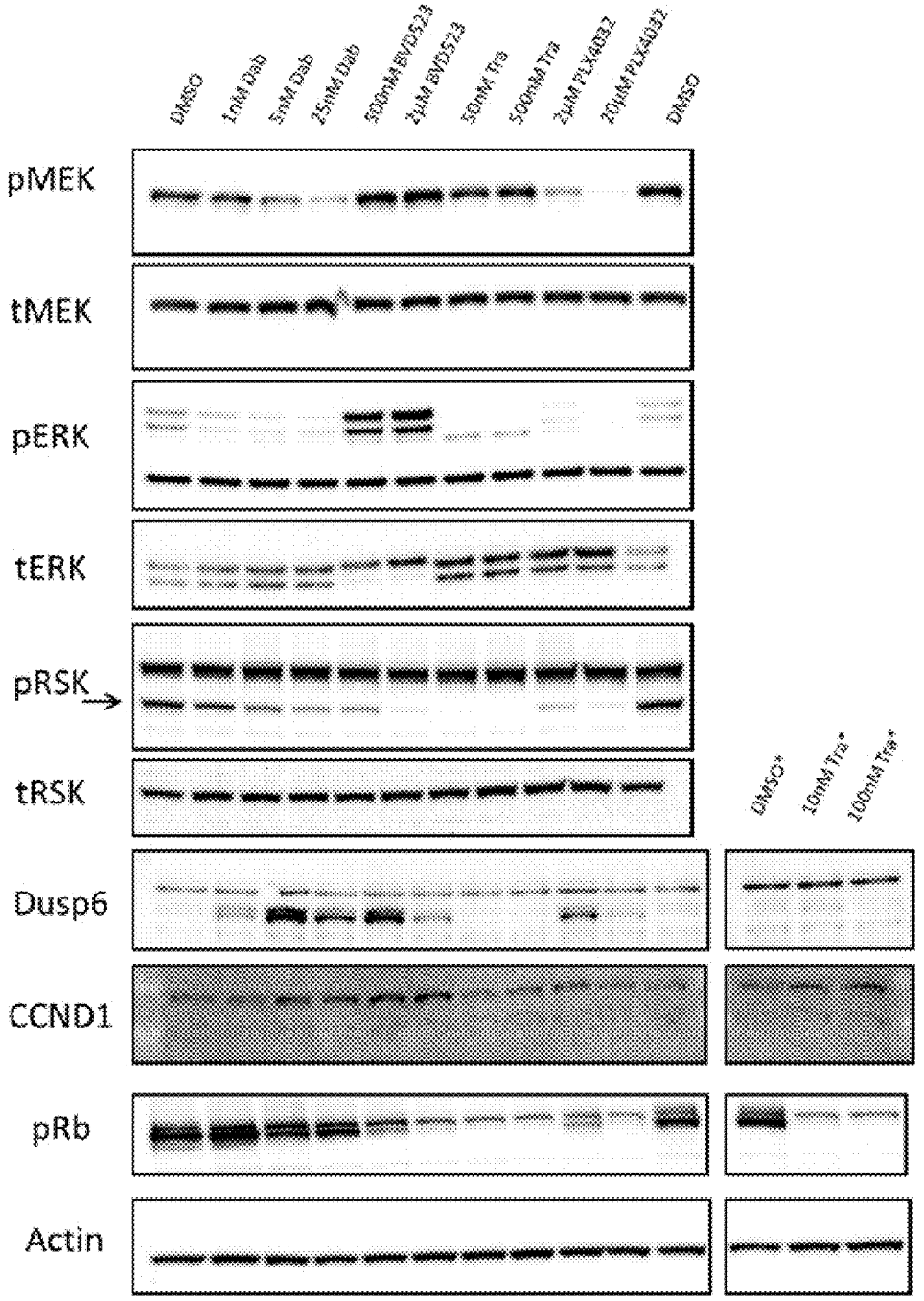

DMSO
1nM Dab
5nM Dab
25nM Dab
500nM BVD523
2μM BVD523
50nM Tra
500nM Tra
2μM PLX4032
10μM PLX4032
DMSO
pMEK
tMEK
pERK
tERK
pRSK
tRSK
Dusp6
CCND1
pRb
Actin
DMSO*
10nM Tra*
100nM Tra*

FIG. 27G

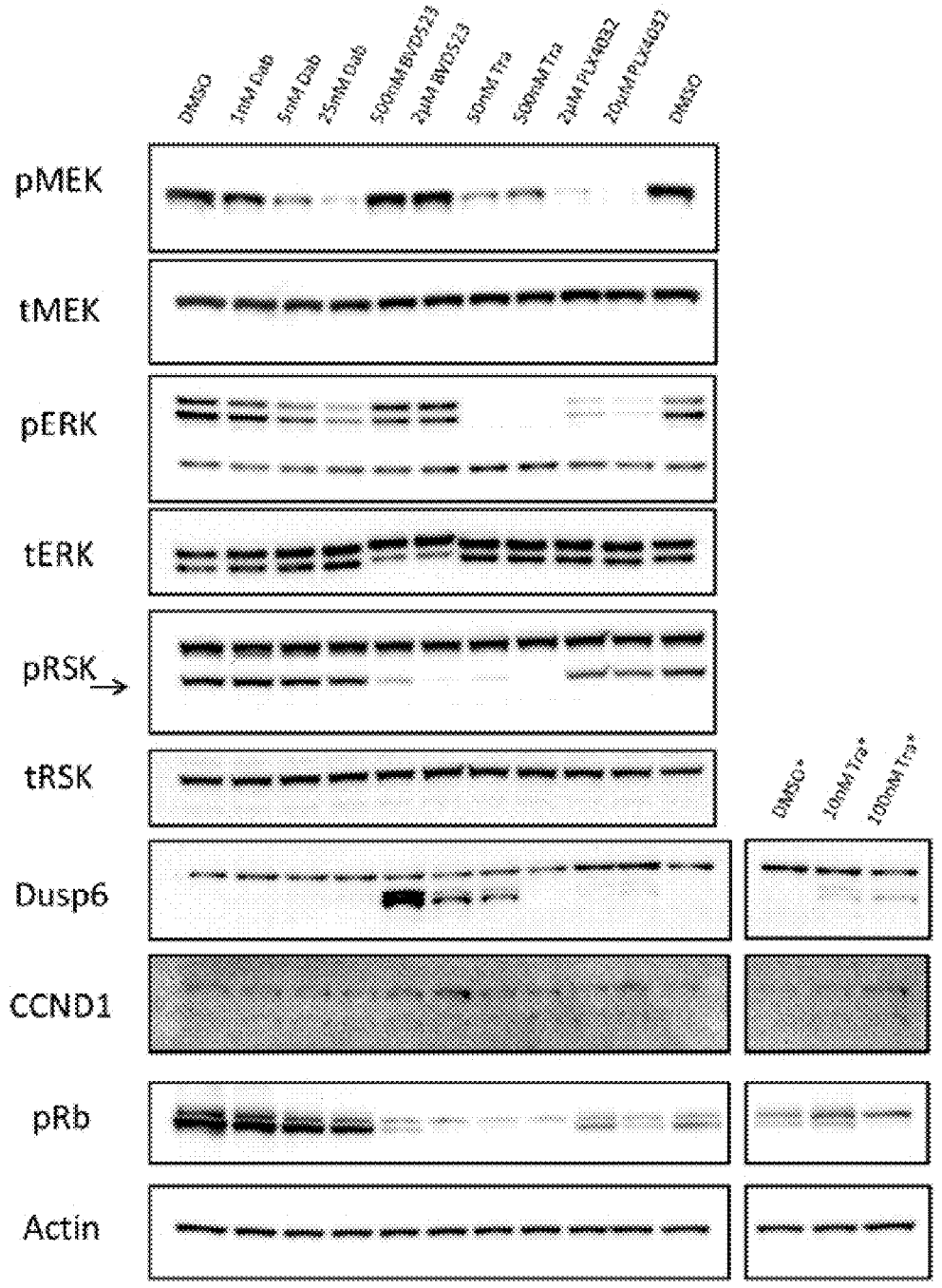

DMSO
1nM Dab
5nM Dab
25nM Dab
500nM BVD523
2μM BVD523
50nM Tra
500nM Tra
2μM PLX4032
10μM PLX4032
DMSO
pMEK
tMEK
pERK
tERK
pRSK
tRSK
DMSO*
10nM Tra*
100nM Tra*
Dusp6
CCND1
pRb
Actin

FIG. 27H

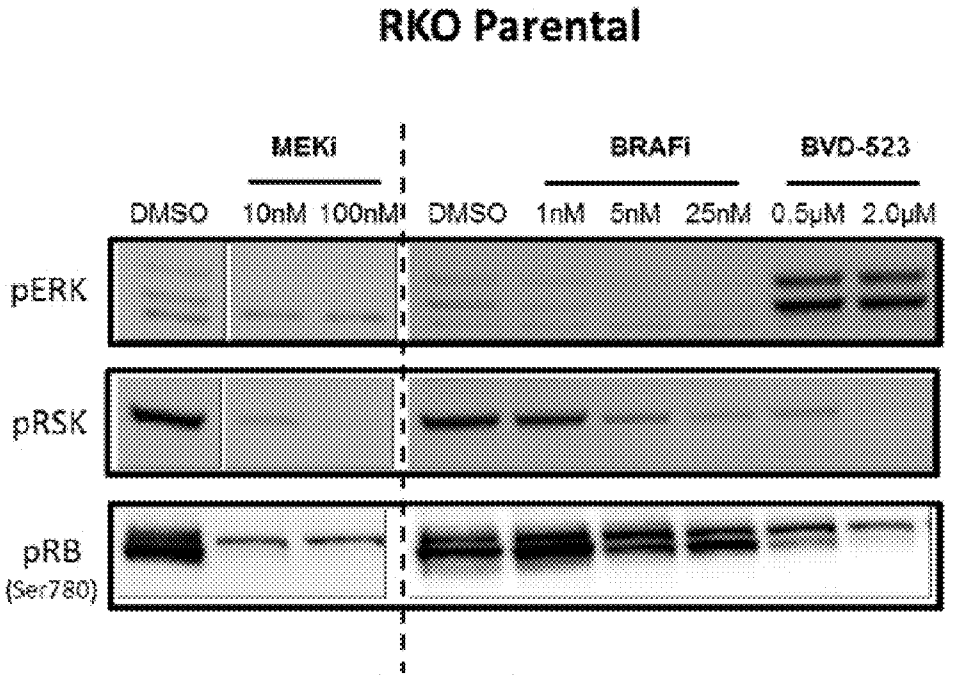


FIG. 27I

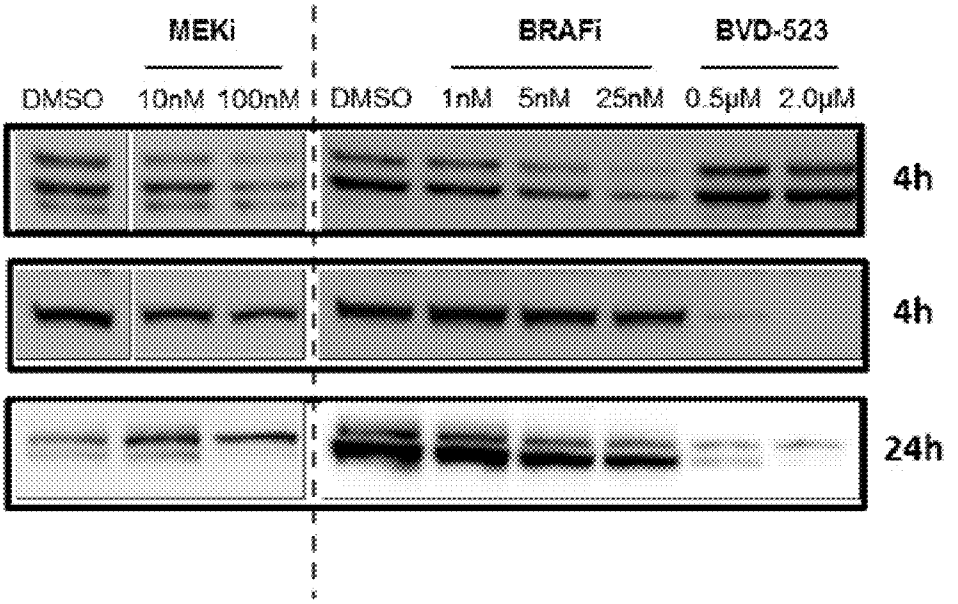


FIG. 28A

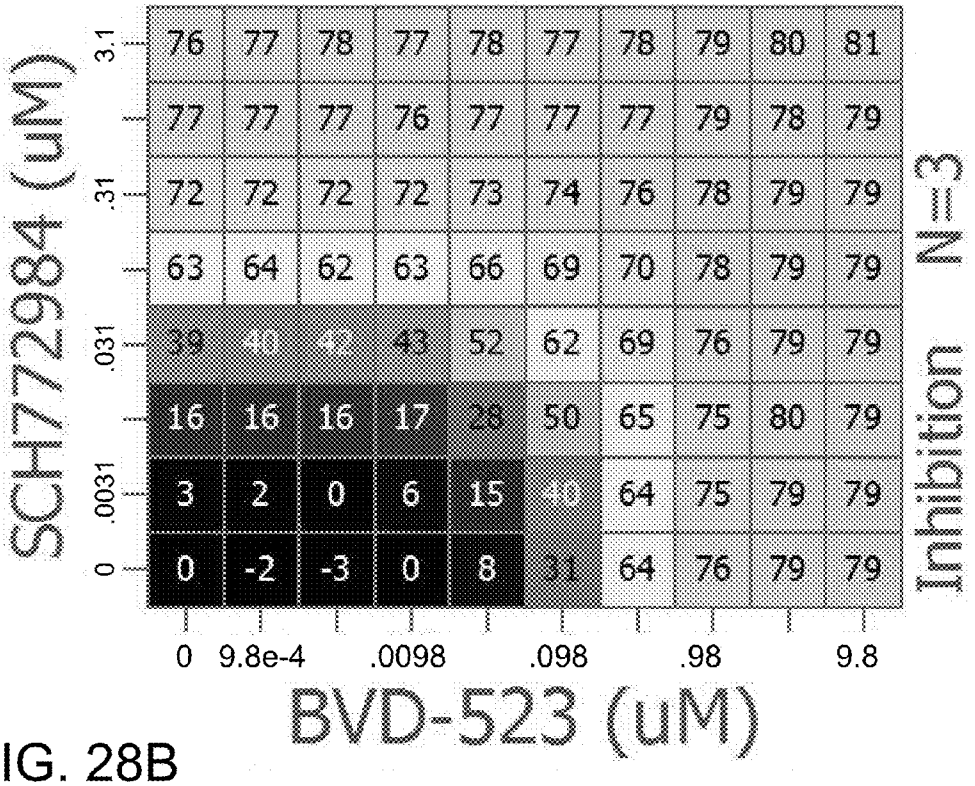


FIG. 28B

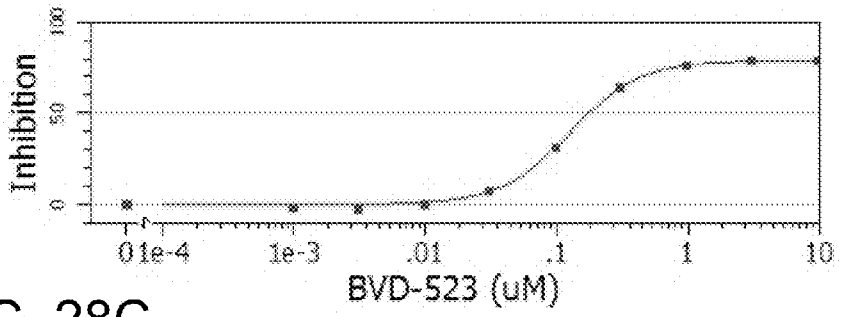


FIG. 28C

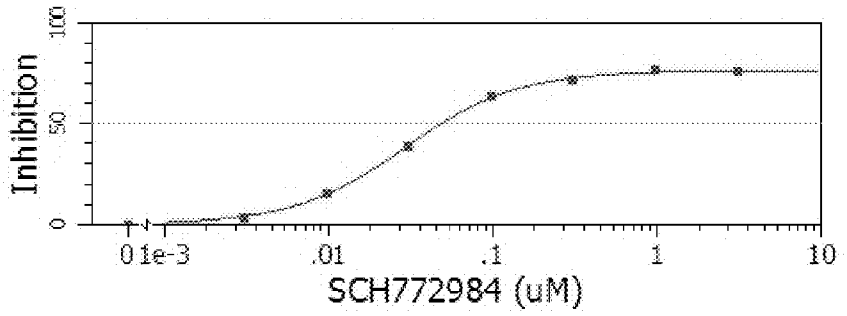


FIG. 28D

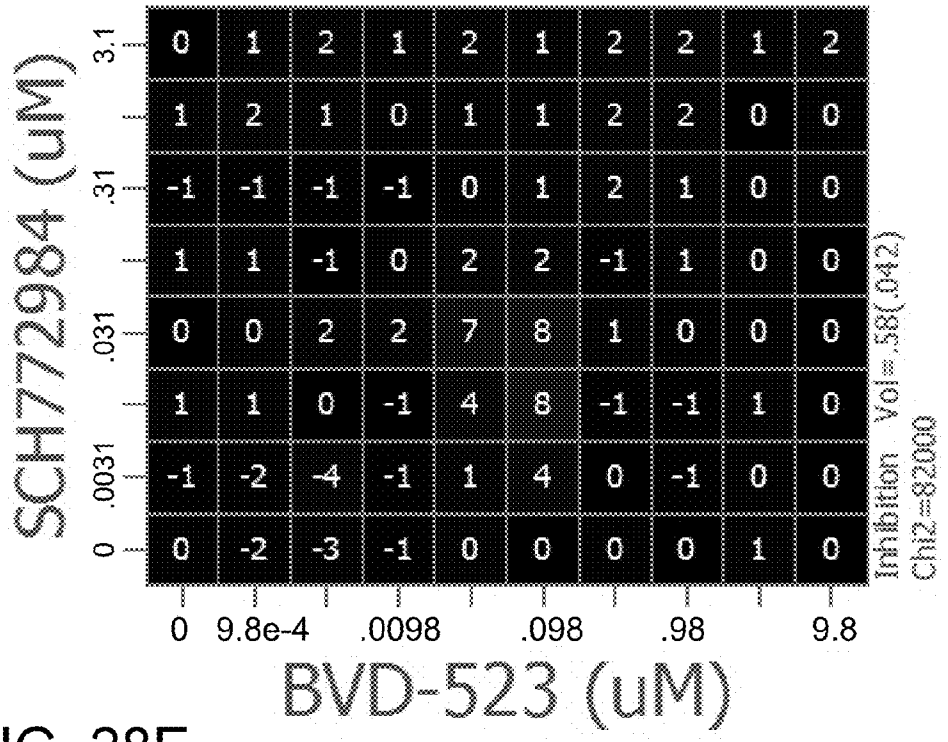


FIG. 28E

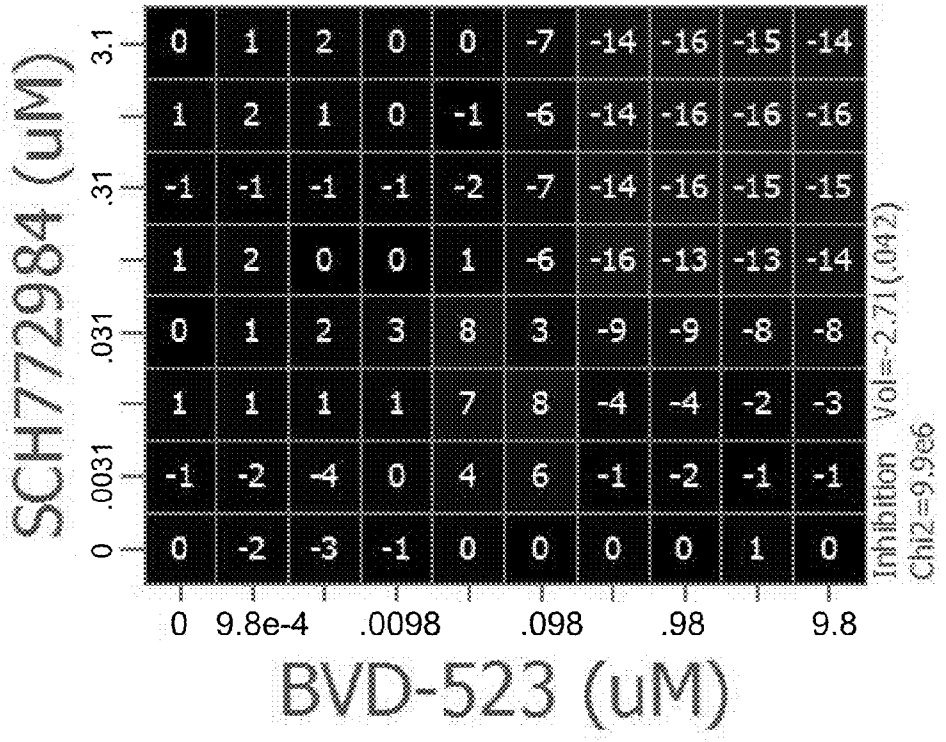


FIG. 29A

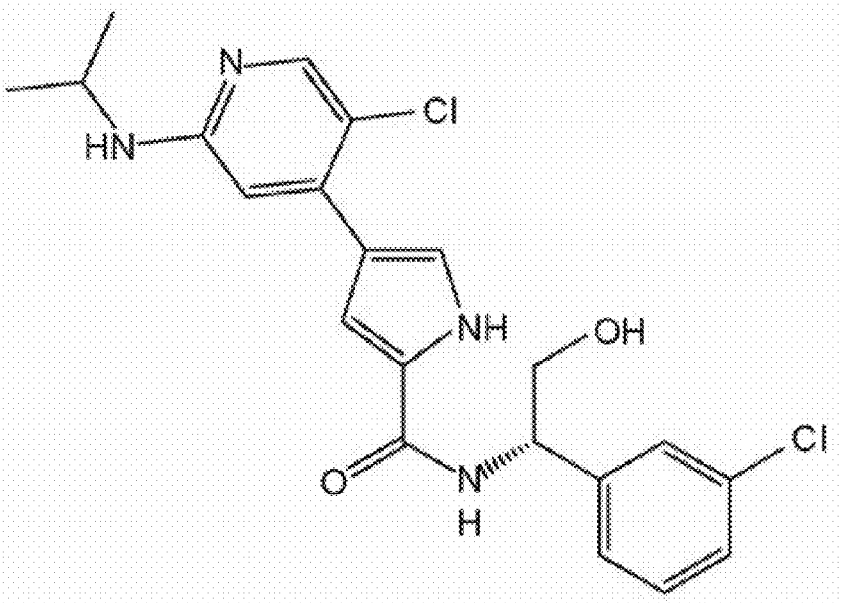


FIG. 29B

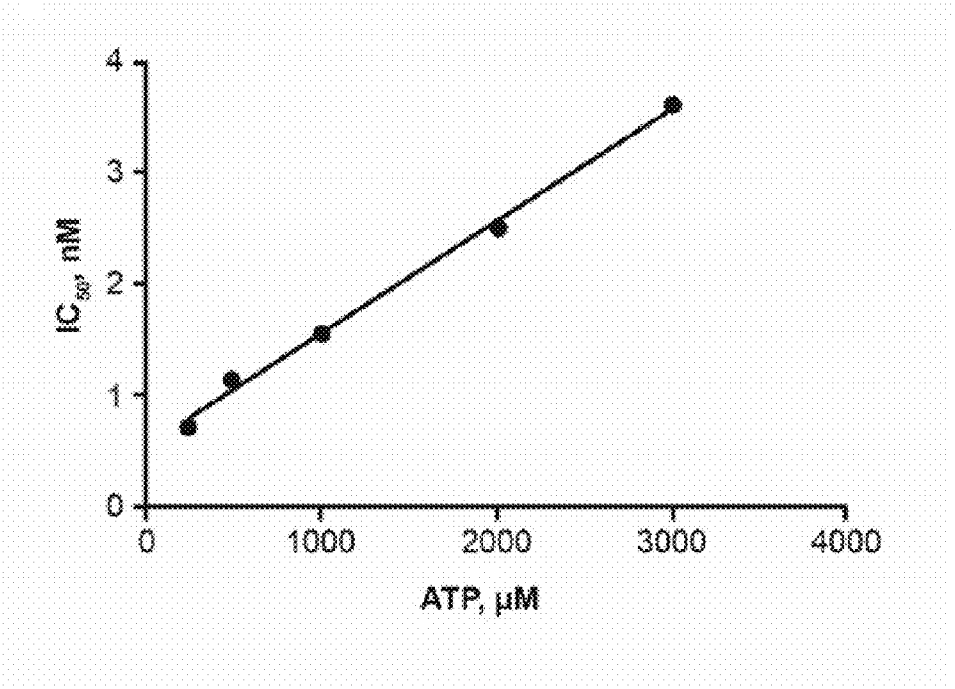


FIG. 29C

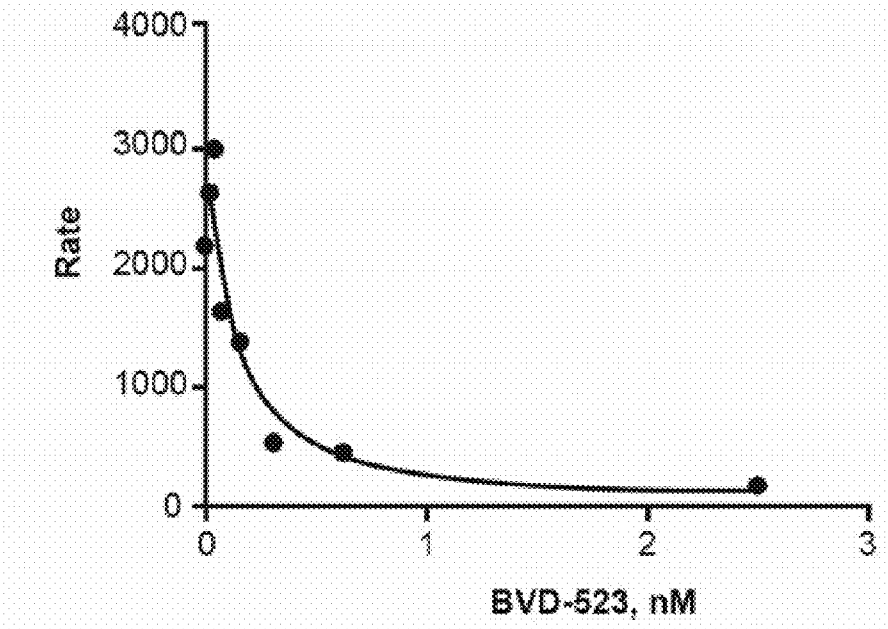


FIG. 29D

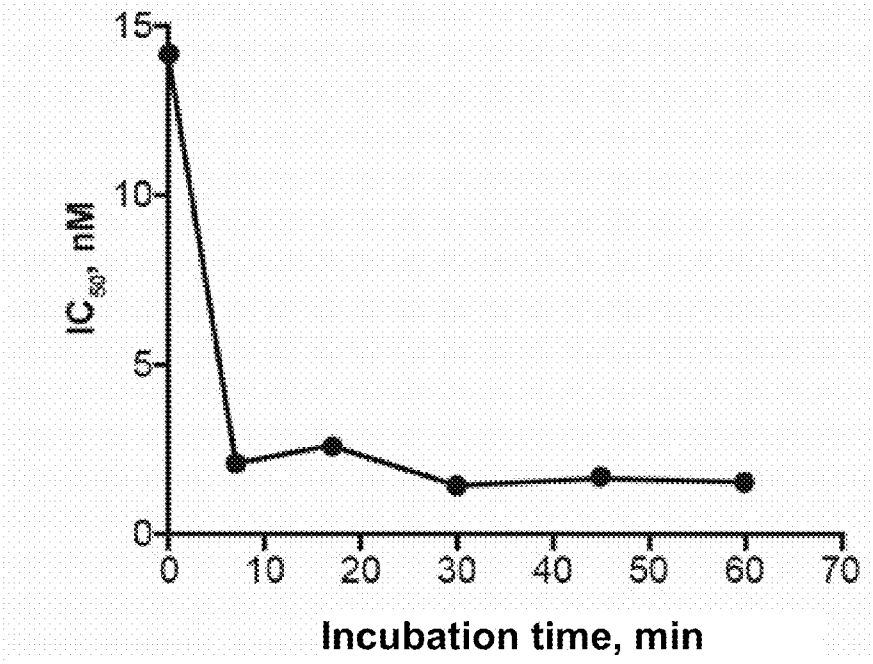


FIG. 29E

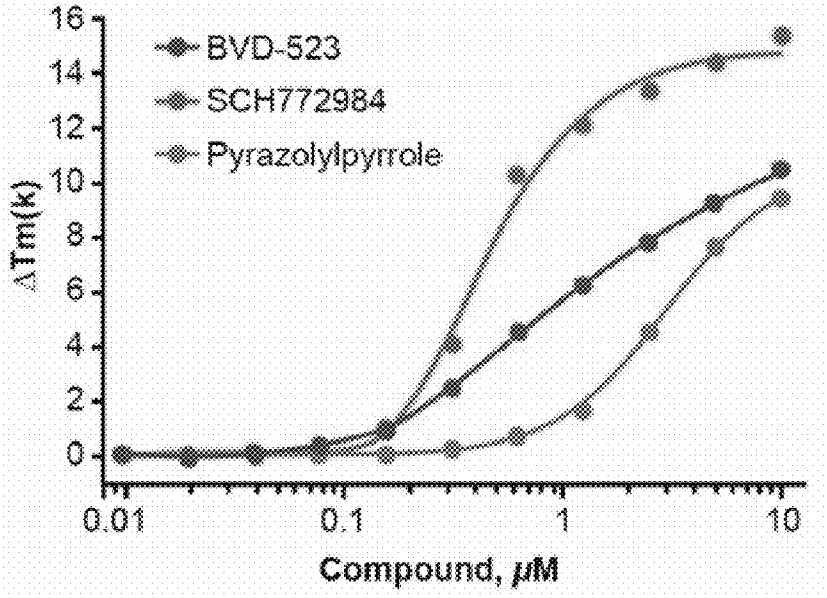


FIG. 29F

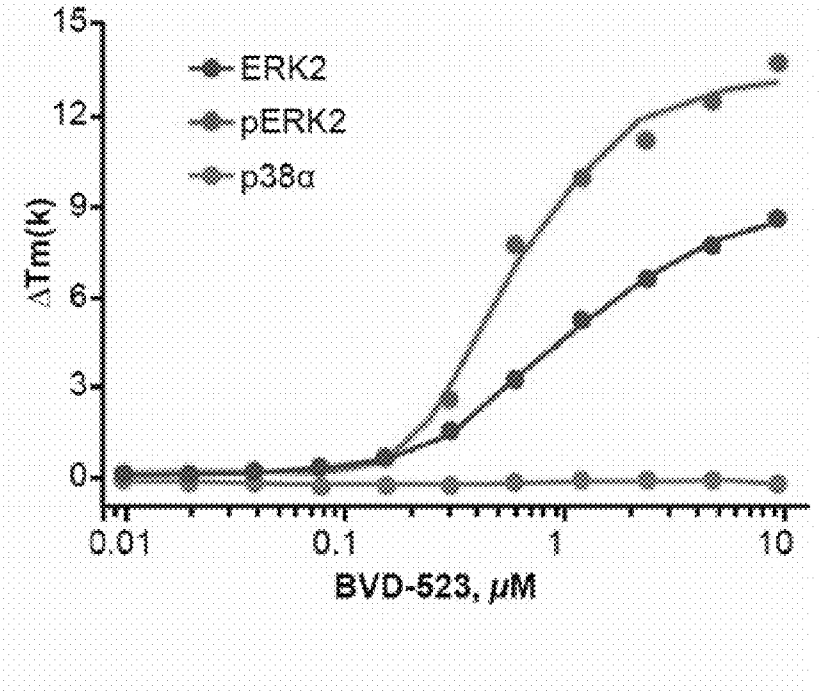


FIG. 30A

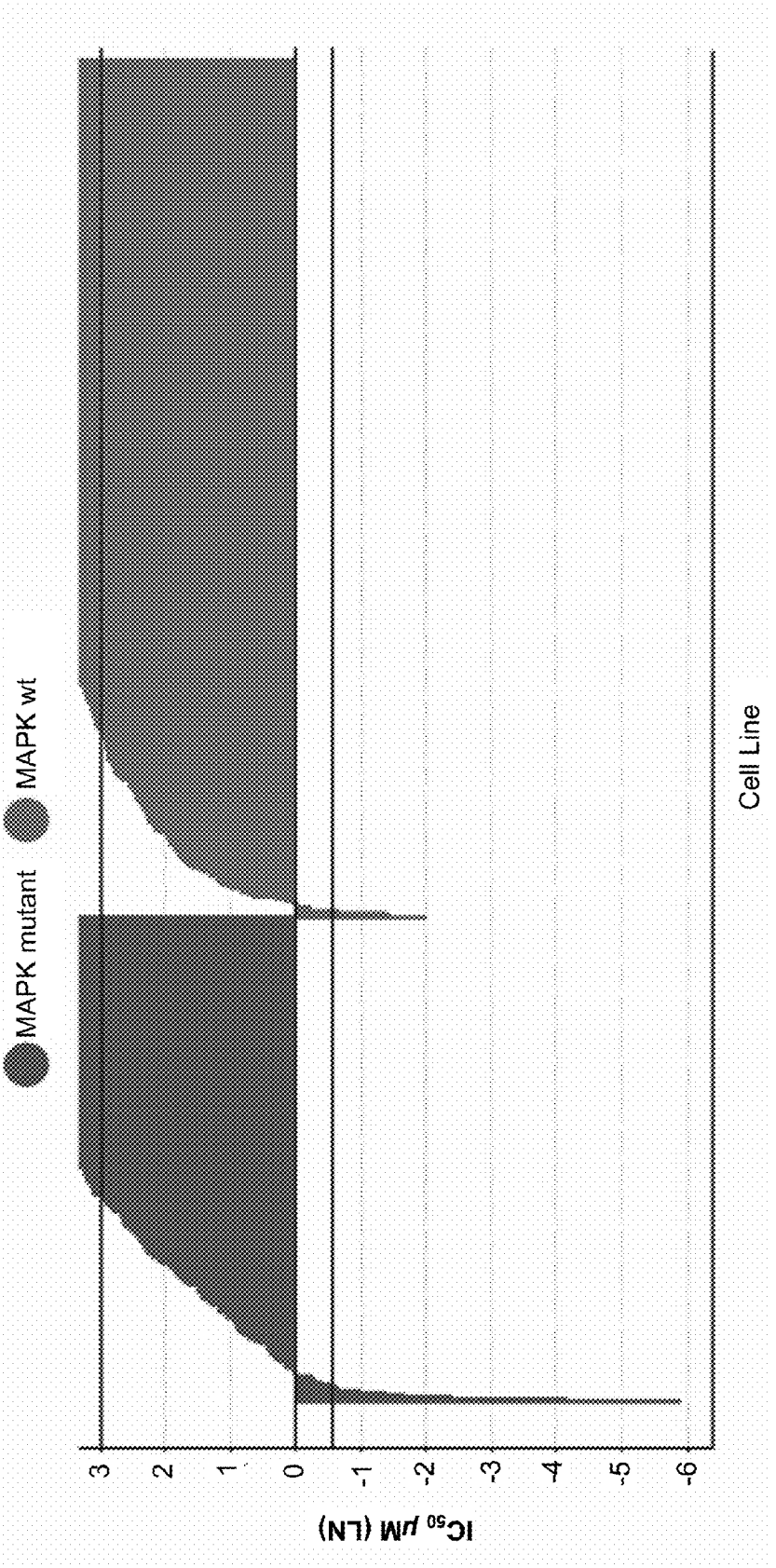


FIG. 30B

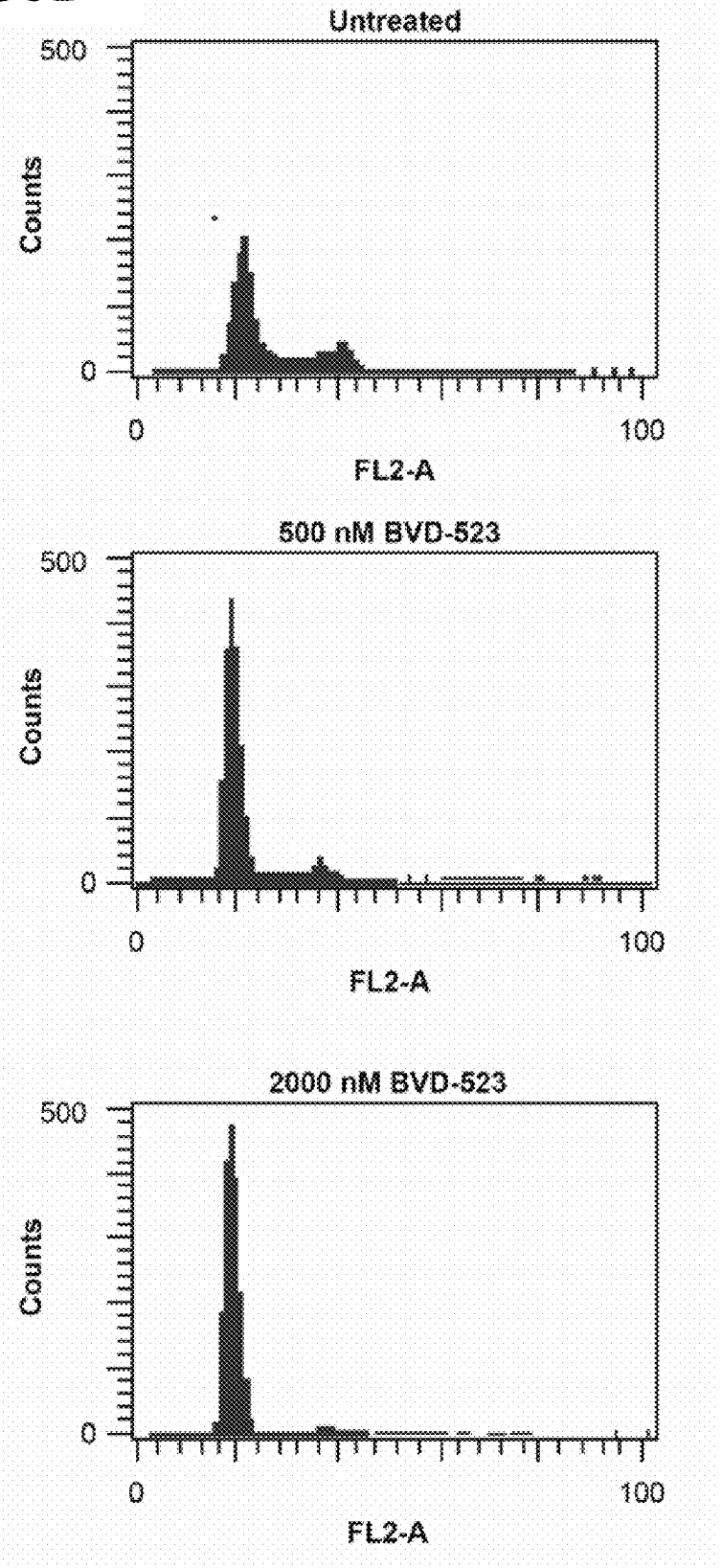

Untreated
500
Counts
0
0
100
FL2-A
500 nM BVD-523
500
Counts
0
0
100
FL2-A
2000 nM BVD-523
500
Counts
0
0
100
FL2-A

FIG. 30C

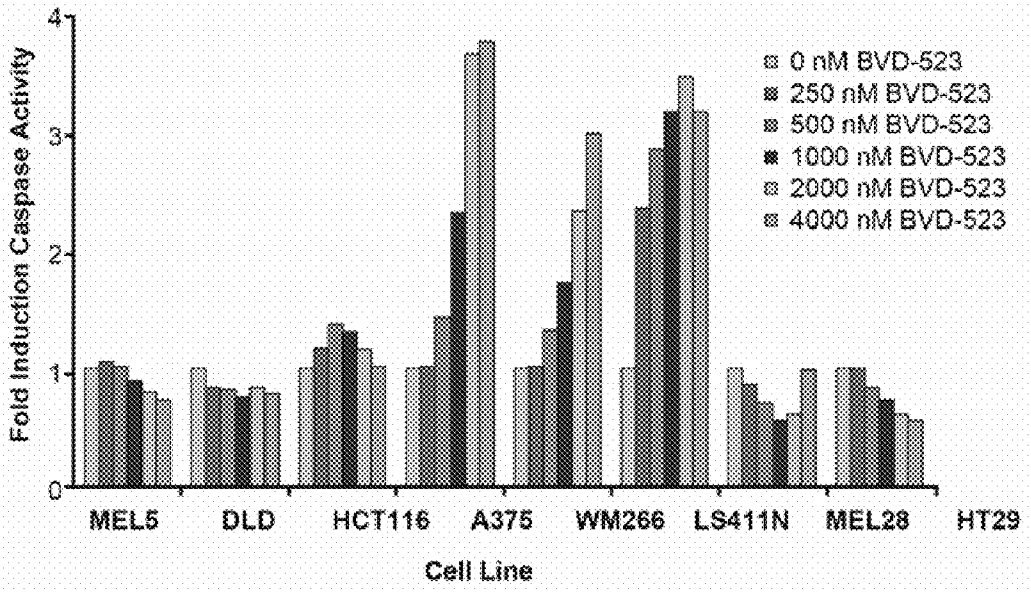


FIG. 30D

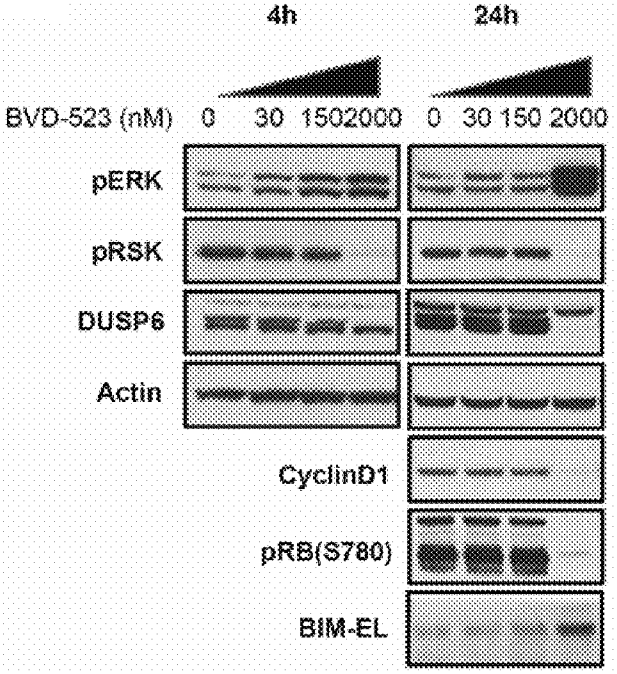


FIG. 31A

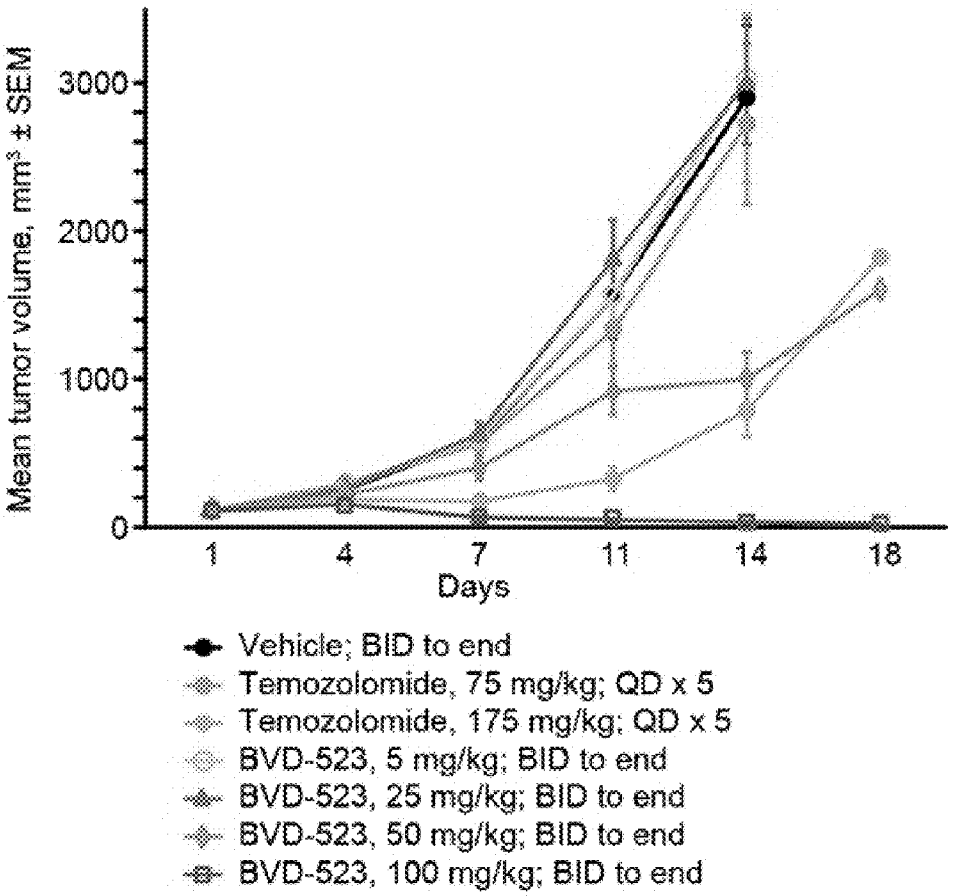

Mean tumor volume, mm³ ± SEM
3000
2000
1000
0
1
4
7
11
14
18
Days
Vehicle; BID to end
Temozolomide, 75 mg/kg; QD x 5
Temozolomide, 175 mg/kg; QD x 5
BVD-523, 5 mg/kg; BID to end
BVD-523, 25 mg/kg; BID to end
BVD-523, 50 mg/kg; BID to end
BVD-523, 100 mg/kg; BID to end

FIG. 31B

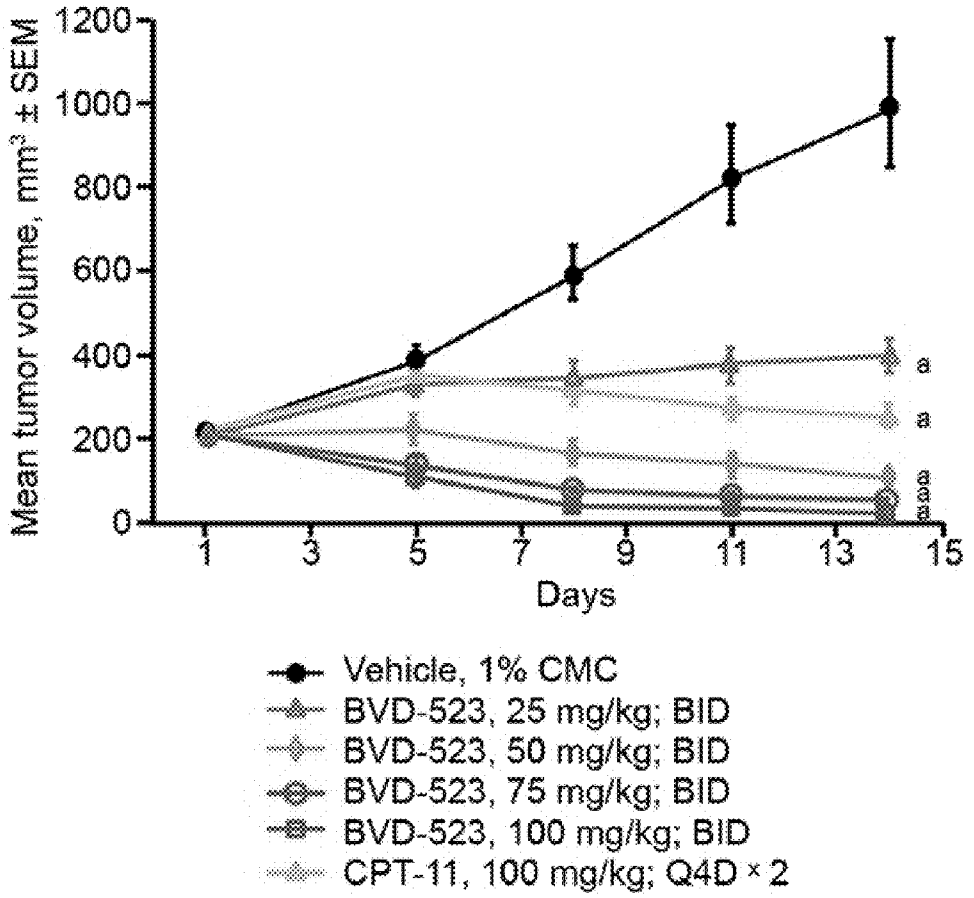

Mean tumor volume, mm³ ± SEM
1200
1000
800
600
400
200
0
1
3
5
7
9
11
13
15
Days
a
a
a
a
Vehicle, 1% CMC
BVD-523, 25 mg/kg; BID
BVD-523, 50 mg/kg; BID
BVD-523, 75 mg/kg; BID
BVD-523, 100 mg/kg; BID
CPT-11, 100 mg/kg; Q4D × 2

FIG. 31C

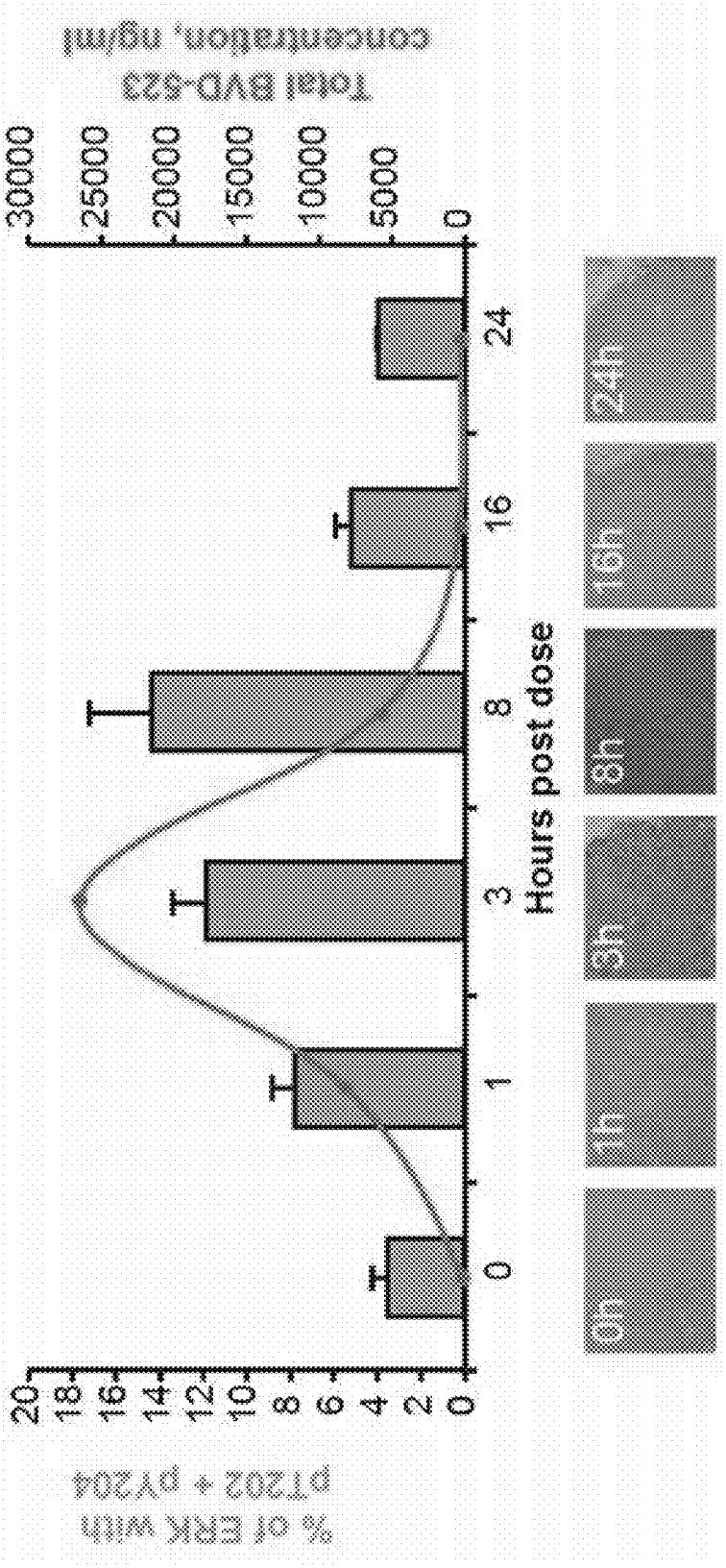

% of ERK with pT202 + pY204
20
18
16
14
12
10
8
6
4
2
0
Total BVD-523 concentration, ng/ml
30000
25000
20000
15000
10000
5000
0
0
1
3
8
16
24
Hours post dose
0h
1h
3h
8h
16h
24h

FIG. 32A

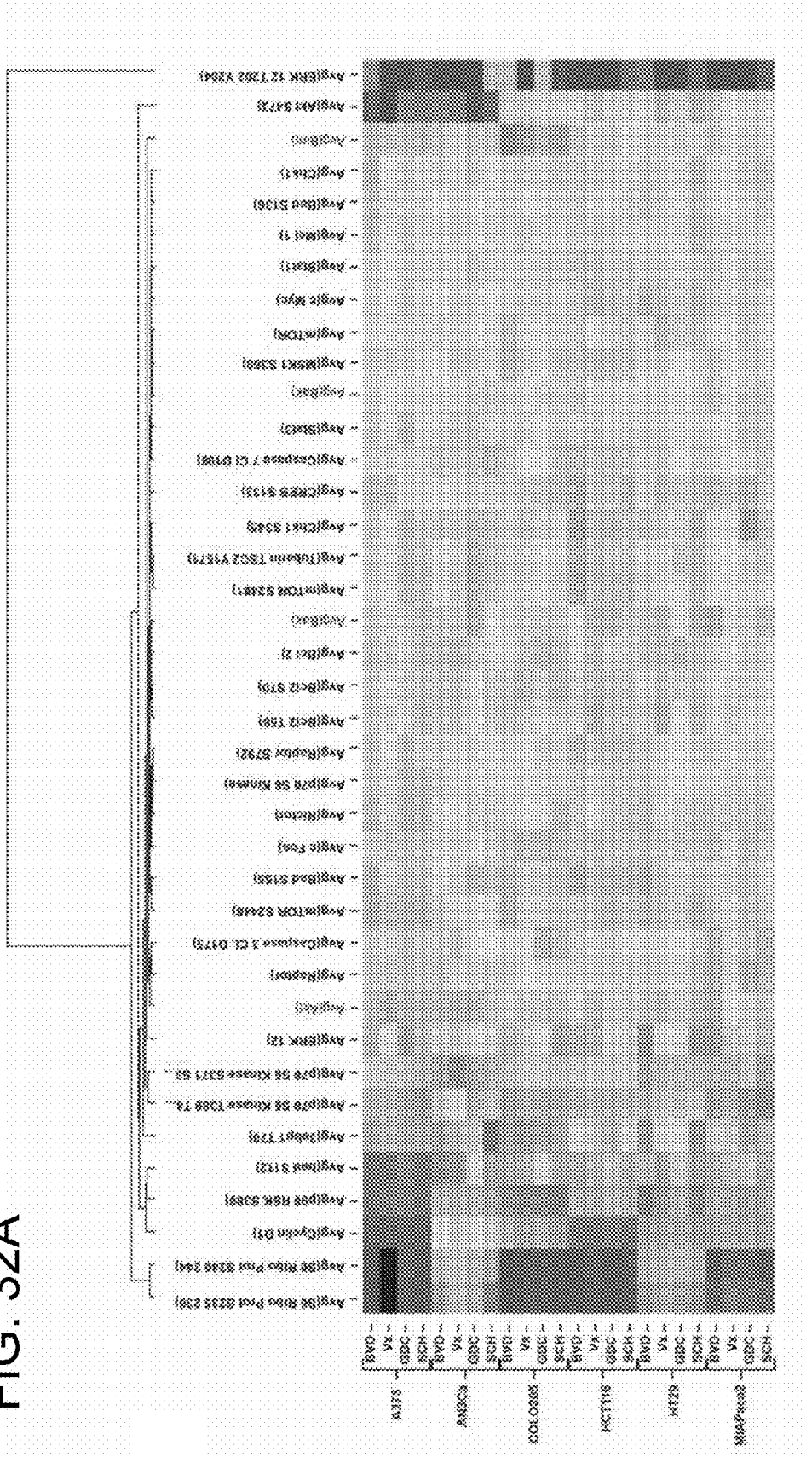

Axl/Src Rico Prot 8235 23s)
Axl/Src Rico Prot 8235 24s)
Axl/Cyclin D1)
Axl/pipe RSK 9385)
Axl/pipe S 1132)
Axl/Jaqt 779)
Axl/pipe 58 Kinase T356 Y4...
Axl/pipe 58 Kinase S371 S3...
Axl/ERK 12)
Axl/pipe)
Axl/Beptor)
Axl/Caspase 3 CL D175)
Axl/mTOR S2448)
Axl/Bad S136)
Axl/pipe Fos)
Axl/Betcin)
Axl/pipe 58 Kinase)
Axl/Beptor S792)
Axl/Bcl2 T56)
Axl/Bcl2 S70)
Axl/pipe Z)
Axl/pipe)
Axl/mTOR S2481)
Axl/Tubulin TSC2 Y1571)
Axl/Chk1 S345)
Axl/CREB S133)
Axl/Caspase 7 CI D198)
Axl/S6K1)
Axl/pipe)
Axl/MSK1 S360)
Axl/mTOR)
Axl/pipe Myc)
Axl/Bad 9)
Axl/Bad S136)
Axl/Chk1)
Axl/pipe)
Axl/Akt S473)
Axl/ERK 12 T202 Y204)
BVD
VX
GDC
SCH
A375
A498
COLO205
HCT116
KP2
MIAPaca2

FIG. 32B

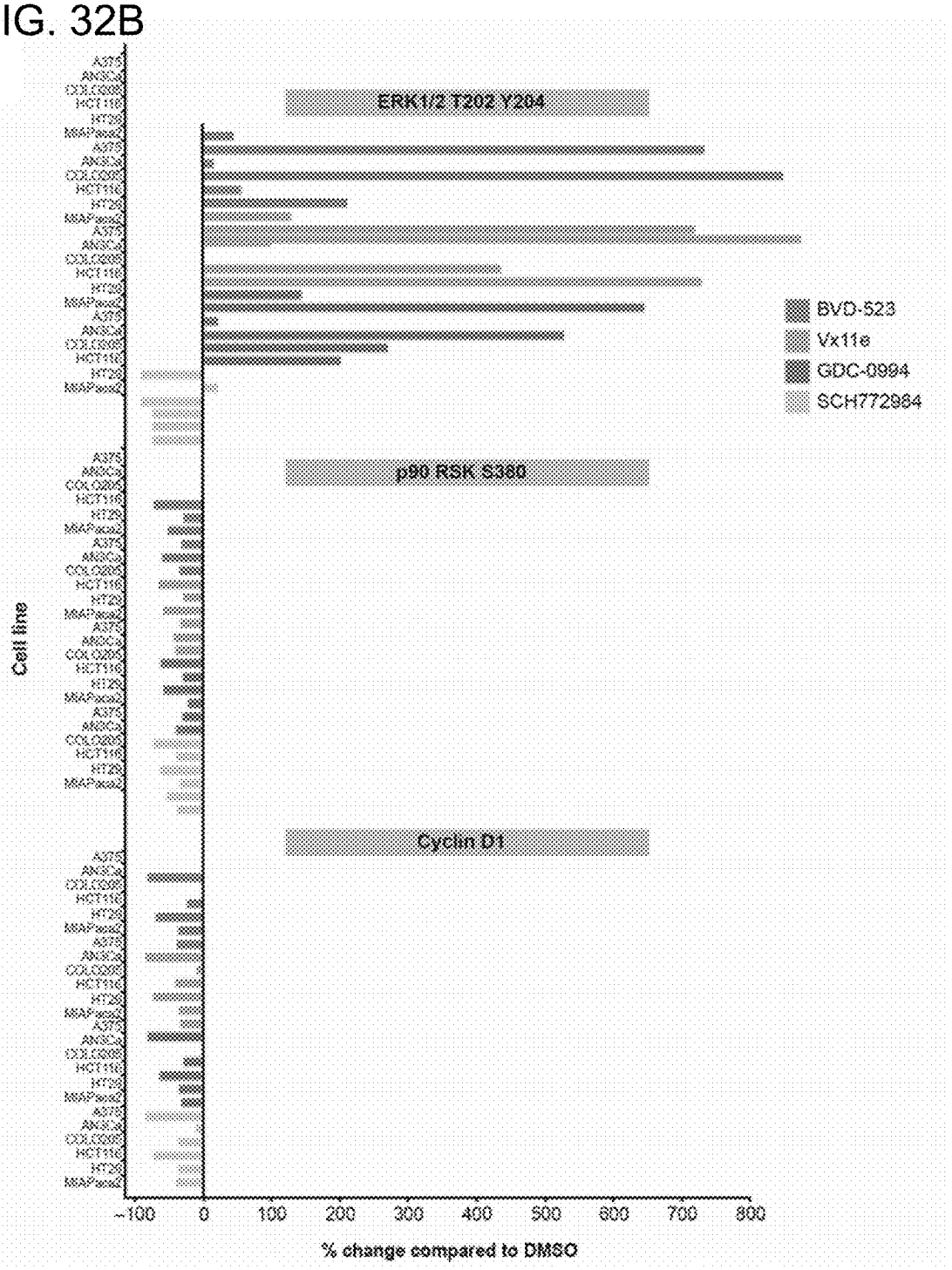

ERK1/2 T202 Y204
p90 RSK S380
Cyclin D1
BVD-523
Vx11e
GDC-0994
SCH772984
Cell line
-100
0
100
200
300
400
500
600
700
800
% change compared to DMSO

FIG. 32C

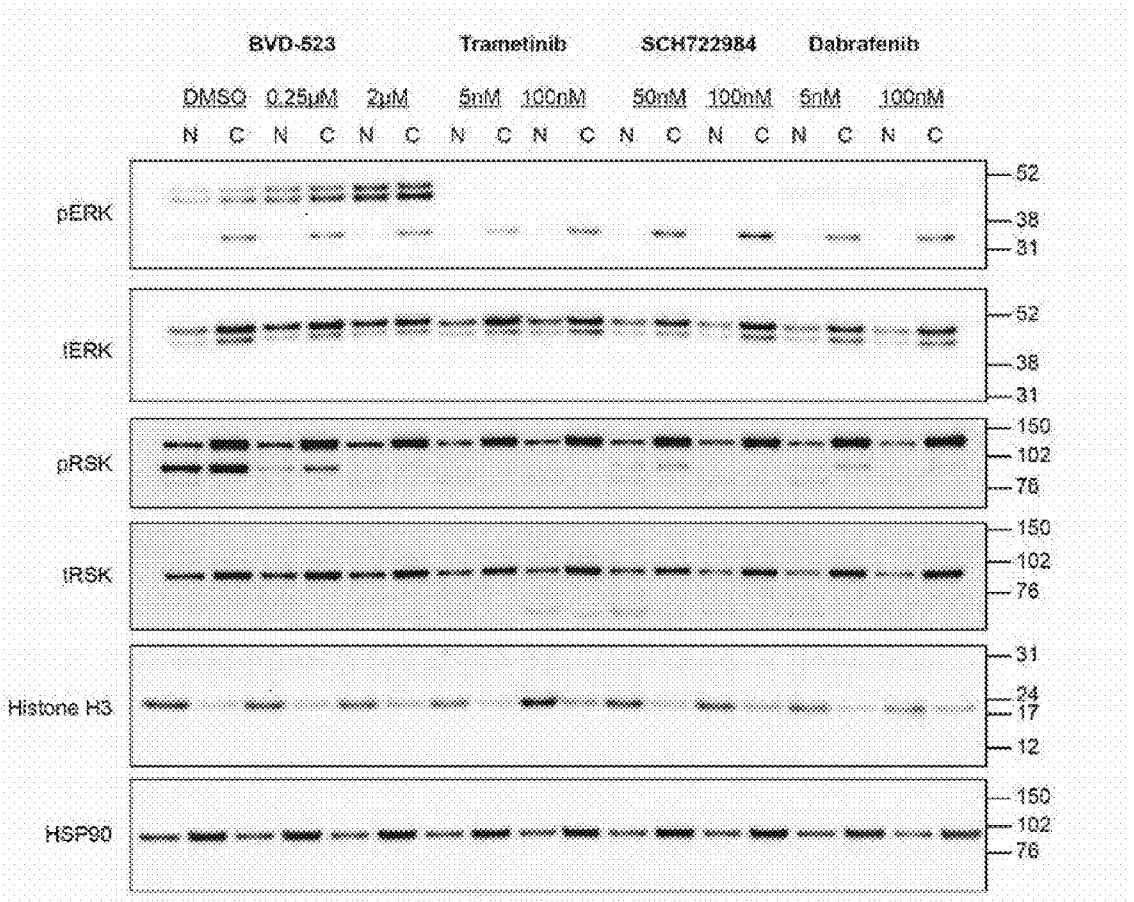

BVD-523
Trametinib
SCH722984
Dabrafenib
DMSO
0.25uM
2uM
5nM
100nM
50nM
100nM
5nM
100nM
N C N C N C N C N C N C N C N C N C
pERK
tERK
pRSK
tRSK
Histone H3
HSP90
52
38
31
150
102
76
24
17
12

FIG. 33

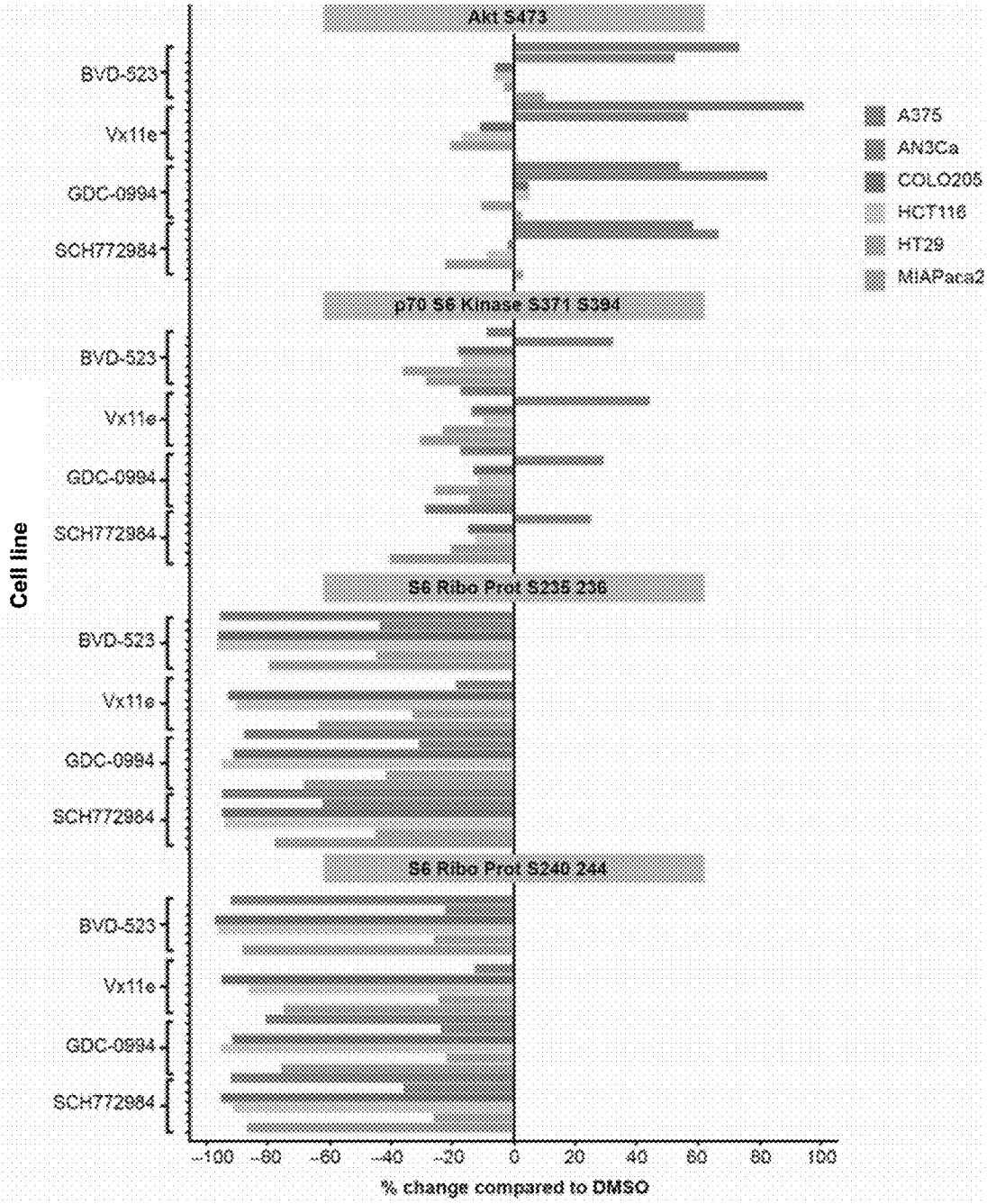

Akt S473
p70 S6 Kinase S371 S394
S6 Ribo Prot S235 236
S6 Ribo Prot S240 244
BVD-523
Vx11e
GDC-0994
SCH772984
Cell line
A375
AN3Ca
COLO205
HCT116
HT29
MIAPaca2
-100 -80 -60 -40 -20 0 20 40 60 80 100
% change compared to DMSO

FIG. 34A

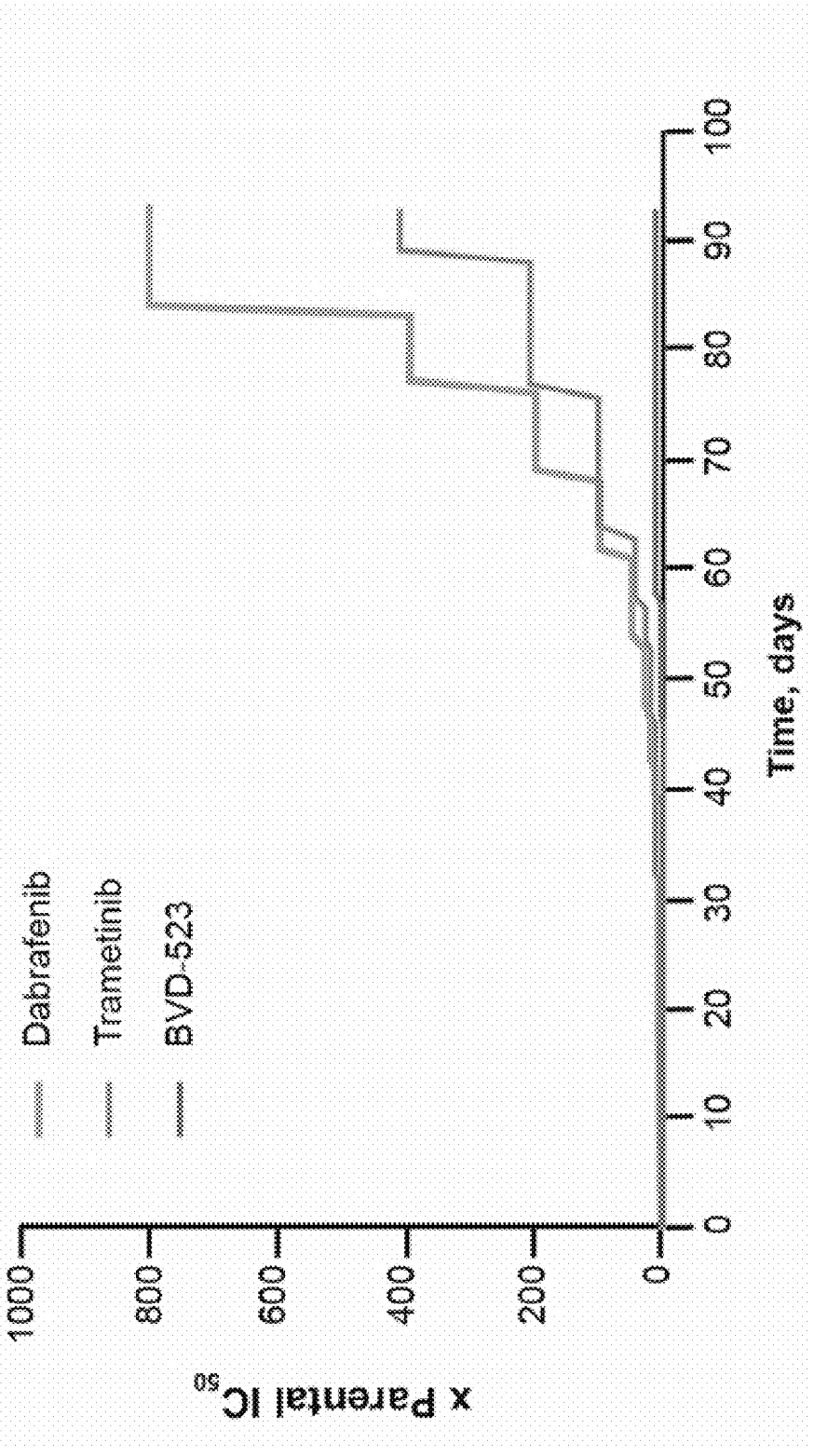

Dabrafenib
Trametinib
BVD-523
x Parental IC50
1000
800
600
400
200
0
0
10
20
30
40
50
60
70
80
90
100
Time, days

FIG. 34B

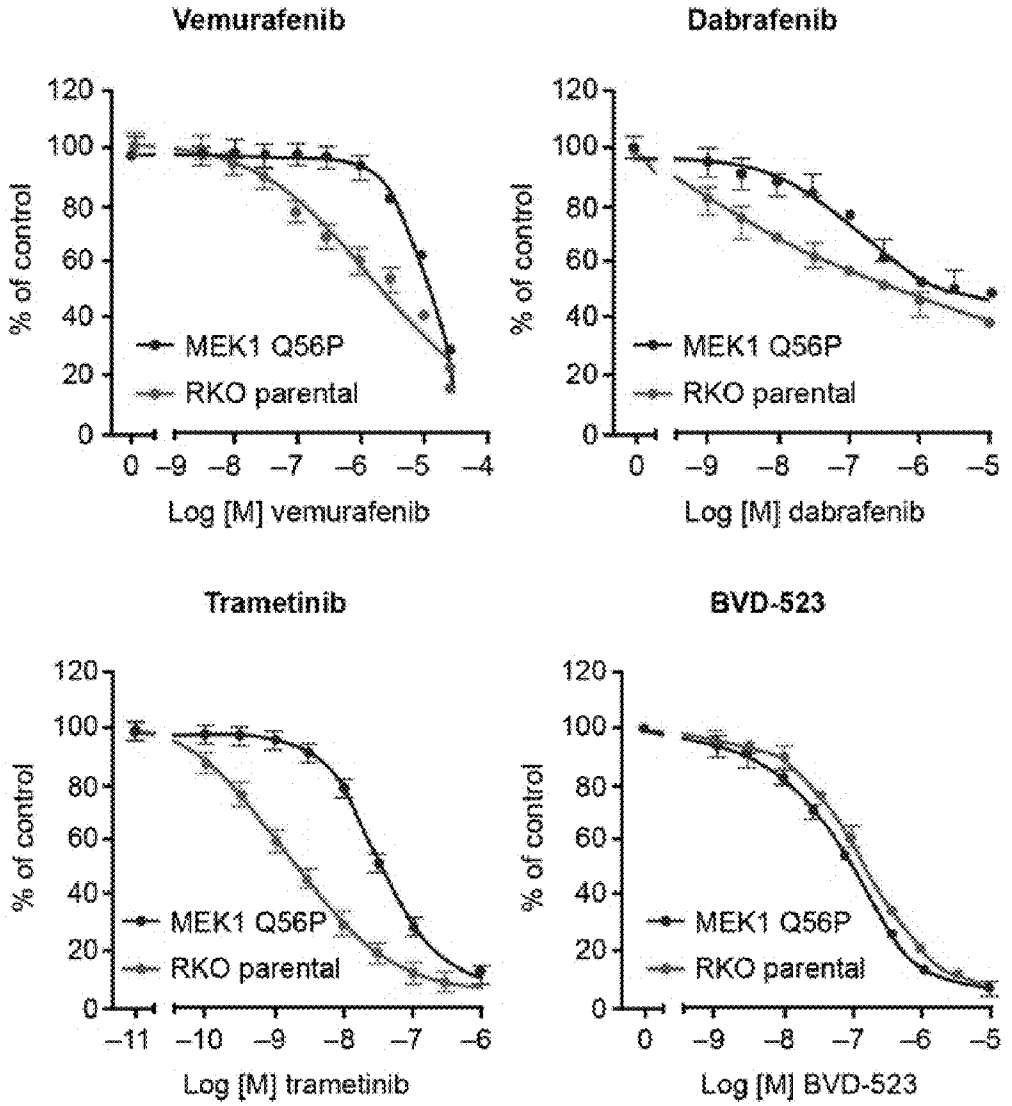

Vemurafenib
Dabrafenib
Trametinib
BVD-523
% of control
MEK1 Q56P
RKO parental
Log [M] vemurafenib
Log [M] dabrafenib
Log [M] trametinib
Log [M] BVD-523

FIG. 34C

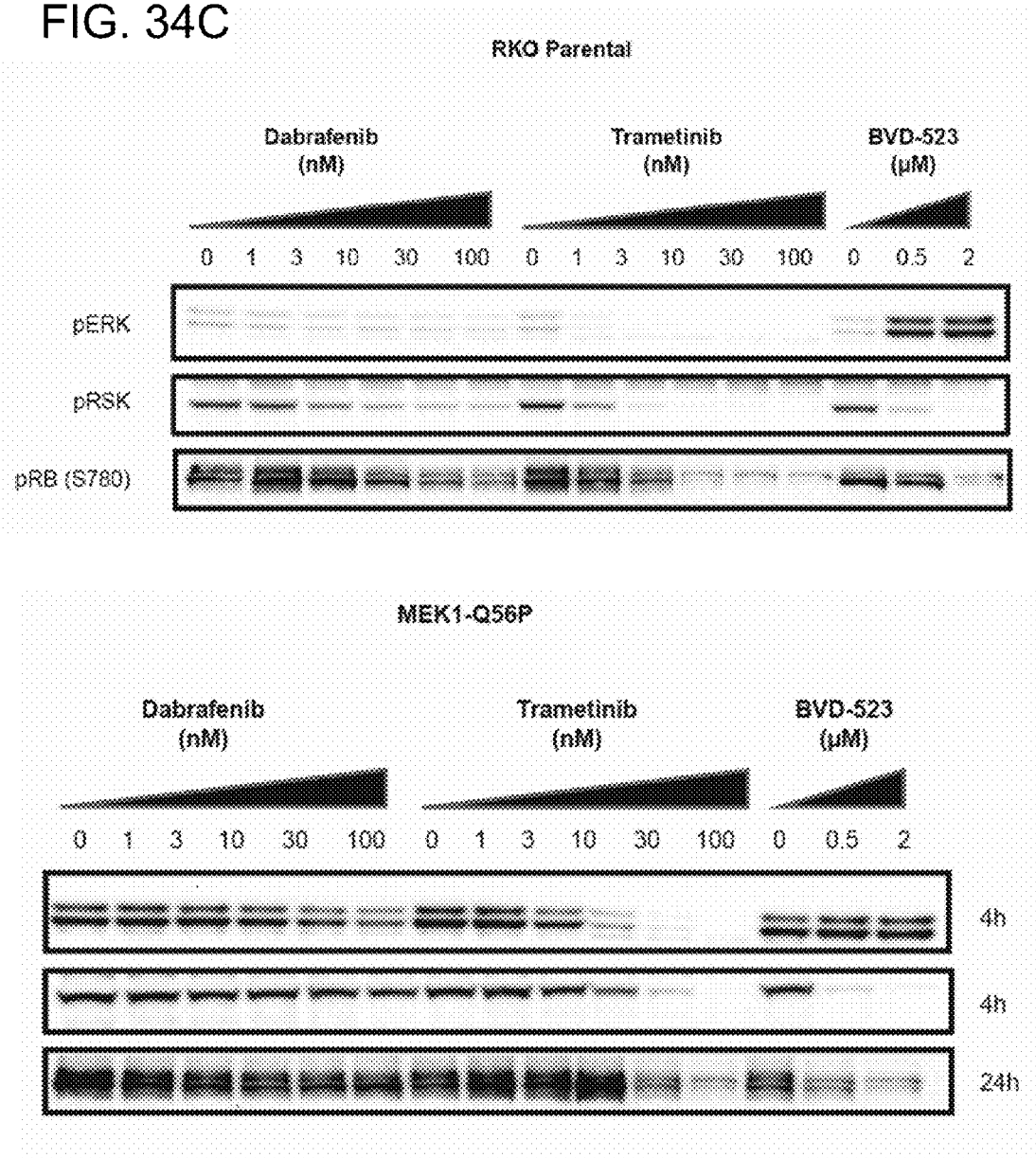

RKO Parental
Dabrafenib (nM)
Trametinib (nM)
BVD-523 (μM)
0 1 3 10 30 100 0 1 3 10 30 100 0 0.5 2
pERK
pRSK
pRB (S780)
MEK1-Q56P
Dabrafenib (nM)
Trametinib (nM)
BVD-523 (μM)
0 1 3 10 30 100 0 1 3 10 30 100 0 0.5 2
4h
4h
24h

FIG. 34D

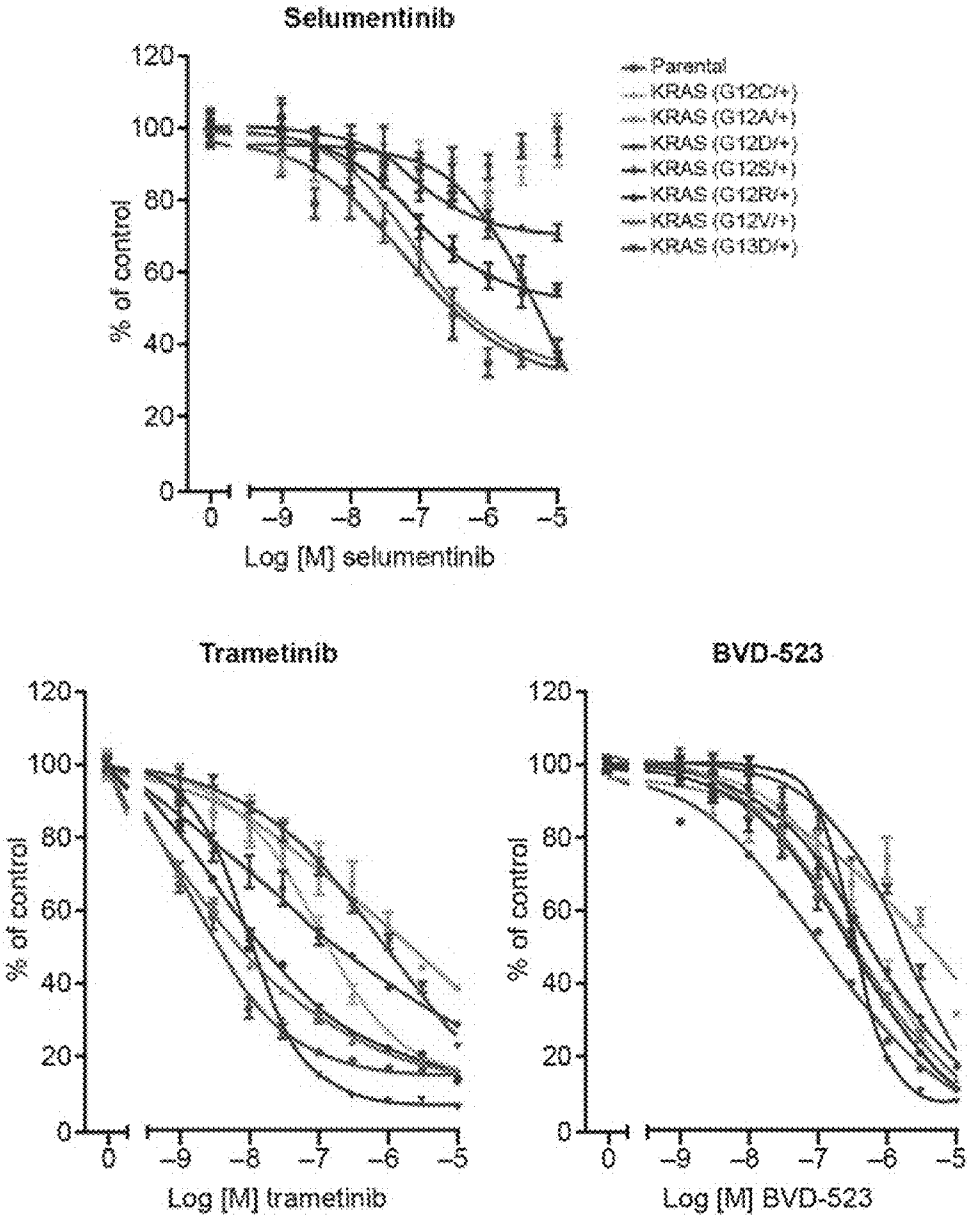

Selumentinib
120
100
80
60
40
20
0
% of control
0
−9
−8
−7
−6
−5
Log [M] selumentinib
Parental
KRAS (G12C/+)
KRAS (G12A/+)
KRAS (G12D/+)
KRAS (G12S/+)
KRAS (G12R/+)
KRAS (G12V/+)
KRAS (G13D/+)
Trametinib
Log [M] trametinib
BVD-523
Log [M] BVD-523

FIG. 35A

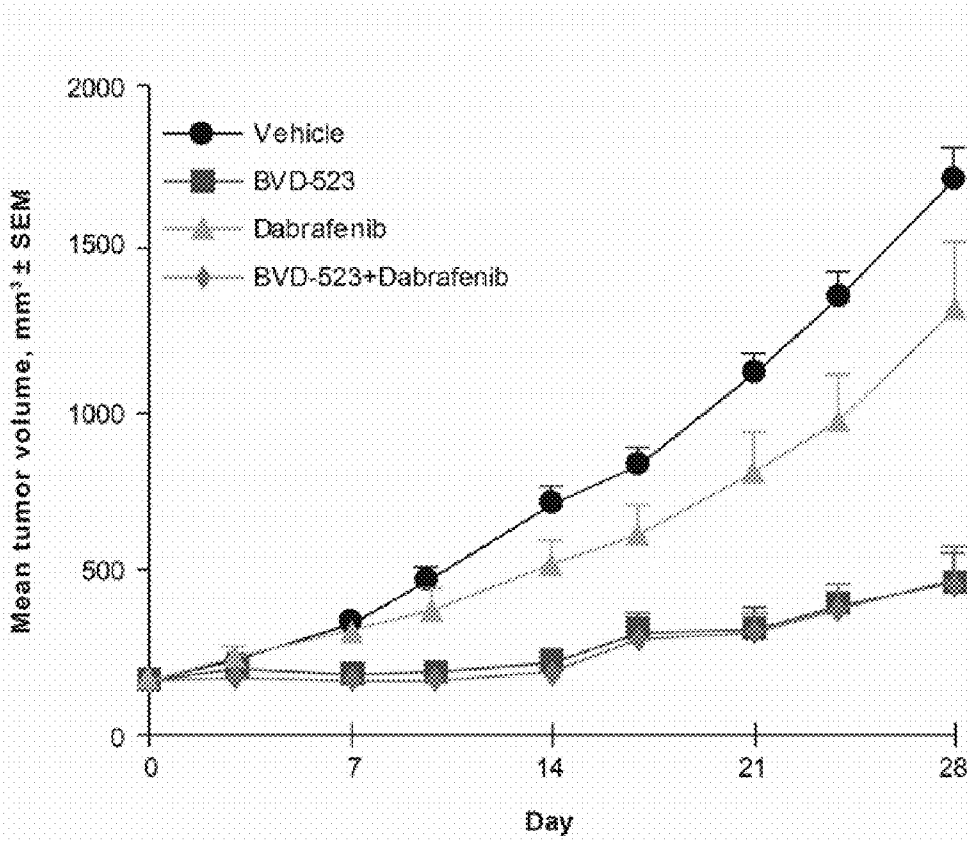

2000
1500
1000
500
0
Mean tumor volume, mm³ ± SEM
Vehicle
BVD-523
Dabrafenib
BVD-523+Dabrafenib
0
7
14
21
28
Day

FIG. 36A

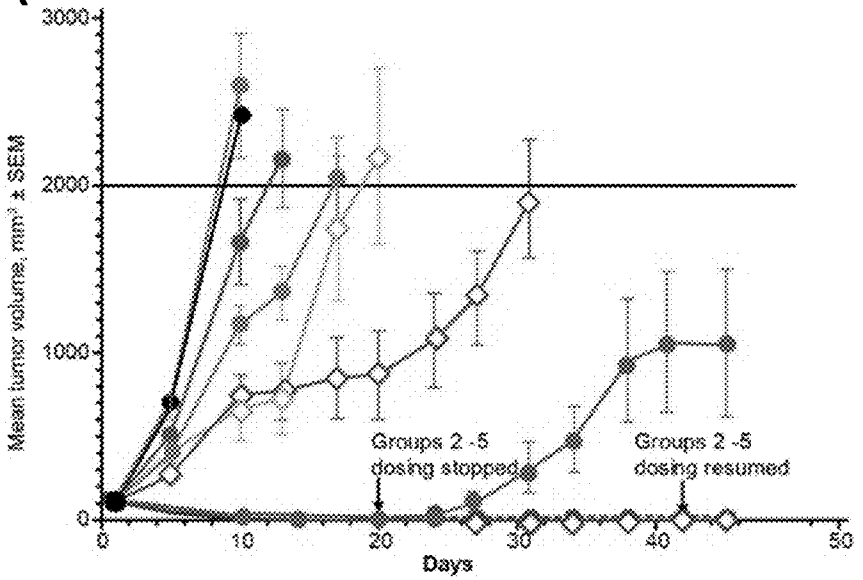
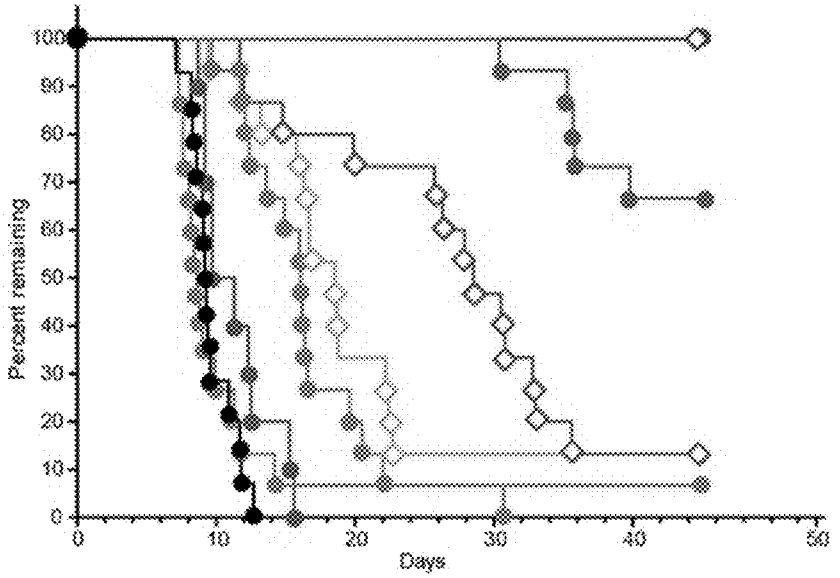


FIG. 36B



G1: Vehicle; QD to end
G2: Dabrafenib, 50 mg/kg + BVD-523, 50 mg/kg
G3: Dabrafenib, 50 mg/kg + BVD-523, 100 mg/kg
G4: Dabrafenib, 100 mg/kg + BVD-523, 50 mg/kg
G5: Dabrafenib, 100 mg/kg + BVD-523, 100 mg/kg
G6: Dabrafenib, 50 mg/kg orally; QD to end
G7: Dabrafenib, 100 mg/kg orally; QD to end
G8: BVD-523, 50 mg/kg orally; BID to end
G9: BVD-523, 100 mg/kg orally; BID to end
G10: Temozolomide, 150 mg/kg orally; QD x 5

FIG. 36C

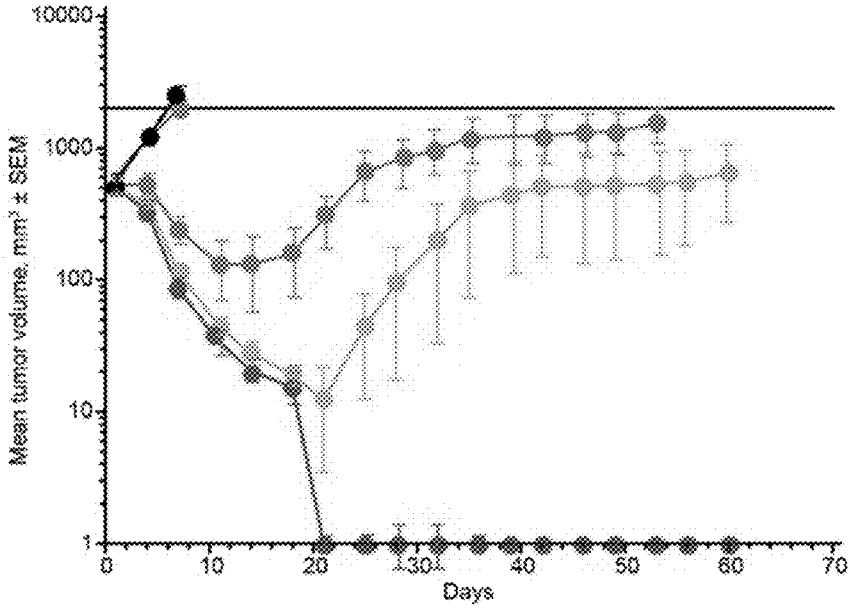


FIG. 36D

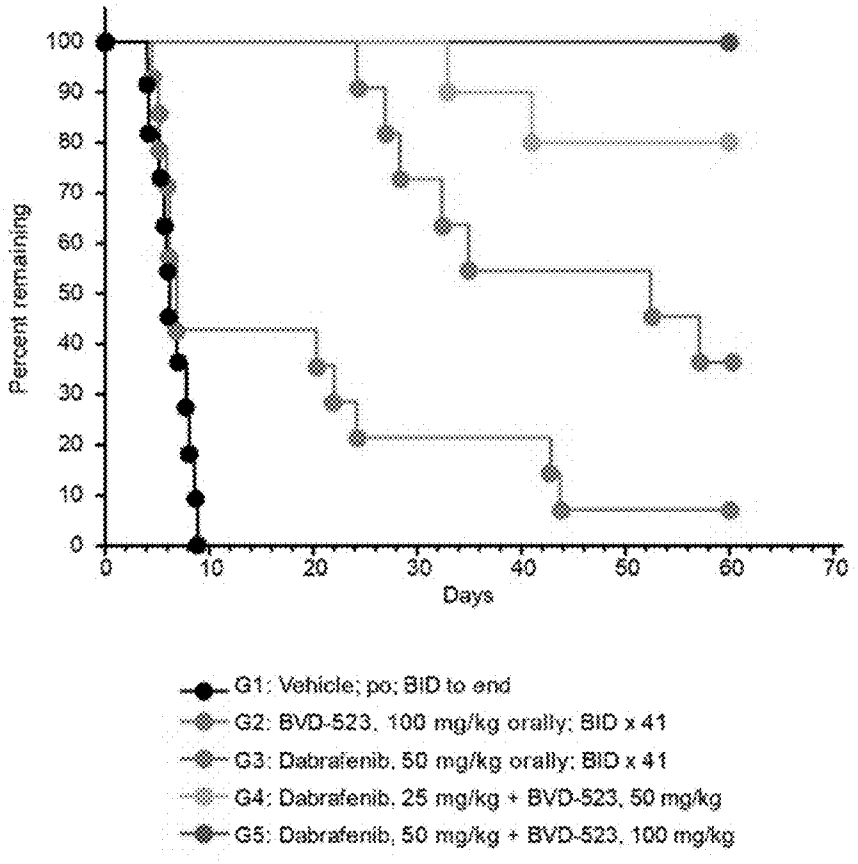


FIG. 37A

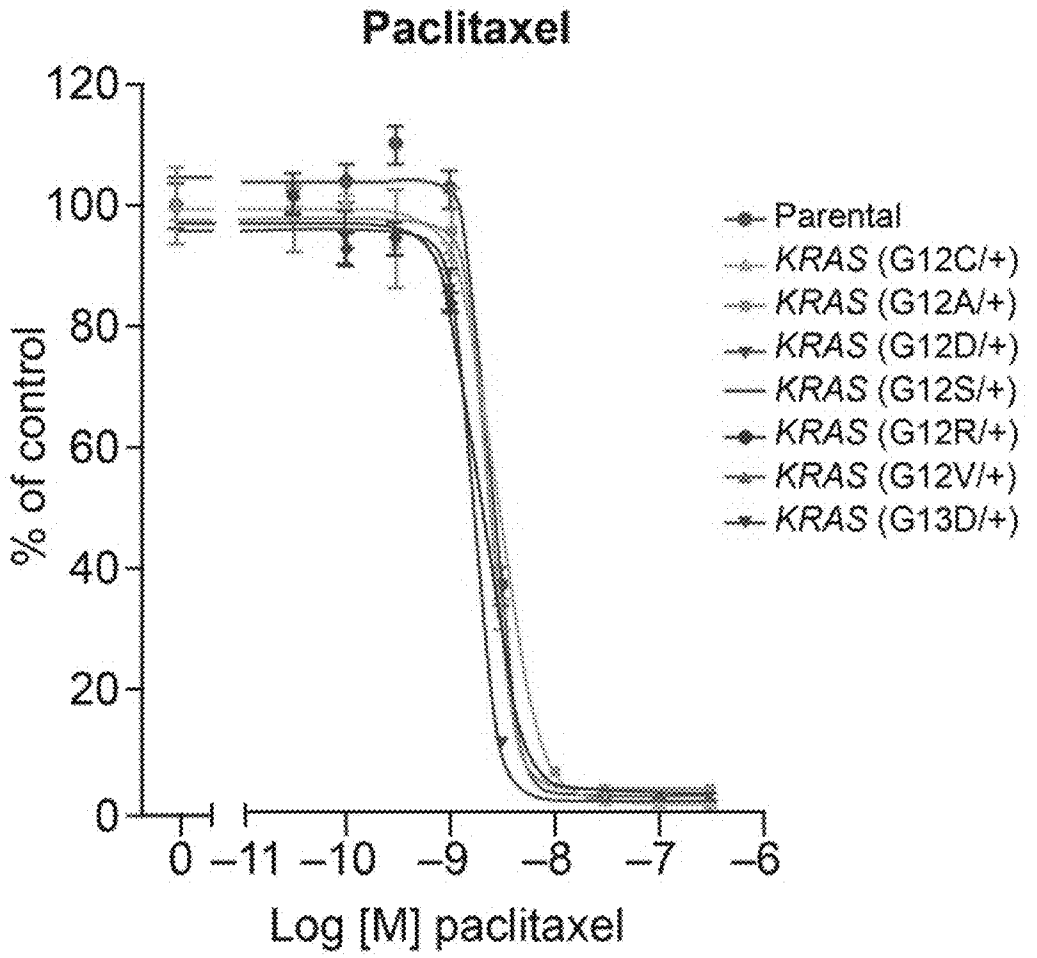
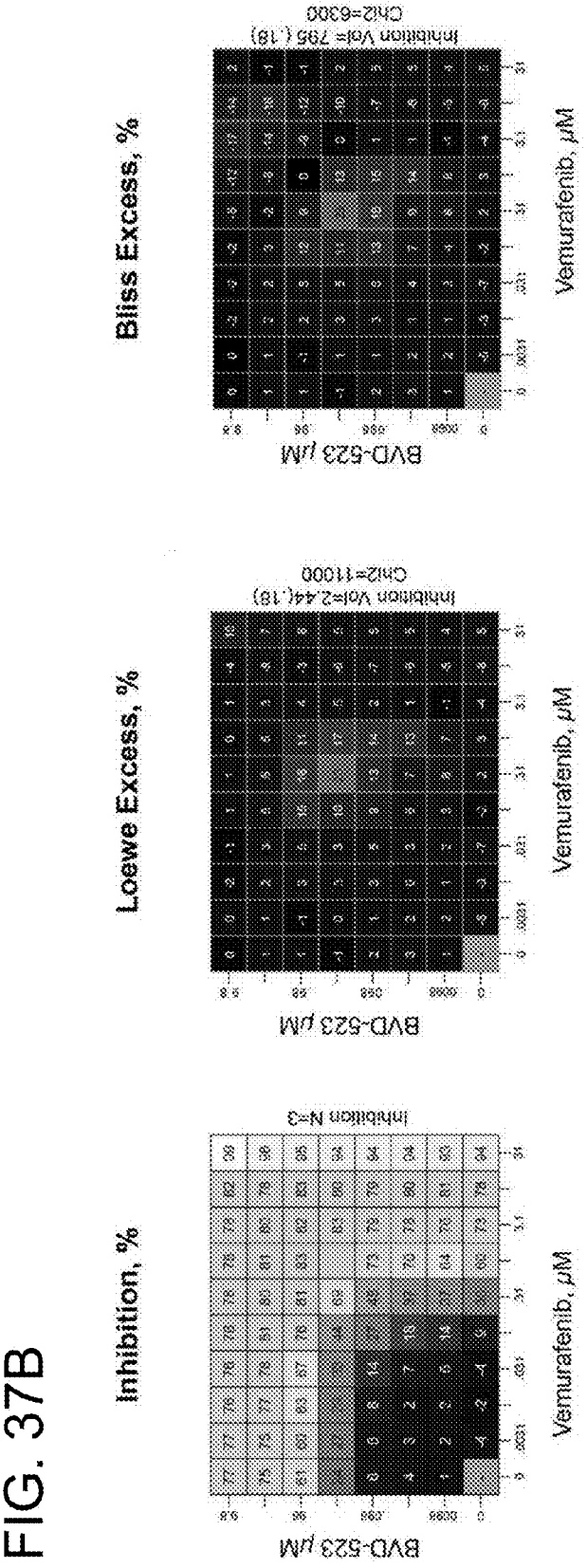

Paclitaxel
120
100
80
60
40
20
0
% of control
0 –11 –10 –9 –8 –7 –6
Log [M] paclitaxel
Parental
KRAS (G12C/+)
KRAS (G12A/+)
KRAS (G12D/+)
KRAS (G12S/+)
KRAS (G12R/+)
KRAS (G12V/+)
KRAS (G13D/+)

FIG. 37B


Bliss Excess, %
Inhibition Vol= 795 (.18)
Ch12=6300
BVD-523 μM
Vemurafenib, μM
Loewe Excess, %
Inhibition Vol=2.44(.18)
Ch12=11000
BVD-523 μM
Vemurafenib, μM
Inhibition, %
Inhibition N=3
BVD-523 μM
Vemurafenib, μM

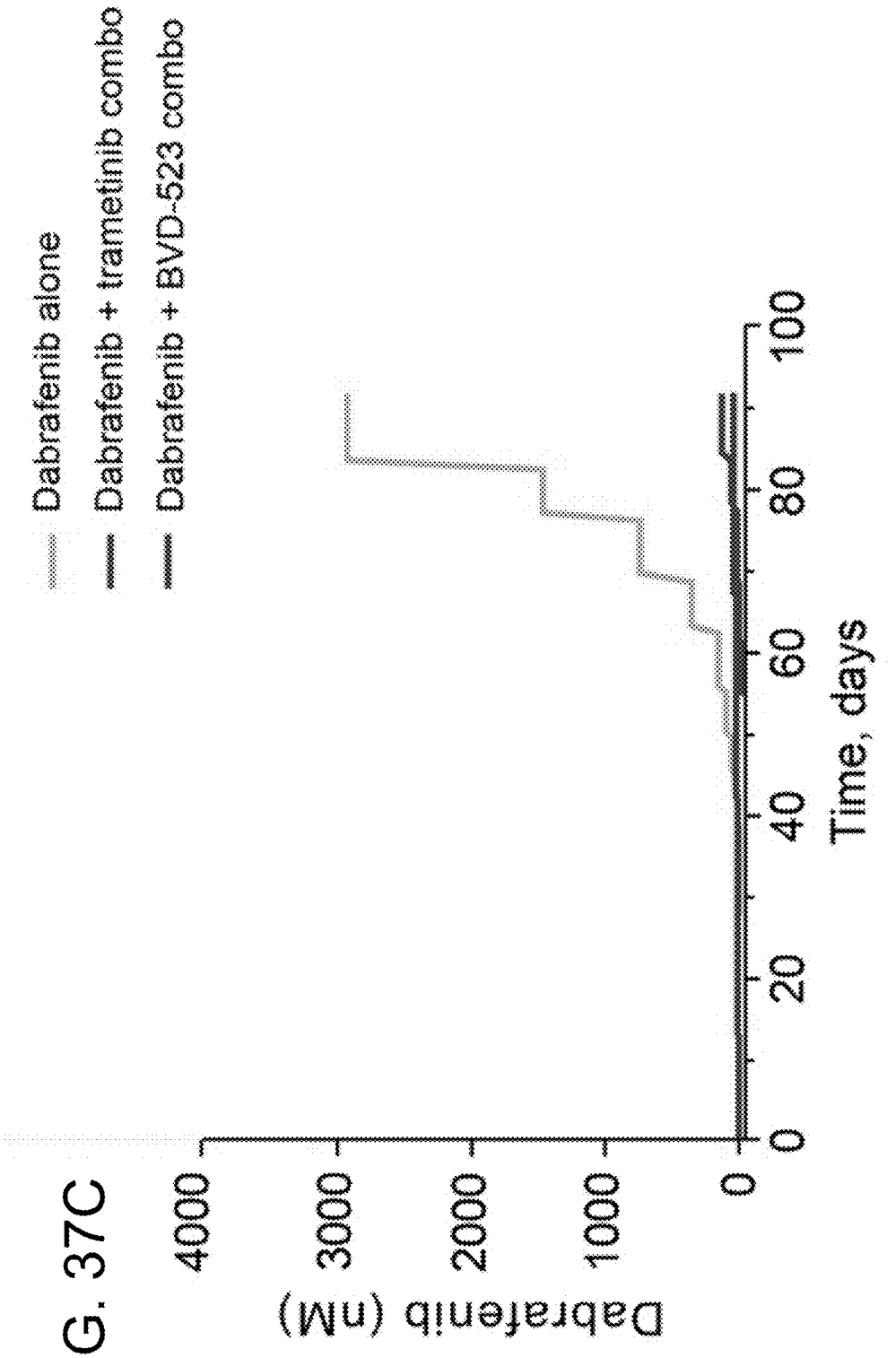

Dabrafenib alone
Dabrafenib + trametinib combo
Dabrafenib + BVD-523 combo
Dabrafenib (nM)
4000
3000
2000
1000
0
0
20
40
60
80
100
Time, days

FIG. 37C

FIG. 38

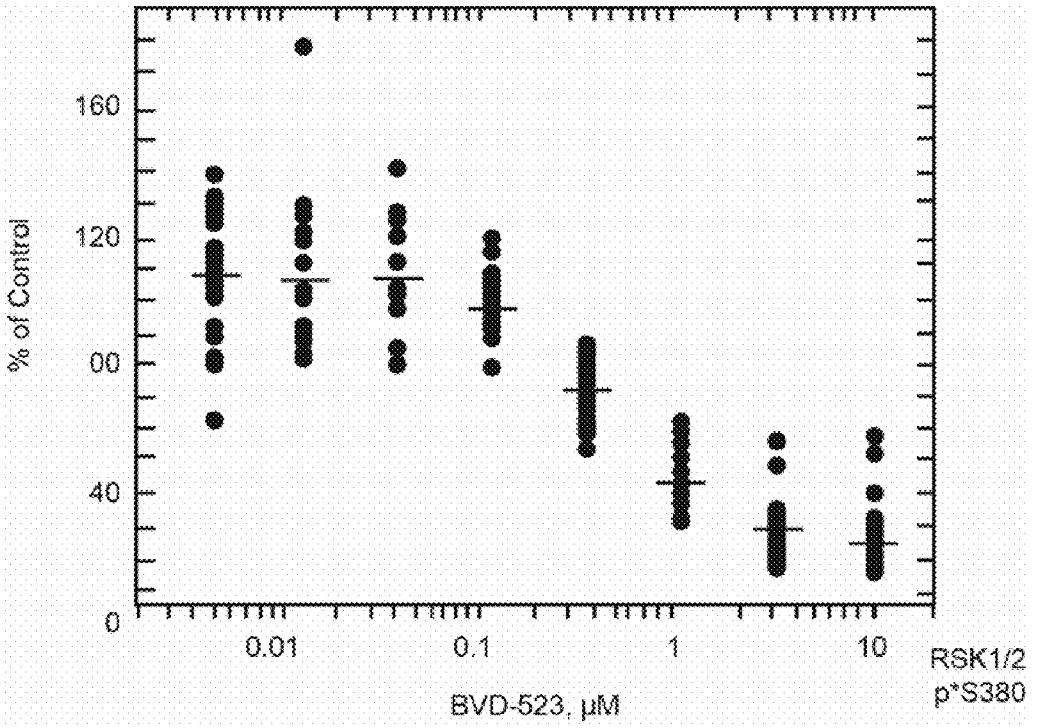
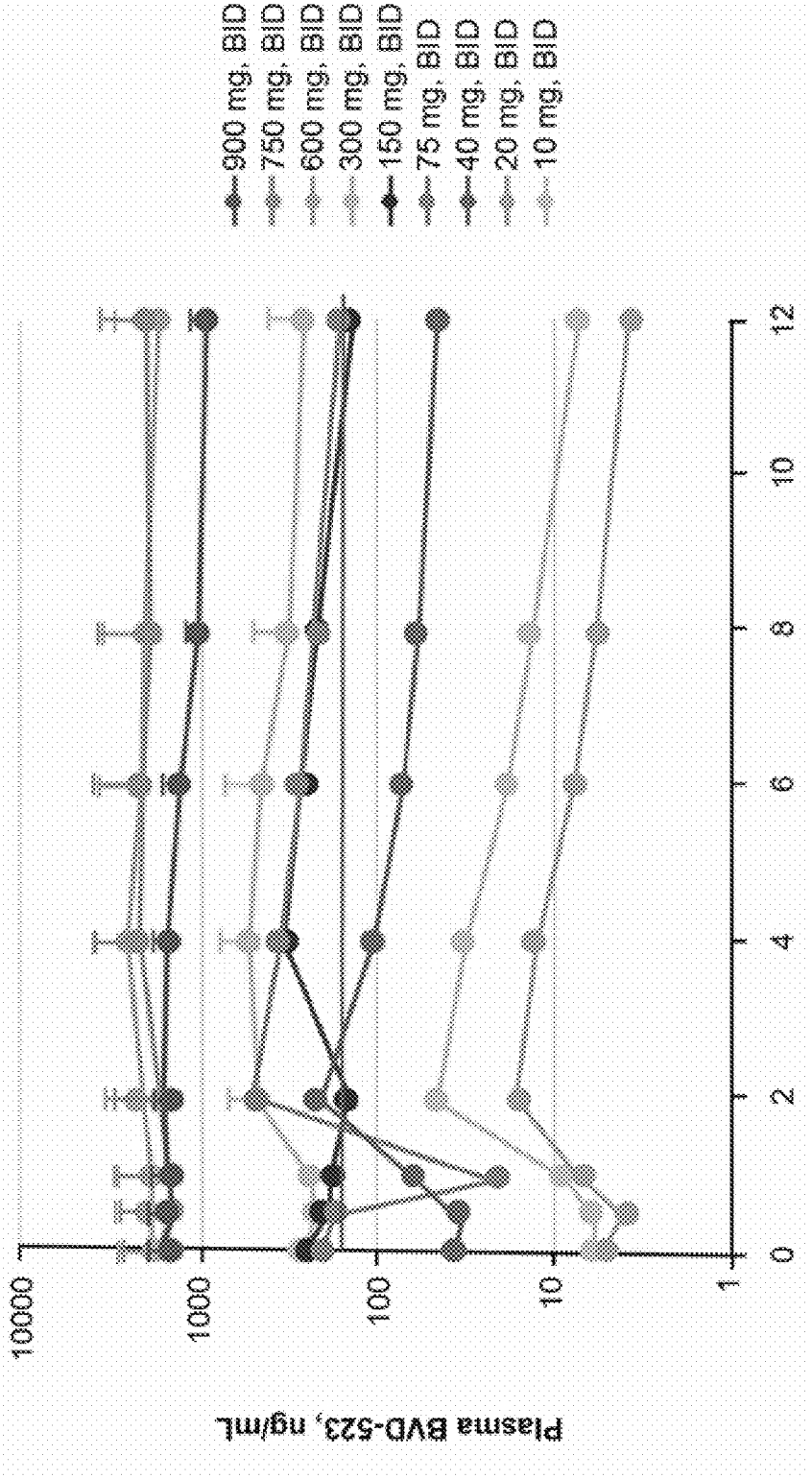


FIG. 39A


900 mg, BID
750 mg, BID
600 mg, BID
300 mg, BID
150 mg, BID
75 mg, BID
40 mg, BID
20 mg, BID
10 mg, BID
Plasma BVD-523, ng/mL
10000
1000
100
10
1
0
2
4
6
8
10
12

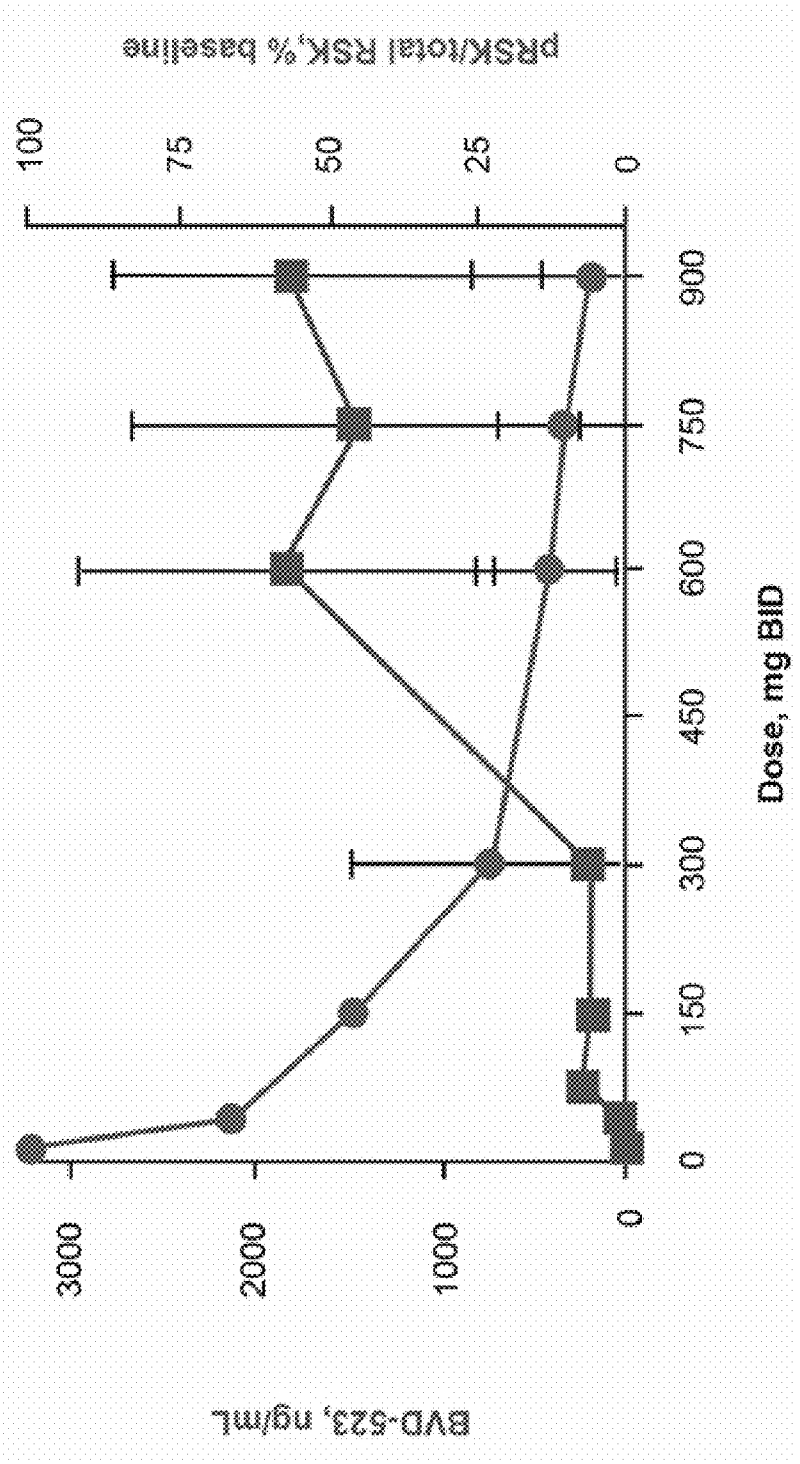

pRSK/total RSK, % baseline
100
75
50
25
0
BVD-523, ng/mL
3000
2000
1000
0
0
150
300
450
600
750
900
Dose, mg BID

FIG. 39B

FIG. 40A

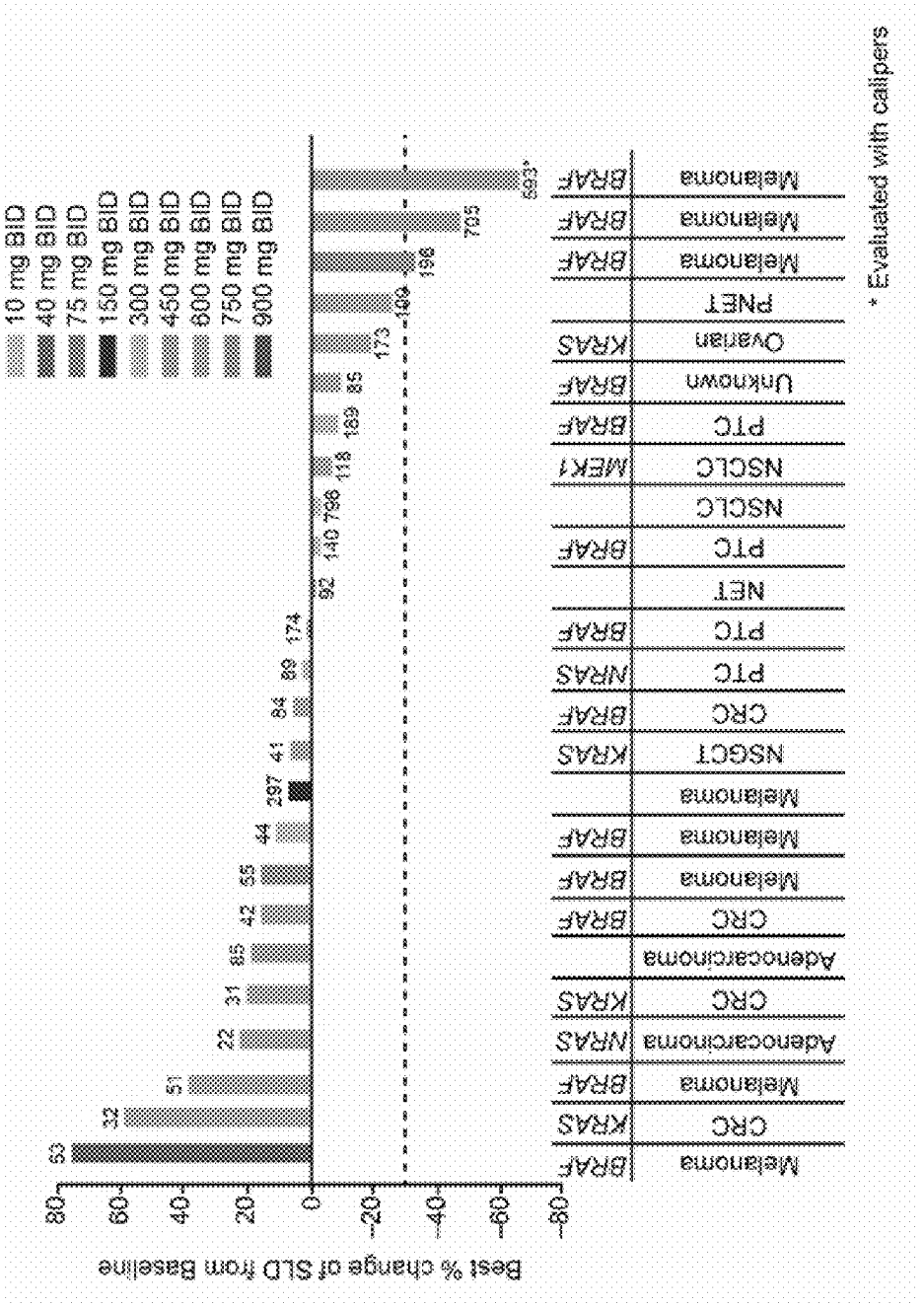

10 mg BID
40 mg BID
75 mg BID
150 mg BID
300 mg BID
450 mg BID
600 mg BID
750 mg BID
900 mg BID
Best % change of SLD from Baseline
80
60
40
20
0
-20
-40
-60
-80
53
32
51
22
31
85
42
55
44
397
41
84
89
174
92
140
796
118
189
85
173
194
198
705
593*
Melanoma BRAF
CRC KRAS
Melanoma BRAF
Adenocarcinoma NRAS
CRC KRAS
Adenocarcinoma
CRC BRAF
Melanoma BRAF
Melanoma BRAF
Melanoma
NSGCT KRAS
CRC BRAF
PTC NRAS
PTC BRAF
NET
PTC BRAF
NSCLC
NSCLC MEK1
PTC BRAF
Unknown BRAF
Ovarian KRAS
PNET
Melanoma BRAF
Melanoma BRAF
Melanoma BRAF
* Evaluated with calipers

FIG. 40B

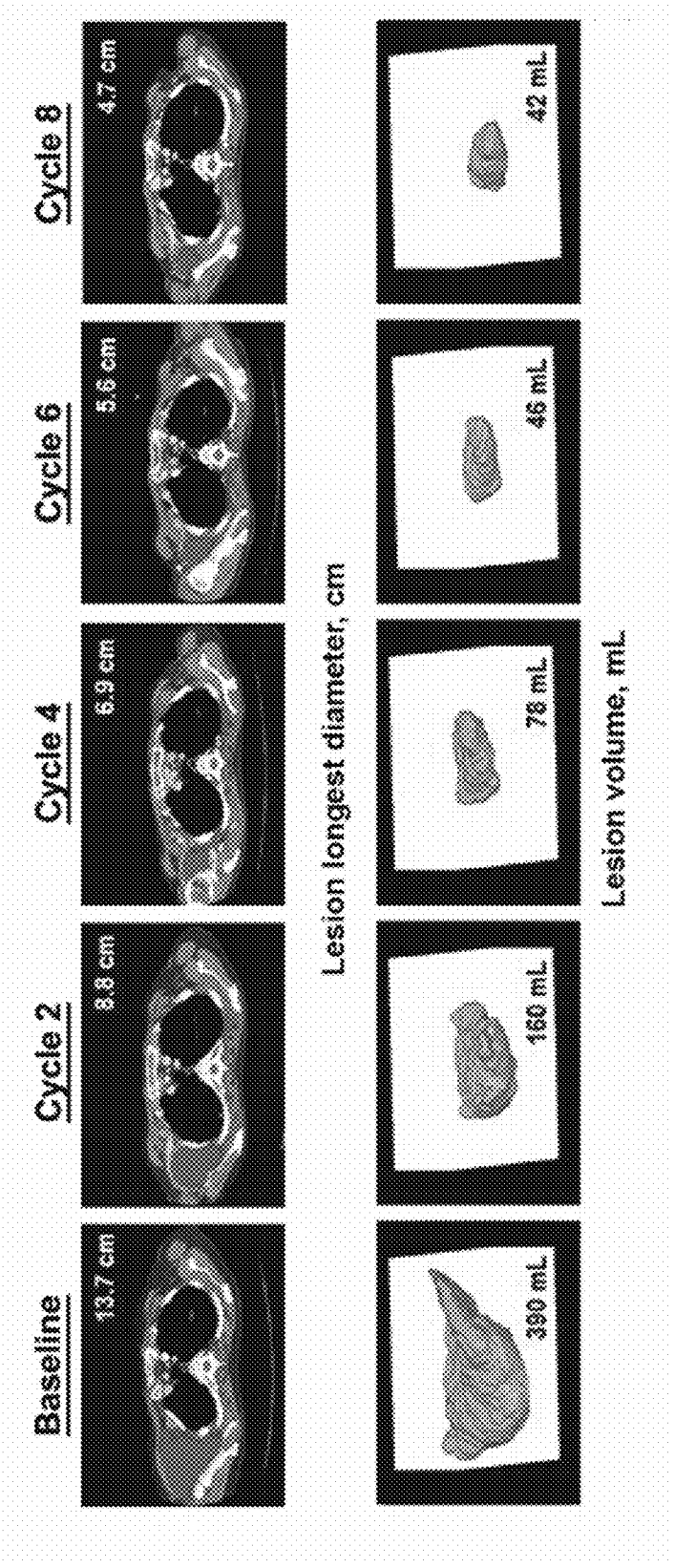
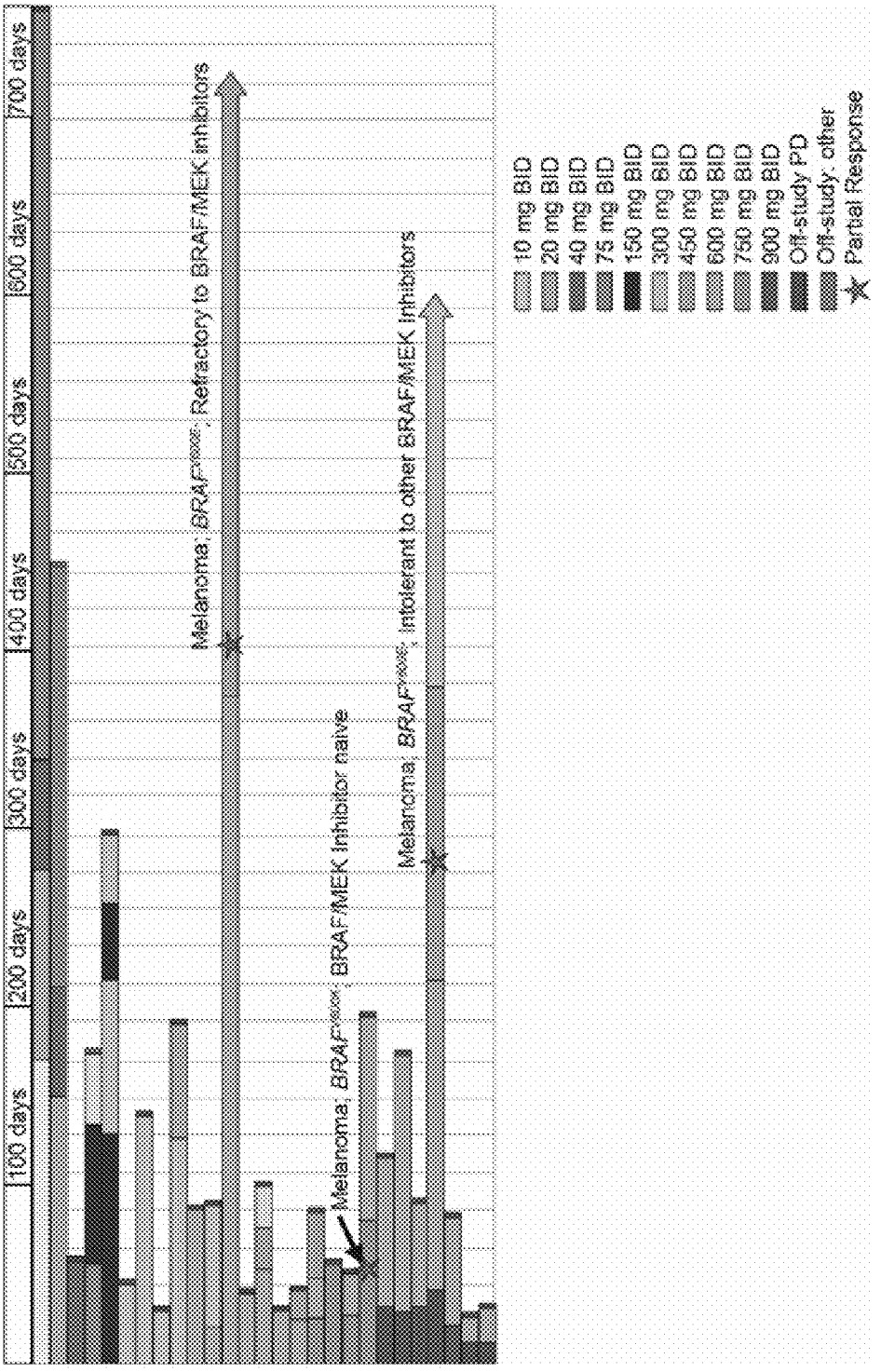

Baseline
Cycle 2
Cycle 4
Cycle 6
Cycle 8
13.7 cm
8.8 cm
6.9 cm
5.6 cm
4.7 cm
Lesion longest diameter, cm
390 mL
168 mL
78 mL
46 mL
42 mL
Lesion volume, mL

FIG. 41


100 days
200 days
300 days
400 days
500 days
600 days
700 days
Melanoma; BRAF V600E; BRAF/MEK inhibitor naive
Melanoma; BRAF V600E; Refractory to BRAF/MEK inhibitors
Melanoma; BRAF V600E; Intolerant to other BRAF/MEK inhibitors
10 mg BID
20 mg BID
40 mg BID
75 mg BID
150 mg BID
300 mg BID
450 mg BID
600 mg BID
750 mg BID
900 mg BID
Off-study PD
Off-study: other
Partial Response

METHODS AND COMPOSITIONS FOR TREATING NON-ERK MAPK PATHWAY INHIBITOR-RESISTANT CANCERS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation in part of PCT international application no. PCT/US2014/071749, filed Dec. 19, 2014, which claims benefit of U.S. Patent Application Ser. No. 61/919,551, filed on Dec. 20, 2013 which, applications are incorporated by reference herein in their entireties.

FIELD OF INVENTION

[0002] The present invention provides, inter alia, methods, pharmaceutical compositions, and kits for treating or ameliorating the effects of a cancer in a subject, which cancer is refractory or resistant to non-ERK MAPK pathway inhibitor therapy.

INCORPORATION BY REFERENCE OF SEQUENCE LISTING

[0003] This application contains references to amino acids and/or nucleic acid sequences that have been filed concurrently herewith as sequence listing text file "0375608.txt", file size of 356 KB, created on Dec. 18, 2014. The aforementioned sequence listing is hereby incorporated by reference in its entirety pursuant to 37 C.F.R. §1.52(e)(5).

BACKGROUND OF THE INVENTION

[0004] Drug inhibitors that target components of the mitogen-activated protein kinases (MAPK) signaling pathway show clinical efficacy in a variety of cancers, particularly those bearing mutations in the BRAF protein kinase. Both RAF and MEK inhibitors are approved for single-agent use in advanced metastatic BRAF mutant melanoma. Either alone or in combination, BRAF and MEK inhibitor activity is unpredictable in other cancers, with promising efficacy in BRAF mutant thyroid and lung cancer, but only marginal activity in BRAF mutant colorectal cancer.

[0005] As with other targeted therapies, patterns of disease response to RAF and MEK inhibitors appear to be influenced by the intrinsic genetic heterogeneity present in the cancers where the drugs are used. For instance, it has been shown that certain genetic alterations, including PTEN and other changes that activate the PI3K cell growth signaling pathway, may predict a poor initial response, and/or relatively rapid progression, in BRAF mutant melanoma treated with the RAF inhibitor vemurafenib. Likewise, direct mutations in MEK gene loci appear to emerge in tumors that have progressed following either BRAF, MEK, or combined drug treatment. Several additional examples, from RAS and RAF gene amplification and splicing mutations, suggest that acquired drug resistance is produced when oncogenic pleiotropy encounters the selective pressure of targeted drug treatment.

[0006] In view of the foregoing, there is a need for novel targeted agents that would ideally inhibit diverse nodes of oncogenic pathways, and also be effective in combinations by inducing a burden of selective pressures that exceeds the adaptive capacity of diverse cancer genomes. The present application is directed to meeting these and other needs.

SUMMARY OF THE INVENTION

[0007] One embodiment of the present invention is a method for treating or ameliorating the effects of a cancer in a subject, which cancer is refractory or resistant to non-ERK MAPK pathway inhibitor therapy. The method comprises administering to the subject an effective amount of BVD-523 or a pharmaceutically acceptable salt thereof.

[0008] Another embodiment of the present invention is a method for treating or ameliorating the effects of a cancer in a subject. The method comprises:

[0009] (a) identifying a subject with cancer that has become refractory or resistant to BRAF inhibitor therapy, MEK inhibitor therapy, or BRAF and MEK inhibitor therapy; and

[0010] (b) administering to the subject with said refractory or resistant cancer an effective amount of an ERK inhibitor, which is BVD-523 or a pharmaceutically acceptable salt thereof.

[0011] A further embodiment of the present invention is a method for treating or ameliorating the effects of cancer in a subject, which cancer is refractory or resistant to BRAF inhibitor therapy, MEK inhibitor therapy, or both. The method comprises administering to the subject an effective amount of BVD-523 or a pharmaceutically acceptable salt thereof.

[0012] Another embodiment of the present invention is a method for identifying a subject having cancer who would benefit from therapy with an ERK inhibitor. The method comprises:

[0013] (a) obtaining a biological sample from the subject; and

[0014] (b) screening the sample to determine whether the subject has one or more of the following markers:

[0015] (i) a switch between RAF isoforms,

[0016] (ii) upregulation of receptor tyrosine kinase (RTK) or NRAS signaling,

[0017] (iii) reactivation of mitogen activated protein kinase (MAPK) signaling,

[0018] (iv) the presence of a MEK activating mutation,

[0019] (v) amplification of mutant BRAF,

[0020] (vi) STAT3 upregulation,

[0021] (vii) mutations in the allosteric pocket of MEK that directly block binding of inhibitors to MEK or lead to constitutive MEK activity, wherein the presence of one or more of the markers confirms that the subject's cancer is refractory or resistant to BRAF and/or MEK inhibitor therapy and that the subject would benefit from therapy with an ERK inhibitor, which is BVD-523 or a pharmaceutically acceptable salt thereof.

[0022] A further embodiment of the present invention is a pharmaceutical composition for treating or ameliorating the effects of a cancer in a subject, which cancer is refractory or resistant to non-ERK MAPK pathway therapy. The composition comprises a pharmaceutically acceptable carrier or diluent and an effective amount of BVD-523 or a pharmaceutically acceptable salt thereof.

[0023] Another embodiment of the present invention is a kit for treating or ameliorating the effects of a cancer in a subject, which cancer is refractory or resistant to non-ERK MAPK pathway therapy. The kit comprises any of the pharmaceutical compositions according to the present invention packaged together with instructions for its use.

[0024] Another embodiment of the present invention is a method for inhibiting phosphorylation of RSK in a cancer cell that is refractory or resistant to a non-ERK MAPK pathway inhibitor. The method comprises contacting the cancer cell with an effective amount of BVD-523 or a pharmaceutically acceptable salt thereof for a period of time sufficient for phosphorylation of RSK in the cancer cell to be inhibited.

[0025] Another embodiment of the present invention is a method of treating a subject having an unresectable or metastatic BRAF600 mutation-positive melanoma comprising administering to the subject 600 mg BID of BVD-523 or a pharmaceutically acceptable salt thereof.

[0026] Another embodiment of the present invention is a composition for treating a subject having an unresectable or metastatic BRAF600 mutation-positive melanoma, the composition comprising 600 mg of BVD-523 or a pharmaceutically acceptable salt thereof and optionally a pharmaceutically acceptable carrier, adjuvant, or vehicle.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0028] FIG. **1**A-FIG. **1**C show the progress of a dose escalation study in a human malignant melanoma cell line (A375 cells) for month 1. Various treatments (trametinib (a type 2 MEK inhibitor), dabrafenib (a BRAF inhibitor), and BVD-523 (an ERK1/2 inhibior)) are as labeled.

[0029] FIG. **2**A-FIG. **2**H show the results of a proliferation assay that tracks changes in sensitivity to the escalated agent(s) at month 1. Various treatments (trametinib, dabrafenib, BVD-523, and pacitaxel) are as labeled on the top of the graph. The caption to the right of the graph shows the various types of cells generated from the dose escalation study. For example, "dabrafenib" refers to the cells that have been treated with the highest dose of dabrafenib from month 1 of the dose escalation study. Parental refers to the control cells that have not been treated with drugs. FIG. **2**A, FIG. **2**C and FIG. **2**G are normalized to control, whereas FIG. **2**D, FIG. **2**F and FIG. **2**H show the raw data.

[0030] FIG. **3**A-FIG. **3**D show the progress of a dose escalation study in A375 cells for month 2. Various treatments (trametinib, dabrafenib, and BVD-523) are as labeled.

[0031] FIG. **4**A-FIG. **4**H show the results of a proliferation assay that tracks changes in sensitivity to the escalated agent(s) at month 2. Various treatments (trametinib, dabrafenib, BVD-523, and pacitaxel) are as labeled on the top of the graph. The caption to the right of the graph shows the various types of cells generated from the dose escalation study. For example, "dabrafenib" refers to the cells that have been treated with the highest dose of dabrafenib from month 2 of the dose escalation study. Parental refers to the control cells that have not been treated with drugs. FIG. **4**A, FIG. **4**C and FIG. **4**G are normalized to control, whereas FIG. **4**D, FIG. **4**F and FIG. **4**H show the raw data.

[0032] FIG. **5**A-FIG. **5**H show only the parental and BVD-523 cell line data from FIG. **4**A-FIG. **4**H. Various treatments (trametinib, dabrafenib, BVD-523, and pacitaxel) are as labeled. FIG. **5**A, FIG. **5**C and FIG. **5**G are normalized to control, whereas FIG. **5**D, FIG. **5**F and FIG. **5**H show the raw data.

[0033] FIG. **6**A-FIG. **6**D show the progress of the dose escalation study in a human malignant cell line (A375 cells) for month 3. Various treatments (trametinib, dabrafenib, and BVD-523) are as labeled.

[0034] FIG. **7** is a histogram showing the results of a proliferation assay as applied to cells grown in the DMSO control wells from the dose escalation assay.

[0035] FIG. **8**A-FIG. **8**D are a set of line graphs showing proliferation assays for month 3 of the study. Various treatments (trametinib, dabrafenib, BVD-523, and pacitaxel) are as labeled on the top of the graph. The caption to the right of the graph shows the various types of cells generated from the dose escalation study. For example, "dabrafenib" refers to the cells that have been treated with the highest dose of dabrafenib from month 3 of the dose escalation study. Parental refers to the control cells that have not been treated with drugs.

[0036] FIG. **9**A-FIG. **9**D show only the parental, dabrafenib, and BVD-523 cell line data from FIG. **8**A-FIG. **8**D.

[0037] FIG. **10**A is a dose matrix showing % inhibition of the trametinib/dabrafenib combination in A375 cells using the Alamar Blue cell viability assay. FIG. **10**B is a dose matrix showing excess over Bliss for the trametinib/dabrafenib combination. FIG. **10**C and FIG. **10**D show % viability relative to DMSO only treated controls for dabrafenib and trametinib single agent treatments in A375 cells using the Alamar Blue cell viability assay. FIG. **10**E shows % viability relative to DMSO only treated controls for dabrafenib and trametinib combination treatments in A375 cells using the Alamar Blue cell viability assay.

[0038] FIG. **11**A is a dose matrix showing % inhibition of the trametinib/dabrafenib combination in A375 cells using the CellTiter-Glo cell viability assay. FIG. **11**B is a dose matrix showing excess over Bliss for the trametinib/dabrafenib combination. FIG. **11**C and FIG. **11**D show % viability relative to DMSO only treated controls for dabrafenib and trametinib single agent treatments in A375 cells using the CellTiter-Glo cell viability assay. FIG. **11**E shows % viability relative to DMSO only treated controls for dabrafenib and trametinib combination treatments in A375 cells using the CellTiter-Glo cell viability assay.

[0039] FIG. **12**A is a dose matrix showing % inhibition of the BVD-523/dabrafenib combination in A375 cells using the Alamar Blue cell viability assay. FIG. **12**B is a dose matrix showing excess over Bliss for the BVD-523/dabrafenib combination. FIG. **12**C and FIG. **12**D show % viability relative to DMSO only treated controls for dabrafenib and BVD-523 single agent treatments in A375 cells using the Alamar Blue cell viability assay. FIG. **12**E shows % viability relative to DMSO only treated controls for dabrafenib and BVD-523 combination treatments in A375 cells using the Alamar Blue cell viability assay.

[0040] FIG. **13**A is a dose matrix showing % inhibition of the BVD-523/dabrafenib combination in A375 cells using the CellTiter-Glo cell viability assay. FIG. **13**B is a dose matrix showing excess over Bliss for the BVD-523/dabrafenib combination. FIG. **13**C and FIG. **13**D show % viability relative to DMSO only treated controls for dabrafenib and BVD-523 single agent treatments in A375 cells using the CellTiter-Glo cell viability assay. FIG. **13**E shows % viability relative to DMSO only treated controls for dabrafenib and BVD-523 combination treatments in A375 cells using the CellTiter-Glo cell viability assay.

[0041] FIG. **14**A is a dose matrix showing % inhibition of the trametinib/BVD-523 combination in A375 cells using the Alamar Blue cell viability assay. FIG. **14**B is a dose matrix showing excess over Bliss for the trametinib/BVD-523 combination. FIG. **14**C and FIG. **14**D show % viability relative to DMSO only treated controls for BVD-523 and trametinib single agent treatments in A375 cells using the Alamar Blue cell viability assay. FIG. **14**E shows % viability relative to DMSO only treated controls for BVD-523 and trametinib combination treatments in A375 cells using the Alamar Blue cell viability assay.

[0042] FIG. **15**A is a dose matrix showing % inhibition of the trametinib/BVD-523 combination in A375 cells using the CellTiter-Glo cell viability assay. FIG. **15**B is a dose matrix showing excess over Bliss for the trametinib/BVD-523 combination. FIG. **15**C and FIG. **15**D show % viability relative to DMSO only treated controls for BVD-523 and trametinib single agent treatments in A375 cells using the CellTiter-Glo cell viability assay. FIG. **15**E shows % viability relative to DMSO only treated controls for BVD-523 and trametinib combination treatments in A375 cells using the CellTiter-Glo cell viability assay.

[0043] FIG. **16**A-FIG. **16**D are a set of images showing Western blot analysis of MAPK signaling in A375 cells after a 4 hour treatment with various concentrations (in nM) of BVD-523, dabrafenib (Dab), and Trametinib (Tram). 40 μg of total protein was loaded in each lane except where indicated otherwise. In this experiment, duplicate samples were collected. FIG. **16**A and FIG. **16**B show results from duplicate samples. Similarly, FIG. **16**C and FIG. **16**D also show results from duplicate samples. In FIG. **16**A and FIG. **16**B, pRSK1 had a relatively weak signal in A375 cells compared to other markers. A different pRSK1-S380 antibody from Cell Signaling (cat. #11989) was tested but did not give a detectable signal (data not shown). In FIG. **16**C and FIG. **16**D, pCRAF-338 gave a minimal signal.

[0044] FIG. **17**A-FIG. **17**D are a set of images showing Western blot analysis of MAPK signaling in a human colorectal carcinoma cell line (HCT116 cells) after a 4 hour treatment with various concentrations (in nM) of BVD-523, dabrafenib (Dab), and Trametinib (Tram). 40 μg of total protein was loaded in each lane except where indicated otherwise. In this experiment, duplicate samples were collected. FIG. **17**A and FIG. **17**B show results from duplicate samples. Similarly, FIG. **17**C and FIG. **17**D also show results from duplicate samples. In FIG. **17**A and FIG. **17**B, pRSK1 levels appear to be very low in HCT116 cells, and in FIG. **17**C and FIG. **17**D, pCRAF-338 signal was also very weak.

[0045] FIG. **18**A-FIG. **18**D are a set of images showing Western blot analysis of cell cycle and apoptosis signaling in A375 melanoma cells after a 24 hour treatment with various concentrations (in nM) of BVD-523 ("BVD523"), trametinib ("tram") and/or dabrafenib ("Dab") as labelled. 50 μg of total protein was loaded in each lane except where indicated otherwise. In this experiment, duplicate samples were collected. FIG. **18**A and FIG. **18**B show results from duplicate samples. Similarly, FIG. **18**C and FIG. **18**D also show results from duplicate samples. In FIG. **18**A and FIG. **18**B, no band of a size corresponding to cleaved PARP (89 kDa) was apparent.

[0046] FIG. **19** shows that BVD-523 can treat acquired resistance to targeted drugs in-vivo. A patient-derived line, ST052C, was isolated from a BRAFV600E melanoma patient that progressed following 10 months of therapy with MAPK-pathway directed therapies. Treated ex vivo, ST052C exhibited acquired cross-resistance to dabrafenib at 50 mg/kg BID. Meanwhile, BVD-523 was effective in ST052C as a single-agent at 100 mg/kg BID.

[0047] FIG. **20** is a flowchart showing the dose escalation protocol used herein.

[0048] FIG. **21** shows a schematic of the mitogen-activated protein kinases (MAPK) pathway.

[0049] FIG. **22**A-FIG. **22**E show the results of single agent proliferation assays. Proliferation results are shown for treatment with BVD-523 (FIG. **22**A), SCH772984 (FIG. **22**B), Dabrafenib (FIG. **22**C), Trametinib (FIG. **22**D), and Paclitaxel (FIG. **22**E).

[0050] FIG. **23**A-FIG. **23**O show the results of the combination of BVD-523 and Dabrafenib. FIG. **23**A shows a dose matrix showing inhibition (%) for the combination in RKO parental cells. FIG. **23**B-FIG. **23**C show the results of single agent proliferation assays for the combination in FIG. **23**A. FIG. **23**D shows Loewe excess for the combination in FIG. **23**A and FIG. **23**E shows Bliss excess for the combination in FIG. **23**A. FIG. **23**F shows a dose matrix showing inhibition (%) for the combination in RKO MEK1 (Q56P/+)-clone 1 cells. FIG. **23**G-FIG. **23**H show the results of single agent proliferation assays for the combination in FIG. **23**F. FIG. **23**I shows Loewe excess for the combination in FIG. **23**F and FIG. **23**J shows Bliss excess for the combination in FIG. **23**F. FIG. **23**K shows a dose matrix showing inhibition (%) for the combination in RKO MEK1 (Q56P/+)-clone 2 cells. FIG. **23**L-FIG. **23**M show the results of single agent proliferation assays for the combination in FIG. **23**K. FIG. **23**N shows Loewe excess for the combination in FIG. **23**K and FIG. **23**O shows Bliss excess for the combination in FIG. **23**K.

[0051] FIG. **24**A-FIG. **24**O show the results of the combination of SCH772984 and Dabrafenib. FIG. **24**A shows a dose matrix showing inhibition (%) for the combination in RKO parental cells. FIG. **24**B-FIG. **24**C show the results of single agent proliferation assays for the combination in FIG. **24**A. FIG. **24**D shows Loewe excess for the combination in FIG. **24**A and FIG. **24**E shows Bliss excess for the combination in FIG. **24**A. FIG. **24**F shows a dose matrix showing inhibition (%) for the combination in RKO MEK1 (Q56P/+)-clone 1 cells. FIG. **24**G-FIG. **24**H show the results of single agent proliferation assays for the combination in FIG. **24**F. FIG. **24**I shows Loewe excess for the combination in FIG. **24**F and FIG. **24**J shows Bliss excess for the combination in FIG. **24**F. FIG. **24**K shows a dose matrix showing inhibition (%) for the combination in RKO MEK1 (Q56P/+)-clone 2 cells. FIG. **24**L-FIG. **24**M show the results of single agent proliferation assays for the combination in FIG. **24**K. FIG. **24**N shows Loewe excess for the combination in FIG. **24**K and FIG. **24**O shows Bliss excess for the combination in FIG. **24**K.

[0052] FIG. **25**A-FIG. **25**O show the results of the combination of Trametinib and Dabrafenib. FIG. **25**A shows a dose matrix showing inhibition (%) for the combination in RKO parental cells. FIG. **25**B-FIG. **25**C show the results of single agent proliferation assays for the combination in FIG. **25**A. FIG. **25**D shows Loewe excess for the combination in FIG. **25**A and FIG. **25**E shows Bliss excess for the combination in FIG. **25**A. FIG. **25**F shows a dose matrix showing inhibition (%) for the combination in RKO MEK1 (Q56P/+)-clone 1 cells. FIG. **25**G-FIG. **25**H show the results

of single agent proliferation assays for the combination in FIG. **25**F. FIG. **25**I shows Loewe excess for the combination in FIG. **25**F and FIG. **25**J shows Bliss excess for the combination in FIG. **25**F. FIG. **25**K shows a dose matrix showing inhibition (%) for the combination in RKO MEK1 (Q56P/+)-clone 2 cells. FIG. **25**L-FIG. **25**M show the results of single agent proliferation assays for the combination in FIG. **25**K. FIG. **25**N shows Loewe excess for the combination in FIG. **25**K and FIG. **25**O shows Bliss excess for the combination in FIG. **25**K.

[0053] FIG. **26**A shows Lowe Volumes for the combinations tested. FIG. **26**B shows Bliss Volumes for the combinations tested. FIG. **26**C shows Synergy Scores for the combinations tested.

[0054] FIG. **27**A-FIG. **27**I show the changes in MAPK and Effector Pathway Signaling in MEK acquired resistance. Isogenic RKO parental and MEK1 (Q56P/+) cells were treated with compound for 4 or 24 h and then immunoblotted with the indicated antibodies. Dabrafenib was the BRAF inhibitor and trametinib was the MEK inhibitor. FIG. **27**A shows increased signaling in RKO MEK1 (Q56P/+) cells. FIG. **27**B-FIG. **27**C show the results of a 4 hour treatment in Experiment 1 (See, Example 7) in RKO Parental (**27**B) and RKO MEK1 (Q56P/+) (**27**C) cells. FIG. **27**D-FIG. **27**E show the results of a 4 hour treatment in Experiment 2 (See, Example 7) in RKO Parental (**27**D) and RKO MEK1 (Q56P/+) (**27**E) cells. FIG. **27**F-FIG. **27**G show the results of a 4 hour treatment in Experiment 2 (See, Example 7) in RKO Parental (**27**F) and RKO MEK1 (Q56P/+) (**27**G) cells. FIG. **27**H-FIG. **27**I show a summary of results in RKO Parental (**27**H) and RKO MEK1 (Q56P/+) (**27**I) cells.

[0055] FIG. **28**A-FIG. **28**E show the results of the combination of BVD-523 and SCH772984. FIG. **28**A shows a dose matrix showing inhibition (%) for the combination in A375 cells. FIG. **28**B-FIG. **28**C show the results of single agent proliferation assays for the combination in FIG. **28**A. FIG. **28**D shows Loewe excess for the combination in FIG. **28**A and FIG. **28**E shows Bliss excess for the combination in FIG. **28**A.

[0056] FIG. **29**A-FIG. **29**F show discovery and characterization of the novel ERK1/2 inhibitor BVD-523 (ulixertinib). FIG. **29**A shows that BVD-523 demonstrates inhibition in a reversible ATP-competitive manner. This is demonstrated by a linear increase in IC_{50} values for inhibition of ERK2 with increasing ATP concentration as shown in FIG. **29**B. FIG. **29**C shows a representative plot of the dose-response curve and FIG. **29**D shows a plot of IC_{50} over time. FIG. **29**E shows BVD-523 binding to ERK2 and phospho-ERK2 (pERK2), compared with negative control protein p38. FIG. **29**F shows BVD-523 binding to ERK2 compared with the ERK inhibitors SCH772984 and pyrazolylpyrrole.

[0057] FIG. **30**A-FIG. **30**D show that BVD 523 inhibits cellular proliferation and enhances caspase 3 and caspase 7 activity in vitro. FIG. **30**A shows that BVD-523 demonstrates preferential activity in cells with MAPK pathway mutations, as defined by the presence of mutations in RAS family members and RAF. In addition, as shown in FIG. **30**B, BVD-523 blocks sensitive cell lines in the G1 phase of the cell cycle. FIG. **30**C shows that BVD-523 induced a concentration- and time-dependent increase in caspase activity in the A375, WM266, and LS411N cancer cell lines after 72 hours of exposure. FIG. **30**D shows that the MAPK pathway and effector proteins are modulated by acute (4-hour) and prolonged (24-hour) BVD-523 treatment in $BRAF^{V600E}$-mutant A375 cells.

[0058] FIG. **31**A-FIG. **31**C show in vivo BVD-523 antitumor activity. BVD-523 monotherapy inhibits tumor growth in (FIG. **31**A) A375 and (FIG. **31**B) Colo205 cell line xenograft models ($^{a}P<0.0001$, compared with vehicle control; CPT-11 dosed on Day 14 and Day 18 only). Abbreviations: BID, twice daily; CMC, carboxymethylcellulose; QD, every day; Q4D, every 4 days. FIG. **31**C shows that in Colo205 xenografts, increased ERK1/2 phosphorylation correlates with BVD-523 concentration.

[0059] FIG. **32**A shows signaling effects of ERK1/2 inhibitors. Using RPPA, effects on proteins are measured in cell lines (A375, AN3Ca, Colo205, HCT116, HT29 and MIAPaca2) following treatment with ERK1/2 inhibitors BVD-523 (BVD), Vx11e (Vx), GDC-0994 (GDC), or SCH722984 (SCH). FIG. **32**B shows that the ERK inhibitors BVD-523, GDC-0994, and Vx11e have differential effects on phospho-ERK (ERK 1/2 T202 Y204) compared with SCH722984; phospho-RSK (p90 RSK 380) and Cyclin D1 are inhibited by the ERK inhibitors tested. Abbreviations: BRAFi, BRAF inhibitors; MEKi, MEK inhibitors. FIG. **32**C shows a western blot assay of cellular and nuclear fractions from a RKO cell line following treatment with BVD-523, trametinib, SCH722984, or dabrafenib. Histone H3 (nuclear localized protein) and HSP90 (cytoplasmically localized protein) were included as positive controls to confirm that the nuclear and cytoplasmic fractions were properly enriched; nuclear fractions have high H3 and cytoplasmic fractions have higher HSP90.

[0060] FIG. **33** shows that the ERK inhibitors BVD-523, Vx11, GDC-0994, and SCH772984 (SCH) demonstrate cell line-dependent changes in phospho-ATK levels. Abbreviation: DMSO, dimethyl sulfoxide.

[0061] FIG. **34**A-FIG. **34**D show that BVD-523 demonstrates activity in models of resistance to BRAF/MEK inhibition. The appearance of resistance to BVD-523, dabrafenib, or trametinib in $BRAF^{V600E}$ A375 cells following exposure to increasing concentrations of drug is indicated. A strict set of "criteria" was applied to determine when the dose could be increased in order to ensure that the kinetics of the acquisition of resistance between treatments was comparable. See, Example 1. Time is shown against multipliers of IC_{50}; each point on the plotted line represents a change of medium or cell split. FIG. **34**A shows that adapting cells to growth in the presence of BVD-523 was more challenging than with either dabrafenib or trametinib. FIG. **34**B shows that BVD-523 sensitivity is retained in A375 cells cultured to acquire resistance to combined BRAF (dabrafenib)+MEK (trametinib) inhibition. In FIG. **34**C, cells were treated with compound for 96 h and viability was assessed using CellTiter-Glo®. BVD-523 activity is retained in $BRAF^{V600E}$ RKO cells cross-resistant to BRAF (dabrafenib) and MEK (trametinib) inhibitors due to endogenous heterozygous knock-in of $MEK1^{Q56P}$. FIG. **34**D shows that BVD-523 inhibition of pRSK in $BRAF^{V600E}$-mutant cell line RKO is maintained in the presence of $MEK1^{Q56P}$, which confers resistance to MEK and BRAF inhibition. Knock-in of KRAS mutant alleles into SW48 cell lines significantly diminishes sensitivity to the MEK inhibitors trametinib and selumetinib, while comparatively sensitivity to BVD-523 is retained.

[0062] FIG. **35**A shows BVD-523 in vivo activity in xenografts derived from a vemurafenib-relapsed patient. Mean tumor volume (±SEM) is shown for BVD-523 100 mg/kg BID alone, dabrafenib 50 mg/kg BID alone, and BVD-523 100 mg/kg BID plus dabrafenib 50 mg/kg BID. Abbreviations: BID, twice daily; SEM, standard error of mean.

[0063] FIG. **36**A-FIG. **36**D show the benefit of combined BVD-523 and BRAF inhibition. FIG. **36**A-FIG. **36**B show that the combination of BVD-523 plus dabrafenib exhibited superior antitumor activity compared with treatment with either agent alone in a A375 $BRAF^{V600E}$-mutant melanoma cell line xenograft model with a tumor start volume of 75-144 mm^3. FIG. **36**C-FIG. **36**D show similar data from the same model with an enlarged tumor volume (700-800 mm^3) at the start of dosing. Plots of mean tumor growth (left panels) and Kaplan-Meier survival (right panels) are presented for each study. Abbreviations: BID, twice daily; QD, once daily.

[0064] FIG. **37**A shows that, in SW48 colorectal cells engineered with KRAS alleles, response to paclitaxel was unaltered compared to control. FIG. **37**B shows combination interactions between BVD-523 and vemurafenib, which were assessed using an 8×10 matrix of concentrations using the Loewe Additivity and Bliss Independence Models, and analyzed with Horizon's Chalice, Bioinformatics Software. Chalice enables potential synergistic interactions to be identified by displaying the calculated excess inhibition over that predicted as being additive across the dose matrix as a heat map, and by reporting a quantitative "Synergy Score" based on the Loewe model. The results suggest that interactions between BVD-523 and vemurafenib are at least additive, and in some cases synergistic in melanoma cell lines carrying a $BRAF^{V600E}$ mutation. FIG. **37**C shows that BVD-523 in combination with dabrafenib markedly delays the onset of acquired resistance in A375 $BRAF^{V600E}$ melanoma cells. The temporal acquisition of resistance in response to escalating concentrations of dabrafenib alone or in combination with BVD-523 or trametinib was assessed. Strict criteria were applied as to when the dose could be increased to ensure that the kinetics of adaptation was comparable between treatments. See, Example 1.

[0065] FIG. **38** shows that BVD-523 inhibits ex vivo PMA-stimulated RSK1/2 phosphorylation in human whole blood. Averages of BVD-523 concentration data set are indicated by (-). n=20 for each concentration of BVD-523. Abbreviations: PBMC, peripheral blood mononuclear cells; RSK, ribosomal S6 kinase.

[0066] FIG. **39**A shows steady-state BVD-523 pharmacokinetics (Cycle 1, Day 15). The dashed red line indicates an EC_{50} 200 ng/mL HWB. Abbreviations: AUC, area under the curve; BID, twice daily; C_{max}, maximum concentration; EC_{50}, 50% maximum effective concentration; HWB, human whole blood; SD, standard deviation. FIG. **39**B shows pharmacodynamic inhibition of ERK phosphorylation by BVD-523 in human whole blood. Abbreviations: BID, twice daily; pRSK, phospho-RSK; RSK, ribosomal S6 kinase.

[0067] FIG. **40**A shows the best radiographic response in patients treated with BVD-523. Included are all patients with disease measured by RECIST v1.1 who received ≥1 dose of study treatment and had >1 on-treatment tumor assessment (25/27; 2 did not receive both scans of target lesions). Response was measured as the change from baseline in the sum of the longest diameter of each target lesion. Dose shown is that which the patient was receiving at the time of response. The dashed line indicates the threshold for a partial response according to RECIST v1.1. Abbreviations: CRC, colorectal cancer; NET, neuroendocrine tumors; NSCLC, non-small cell lung cancer; NSGCT, nonseminomatous germ cell tumors; PNET, pancreatic NET; PTC, papillary thyroid cancer; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SLD, sum of the largest diameter. FIG. **40**B shows a computerized tomography scan of a confirmed partial response in a 61-year-old patient with a BRAF-mutant melanoma treated with BVD-523.

[0068] FIG. **41** shows tumor response and tumor progression. Shown is a swimmer plot of tumor response, tumor progression, and duration of treatment in response-evaluable patients treated with BVD-523. Origin of the vertical axis corresponds to randomization date or reference start date. Analysis cut-off date: Dec. 1, 2015. Abbreviation: BID, twice daily.

DETAILED DESCRIPTION OF THE INVENTION

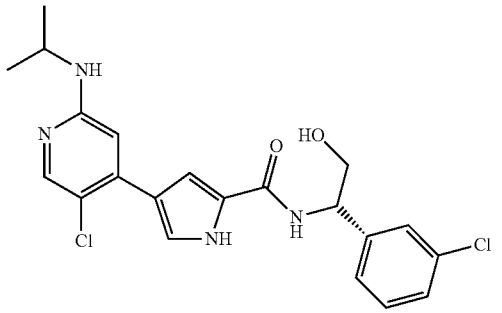
[0069] One embodiment of the present invention is a method for treating or ameliorating the effects of a cancer in a subject, which cancer is refractory or resistant to non-ERK MAPK pathway inhibitor therapy. The method comprises administering to the subject an effective amount of BVD-523 or a pharmaceutically acceptable salt thereof.

[0070] As used herein, the terms "treat," "treating," "treatment" and grammatical variations thereof mean subjecting an individual subject to a protocol, regimen, process or remedy, in which it is desired to obtain a physiologic response or outcome in that subject, e.g., a patient. In particular, the methods and compositions of the present invention may be used to slow the development of disease symptoms or delay the onset of the disease or condition, or halt the progression of disease development. However, because every treated subject may not respond to a particular treatment protocol, regimen, process or remedy, treating does not require that the desired physiologic response or outcome be achieved in each and every subject or subject population, e.g., patient population. Accordingly, a given subject or subject population, e.g., patient population may fail to respond or respond inadequately to treatment.

[0071] As used herein, the terms "ameliorate", "ameliorating" and grammatical variations thereof mean to decrease the severity of the symptoms of a disease in a subject.

[0072] As used herein, a "subject" is a mammal, preferably, a human. In addition to humans, categories of mammals within the scope of the present invention include, for example, farm animals, domestic animals, laboratory animals, etc. Some examples of farm animals include cows, pigs, horses, goats, etc. Some examples of domestic animals include dogs, cats, etc. Some examples of laboratory animals include primates, rats, mice, rabbits, guinea pigs, etc.

[0073] In the present invention, BVD-523 corresponds to a compound according to formula (I):



and pharmaceutically acceptable salts thereof. BVD-523 may be synthesized according to the methods disclosed, e.g., in U.S. Pat. No. 7,354,939. Enantiomers and racemic mixtures of both enantiomers of BVD-523 are also contemplated within the scope of the present invention. BVD-523 is an ERK1/2 inhibitor with a mechanism of action that is believed to be, e.g., unique and distinct from certain other ERK1/2 inhibitors, such as SCH772984 and the pyrimidinal structure used by Hatzivassiliou et al. (2012). For example, other ERK1/2 inhibitors, such as SCH772984, inhibit autophosphorylation of ERK (Morris et al., 2013), whereas BVD-523 allows for the autophosphorylation of ERK while still inhibiting ERK. (See, e.g., FIG. **18**).

[0074] As used herein, the words "resistant" and "refractory" are used interchangeably. Being "resistant" to non-ERK MAPK pathway inhibitor therapy treatments means that non-ERK MAPK inhibitors have reduced efficacy in treating cancer.

[0075] As used herein, a "non-ERK MAPK inhibitor" means any substance that reduces the activity, expression or phosphorylation of proteins or other members of the MAPK pathway that results in a reduction of cell growth or an increase in cell death, with the exception of ERK1/2 inhibitors. As used herein, an "ERK1/2 inhibitor" means those substances that (i) directly interact with ERK1 and/or ERK2, e.g., by binding to ERK1/2 and (ii) decrease the expression or the activity of ERK1 and/or ERK2 protein kinases. Therefore, inhibitors that act upstream of ERK1/2, such as MEK inhibitors and RAF inhibitors, are not ERK1/2 inhibitors according to the present invention (but they are non-ERK MAPK inhibitors). Non-limiting examples of ERK1/2 inhibitors according to the present invention include AEZS-131 (Aeterna Zentaris), AEZS-136 (Aeterna Zentaris), BVD-523 (BioMed Valley Discoveries, Inc.), SCH-722984 (Merck & Co.), SCH-772984 (Merck & Co.), SCH-900353 (MK-8353) (Merck & Co.), pharmaceutically acceptable salts thereof, and combinations thereof.

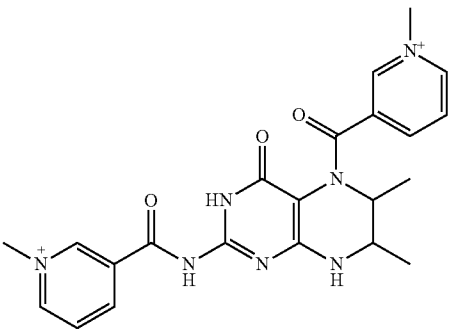
[0076] An overview of the mammalian MAPK cascades is shown in FIG. **21**. The MAPK pathway is reviewed in e.g., Akinleye et al., 2013. Briefly, with respect to the ERK1/2 module in FIG. **21** (light purple box), the MAPK 1/2 signaling cascade is activated by ligand binding to receptor tyrosine kinases (RTK). The activated receptors recruit and phosphorylate adaptor proteins Grb2 and SOS, which then interact with membrane-bound GTPase Ras and cause its activation. In its activated GTP-bound form, Ras recruits and activates RAF kinases (A-RAF, B-RAF, and C-RAF/RAF-1). The activated RAF kinases activate MAPK 1/2 (MKK1/2), which in turn catalyzes the phosphorylation of threonine and tyrosine residues in the activation sequence Thr-Glu-Tyr of ERK1/2. With respect to the JNK/p38 module (yellow box in FIG. **21**), upstream kinases, MAP3Ks, such as MEKK1/4, ASK1/2, and MLK1/2/3, activate MAP2K3/6 (MKK3/6), MAP2K4 (MKK4), and MAP2K7 (MKK7). These MAP2K's then activate JNK protein kinases, including JNK1, JNK2, and JNK3, as well as p38 α/β/γ/δ. To execute their functions, JNKs activate several transcription factors, including c-Jun, ATF-2, NF-ATc1, HSF-1 and STAT3. With respect to the ERK5 module (blue box in FIG. **21**), the kinases upstream of MAP2K5 (MKK5) are MEKK2 and MEKK3. The best characterized downstream target of MEK5 is ERK5, also known as big MAP kinase 1 (BMK1) because it is twice the size of other MAPKs.

[0077] Non-limiting examples of non-ERK MAPK pathway inhibitors according to the present invention include RAS inhibitors, RAF inhibitors (such as, e.g., inhibitors of A-RAF, B-RAF, C-RAF (RAF-1)), MEK inhibitors, and combinations thereof. Preferably, the non-ERK MAPK pathway inhibitors are BRAF inhibitors, MEK inhibitors, and combinations thereof.

[0078] As used herein, a "RAS inhibitor" means those substances that (i) directly interact with RAS, e.g., by binding to RAS and (ii) decrease the expression or the activity of RAS. Non-limiting exemplary RAS inhibitors include, but are not limited to, farnesyl transferase inhibitors (such as, e.g., tipifarnib and lonafarnib), farnesyl group-containing small molecules (such as, e.g., salirasib and TLN-4601), DCAI, as disclosed by Maurer (Maurer et al., 2012), Kobe0065 and and Kobe2602, as disclosed by Shima (Shima et al., 2013), HBS 3 (Patgiri et al., 2011), and AIK-4 (Allinky).

[0079] As used herein, a "RAF inhibitor" means those substances that (i) directly interact with RAF, e.g., by binding to RAF and (ii) decrease the expression or the activity of RAF, such as, e.g., A-RAF, B-RAF, and C-RAF (RAF-1). Non-limiting exemplary RAF inhibitors, including BRAF inhibitors, include:

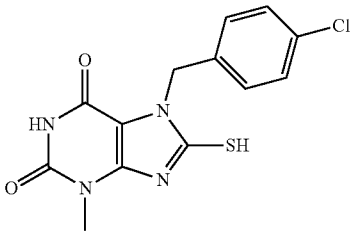
Compound 7



(Li et al.),

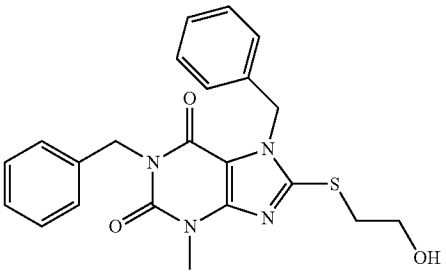
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Compound 9



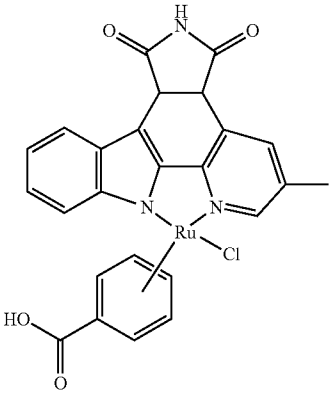
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Compound 10



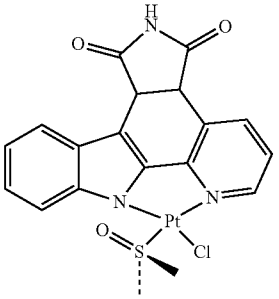
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Compound 13



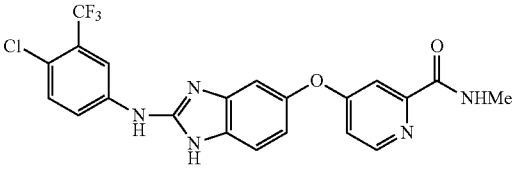
(Id.),

Compound 14



(Id.),

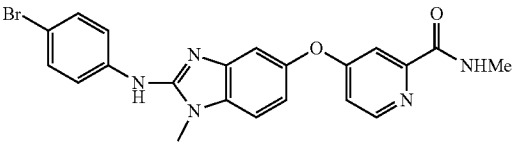
Compound 15



(Id.),

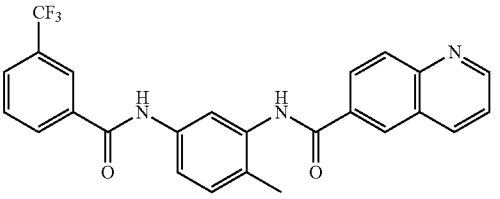
-continued

Compound 16



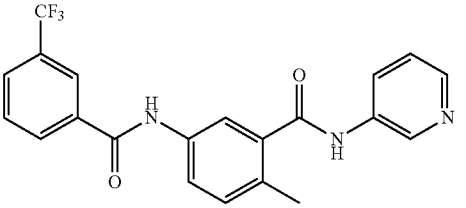
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Compound 18



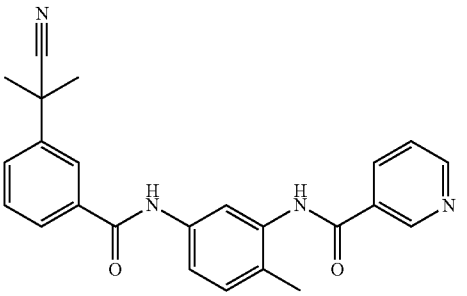
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Compound 19



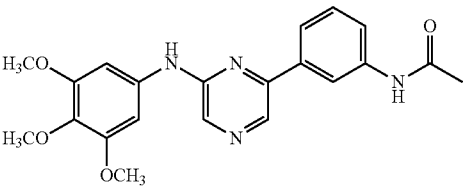
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Compound 20



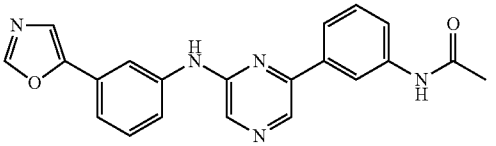
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Compound 21



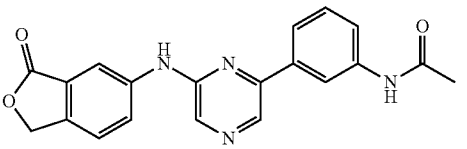
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Compound 22



(Id.),

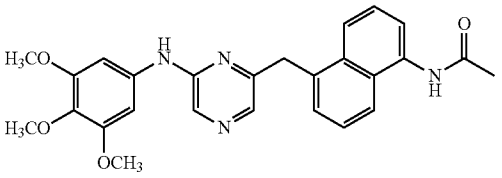
Compound 23



(Id.),

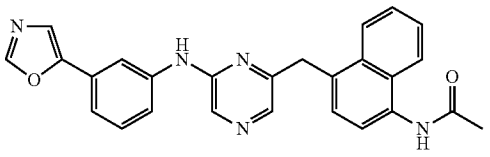
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Compound 24



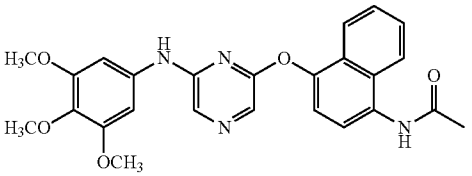
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Compound 25



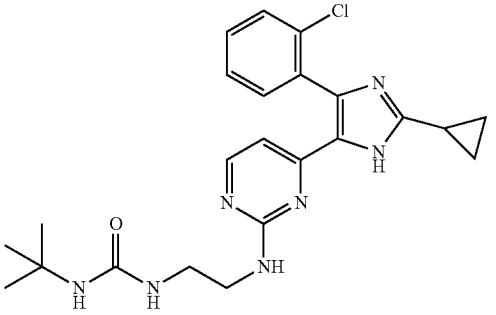
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Compound 26



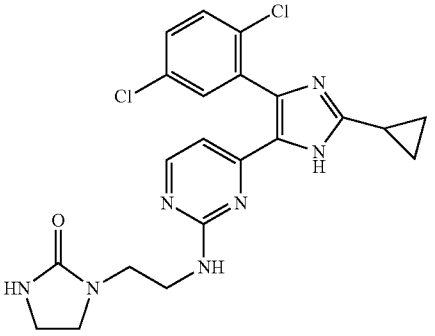
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Compound 27



(Id.),

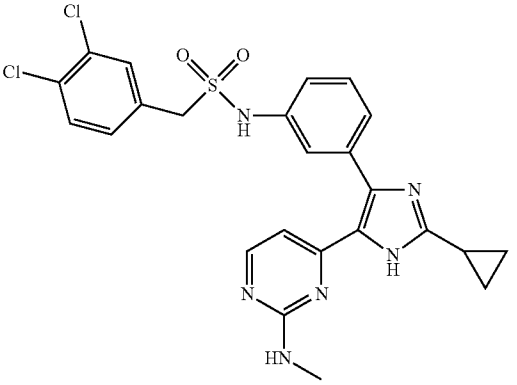
Compound 28



(Id.),

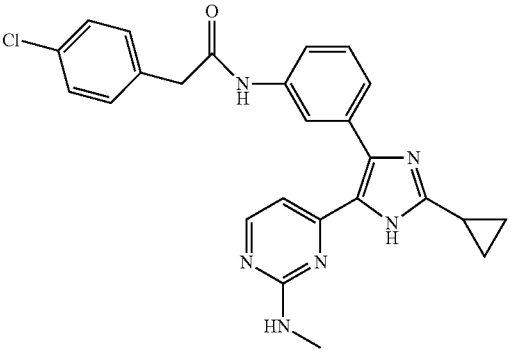
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Compound 30



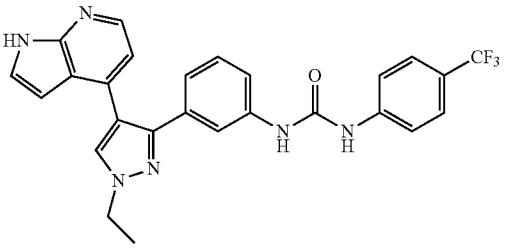
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Compound 31



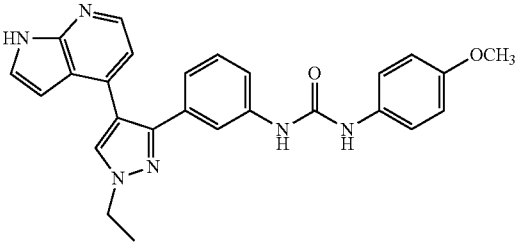
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Compound 32



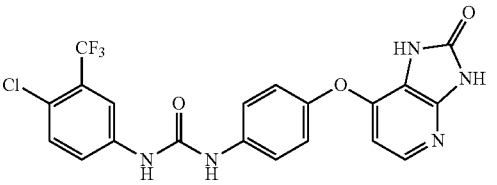
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Compound 33



(Id.),

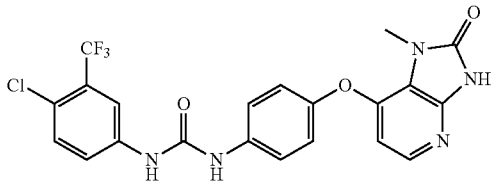
Compound 34



(Id.),

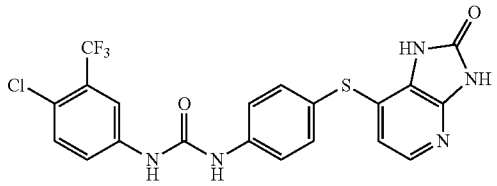
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Compound 35



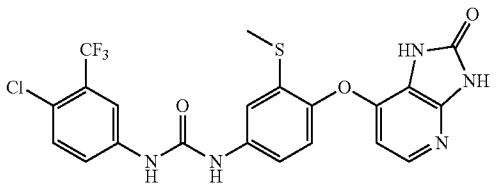
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Compound 36



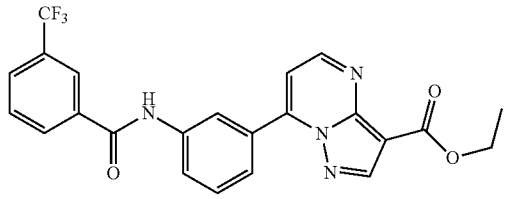
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Compound 37



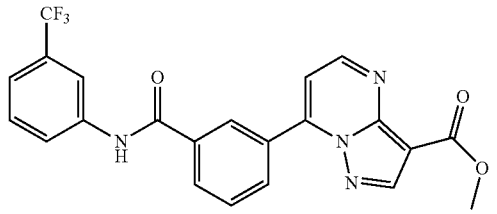
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Compound 38



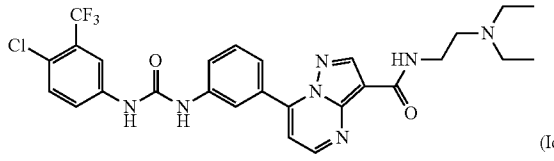
(Id.),

Compound 39



(Id.),

Compound 40



(Id.),

AAL881 (Novartis); AB-024 (Ambit Biosciences), ARQ-736 (ArQule), ARQ-761 (ArQule), AZ628 (Axon Medchem BV), BeiGene-283 (BeiGene), BIIB-024 (MLN 2480) (Sunesis & Takeda), b-raf inhibitor (Sareum), BRAF kinase inhibitor (Selexagen Therapeutics), BRAF siRNA 313 (tacaccagcaagctagatgca) and 523 (cctatcgttagagtcttcctg) (Liu et al., 2007), CTT239065 (Institute of Cancer Research), dabrafenib (GSK2118436), DP-4978 (Deciphera Pharmaceuticals), HM-95573 (Hanmi), GDC-0879 (Genentech), GW-5074 (Sigma Aldrich), ISIS 5132 (Novartis), L779450 (Merck), LBT613 (Novartis), LErafAON (NeoPharm, Inc.), LGX-818 (Novartis), pazopanib (GlaxoSmithKline), PLX3202 (Plexxikon), PLX4720 (Plexxikon), PLX5568 (Plexxikon), RAF-265 (Novartis), RAF-365 (Novartis), regorafenib (Bayer Healthcare Pharmaceuticals, Inc.), RO 5126766 (Hoffmann-La Roche), SB-590885 (GlaxoSmith-Kline), SB699393 (GlaxoSmithKline), sorafenib (Onyx Pharmaceuticals), TAK 632 (Takeda), TL-241 (Teligene), vemurafenib (RG7204 or PLX4032) (Daiichi Sankyo), XL-281 (Exelixis), ZM-336372 (AstraZeneca), pharmaceutically acceptable salts thereof, and combinations thereof.

[0080] As used herein, a "MEK inhibitor" means those substances that (i) directly interact with MEK, e.g., by binding to MEK and (ii) decrease the expression or the activity of MEK. Thus, inhibitors that act upstream of MEK, such as RAS inhibitors and RAF inhibitors, are not MEF inhibitors according to the present invention. Non-limiting examples of MEK inhibitors include anthrax toxin, antroquinonol (Golden Biotechnology), ARRY-142886 (6-(4-bromo-2-chloro-phenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxy-ethoxy)-amide) (Array BioPharma), ARRY-438162 (Array BioPharma), AS-1940477 (Astellas), AS-703988 (Merck KGaA), bentamapimod (Merck KGaA), BI-847325 (Boehringer Ingelheim), E-6201 (Eisai), GDC-0623 (Hoffmann-La Roche), GDC-0973 (cobimetinib) (Hoffmann-La Roche), L783277 (Merck), lethal factor portion of anthrax toxin, MEK162 (Array BioPharma), PD 098059 (2-(2'-amino-3'-methoxyphenyl)-oxanaphthalen-4-one) (Pfizer), PD 184352 (CI-1040) (Pfizer), PD-0325901 (Pfizer), pimasertib (Santhera Pharmaceuticals), RDEA119 (Ardea Biosciences/Bayer), refametinib (AstraZeneca), RG422 (Chugai Pharmaceutical Co.), RO092210 (Roche), RO4987655 (Hoffmann-La Roche), RO5126766 (Hoffmann-La Roche), selumetinib (AZD6244) (AstraZeneca), SL327 (Sigma), TAK-733 (Takeda), trametinib (Japan Tobacco), U0126 (1,4-diamino-2,3-dicyano-1,4-bis(2-aminophenylthio)butadiene) (Sigma), WX-554 (Wilex), YopJ polypeptide (Mittal et al., 2010), pharmaceutically acceptable salts thereof, and combinations thereof.

[0081] In one aspect of this embodiment, substantially all phosphorylation of ribosomal s6 kinase (RSK) is inhibited after administration of BVD-523 or a pharmaceutically acceptable salt thereof. As used herein in the context of RSK phosphorylation, "substantially all" means a reduction of greater than 50% reduction, preferably greater than 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% reduction.

[0082] In another aspect of this embodiment, the cancer has MAPK activity. As used herein, having "MAPK activity" means that proteins downstream of ERK are still active, even if proteins upstream of ERK may not be active. Such a cancer may be a solid tumor cancer or a hematologic cancer.

[0083] In the present invention, cancers include both solid and hemotologic cancers. Non-limiting examples of solid cancers include adrenocortical carcinoma, anal cancer, bladder cancer, bone cancer (such as osteosarcoma), brain cancer, breast cancer, carcinoid cancer, carcinoma, cervical cancer, colon cancer, endometrial cancer, esophageal cancer, extrahepatic bile duct cancer, Ewing family of cancers, extracranial germ cell cancer, eye cancer, gallbladder cancer, gastric cancer, germ cell tumor, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma, kidney cancer, large intestine cancer, laryn-

geal cancer, leukemia, lip and oral cavity cancer, liver tumor/cancer, lung tumor/cancer, lymphoma, malignant mesothelioma, Merkel cell carcinoma, mycosis fungoides, myelodysplastic syndrome, myeloproliferative disorders, nasopharyngeal cancer, neuroblastoma, oral cancer, oropharyngeal cancer, osteosarcoma, ovarian epithelial cancer, ovarian germ cell cancer, pancreatic cancer, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pituitary cancer, plasma cell neoplasm, prostate cancer, rhabdomyosarcoma, rectal cancer, renal cell cancer, transitional cell cancer of the renal pelvis and ureter, salivary gland cancer, Sezary syndrome, skin cancers (such as cutaneous t-cell lymphoma, Kaposi's sarcoma, mast cell tumor, and melanoma), small intestine cancer, soft tissue sarcoma, stomach cancer, testicular cancer, thymoma, thyroid cancer, urethral cancer, uterine cancer, vaginal cancer, vulvar cancer, and Wilms' tumor.

[0084] Examples of hematologic cancers include, but are not limited to, leukemias, such as adult/childhood acute lymphoblastic leukemia, adult/childhood acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia, lymphomas, such as AIDS-related lymphoma, cutaneous T-cell lymphoma, adult/childhood Hodgkin lymphoma, mycosis fungoides, adult/childhood non-Hodgkin lymphoma, primary central nervous system lymphoma, Sezary syndrome, cutaneous T-cell lymphoma, and Waldenstrom macroglobulinemia, as well as other proliferative disorders such as chronic myeloproliferative disorders, Langerhans cell histiocytosis, multiple myeloma/plasma cell neoplasm, myelodysplastic syndromes, and myelodysplastic/myeloproliferative neoplasms.

[0085] Preferably, the cancer is selected from the group consisting of a cancer of the large intestine, breast cancer, pancreatic cancer, skin cancer, and endometrial cancers. More preferably, the cancer is melanoma.

[0086] In another aspect of this embodiment, the method further comprises administering to the subject at least one additional therapeutic agent effective for treating or ameliorating the effects of the cancer. The additional therapeutic agent may be selected from the group consisting of an antibody or fragment thereof, a cytotoxic agent, a toxin, a radionuclide, an immunomodulator, a photoactive therapeutic agent, a radiosensitizing agent, a hormone, an anti-angiogenesis agent, and combinations thereof.

[0087] As used herein, an "antibody" encompasses naturally occurring immunoglobulins as well as non-naturally occurring immunoglobulins, including, for example, single chain antibodies, chimeric antibodies (e.g., humanized murine antibodies), and heteroconjugate antibodies (e.g., bispecific antibodies). Fragments of antibodies include those that bind antigen, (e.g., Fab', $F(ab')_2$, Fab, Fv, and rIgG). See also, e.g., Pierce Catalog and Handbook, 1994-1995 (Pierce Chemical Co., Rockford, Ill.); Kuby, J., Immunology, 3rd Ed., W.H. Freeman & Co., New York (1998). The term antibody also includes bivalent or bispecific molecules, diabodies, triabodies, and tetrabodies. The term "antibody" further includes both polyclonal and monoclonal antibodies.

[0088] Examples of therapeutic antibodies that may be used in the present invention include rituximab (Rituxan), Cetuximab (Erbitux), bevacizumab (Avastin), and Ibritumomab (Zevalin).

[0089] Cytotoxic agents according to the present invention include DNA damaging agents, antimetabolites, anti-microtubule agents, antibiotic agents, etc. DNA damaging agents include alkylating agents, platinum-based agents, intercalating agents, and inhibitors of DNA replication. Non-limiting examples of DNA alkylating agents include cyclophosphamide, mechlorethamine, uramustine, melphalan, chlorambucil, ifosfamide, carmustine, lomustine, streptozocin, busulfan, temozolomide, pharmaceutically acceptable salts thereof, prodrugs, and combinations thereof. Non-limiting examples of platinum-based agents include cisplatin, carboplatin, oxaliplatin, nedaplatin, satraplatin, triplatin tetranitrate, pharmaceutically acceptable salts thereof, prodrugs, and combinations thereof. Non-limiting examples of intercalating agents include doxorubicin, daunorubicin, idarubicin, mitoxantrone, pharmaceutically acceptable salts thereof, prodrugs, and combinations thereof. Non-limiting examples of inhibitors of DNA replication include irinotecan, topotecan, amsacrine, etoposide, etoposide phosphate, teniposide, pharmaceutically acceptable salts thereof, prodrugs, and combinations thereof. Antimetabolites include folate antagonists such as methotrexate and premetrexed, purine antagonists such as 6-mercaptopurine, dacarbazine, and fludarabine, and pyrimidine antagonists such as 5-fluorouracil, arabinosylcytosine, capecitabine, gemcitabine, decitabine, pharmaceutically acceptable salts thereof, prodrugs, and combinations thereof. Anti-microtubule agents include without limitation vinca alkaloids, paclitaxel (Taxol®), docetaxel (Taxotere®), and ixabepilone (Ixempra®). Antibiotic agents include without limitation actinomycin, anthracyclines, valrubicin, epirubicin, bleomycin, plicamycin, mitomycin, pharmaceutically acceptable salts thereof, prodrugs, and combinations thereof.

[0090] Cytotoxic agents according to the present invention also include an inhibitor of the PI3K/Akt pathway. Non-limiting examples of an inhibitor of the PI3K/Akt pathway include A-674563 (CAS #552325-73-2), AGL 2263, AMG-319 (Amgen, Thousand Oaks, Calif.), AS-041164 (5-benzo [1,3]dioxol-5-ylmethylene-thiazolidine-2,4-dione), AS-604850 (5-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethylene)-thiazolidine-2,4-dione), AS-605240 (5-quinoxilin-6-methylene-1,3-thiazolidine-2,4-dione), AT7867 (CAS #857531-00-1), benzimidazole series, Genentech (Roche Holdings Inc., South San Francisco, Calif.), BML-257 (CAS #32387-96-5), CAL-120 (Gilead Sciences, Foster City, Calif.), CAL-129 (Gilead Sciences), CAL-130 (Gilead Sciences), CAL-253 (Gilead Sciences), CAL-263 (Gilead Sciences), CAS #612847-09-3, CAS #681281-88-9, CAS #75747-14-7, CAS #925681-41-0, CAS #98510-80-6, CCT128930 (CAS #885499-61-6), CH5132799 (CAS #1007207-67-1), CHR-4432 (Chroma Therapeutics, Ltd., Abingdon, UK), FPA 124 (CAS #902779-59-3), GS-1101 (CAL-101) (Gilead Sciences), GSK 690693 (CAS #937174-76-0), H-89 (CAS #127243-85-0), Honokiol, IC87114 (Gilead Science), IPI-145 (Intellikine Inc.), KAR-4139 (Karus Therapeutics, Chilworth, UK), KAR-4141 (Karus Therapeutics), KIN-1 (Karus Therapeutics), KT 5720 (CAS #108068-98-0), Miltefosine, MK-2206 dihydrochloride (CAS #1032350-13-2), ML-9 (CAS #105637-50-1), Naltrindole Hydrochloride, OXY-111A (NormOxys Inc., Brighton, Mass.), perifosine, PHT-427 (CAS #1191951-57-1), PI3 kinase delta inhibitor, Merck KGaA (Merck & Co., Whitehouse Station, N.J.), PI3 kinase delta inhibitors, Genentech (Roche Holdings Inc.), PI3 kinase delta inhibitors, Incozen (Incozen Therapeutics, Pvt. Ltd., Hydrabad, India), PI3 kinase delta inhibitors-2, Incozen (Incozen Therapeutics), PI3 kinase inhibitor, Roche-4 (Roche Holdings Inc.), PI3

kinase inhibitors, Roche (Roche Holdings Inc.), PI3 kinase inhibitors, Roche-5 (Roche Holdings Inc.), PI3-alpha/delta inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd., South San Francisco, Calif.), PI3-delta inhibitors, Cellzome (Cellzome AG, Heidelberg, Germany), PI3-delta inhibitors, Intellikine (Intellikine Inc., La Jolla, Calif.), PI3-delta inhibitors, Pathway Therapeutics-1 (Pathway Therapeutics Ltd.), PI3-delta inhibitors, Pathway Therapeutics-2 (Pathway Therapeutics Ltd.), PI3-delta/gamma inhibitors, Cellzome (Cellzome AG), PI3-delta/gamma inhibitors, Cellzome (Cellzome AG), PI3-delta/gamma inhibitors, Intellikine (Intellikine Inc.), PI3-delta/gamma inhibitors, Intellikine (Intellikine Inc.), PI3-delta/gamma inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd.), PI3-delta/gamma inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd.), PI3-gamma inhibitor Evotec (Evotec), PI3-gamma inhibitor, Cellzome (Cellzome AG), PI3-gamma inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd.), PI3K delta/gamma inhibitors, Intellikine-1 (Intellikine Inc.), PI3K delta/gamma inhibitors, Intellikine-1 (Intellikine Inc.), pictilisib (Roche Holdings Inc.), PIK-90 (CAS #677338-12-4), SC-103980 (Pfizer, New York, N.Y.), SF-1126 (Semafore Pharmaceuticals, Indianapolis, Ind.), SH-5, SH-6, Tetrahydro Curcumin, TG100-115 (Targegen Inc., San Diego, Calif.), Triciribine, X-339 (Xcovery, West Palm Beach, Fla.), XL-499 (Evotech, Hamburg, Germany), pharmaceutically acceptable salts thereof, and combinations thereof.

[0091] In the present invention, the term "toxin" means an antigenic poison or venom of plant or animal origin. An example is diphtheria toxin or portions thereof.

[0092] In the present invention, the term "radionuclide" means a radioactive substance administered to the patient, e.g., intravenously or orally, after which it penetrates via the patient's normal metabolism into the target organ or tissue, where it delivers local radiation for a short time. Examples of radionuclides include, but are not limited to, I-125, At-211, Lu-177, Cu-67, I-131, Sm-153, Re-186, P-32, Re-188, In-114m, and Y-90.

[0093] In the present invention, the term "immunomodulator" means a substance that alters the immune response by augmenting or reducing the ability of the immune system to produce antibodies or sensitized cells that recognize and react with the antigen that initiated their production. Immunomodulators may be recombinant, synthetic, or natural preparations and include cytokines, corticosteroids, cytotoxic agents, thymosin, and immunoglobulins. Some immunomodulators are naturally present in the body, and certain of these are available in pharmacologic preparations. Examples of immunomodulators include, but are not limited to, granulocyte colony-stimulating factor (G-CSF), interferons, imiquimod and cellular membrane fractions from bacteria, IL-2, IL-7, IL-12, CCL3, CCL26, CXCL7, and synthetic cytosine phosphate-guanosine (CpG).

[0094] In the present invention, the term "photoactive therapeutic agent" means compounds and compositions that become active upon exposure to light. Certain examples of photoactive therapeutic agents are disclosed, e.g., in U.S. Patent Application Serial No. 2011/0152230 A1, "Photoactive Metal Nitrosyls For Blood Pressure Regulation And Cancer Therapy."

[0095] In the present invention, the term "radiosensitizing agent" means a compound that makes tumor cells more sensitive to radiation therapy. Examples of radiosensitizing agents include misonidazole, metronidazole, tirapazamine, and trans sodium crocetinate.

[0096] In the present invention, the term "hormone" means a substance released by cells in one part of a body that affects cells in another part of the body. Examples of hormones include, but are not limited to, prostaglandins, leukotrienes, prostacyclin, thromboxane, amylin, antimullerian hormone, adiponectin, adrenocorticotropic hormone, angiotensinogen, angiotensin, vasopressin, atriopeptin, brain natriuretic peptide, calcitonin, cholecystokinin, corticotropin-releasing hormone, encephalin, endothelin, erythropoietin, follicle-stimulating hormone, galanin, gastrin, ghrelin, glucagon, gonadotropin-releasing hormone, growth hormone-releasing hormone, human chorionic gonadotropin, human placental lactogen, growth hormone, inhibin, insulin, somatomedin, leptin, liptropin, luteinizing hormone, melanocyte stimulating hormone, motilin, orexin, oxytocin, pancreatic polypeptide, parathyroid hormone, prolactin, prolactin releasing hormone, relaxin, renin, secretin, somatostain, thrombopoietin, thyroid-stimulating hormone, testosterone, dehydroepiandrosterone, androstenedione, dihydrotestosterone, aldosterone, estradiol, estrone, estriol, cortisol, progesterone, calcitriol, and calcidiol.

[0097] Some compounds interfere with the activity of certain hormones or stop the production of certain hormones. These hormone-interfering compounds include, but are not limited to, tamoxifen (Nolvadex®), anastrozole (Arimidex®), letrozole (Femara®), and fulvestrant (Faslodex®). Such compounds are also within the meaning of hormone in the present invention.

[0098] As used herein, an "anti-angiogenesis" agent means a substance that reduces or inhibits the growth of new blood vessels, such as, e.g., an inhibitor of vascular endothelial growth factor (VEGF) and an inhibitor of endothelial cell migration. Anti-angiogenesis agents include without limitation 2-methoxyestradiol, angiostatin, bevacizumab, cartilage-derived angiogenesis inhibitory factor, endostatin, IFN-α, IL-12, itraconazole, linomide, platelet factor-4, prolactin, SU5416, suramin, tasquinimod, tecogalan, tetrathiomolybdate, thalidomide, thrombospondin, thrombospondin, TNP-470, ziv-aflibercept, pharmaceutically acceptable salts thereof, prodrugs, and combinations thereof.

[0099] Another embodiment of the present invention is a method for treating or ameliorating the effects of a cancer in a subject. The method comprises:

[0100] (a) identifying a subject with cancer that has become refractory or resistant to BRAF inhibitor therapy, MEK inhibitor therapy, or BRAF and MEK inhibitor therapy; and

[0101] (b) administering to the subject with said refractory or resistant cancer an effective amount of an ERK inhibitor, which is BVD-523 or a pharmaceutically acceptable salt thereof.

[0102] Suitable and preferred subjects are as disclosed herein. In this embodiment, the methods may be used to treat the cancers disclosed above. In accordance with the present invention, the cancer may have MAPK activity.

[0103] In one aspect of this embodiment, identifying a subject with cancer that is refractory or resistant to BRAF and/or MEK inhibitor therapy comprises:

[0104] (a) obtaining a biological sample from the subject; and

[0105] (b) screening the sample to determine whether the subject has become resistant to an inhibitor therapy selected from the group consisting of BRAF inhibitor therapy, MEK inhibitor therapy, and combinations thereof.

[0106] In the present invention, biological samples include, but are not limited to, blood, plasma, urine, skin, saliva, and biopsies. Biological samples are obtained from a subject by routine procedures and methods which are known in the art.

[0107] Preferably, screening for a cancer that is refractory or resistant to BRAF inhibitor therapy may comprise, e.g., identifying (i) a switch between RAF isoforms, (ii) upregulation of RTK or NRAS signaling, (iii) reactivation of mitogen activated protein kinase (MAPK) signaling, (iv) the presence of a MEK activating mutation, and combinations thereof.

[0108] A switch between RAF isoforms may occur in subjects having acquired resistance to BRAF inhibitor therapy. To detect such a switch, BRAF inhibitor-resistant tumor cells may be retrieved from a patient and analyzed via Western blotting for ERK and phospho-ERK levels in the presence of a BRAF inhibitor. Comparison with BRAF inhibitor-sensitive cells treated with a BRAF inhibitor may reveal higher levels of phospho-ERK in BRAF inhibitor-resistant tumor cells, implying that a switch has taken place in which another RAF isoform phosphorylates ERK in place of BRAF. Confirmation of which RAF isoform has taken over may involve sh/siRNA-mediated knockdown of ARAF and CRAF individually in BRAF inhibitor-resistant cells exposed to a BRAF inhibitor, followed by subsequent Western blotting for ERK and phospho-ERK levels. If, for example, ARAF knockdown in BRAF inhibitor-resistant cells exposed to a BRAF inhibitor still results in high levels of phospho-ERK, it would indicate that CRAF has taken over phosphorylating ERK. Likewise, if CRAF was knocked down in BRAF inhibitor-resistant cells exposed to BRAF inhibitor and ERK was still highly phosphorylated, it would mean that ARAF has taken over ERK phosphorylation. RAF isoform switching may also involve simultaneous knockdown of ARAF and CRAF in BRAF inhibitor-resistant cells in the presence of BRAF inhibitor, effectively blocking all RAF-mediated phosphorylation. A resulting decrease in ERK phosphorylation would indicate that the BRAF inhibitor-resistant cells have the capacity to switch between RAF isoforms in order to phosphorylate ERK (Villanueva, et al., 2010).

[0109] Upregulation of RTK or NRAS signaling may also be a cause of BRAF inhibitor resistance. Detection may, e.g., first involve using Western blotting protocols with phospho-specific antibodies to analyze the activation of the downstream RAF effectors MEK1/2 and ERK1/2. If BRAF inhibitor-resistant cells show high activation levels of these proteins in the presence of a BRAF inhibitor, RTK or NRAS upregulation may be the cause. Gene expression profiling (or other related methods) of BRAF inhibitor-resistant cells in the presence of a BRAF inhibitor may reveal higher expression levels of KIT, MET, EGFR, and PDGFRβ RTKs as compared to BRAF inhibitor-sensitive cells. Real-time quantitative polymerase chain reaction experiments, or other similar procedures, focusing on any of these genes may confirm higher expression levels while phospho-RTK arrays (R&D Systems, Minneapolis, Minn.) may show elevated activation-associated tyrosine phosphorylation. Alternatively, NRAS activation may be detected by various gene sequencing protocols. Activating mutations in NRAS, particularly Q61K, may indicate that B-RAF signaling has been bypassed. In melanoma cells, activated NRAS uses C-RAF to signal to MEK-ERK. Thus, activated NRAS may enable a similar bypass pathway in BRAF inhibitor-resistant cells exposed to BRAF inhibitor. Further confirmation of these mechanisms in a given BRAF inhibitor-resistant sample may be accomplished, for example, using sh/siRNA-mediated knockdown of upregulated RTKs or activated NRAS in the presence of BRAF inhibitor. Any significant levels of growth inhibition may indicate that upregulation of RTK or NRAS signaling is the cause of BRAF inhibition in that particular sample (Nazarian, et al., 2010).

[0110] Detecting reactivation of MAPK signaling in BRAF inhibitor-resistant cells may indicate another bypass mechanism for BRAF inhibitor resistance. COT and C-RAF have been shown to be upregulated in a BRAF V600E background exposed to BRAF inhibitor. Quantitative real-time RT-PCR, e.g., may reveal increased COT expression in BRAF inhibitor-resistant cells in the presence of BRAF inhibitor. Furthermore, sh/siRNA-mediated knockdown of COT in BRAF inhibitor-resistant cells in the presence of BRAF inhibitor may reduce the viability of BRAF inhibitor-resistant cells, indicating that these particular cells may be sensitive to COT inhibition and/or combination BRAF inhibitor/MEK inhibitor treatments (Johannessen, et al., 2010).

[0111] Reactivation of MAPK signaling may also be accomplished in a BRAF inhibitor-resistant background by activating mutations in MEK1. Targeted, massively parallel sequencing of genomic DNA from a BRAF inhibitor-resistant tumor may reveal activating mutations in MEK1, such as C121S, G128D, N122D, and Y130, among others. Other, undocumented mutations in MEK1 may be analyzed by, for example, expressing the particular mutation in a BRAF inhibitor-sensitive cell line such as A375. Determining levels of growth inhibition in these cells upon exposure to BRAF inhibitor may indicate if the MEK1 mutation is causing resistance to BRAF inhibitory therapy. To confirm such a finding, Western blotting for elevated levels of phospho-ERK1/2 in cells ectopically expressing the MEK1 mutation may indicate that the MEK1 mutation is allowing the BRAF inhibitor-resistant tumor to bypass BRAF and promote phosphorylation of ERK through MEK1 (Wagle, et al., 2011).

[0112] In accordance with the present invention, screening for a cancer that is refractory or resistant to MEK inhibitor therapy may comprise, e.g., identifying (i) amplification of mutant BRAF, (ii) STAT3 upregulation, (iii) mutations in the allosteric pocket of MEK that directly block binding of inhibitors to MEK or lead to constitutive MEK activity, and combinations thereof.

[0113] Amplification of mutant BRAF may cause MEK inhibitor resistance. MEK inhibitor resistance is typically associated with high levels of phosphorylated ERK and MEK in the presence of a MEK inhibitor, which may be assessed via, for example, Western blotting. Amplification of mutant BRAF in MEK inhibitor-resistant cell lines may be detected by, for example, fluorescence in situ hybridization (FISH) or quantitative PCR from genomic DNA of the resistant cell lines. Confirmation that BRAF amplification is a primary cause of MEK inhibitor resistance may entail using BRAF-targeted sh/siRNAs in resistant cells. If a significant decrease in MEK or ERK phosphorylation is

observed, BRAF amplification may be a suitable target for further therapeutic approaches. (Corcoran, et al., 2010).

[0114] Identifying STAT3 upregulation may indicate that a particular tumor sample is resistant to MEK inhibitor therapy. Genome-wide expression profiling may reveal the STAT3 pathway to be upregulated in a tumor. Other techniques, such as Western blotting for phospho-STAT3 and real-time qPCR for the STAT pathway-associated genes JAK1 and IL6ST may reveal upregulated STAT3. Further confirmation that STAT3 upregulation causes MEK inhibitor resistance in a particular sample may comprise the use of sh/siRNAs against STAT3 in the sample followed by appropriate Western blotting for MEK and ERK activation as well as phospho-STAT3 and total STAT3. Growth inhibition studies may show that STAT3 knockdown sensitizes previously MEK inhibitor-resistant cells to MEK inhibition. A similar effect may be seen if the sample were exposed to a STAT3 inhibitor such as JSI-124. Additional confirmation that STAT3 upregulation is the cause of MEK inhibitor resistance in a particular tumor could arise from Western blotting for BIM expression, including BIM-EL, BIM-L, and BIM-SL. BIM expression leads to MEK inhibitor-induced apoptosis, thus STAT3 upregulation may lower BIM levels. STAT3 is known to regulate the expression of miR 17-92, which suppresses BIM expression. Upregulated STAT3 may lead to higher levels of miR 17-92, which will lower BIM levels and promote resistance to MEK inhibition. Thus, real-time qPCR of miR 17-92 levels may also assist in assessing whether STAT3 upregulation is causing MEK inhibition resistance in a particular sample. (Dai, et al., 2011).

[0115] Mutations in the allosteric pocket of MEK that can directly block binding of inhibitors to MEK or lead to constitutive MEK activity may be detected by methods disclosed below. Such mutations have been identified previously by Emery and colleagues (Emery, et al., 2009) as well as Wang and colleagues (Wang et al., 2011). Other mutations may affect MEK1 codons located within or abutting the N-terminal negative regulatory helix, such as P124L and Q56P. (Id.).

[0116] Methods for identifying mutations in nucleic acids, such as the above identified MEK genes, are known in the art. Nucleic acids may be obtained from biological samples. In the present invention, biological samples include, but are not limited to, blood, plasma, urine, skin, saliva, and biopsies. Biological samples are obtained from a subject by routine procedures and methods which are known in the art.

[0117] Non-limiting examples of methods for identifying mutations include PCR, sequencing, hybrid capture, in-solution capture, molecular inversion probes, fluorescent in situ hybridization (FISH) assays, and combinations thereof.

[0118] Various sequencing methods are known in the art. These include, but are not limited to, Sanger sequencing (also referred to as dideoxy sequencing) and various sequencing-by-synthesis (SBS) methods as disclosed in, e.g., Metzker 2005, sequencing by hybridization, by ligation (for example, WO 2005021786), by degradation (for example, U.S. Pat. Nos. 5,622,824 and 6,140,053) and nanopore sequencing (which is commercially available from Oxford Nanopore Technologies, UK). In deep sequencing techniques, a given nucleotide in the sequence is read more than once during the sequencing process. Deep sequencing techniques are disclosed in e.g., U.S. Patent Publication No. 20120264632 and International Patent Publication No. WO2012125848.

[0119] PCR-based methods for detecting mutations are known in the art and employ PCR amplification, where each target sequence in the sample has a corresponding pair of unique, sequence-specific primers. For example, the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method allows for rapid detection of mutations after the genomic sequences are amplified by PCR. The mutation is discriminated by digestion with specific restriction endonucleases and is identified by electrophoresis. See, e.g., Ota et al., 2007. Mutations may also be detected using real time PCR. See, e.g., International Application publication No. WO2012046981.

[0120] Hybrid capture methods are known in the art and are disclosed in e.g., U.S. Patent Publication No. 20130203632 and U.S. Pat. Nos. 8,389,219 and 8,288,520. These methods are based on the selective hybridization of the target genomic regions to user-designed oligonucleotides. The hybridization can be to oligonucleotides immobilized on high or low density microarrays (on-array capture), or solution-phase hybridization to oligonucleotides modified with a ligand (e.g. biotin) which can subsequently be immobilized to a solid surface, such as a bead (in-solution capture).

[0121] Molecular Inversion Probe (MIP) techniques are known in the art and are disclosed in e.g., Absalan et al., 2008. This method uses MIP molecules, which are special "padlock" probes (Nilsson et al, 1994) for genotyping. A MIP molecule is a linear oligonucleotide that contains specific regions, universal sequences, restriction sites and a Tag (index) sequence (16-22 bp). A MIP hybridizes directly around the genetic marker/SNP of interest. The MIP method may also use a number of "padlock" probe sets that hybridize to genomic DNA in parallel (Hardenbol et al., 2003). In case of a perfect match, genomic homology regions are ligated by undergoing an inversion in configuration (as suggested by the name of the technique) and creating a circular molecule. After the first restriction, all molecules are amplified with universal primers. Amplicons are restricted again to ensure short fragments for hybridization on a microarray. Generated short fragments are labeled and, through a Tag sequence, hybridized to a cTag (complementary strand for index) on an array. After the formation of Tag-cTag duplex, a signal is detected.

[0122] The following Tables 1, 2, and 3 show the SEQ ID Nos. of representative nucleic acid and amino acid sequences of wild type BRAF, N-RAS, and MEK1 from various animals in the sequence listing. These sequences may be used in methods for identifying subjects with mutant BRAF, N-RAS, and MEK1 genotypes.

TABLE 1

BRAF sequences

SEQ ID NO.	polypeptide or nucleic acid sequence	Organism	Other information
1	nucleic acid	human	
2	polypeptide	human	
3	nucleic acid	rat (*Rattus norvegicus*)	

TABLE 1-continued

BRAF sequences

SEQ ID NO.	polypeptide or nucleic acid sequence	Organism	Other information
4	polypeptide	rat (*Rattus norvegicus*)	
5	nucleic acid	mouse, *Mus musculus*	
6	polypeptide	mouse, *Mus musculus*	
7	nucleic acid	rabbit, *Oryctolagus cuniculus*	
8	polypeptide	rabbit, *Oryctolagus cuniculus*	
9	nucleic acid	guinea pig, *Cavia porcellus*	
10	polypeptide	guinea pig, *Cavia porcellus*	
11	nucleic acid	dog, *Canis lupus familiaris*	variant x1
12	polypeptide	dog, *Canis lupus familiaris*	variant x1
13	nucleic acid	dog, *Canis lupus familiaris*	variant x2
14	polypeptide	dog, *Canis lupus familiaris*	variant x2
15	nucleic acid	cat, *Felis catus*	
16	polypeptide	cat, *Felis catus*	
17	nucleic acid	cow, *Bos taurus*	variant X1
18	polypeptide	cow, *Bos taurus*	variant X1
19	nucleic acid	cow, *Bos taurus*	variant X2
20	polypeptide	cow, *Bos taurus*	variant X2
21	nucleic acid	cow, *Bos taurus*	variant X3
22	polypeptide	cow, *Bos taurus*	variant X3
23	nucleic acid	cow, *Bos taurus*	variant X4
24	polypeptide	cow, *Bos taurus*	variant X4
25	nucleic acid	cow, *Bos taurus*	variant X5
26	polypeptide	cow, *Bos taurus*	variant X5
27	nucleic acid	cow, *Bos taurus*	variant X6
28	polypeptide	cow, *Bos taurus*	variant X6
29	nucleic acid	cow, *Bos taurus*	variant X7
30	polypeptide	cow, *Bos taurus*	variant X7
31	nucleic acid	cow, *Bos taurus*	variant X8
32	polypeptide	cow, *Bos taurus*	variant X8
33	nucleic acid	cow, *Bos taurus*	variant X9
34	polypeptide	cow, *Bos taurus*	variant X9
35	nucleic acid	cow, *Bos taurus*	variant X10
36	polypeptide	cow, *Bos taurus*	variant X10
37	nucleic acid	cow, *Bos taurus*	variant X11
38	polypeptide	cow, *Bos taurus*	variant X11
39	nucleic acid	cow, *Bos taurus*	variant 2
40	polypeptide	cow, *Bos taurus*	variant 2
41	nucleic acid	horse, *Equus caballus*	
42	polypeptide	horse, *Equus caballus*	
43	nucleic acid	chicken, *Gallus gallus*	
44	polypeptide	chicken, *Gallus gallus*	

TABLE 2

N-RAS sequences

SEQ ID NO.	polypeptide or nucleic acid sequence	Organism	Other information
45	nucleic acid	human	
46	polypeptide	human	
47	nucleic acid	rat (*Rattus norvegicus*)	

TABLE 2-continued

N-RAS sequences

SEQ ID NO.	polypeptide or nucleic acid sequence	Organism	Other information
48	polypeptide	rat (*Rattus norvegicus*)	
49	nucleic acid	mouse, *Mus musculus*	
50	polypeptide	mouse, *Mus musculus*	
51	nucleic acid	guinea pig, *Cavia porcellus*	
52	polypeptide	guinea pig, *Cavia porcellus*	
53	nucleic acid	guinea pig, *Cavia porcellus*	variant X1
54	polypeptide	guinea pig, *Cavia porcellus*	variant X1
55	nucleic acid	dog, *Canis lupus familiaris*	
56	polypeptide	dog, *Canis lupus familiaris*	
57	nucleic acid	cat, *Felis catus*	
58	polypeptide	cat, *Felis catus*	
59	nucleic acid	cow, *Bos taurus*	
60	polypeptide	cow, *Bos taurus*	
61	nucleic acid	chicken, *Gallus gallus*	
62	polypeptide	chicken, *Gallus gallus*	

TABLE 3

MEK1 sequences

SEQ ID NO.	polypeptide or nucleic acid sequence	Organism
63	nucleic acid	human
64	polypeptide	human
65	nucleic acid	rat (*Rattus norvegicus*)
66	polypeptide	rat (*Rattus norvegicus*)
67	nucleic acid	mouse, *Mus musculus*
68	polypeptide	mouse, *Mus musculus*
69	nucleic acid	rabbit, *Oryctolagus cuniculus*
70	polypeptide	rabbit, *Oryctolagus cuniculus*
71	nucleic acid	guinea pig, *Cavia porcellus*
72	polypeptide	guinea pig, *Cavia porcellus*
73	nucleic acid	dog, *Canis lupus familiaris*
74	polypeptide	dog, *Canis lupus familiaris*
75	nucleic acid	cat, *Felis catus*
76	polypeptide	cat, *Felis catus*
77	nucleic acid	cow, *Bos taurus*
78	polypeptide	cow, *Bos taurus*
79	nucleic acid	horse, *Equus caballus*
80	polypeptide	horse, *Equus caballus*
81	nucleic acid	chicken, *Gallus gallus*
82	polypeptide	chicken, *Gallus gallus*

[0123] In another aspect of this embodiment, the method further comprises administering at least one additional therapeutic agent, preferably an inhibitor of the PI3K/Akt pathway, as disclosed herein.

[0124] A further embodiment of the present invention is a method for treating or ameliorating the effects of cancer in a subject, which cancer is refractory or resistant to BRAF inhibitor therapy, MEK inhibitor therapy, or both. The method comprises administering to the subject an effective amount of BVD-523 or a pharmaceutically acceptable salt thereof.

[0125] Suitable and preferred subjects are as disclosed herein. In this embodiment, the methods may be used to treat the cancers disclosed above, including those cancers with the mutational backgrounds, resistance profiles, and MAPK activity identified above. Methods of identifying such mutations are also as set forth above.

[0126] In a further aspect of this embodiment, the method further comprises administering to the subject at least one additional therapeutic agent, preferably an inhibitor of the PI3K/Akt pathway, as disclosed herein.

[0127] Another embodiment of the present invention is a method for identifying a subject having cancer who would benefit from therapy with an ERK inhibitor. The method comprises:

[0128] (a) obtaining a biological sample from the subject; and

[0129] (b) screening the sample to determine whether the subject has one or more of the following markers:

[0130] (i) a switch between RAF isoforms,

[0131] (ii) upregulation of RTK or NRAS signaling,

[0132] (iii) reactivation of mitogen activated protein kinase (MAPK) signaling,

[0133] (iv) the presence of a MEK activating mutation,

[0134] (v) amplification of mutant BRAF,

[0135] (vi) STAT3 upregulation,

[0136] (vii) mutations in the allosteric pocket of MEK that directly block binding of inhibitors to MEK or lead to constitutive MEK activity,

wherein the presence of one or more of the markers confirms that the subject's cancer is refractory or resistant to BRAF and/or MEK inhibitor therapy and that the subject would benefit from therapy with an ERK inhibitor, which is BVD-523 or a pharmaceutically acceptable salt thereof.

[0137] Suitable and preferred subjects are as disclosed herein. In this embodiment, the methods may be used to identify a subject having cancers disclosed above, including those cancers with the mutational backgrounds, resistance profiles, and MAPK activity identified above. Methods of identifying such mutations are also as set forth above.

[0138] In one aspect of this embodiment, the method further comprises administering BVD-523 or a pharmaceutically acceptable salt thereof to a subject having one or more of the markers. Preferably, the method additionally comprises administering to the subject having one or more of the markers at least one additional therapeutic agent, preferably an inhibitor of the PI3K/Akt pathway, as disclosed herein.

[0139] An additional embodiment of the present invention is a pharmaceutical composition for treating or ameliorating the effects of a cancer in a subject, which cancer is refractory or resistant to non-ERK MAPK pathway therapy. The composition comprises a pharmaceutically acceptable carrier or diluent and an effective amount of BVD-523 or a pharmaceutically acceptable salt thereof.

[0140] Suitable and preferred subjects and types of non-ERK MAPK pathway inhibitor therapy are as disclosed herein. In this embodiment, the pharmaceutical composition may be used to treat the cancers disclosed above, including those cancers with the mutational backgrounds, resistance profiles, and MAPK activity identified above. Methods of identifying such mutations are also as set forth above.

[0141] In one aspect of this embodiment, the pharmaceutical composition further comprises at least one additional therapeutic agent, preferably an inhibitor of the PI3K/Akt pathway, as disclosed herein.

[0142] Another embodiment of the present invention is a kit for treating or ameliorating the effects of a cancer in a subject, which cancer is refractory or resistant to non-ERK MAPK pathway therapy. This kit comprises any pharmaceutical composition according to the present invention packaged together with instructions for its use.

[0143] The kits may also include suitable storage containers, e.g., ampules, vials, tubes, etc., for each pharmaceutical composition and other reagents, e.g., buffers, balanced salt solutions, etc., for use in administering the pharmaceutical compositions to subjects. The pharmaceutical compositions and other reagents may be present in the kits in any convenient form, such as, e.g., in a solution or in a powder form. The kits may further include a packaging container, optionally having one or more partitions for housing the pharmaceutical composition and other optional reagents.

[0144] Suitable and preferred subjects and types of non-ERK MAPK pathway inhibitor therapy are as disclosed herein. In this embodiment, the kit may be used to treat the cancers disclosed above, including those cancers with the mutational backgrounds, resistance profiles, and MAPK activity identified herein. Methods of identifying such mutations are as set forth above.

[0145] In one aspect of this embodiment, the kit further comprises at least one additional therapeutic agent, preferably an inhibitor of the PI3K/Akt pathway, as disclosed herein.

[0146] Another embodiment of the present invention is a method for inhibiting phosphorylation of RSK in a cancer cell that is refractory or resistant to a non-ERK MAPK pathway inhibitor. The method comprises contacting the cancer cell with an effective amount of BVD-523 or a pharmaceutically acceptable salt thereof for a period of time sufficient for phosphorylation of RSK in the cancer cell to be inhibited. In this embodiment, "contacting" means bringing BVD-523 or a pharmaceutically acceptable salt thereof and optionally one or more additional therapeutic agents into close proximity to the cancer cells. This may be accomplished using conventional techniques of drug delivery to mammals, or in the in vitro situation by, e.g., providing BVD-523 or a pharmaceutically acceptable salt thereof and optionally other therapeutic agents to a culture media in which the cancer cells are located. In the ex vivo situation, contacting may be carried out by, e.g., providing BVD-523 or a pharmaceutically acceptable salt thereof and optionally other therapeutic agents to a cancerous tissue.

[0147] Suitable and preferred types of non-ERK MAPK pathway inhibitors are as disclosed herein. In this embodiment, effecting cancer cell death may be accomplished in cancer cells having various mutational backgrounds, resistance profiles, and MAPK activity as disclosed above. Methods of identifying such mutations are also as set forth above.

[0148] The methods of this embodiment, which may be carried out in vitro, ex vivo, or in vivo, may be used to effect cancer cell death, by e.g., killing cancer cells, in cells of the types of cancer disclosed herein.

[0149] In one aspect of this embodiment, greater than 50% of RSK phosphorylation is inhibited. In another aspect of this embodiment, greater than 75% of RSK phosphorylation is inhibited. In an additional aspect of this embodiment, greater than 90% of RSK phosphorylation is inhibited. In a further aspect of this embodiment, greater than 95% of RSK phosphorylation is inhibited. In another aspect of this embodiment, greater than 99% of RSK phosphorylation is inhibited. In an additional aspect of this embodiment, 100% of RSK phosphorylation is inhibited.

[0150] In a further aspect of this embodiment, the cancer cell is a mammalian cancer cell. Preferably, the mammalian cancer cell is obtained from a mammal selected from the group consisting of humans, primates, farm animals, and domestic animals. More preferably, the mammalian cancer cell is a human cancer cell.

[0151] In a further aspect of this embodiment, the contacting step comprises administering BVD-523 or a pharmaceutically acceptable salt to a subject from whom the cancer cell was obtained.

[0152] In the present invention, an "effective amount" or a "therapeutically effective amount" of a compound or composition disclosed herein is an amount of such compound or composition that is sufficient to effect beneficial or desired results as described herein when administered to a subject. Effective dosage forms, modes of administration, and dosage amounts may be determined empirically, and making such determinations is within the skill of the art. It is understood by those skilled in the art that the dosage amount will vary with the route of administration, the rate of excretion, the duration of the treatment, the identity of any other drugs being administered, the age, size, and species of mammal, e.g., human patient, and like factors well known in the arts of medicine and veterinary medicine. In general, a suitable dose of a compound or composition according to the invention will be that amount of the composition, which is the lowest dose effective to produce the desired effect. The effective dose of a compound or composition of the present invention may be administered as two, three, four, five, six or more sub-doses, administered separately at appropriate intervals throughout the day.

[0153] A suitable, non-limiting example of a dosage of a BVD-523 and other anti-cancer agents disclosed herein is from about 1 mg/kg to about 2400 mg/kg per day, such as from about 1 mg/kg to about 1200 mg/kg per day, 75 mg/kg per day to about 300 mg/kg per day, including from about 1 mg/kg to about 100 mg/kg per day. Other representative dosages of such agents include about 1 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 60 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 90 mg/kg, 100 mg/kg, 125 mg/kg, 150 mg/kg, 175 mg/kg, 200 mg/kg, 250 mg/kg, 300 mg/kg, 400 mg/kg, 500 mg/kg, 600 mg/kg, 700 mg/kg, 800 mg/kg, 900 mg/kg, 1000 mg/kg, 1100 mg/kg, 1200 mg/kg, 1300 mg/kg, 1400 mg/kg, 1500 mg/kg, 1600 mg/kg, 1700 mg/kg, 1800 mg/kg, 1900 mg/kg, 2000 mg/kg, 2100 mg/kg, 2200 mg/kg, and 2300 mg/kg per day. The effective dose of BVD-523 and other anti-cancer agents disclosed herein, may be administered as two, three, four, five, six or more sub-doses, administered separately at appropriate intervals throughout the day.

[0154] The BVD-523, other inhibitors, and various other anti-cancer agents disclosed herein, or a pharmaceutical composition of the present invention may be administered in any desired and effective manner: for oral ingestion, or as an ointment or drop for local administration to the eyes, or for parenteral or other administration in any appropriate manner such as intraperitoneal, subcutaneous, topical, intradermal, inhalation, intrapulmonary, rectal, vaginal, sublingual, intramuscular, intravenous, intraarterial, intrathecal, or intralymphatic. Further, BVD-523, other inhibitors, and various other anti-cancer agents disclosed herein, or a pharmaceutical composition of the present invention may be administered in conjunction with other treatments. BVD-523, other inhibitors, and various other anti-cancer agents disclosed herein, or a pharmaceutical composition of the present invention may be encapsulated or otherwise protected against gastric or other secretions, if desired.

[0155] The pharmaceutical compositions of the invention comprise one or more active ingredients in admixture with one or more pharmaceutically-acceptable diluents or carriers and, optionally, one or more other compounds, drugs, ingredients and/or materials. Regardless of the route of administration selected, the agents/compounds of the present invention are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art. See, e.g., Remington, The Science and Practice of Pharmacy (21st Edition, Lippincott Williams and Wilkins, Philadelphia, Pa.).

[0156] Pharmaceutically acceptable diluents or carriers are well known in the art (see, e.g., Remington, The Science and Practice of Pharmacy (21st Edition, Lippincott Williams and Wilkins, Philadelphia, Pa.) and The National Formulary (American Pharmaceutical Association, Washington, D.C.)) and include sugars (e.g., lactose, sucrose, mannitol, and sorbitol), starches, cellulose preparations, calcium phosphates (e.g., dicalcium phosphate, tricalcium phosphate and calcium hydrogen phosphate), sodium citrate, water, aqueous solutions (e.g., saline, sodium chloride injection, Ringer's injection, dextrose injection, dextrose and sodium chloride injection, lactated Ringer's injection), alcohols (e.g., ethyl alcohol, propyl alcohol, and benzyl alcohol), polyols (e.g., glycerol, propylene glycol, and polyethylene glycol), organic esters (e.g., ethyl oleate and tryglycerides), biodegradable polymers (e.g., polylactide-polyglycolide, poly(orthoesters), and poly(anhydrides)), elastomeric matrices, liposomes, microspheres, oils (e.g., corn, germ, olive, castor, sesame, cottonseed, and groundnut), cocoa butter, waxes (e.g., suppository waxes), paraffins, silicones, talc, silicylate, etc. Each pharmaceutically acceptable diluent or carrier used in a pharmaceutical composition of the invention must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject. Diluents or carriers suitable for a selected dosage form and intended route of administration are well known in the art, and acceptable diluents or carriers for a chosen dosage form and method of administration can be determined using ordinary skill in the art.

[0157] The pharmaceutical compositions of the invention may, optionally, contain additional ingredients and/or materials commonly used in pharmaceutical compositions. These ingredients and materials are well known in the art and include (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (2) binders, such as carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, hydroxypropylmethyl cellulose, sucrose and acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, sodium starch glycolate, cross-linked sodium carboxymethyl cellulose and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, and sodium lauryl sulfate; (10) suspending agents, such as ethoxylated isostearyl alcohols, polyoxyethylene

sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth; (11) buffering agents; (12) excipients, such as lactose, milk sugars, polyethylene glycols, animal and vegetable fats, oils, waxes, paraffins, cocoa butter, starches, tragacanth, cellulose derivatives, polyethylene glycol, silicones, bentonites, silicic acid, talc, salicylate, zinc oxide, aluminum hydroxide, calcium silicates, and polyamide powder; (13) inert diluents, such as water or other solvents; (14) preservatives; (15) surface-active agents; (16) dispersing agents; (17) control-release or absorption-delaying agents, such as hydroxypropylmethyl cellulose, other polymer matrices, biodegradable polymers, liposomes, microspheres, aluminum monostearate, gelatin, and waxes; (18) opacifying agents; (19) adjuvants; (20) wetting agents; (21) emulsifying and suspending agents; (22), solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan; (23) propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane; (24) antioxidants; (25) agents which render the formulation isotonic with the blood of the intended recipient, such as sugars and sodium chloride; (26) thickening agents; (27) coating materials, such as lecithin; and (28) sweetening, flavoring, coloring, perfuming and preservative agents. Each such ingredient or material must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject. Ingredients and materials suitable for a selected dosage form and intended route of administration are well known in the art, and acceptable ingredients and materials for a chosen dosage form and method of administration may be determined using ordinary skill in the art.

[0158] The pharmaceutical compositions of the present invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, powders, granules, a solution or a suspension in an aqueous or non-aqueous liquid, an oil-in-water or water-in-oil liquid emulsion, an elixir or syrup, a pastille, a bolus, an electuary or a paste. These formulations may be prepared by methods known in the art, e.g., by means of conventional pan-coating, mixing, granulation or lyophilization processes.

[0159] Solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like) may be prepared, e.g., by mixing the active ingredient(s) with one or more pharmaceutically-acceptable diluents or carriers and, optionally, one or more fillers, extenders, binders, humectants, disintegrating agents, solution retarding agents, absorption accelerators, wetting agents, absorbents, lubricants, and/or coloring agents. Solid compositions of a similar type may be employed as fillers in soft and hard-filled gelatin capsules using a suitable excipient. A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using a suitable binder, lubricant, inert diluent, preservative, disintegrant, surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine. The tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein. They may be sterilized by, for example, filtration through a bacteria-retaining filter. These compositions may also optionally contain opacifying agents and may be of a composition such that they release the active ingredient only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. The active ingredient can also be in microencapsulated form.

[0160] Liquid dosage forms for oral administration include pharmaceutically-acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. The liquid dosage forms may contain suitable inert diluents commonly used in the art. Besides inert diluents, the oral compositions may also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents. Suspensions may contain suspending agents.

[0161] The pharmaceutical compositions of the present invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more active ingredient(s) with one or more suitable nonirritating diluents or carriers which are solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound. The pharmaceutical compositions of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such pharmaceutically-acceptable diluents or carriers as are known in the art to be appropriate.

[0162] Dosage forms for the topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, drops and inhalants. The active agent(s)/compound(s) may be mixed under sterile conditions with a suitable pharmaceutically-acceptable diluent or carrier. The ointments, pastes, creams and gels may contain excipients. Powders and sprays may contain excipients and propellants.

[0163] The pharmaceutical compositions of the present invention suitable for parenteral administrations may comprise one or more agent(s)/compound(s) in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain suitable antioxidants, buffers, solutes which render the formulation isotonic with the blood of the intended recipient, or suspending or thickening agents. Proper fluidity can be maintained, for example, by the use of coating materials, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. These pharmaceutical compositions may also contain suitable adjuvants, such as wetting agents, emulsifying agents and dispersing agents. It may also be desirable to include isotonic agents. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption.

[0164] In some cases, in order to prolong the effect of a drug (e.g., pharmaceutical formulation), it is desirable to slow its absorption from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility.

[0165] The rate of absorption of the active agent/drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered agent/drug may be accomplished by dissolving or suspending the active agent/drug in an oil vehicle. Injectable depot forms may be made by forming microencapsule matrices of the active ingredient in biodegradable polymers. Depending on the ratio of the active ingredient to polymer, and the nature of the particular polymer employed, the rate of active ingredient release can be controlled. Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue. The injectable materials can be sterilized for example, by filtration through a bacterial-retaining filter.

[0166] The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampules and vials, and may be stored in a lyophilized condition requiring only the addition of the sterile liquid diluent or carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the type described above.

[0167] The present invention provides treatment of cancer which is refractory or resistant to non-ERK MAPK pathway inhibitor therapy and discloses combinations shown to enhance the effects of ERK inhibitors. Herein, applicants have also shown that the combination of different ERK inhibitors is likewise synergistic. Therefore, it is contemplated that the effects of the combinations described herein can be further improved by the use of one or more additional ERK inhibitors. Accordingly, some embodiments of the present invention include one or more additional ERK inhibitors.

[0168] The present invention also provides a method of treating a subject having an unresectable or metastatic BRAF600 mutation-positive melanoma comprising administering to the subject 600 mg BID of BVD-523 or a pharmaceutically acceptable salt thereof.

[0169] In some embodiments of the invention, the mutation is a $BRAF^{V600E}$ mutation.

[0170] The present invention also provides a composition for treating a subject having an unresectable or metastatic BRAF600 mutation-positive melanoma, the composition comprising 600 mg of BVD-523 or a pharmaceutically acceptable salt thereof and optionally a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0171] The following examples are provided to further illustrate the methods of the present invention. These examples are illustrative only and are not intended to limit the scope of the invention in any way.

EXAMPLES

Example 1

Materials and Methods

[0172] Cancer cell lines were maintained in cell culture under standard media and serum conditions. For dose escalation studies, A375 cells were split, grown to about 40-60% confluence, and then treated with the initial dose of the specified drug. Table 4 shows a summary of drug treatments that were escalated.

TABLE 4

Summary of Treatments Being Escalated

Treatment	Inhibitor
1	Trametinib (MEKi)
2	Dabrafenib (BRAFi)
3	BVD-523 (ERKi)
4	Dabrafenib (BRAFi) + Trametinib (MEKi)
5	Dabrafenib (BRAFi) + BVD-523 (ERKi)
6	Trametinib (MEKi) + BVD-523 (ERKi)

[0173] Single agent dose escalations were performed based on Little et al., 2011 and are outlined in FIG. **20**. Cells were then allowed to grow until 70-90% confluence and split. Split ratios were kept as "normal" as possible and reasonably consistent between treatments (e.g. a minimum of 50% of the normal split ratio of the parentals). Medium was refreshed every 3-4 days. When cells again reached about 40-60% confluence, the dose was escalated. In the event that the 40-60% window was missed, the cells were split again and dosed once they reached 40-60% confluence. Again, medium was refreshed every 3-4 days. The process was repeated as required (FIG. **20**).

[0174] For single agent treatments, starting concentrations and dose increases were conducted by starting with the approximate IC_{50}, escalating in small increments or, gently, for the initial 4-5 doses, doubling the dose, increasing by the same increment for the next 4 doses, then moving to 1.5-fold increases in concentration for subsequent doses.

[0175] For combination treatments, starting concentrations and dose increases were conducted by starting with half of the approximate IC_{50} of each compound (combination assay suggests this will result in about 40-70% inhibition range), escalating as per single agents (i.e. doing an initial doubling and then increasing by the same increment for the next 4 doses, then moving to 1.5-fold increases in concentration). Table 5 shows the projected dose increases using these schemes.

TABLE 5

Projected Dose Increases—Month 1

				Dab/Tram		Dab/523		Tram/523	
Dose	Tram (nM)	Dab (nM)	BVD-523 (μM)	Dab (nM)	Tram (nM)	Dab (nM)	523 (μM)	Tram (nM)	523 (μM)
1	1	5	0.16	2.5	0.5	2.5	0.08	0.5	0.08
2	2	10	0.32	5	1	5	0.16	1	0.16
3	3	15	0.48	7.5	1.5	7.5	0.24	1.5	0.24
4	4	20	0.64	10	2	10	0.32	2	0.32
5	5	25	0.80	12.5	2.5	12.5	0.40	2.5	0.40
6	8	38	1.2	19	4	19	0.6	4	0.6
7	11	56	1.8	28	6	28	0.9	6	0.9
8	17	84	2.7	42	8	42	1.4	8	1.4
9	25	127	4.1	63	13	63	2.0	13	2.0
10	38	190	6.1	95	19	95	3.0	19	3.0
11	57	285	9.1	142	28	142	4.6	28	4.6
12	85	427	13.7	214	43	214	6.8	43	6.8
13	128	641	20.5	320	64	320	10.3	64	10.3
14	192	961	30.8	481	96	481	15.4	96	15.4
15	288	1442	46.1	721	144	721	23.1	144	23.1
16	432	2162	69.2	1081	216	1081	34.6	216	34.6
17	649	3244	103.8	1622	324	1622	51.9	324	51.9
18	973	4865	155.7	2433	487	2433	77.8	487	77.8
19	1460	7298	233.5	3649	730	3649	116.8	730	116.8
20	2189	10947	350.3	5474	1095	5474	175.2	1095	175.2

[0176] Clonal resistant cell populations were derived from resistant cell pools by limiting dilution.

[0177] Proliferation assays were used to track changes in sensitivity to the escalated agent(s) at appropriate time intervals (e.g. each month, although the timing is dependent on adequate cell numbers being available). For proliferation assays, cells were seeded in 96-well plates at 3000 cells per well in drug-free DMEM medium containing 10% FBS and allowed to adhere overnight prior to addition of compound or vehicle control. Compounds were prepared from DMSO stocks to give a final concentration range as shown in FIG. **2**A-FIG. **2**H. The final DMSO concentration was constant at 0.1%. Test compounds were incubated with the cells for 96 hours at 37° C. and 5% CO_2 in a humidified atmosphere. Alamar Blue 10% (v/v) was then added and incubated for 4 hours and fluorescent product was detected using a BMG FLUOstar plate reader. The average media only background value was deducted and the data analyzed using a 4-parameter logistic equation in GraphPad Prism. Paclitaxel was used as a positive control.

[0178] Proliferation assays for month 1 were initiated at day 28 using cells growing in the concentrations of each agent indicated in Table 6.

TABLE 6

Initial Concentrations of Drugs Used in Proliferation Assays - Month 1

Line	Dab	Tram	BVD-523
Parental	—	—	—
Tram	—	2 nM	—
Dab	15 nM	—	—
BVD-523	—	—	0.48 μM
Tram + Dab	5 nM	1 nM	—
Dab + BVD-523	7.5 nM	—	0.24 μM
Tram + BVD-523	—	1 nM	0.16 μM

[0179] Proliferation assays for month 2 were initiated at day 56 using cells growing in the concentrations of each agent indicated in Table 7.

TABLE 7

Initial Concentrations of Drugs Used in Proliferation Assays - Month 2

Line	Dab	Tram	BVD-523
Parental	—	—	—
Tram	—	8 nM	—
Dab	127 nM	—	—
BVD-523	—	—	0.8 μM
Tram + Dab	10 nM	2 nM	—
Dab + BVD-523	12.5 nM	—	0.4 μM
Tram + BVD-523	—	2 nM	0.32 μM

[0180] At the end of the 3 month escalation period, cultures were maintained at the top concentration for 2 weeks prior to the final round of proliferation assays and potential single cell cloning. As the proliferation assays/single cell cloning required actively proliferating cells, for treatments where cells were proliferating very slowly at the top concentration or that were only recently escalated, a backup culture was also maintained at a lower concentration (Table 8). For the BVD-523 treatment, where cells appeared to have almost completely stopped growing and looked particularly fragile at the top concentration (1.8 μM), cultures were maintained at a lower concentration for the 2 week period.

TABLE 8

Details of Treatments Being Cultured at a Fixed Concentration for 2 Weeks

Treatment	Inhibitor	Culture 1	Backup Culture
1	Tram	160 nM	80 nM
2	Dab	3.2 μM	—
3	BVD-523	1.2 μM	0.8 μM
4	Dab + Tram	D: 160 nM	D: 80 nM
		T: 30 nM	T: 16 nM
5	Dab + BVD-523	D: 42 nM	D: 28 nM
		523: 1.4 μM	523: 0.9 μM
6	Tram + BVD-523	T: 4 nM	T: 2.5 nM
		523: 0.6 μM	523: 0.4 μM

[0181] Proliferation assays for month 3 used cells growing in the concentrations of each agent indicated in Table 9.

TABLE 9

Initial Concentrations of Drugs Used in Proliferation Assays - Month 3

Line	Dab	Tram	BVD-523
Parental	—	—	—
Tram	—	160 nM	—
Dab	3.2 μM	—	—
BVD-523	—	—	1.2 μM
Tram + Dab	80 nM	16 nM	—
Dab + BVD-523	28 nM	—	0.9 μM
Tram + BVD-523	—	2.5 nM	0.4 μM

[0182] For combination studies, A375 cells (ATCC) were seeded into triplicate 96-well plates at a cell density of 3000 cells/well in DMEM plus 10% FBS and allowed to adhere overnight prior to addition of test compound or vehicle control. Combinations were tested using a 10×8 dose matrix with a final DMSO concentration of 0.2%. A 96 hour assay incubation period followed, with subsequent addition of Alamar Blue 10% (v/v) and 4 hours incubation prior to reading on a fluorescent plate reader. After reading Alamar Blue, the medium/Alamar Blue mix was flicked off and 100 μl of CellTiter-Glo/PBS (1:1) added and the plates processed as per the manufacturers instructions (Promega). Media only background values were subtracted before the data was analysed. The Bliss additivity model was then applied.

[0183] In brief, predicted fractional inhibition values for combined inhibition were calculated using the equation C_{bliss}=A+B−(A×B) where A and B are the fractional inhibitions obtained by drug A alone or drug B alone at specific concentrations. C_{bliss} is the fractional inhibition that would be expected if the combination of the two drugs were exactly additive. C_{bliss} values are subtracted from the experimentally observed fractional inhibition values to give an 'excess over Bliss' value. Excess over Bliss values greater than 0 indicate synergy, whereas values less than 0 indicate antagonism. Excess over Bliss values are plotted as heat maps±SD.

[0184] The single and combination data are also presented as dose-response curves generated in GraphPad Prism (plotted using % viability relative to DMSO only treated controls).

[0185] For focused combination studies, the Alamar Blue viability assays were performed as described above for combination studies. Additionally, Caspase-Glo 3/7 assays were performed. In brief, HCT116 cells were seeded in triplicate in white 96-well plates at a cell density of 5000 cells/well in McCoy's 5A plus 10% FBS. A375 cells were seeded at a density of 5000 cells/well in DMEM plus 10% FBS. Cells were allowed to adhere overnight prior to addition of test compound or vehicle control. The final concentration of DMSO was 0.2%, and 800 nM staurosporine was included as a positive control. 24 and 48 hour assay incubation periods were used. Then, Caspase-Glo® 3/7 50% (v/v) was added, plates were mixed for 5 minutes on an orbital shaker and incubated for 1 hour at room temperature prior to reading on a luminescent plate reader. Media only background values were subtracted before the data was analysed.

[0186] For Differential Scanning Fluorimetry, SYPRO orange (5,000× solution, Invitrogen) was diluted (1:1,000) in buffer solution (10 mM HEPES, 150 mM NaCl, pH 7.5). HisX6 tagged proteins included inactive ERK2, active ERK2 (ppERK2), or p38a at a final concentration of 1 μM. The protein/dye solution and compounds in 100% DMSO were added to wells (2% v/v final DMSO concentration) to achieve the desired final concentrations, mixed, and placed into an RT-PCR instrument. Next, a melting curve was run from 25-95° C. at a rate of 1° C. per minute and the melting temperature (Tm) was determined for each protein in the absence or presence of compounds. The change in Tm (ΔTm) in the presence of various drug concentrations is presented.

[0187] For Ki determination of ERK1, activated ERK1 (10 nM) was incubated with various concentrations of the compounds in 2.5% (v/v) DMSO for 10 minutes at 30° C. in 0.1 M HEPES buffer (pH 7.5), 10 mM $MgCl_2$, 2.5 mM phosphoenolpyruvate, 200 μM nicotinamide adenine dinucleotide (NADH), 150 μg/mL pyruvate kinase, 50 μg/mL lactate dehydrogenase, and 200 μM Erktide peptide. The reaction was initiated by the addition of 65 μM of ATP. Decreased absorbance rate (340 nm) was monitored and the IC_{50} was determined as a function of inhibitor concentration.

[0188] For Ki determination of ERK2, the inhibitory activity of BVD-523 against ERK2 was determined using a radiometric assay, with final concentration of the components being 100 mM HEPES (pH 7.5), 10 mM $MgCl_2$, 1 mM dithiothreitol (DTT), 0.12 nM ERK2, 10 μM myelin basic protein (MBP), and 50 μM ^{33}P-γ-ATP. All reaction components, with the exception of ATP and MBP, were premixed and aliquoted (33 μL) into a 96-well plate. A stock solution of compound in DMSO was used to make up to 500-fold dilutions; a 1.5-μL aliquot of DMSO or inhibitor in DMSO was added to each well. The reaction was initiated by adding the substrates ^{33}P-γ-ATP and MBP (33 μL). After 20 minutes the reaction was quenched with 20% (w/v) tricholoracetic acid (TCA) (55 μL) containing 4 mM ATP, transferred to the GF/B filter plates, and washed 3 times with 5% (w/v) TCA). Following the addition of Ultimate Gold™ scintillant (50 μL), the samples were counted in a Packard TopCount. From the activity versus concentration titration curve, the Ki value was determined by fitting the data to an equation for competitive tight binding inhibition kinetics using Prism software, version 3.0.

[0189] For IC_{50} determination of ERK2, activity was assayed by a standard coupled-enzyme assay. The final concentrations were as follows: 0.1 M HEPES (pH 7.5), 10 mM $MgCl_2$, 1 mM DTT, 2.5 mM phosphoenolpyruvate, 200 μM NADH, 50 μg/mL pyruvate kinase, 10 μg/mL lactate dehydrogenase, 65 μM ATP, and 800 μM peptide (ATGPL-SPGPFGRR). All of the reaction components except ATP were premixed with ERK and aliquoted into assay-plate wells. BVD-523 in DMSO was introduced into each well, keeping the concentration of DMSO per well constant. BVD-523 concentrations spanned a 500-fold range for each titration. The assay-plate was incubated at 30° C. for 10 minutes in the plate reader compartment of the spectrophotometer (molecular devices) before initiating the reaction by adding ATP. The absorbance change at 340 nm was monitored as a function of time; the initial slope corresponds to the rate of the reaction. The rate versus concentration of the BVD-523 titration curve was fitted either to an equation for competitive tight-binding inhibition kinetics to determine a value for Ki or to a 3-parameter fit to determine the IC_{50} using Prism software, version 3.0.

[0190] For apoptosis assays, cells were plated at 2×10^4 cells per well in a 96-well plate and allowed to attach overnight or grow to 50% confluency. Cells were treated with a serial dilution of BVD-523 in media (final volume 200 μL, concentration ranges 4-0.25 μM) and incubated for 48 hours in a 37° C. CO_2 incubator. Cells were washed with 100 μL of PBS, and 60 μL of radioimmunoprecipitation assay buffer was added (50 mM Tris-HCl, pH 8.0, 150 mM NaCl, 1.0% [w/v] NP-40, 0.5% [w/v] sodium deoxycholate, 1% [w/v] SDS), then incubated for 10 minutes at 4° C. to lyse the cells. A 30-μL lysate aliquot was added to 100 μL of caspase assay buffer (120 mM HEPES, 12 mM EDTA, 20 mM dithiothreitol, 12.5 μg/mL AC-DEVD-AMC caspase substrate) and incubated at RT from 4 hours to overnight. The plate was read in a fluorimeter (excitation wavelength 360 nm, emission wavelength 460 mm). The remaining 30 μL of lysate was analyzed for total protein content using the BioRad Protein Assay Kit (sample-to-working reagent ratio of 1:8). Final normalized caspase activity was derived as fluorescence units per μg protein and converted to a fold increase in caspase activity when compared with DMSO controls.

[0191] For measurement of antitumor activity in A375 xenografts, xenografts were initiated with A375 cells maintained by serial subcutaneous transplantation in female athymic nude mice. Each test mouse received an A375 tumor fragment (1 mm^3) implanted subcutaneously in the right flank. Once tumors reached target size (80-120 mm^3), animals were randomized into treatment and control groups, and drug treatment was initiated.

[0192] To evaluate BVD-523 monotherapy, BVD-523 in 1% (w/v) carboxymethylcellulose (CMC) was administered orally, per os (p.o.), BID at doses of 5, 25, 50, 100, or 150 mg/kg. Oral temozolomide was administered as a positive reference compound at 75 or 175 mg/kg once daily (QD) for a total of five treatments (QD×5).

[0193] The efficacy of BVD-523 in combination with dabrafenib was evaluated in mice randomized into 9 groups of 15 and 1 group of 10 (Group 10). Dabrafenib was administered p.o. at 50 or 100 mg/kg QD and BVD-523 was administered p.o. at 50 or 100 mg/kg BID, alone and in combination, until study end; vehicle-treated and temozolomide-treated (150 mg/kg QD×5) control groups were also included. Combination dosing was stopped on Day 20 to monitor for tumor regrowth. Animals were monitored indi-

vidually and euthanized when each tumor reached an endpoint volume of 2000 mm^3, or the final day (Day 45), whichever came first, and median time to endpoint (TTE) calculated. The combination was also evaluated in an upstaged A375 model where larger tumors in the range 228-1008 mm^3 were evaluated. Here, mice were randomized into 1 group (Group 1) of 14 and 4 groups (Groups 2-5) of 20. Dosing was initiated on Day 1 with dabrafenib plus BVD-523 (25 mg/kg dabrafenib+50 mg/kg BVD-523 or 50 mg/kg dabrafenib+100 mg/kg BVD-523), with each agent given p.o. BID until study end. The study included 50-mg/kg dabrafenib and 100-mg/kg BVD-523 monotherapy groups as well as a vehicle-treated control group. Tumors were measured twice weekly. Combination dosing was stopped on Day 42 to monitor for tumor regrowth through study end (Day 60). Treatment outcome was determined from % TGD, defined as the percent increase in median TTE for treated versus control mice, with differences between groups analyzed via log rank survival analysis. For TGI analysis, % TGI values were calculated and reported for each treatment (T) group versus the control (C) using the initial (i) and final (f) tumor measurements based on the following formula: % TGI=1−Tf−Ti/Cf−C. Mice were also monitored for CR and PR responses. Animals with a CR at the end of the study were additionally classified as TFS.

[0194] For measurement of BVD-523 activity in Colo205 xenografts, human Colo205 cells were cultured in RPMI 1640 supplemented with 10% (v/v) fetal bovine serum (FBS), 100 units/mL penicillin, 100 μg/mL streptomycin (Invitrogen), and 2 mM L-glutamine. Cells were cultured for fewer than four passages prior to implantation. Female athymic nude mice (19-23 g) were injected subcutaneously with 2×10^6 Colo205 cells into the right dorsal axillary region on Day 0.

[0195] Mice with an approximate tumor volume of 200 mm^3 were randomized into 6 experimental groups. Vehicle control, 1% CMC (w/v), was prepared weekly. BVD-523 was suspended in 1% (w/v) CMC at the desired concentration and homogenized on ice at 6,500 rpm for 50 minutes. BVD-523 suspensions were prepared weekly and administered p.o. BID at total daily doses of 50, 100, 150, and 200 mg/kg (n=12/group) on an 8- or 16-hour dosing schedule for 13 days. The vehicle control (n=12) was administered using the same dosing regimen. CPT-11 was administered as a positive reference compound (n=12). Each 1 mL of CPT-11 injection contained 20 mg irinotecan, 45 mg sorbitol, and 0.9 mg lactic acid. CPT-11 was administered at 100 mg/kg/day intraperitoneally every 4 days for 2 consecutive doses.

[0196] For measurement of ERK1/2 Isotope-Tagged Internal Standard (ITIS) Mass Spectrometry in Colo205 Xenografts, frozen tumors were lysed in 10 volumes of ice cold lysis buffer (10 mM TRIS-HCl, pH 8.0, 10 mM $MgCl_2$, 1% (v/v) Triton X-100, Complete™ Protease Inhibitor Cocktail [Roche, cat. No. 1836170], Phosphatase Inhibitor Cocktail I [Sigma, cat. No. P-2850], Phosphatase Inhibitor Cocktail II [Sigma cat. No. 5726], and benzonase [Novagen cat. No. 70664]). Lysates were clarified by centrifugation (100, 000×g for 60 minutes at 4° C.) and the supernatants adjusted to 2 mg/mL with lysis buffer. ERK1 was immunoprecipitated using agarose-coupled and pan-anti-ERK1 (Santa Cruz Biotechnology cat. No. sc-93ac) antibodies. Immunoprecipitated proteins were resolved by SDS-PAGE and stained with SYPRO Ruby (Invitrogen), and the ERK bands excised via razor. Gel slices were washed in 300 μL of 20 mM NH_4HCO_3, diced into small pieces, and placed in Page Eraser Tip (The Nest Group cat no. SEM0007). Gel fragments were reduced and alkylated prior to trypsin digestion. Tryptic fragments were isolated in 75 μL of 50% (v/v) Acetonitrile, 0.2% (v/v) trifluoroacetic acid and the resulting sample concentrated to 0-10 μL in a SpeedVac.

[0197] For ITIS analysis, digested samples were spiked with heavy-atom labeled peptide standards and fractional phosphorylation was quantified by coupled liquid chromatography-tandem mass spectrometry (MS). Nanocapillary chromatography was performed using a Rheos 2000 binary pump from Flux Instruments delivering nanoscale flow after 1:750 splitting, an LC Packings Inertsil nano-precolumn (C18, 5 mm, 100 Å, 30 mm ID×1 mm), and a New Objective PicoFrit AQUASIL resolving column (C18, 5 mm, 75/15 mm ID×10 cm), which also served as an electrospray ionization (ESI) emitter. An Applied Biosystem API 3000 mass spectrometer coupled with a nano-ESI source was used for MS analysis. An in-house-made gas nozzle connected to a nebulizing gas source was used to help steady nano-flow spray. Data were acquired in a multiple reaction monitoring (MRM) mode: nebulizing gas at 3; curtain gas at 7; collision gas at 5; ion spray voltage at 2150 volts, exit potential at 10 volts; Q1/Q3 resolution Low/Unit; and dwell time of 65 msec for all MRM channels. All raw MS data were processed using a combination of the Analyst software suite from Applied Biosystem and custom tools.

[0198] For assessment of drug sensitivity in cell-line models of acquired resistance, drug sensitivity of dose-escalated A375 cells and isogenic RKO cells was assessed in 96-hour proliferation assays. RKO isogenic cells (McCoy's 5A containing 10% [v/v] FBS) or dose-escalated A375 cells (DMEM containing 10% FBS were seeded into 96-well plates and allowed to adhere overnight prior to addition of compound or vehicle control. Note that the dose-escalated A375 cells were seeded in the absence of inhibitor. Compounds were prepared from 0.1% (v/v) DMSO stocks to give a final concentration as indicated. Test compounds were incubated with the cells for 96 hours at 37° C. in a 5% CO_2 humidified atmosphere. For the RKO cells, CellTiter-Glo® reagent (Promega) was added according to manufacturer's instructions and luminescence detected using a BMG FLUOstar plate reader. For the A375 assays Alamar blue (ThermoFisher) 10% (v/v) was added and incubated for 4 h, and fluorescent product was then detected using a BMG FLUOstar. The average media only background value was deducted and the data analyzed using a 4-parameter logistic equation in GraphPad Prism.

[0199] IC_{50} Determination of ERK1 was measured in a final reaction volume of 25 μL. ERK1 (human) (5-10 mU) was incubated with 25 mM Tris (pH 7.5), 0.02 mM ethyleneglycoltetracetic acid, 250 μM peptide, 10 mM Mg acetate, and γ-^{33}P-ATP (specific activity approximately 500 cpm/pmol, concentration as required). Adding Mg ATP initiated the reaction. After incubation for 40 minutes at room temperature (RT), the reaction was stopped by adding 5 μL of a 3% (w/v) phosphoric acid solution. Then, 10 μL of the reaction was spotted onto a P30 filtermat, and washed 3 times for 5 minutes in 75 mM of phosphoric acid then once in methanol before drying and scintillation counting.

[0200] RKO MEK1 Q56P Isogenic cells were produced by Horizon Discovery (Cambridge, UK; #HD 106-019) using a recombinant AAV-mediated gene targeting strategy. Briefly, rAAV virus was generated following transfection of

the appropriate targeting vector and helper vectors in HEK293T cells, purified using an AAV purification kit (Virapur, San Diego, USA) and titrated using qPCR. Parental homozygous RKO cells (homozygous wild type for MEK1) were then infected with rAAV virus and clones that had integrated the selection cassette were identified by G418 selection and expanded. Correctly targeted clones that were heterozygous for knock-in of the MEK1 Q56P point mutation into a single allele were identified by PCR and sequencing.

[0201] Isogenic SW48 cell lines heterozygous for knock-in of mutant KRAS (De Roock et al 2010, JAMA, 304, 1812-1820) were obtained from Horizon Discovery (Catalogue numbers; HD 103-002, HD 103-006 HD 103-007, HD 103-009, HD 103-010, HD 103-011, HD 103-013). For proliferation assay, cells were seeded into 96-well plates in McCoy's 5A medium supplemented with 10% FBS and allowed to adhere overnight prior to addition of compound or vehicle control. Test compounds were incubated with the cells for 96 hours at 37° C. in a 5% CO_2 atmosphere. Viability was then assessed using Alamar blue.

[0202] The proprietary KinaseProfiler assay was conducted at Upstate Discovery and employed radiometric detection similar to that employed by Davies et al, was used to profile the selectivity of BVD-523 against a panel of 70 kinases.

[0203] A drug sensitivity analysis was carried out as part of The Genomics of Drug Sensitivity in Cancer Project using high-throughput screening, as previously described (Yang et al. 2013).

[0204] For Western blot analysis, A375 cells were seeded onto 10 cm dishes in Dulbecco's Modified Eagle's Medium plus 10% (v/v) FBS. Cells were allowed to adhere overnight prior to the addition of test compound or vehicle. For experiments with RKO cells, these cells were seeded in 6-well plates or 10 cm dishes with McCoy's 5A+10% (v/v) FBS. Cells were then treated at the desired concentration and duration. Cells were harvested by trypsinization, pelleted, and snap frozen. Lysates were prepared with RIPA buffer supplemented with protease and phosphatase inhibitor cocktails (Roche), clarified by centrifugation at 11,000 rpm for 10 minutes, and quantitated by bicinchoninic acid assay. Samples were resolved by SDS-PAGE, blotted onto polyvinylidene difluoride membranes, and probed using antibodies (i.e., pRB [Ser780], cat. no. 9307; CCND1, cat. no. ab6152; BCL-xL, cat. no. 2762; PARP, cat. no. 9542; DUSP6, cat. no. 3058S) directed to the indicated targets.

[0205] For Reverse Phase Protein Analysis (RPPA), A375, MIAPaCa-2, HCT116, Colo205, HT-29, and AN3Ca cells (ATCC) were plated at 80% confluence, allowed to recover overnight (MIAPaCa-2 cells were plated at 30% confluence and allowed to recover for 3 days), then treated with 10 μM of each compound (i.e., BVD-523, SCH722984, GDC-0994, or Vx-11e) for 6 hours at 37° C. Control wells were treated with DMSO at 0.1% (v/v) for 6 hours prior to cell lysate generation. Samples were then analyzed using reverse-phase protein microarray technology (Theranostics Health).

[0206] For analysis of pERK IHC in Colo205 xenografts, xenograft tumors were processed overnight in 70% through 100% graded ethanols, cleared in two changes of xylene, infiltrated with paraffin, and embedded into paraffin blocks. Then, 5-μm sections were cut and placed onto positively charged glass slides and baked for at least 30 minutes, but not longer than 1 hour, at 60° C. A single section from each animal and dose group was probed with anti-phospho p42/p44 MAPK antibody (pERK [1:100], CST; Cat no. 9101; Lot no. 16), counterstained with hematoxylin, and then analyzed microscopically using a Zeiss Axioplan 2 microscope. An isotype control (rabbit, Zymed laboratories, catalog no. 08-6199, lot no. 40186458) was run as a negative control.

[0207] For FACS analysis, cells were scraped and pelleted at 1,500 rpm for 5 minutes, then re-suspended in 1 mL of buffer and frozen at −70° C. The frozen cells were thawed and centrifuged again, followed by 10 minutes of re-suspension in 0.25 mL of Buffer A (trypsin in spermine tetrahydrochloride detergent buffer) to disaggregate cell clumps and digest cell membranes and cytoskeletons. Buffer B (trypsin inhibitor and Ribonuclease I in buffer, 0.2 mL) was added for 10 minutes in the dark. The resulting DNA-stained nuclei were filtered and analyzed by FACS. The histograms were analyzed to establish the proportion of cells in the G1, S, and G2/M phases of the cell cycle based on the presence of n and 2n DNA (or higher) content.

[0208] For measurement of in vitro combination activity, five thousand G-361 cells were seeded into triplicate 96-well plates containing McCoy's 5A with 10% (v/v) FBS and allowed to adhere overnight. The vemurafenib/BVD-523 combination was tested using a 10×8 dose matrix. Compounds were incubated with the cells for 72 hours at 37° C. in a 5% CO_2 humidified atmosphere. CellTiter-Glo reagent was added according to manufacturer's instructions and luminescence detected using a MBG FLUOstar plate reader. The interactions across the dose matrix were determined by the Loewe Additivity and Bliss independence models using Horizon's Chalice Combination Analysis Software.

[0209] For generating compound resistance in vitro by dose escalation, A375 parental cells (ATCC CRL-1619) were grown to ~40-60% confluence in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% heat-inactivated FBS and penicillin/streptomycin, then treated with initial doses of BVD-523, trametinib, or dabrafenib either alone or in combination at or slightly below each compound's IC_{50}; for combination studies, initial dosing was half of each compound's IC_{50}. Cells were allowed to grow until ~70-90% confluence and split; medium was refreshed every 3-4 days. When cells again reached ~40-60% confluence, the dose was escalated by the same increment (equivalent to the starting concentration) then moved to 1.5-fold increases in concentration followed by a further move to 2-fold increases if the cells continued to adapt rapidly (e.g., the first six doses of the dabrafenib escalation were: 5, 10, 15, 20, 25, and 37.5 nM). This process was repeated as required.

[0210] Cell viability assays for FIG. **30**A were performed by a Resazurin (Alamar Blue) metabolic assay after 5 days in drug in full serum under high glucose conditions. Cells were seeded in 384-well microplates at ~15%-50% confluence in medium with 10% FBS and penicillin/streptavidin plus high glucose (18-25 mM). The optimal cell number for each cell line was determined to optimize growth during drugging. For adherent cell lines, after overnight incubation cells were treated with 9 concentrations of each compound (2-fold dilutions series) using liquid handling robotics, and returned to the incubator for assay at a 96-h time point. For suspension cell lines, cells were treated with compound immediately after plating and returned to the incubator for a 96-h time point. Cells were then stained with 55 μg/ml

Resazurin (Sigma) prepared in glutathione-free media for 4 hours. Quantitation of fluorescent signal intensity was performed using a fluorescent plate reader at excitation and emission wavelengths of 535/595 nm for Resazurin. All screening plates were subjected to stringent quality control measures. Effects on cell viability were measured and a curve-fitting algorithm was applied to the raw dataset to derive a multi-parameter description of drug response, including the half maximal inhibitory concentration (IC_{50}). IC_{50} is expressed in natural log of the IC_{50} in μM (LN_IC_{50}; EXP returns IC_{50} in μM). Extrapolation of the IC_{50} was allowed for where it yielded very high values. If desired the data was restricted to the tested concentration range by capping IC_{50} values at the maximum tested concentration (and the minimum tested concentration for low values).

[0211] For efficacy testing of BVD-523 in a patient-derived xenograft (AT052C) representing melanoma from a $BRAF^{V600E}$ patient that had become clinically refractory to vemurafenib. Tumor fragments were harvested from host animals and implanted into immune-deficient mice. The study was initiated at a mean tumor volume of approximately 170 mm^3, at which point the animals were randomized into four groups including a control (1% [v/v] CMC p.o., BID×31) and three treatment groups (BVD-523 [100 mg/kg], dabrafenib [50 mg/kg], or BVD-523/dabrafenib [100/50 mg/kg], n=10/group); All treatment drugs were administered p.o. on a BID×31 schedule.

[0212] For IC_{50} determination for the inhibition of PMA-stimulated RSK1 phosphorylation by BVD-523 in human whole blood samples, IC_{50} values for the inhibition of PMA stimulated RSK1 phosphorylation by BVD-523 were determined for 10 healthy donors (aged 22-61 years) using an 8-point concentration curve ranging from 10 μM to 5 nM of BVD-523. Controls consisted of 3 unstimulated samples and 3 PMA-stimulated samples for each donor. Both phosphor-RSK (pRSK) and total RSK levels were determined and data were calculated using pRSK/RSK levels for each sample.

[0213] Thirty milliliters of blood was drawn from each donor into sodium heparin vacutainers. One mL of whole blood was added to each of twenty-two 2-mL microtubes per donor. The microtubes tubes were labeled with the donor number (1 through 10) and the subsequent treatment designation: "A" for PMA stimulation only (maximum), "B" for BVD-523-containing samples that received PMA stimulation; and "C" for the unstimulated samples (minimum). Dimethyl sulfoxide (DMSO) was added to all tubes in groups A and C to a final concentration of 0.1%. Samples were then rocked gently at room temperature.

[0214] BVD-523 (10 mM in 100% DMSO) was serially diluted with 3-fold dilutions into 100% DMSO. These serially diluted BVD-523 samples in 100% DMSO were then diluted 10-fold in Dulbecco's Modified Eagle Medium containing 10% fetal bovine serum and penicillin/streptomycin/glutamine, and 10 μL of each of these working solutions was added per mL of blood for each designated BVD-523 concentration. Each concentration of BVD-523 was run in duplicate, two 1-mL blood samples each, yielding 16 total samples for the full 8-point concentration curve. Samples were then rocked gently at room temperature for a minimum of 2 hours but not longer than 3 hours.

[0215] Human whole blood samples in groups A and B for all donors were stimulated with PMA at a final concentration of 100 nM for 20 minutes at room temperature. Samples in group C were not treated with PMA but were rocked and handled as all other samples.

[0216] Upon completion of PMA treatment for each sample, peripheral blood mononuclear cells were isolated from the human whole blood. One mL of blood from each sample was gently layered onto 0.75 mL of room-temperature Histopaque 1077 in a 2-mL microcentrifuge tube. The samples were centrifuged for 2 minutes at 16,000×g in an Eppendorf microcentrifuge. The interface and upper layers were removed and added to tubes containing 1 mL of cold Dulbecco's phosphate-buffered saline (DPBS). These samples were then centrifuged for 30 seconds at 16,000×g to pellet the cells. The buffer supernatant was removed by aspiration and the pellets were re-suspended in 1 mL of cold DPBS. The pellets from each sample were then re-pelleted as above. The buffer was removed by aspiration and the pellets were lysed as indicated below.

[0217] Complete lysis buffer consisted of Meso Scale Discovery Tris lysis buffer, 1× Halt Protease inhibitor cocktail, 1× Phosphatase inhibitor cocktail 2, 1× Phosphatase inhibitor cocktail 3, 2 mM phenylmethanesulfonyl fluoride, and 0.1% sodium dodecyl sulfate. Lysis buffer was kept on ice and made fresh for each sample group. Final cell pellets were lysed by the addition of 120 L of complete lysis buffer. Samples were vortexed until the cell pellet disappeared and then flash frozen on dry ice. Samples were stored at −20° C. prior to measurement of pRSK and total RSK by ELISA.

[0218] For the pRSK ELISA (PathScan), thawed lysates were combined 1:1 with sample diluent (provided in ELISA kit): 120 μL of lysate added to 120 μL of sample diluent in a round bottom 96-well plate. This combination was then transferred to the pRSK microwells at 100 μL per well. For the total RSK ELISA (PathScan), 20 μL of the lysate already diluted 1:1 in sample diluent was further diluted in 200 μL of sample diluent in a round bottom 96-well plate. This combination was then transferred to the total RSK microwells at 100 μL per well. The plates were sealed with a plate seal and incubated 16 to 18 hours at 4° C., a time that was shown to yield the best detection of the target protein. Both ELISAs were developed according to the kit instructions.

[0219] Patients aged ≥18 years were eligible for participation if they had noncurable, histologically confirmed metastatic or advanced stage malignant tumors; an ECOG performance status of 0 or 1; adequate renal, hepatic, bone marrow, and cardiac function; and a life expectancy ≥3 months. Patients may have received up to 2 prior lines of chemotherapy for their metastatic disease. Exclusion criteria were known uncontrolled brain metastases; gastrointestinal conditions which could impair absorption of study medication; history or current evidence/risk of retinal vein occlusion or central serous retinopathy; and concurrent therapy with drugs known to be strong inhibitors of CYP1A2, CYP2D6, and CYP3A4 or strong inducers of CYP3A4. All participants provided informed consent prior to initiation of any study procedures.

[0220] Patients that received at least one dose of BVD-523 were included in the analysis using SAS (version 9.3) software. The data cutoff was Dec. 1, 2016. This study is registered with ClinicalTrials.gov, number NCT01781429.

[0221] The present invention presents data from an open-label, multicenter phase I study to assess the safety, pharmacokinetics, and pharmacodynamics of escalating doses of BVD-523 in patients with advanced malignancies. The

dosing regimen combined both accelerated titration and standard cohort 3+3 dose escalation schema, which were used jointly to identify the MTD and RP2D of BVD-523 in patients with advanced solid tumors. One to 6 patients per treatment cohort were assigned to receive sequentially higher oral doses of BVD-523 on a BID schedule (12-hour intervals) in 21-day cycles, starting at a dose of 10 mg BID. BVD-523 was administered BID continuously in 21-day cycles at the following doses: 10 mg (n=1); 20 mg (n=1); 40 mg (n=1); 75 mg (n=1); 150 mg (n=1); 300 mg (n=4); 600 mg (n=7); 750 mg (n=4); and 900 mg (n=7).

[0222] Patients received BID oral doses until disease progression, unacceptable toxicity, or a clinical observation satisfying another withdrawal criterion. Dose escalations occurred in up to 100% increments in single-patient cohorts until 1 patient experienced a ≥Grade 2 toxicity (excluding alopecia or diarrhea). Cohorts were then expanded to at least 3 patients each and subsequent dose-escalation increments were reduced from up to 100% to a maximum of 50%. When at least 1 patient in a 3-patient cohort experienced a DLT, up to 3 additional patients were treated at this dose level. When more than 1 DLT occurred in ≤6 patients, this dose level was defined as the nontolerated dose and dose escalation was stopped. Intrapatient dose escalation was allowed, provided the patients receiving the highest current dose had been observed for at least 3 weeks and dose-limiting side effects were reported in fewer than 2 of 6 patients assigned to a given dose. Patients experiencing DLTs or unacceptable toxicity had their treatment interrupted until the toxicity returned to ≤Grade 1. Resumption of BVD-523 treatment was then initiated at the next lower dose level tested or at a 20% to 30% dose decrease, aligning with capsule dosage.

[0223] The primary objective of the phase I study was to define the safety and tolerability of BVD-523 by determining the dose-limiting toxicities, the MTD, and the RP2D. The secondary objectives included the determination of the pharmacokinetic profile of BVD-523 in patients with advanced malignancies and the investigation of any preliminary clinical effects on tumor response, as assessed by physical or radiologic exam using RECIST v1.1. The exploratory objectives included evaluation of pharmacodynamic marker (biomarker) measures and investigation of preliminary clinical effects on tumor response assessed by ^{18}F-FDG-PET as indicated.

[0224] For determination of MTD, DLT, and RP2D, MTD was defined as the highest dose cohort at which ≤33% of patients experienced BVD-523-related DLTs in the first 21 days of treatment. DLT was defined as a BVD-related toxicity in the first 21 days of treatment that resulted in ≥Grade 4 hematologic toxicity for >1 day; Grade 3 hematologic toxicity with complications (e.g., thrombocytopenia with bleeding); ≥Grade 3 nonhematologic toxicity, except untreated nausea, vomiting, constipation, pain, and rash (these become DLTs if the AE persisted despite adequate treatment); or a treatment interruption exceeding 3 days in Cycle 1 (or the inability to being in Cycle 2 for >7 days) due to BVD-523-related toxicity.

[0225] The RP2D could be as high as the MTD and was determined in discussion with the clinical investigators, the medical monitor, and the sponsor. Observations related to pharmacokinetics, pharmacodynamics, and any cumulative toxicity observed after multiple cycles were included in the rationale supporting the RP2D.

[0226] With regard to safety assessments, AEs were defined as any untoward medical occurrence in a patient who was administered a medicinal product that does not necessarily have a causal relationship with BVD-523, and was coded using the MedDRA coding dictionary. An SAE was any untoward medical occurrence that occurred at any dose that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability/incapacity or a congenital anomaly/birth defect. The severity of AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Grading Scale, version 4.

[0227] Safety evaluations were conducted at baseline, on Days 8, 15, 22, 29, 36, and 43, and, in patients who continued treatment, every 3 weeks or if clinically indicated thereafter. Each evaluation included a physical examination and clinical laboratory studies. Electrocardiograms were repeated if clinically significant and at the discretion of the investigator. The investigators made judgments regarding whether or not AEs were related to study drug and followed up until resolution or stabilization, or the AE was judged to be no longer clinically significant.

[0228] For pharmacokinetic analysis, the pharmacokinetic population consisted of patients who received at least one dose of BVD-523 and had evaluable pharmacokinetic data for plasma and/or urine. Blood samples were collected prior to dosing, and then at 0.5 (±5 min), 1 (±5 min), 2 (±10 min), 4 (±10 min), 6 (±10 min), 8 (±10 min), and 12 (±2 hr) hours on Day 1 (Visit 2; baseline/initiation of treatment) and Day 15 (Visit 4; at steady state) after the morning dose. On Day 22, prior to dose administration, a final blood sample was collected for pharmacokinetic analyses. Urine samples were collected predose and at the 1- to 6-hour and 6- to 12-±2-hour intervals postdose on Days 1 and 15. Plasma and urine samples were analyzed for BVD-523 and metabolites using validated LC/MS/MS methods. Standard pharmacokinetic parameters were obtained using Phoenix WinNonlin (Pharsight) with a noncompartmental method. Relationship between dose and exposure was calculated using standard least-squares regression analysis.

[0229] For pharmacodynamic confirmation of target inhibition by BVD-523, targeted ERK inhibition by BVD-523 was determined by examining pRSK as a target biomarker in human whole blood samples obtained from patients with advanced solid tumors (N=27) who had received different doses of BVD-523 (10-900 mg BID) during the phase I study. The activity of BVD-523 from 4 timepoints (baseline predose, baseline 4 hours postdose, Day 15 predose, and Day 15 4 hours postdose) was expressed as a percent activity (pRSK) of PMA-stimulated blood incubated with BVD-523.

[0230] For measurement of antitumor response, tumor measurements based on physical examination occurred at baseline and on the first day of each treatment cycle. CT and other assessments were made every 2 to 3 cycles. Findings were assessed in accordance with RECIST v1.1: CR was defined as disappearance of all target lesions; PR was defined as a ≥30% decrease in the sum of the longest diameters of target lesions, taking baseline measurements as reference; stable disease was defined as being of neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the baseline measurement. Metabolic response was assessed by

visualizing tumor uptake of ^{18}F-glucose via ^{18}F-FDG-PET scanning prior to receiving the first dose of BVD-523 and at Day 15 (Visit 4).

Example 2

Dose Escalation and Proliferation Assays

Month 1

Dose Escalation Progress—Month 1

[0231] A375 cells were dose escalated using BVD-523, dabrafenib, and trametinib either as single agents or in combination. Doses were increased in small increments during the first month. Other than a marked reduction in growth rate, cells generally tolerated the escalations well and the doses were planned to be more aggressively escalated using larger increments in month 2. FIG. **1**A-FIG. **1**C show month 1 progress for the dose escalation studies.

Proliferation Assay Results—Month 1

[0232] Proliferation assays were performed to assess the response of the escalated cells lines vs. parental cell line, to BVD-523, dabrafenib, and trametinib treatments.

[0233] FIG. **2**A-FIG. **2**H show normalized and raw proliferation assay results from month 1 of the studies. Note that differences in max signals in DMSO controls between different treatments (FIG. **2**D, FIG. **2**F, and FIG. **2**H) suggest differential growth rates between treatments. These differences may influence the responses of lines to inhibitors in the proliferation assays.

[0234] Table 10 shows IC_{50} data for month 1 of the studies.

TABLE 10

IC_{50} Data—Month 1

	Cell Line, Relative IC_{50} (nM)						
Compound	Par*	Tram	Dab	BVD-523	Dab/Tram	Dab/523	Tram/523
Dabrafenib	6	29	about 161	8	58	68	11
Trametinib	0.5	2.2	2.5	0.7	3.9	3.1	2.5
BVD-523	189	335	350	268	300	412	263
Paclitaxel	2.2	3.0	3.3	3.4	3.5	3.4	3.4

*Par = Parental cell line

[0235] There were early hints that cells grown in the presence of escalating doses of dabrafenib or trametinib, either as single agents or in combinations, were exhibiting decreased responses to these two agents in proliferation assays.

[0236] In the early stages of month 2, the growth rate of cells in the dabrafenib only treatment notably increased relative to the early stages of month 1. This enabled an increased rate of progression and suggested that resistance was becoming apparent.

Example 3

Dose Escalation and Proliferation Assays

Month 2

Dose Escalation Progress—Month 2

[0237] The second month of studies saw most treatments move into a phase where doses were increased in greater increments (1.5-fold) compared to the initial gentle escalation phase. The single agent escalation of dabrafenib and trametinib was quickest, with cells growing in concentrations equivalent to 100× parental cell IC_{50} (FIG. **3**A and FIG. **3**B). The single agent escalation of BVD-523 progressed more slowly compared to dabrafenib and trametinib (FIG. **3**C). See FIG. **3**D for a comparison of the single agent escalations. BVD-523 escalated cells had a more "fragile" appearance and there was a greater number of floating cells compared to the dabrafenib and trametinib escalated populations.

[0238] The combined agent escalations progressed more slowly than the single agent treatments. The BVD-523/trametinib combination was particularly effective in preventing cells from progressing.

Proliferation Assay Results—Month 2

[0239] Proliferation assays on single agent escalated dabrafenib and trametinib cell populations revealed modest shifts in the dose response curves, suggesting that an additional period of escalation would be beneficial to further enrich for resistant cells. Interestingly, in the proliferations assay, there was evidence to suggest that cells exposed to BVD-523 grew less well upon inhibitor withdrawal, perhaps indicating a level of addiction.

[0240] FIG. **4**A-FIG. **4**H show normalized and raw proliferation assay results from month 2 of the studies. Note that differences in max signals in DMSO controls between different treatments (FIG. **4**D, FIG. **4**F, and FIG. **4**H) suggest differential growth rates between treatments. These differences may influence the responses of lines to inhibitors in the proliferation assays.

[0241] FIG. **5**A-FIG. **5**H show normalized and raw proliferation assay results from month 2 of the studies with a focus on parental and BVD-523 line data only.

TABLE 11

IC_{50} Data—Month 2

	Cell Line, Relative IC_{50} (nM)						
Compound	Par*	Tra	Dab	BVD-523	Dab/Tram	Dab/523	Tram/523
Dabrafenib	4.1	6.2	11.5	697	256	218	68
Trametinib	0.4	0.7	1.1	24.3	12.6	6.2	4.6
BVD-523	187	252	284	1706	561	678	435
Paclitaxel	3.7	8.9	1.9	6.5	4.7	4.2	8.9

*Par = Parental cell line

Example 4

Dose Escalation and Proliferation Assays

Month 3

Dose Escalation Progress—Month 3

[0242] FIG. **6**A-FIG. **6**C show single and combination agent escalation for month 3 of the studies. FIG. **6**D shows a comparison of single agent escalations.

Proliferation Assay Results—Month 3

[0243] FIG. **7** shows an assessment of growth during the proliferation assay in DMSO control wells. FIG. **8**A-FIG. **8**D show results from month 3 of the studies. FIG. **9**A-FIG. **9**D show results from month 3 of the studies with a focus on single treatment cell lines.

[0244] Table 12 shows IC_{50} data for month 3 of the studies. Relative IC_{50}s were determined from 4-parameter curve fits in Prism. IC_{50} values were not determined for the cell line escalated with trametinib due to a lack of growth during the assay (ND: not done).

TABLE 12

IC_{50} Data—Month 3

	Cell Line, Relative IC_{50} (nM)						
Compound	Par*	Tram	Dab	BVD-523	Dab/Tram	Dab/523	Tram/523
Dabrafenib	2.1	ND	2.5	18.4	17.9	337	73
Trametinib	0.2	ND	0.4	1.7	2.7	90	11.2
BVD-523	129	ND	198	433	323	1151	296
Paclitaxel	1.9	ND	1.9	6.5	4.7	4.2	8.9

*Par = Parental cell line

[0245] FIG. **19** shows single and combination agent escalation for month 3 of the studies. Cell line variants were obtained that could grow in the presence of dabrafenib or trametinib at concentrations greater than 100 times the IC_{50} of these agents in parental A375 cell. In comparison, cell lines resistant to BVD-523 could only be maintained in less than 10× of parental IC_{50} concentration. Sensitivity testing suggested dabrafenib and trametinib-resistant cell lines remained relatively sensitive to BVD-523; the increased IC_{50} "shift" for BVD-523 in resistant cell lines was more modest than those corresponding IC_{50} increases following dabrafenib or trametinib treatment. Likewise, compared to dabrafenib or trametinib treatment, more complete inhibition of cell growth was observed when resistant cell lines were treated with BVD-523 at concentrations 10-fold above its IC_{50} in the parental A375 line. In total, patterns of resistance and cross-sensitivity suggest BVD-523 may remain effective in settings of acquired resistance.

Example 5

Combination Study Results

[0246] As expected, A375 cells, which carry a BRAF (V600E) mutation, were sensitive to dabrafenib. Single agent IC_{50} values calculated using Alamar Blue (FIG. **10**A-FIG. **10**E, FIG. **12**A-FIG. **12**E, and FIG. **14**A-FIG. **14**E) were generally slightly lower for Dabrafenib and BVD-523 compared to those derived using CellTiter-Glo (FIG. **11**A-FIG. **11**E, FIG. **13**A-FIG. **13**E, and FIG. **15**A-FIG. **15**E). Published IC_{50} values for Dabrafenib and Trametinib in a 72 hour CellTiter-Glo assay were 28±16 nM and 5±3 nM respectively (Greger et al., 2012; King et al., 2013)—the single agent results reported here are consistent with these values. There was some evidence for a window of synergy in all treatments. Variation between triplicates was low, however, there was some evidence of edge effects that likely explains the apparent enhanced growth observed in some treatments versus the no drug control (e.g. particularly apparent in the Trametinib/BVD-523 combination). This makes the interpretation of the Bliss analysis more challenging as in some treatments it may have resulted in the artefactual enhancement in the level of synergy.

[0247] The combination assays were repeated for A375 cells. Single agent BVD-523, Trametinib and Dabrafenib potencies were consistent with those reported in the previous studies disclosed herein.

[0248] In sum, taken together the data show that MEK and BRAF resistant cells could be overcome by treatment with the ERK inhibitor, BVD-523.

Example 6

BVD-523 Altered Markers of MAPK Kinase Activity and Effector Function

[0249] For Western blot studies, HCT116 cells (5×10^6) were seeded into 10 cm dishes in McCoy's 5A plus 10% FBS. A375 cells (2.5×10^6) were seeded into 10 cm dishes in DMEM plus 10% FBS. Cells were allowed to adhere overnight prior to addition of the indicated amount of test compound (BVD-523) or vehicle control. Cells were treated for either 4 or 24 hours before isolation of whole-cell protein lysates, as specified below. Cells were harvested by trypsinisation, pelleted and snap frozen. Lysates were prepared with RIPA (Radio-Immunoprecipitation Assay) buffer, clarified by centrifugation and quantitated by bicinchoninic acid assay (BCA) assay. 20-50 μg of protein was resolved by SDS-PAGE electrophoresis, blotted onto PVDF membrane and probed using the antibodies detailed in Table 13 (for the 4-hour treatment) and Table 14 (for the 24-hour treatment) below.

TABLE 13

Antibody Details

Antigen	Size (kDa)	Supplier	Cat No	Dilution	Incubation/Block Conditions	Secondary
pRSK1/2 pS380	90	Cell Signaling	9335	1:1000	o/n 4° C. 5% BSA	anti-rabbit
pRSK1/2 pS380	90	Cell Signaling	11989	1:2000	o/n 4° C. 5% BSA	anti-rabbit
pRSK-T359/5363	90	Millipore	04-419	1:40000	o/n 4° C. 5% BSA	anti-rabbit
Total RSK	90	Cell Signaling	9333	1:1000	o/n 4° .C 5% BSA	anti-rabbit
pErk 1/2	42/44	Cell Signaling	9106S	1:500	o/n 4° C. 5% milk	anti-mouse

TABLE 13-continued

Antibody Details

Antigen	Size (kDa)	Supplier	Cat No	Dilution	Incubation/Block Conditions	Secondary
Total ERK	42/44	Cell Signaling	9102	1:2000	o/n 4° C. 5% milk	anti-rabbit
pMEK1/2	45	Cell Signaling	9154	1:1000	o/n 4° C. 5% BSA	anti-rabbit
Total MEK	45	Cell Signaling	9126	1:1000	o/n 4° C. 5% BSA	anti-rabbit
pS6-pS235	32	Cell Signaling	2211S	1:3000	o/n 4° C. 5% milk	anti-rabbit
Total S6	32	Cell Signaling	2217	1:2000	o/n 4° C. 5% milk	anti-rabbit
DUSP6	48	Cell Signaling	3058S	1:1000	o/n 4° C. 5% BSA	anti-rabbit
Total CRAF	73	BD Bio-sciences	610152	1:2000	o/n 4° C. 5% milk	anti-mouse
pCRAF-Ser338	73	Cell Signaling	9427	1:1000	o/n 4° C. 5% BSA	anti-rabbit
pRB (Ser780)	105	Cell Signaling	9307	1:2000	o/n 4° C. 5% BSA	anti-rabbit
β-Actin	42	Sigma	A5441	1:500,000	o/n 4° C. 5% milk	anti-mouse

TABLE 14

Antibody details

Antigen	Size (kDa)	Supplier	Cat No	Dilution	Incubation/Block Conditions	Secondary
pRB (Ser780)	105	Cell Signaling	9307	1:2000	o/n 4° C. 5% BSA	anti-rabbit
CCND1	34	Abcam	ab6152	1:500	o/n 4° C. 5% milk	anti-mouse
Bim-EL	23	Millipore	AB17003	1:1000	o/n 4° C. 5% BSA	anti-rabbit
Bim-EL	23	Cell Signaling	2933	1:1000	o/n 4° C. 5% BSA	anti-rabbit
BCL-xL	30	Cell Signaling	2762	1:2000	o/n 4° C. 5% BSA	anti-rabbit
PARP	116/89	Cell Signaling	9542	1:1000	o/n 4° C. 5% milk	anti-rabbit
Cleaved Caspase 3	17, 19	Cell Signaling	9664X	1:1000	o/n 4° C. 5% milk	anti-rabbit
DUSP6	48	Cell Signaling	3058S	1:1000	o/n 4° C. 5% BSA	anti-rabbit
pRSK1/2 pS380	90	Cell Signaling	9335	1:1000	o/n 4° C. 5% BSA	anti-rabbit
pRSK1/2 pS380	90	Cell Signaling	11989	1:2000	o/n 4° C. 5% BSA	anti-rabbit
pRSK-T359/5363	90	Millipore	04-419	1:40000	o/n 4° C. 5% BSA	anti-rabbit
Total RSK	90	Cell Signaling	9333	1:1000	o/n 4° C. 5% BSA	anti-rabbit
pErk 1/2	42/44	Cell Signaling	9106S	1:500	o/n 4° C. 5% milk	anti-mouse
Total ERK	42/44	Cell Signaling	9102	1:2000	o/n 4° C. 5% milk	anti-rabbit
B-Actin	42	Sigma	A5441	1:500,000	o/n 4° C. 5% milk	anti-mouse

[0250] FIG. **16**A-FIG. **16**D, FIG. **17**A-FIG. **17**D, and FIG. **18**A-FIG. **18**D show Western blot analyses of cells treated with BVD-523 at various concentrations for the following: 1) MAPK signaling components in A375 cells after 4 hours; 2) cell cycle and apoptosis signaling in A375 24 hours treatment with various amounts of BVD-523; and 3) MAPK signaling in HCT-116 cells treated for 4 hours. The results show that acute and prolonged treatment with BVD-523 in RAF and RAS mutant cancer cells in-vitro affects both substrate phosphorylation and effector targets of ERK kinases. The concentrations of BVD-523 required to induce these changes is typically in the low micromolar range.

[0251] Changes in several specific activity markers are noteworthy. First, the abundance of slowly migrating isoforms of ERK kinase increase following BVD-523 treatment; modest changes can be observed acutely, and increase

following prolonged treatment. While this could indicate an increase in enzymatically active, phosphorylated forms of ERK, it remains noteworthy that multiple proteins subject to both direct and indirect regulation by ERK remain "off" following BVD-523 treatment. First, RSK1/2 proteins exhibit reduced phosphorylation at residues that are strictly dependent on ERK for protein modification (T359/S363). Second, BVD-523 treatment induces complex changes in the MAPK feedback phosphatase, DUSP6: slowly migrating protein isoforms are reduced following acute treatment, while total protein levels are greatly reduced following prolonged BVD-523 treatment. Both of these findings are consistent with reduced activity of ERK kinases, which control DUSP6 function through both post-translational and transcriptional mechanisms. Overall, despite increases in cellular forms of ERK that are typically thought to be active, it appears likely that cellular ERK enzyme activity is fully inhibited following either acute or prolonged treatment with BVD-523.

[0252] Consistent with these observations, effector genes that require MAPK pathway signaling are altered following treatment with BVD-523. The G1/S cell-cycle apparatus is regulated at both post-translational and transcriptional levels by MAPK signaling, and cyclin-D1 protein levels are greatly reduced following prolonged BVD-523 treatment. Similarly, gene expression and protein abundance of apoptosis effectors often require intact MAPK signaling, and total levels of Bim-EL increase following prolonged BVD-523 treatment. As noted above, however, PARP protein cleavage and increased apoptosis were not noted in the A375 cell background; this suggests that additional factors may influence whether changes in BVD-523/ERK-dependent effector signaling are translated into definitive events such as cell death and cell cycle arrest.

[0253] Consistent with the cellular activity of BVD-523, marker analysis suggests that ERK inhibition alters a variety of molecular signaling events in cancer cells, making them susceptible to both decreased cell proliferation and survival.

[0254] In sum, FIG. **16**A-FIG. **16**D, FIG. **17**A-FIG. **17**D, and FIG. **18**A-FIG. **18**D show that BVD-523 inhibits the MAPK signaling pathway and may be more favorable compared to RAF or MEK inhibition in this setting.

[0255] Finally, properties of BVD-523 may make this a preferred agent for use as an ERK inhibitor, compared to other agents with a similar activity. It is known that kinase inhibitor drugs display unique and specific interactions with their enzyme targets, and that drug efficacy is strongly influenced by both the mode of direct inhibition, as well as susceptibility to adaptive changes that occur following treatment. For example, inhibitors of ABL, KIT, EGFR and ALK kinases are effective only when their cognate target is found in active or inactive configurations. Likewise, certain of these inhibitors are uniquely sensitive to either secondary genetic mutation, or post-translational adaptive changes, of the protein target. Finally, RAF inhibitors show differential potency to RAF kinases present in certain protein complexes and/or subcellular localizations. In summary, as ERK kinases are similarly known to exist in diverse, variable, and complex biochemical states, it appears likely that BVD-523 may interact with and inhibit these targets in a fashion that is distinct and highly preferable to other agents.

Example 7

Effects of BVD-523 and Benchmark ERK BRAF and MEK Inhibitors on Viability and MAPK Signalling Single Agent Proliferation Assay

[0256] Cells were seeded in 96-well plates at the densities indicated in Table 15 in McCoy's 5A containing 10% FBS and allowed to adhere overnight prior to addition of compound or vehicle control. Compounds were prepared from DMSO stocks to give the desired final concentrations. The final DMSO concentration was constant at 0.1%. Test compounds were incubated with the cells for 96 h at 37° C., 5% CO_2 in a humidified atmosphere. CellTiter-Glo® reagent (Promega, Madison, Wis.) was added according to manufacturer's instructions and luminescence detected using the BMG FLUOstar plate reader (BMG Labtech, Ortenberg, Germany). The average media only background value was deducted and the data analysed using a 4-parameter logistic equation in GraphPad Prism (GraphPad Software, La Jolla, Calif.).

Combination Proliferation Assay

[0257] Cells were seeded into triplicate 96-well plates at the densities indicated in Table 15 in McCoy's 5A containing 10% FBS and allowed to adhere overnight prior to addition of test compound or vehicle control. Combinations were tested using a 10×8 dose matrix. The final DMSO concentration was constant at 0.2%.

[0258] Test compounds were incubated with the cells for 96 h at 37° C., 5% CO_2 in a humidified atmosphere. Cells were stained with Hoechst stain and fluorescence detected as described above. The average media only background value was deducted and the data analysed.

[0259] Combination interactions across the dose matrix were determined by the Loewe Additivity and Bliss independence models using Chalice™ Combination Analysis Software (Horizon Discovery Group, Cambridge, Mass.) as outlined in the user manual (available at chalice.horizondiscovery.com/chalice-portal/documentation/analyzer/home.jsp). Synergy is determined by comparing the experimentally observed level of inhibition at each combination point with the value expected for additivity, which is derived from the single-agent responses along the edges of the matrix. Potential synergistic interactions were identified by displaying the calculated excess inhibition over that predicted as being additive across the dose matrix as a heat map, and by reporting a quantitative 'Synergy Score' based on the Loewe model. The single agent data derived from the combination assay plates were presented as dose-response curves generated in Chalice™

TABLE 15

	Cell Line Seeding Density		
	Seeding density (cells/well)		
Cell Line	96-well Proliferation	6-Well Western	10 cm dish Westerns
RKO Parental	1000	1×10^6	2.9×10^6
RKO MEK1 (Q56P/+) Clone 1	1250	Not tested	Not tested
RKO MEK1 (Q56P/+) Clone 2	1000	7.5×10^5	2×10^6

Western Blotting

[0260] Cells were seeded into 6-well plates (Experiment 1) or 10 cm dishes (Experiment 2) at the densities indicated in Table 15 in McCoy's 5A containing 10% FBS and allowed to adhere overnight prior to addition of compound or vehicle control. Test compounds were added and incubated with the cells for 4 or 24 h at 37° C., 5% CO_2 in a humidified atmosphere. Cells were harvested by trypsinisation, pelleted by centrifugation and snap frozen on dry ice.

[0261] Lysates were prepared using RIPA buffer (50 mM Tris-hydrochloride, pH 8.0; 150 mM sodium chloride; 1.0% Igepal CA-630 (NP-40); 0.5% sodium deoxycholate; 0.1% sodium dodecyl sulphate; 1× complete EDTA-free protease inhibitor cocktail (Roche, Nutley, N.J.; cat 05 892 791 001); 1× phosSTOP phosphatase inhibitor cocktail (Roche Nutley, N.J.; cat. 04 906 837 001)) and clarified by centrifugation at 11,000 rpm for 10 min in a bench-top centrifuge.

[0262] Total protein in the lysates was quantitated by BCA assay according to the manufacturer's instructions (Pierce™ BCA Protein Assay Kit; Thermo Scientific, Waltham, Mass.; cat. 23225), boiled in sample buffer (NuPAGE LDS Sample Buffer; (Invitrogen, Carlsbad, Calif.; cat. NP0007)) and stored at −80° C.

[0263] Equal amounts of protein (40 μg) were resolved on NuPAGE 4-12% Bis-Tris gels (Invitrogen, Carlsbad, Calif.; cat. WG1402BOX) and blotted onto PVDF membranes using iBlot gel transfer stacks (Invitrogen, Carlsbad, Calif.; cat. IB4010-01) on an iBlot gel transfer device (Invitrogen Carlsbad, Calif.) according to the manufacturer's instructions.

[0264] Blots were probed using the antibodies and block conditions detailed in Table 16. Western blots were developed using Pierce™ ECL2 Western blotting substrate (Thermo Scientific, Waltham, Mass.; cat. 80196) and imaged using a FluorChem M Western blot imager (ProteinSimple, San Jose, Calif.).

TABLE 16

Antibodies and Western Blotting Conditions

Antigen	Size (kDa)	Supplier	Cat No	Dilution	Incubation/block Conditions	Secondary
pRSK-T359/S353	90	Millipore	04-419	1:20000	o/n 4° C. 5% BSA	anti-rabbit
Total RSK	90	Cell Signaling	9333	1:1000	o/n: 4° C. 5% BSA	anti-rabbit
pErk 1/2	42/44	Cell Signaling	9106S	1:500	o/n 4° C. 5% milk	anti-mouse
Total ERK	42/44	Cell Signaling	9102	1:2000	o/n 4° C. 5% milk	anti-rabbit
pMEK1/2	45	Cell Signaling	9154	1:1000	o/n 4° C. 5% BSA	anti-rabbit
Total MEK	45	Cell Signaling	9126	1:1000	o/n 4° C. 5% BSA	anti-rabbit
DUSP6	45	Cell Signaling	3058S	1:1000	o/n 4° C. 5% BSA	anti-rabbit
pRB (Ser780)	105	Cell Signaling	9307	1:2000	o/n 4° C. 5% BSA	anti-rabbit
CCND1	34	Abcam	ab6152	1:500	o/n 4° C. 5% milk	anti-mouse
B-Actin	42	Sigma	A5441	1:100,000	o/n 4° C. 5% milk	anti-mouse
Anti-rabbit HRP-conjugated secondary	—	Cell Signaling	7074S	1:2000	1 h room temp. Block matched to primary Antibody	—
Anti-mouse HRP-conjugated secondary	—	Cell Signaling	7076	1:5000	1 h room temp. Block matched to primary Antibody	—

[0265] The MEK1 (Q56P) mutation exemplifies a class of clinically relevant MEK1/2 activating mutations known to up-regulate the MAPK pathway and drive acquired resistance to BRAF or MEK inhibitors.

[0266] This study used a pair of RKO BRAF(V600E) cell lines that are isogenic for the presence or absence of a MEK1 (Q56P) activating mutation, to assess the effect that activating MEK mutations have in response to the novel ERK inhibitor BVD-523 versus other benchmark MAPK inhibitors.

[0267] Effects of on cell viability were assessed by quantitating cellular ATP levels using CellTiter-Glo® after 96 h. Single agent assays demonstrated that the double mutant BRAF(V600E)::MEK1(Q56P) cells displayed a markedly reduced sensitivity to inhibition with benchmark clinical BRAF (exemplified by Dabrafenib) or MEK (exemplified by Trametinib) inhibitors relative to the parental BRAF (V600E) cells, which demonstrates the suitability of this isogenic model for recapitulating the acquired resistance known to be associated with this class of mutation in the clinic (Table 17).

TABLE 17

Single Agent IC_{50} Values

Compound	RKO Parental	RKO MEK1 Q56P/+ Cl. 1	RKO MEK1 Q56P/+ Cl. 2
BVD-523	0.20	0.17	0.18
SCH772984	0.04	0.14	0.12
Dabrafenib	n.d.	n.d.	n.d.
Trametinib	0.006	0.093	0.080
Paclitaxel	0.002	0.002	0.002

n.d.—not determined, only a partial dose response achieved

[0268] In contrast, response to BVD-523 was identical in both the parental and double mutant cells, indicating that BVD-523 is not susceptible to this mechanism of acquired resistance.

[0269] These results were identical in two independently derived double mutant BRAF(V600E)::MEK1(Q56P) cell line clones confirming that these differences in response versus the parental cells were specifically related to the

presence of the MEK1 mutation rather than an unrelated clonal artifact (FIG. **22**A-FIG. **22**E). Similar results were also observed with a second mechanistically distinct benchmark ERK inhibitor (SCH772984), which supports the notion that these observations are specifically related to inhibition of ERK and not due to an off-target effect.

[0270] The effect of combining BVD-523 with a BRAF inhibitor (exemplified by Dabrafenib) was also assessed in these cell lines across a matrix of concentrations using the Loewe Addivity or Bliss Independence models with Horizon's Chalice™ combination analysis software (FIG. **23**-FIG. **23**O and FIG. **24**A-FIG. **24**O). The presence of potentially synergistic interactions was then assessed by displaying the calculated excess inhibition over that predicted as being additive across the dose matrix as a heat map, and by calculating a 'Volume Score' that shows whether the overall response to a combination is synergistic (positive values), antagonistic (negative values) or additive (~0).

[0271] The results suggest that the BVD-523::Dabrafenib combination was mainly additive in the parental and mutant cell line. In contrast, the combination of a MEK inhibitor (trametinib) plus Dabrafenib, while being mostly additive in the parental cell line, showed strong synergy in the double mutant BRAF(V600E)::MEK1(Q56P) cell line (FIG. **25**A-FIG. **25**O). Loewe Volumes, Bliss Volumes and Synergy scores for the combinations tested are shown in Tables 18-20, respectively and are shown graphed in FIG. **26**A-FIG. **26**C.

TABLE 18

Loewe Volumes

	RKO Parental	RKO MEK1 (Q56P) - Clone 1	RKO MEK1 (Q56P) - Clone 2
BVD-523 × Dabrafenib	3.54	2.88	2.35
Dabrafenib × SCH772984	5.2	6.79	6.14
Dabrafenib × Trametinib	5.68	12.6	11.6

TABLE 19

Bliss Volumes

	RKO Parental	RKO MEK1 (Q56P) - Clone 1	RKO MEK1 (Q56P) - Clone 2
BVB-523 × Dabrafenib	−0.894	0.527	1.42
Dabrafenib × SCH772984	0.209	4.3	5.07
Dabrafenib × Trametinib	0.353	10.8	9.87

TABLE 20

Synergy Scores

	RKO Parental	RKO MEK1 (Q56P) - Clone 1	RKO MEK1 (Q56P) - Clone 2
BVD-523 × Dabrafenib	3.18	2.31	1.77
Dabrafenib × SCH772984	4.56	5.57	4.36
Dabrafenib × Trametinib	5.58	11	9.83

[0272] Effects on MAPK pathway signally was assessed by Western blotting. The levels of basal ERK phosphorylation (DMSO samples) was markedly up-regulated in the MEK1(Q56P)-expressing line relative to parental further confirming that this isogenic model faithfully recapitulates the expected phenotype for the expression of MEK activating acquired resistance mutations.

[0273] In the parental BRAF(V600E) RKO cells, a reduced level of RSK1/2 phosphorylation is observed following acute treatment with RAF, MEK and ERK kinase inhibitors at pharmacologically active concentrations. In contrast, isogenic, double mutant BRAFV600E::MEK1Q56P cells do not exhibit reduced RSK phosphorylation following BRAF or MEK inhibitor treatment, while BVD-523 remains effective at similar concentrations (FIG. **27**A-FIG. **27**I). The dotted lines indicate that the trametinib-treated samples (plus matched DMSO control) and blots are derived from a separate experiment to the BRAFi and BVD-523 treated samples.

[0274] Changes in effector gene signaling consistent with cell growth inhibition patterns are observed following prolonged inhibitor treatment. In parental RKO lines, a reduced level of phosphorylated pRB is observed following prolonged MEK and ERK inhibitor treatment. At the level of pRB modulation, MEK1 mutant lines appear insensitive to low concentration MEK inhibitor treatment, while higher concentrations remain effective. Critically, BVD-523 potency against pRB activity does not appear to be strongly affected by MEK mutation. Surprisingly, RAF inhibitor treatment does not affect pRB status, despite potent inhibition of upstream signaling, in both parental and MEK mutant backgrounds.

[0275] In summary, these results show that BVD-523 is not susceptible to acquired resistance driven by MEK activating mutations such as MEK1 (Q56P). In addition they suggest that in combination the interactions between BVD-523 and BRAFi (exemplified by Dabrafenib) are additive irrespective of the presence of a MEK activating mutation.

Example 8

Combination Interactions Between ERK Inhibitors

[0276] RAF mutant melanoma cell line A375 cells were cultured in DMEM with 10% FBS and seeded into triplicate 96-well plates at an initial density of 2000 cells per well. Combination interactions between ERK inhibitors BVD-523 and SCH772984 were analized after 72 hours as described above in Example 4. Viability was determined using CellTiter-Glo® reagent (Promega, Madison, Wis.) according to manufacturer's instructions and luminescence was detected using the BMG FLUOstar plate reader (BMG Labtech, Ortenberg, Germany).

[0277] Visualization of the Loewe and Bliss 'excess inhibition' heat maps suggested that the combination of BVD-523 and SCH772984 was mainly additive with windows of potential synergy in mid-range doses (FIG. **28**A-FIG. **28**E).

[0278] In summary, these results suggest that interactions between BVD-523 and SCH772984 are at least additive, and in some cases synergistic.

Example 9

Targeting the MAPK Signaling Pathway in Cancer

Promising Activity with the Novel Selective ERK1/2 Inhibitor BVD-523 (Ulixertinib)

[0279] Treatment strategies for cancer have evolved from classic cytotoxic-based approaches to agents that counteract

the effects of genetic lesions that drive aberrant signaling essential to tumor proliferation and survival. For example, the ERK module of the mitogen-activated protein kinase (MAPK) signaling cascade (RAS-RAF-MEK-ERK) (Cargnello and Rouxx 2011) can be engaged by several receptor tyrosine kinases (e.g., EGFR and ErbB-2) in addition to constitutively activated mutations of pathway components such as RAS and BRAF (Gollob et al. 2006). Through aberrant activation of ERK signaling, genetic alterations in RAS or BRAF result in rapid tumor growth, increased cell survival, and resistance to apoptosis (Poulikakos et al. 2011, Corcoran et al. 2010, Nazarian et al. 2010, Shi et al. 2014, Wagle et al. 2011). Activating mutations of RAS family members KRAS and NRAS are found in ~30% of all human cancers, with particularly high incidence in pancreatic (Kanda et al. 2012) and colorectal cancer (Arrington et al. 2014). Constitutively activating mutations in the BRAF gene that normally encodes for valine at amino acid 600 have been observed in melanoma, thyroid carcinoma, colorectal cancer, and non-small cell lung cancer (Hall et al. 2014). Cancers bearing genetic mutations that result in changes of the downstream components ERK and MEK have also been reported (Ojesina et al. 2014, Arcila et al. 2015). Alterations that activate the MAPK pathway are also common in the setting of resistance to targeted therapies (Groenendijk et al. 2014). Thus, targeting the MAPK pathway terminal master kinases (ERK1/2) is a promising strategy for tumors harboring such pathway activating alterations (e.g., BRAF, NRAS, and KRAS).

[0280] Three MAPK pathway-targeting drugs have been approved by the US Food and Drug Administration (FDA) for single-agent treatment of nonresectable or metastatic cutaneous melanoma with $BRAF^{V600}$ mutations: the BRAF inhibitors vemurafenib and dabrafenib and the MEK inhibitor trametinib. Furthermore, the combination of dabrafenib and trametinib is also approved in this indication (Queirolo et al. 2015 and Massey et al. 2015). An additional MEK inhibitor, cobimetinib, is approved in this indication as part of a combination regimen with BRAF inhibitors. Clinical experience with these drugs validates the MAPK pathway as a therapeutic target. In phase III trials of patients with $BRAF^{V600}$-mutant melanoma, the single agents vemurafenib and dabrafenib demonstrated superior response rates (approximately 50% vs. 5-19%) and median progression-free survival (PFS, 5.1-5.3 months vs. 1.6-2.7 months) over cytotoxic chemotherapy (dacarbazine) (Chapman et al. 2011 and Hauschild et al. 2012). Furthermore, clinical use of concomitant BRAF-plus MEK-targeted therapies has demonstrated that simultaneous targeting of different nodes in the MAPK pathway can enhance the magnitude and duration of response. First-line use of BRAF plus MEK-targeted agents (dabrafenib/trametinib or cobimetinib/vemurafenib) further improved median overall survival compared with single-agent BRAF inhibition (Robert et al. 2015, Long et al. 2015, Larkin et al. 2014). Thus, combined BRAF-/MEK-targeted therapy is a valuable treatment option for patients with metastatic melanoma with $BRAF^{V600}$ mutations.

[0281] Despite improvements in clinical outcomes seen with BRAF-/MEK-inhibitor combination therapies, durable benefit is limited by the eventual development of acquired resistance and subsequent disease progression, with median PFS ranging from approximately 9 to 11 months. (Robert et al. 2015, Long et al. 2015, Larkin et al. 2014, and Flaherty et al. 2012). Genetic mechanisms of acquired resistance to single-agent BRAF inhibition have been intensely studied, and identification of resistance mechanisms include splice variants of BRAF (Poulikakos et al. 2011), $BRAF^{V600E}$ amplification (Corcoran et al. 2010), MEK mutations (Wagle et al. 2014), NRAS mutations, and RTK activation (Nazarian et al. 2010 and Shi et al. 2014). Resistance mechanisms in the setting of BRAF-/MEK-inhibitor combination therapy are beginning to emerge and mirror that of BRAF single-agent resistance (Wagle et al. 2014 and Long et al. 2014). These genetic events all share in common the ability to reactivate ERK signaling. Indeed, reactivated MAPK pathway signaling as measured by ERK transcriptional targets is common in tumor biopsies from BRAF inhibitor-resistant patients (Rizos et al. 2014). Furthermore, ERK1/2 reactivation has been observed in the absence of a genetic mechanism of resistance (Carlino et al. 2015). Therefore, the quest to achieve durable clinical benefit has led researchers to focus on evaluating additional agents that target the downstream MAPK components ERK1/2. Inhibiting ERK may provide important clinical benefit to patients with acquired resistance to BRAF/MEK inhibition. ERK family kinases have shown promise as therapeutic targets in preclinical cancer models, including those cancers resistant to BRAF or MEK inhibitors (Morris et al. 2013 and Hatzivassiliou et al. 2012). However, the potential use of such ERK1/2 inhibitors expands beyond acquired-resistance in melanoma.

[0282] Targeting ERK1/2 is a rational strategy in any tumor type harboring known drivers of MAPK, not only BRAF/MEK therapy-relapsed patients. As ERK1 and ERK2 reside downstream in the pathway, they represent a particularly attractive treatment strategy within the MAPK cascade that may avoid upstream resistance mechanisms. Here, preclinical characterization of BVD-523 (ulixertinib) in models of MAPK pathway-dependent cancers is reported, including drug-naïve and BRAF/MEK therapy acquired-resistant models. Results of a phase I dose-finding study of BVD-523 are included as a companion publication in this journal. See, Examples 17-24.

[0283] In the present invention, BVD-523 was shown to be a potent, highly selective, reversible, small molecule ATP-competitive inhibitor of ERK1/2 with in vitro and in vivo anticancer activity.

[0284] BVD-523 (ulixertinib) was identified and characterized as a novel, reversible, ATP-competitive ERK1/2 inhibitor with high potency and ERK1/2 selectivity. BVD-523 caused reduced proliferation and enhanced caspase activity, most notably in cells harboring MAPK (RAS-RAF-MEK) pathway mutations. In in vivo $BRAF^{V600E}$ xenograft studies, BVD-523 showed dose-dependent growth inhibition and tumor regressions. Interestingly, BVD-523 inhibited phosphorylation of target substrates despite increased phosphorylation of ERK1/2. BVD-523 also demonstrated antitumor activity in models of acquired resistance to single-agent and combination BRAF/MEK targeted therapy. Synergistic antiproliferative effects in a $BRAF^{V600E}$-mutant melanoma cell line xenograph model were also demonstrated when BVD-523 was used in combination with BRAF inhibition. These studies suggest that BVD-523 holds promise as a treatment for ERK-dependent cancers, including those whose tumors have acquired resistance to other treatments targeting upstream nodes of the MAPK pathway.

Example 10

Discovery and Initial Characterization of a Novel ERK1/2 Inhibitor, BVD-523 (Ulixertinib)

[0285] Following extensive optimization of leads originally identified using a high-throughput, small-molecule screen (Aronov et al. 2009), a novel adenosine triphosphate (ATP)-competitive ERK1/2 inhibitor, BVD-523 (ulixertinib) was identified (FIG. **29** A). BVD-523 is a potent ERK inhibitor with a K_i of 0.04±0.02 nM against ERK2. It was shown to be a reversible, competitive inhibitor of ATP, as the IC_{50} values for ERK2 inhibition increased linearly with increasing ATP concentration (FIG. **29**B and FIG. **29**C). The IC_{50} remained nearly constant for incubation times 210 minutes, suggesting rapid equilibrium and binding of BVD-523 with ERK2 (FIG. **29**D). BVD-523 is also a tight-binding inhibitor of recombinant ERK1 (Rudolph et al. 2015), exhibiting a K_i of <0.3 nM.

[0286] Binding of BVD-523 to ERK2 was demonstrated using calorimetric studies and compared to data generated using the ERK inhibitors SCH772984 and pyrazolylpyrrole (Arovov et al. 2007). All compounds bound and stabilized inactive ERK2 with increasing concentration, as indicated by positive ΔTm values (FIG. **29**E). The 10- to 15-degree change in ΔTm observed with BVD-523 and SCH-772984 is consistent with compounds that have low-nanomolar binding affinities (Fedorov et al. 2012). BVD-523 demonstrated a strong binding affinity to both phosphorylated active ERK2 (pERK2) and inactive ERK2 (FIG. **29**F). A stronger affinity to pERK2 compared with inactive ERK2 was observed. BVD-523 did not interact with the negative control protein p38a MAP kinase (FIG. **29**F).

[0287] BVD-523 demonstrated excellent ERK1/2 kinase selectivity based on biochemical counter-screens against 75 kinases in addition to ERK1 and ERK2. The ATP concentrations were approximately equal to the K_m in all assays. Kinases inhibited to greater than 50% by 2 μM BVD-523 were retested to generate K_i values (or apparent Ki; Table 21). Twelve of the 14 kinases had a K_i of <1 μM. The selectivity of BVD-523 for ERK2 was >7000-fold for all kinases tested except ERK1, which was inhibited with a Ki of <0.3 nM (10-fold). Therefore, BVD-523 is a highly potent and selective inhibitor of ERK1/2.

TABLE 21

BVD-523 displays selectivity for ERK1 and ERK2 kinases.

Kinase	Ki (μM)
CDK1/cyclinB	0.07[a]
CDK2/cyclinA	0.36
CDK5/p35	0.09[a]
CDK6/cycinD3	0.09[a]
ERK1	0.0003
ERK2	0.00004
GSK3b	0.32
JNK2α	0.65[a]
JNK3	1.3
P38γ	0.45[a]
P38δ	0.24[a]

TABLE 21-continued

BVD-523 displays selectivity for ERK1 and ERK2 kinases.

Kinase	Ki (μM)
ROCKI	11.1
ROCKII	0.27[a]
RSK3	0.45

[a]Apparent.

<50% inhibition at 2 μM: ABL, AKT3, AMPK, AUR1, AUR2, AXL, BLK, CAMKII, CAMKIV, CHK1, CHK2, CK1, CK2, CSK, EGFR, EPHB4, FES, FGFR3, FLT3, FYN, IGF1R, IKKα, IKKβ, IKKi, IRAK4, IRTK, ITK, JAK3, JNK1α 1, KDR, LCK, LYN, cMET, MKK4, MKK6, MKK7β, MLK2, MSK1, MST2, NAK, NEK2, p38α, p38β, p70S6K, PAK2, PDGFRα, PDK1, PKA, PKCα, PKCβ II, PKCγ, PKCi, PKCθ, PRAK, PRK2, cRAF, SGK, SRC, SYK, TAK1, TIE2, ZAP70

Example 11

BVD-523 Preferentially Inhibits Cellular Proliferation and Enhances Caspase-3/7 Activity In Vitro in Cancer Cell Lines with MAPK Pathway-Activating Mutations

[0288] BVD-523 cellular activity was assessed in a panel of approximately 1,000 cancer cell lines of various lineages and genetic backgrounds (FIG. **30**A and Table 22). Cell lines were classified as MAPK wild type (wt) or mutant depending on the absence or presence of mutations in RAS family members and BRAF. Although some MAPK-wt cell lines were sensitive to BVD-523, generally BVD-523 inhibited proliferation preferentially in cells with MAPK pathway alterations.

[0289] Next, the growth and survival impact of BVD-523 treatment on sensitive cells was characterized. Fluorescence activated cell sorting (FACS) analysis was performed on $BRAF^{V600E}$-mutant melanoma cell line UACC-62 following treatment with BVD-523 at 500 nM or 2000 nM for 24 hours. Treated cells were arrested in the G1 phase of the cell cycle in a concentration-dependent manner (FIG. **30**B).

[0290] In addition, caspase-3/7 activity was analyzed as a measure of apoptosis in multiple human cancer cell lines. A concentration- and cell-line-dependent increase in caspase 3/7 was observed following treatment with BVD-523 for 72 hours (FIG. **30**C). BVD-523 treatment resulted in pronounced caspase-3/7 induction in a subset of MAPK-activated cell lines harboring a $BRAF^{V600}$ mutation (A375, WM266, and LS411N). This is consistent with earlier observations for preferential inhibition of proliferation by BVD-523 in MAPK pathway-mutant cancer cell lines (FIG. **30**A).

[0291] To further characterize the mechanism of action and effects on signaling elicited by BVD-523, the levels of various effector and MAPK-related proteins were assessed in BVD-523-treated $BRAF^{V600E}$-mutant A375 melanoma cells (FIG. **30**D). Phospho-ERK1/2 levels increased in a concentration-dependent manner after 4 and 24 hours of BVD-523 treatment. Despite prominent concentration-dependent increases in pERK1/2 observed with 2 μM BVD-523 treatment, phosphorylation of the ERK1/2 target RSK1/2 was reduced at both 4 and 24 hours, which is consistent with sustained inhibition. Total protein levels of DUSP6, a distal marker of ERK1/2 activity, were also attenuated at 4 and 24 hours. Following 24 hours of treatment with BVD-523, the apoptotic marker BIM-EL increased in a dose-dependent manner, while cyclin D-1 and pRB was attenuated at 2 μM. All effects are consistent with on-target ERK1/2 inhibition.

TABLE 22

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_8049_00277140	Biliary Tract	8049	ETK-1	456	3.525905	0.587	0.805	0.874	0.9304	0.8796	0.954	1.0285	1.094	0.9918
026_664_00277150	Biliary Tract	664	HuCCT1	456	3.600435	0.663	0.734	0.847	0.9661	0.9652	1.029	0.9656	1.0172	0.9981
026_653_00278500	Biliary Tract	653	EGI-1	456	4.229085	0.693	0.686	0.74	0.7843	0.8546	0.889	0.967	0.9286	0.9525
026_8204_00278540	Biliary Tract	8204	TGBC24TKB	456	5.609877	0.768	0.875	0.826	0.8122	0.8629	0.862	0.8909	0.9353	0.9353
026_8188_00293390	Biliary Tract	8188	TGBC1TKB	456	6.179372	0.915	0.929	0.913	0.9808	0.9201	1.144	1.0128	0.9048	0.9496
026_330_00278580	Bone	330	H-EMC-SS	456	0.038629	0.36	0.392	0.383	0.4615	0.437	0.566	0.7772	0.9442	0.9662
026_8047_00283120	Bone	8047	ES7	456	1.846677	0.515	0.521	0.539	0.5362	0.7569	0.769	0.8353	0.9371	0.9503
026_8053_00287650	Bone	8053	EW-13	456	2.197657	0.333	0.545	0.665	0.8165	0.9099	0.962	0.9571	0.9945	1.0406
026_8227_00288230	Bone	8227	CADO-ES1	456	2.29467	0.359	0.554	0.585	1.0389	0.9034	0.952	1.1264	1.2671	1.0023
026_8050_00279380	Bone	8050	EW-1	456	2.409222	0.487	0.555	0.593	0.6879	0.6908	0.788	0.8057	0.892	0.9331
026_306_00278530	Bone	306	SK-ES-1	456	2.4607	0.527	0.556	0.577	0.682	0.673	0.855	0.8706	0.8641	0.8867
026_305_00277180	Bone	305	U-2 OS	456	2.847932	0.145	0.599	0.657	0.7441	0.8231	0.793	0.8449	0.9969	0.8925
026_337_00283440	Bone	337	HuO9	456	2.916396	0.448	0.696	0.939	0.8026	0.8478	0.903	0.9796	0.8682	1.0954
26_8227_00304340	Bone	8227	CADO-ES1	456	2.975471	0.542	0.666	0.884	0.8971	0.9918	0.974	1.0247	1.0031	1.0728
026_8043_00283110	Bone	8043	ES1	456	2.981717	0.543	0.663	0.705	0.7865	0.811	0.835	0.7995	0.9278	0.8292
026_8142_00282550	Bone	8142	NOS-1	456	3.203574	0.547	0.775	0.825	0.892	0.7556	0.894	0.8477	1.1038	0.9881
026_8055_00290580	Bone	8055	EW-18	456	3.311765	0.638	0.688	0.718	1.1012	0.9293	0.993	1.0646	1.1078	1.0895
026_8058_00293350	Bone	8058	EW-3	456	3.365484	0.715	0.595	0.72	0.7195	0.8774	0.8	0.8628	0.9101	1.2148
026_339_00277160	Bone	339	NY	456	3.400937	0.59	0.789	0.875	0.9222	0.9594	0.975	0.933	1.1433	0.9637
026_8165_00287690	Bone	8165	SK-PN-DW	456	3.476926	0.621	0.812	0.933	0.9706	0.9188	0.991	1.0026	1.0012	1.0432
026_326_00282540	Bone	326	MHH-ES-1	456	3.524605	0.618	0.719	0.824	0.8235	0.8745	0.966	1.1187	1.0416	0.913
026_8048_00279370	Bone	8048	ES8	456	3.530755	0.572	0.698	0.765	0.8053	0.8255	0.912	0.931	0.9069	0.9095
026_331_00278590	Bone	331	HOS	456	3.602447	0.53	0.798	0.749	0.7609	0.8727	0.839	0.8786	0.8236	0.972
026_8045_00282660	Bone	8045	ES5	456	3.665641	0.704	0.653	0.874	0.8827	0.7407	0.913	0.8294	1.0585	1.162
026_8059_00283090	Bone	8059	EW-7	456	3.827217	0.662	0.72	0.76	0.831	0.8857	0.95	0.9309	0.9266	0.9963
026_8201_00282520	Bone	8201	ES3	456	3.982944	0.707	0.721	0.778	0.8414	0.8385	0.989	0.9588	1.0248	1.0261
026_8056_00314310	Bone	8056	EW-22	456	4.196343	0.701	0.827	0.819	0.8824	0.9413	0.894	0.9848	1.0221	1.1139
026_329_00282700	Bone	329	G-292 Clone A141B1	456	4.264519	0.705	0.918	0.893	0.949	1.0435	1.016	0.9814	0.9215	1.1209
026_324_00278550	Bone	324	CAL-72	456	4.286956	0.731	0.942	0.942	0.9262	0.9863	0.966	0.9797	0.9547	1.0113
026_304_00283460	Bone	304	Saos-2	456	4.597501	0.742	0.784	0.9	0.8765	0.9306	0.926	0.9516	0.95	1.0352
026_325_00283060	Bone	325	CAL-78	456	4.650689	0.727	0.913	0.918	0.9149	0.8999	0.897	0.9065	1.0242	1.0181
026_1138_00278560	Bone	1138	CS1	456	4.765346	0.744	0.848	0.864	0.8601	0.8818	1.016	1.0005	0.9749	0.977
026_8162_00282560	Bone	8162	SJSA-1	456	4.867747	0.802	0.803	0.805	0.7765	0.762	0.974	1.0651	1.0412	1.0623
026_336_00283430	Bone	336	HuO-3N1	456	4.900372	0.724	0.86	0.806	0.8427	0.8308	0.87	0.8972	0.9772	1.0073
026_328_00278600	Bone	328	TC-71	456	5.117725	0.844	0.939	0.97	1.0221	0.9857	1.072	1.023	1.0842	1.0771
026_8054_00282530	Bone	8054	EW-16	456	5.180986	0.835	0.775	0.925	0.8021	0.8155	0.934	0.9339	1.058	1.1414
026_335_00308220	Bone	335	MG-63	456	5.257203	0.884	0.841	0.852	0.8745	1.0185	1.081	1.1007	1.0325	1.0709
026_1241_00283070	Bone	1241	CHSA8926	456	5.394244	0.883	0.851	0.947	0.9788	0.9327	1.019	1.0879	1.0294	1.119
026_8044_00279340	Bone	8044	ES4	456	6.158016	0.822	0.876	0.92	0.8612	0.8592	0.873	0.8969	0.9914	0.9632
026_8057_00283080	Bone	8057	EW-24	456	6.273162	0.927	0.899	0.97	0.9817	0.9704	1.012	0.9822	0.9596	0.9793
026_8051_00285230	Bone	8051	EW-11	456	6.340509	0.924	1.008	0.846	0.9309	1.047	0.868	0.9762	1.0834	1.048
026_8046_00279351	Bone	8046	ES6	456	6.745328	0.882	1.065	1.046	1.0203	1.0617	0.85	0.8881	1.0547	0.9578
026_8146_00285140	Brain	8146	ONS-76	456	1.017095	0.362	0.369	0.387	0.52	0.6146	0.733	0.8773	0.9176	1.1016
026_8009_00285111	Brain	8009	AM-38	456	2.859683	0.545	0.617	0.664	0.5881	0.5592	0.692	0.826	0.9522	1.078
026_8091_00285281	Brain	8091	KS-1	456	2.979142	0.617	0.59	0.62	0.7057	0.7844	0.875	0.9025	1.0584	1.1343
026_388_00285240	Brain	388	MOG-G-CCM	456	3.029922	0.505	0.754	0.852	0.977	0.9597	0.989	1.1211	1.0361	1.0747
026_352_00283150	Brain	352	LN-229	456	3.053877	0.552	0.647	0.662	0.7206	0.8119	0.932	0.9285	1.0381	1.0748

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio								
						20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_8214_00290680	Brain	8214	YH-13	456	3.068585	0.558	0.628	0.773	1.0443	0.9614	1.113	1.1139	1.093	1.2619
026_8214_00288290	Brain	8214	YH-13	456	3.531592	0.627	0.651	0.866	0.8387	0.8073	0.922	1.077	1.0619	1.1182
026_358_00293700	Brain	358	D283 Med	456	3.551231	0.64	0.743	0.916	0.9078	0.9464	0.928	0.871	0.9767	1.4204
026_8061_00290830	Brain	8061	GB-1	456	3.686496	0.613	0.692	0.809	0.8255	0.8977	0.877	0.9922	0.9416	0.8923
026_374_00283180	Brain	374	U-251 MG	456	3.933399	0.654	0.733	0.861	0.8164	0.8981	0.891	0.9222	0.9976	1.1342
026_343_00283160	Brain	343	PFSK-1	456	3.963833	0.626	0.904	1.007	1.0229	0.934	1.078	1.0411	1.0084	1.052
026_393_00283190	Brain	393	YKG-1	456	3.987729	0.646	0.714	0.77	0.8178	0.8374	0.848	0.953	0.8805	1.0209
026_8028_00287630	Brain	8028	D-263MG	456	4.157483	0.662	0.709	0.734	0.7813	0.8341	0.839	0.9023	0.9333	1.0435
026_379_00283140	Brain	379	GAMG	456	4.214093	0.681	0.701	0.829	0.8043	0.8412	0.83	0.9322	0.8908	1.046
026_8019_00293320	Brain	8019	CAS-1	456	4.309856	0.732	0.772	0.825	0.9222	0.9783	1.227	0.8865	0.8407	1.1628
026_8001_00285100	Brain	8001	8-MG-BA	456	4.345495	0.688	0.845	0.88	0.8958	0.9285	0.912	0.9148	0.9398	1.07
026_351_00283450	Brain	351	LN-18	456	4.481815	0.685	0.822	0.862	0.8746	0.8966	0.902	0.9022	0.9311	0.9325
026_357_00283410	Brain	357	H4	456	4.481909	0.721	0.808	0.876	0.858	0.8822	0.94	1.0232	0.9287	1.0614
026_8085_00293731	Brain	8085	KINGS-1	456	4.48888	0.797	0.781	0.82	0.9645	0.9641	1.015	0.9981	1.0442	0.974
026_350_00284910	Brain	350	M059J	456	4.537622	0.723	0.834	0.869	0.8888	0.9473	0.909	0.9144	1.0191	1.0818
026_8015_00308070	Brain	8015	Becker	456	4.548091	0.696	0.814	0.876	0.8121	0.825	0.889	0.917	0.9113	1.0138
026_8160_00287680	Brain	8160	SF539	456	4.738405	0.726	0.919	0.827	0.8875	0.9392	0.934	0.952	1.0525	0.9285
026_8159_00287670	Brain	8159	SF268	456	4.804304	0.786	0.825	0.923	0.9225	0.9772	0.99	0.978	0.9754	0.9699
026_359_00283100	Brain	359	Daoy	456	4.81575	0.683	0.74	0.796	0.8102	0.876	0.896	0.9135	0.9254	0.9257
026_8217_00290890	Brain	8217	SK-MG-1	456	4.83361	0.725	0.784	0.83	0.844	0.8849	0.901	0.9119	0.9353	0.9859
026_342_00285160	Brain	342	SW 1783	456	4.84471	0.796	0.905	0.896	0.9349	1.0662	0.935	1.0347	1.0148	1.08
026_8029_00288240	Brain	8029	D-336MG	456	4.925588	0.792	0.892	0.997	0.8872	0.9556	0.944	1.105	1.0724	1.1057
026_8030_00295500	Brain	8030	D-392MG	456	4.966575	0.791	0.866	0.824	0.9331	0.8638	1.022	0.9531	0.9688	1.0531
026_8089_00287440	Brain	8089	KNS-81-FD	456	5.077406	0.804	0.89	0.869	0.8138	0.8421	1.049	1.0747	0.9317	1.1222
026_8138_00285290	Brain	8138	NMC-G1	456	5.086457	0.771	0.817	0.763	0.762	0.8138	0.887	0.968	1.0104	1.049
026_8139_00285130	Brain	8139	no-10	456	5.147267	0.824	0.888	0.928	0.9069	0.9436	1.031	0.943	1.05	1.0543
026_8083_00293720	Brain	8083	KALS-1	456	5.203248	0.817	0.765	0.902	0.9843	0.9376	0.915	0.9382	1.0116	0.9496
026_378_00284880	Brain	378	DK-MG	456	5.2953	0.789	0.757	0.713	0.7179	0.7297	0.849	0.8425	0.9101	1.0114
026_383_00284900	Brain	383	LN-405	456	5.313289	0.839	0.886	0.901	0.937	0.8868	1.041	0.949	1.0816	1.0986
026_8032_00293340	Brain	8032	D-542MG	456	5.342096	0.822	0.856	0.927	0.9108	0.8977	0.934	0.9191	0.9743	0.9895
026_344_00282720	Brain	344	LNZTA3WT4	456	5.43481	0.777	1.136	0.931	0.9386	0.9371	1.018	1.0441	1.0001	0.9944
026_8167_00290910	Brain	8167	SNB75	456	5.474524	0.76	0.772	0.83	0.8023	0.8147	1.01	0.8804	1.0523	0.9382
026_8087_00285270	Brain	8087	KNS-42	456	5.484622	0.862	0.858	0.846	0.8777	0.9301	0.972	0.9923	1.0701	1.0135
026_354_00287481	Brain	354	U-87 MG	456	5.588679	0.851	0.949	0.942	0.9605	0.9939	1.004	1.0222	0.9964	1.0855
026_8140_00285300	Brain	8140	no-11	456	5.608459	0.844	0.885	0.896	0.959	0.9411	0.893	0.9627	1.0352	0.9432
026_8221_00284860	Brain	8221	D-423MG	456	5.731372	0.807	0.783	0.798	0.8469	0.8833	0.945	0.9877	0.9131	0.9215
026_348_00283400	Brain	348	DBTRG-05MG	456	5.749405	0.792	0.75	0.763	0.7919	0.7917	0.856	0.9393	0.9013	0.9922
026_341_00285310	Brain	341	SW 1088	456	5.805148	0.869	0.907	0.895	0.8893	0.9105	0.919	0.966	0.8961	1.0957
026_356_00283420	Brain	356	Hs 683	456	5.858982	0.841	0.993	0.888	0.8789	0.8908	1.04	0.8743	0.906	1.058
026_8031_00287640	Brain	8031	D-502MG	456	5.99897	0.825	0.819	0.771	0.7649	0.8658	0.834	0.9457	0.9922	0.9572
026_8224_00284870	Brain	8224	D-566MG	456	6.026403	0.839	0.84	0.858	0.8841	0.9252	0.941	0.968	0.9815	0.9816
026_389_00284920	Brain	389	MOG-G-UVW	456	6.074777	0.861	0.876	0.879	0.9129	0.9004	0.902	1.0597	0.9108	1.0304
026_341_00283470	Brain	341	SW 1088	456	6.105387	0.913	0.89	0.897	0.897	0.9463	0.931	0.9486	0.9506	1.1024
026_375_00284850	Brain	375	42-MG-BA	456	6.106423	0.896	0.892	0.932	0.944	0.9633	0.976	0.9735	0.9871	1.0285
026_1122_00283170	Brain	1122	SF-295	456	6.112956	0.879	0.909	0.909	0.9301	0.9215	0.946	0.9199	0.9433	1.0329
026_8158_00290650	Brain	8158	SF126	456	6.158755	0.86	0.97	1	1.0676	1.0025	1.187	0.9851	0.9627	1.1324
026_340_00285250	Brain	340	CCF-STTG1	456	6.170298	0.851	0.911	0.916	0.9011	0.9748	0.919	0.9109	0.9323	0.9837
026_380_00284890	Brain	380	GMS-10	456	6.23472	0.842	0.885	0.853	0.8466	0.8914	0.914	0.8882	1.0019	1.0545
026_354_00290361	Brain	354	U-87 MG	456	6.315816	0.93	0.874	0.977	0.9346	0.9336	1.084	0.9295	1.062	1.073

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_8063_00290841	Brain	8063	GI-1	456	6.443002	0.809	0.877	0.913	0.9018	0.9184	0.86	0.9241	0.9072	0.9709
026_8027_00293330	Brain	8027	D-247MG	456	6.453915	0.928	0.905	0.908	0.8398	0.8592	0.911	0.9463	0.9529	0.9044
026_346_00283390	Brain	346	A172	456	6.640511	0.941	0.953	0.995	1.0208	0.9242	1.026	1.0141	1.0236	1.0356
026_8089_00291170	Brain	8089	KNS-81-FD	456	7.067458	0.854	0.823	0.854	0.8437	0.8524	0.889	0.8917	0.9075	0.9111
026_355_00285180	Brain	355	U-118 MG	456	7.408088	0.965	1.005	0.945	0.9352	0.9307	0.932	0.9407	0.945	0.9851
026_347_00282740	Brain	347	T98G	456	7.802123	0.986	1.098	0.951	1.0602	0.9957	1.038	1.0462	0.9753	0.982
026_417_00271110	Breast	417	DU4475	456	−3.0044	0.119	0.118	0.124	0.1202	0.1235	0.121	0.164	0.4789	0.6922
26_465_00271670	Breast	465	MRK-nu-1	456	1.744742	0.115	0.398	0.572	0.6893	0.7807	0.868	0.921	0.9463	1.1175
026_438_00273540	Breast	438	HCC1599	456	1.968855	0.352	0.459	0.617	0.7517	0.8021	0.899	0.9102	0.9757	1.0216
026_435_00271290	Breast	435	HCC1187	456	2.132259	0.375	0.482	0.801	0.7466	0.7917	0.794	0.9164	0.9352	0.9707
026_403_00271400	Breast	403	MCF7	456	2.857648	0.493	0.634	0.765	0.8761	0.9706	0.973	1.0249	1.0247	1.0456
026_401_00273450	Breast	401	MDA-MB-468	456	3.05753	0.415	0.718	0.931	0.9526	0.909	0.954	0.9512	1.0282	0.9601
26_451_00271640	Breast	451	CAL-85-1	456	3.06898	0.489	0.695	0.808	0.7646	0.8147	0.885	0.8459	1.0885	0.9906
026_404_00273430	Breast	404	MDA-MB-231	456	3.086092	0.483	0.731	0.783	0.824	0.8358	0.874	0.9446	0.9609	1.0599
026_418_00271550	Breast	418	Hs 578T	456	3.125956	0.071	0.614	0.832	0.7916	0.8611	0.836	0.9569	0.9556	1.0186
026_402_00272120	Breast	402	CAMA-1	456	3.166443	0.55	0.636	0.773	0.8152	0.9017	0.886	0.906	0.9417	0.9695
026_426_00274200	Breast	426	HCC1569	456	3.228782	0.571	0.713	0.945	0.9056	0.9414	0.938	0.9814	1.028	1.0046
026_431_00271130	Breast	431	HCC1806	456	3.337319	0.566	0.672	0.68	0.6852	0.6987	0.765	0.8378	1.0081	1.1468
026_414_00271900	Breast	414	AU565	456	3.409308	0.533	0.816	0.949	0.9831	0.9841	0.924	0.9729	0.9876	1.1475
026_452_00272130	Breast	452	COLO-824	456	3.645131	0.358	0.743	0.843	0.9519	0.9643	0.904	0.9021	1.0288	0.9665
026_416_00271360	Breast	416	BT-549	456	3.723874	0.659	0.818	0.911	0.9492	0.9446	0.965	0.9707	0.9785	1.0314
026_8144_00274240	Breast	8144	OCUB-M	456	3.727884	0.44	0.801	0.89	0.9127	1.0139	1.046	0.9729	0.96	1.0167
026_432_00271960	Breast	432	HCC70	456	3.73179	0.605	0.733	0.855	0.8647	0.8214	0.887	0.9582	0.9394	1.1987
026_457_00273420	Breast	457	EVSA-T	456	3.968951	0.686	0.879	0.927	0.9385	0.9505	0.975	0.9713	0.9606	1.0214
026_466_00274370	Breast	466	YMB-1-E	456	3.997753	0.654	0.836	0.87	0.9113	0.9082	0.908	0.9623	1.0457	0.9738
026_441_00285120	Breast	441	HCC2157	456	3.997874	0.474	1.044	0.849	0.8244	0.6122	0.948	1.0739	0.6695	1.0405
026_443_00271990	Breast	443	MDA-MB-330	456	4.004084	0.601	0.92	0.94	0.9085	0.9663	0.971	0.9817	0.9257	1.0607
026_436_00271300	Breast	436	HCC1395	456	4.036641	0.703	0.897	0.946	0.9395	1.0136	1.033	1.0207	1.0407	1.1296
026_412_00277190	Breast	412	UACC-893	456	4.234383	0.421	0.859	0.854	0.8448	0.9188	0.999	0.9512	1.0422	0.9971
026_450_00271390	Breast	450	CAL-51	456	4.319545	0.678	0.725	0.783	0.8043	0.8395	0.899	0.9313	0.9642	1.0975
026_449_00271380	Breast	449	CAL-148	456	4.389344	0.747	0.676	1.08	0.9571	0.7093	0.888	0.981	0.8213	1.2196
026_434_00271920	Breast	434	HCC1143	456	4.464516	0.726	0.808	0.808	0.822	0.8993	0.923	0.919	0.949	1.1427
026_433_00276270	Breast	433	HCC202	456	4.571252	0.686	0.9	0.944	0.8549	0.8115	0.943	0.972	0.9241	0.9618
026_422_00274230	Breast	422	MDA-MB-175-VII	456	4.594595	0.7	0.73	0.74	0.7666	0.8545	0.848	0.9155	0.9541	0.9487
026_461_00272170	Breast	461	MFM-223	456	4.656681	0.787	0.875	0.908	0.9465	0.988	1.047	1.0015	1.1431	1.0159
026_427_00271330	Breast	427	MDA-MB-453	456	4.669025	0.795	0.819	0.921	0.9998	0.9757	0.998	1.0349	1.0264	1.1651
026_448_00271370	Breast	448	CAL-120	456	4.779687	0.744	0.746	0.796	0.8032	0.8728	0.85	0.9852	1.0071	1.0287
026_411_00271420	Breast	411	UACC-812	456	5.072094	0.82	0.894	0.873	0.9564	0.9958	0.944	0.9931	1.0326	0.9659
026_442_00273480	Breast	442	HCC2218	456	5.225292	0.614	0.923	0.963	1.0597	1.042	1.043	1.0714	1.0498	1.0318
026_398_00272150	Breast	398	HCC1428	456	5.256241	0.85	0.899	1.013	0.8915	0.9851	0.983	0.9959	0.9937	1.0331
026_464_00308490	Breast	464	T47D	456	5.26439	0.825	0.853	0.869	0.8588	0.823	0.978	0.9397	0.9562	0.968
026_400_00273440	Breast	400	MDA-MB-436	456	5.286367	0.725	0.844	0.848	0.8326	0.8721	0.851	0.8881	0.9805	0.933
026_437_00280161	Breast	437	HCC1500	456	5.288806	0.796	0.982	0.913	0.8847	0.9397	1.088	0.8523	0.9109	0.9883
026_440_00271950	Breast	440	HCC1954	456	5.303093	0.807	0.813	0.885	0.8155	0.8463	0.861	1.0199	1.0209	0.9481
026_413_00271930	Breast	413	HCC1419	456	5.337084	0.839	0.926	0.932	0.9634	0.9633	0.941	0.9595	0.9516	1.1518
026_410_00272180	Breast	410	ZR-75-30	456	5.373081	0.83	0.857	0.88	0.8529	0.9183	0.913	0.911	1.03	0.9685
026_439_00271940	Breast	439	HCC1937	456	5.44243	0.841	0.952	0.975	1.0253	0.9632	0.953	1.0302	1.0262	1.0774
026_408_00271350	Breast	408	BT-20	456	5.735872	0.871	0.955	0.93	0.9913	0.9764	0.972	1.0674	0.9818	1.1818
026_399_00272160	Breast	399	MDA-MB-415	456	5.879088	0.884	0.875	0.885	0.8851	0.9175	0.914	0.9179	0.9049	0.9735

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_458_00274220	Breast	458	HDQ-P1	456	6.259493	0.84	1.072	1.136	1.0763	1.0797	1.042	1.0437	1.0231	1.0073
026_397_00274350	Breast	397	HCC38	456	6.744219	0.874	1.053	1.023	1.0222	0.9856	0.93	0.9274	0.9402	0.9941
026_405_00274360	Breast	405	MDA-MB-361	456	6.792889	0.935	0.959	0.987	0.9819	0.9119	0.921	0.9597	0.998	0.9922
026_425_00280231	Breast	425	MDA-MB-157	456	7.000504	0.906	1.069	1.05	0.9597	0.9229	0.966	0.9422	0.9712	0.9545
026_454_00272140	Breast	454	EFM-192A	456	7.097342	0.942	1.032	1.041	1.0545	0.9812	0.979	1.0186	1.0191	0.9742
026_420_00271541	Breast	420	BT-474	456	7.458914	0.191	1.089	1.053	1.0824	1.0008	0.955	0.9764	0.9678	1.0149
026_453_00273410	Breast	453	EFM-19	456	8.207256	1.096	1.286	1.208	1.1112	1.0544	1.042	1.0064	1.0474	1.0572
026_415_00316440	Breast	415	BT-483	456	8.21654	1.148	1.275	1.181	1.1462	1.089	1.147	1.0671	1.0911	1.1123
026_8176_00316650	Cervix	8176	TC-YIK	456	0.842618	0.29	0.416	0.488	0.5211	0.5993	0.669	0.7672	0.7877	1.0572
026_479_00264920	Cervix	479	HT-3	456	1.420025	0.257	0.608	0.574	0.5844	0.5901	0.637	0.8649	0.8189	0.8617
026_478_00271910	Cervix	478	C-33 A	456	2.72591	0.472	0.615	0.658	0.6776	0.6753	0.734	0.7964	0.8383	0.9143
026_478_00269410	Cervix	478	C-33 A	456	2.976483	0.445	0.701	0.714	0.731	0.8172	0.771	0.9038	0.852	0.9634
026_493_00268830	Cervix	493	ME-180	456	3.07379	0.509	0.667	0.695	0.7355	0.6828	0.732	0.7953	0.9097	1.0456
026_476_00269050	Cervix	476	C-4 I	456	3.232632	0.508	0.792	0.857	0.8645	0.8671	0.933	1.0078	1.0484	1.1636
026_8145_00271140	Cervix	8145	OMC-1	456	3.295968	0.531	0.786	0.84	0.8546	0.9307	0.911	1.0261	1.0441	1.0392
026_484_00263710	Cervix	484	Ca Ski	456	3.639931	0.327	0.715	0.879	0.8811	0.8284	0.817	0.9599	1.0361	1.165
026_469_00264610	Cervix	469	HeLa	456	3.981495	0.311	0.783	0.933	0.9784	0.9807	0.982	0.9321	0.9429	0.9946
026_493_00262480	Cervix	493	ME-180	456	4.007923	0.639	0.799	0.885	0.9474	0.9337	0.873	0.9457	0.8694	0.8949
026_474_00269100	Cervix	474	SiHa	456	4.596545	0.742	0.846	0.832	0.8807	0.9276	0.898	1.0004	0.9967	1.1646
026_482_00262520	Cervix	482	SISO	456	5.313141	0.851	0.946	0.96	0.9752	0.9888	0.276	0.975	0.947	0.9669
026_482_00274250	Cervix	482	SISO	456	5.375837	0.842	0.881	0.887	0.9541	0.9605	0.96	0.9679	1.044	1.0481
026_482_00269740	Cervix	482	SISO	456	5.709731	0.838	0.89	0.925	0.9202	0.9445	0.931	0.9609	0.9695	0.9938
026_468_00264600	Cervix	468	DoTc2 4510	456	5.749229	0.363	0.92	0.961	0.9796	0.9907	0.984	1.01	0.9525	0.9858
026_473_00264650	Cervix	473	SW756	456	5.953892	0.162	0.868	0.813	0.7938	0.8104	0.779	0.9163	0.8951	0.9568
026_491_00264830	Cervix	491	5KG-IIIa	456	6.261878	0.721	1.002	1.008	1.007	1.0125	0.97	1.0049	0.9721	0.9931
026_476_00264900	Cervix	476	C-4 I	456	6.792994	0.225	0.991	0.994	0.9083	0.8797	0.89	0.982	0.9123	0.9144
026_474_00264930	Cervix	474	SiHa	456	7.505839	0.532	0.824	0.865	0.9092	0.9029	0.879	0.8904	0.8746	0.8785
026_472_00264630	Cervix	472	MS751	456	7.679336	1.023	0.945	0.949	0.9806	0.9744	0.979	0.9915	0.9775	0.9824
026_8180_00276230	Esophagus	8180	TE-15	456	0.823778	0.313	0.365	0.448	0.4963	0.618	0.64	0.8902	0.6859	1.0361
026_502_00276550	Esophagus	502	KYSE-450	456	1.219587	0.422	0.41	0.448	0.5484	0.5334	0.703	0.7332	0.8892	0.853
026_497_00274050	Esophagus	497	KYSE-150	456	1.304746	0.328	0.402	0.467	0.567	0.6585	0.801	0.8957	0.9976	0.9719
026_8252_00276570	Esophagus	8252	OACp4C	456	1.678468	0.101	0.3	0.567	0.6503	0.7826	0.861	0.8531	0.9243	0.9446
026_496_00276530	Esophagus	496	KYSE-140	456	2.209734	0.522	0.516	0.476	0.5824	0.6741	0.815	0.8515	0.806	0.8896
026_8233_00278570	Esophagus	8233	ESO26	456	2.595405	0.493	0.568	0.679	0.7293	0.7791	0.852	0.8801	1.0449	0.8251
026_8184_00282680	Esophagus	8184	TE-6	456	2.946928	1.152	0.677	0.704	0.6755	0.7901	0.89	1.1989	1.0724	0.9825
026_8277_00276670	Esophagus	8277	TE-4	456	3.072573	0.518	0.605	0.768	0.8018	0.8549	0.883	0.9093	0.8952	0.9579
026_506_00277170	Esophagus	506	OE19	456	3.143883	0.544	0.752	0.743	0.8799	1.0437	0.937	1.0332	1.0004	1.0701
026_8179_00276220	Esophagus	8179	TE-12	456	3.163617	0.183	0.742	0.633	0.6476	0.7356	0.839	0.7964	0.8189	0.8318
026_8185_00276250	Esophagus	8185	TE-8	456	3.50176	0.201	0.606	0.658	0.7374	0.6587	0.744	0.775	0.681	0.9258
026_8184_00293680	Esophagus	8184	TE-6	456	3.545508	0.552	0.767	0.935	0.8745	0.8626	0.742	1.0239	0.863	0.9232
026_8178_00280260	Esophagus	8178	TE-10	456	3.804003	0.664	0.735	0.78	0.9124	0.8781	1.01	1.0331	0.9777	1.0127
026_499_00276630	Esophagus	499	KYSE-270	456	4.027681	0.678	0.727	0.767	0.7928	0.8774	0.984	0.9911	1.0386	1.0007
026_509_00276620	Esophagus	509	KYSE-220	456	4.075564	0.637	0.656	0.682	0.7368	0.7969	0.844	0.873	0.9181	0.9229
026_8235_00276520	Esophagus	8235	FLO-1	456	4.100409	0.604	0.732	0.778	0.7882	0.8071	0.864	0.8729	0.8842	0.9483
026_8251_00276640	Esophagus	8251	OACM5-1	456	4.181038	0.673	0.784	0.878	0.8883	0.9366	0.926	0.9214	0.9309	0.9714
026_8186_00282690	Esophagus	8186	TE-9	456	4.291684	0.689	0.795	0.742	0.8146	0.856	0.846	1.0123	0.8588	1.0654
026_495_00274190	Esophagus	495	COLO-680N	456	4.332573	0.742	0.818	0.865	0.9122	0.97	0.96	1.1262	0.9684	1.0444
026_510_00273560	Esophagus	510	KYSE-50	456	4.431288	0.658	0.743	0.781	0.8044	0.8395	0.815	0.8665	0.9009	1.0802
026_8186_00292740	Esophagus	8186	TE-9	456	4.438695	0.739	0.769	0.893	0.8667	0.8573	0.944	1.0623	1.0025	1.1458

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_503_00274070	Esophagus	503	KYSE-510	456	4.484808	0.731	0.796	0.816	0.8942	0.9487	0.912	0.9785	1.0104	1.0221
026_504_00276560	Esophagus	504	KYSE-520	456	4.773857	0.716	0.731	0.748	0.7768	0.8124	0.867	0.9459	0.995	0.9576
026_8208_00276600	Esophagus	8208	HCE-4	456	4.88732	0.748	0.785	0.808	0.8645	0.9033	0.954	0.9197	0.9231	0.9878
026_512_00274080	Esophagus	512	T.T	456	4.943912	0.781	0.839	0.89	0.9002	0.9769	0.929	0.9845	0.9744	1.0152
026_8268_00276650	Esophagus	8268	SK-GT-4	456	5.079273	0.835	0.788	0.758	0.735	0.7503	0.833	0.9063	0.9163	0.972
026_505_00274210	Esophagus	505	KYSE-70	456	5.137973	0.794	0.857	0.892	0.8943	0.9411	0.957	0.9493	0.9907	1.0431
026_508_00278520	Esophagus	508	OE33	456	5.424479	0.701	0.81	0.783	0.7873	0.7763	0.833	0.8596	0.903	0.9287
026_498_00276540	Esophagus	498	KYSE-180	456	5.533652	0.84	0.853	0.898	0.9109	0.9353	0.924	0.9336	0.9199	0.942
026_8202_00276660	Esophagus	8202	TE-11	456	5.740526	0.822	0.845	0.848	0.8684	0.8821	0.913	0.9297	0.9627	1.0605
026_8039_00276580	Esophagus	8039	EC-GI-10	456	5.844841	0.878	0.905	0.892	0.951	0.9277	0.926	0.9555	1.04	1.0068
026_501_00274060	Esophagus	501	KYSE-410	456	6.135532	0.762	0.836	0.846	0.8398	0.8691	0.887	0.9278	0.9729	0.9854
026_8246_00276610	Esophagus	8246	KYAE-1	456	6.1525	0.887	0.93	0.92	0.9326	0.9185	0.978	0.97	0.9663	0.9315
026_507_00278510	Esophagus	507	OE21	456	6.23551	0.922	0.838	0.875	0.7771	0.8079	0.985	0.9753	0.9667	0.9919
026_8183_00276240	Esophagus	8183	TE-5	456	6.777236	0.111	1.028	0.936	1.0341	1.0898	0.876	0.8843	0.9699	0.8561
026_8177_00282670	Esophagus	8177	TE-1	456	7.848711	1.022	1.1	0.912	1.0973	1.0839	1.065	1.0874	1.0775	1.0749
026_545_00260020	Head & Neck	545	DOK	456	−0.22061	0.308	0.451	0.33	0.4014	0.4436	0.534	0.6634	0.7589	0.8693
026_1217_00255750	Head & Neck	1217	H3118	456	0.314816	0.254	0.413	0.453	0.4692	0.5199	0.565	0.691	0.6788	0.7738
026_526_00308740	Head & Neck	526	PCI-4B	456	1.887412	0.418	0.409	0.489	0.7595	0.7429	0.873	0.9067	0.918	1.0403
026_530_00260620	Head & Neck	530	PCI-30	456	1.98819	0.142	0.356	0.628	0.7119	0.7851	0.825	0.9139	0.8747	0.8098
026_552_00252890	Head & Neck	552	SAT	456	2.534279	0.382	0.613	0.727	0.8554	0.7778	0.977	0.8474	0.7957	0.9605
026_550_00258980	Head & Neck	550	SCC-4	456	2.544916	0.464	0.564	0.904	0.7519	0.7827	0.709	0.7715	0.8596	0.9574
026_1224_00256200	Head & Neck	1224	SCC-9	456	2.68588	0.466	0.633	0.641	0.6635	0.6231	0.758	0.8287	0.8854	0.9263
026_1223_00259190	Head & Neck	1223	SCC-25	456	2.934793	0.193	0.664	0.718	0.8957	0.937	0.932	1.0111	0.988	1.0055
026_548_00261030	Head & Neck	548	RPMI 2650	456	3.095229	0.489	0.696	0.761	0.8664	0.8685	0.911	0.9177	0.9218	0.9624
026_517_00308680	Head & Neck	517	JHU-011	456	3.112112	0.536	0.616	0.696	0.7845	0.8433	0.813	0.9157	0.9495	1.0827
026_8011_00257080	Head & Neck	8011	BB30-HNC	456	3.217966	0.541	0.677	0.734	0.7445	0.7909	0.917	0.9622	0.9832	1.0203
026_553_00259140	Head & Neck	553	OSC-20	456	3.378306	0.587	0.751	0.792	0.8761	0.9722	0.983	1.0097	0.974	0.999
026_556_00257220	Head & Neck	556	SKN-3	456	3.392608	0.207	0.626	0.805	0.7174	0.6353	0.718	0.757	0.8593	0.8383
026_536_00256080	Head & Neck	536	BHY	456	3.443799	0.593	0.821	0.877	0.8931	0.9405	1.049	1.0289	0.9991	1.0281
026_561_00257110	Head & Neck	561	Ca9-22	456	3.710495	0.634	0.867	0.849	0.916	0.9493	0.99	1.0155	1.0225	1.0222
026_532_00308750	Head & Neck	532	PCI-6A	456	3.742916	0.628	0.684	0.811	0.8452	0.8862	0.945	0.9298	0.9056	0.9974
026_8012_00266550	Head & Neck	8012	BB49-HNC	456	3.77782	0.46	0.775	0.9	0.8967	0.924	0.968	0.9717	1.0116	0.9946
026_8100_00256170	Head & Neck	8100	LB771 -HNC	456	3.926882	0.701	0.899	0.929	0.9987	0.9867	0.989	1.0145	0.9621	0.9588
026_1222_00253030	Head & Neck	1222	SCC-15	456	4.189701	0.411	0.772	0.855	0.8291	0.7747	1.02	0.8664	0.932	0.9717
026_533_00260900	Head & Neck	533	PCI-15A	456	4.236361	1.325	1.15	0.832	0.8691	0.8188	0.863	0.9549	1.0427	1.0471
26_547_00314070	Head & Neck	547	KOSC-2 cl3-43	456	4.563275	0.708	0.872	0.897	0.9	0.8378	0.941	1.0131	0.9825	0.9292
026_544_00256140	Head & Neck	544	Detroit 562	456	4.601961	0.746	0.964	0.951	0.9801	0.9656	0.961	0.9765	0.9793	0.9061
026_543_00256100	Head & Neck	543	BICR 78	456	4.851894	0.728	0.818	0.868	0.8349	0.9283	0.925	0.9696	0.966	0.9649
026_537_00256120	Head & Neck	537	CAL-33	456	5.580216	0.834	0.892	0.921	0.9097	0.9511	0.935	0.9977	1.0062	0.9837
026_549_00256220	Head & Neck	549	HO-1-N-1	456	5.63511	0.866	0.873	0.883	0.8726	0.8907	0.97	0.987	0.9898	1.0714
026_557_00259180	Head & Neck	557	SAS	456	6.035072	0.913	0.97	0.967	0.9738	0.9866	1.043	1.0896	1.0407	1.0277
026_534_00256110	Head & Neck	534	CAL 27	456	6.045151	0.85	0.904	0.912	0.9312	0.925	0.939	0.9758	0.9901	0.9927
026_542_00269190	Head & Neck	542	BICR 31	456	6.045414	0.903	0.908	0.952	0.9408	0.977	0.97	0.9966	1.0002	1.0269
026_530_00262500	Head & Neck	530	PCI-30	456	6.119674	0.884	0.955	1.145	0.9682	1.009	0.988	0.9261	1.0121	0.9861
026_540_00258490	Head & Neck	540	BICR 10	456	6.128463	0.839	1.048	1.049	1.0556	1.0464	1.041	1.0301	0.974	0.9953
026_541_00256090	Head & Neck	541	BICR 22	456	6.156446	0.828	1.076	1.058	0.9602	1.0898	1.064	1.0874	0.9689	1.0462
026_8003_00263440	Head & Neck	8003	A253	456	6.291179	0.877	0.857	0.859	0.8594	0.9753	0.982	0.9985	0.9367	0.969
026_535_00256160	Head & Neck	535	FaDu	456	6.303565	0.841	1.063	1.091	1.0795	1.0793	1.034	1.0404	1.0191	1.0095
026_554_00257210	Head & Neck	554	OSC-19	456	6.322489	0.938	0.942	0.914	0.9247	0.9682	1.004	1.0285	1.0504	1.0506

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_559_00256250	Head & Neck	559	HSC-3	456	6.797258	0.909	1.024	1.057	1.0632	1.0572	1.029	1.0059	0.9701	0.9782
026_8071_00256760	Head & Neck	8071	HCE-T	456	6.917353	0.576	1.146	1.274	1.3514	1.1688	1.173	1.0336	1.1999	0.8849
026_521_00257180	Head & Neck	521	JHU-022	456	7.049785	0.896	0.846	0.901	0.8757	0.9278	0.886	0.9103	0.9436	0.9699
026_555_00256270	Head & Neck	555	KON	456	7.114386	0.946	0.982	0.977	0.9826	0.9957	0.96	0.9991	0.961	0.9207
026_538_00258510	Head & Neck	538	HN	456	7.118392	0.947	1.007	0.984	1.0014	1.0052	0.998	1.0105	0.9648	0.9952
026_546_00259150	Head & Neck	546	PE/CA-PJ15	456	7.26219	0.96	0.963	0.931	0.9179	0.9698	0.969	0.9884	1.006	0.9974
026_560_00256260	Head & Neck	560	HSC-4	456	7.41962	1.005	0.994	1.003	0.9486	1.2114	0.897	0.9756	0.9433	0.9255
026_551_00259130	Head & Neck	551	HO-1-u-1	456	7.903602	0.999	1.037	1.039	1.0722	1.0616	1.067	1.0655	1.0038	0.9405
026_558_00256240	Head & Neck	558	HSC-2	456	8.185707	1.148	1.077	0.985	1.1269	1.0034	1.093	0.9608	0.9252	0.9888
026_531_00258970	Head & Neck	531	PCI-38	456	8.493869	1.046	1.067	1.063	1.0751	1.0712	0.965	1.0236	1.0421	0.9848
026_570_00293670	Intestine	570	SK-CO-1	456	−0.30187	0.268	0.258	0.267	0.2555	0.3743	0.418	0.7306	0.9824	0.9276
026_8153_00295901	Intestine	8153	RKO	456	0.044041	0.222	0.197	0.246	0.3161	0.4612	0.693	0.7818	0.9061	1.1131
18	Intestine	586	COLO 205	456	0.350012	0.083	0.182	0.268	0.3978	0.5206	0.706	0.8518	0.9472	0.9745
026_582_00295550	Intestine	582	LoVo	456	0.399717	0.325	0.396	0.385	0.4168	0.4097	0.533	0.75	0.8239	0.9276
026_8108_00298530	Intestine	8108	LS-513	456	0.423432	0.094	0.146	0.195	0.2527	0.5673	0.876	1.1755	1.0179	1.1926
026_8274_00258540	Intestine	8274	SNU-61	456	0.467862	0.432	0.599	0.539	0.5369	0.5735	0.603	0.7283	0.7462	0.9243
026_8136_00260060	Intestine	8136	NCI-H747	456	0.578701	0.356	0.465	0.488	0.5338	0.5471	0.613	0.7238	0.8107	0.9473
026_574_00298390	Intestine	574	CL-11	456	0.894127	0.381	0.401	0.395	0.4593	0.6002	0.69	0.749	0.8474	0.9789
026_589_00295371	Intestine	589	HCT 116	456	0.931657	0.336	0.381	0.435	0.4732	0.5791	0.862	1.1049	1.0627	1.1072
026_608_00293620	Intestine	608	CCK-81	456	1.046144	0.242	0.394	0.399	0.4912	0.6325	0.738	0.9653	0.9069	0.9123
026_610_00293660	Intestine	610	RCM-1	456	1.475794	0.45	0.416	0.414	0.6252	0.6775	0.804	0.981	1.0277	1.0565
026_569_00295390	Intestine	569	HT-29	456	1.526342	0.48	0.464	0.5	0.5547	0.5893	0.74	0.9536	0.9048	0.9241
026_8271_00314300	Intestine	8271	SNU-175	456	1.739925	0.382	0.522	0.535	0.5651	0.6481	0.701	0.7957	0.9458	0.9851
026_8108_00296610	Intestine	8108	LS-513	456	1.815428	0.37	0.448	0.511	0.6156	0.8074	0.933	0.9905	0.9579	0.9991
026_592_00295380	Intestine	592	HT115	456	1.869689	0.377	0.436	0.5	0.6258	0.8213	1.101	1.0858	1.0169	1.1148
026_606_00293630	Intestine	606	HCC-56	456	1.929923	0.646	0.514	0.536	0.5915	0.7207	0.867	0.8829	0.9131	0.9417
026_8107_00296450	Intestine	8107	LS-411N	456	2.297731	0.497	0.55	0.585	0.5585	0.6884	0.755	0.8626	0.8921	0.9253
026_595_00295420	Intestine	595	LS180	456	2.32965	0.453	0.515	0.551	0.6999	0.8666	0.91	1.0102	0.9178	1.1155
026_8169_00295910	Intestine	8169	SNU-C2B	456	2.617884	0.503	0.566	0.598	0.7373	0.671	0.774	0.9066	0.8796	0.9886
026_564_00292860	Intestine	564	NCI-H630	456	2.627492	0.496	0.556	0.55	0.7713	1.0007	0.964	0.9563	0.8783	0.9169
026_603_00292731	Intestine	603	SW837	456	2.797981	0.525	0.597	0.586	0.7811	0.7763	1.002	1.023	1.0218	1.0696
026_588_00295360	Intestine	588	GP5d	456	2.925873	0.521	0.65	0.67	0.679	0.8325	0.964	1.0479	1.1013	1.0678
026_598_00302650	Intestine	598	SW 1417	456	3.077195	0.616	0.696	0.742	0.6531	1.034	1.029	1.0798	0.8321	1.2207
026_8276_00296000	Intestine	8276	SNU-C5	456	3.153347	0.603	0.592	0.612	0.6327	0.7283	0.812	0.8824	0.9411	0.9768
026_593_00295530	Intestine	593	HT55	456	3.164186	0.589	0.646	0.61	0.7857	0.7974	1.03	1.1134	1.0941	1.1175
026_8106_00264670	Intestine	8106	LS-123	456	3.191118	0.547	0.687	0.783	0.7554	0.8823	0.879	0.9202	0.965	0.9375
026_599_00296340	Intestine	599	SW 1463	456	3.237942	0.572	0.642	0.631	0.6255	0.6275	0.757	0.9237	0.9401	0.9681
026_8086_00296431	Intestine	8086	KM12	456	3.240654	0.564	0.657	0.65	0.6739	0.8062	0.903	0.8847	0.9825	0.9793
026_587_00302320	Intestine	587	COLO 741	456	3.269221	0.615	0.622	0.694	0.6624	0.7236	0.816	1.1047	1.0995	1.0783
026_8273_00295970	Intestine	8273	SNU-407	456	3.390403	0.577	0.622	0.663	0.7325	0.7399	0.745	0.8059	0.8644	1.0342
026_8270_00304630	Intestine	8270	SNU-1040	456	3.643993	0.604	0.78	0.799	0.8256	0.8028	0.92	0.9246	0.9919	1.2066
026_8168_00295990	Intestine	8168	SNU-C1	456	3.717495	0.645	0.673	0.685	0.6875	0.8368	0.739	0.8513	1.1115	1.0883
026_8275_00256210	Intestine	8275	SNU-81	456	3.903109	0.338	0.659	0.68	0.6942	0.7065	0.761	0.7749	0.8653	0.9224
026_583_00295921	Intestine	583	SW-948	456	3.908038	0.735	0.672	0.851	0.9918	1.0392	0.979	0.9178	0.9736	0.9758
026_8274_00295980	Intestine	8274	SNU-61	456	4.14154	0.663	0.72	0.672	0.6639	0.7521	0.794	0.8775	0.8761	0.9371
026_8105_00296440	Intestine	8105	LS-1034	456	4.222062	0.732	0.754	0.781	0.8085	0.8857	1.006	1.1032	1.0973	1.0698
026_580_00295930	Intestine	580	COLO-678	456	4.449849	0.891	0.793	0.767	0.8394	0.8741	0.917	1.0326	0.9344	1.0884
026_580_00266560	Intestine	580	COLO-678	456	4.550688	0.724	0.686	0.785	0.8147	0.8701	0.885	0.9546	0.9558	0.9803
026_581_00295830	Intestine	581	HCT-15	456	4.608693	0.811	0.75	0.973	0.9405	1.0972	0.98	1.098	1.0722	1.1405

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_573_00296370	Intestine	573	SW620	456	4.816766	0.775	0.787	0.797	0.8519	0.8683	0.915	0.9626	1.0901	1.097
026_8021_00296390	Intestine	8021	COLO-320-HSR	456	4.87923	0.817	0.861	0.828	1.0219	0.8974	1.103	1.0927	0.9967	1.1145
026_8106_00298521	Intestine	8106	LS-123	456	4.895207	0.706	0.749	0.852	0.7598	0.7605	0.923	0.8934	0.9319	1.0175
026_600_00296361	Intestine	600	SW 48	456	4.951306	0.706	0.776	0.775	0.7937	0.8445	0.857	0.9382	0.915	0.9609
026_8070_00296411	Intestine	8070	HCC2998	456	4.984157	0.701	0.788	0.743	0.7463	0.8151	0.891	0.9115	0.9572	0.9432
026_8135_00295950	Intestine	8135	NCI-H716	456	4.988916	0.813	0.864	0.948	0.9832	0.9658	0.94	0.9372	0.9633	1.1237
026_8136_00295961	Intestine	8136	NCI-H747	456	5.220086	0.699	0.693	0.763	0.7315	0.7863	0.815	0.8715	0.8842	1.1461
026_574_00263900	Intestine	574	CL-11	456	5.294016	0.826	0.812	0.761	0.7543	0.8087	0.891	0.9784	0.9577	0.9649
026_8026_00300671	Intestine	8026	CW-2	456	5.403672	0.827	0.955	0.974	0.9551	0.9288	0.954	0.9824	0.9866	1.0636
026_607_00293610	Intestine	607	CaR-1	456	5.551737	0.834	0.873	0.912	0.8795	0.9318	0.939	0.9636	0.9483	0.9415
026_8074_00296420	Intestine	8074	HUTU-80	456	5.701754	0.841	0.852	0.876	0.9027	0.8952	1.007	1.0026	0.966	0.9322
026_563_00316540	Intestine	563	C2BBe1	456	5.783056	0.853	0.949	0.926	0.9333	0.9253	0.879	0.9164	1.0369	1.0733
026_596_00296280	Intestine	596	MDST8	456	6.402689	0.885	0.885	0.874	0.8768	0.9374	0.931	0.9758	0.9779	1.0734
026_597_00300651	Intestine	597	SW 1116	456	6.447765	0.647	1.058	0.925	1.031	0.9839	0.997	1.0631	1.0277	0.905
026_601_00296480	Intestine	601	T84	456	7.233631	0.973	0.939	0.93	0.9736	0.9545	0.891	0.964	0.9372	1.0259
026_622_00288160	Kidney	622	G-401	456	1.158385	0.353	0.358	0.433	0.5045	0.6202	0.865	0.8778	1.0261	1.0061
026_626_00298790	Kidney	626	BFTC-909	456	1.589633	0.292	0.387	0.526	0.5522	0.8154	0.895	0.9347	1.005	1.054
026_623_00288201	Kidney	623	SK-NEP-1	456	1.837955	0.412	0.444	0.507	0.7421	0.8141	0.813	0.9099	0.9209	0.981
026_8264_00290630	Kidney	8264	RCC-JF	456	2.377362	0.452	0.535	0.585	0.6574	0.9675	0.851	0.9828	1.0591	1.0712
026_619_00290290	Kidney	619	769-P	456	2.463867	0.439	0.58	0.576	0.7655	0.8898	0.994	1.0776	1.0508	1.1513
026_627_00291130	Kidney	627	CAL-54	456	2.931844	0.586	0.588	0.649	0.6813	0.7826	0.858	0.9811	0.9726	1.0003
026_617_00290310	Kidney	617	ACHN	456	2.983353	0.545	0.592	0.627	0.7345	0.7447	0.733	0.7712	0.919	1.1152
026_8263_00290620	Kidney	8263	RCC-FG2	456	3.111338	0.517	0.689	0.691	0.7857	0.7896	0.884	0.8746	0.9754	1.0284
026_8190_00290280	Kidney	8190	TK10	456	3.318654	0.638	0.654	0.671	0.7606	0.892	0.932	1.0085	1.0009	0.9983
026_638_00288220	Kidney	638	VMRC-RCZ	456	3.36569	0.14	0.709	0.838	0.9211	0.92	0.981	0.9922	0.9588	0.989
026_8261_00308760	Kidney	8261	RCC-AB	456	3.394556	0.566	0.724	0.758	0.85	0.8258	0.948	0.9492	0.9471	0.9351
026_628_00288210	Kidney	628	SW 13	456	3.41636	0.454	0.733	0.735	0.7572	0.8068	0.826	0.8584	0.9361	1.0195
026_8262_00290610	Kidney	8262	RCC-ER	456	3.745967	0.583	0.783	0.794	0.8415	0.9082	0.87	0.8861	0.9471	0.9855
026_8265_00302360	Kidney	8265	RCC-JW	456	3.749626	0.686	0.758	0.874	0.9595	1.0107	1.003	1.0135	1.0068	1.0345
026_8261_00311200	Kidney	8261	RCC-AB	456	3.919417	0.288	0.72	0.73	0.765	0.8515	0.878	0.9287	0.8965	0.9174
026_618_00290300	Kidney	618	786-O	456	3.967789	0.657	0.719	0.822	0.8016	0.8829	0.898	1.0239	0.917	1.0472
026_625_00290670	Kidney	625	UO-31	456	3.998088	0.662	0.756	0.767	0.9002	0.8304	0.876	0.9012	1.0588	1.1507
026_8096_00290860	Kidney	8096	LB2241-RCC	456	3.99857	0.643	0.686	0.74	0.8137	0.8533	0.902	0.9235	0.9107	0.9322
026_614_00291210	Kidney	614	SW 156	456	4.137243	0.651	0.665	0.71	0.7683	0.8365	0.896	0.903	0.9074	0.9013
026_8249_00295560	Kidney	8249	NCC021	456	4.201277	0.701	0.897	0.903	0.9199	0.9735	0.942	0.9933	1.0276	1.0113
026_633_00290250	Kidney	633	KMRC-20	456	4.24311	0.713	0.872	0.83	0.9644	0.8737	1.135	1.027	1.0923	1.0373
026_8068_00290231	Kidney	8068	HA7-RCC	456	4.403879	0.761	0.764	0.7	0.8322	0.7944	0.89	1.0474	1.1224	1.0563
026_8095_00290260	Kidney	8095	LB1047-RCC	456	4.460236	0.772	0.824	0.914	1.0356	1.0154	1.004	1.0739	1.1192	1.1745
026_626_00258890	Kidney	626	BFTC-909	456	4.464205	0.741	0.932	1.057	1.0395	1.0888	1.03	1.0217	1.0625	1.0049
026_8147_00290270	Kidney	8147	OS-RC-2	456	4.480976	0.767	0.794	0.799	0.8302	0.9419	1.023	1.0718	1.0847	1.1694
026_8013_00290220	Kidney	8013	BB65-RCC	456	4.50555	0.714	0.769	0.765	0.8909	0.8509	0.865	0.9509	1.0096	0.903
026_8006_00293300	Kidney	8006	A704	456	4.630889	0.755	0.917	0.918	0.9328	0.9788	1.112	0.981	0.9813	1.0413
026_637_00290240	Kidney	637	KMRC-1	456	4.786417	0.748	0.889	0.97	0.9322	0.836	1.012	1.0239	0.9503	1.088
026_624_00290320	Kidney	624	Caki-1	456	4.808296	0.821	0.803	0.908	0.9738	0.9722	1.083	1.1676	1.1464	1.1228
026_8266_00290640	Kidney	8266	RCC-MF	456	4.811179	0.754	0.903	0.819	0.8455	0.8764	0.999	0.9885	0.935	1.1762
026_620_00288170	Kidney	620	G-402	456	4.865533	0.694	0.721	0.686	0.7919	0.7766	0.804	0.8404	0.885	0.9093
026_8152_00293381	Kidney	8152	RCC10RGB	456	5.110675	0.821	0.719	0.783	0.9032	0.8829	0.858	0.8991	0.9287	1.0343
026_640_00291220	Kidney	640	VMRC-RCW	456	5.287926	0.73	0.737	0.793	0.8088	0.8744	0.905	0.9003	0.9127	0.9163
026_8102_00293360	Kidney	8102	LB996-RCC	456	5.484542	0.855	0.901	0.954	0.9116	0.9754	0.98	0.958	0.9786	0.9921

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_1119_00290901	Kidney	1119	SN-12C	456	5.586587	0.818	0.749	0.747	0.783	0.8058	0.856	0.9038	0.9508	0.9573
026_626_00290810	Kidney	626	BFTC-909	456	5.753321	0.799	0.854	0.903	0.9293	0.9289	0.92	0.9333	0.9322	0.9535
026_8005_00266530	Kidney	8005	A498	456	5.843211	0.594	0.917	1.009	1.0079	0.9307	0.996	1.0002	1.0033	0.9941
026_8157_00296471	Kidney	8157	RXF393	456	6.166218	0.853	0.878	0.91	0.8924	0.9071	0.932	0.9081	0.9505	0.9889
026_8102_00253000	Kidney	8102	LB996-RCC	456	6.306723	0.959	0.873	0.878	0.9741	0.9596	1.025	0.9525	0.9849	0.9931
026_8006_00263880	Kidney	8006	A704	456	6.969306	1.351	0.929	1.157	0.9881	1.0206	0.957	1.0009	0.9583	0.9931
026_8152_00256190	Kidney	8152	RCC10RGB	456	7.15535	1.178	0.835	1.176	0.846	0.8683	1.123	1.1733	1.1056	1.0876
026_8005_00296380	Kidney	8005	A498	456	8.190783	1.022	1.025	1.024	1.0158	1.03	1.032	1.0128	1.0239	1.0104
026_233_00277420	Leukemia	233	SIG-M5	456	−5.883853	0.228	0.243	0.233	0.2401	0.2362	0.247	0.2641	0.2732	0.4405
026_217_00277380	Leukemia	217	OCI-AML2	456	−1.42786	0.09	0.102	0.106	0.1256	0.1044	0.132	0.3277	0.8333	0.8618
026_179_00314500	Leukemia	179	KMOE-2	456	−0.249088	0.13	0.135	0.138	0.1591	0.3658	0.608	0.865	0.8967	1.0615
026_214_00285590	Leukemia	214	NB-4	456	−0.011745	0.18	0.323	0.315	0.3611	0.4215	0.592	0.8144	0.8865	0.9464
026_168_00280410	Leukemia	168	JURL-MK1	456	0.181843	0.145	0.179	0.186	0.2526	0.4638	0.727	0.9379	0.904	0.9907
026_194_00280680	Leukemia	194	ML-2	456	0.294246	0.418	0.395	0.379	0.4439	0.4739	0.633	0.7874	0.8519	1.0223
026_186_00280670	Leukemia	186	LAMA-84	456	0.295979	0.152	0.15	0.191	0.3623	0.6147	0.774	0.777	0.8716	0.8816
026_234_00314650	Leukemia	234	SKM-1	456	0.349518	0.37	0.347	0.369	0.4439	0.4995	0.57	0.729	0.9566	1.2103
026_221_00280300	Leukemia	221	OCI-M1	456	0.656393	0.183	0.235	0.344	0.5052	0.5942	0.759	0.8267	0.8418	1.1212
026_260_00280430	Leukemia	260	KO52	456	0.674413	0.348	0.376	0.357	0.3446	0.4195	0.753	0.7217	0.7637	1.0996
026_45_00274530	Leukemia	45	HL-60	456	0.756274	0.344	0.389	0.403	0.4669	0.6154	0.78	0.9211	0.9579	1.0107
026_218_00279140	Leukemia	218	OCI-AML3	456	0.868641	0.368	0.38	0.401	0.4571	0.5459	0.76	0.8359	0.9311	0.9403
026_219_00280290	Leukemia	219	OCI-AML5	456	0.879404	0.245	0.404	0.427	0.4943	0.686	0.712	0.8112	0.9498	0.9021
026_199_00314510	Leukemia	199	MOLT-13	456	0.892109	0.227	0.339	0.454	0.5097	0.5774	0.766	0.8101	0.9633	1.1416
026_226_00280310	Leukemia	226	PL-21	456	0.938066	0.406	0.425	0.463	0.4834	0.537	0.657	0.7338	0.7978	0.8482
026_8141_00274380	Leukemia	8141	NOMO-1	456	1.040856	0.375	0.445	0.435	0.4798	0.5465	0.636	0.9597	0.9214	0.9288
026_8069_00279180	Leukemia	8069	HAL-01	456	1.147185	0.349	0.345	0.454	0.634	0.6764	1.103	0.7322	0.8261	1.0097
026_68_00273640	Leukemia	68	MV-4-11	456	1.155322	0.061	0.367	0.445	0.5488	0.6586	0.777	0.8697	0.9167	1.045
026_175_00282940	Leukemia	175	KARPAS-620	456	1.190853	0.562	0.517	0.444	0.6051	0.7411	0.916	0.9551	1.1003	1.0193
026_89_00278880	Leukemia	89	MEG-01	456	1.211836	0.223	0.376	0.433	0.6062	0.6931	0.86	0.9075	0.9993	1.0376
026_8017_00279150	Leukemia	8017	BV-173	456	1.464827	0.147	0.454	0.57	0.8503	0.5534	0.638	0.7679	0.8629	1.0089
026_225_00277400	Leukemia	225	PF-382	456	1.646942	0.317	0.403	0.525	0.6985	0.7396	0.932	0.9611	0.9018	1.0833
026_285_00282960	Leukemia	285	KY821A3	456	1.656661	0.422	0.426	0.445	0.6672	0.7837	0.935	1.0015	1.0293	1.0583
026_8008_00280620	Leukemia	8008	ALL-PO	456	1.659142	0.143	0.469	0.549	0.6225	0.6911	0.725	0.845	0.8482	1.019
026_177_00276860	Leukemia	177	KE-37	456	1.711407	0.195	0.451	0.523	0.6745	0.9068	0.897	0.9087	0.9169	1.0477
026_126_00280270	Leukemia	126	GDM-1	456	1.723253	0.297	0.444	0.595	0.682	0.7944	0.786	0.9053	0.9081	0.8666
026_261_00274440	Leukemia	261	MY-M12	456	1.811821	0.395	0.471	0.59	0.6443	0.7461	0.832	0.8778	1.0023	1.0569
026_201_00277390	Leukemia	201	MOLT-16	456	1.821177	0.276	0.43	0.578	0.7394	0.7801	0.857	0.9379	1.0322	0.9678
026_148_00277330	Leukemia	148	CMK	456	1.894859	0.275	0.484	0.637	0.6101	0.744	0.771	0.9002	0.8949	0.8668
026_28_00280320	Leukemia	28	SUP-B15	456	1.921651	0.261	0.506	0.579	0.7214	0.7165	0.82	0.908	0.9679	0.9913
026_190_00287920	Leukemia	190	ME-1	456	1.924633	0.611	0.596	0.587	0.5806	0.5987	0.684	0.7906	0.8581	0.9106
026_8150_00273700	Leukemia	8150	QIMR-WIL	456	1.928333	0.441	0.546	0.595	0.6574	0.7011	0.771	0.852	0.962	0.9148
026_8156_00273710	Leukemia	8156	RPMI-8866	456	1.939976	0.339	0.474	0.598	0.694	0.7428	0.867	0.9518	0.9936	0.9682
026_161_00277350	Leukemia	161	HC-1	456	1.948766	0.447	0.517	0.568	0.6165	0.6342	0.768	0.7642	0.9074	1.0155
026_195_00279120	Leukemia	195	MOLM-13	456	1.961596	0.394	0.455	0.518	0.6868	0.817	0.872	0.9157	0.983	1.0345
026_209_00279130	Leukemia	209	NALM-6	456	2.000316	0.14	0.471	0.592	0.6915	0.7587	0.808	0.8658	0.9205	0.9768
026_127_00278810	Leukemia	127	CESS	456	2.000616	0.342	0.505	0.625	0.6869	0.7679	0.843	0.9355	0.9565	0.9827
026_8196_00278790	Leukemia	8196	697	456	2.032634	0.337	0.476	0.617	0.7249	0.8167	0.885	1.0481	1.0695	1.0723
026_223_00276841	Leukemia	223	P12-ICHIKAWA	456	2.094412	0.266	0.472	0.62	1.0139	0.9551	0.864	0.9219	1.0283	0.907
026_157_00279291	Leukemia	157	DND-41	456	2.109279	0.354	0.498	0.624	0.7174	0.8189	0.89	0.9495	0.9928	1.0144
026_174_00276850	Leukemia	174	KARPAS-45	456	2.156973	0.368	0.541	0.63	0.778	0.8566	0.998	1.0142	0.9561	0.9985

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_223_00274461	Leukemia	223	P12-ICHIKAWA	456	2.170641	0.274	0.465	0.567	0.909	0.9914	1.041	1.0272	0.9908	1.0038
026_231_00277410	Leukemia	231	RPMI-8402	456	2.171412	0.292	0.525	0.673	0.8379	0.894	0.956	1.0525	1.0069	1.0163
026_176_00278840	Leukemia	176	KCL-22	456	2.178418	0.342	0.551	0.66	0.7185	0.7521	0.822	0.8942	1.034	0.9817
026_198_00279320	Leukemia	198	MOLP-8	456	2.182175	0.422	0.613	0.604	0.6789	0.7123	0.753	0.8469	0.8678	0.9555
026_35_00274541	Leukemia	35	MOLT-4	456	2.185513	0.368	0.518	0.657	0.7557	0.8266	0.893	0.9057	1.0649	1.0505
26_256_00273800	Leukemia	256	U266B1	456	2.191112	0.423	0.53	0.596	0.6351	0.7316	0.782	0.8701	0.9616	0.9089
026_41_00278850	Leukemia	41	KG-1	456	2.260524	0.445	0.507	0.569	0.7321	0.8443	0.89	0.9006	0.9237	0.9648
026_38_00278900	Leukemia	38	THP-1	456	2.296961	0.389	0.568	0.692	0.7667	0.7899	0.895	0.9332	0.9649	0.9902
026_153_00277340	Leukemia	153	CTV-1	456	2.301756	0.308	0.563	0.682	0.7882	0.8949	0.972	1.0362	1.0213	1.0568
26_284_00273770	Leukemia	284	KY821	456	2.31293	0.459	0.524	0.599	0.642	0.7677	0.831	0.9119	0.9596	0.9938
026_256_00304780	Leukemia	256	U266B1	456	2.374209	0.453	0.543	0.608	0.6629	0.7604	0.806	0.9117	0.9547	0.9487
026_8033_00279160	Leukemia	8033	DEL	456	2.390133	0.433	0.595	0.647	0.7617	0.7648	0.851	0.9096	0.9116	0.9641
026_227_00314640	Leukemia	227	RCH-ACV	456	2.405281	0.39	0.571	0.742	0.8517	0.9043	0.946	0.9917	1.0175	1.1197
026_33_00274521	Leukemia	33	CCRF-CEM	456	2.408403	0.354	0.606	0.685	0.7594	0.8191	0.904	0.9597	0.9629	1.0269
026_141_00276820	Leukemia	141	K-562	456	2.457405	0.51	0.504	0.624	0.8081	0.8379	1.163	0.9404	1.0057	1.0193
026_8137_00273680	Leukemia	8137	NKM-1	456	2.543263	0.464	0.601	0.622	0.6486	0.7425	0.801	0.8993	0.9038	0.9449
026_36_00274550	Leukemia	36	Reh	456	2.569808	0.418	0.628	0.742	0.8367	0.88	0.896	0.9262	0.8979	0.9849
026_8042_00285400	Leukemia	8042	EoL-1 -cell	456	2.64235	0.232	0.569	0.651	0.7409	0.7743	0.894	0.8333	0.905	0.9094
026_281_00273690	Leukemia	281	P30/OHK	456	2.804566	0.473	0.654	0.769	0.9121	0.8865	1.022	1.0746	1.0233	1.0407
026_59_00278820	Leukemia	59	J.RT3-T3.5	456	2.830428	0.457	0.659	0.795	0.8429	0.9259	1.002	1.0587	0.9873	1.1396
026_164_00277360	Leukemia	164	HEL	456	2.835925	0.426	0.745	0.939	0.9081	1.0194	0.987	1.0611	1.0159	0.9841
026_183_00277370	Leukemia	183	L-363	456	2.864138	0.468	0.685	0.82	0.9025	0.9548	1.046	1.0249	0.9812	1.02
026_90_00282840	Leukemia	90	KU812	456	2.874545	0.446	0.74	0.806	0.917	0.9589	0.978	0.9646	1.0111	1.0409
026_27_00278890	Leukemia	27	RS4; 11	456	2.914096	0.47	0.684	0.809	0.8895	0.9144	0.975	0.9547	0.9619	1.0194
026_167_00314490	Leukemia	167	JURKAT	456	2.954834	0.503	0.713	0.842	0.9399	0.9544	0.985	0.9987	1.034	1.0702
026_181_00278860	Leukemia	181	KOPN-8	456	2.957727	0.484	0.669	0.731	0.7843	0.8662	0.92	0.9473	0.9339	0.9555
026_8155_00309110	Leukemia	277	RPMI 8226	456	2.959542	0.648	0.63	0.689	0.8376	0.888	0.99	0.9938	1.0182	1.0157
026_8041_00280640	Leukemia	8041	EM-2	456	3.022652	0.557	0.687	0.614	0.634	0.706	0.679	0.8613	0.8617	1.9538
026_142_00279280	Leukemia	142	ALL-SIL	456	3.085854	0.187	0.624	0.769	0.7092	0.7975	0.937	0.9525	0.9717	0.8276
026_277_00280420	Leukemia	277	RPMI 8226	456	3.102844	0.659	0.636	0.566	0.6117	0.6594	0.722	0.8693	0.9508	0.9057
026_180_00279310	Leukemia	180	KMS-12-BM	456	3.125028	0.512	0.704	0.788	0.8503	0.8703	0.949	0.905	0.9806	0.9931
026_8066_00279170	Leukemia	8066	GR-ST	456	3.192114	0.532	0.681	0.762	0.8318	0.8448	0.865	1.0258	0.9609	0.9989
26_283_00273780	Leukemia	283	LC4-1	456	3.243599	0.592	0.732	0.916	0.9522	1.0268	1.078	0.9517	1.0295	1.0135
026_114_00273650	Leukemia	114	SUP-T1	456	3.397019	0.637	0.807	0.908	1.0154	0.984	1.031	0.99	0.9877	1.0134
026_138_00287901	Leukemia	138	Loucy	456	3.501279	0.289	0.749	0.772	0.942	0.9225	0.948	0.9678	0.9653	1.0654
026_8014_00282911	Leukemia	8014	BE-13	456	3.615529	0.68	0.757	0.965	1.1246	1.0528	1.075	1.0884	1.0694	1.1037
26_274_00273860	Leukemia	274	BALL-1	456	3.704228	0.65	0.709	0.777	0.8768	0.9725	0.983	0.9819	0.9839	0.9978
026_222_00280480	Leukemia	222	OPM-2	456	3.757754	0.681	0.619	0.771	0.9443	0.8789	1.073	0.9014	0.9191	0.9051
026_8164_00283540	Leukemia	8164	SK-MM-2	456	3.790344	0.669	0.788	0.861	0.8903	0.938	0.941	1.0087	0.9277	0.9972
026_166_00278830	Leukemia	166	JJN-3	456	3.901981	0.636	0.791	0.85	0.8566	0.8711	0.916	0.9455	0.9892	1.057
026_230_00282970	Leukemia	230	ROS-50	456	4.130585	0.741	0.775	0.805	0.9413	0.9813	1.11	1.1334	1.0559	0.999
026_159_00314480	Leukemia	159	EJM	456	4.251735	0.714	0.845	0.899	0.9099	1.0285	0.923	1.0677	1.0768	1.0543
026_278_00304730	Leukemia	278	KMS-12-PE	456	4.269602	0.765	0.814	0.84	1.0641	0.988	1.023	1.0045	1.0284	1.0665
026_8219_00282850	Leukemia	8219	Mo-T	456	4.313664	0.73	0.825	0.804	0.9425	0.9233	1.033	0.8454	1.1551	1.0561
026_279_00274450	Leukemia	279	P31/FUJ	456	4.386897	0.705	0.805	0.799	0.819	0.8632	1.043	1.0364	0.9822	1.0363
026_171_00285190	Leukemia	171	KARPAS-231	456	4.404825	0.703	0.9	0.906	0.9339	0.9295	0.904	0.9725	0.9496	0.9164
026_244_00273660	Leukemia	244	TALL-1	456	4.411016	0.698	0.758	0.785	0.8345	0.8593	0.861	1.0445	1.0026	1.0194
026_158_00291340	Leukemia	158	EHEB	456	4.509743	0.665	0.745	0.765	0.7841	0.8282	0.839	0.92	0.9348	1.0344
026_134_00278800	Leukemia	134	ARH-77	456	4.545002	0.781	0.856	0.96	0.848	1.0568	1.029	1.0104	1.0156	1.0086

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_246_00273670	Leukemia	246	U-698-M	456	4.580953	0.754	0.891	0.936	0.9419	0.9607	0.937	1.032	0.9352	1.0229
026_8113_00280440	Leukemia	8113	MHH-CALL-2	456	4.648418	0.771	0.883	0.929	0.9704	0.9337	0.987	1.0345	1.0223	1.0471
026_159_00311690	Leukemia	159	EJM	456	4.699945	0.746	0.894	0.921	0.9275	0.9393	0.941	0.9575	0.9338	0.9675
026_159_00282920	Leukemia	159	EJM	456	4.832393	0.746	0.976	1.016	0.9859	1.0015	1.002	1.1587	1.1041	1.0548
026_8115_00280450	Leukemia	8115	MN-60	456	4.861437	0.826	0.804	0.822	1.0586	0.9555	0.947	1.0471	1.128	1.0314
026_204_00280460	Leukemia	204	MONO-MAC-6	456	4.946039	0.736	0.802	0.771	0.8409	0.8712	0.833	0.8634	1.0677	0.855
026_8117_00280470	Leukemia	8117	MUTZ-1	456	5.304526	0.823	0.984	1.063	1.051	1.0142	1.007	0.9986	0.9654	0.9525
026_188_00282930	Leukemia	188	LP-1	456	5.373997	0.831	0.887	0.972	0.8808	0.9105	0.886	0.9533	0.9576	1.138
026_8081_00285580	Leukemia	8081	JVM-3	456	5.581328	0.884	0.904	0.907	0.9131	1.01	1.097	1.0593	0.9629	1.0333
026_159_00309070	Leukemia	159	EJM	456	5.810283	0.882	0.986	0.998	1.0992	1.0048	1.045	1.0126	1.024	1.0649
026_8080_00280660	Leukemia	8080	JVM-2	456	5.982881	0.867	0.876	0.901	0.8865	0.9235	0.909	0.9782	0.8964	0.9789
026_278_00306920	Leukemia	278	KMS-12-PE	456	6.629507	0.971	0.92	0.95	0.9554	0.9046	0.905	0.9657	1.0243	0.9236
026_8010_00280630	Leukemia	8010	ATN-1	456	7.14863	1.03	0.958	0.835	0.8896	0.8651	0.907	0.9392	0.8582	0.9763
26_262_00273790	Leukemia	262	MLMA	456	7.68552	0.485	1.033	1.077	1.0216	1.0341	0.962	1.0378	0.9821	1.0245
026_278_00282950	Leukemia	278	KMS-12-PE	456	7.74945	0.958	1.101	1.04	1.1177	1.0046	1.029	1.0272	1.0311	1.0037
026_649_00264910	Liver	649	Hep 3B2.1-7	456	−0.30042	0.134	0.098	0.087	0.1121	0.2203	0.601	0.8432	0.8926	0.9089
026_658_00262810	Liver	658	JHH-1	456	−0.185127	0.054	0.329	0.515	0.3993	0.5194	0.524	0.6608	0.6499	0.6863
026_649_00266180	Liver	649	Hep 3B2.1-7	456	−0.037335	0.073	0.105	0.093	0.0908	0.1037	0.202	0.8123	0.9207	1.007
026_667_00273550	Liver	667	HuH-7	456	1.289162	0.279	0.565	0.539	0.5535	0.7134	0.77	0.8626	0.9675	0.9662
026_659_00255780	Liver	659	JHH-2	456	1.758427	0.283	0.473	0.657	0.7149	0.551	0.819	0.8858	0.8891	1.0202
026_643_00266460	Liver	643	SNU-398	456	2.578054	0.415	0.687	0.643	0.6854	0.6879	0.717	0.7896	0.8076	0.9193
026_667_00269210	Liver	667	HuH-7	456	2.760591	0.501	0.59	0.665	0.6852	0.6886	0.781	0.95	1.0287	1.0142
026_647_00269110	Liver	647	SNU-387	456	2.930627	0.494	0.772	0.829	0.9402	0.9686	1.046	1.0372	1.0223	1.2144
026_661_00252500	Liver	661	JHH-7	456	3.286573	0.539	0.889	0.794	0.8777	1.0776	0.953	0.9918	1.037	0.9476
026_643_00263980	Liver	643	SNU-398	456	3.293137	0.487	0.768	0.854	0.8235	0.8763	0.883	0.9616	1.068	1.0718
026_642_00308440	Liver	642	C3A	456	3.554832	0.587	0.68	0.706	0.7687	0.817	0.878	0.9697	0.9574	0.9245
026_648_00258350	Liver	648	SNU-423	456	3.576003	0.139	0.699	0.902	0.9157	0.9485	0.909	0.9218	0.9469	1.0028
026_656_00252510	Liver	656	JHH-4	456	3.61979	0.701	0.653	0.631	0.8187	0.7968	0.977	0.9161	0.9897	0.9288
026_660_00252490	Liver	660	JHH-6	456	3.831185	0.696	0.88	1.034	0.9294	0.9465	1.04	0.9417	1.0528	0.952
026_644_00252750	Liver	644	SNU-449	456	4.40481	0.664	0.733	0.764	0.7954	0.8597	0.896	0.9485	0.9457	0.9162
026_644_00306170	Liver	644	SNU-449	456	6.450644	0.96	0.961	0.745	1.0716	1.0197	1.08	0.991	0.9007	0.9369
26_646_00314060	Liver	646	SNU-475	456	6.501654	0.181	0.97	0.971	0.9863	1.0061	1.007	1.0271	1.0202	0.057
026_654_00255800	Liver	654	SK-HEP-1	456	6.515068	0.927	0.956	0.961	0.9827	0.9589	0.98	0.9783	0.9726	0.9998
026_668_00252690	Liver	668	HLE	456	7.25378	0.434	1.006	1.087	0.9897	1.1103	0.964	1.006	1.106	0.9541
026_662_00252460	Liver	662	huH-1	456	7.722693	0.466	1.165	1.072	1.0401	1.0408	1.136	1.015	1.123	0.9778
026_645_00306160	Liver	645	SNU-182	456	7.852049	1.105	1.061	1.063	1.0055	1.0268	1.053	1.0365	1.0318	1.0842
026_642_00252670	Liver	642	C3A	456	7.864415	0.386	1.1	1.007	1.108	0.9463	1.051	0.9803	1.029	0.9218
026_830_00304760	Lung	830	NCI-H2135	456	−0.374655	0.298	0.262	0.246	0.3049	0.3692	0.528	0.7269	0.8905	0.977
026_698_00300170	Lung	698	NCI-H524	456	2.279246	0.443	0.506	0.63	0.8741	0.9302	1.005	1.0131	1.0304	1.0567
026_672_00314460	Lung	672	NCI-H510A	456	2.367223	0.323	0.585	0.763	0.783	0.8906	0.969	0.9972	1.1809	1.0131
026_761_00300410	Lung	761	COR-L279	456	3.131703	0.559	0.745	0.868	0.9821	1.0079	1.06	1.0144	1.0182	1.0709
026_726_00304770	Lung	726	NCI-H2171	456	3.185965	0.524	0.729	0.842	0.8655	0.9088	0.871	1.0252	0.9207	1.129
026_740_00302760	Lung	740	NCI-H82	456	3.210581	0.542	0.755	0.865	0.9592	1.0522	0.888	0.9137	1.004	1.0151
026_787_00302910	Lung	787	SBC-3	456	3.410219	0.582	0.655	0.694	0.802	0.8502	0.902	0.9485	0.9451	0.9885
026_695_00300150	Lung	695	NCI-H211	456	3.515811	0.644	0.645	0.719	0.8327	0.8177	0.933	0.9519	0.9812	1.0305
026_721_00302860	Lung	721	NCI-H2029	456	3.591515	0.606	0.8	0.891	0.9011	0.8579	0.931	0.9429	1.0032	1.0011
026_776_00303250	Lung	776	MS-1-L	456	3.614256	0.642	0.767	0.855	0.8458	1.1115	0.929	1.0414	1.0285	1.162
026_8197_00304741	Lung	8197	LU-139	456	3.667637	0.66	0.84	0.901	1.0158	0.9097	0.912	1.0844	1.1048	1.0641
026_702_00302900	Lung	702	NCI-H847	456	3.686524	0.818	0.707	0.668	0.6815	0.7184	0.743	0.7999	0.9145	0.9524

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_8203_00309050	Lung	8203	IST-SL1	456	3.697133	0.635	0.801	0.87	0.931	0.9112	1	1.0127	0.9507	1.0704
026_724_00300140	Lung	724	NCI-H2081	456	3.857634	0.623	0.866	0.895	0.9027	0.9349	0.948	0.969	0.9681	1.0072
026_765_00300050	Lung	765	DMS 273	456	3.890251	0.702	0.844	0.904	0.9648	1.028	0.968	1.0795	1.0165	1.0825
026_829_00305160	Lung	829	NCI-H2110	456	3.972695	0.67	0.694	0.776	0.8765	0.8765	0.946	1.0573	0.91	0.9398
026_742_00303230	Lung	742	DMS 53	456	3.990104	0.711	0.802	0.867	0.9734	1.0075	1.037	1.0307	1.0204	1.0405
026_710_00316710	Lung	710	NCI-H1341	456	4.024081	0.591	0.852	0.7	0.7407	0.8259	0.789	0.8069	0.8386	0.865
026_738_00302800	Lung	738	NCI-H446	456	4.043153	0.692	0.871	0.917	1.0421	0.9341	0.915	1.0657	0.9649	1.0382
026_751_00308570	Lung	751	NCI-H209	456	4.061511	0.657	0.848	0.89	0.9403	0.8939	0.91	0.9316	0.9524	0.9513
026_716_00298900	Lung	716	NCI-H1876	456	4.083964	0.744	0.866	0.936	0.9448	0.9881	0.979	0.9782	0.9994	1.0261
026_725_00303280	Lung	725	NCI-H2141	456	4.09696	0.711	0.842	0.928	0.9702	0.9155	0.924	1.0044	1.0101	0.9559
026_688_00302810	Lung	688	SW 1271	456	4.124557	0.602	0.761	0.79	0.8093	0.807	0.823	0.896	0.8782	0.9341
026_720_00302380	Lung	720	NCI-H1994	456	4.130367	0.696	0.694	0.73	0.8114	0.9245	0.935	0.9484	0.9393	0.9738
026_811_00311720	Lung	811	NCI-H1435	456	4.138326	0.635	0.803	0.855	0.8503	0.8571	0.89	0.8912	0.955	0.9956
026_704_00300250	Lung	704	NCI-H1048	456	4.178908	0.166	0.762	0.867	0.8914	0.9318	0.923	0.9201	1.0122	0.9635
026_746_00302780	Lung	746	SHP-77	456	4.20487	0.79	0.843	0.955	1.029	0.9896	1.021	1.0111	0.9931	1.0025
026_829_00311740	Lung	829	NCI-H2110	456	4.22315	0.739	0.83	0.914	0.9675	0.9597	0.983	0.9791	1.032	0.9995
026_736_00300181	Lung	736	NCI-H69	456	4.26966	0.798	0.87	0.945	1.0535	1.0472	1.143	1.0521	1.0846	1.1743
026_724_00303270	Lung	724	NCI-H2081	456	4.274134	0.708	0.95	1.023	0.9666	1.0134	0.99	1.0037	1.0388	1.0531
026_714_00300260	Lung	714	NCI-H1694	456	4.276996	0.701	0.831	0.843	0.8708	0.9426	0.93	0.9095	1.1071	1.0848
026_715_00298890	Lung	715	NCI-H1836	456	4.291554	0.73	0.833	0.997	0.9315	0.9434	0.955	0.9291	0.9423	1
026_757_00302870	Lung	757	CPC-N	456	4.345126	0.718	0.819	0.887	0.8883	0.9167	0.938	0.9641	1.0154	1.0153
026_8229_00304990	Lung	8229	COR-L303	456	4.468573	0.685	0.828	0.788	0.868	0.6881	0.855	0.9579	0.8466	0.9772
026_691_00308560	Lung	691	NCI-H526	456	4.602758	0.748	0.932	0.944	0.9861	0.9744	0.954	1.0035	1.0955	1.0007
026_8099_00316740	Lung	8099	LB647-SCLC	456	4.613258	0.755	0.954	0.998	0.9372	0.957	1.041	1.0171	1.0259	0.9506
026_725_00302750	Lung	725	NCI-H2141	456	4.618451	0.747	0.869	0.906	0.9009	0.9283	0.901	1.003	0.9238	1.1424
026_705_00314520	Lung	705	NCI-H1092	456	4.678169	0.77	0.861	0.911	1.02	0.9158	1.082	0.9997	0.9139	0.961
026_684_00303260	Lung	684	NCI-H1688	456	4.865947	0.832	0.831	0.988	1.0672	0.9906	1.099	1.0391	1.0378	1.0698
026_725_00300160	Lung	725	NCI-H2141	456	4.894458	0.785	0.908	0.936	0.9468	0.9309	0.94	0.9635	1.0477	0.9963
026_8281_00300930	Lung	8281	COR-L311	456	5.024667	0.792	0.892	0.947	0.9155	0.8604	0.871	1.0268	1.0989	1.045
026_757_00300940	Lung	757	CPC-N	456	5.046784	0.796	0.904	0.984	1.0041	1.0137	0.919	0.905	0.9063	1.0167
026_701_00309060	Lung	701	NCI-H841	456	5.157768	0.826	0.808	0.939	0.891	0.8811	0.919	0.9514	1.0474	1.0933
026_814_00304750	Lung	814	NCI-H1568	456	5.159278	0.784	0.726	0.739	0.745	0.7127	0.774	0.9411	0.9	0.9817
026_741_00305010	Lung	741	NCI-H345	456	5.184481	0.801	0.818	0.835	0.9503	0.9116	0.894	0.8849	0.9853	1.083
026_705_00311700	Lung	705	NCI-H1092	456	5.191642	0.849	0.892	0.945	1.0426	0.9184	0.981	1.0366	1.0158	1.0581
026_786_00300950	Lung	786	SBC-5	456	5.281883	0.841	1.002	0.991	1.0148	0.9974	0.998	1.0298	1.0075	1.0015
026_723_00316720	Lung	723	NCI-H2066	456	5.313778	0.793	0.815	0.866	0.86	0.9117	0.892	0.9084	0.923	0.9757
026_705_00309080	Lung	705	NCI-H1092	456	5.329516	0.829	0.941	0.999	0.9672	0.8963	0.935	0.9991	0.9888	1.0506
026_709_00305000	Lung	709	NCI-H1304	456	5.330039	0.838	0.882	0.906	0.8939	0.9384	0.978	1.0127	1.0322	1.0575
026_739_00314630	Lung	739	NCI-H146	456	5.38813	0.858	0.893	0.978	1.0115	1.0583	0.937	0.9685	1.0018	1.0831
026_8110_00314450	Lung	8110	LU-165	456	5.539798	0.87	0.909	0.986	0.9964	0.9809	1.094	0.9305	0.9513	1.1416
026_811_00305140	Lung	811	NCI-H1435	456	5.586661	0.886	0.953	0.978	0.9914	1.0102	0.994	0.9871	0.9783	0.9731
026_711_00311710	Lung	711	NCI-H1417	456	5.606717	0.875	0.91	0.911	0.9612	1.0374	0.917	1.267	1.0195	0.9447
026_712_00309090	Lung	712	NCI-H1436	456	5.636542	0.85	0.918	0.976	0.9527	0.9331	0.932	0.9583	0.9477	1.0343
026_711_00305130	Lung	711	NCI-H1417	456	5.804325	0.849	1.022	0.916	0.9247	0.9771	0.939	0.9326	1.0168	1.0143
026_728_00311760	Lung	728	NCI-H2196	456	5.845371	0.89	0.908	0.918	0.9801	0.875	1.033	0.9519	0.931	1.0431
026_831_00311750	Lung	831	NCI-H2172	456	5.851811	0.879	0.986	1.002	0.9709	0.9562	0.984	0.9781	1.0144	0.974
026_1216_00300060	Lung	1216	H292	456	5.909493	0.869	0.823	0.808	0.8192	0.8429	0.864	0.9245	0.9789	1.0777
026_8109_00314440	Lung	8109	LU-134-A	456	5.930549	0.868	0.95	0.972	0.9375	0.9332	0.959	0.9516	1.1207	1.1025
026_831_00305170	Lung	831	NCI-H2172	456	6.053261	0.837	0.856	0.908	0.8908	0.9397	0.905	0.9677	0.9512	0.9839

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_728_00305180	Lung	728	NCI-H2196	456	6.171009	0.9	0.903	0.976	0.9979	0.9199	0.928	0.9453	0.9369	0.941
026_689_00300910	Lung	689	NCI-H187	456	6.191556	0.887	1.009	0.976	0.9779	0.9535	1.047	1.021	1.0846	0.959
026_785_00302770	Lung	785	SBC-1	456	6.234067	0.875	1.037	1.061	0.9376	1.0385	0.937	0.9403	1.0039	1.1602
026_8280_00306910	Lung	8280	COR-L321	456	6.254083	0.965	0.937	1.019	0.8492	0.948	1.048	1.0366	1.0761	0.9586
026_706_00318720	Lung	706	NCI-H1105	456	6.355	0.897	0.965	1.009	0.9821	0.9646	1.037	0.9974	0.9667	0.9589
026_712_00305150	Lung	712	NCI-H1436	456	6.498513	0.959	0.818	0.938	1.1033	0.9924	0.922	1.0128	1.0035	0.9263
026_8079_00306720	Lung	8079	IST-SL2	456	6.56418	0.947	0.972	0.935	0.9658	0.9445	0.966	0.9554	1.0191	1.0006
026_743_00303220	Lung	743	DMS 114	456	6.614771	0.862	0.853	0.785	0.7831	0.861	0.851	0.8815	0.9129	1.0374
026_8022_00306711	Lung	8022	COLO-668	456	6.912523	0.97	0.968	0.956	1	0.9608	0.917	1.0093	0.9217	0.9308
026_8109_00308510	Lung	8109	LU-134-A	456	6.98132	0.924	1.012	1.105	0.9946	0.9684	1.081	0.9878	0.9397	0.9606
026_758_00303240	Lung	758	HCC-33	456	7.022636	0.931	1.056	1.002	1.0822	1.0508	1.011	1.0081	1.1612	1.1932
026_771_00306940	Lung	771	Lu-135	456	7.040802	0.988	0.969	0.972	1.0271	0.9989	1.006	0.993	1.0649	1.0235
026_694_00302790	Lung	694	NCI-H196	456	7.041262	0.976	0.954	0.975	0.9548	0.9357	0.922	0.9564	0.9433	1.019
026_764_00308550	Lung	764	COR-L95	456	7.251052	0.978	1.021	0.944	1.002	1.0708	0.947	0.9637	0.9383	0.903
026_763_00300900	Lung	763	COR-L88	456	7.365052	0.96	1.168	0.891	1.1434	1.1503	0.976	1.0066	1.0636	1.052
026_8134_00306730	Lung	8134	NCI-H64	456	7.782872	1.026	1.003	0.976	1.0025	0.951	1.047	0.9338	0.8997	1.0076
026_712_00311730	Lung	712	NCI-H1436	456	7.804947	1.019	1.049	0.947	0.9403	0.9104	0.931	0.9349	0.9472	0.9659
026_8018_00304801	Lung: NSCLC	8018	Calu-6	456	−0.899538	0.106	0.165	0.183	0.2075	0.2699	0.394	0.8182	0.9121	1.0531
026_1246_00304570	Lung: NSCLC	1246	NCI-H1770	456	−0.072444	0.109	0.175	0.267	0.3543	0.4184	0.552	0.6475	1.0183	0.9838
026_847_00304580	Lung: NSCLC	847	NCI-H2087	456	1.048994	0.368	0.402	0.458	0.4756	0.5065	0.683	0.7888	0.9774	0.9846
026_680_00298830	Lung: NSCLC	680	NCI-H727	456	1.334143	0.329	0.434	0.475	0.4492	0.5064	0.604	0.8522	0.9134	0.98
026_748_00304590	Lung: NSCLC	748	NCI-H226	456	1.690128	0.342	0.457	0.514	0.5901	0.7687	0.757	0.7854	1.0039	0.932
026_851_00298380	Lung: NSCLC	851	CAL-12T	456	1.708943	0.452	0.449	0.49	0.5839	0.7337	0.842	0.9205	0.938	0.9948
026_861_00300230	Lung: NSCLC	861	LCLC-97TM1	456	2.249036	0.424	0.573	0.622	0.7209	0.7517	0.873	1.0412	0.9724	0.974
026_1245_00304550	Lung: NSCLC	1245	NCI-H1648	456	2.511131	0.507	0.571	0.662	0.5623	0.7611	0.961	1.0696	1.0483	1.4204
026_1180_00308140	Lung: NSCLC	1180	NCI-H3122	456	2.550953	0.534	0.517	0.616	0.6044	0.7162	0.883	0.9512	0.9659	0.9657
026_802_00298451	Lung: NSCLC	802	NCI-H358	456	2.662533	0.509	0.53	0.626	0.7229	0.8072	0.806	0.8743	0.9218	0.9534
026_815_00311140	Lung: NSCLC	815	NCI-H1623	456	2.802368	0.523	0.592	0.685	0.6168	0.6264	0.746	0.872	0.8493	1.0805
026_1180_00302350	Lung: NSCLC	1180	NCI-H3122	456	2.945291	0.724	0.649	0.605	0.75	0.7455	0.913	0.9083	1.0538	1.1763
026_8040_00304501	Lung: NSCLC	8040	EKVX	456	3.134434	0.532	0.642	0.782	0.752	0.7074	0.804	0.9087	1.0521	1.0032
026_865_00308451	Lung: NSCLC	865	COR-L23	456	3.225036	0.58	0.657	0.735	0.83	0.9489	0.935	1.0144	1.0355	1.0002
026_1243_00304541	Lung: NSCLC	1243	NCI-H1395	456	3.23207	0.553	0.739	0.944	0.948	0.9289	0.926	0.9919	1.0441	1.1113
026_884_00308160	Lung: NSCLC	884	RERF-LC-MS	456	3.239905	0.585	0.663	0.662	0.6574	0.7423	0.886	0.9636	0.9621	0.9957
026_796_00295871	Lung: NSCLC	796	NCI-H2009	456	3.244878	0.582	0.62	0.631	0.635	0.7036	0.747	0.8586	0.9443	0.9943
026_799_00295880	Lung: NSCLC	799	NCI-H661	456	3.295179	0.667	0.587	0.685	0.6862	0.8151	0.782	1.0055	0.9053	0.9863
026_822_00311150	Lung: NSCLC	822	NCI-H1869	456	3.570833	0.153	0.716	0.736	0.7399	0.8095	0.819	1.026	0.9674	1.0055
026_756_00302670	Lung: NSCLC	756	BEN	456	3.65632	0.639	0.833	0.942	0.9322	0.9128	0.965	0.9486	1.0116	1.0192
026_876_00299781	Lung: NSCLC	876	LU65	456	3.69068	0.635	0.695	0.704	0.7208	0.8211	0.878	0.9851	1.0211	1.0551
026_805_00304531	Lung: NSCLC	805	NCI-H1155	456	3.716538	0.61	0.788	0.787	0.8467	0.9573	0.91	0.953	1.0683	1.0508
026_834_00304610	Lung: NSCLC	834	NCI-H2347	456	3.72347	0.653	0.736	0.756	0.8026	0.8524	0.984	0.9516	1.2251	1.0554
026_822_00304840	Lung: NSCLC	822	NCI-H1869	456	3.749478	0.594	0.736	0.791	0.7802	0.8592	0.824	0.8872	0.9703	1.0592
026_835_00302390	Lung: NSCLC	835	NCI-H2405	456	3.789193	0.693	0.659	0.651	0.6574	0.7337	0.768	0.8849	0.9046	1.0375
026_678_00304981	Lung: NSCLC	678	UMC-11	456	3.815948	0.655	0.751	0.848	0.8851	0.9411	1.013	0.9806	1.0842	1.1132
026_807_00314280	Lung: NSCLC	807	NCI-H650	456	3.884087	0.604	0.778	0.772	0.8577	0.8346	0.815	1.0068	0.831	0.9772
026_871_00299771	Lung: NSCLC	871	LK-2	456	3.898613	0.684	0.806	0.903	0.9071	0.958	1.018	0.9981	1.0604	1.0786
026_1249_00308150	Lung: NSCLC	1249	NCI-H720	456	3.907633	0.632	0.829	0.932	1.0847	1.526	0.799	0.8751	1.2042	1.1215
026_8231_00304510	Lung: NSCLC	8231	EMC-BAC-1	456	3.943946	0.675	0.713	0.751	0.8781	0.831	0.931	0.976	1.0569	1.0459
026_820_00304560	Lung: NSCLC	820	NCI-H1755	456	3.964037	0.658	0.769	0.785	0.8744	0.8799	0.931	0.9563	1.1261	1.0206
026_815_00304830	Lung: NSCLC	815	NCI-H1623	456	3.981628	0.646	0.709	0.712	0.7108	0.8124	0.879	0.7844	1.0245	1.0786

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_839_00302410	Lung: NSCLC	839	SW 900	456	3.982367	0.65	0.725	0.782	0.8242	0.8576	0.897	0.9535	1.0086	0.9978
026_804_00308480	Lung: NSCLC	804	NCI-H810	456	4.03318	0.731	0.763	0.91	0.9442	0.9087	1.003	0.9482	0.9716	1.0139
026_678_00309011	Lung: NSCLC	678	UMC-11	456	4.0744	0.514	0.846	0.86	0.931	0.9037	0.925	0.9312	0.9354	1.0786
026_842_00298540	Lung: NSCLC	842	NCI-H520	456	4.082969	0.729	0.811	0.916	1.0516	1.0142	1.002	1.0457	1.0025	0.9761
026_824_00314260	Lung: NSCLC	824	NCI-H1944	456	4.107799	0.695	0.731	0.691	0.7704	0.893	0.886	0.905	0.9791	1.0866
026_888_00298370	Lung: NSCLC	888	ABC-1	456	4.123019	0.64	0.676	0.717	0.7343	0.8328	0.84	0.8774	0.9195	0.9448
026_823_00298430	Lung: NSCLC	823	NCI-H1915	456	4.260241	0.691	0.707	0.702	0.7393	0.7957	0.834	0.9053	0.9612	0.9902
026_8232_00304520	Lung: NSCLC	8232	EMC-BAC-2	456	4.327709	0.712	0.795	0.825	0.8558	0.8815	0.959	0.9014	1.1842	1.0135
026_755_00300611	Lung: NSCLC	755	NCI-H1975	456	4.450033	0.666	0.968	0.963	0.9052	0.9346	0.928	0.9969	0.9681	0.973
026_868_00295440	Lung: NSCLC	868	PC-14	456	4.458594	0.726	0.893	0.842	0.8971	0.9361	1.057	0.9146	1.1281	0.933
026_872_00299750	Lung: NSCLC	872	HARA	456	4.480998	0.731	0.742	0.798	0.8152	0.8972	0.941	0.9735	1.0074	1.0301
026_800_00298441	Lung: NSCLC	800	NCI-H23	456	4.511394	0.702	0.698	0.786	0.7938	0.8549	0.889	0.9216	0.9447	1.013
026_836_00304620	Lung: NSCLC	836	NCI-H2444	456	4.530511	0.684	0.798	0.819	0.8507	0.863	0.86	0.9116	1.0106	1.0518
026_865_00296401	Lung: NSCLC	865	COR-L23	456	4.577187	0.791	0.78	0.815	0.8605	0.9148	0.924	1.1179	1.1287	1.1293
026_858_00300591	Lung: NSCLC	858	HCC-78	456	4.583505	0.703	0.983	0.936	1.06	0.9813	0.96	1.0028	0.9854	1.0584
026_854_00300681	Lung: NSCLC	854	EPLC-272H	456	4.590654	0.736	0.914	0.943	1.0019	1.0017	0.864	0.8937	0.9686	1.0373
026_837_00311160	Lung: NSCLC	837	NCI-H2122	456	4.595192	0.771	0.917	0.969	0.9878	0.9667	1.017	1.0165	1.0062	1.0324
026_8111_00308110	Lung: NSCLC	8111	LXF-289	456	4.689278	0.711	0.796	0.884	0.8648	0.868	0.89	0.9108	0.8979	0.9642
026_1136_00308471	Lung: NSCLC	1136	NCI-H1993	456	4.705234	0.725	0.768	0.682	0.7469	0.7866	0.883	0.9296	0.914	0.9652
026_827_00308860	Lung: NSCLC	827	NCI-H2085	456	4.711775	0.79	0.823	0.87	0.9311	0.924	1.007	0.967	1.0124	1.1093
026_859_00311090	Lung: NSCLC	859	HCC-827	456	4.735253	0.737	0.86	0.852	0.7863	0.8298	0.853	1.0366	1.1949	0.9783
026_886_00296261	Lung: NSCLC	886	EBC-1	456	4.744821	0.761	0.848	0.884	0.9053	0.9307	0.969	0.9903	0.9432	1.0947
026_8132_00308130	Lung: NSCLC	8132	NCI-H2126	456	4.781635	0.749	0.796	0.839	0.8331	0.8916	0.939	0.9049	0.9661	0.9286
026_793_00299711	Lung: NSCLC	793	NCI-H1781	456	4.904802	0.775	0.801	0.686	0.7429	0.7804	0.897	0.9136	0.9608	1.0112
026_1247_00314271	Lung: NSCLC	1247	NCI-H2291	456	4.945975	0.773	0.893	0.836	0.831	0.851	1.029	1.0615	0.9828	1.0493
026_860_00298400	Lung: NSCLC	860	LCLC-103H	456	4.97209	0.751	0.819	0.803	0.8985	0.8725	0.898	0.9606	0.9519	1.061
026_806_00300270	Lung: NSCLC	806	NCI-H647	456	5.044917	0.792	0.845	0.882	0.8698	0.8856	0.881	1.0769	0.9333	1.0648
026_877_00300630	Lung: NSCLC	877	PC-3 [JPC-3]	456	5.056812	0.847	0.832	0.968	0.9943	1.0985	1.01	1.0152	1.0063	1.1608
026_753_00298460	Lung: NSCLC	753	NCI-H460	456	5.061076	0.839	0.888	0.945	0.9015	1.041	1.039	1.021	0.9905	1.0126
026_844_00295461	Lung: NSCLC	844	SW 1573	456	5.077017	0.798	0.834	0.833	0.8824	0.8946	0.971	1.0223	0.9943	1.0074
026_8088_00314320	Lung: NSCLC	8088	KNS-62	456	5.130485	0.86	0.847	0.879	0.9874	0.9738	1.047	1.0602	1.0303	0.9876
026_848_00300641	Lung: NSCLC	848	SK-LU-1	456	5.2771	0.811	0.91	0.946	0.9174	0.9429	0.922	0.9544	1.0372	1.0115
026_864_00304961	Lung: NSCLC	864	COR-L 105	456	5.319498	0.718	0.78	0.762	0.8018	0.7683	0.837	0.9721	0.8644	0.9527
026_677_00298361	Lung: NSCLC	677	A549	456	5.414187	0.763	0.799	0.843	0.8595	0.9001	0.919	0.9405	0.9783	0.996
026_8207_00304810	Lung: NSCLC	8207	LC-1F	456	5.423228	0.825	0.794	0.845	0.8457	0.8483	0.976	0.8421	0.8626	0.9602
026_833_00299790	Lung: NSCLC	833	NCI-H2342	456	5.548934	0.856	0.888	0.917	0.9241	0.9293	1.015	0.9449	1.0616	0.9624
026_870_00299801	Lung: NSCLC	870	RERF-LC-KJ	456	5.685511	0.892	0.96	0.999	0.9623	1.0469	1.054	1.0305	1.0128	1.0476
026_845_00311341	Lung: NSCLC	845	NCI-H1838	456	5.711103	0.847	0.867	0.909	0.9088	0.9208	0.932	0.9775	0.9857	0.9755
026_8103_00306210	Lung: NSCLC	8103	LC-2-ad	456	5.718708	0.836	0.96	1.004	0.9427	1.0257	1.064	1.0682	0.9834	1.007
026_794_00300601	Lung: NSCLC	794	NCI-H1792	456	5.721238	0.339	0.904	0.992	0.9248	0.9615	1.005	0.9405	0.9595	1.0225
026_890_00300220	Lung: NSCLC	890	H3255	456	5.722728	0.903	0.862	0.844	0.9926	1.005	0.998	1.1503	1.1306	1.1501
026_862_00304820	Lung: NSCLC	862	LOU-NH91	456	5.738178	0.886	0.864	0.837	0.9386	0.9258	0.887	0.948	1.0561	1.1752
026_812_00298410	Lung: NSCLC	812	NCI-H1437	456	5.791603	0.894	0.946	0.993	0.9231	0.9704	1.003	1.0591	1.0305	1.0361
026_862_00316560	Lung: NSCLC	862	LOU-NH91	456	5.867157	0.871	0.905	0.923	0.9415	0.9143	0.955	0.9491	0.9721	0.9923
026_857_00296270	Lung: NSCLC	857	HCC-44	456	5.930045	0.904	0.868	0.893	0.9249	0.9348	0.956	1.0259	0.9727	1.0027
026_679_00296240	Lung: NSCLC	679	ChaGo-K-1	456	5.965866	0.878	0.915	0.949	0.8968	0.942	0.953	0.9732	0.9711	1.0338
026_791_00298421	Lung: NSCLC	791	NCI-H1650	456	5.971987	0.888	0.896	0.979	0.9429	0.9543	0.921	0.9516	0.9551	0.9966
026_864_00311551	Lung: NSCLC	864	COR-L 105	456	5.975297	0.765	0.838	0.843	0.8384	0.8225	0.848	0.8917	0.8749	0.9811
026_846_00300620	Lung: NSCLC	846	NCI-H2030	456	6.014339	0.886	0.979	0.985	0.9316	1.0428	0.925	0.9778	1.056	0.9904

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_841_00296291	Lung: NSCLC	841	NCI-H2170	456	6.01763	0.897	0.938	0.928	0.9356	0.9557	0.955	1.0968	1.0708	1.0963
026_813_00308231	Lung: NSCLC	813	NCI-H1563	456	6.06364	0.856	0.979	0.977	0.9369	0.9242	0.912	0.8859	0.9059	0.8856
026_816_00295860	Lung: NSCLC	816	NCI-H1651	456	6.160326	0.864	1.039	1.026	1.008	1.0776	0.871	1.0553	1.0199	0.9978
026_818_00308241	Lung: NSCLC	818	NCI-H1703	456	6.172519	0.946	0.829	0.858	0.9042	0.9197	0.887	0.9097	0.9729	0.9634
026_808_00296300	Lung: NSCLC	808	NCI-H838	456	6.172929	0.922	0.941	0.955	1.022	0.964	1.043	1.0358	1.0134	1.0658
026_855_00302330	Lung: NSCLC	855	HCC-15	456	6.195295	0.868	0.911	0.901	0.8895	0.9071	0.95	0.9608	1.0091	1.0383
026_803_00298470	Lung: NSCLC	803	NCI-H522	456	6.200929	0.878	0.933	0.953	0.8695	0.9015	0.833	0.8882	0.8789	1.1066
026_832_00303110	Lung: NSCLC	832	NCI-H2228	456	6.240586	0.908	0.872	0.907	0.9005	0.9724	0.974	0.9776	0.9706	0.968
026_874_00308171	Lung: NSCLC	874	RERF-LC-Sql	456	6.282697	1.064	0.854	0.829	0.8009	0.8914	0.943	0.8612	0.9931	0.9393
026_879_00308101	Lung: NSCLC	879	LU99A	456	6.327465	0.881	0.987	0.995	1.0199	0.9725	0.948	0.9588	0.9756	0.9692
026_856_00299760	Lung: NSCLC	856	HCC-366	456	6.328052	0.936	0.943	0.959	1.0286	0.9991	1.002	1.0072	1.0077	1.0015
026_798_00304790	Lung: NSCLC	798	Calu-3	456	6.338698	0.926	0.986	0.869	0.9635	1.0683	1.166	1.1053	1.1123	1.1003
026_825_00308250	Lung: NSCLC	825	NCI-H2023	456	6.435057	0.938	0.885	0.929	0.961	0.9166	0.959	0.9502	0.9835	0.9846
026_8072_00306200	Lung: NSCLC	8072	HOP-62	456	6.481774	0.973	0.958	0.931	0.9405	0.9799	0.901	1.0374	0.9717	1.1512
026_843_00296331	Lung: NSCLC	843	SK-MES-1	456	6.499026	0.91	0.99	0.934	0.9509	0.9694	1.003	0.9804	0.9674	1.0295
026_1251_00318710	Lung: NSCLC	1251	NCI-H835	456	6.684349	0.964	1.054	0.854	0.9853	0.77	0.963	0.8714	0.9637	1.1416
026_816_00302370	Lung: NSCLC	816	NCI-H1651	456	6.769433	0.903	1.072	1.021	1.002	1.0583	0.94	1.0664	1.0462	1.0774
026_801_00295941	Lung: NSCLC	801	NCI-H1299	456	6.808075	1.036	0.898	0.912	0.9194	0.9832	0.955	1.0252	0.9946	1.085
026_850_00311050	Lung: NSCLC	850	201T	456	6.874432	0.942	0.957	0.988	0.989	0.9596	0.985	0.9759	0.9839	0.9726
026_818_00309001	Lung: NSCLC	818	NCI-H1703	456	7.192409	0.889	0.857	0.855	0.8355	0.8207	0.856	0.8191	0.9124	0.9468
026_1247_00304851	Lung: NSCLC	1247	NCI-H2291	456	7.252153	1.162	1.047	0.877	1.034	0.8759	0.694	1.2149	1.0391	1.1021
026_819_00306250	Lung: NSCLC	819	NCI-H1734	456	7.342705	1.046	1.007	1.012	1.018	0.9902	0.945	0.9742	0.9718	1.0221
026_821_00306261	Lung: NSCLC	821	NCI-H1793	456	7.345651	1.015	1.1	1.058	1.0171	1.0121	1.065	1.0342	1.0776	1.0468
026_798_00308080	Lung: NSCLC	798	Calu-3	456	7.389624	1.032	1	0.914	0.9927	1.0342	1.004	1.0095	0.9327	0.938
026_678_00306181	Lung: NSCLC	678	UMC-11	456	7.458364	1.03	1.058	1.054	1.0958	1.0021	1.03	1.0784	1.0779	1.0688
026_797_00308730	Lung: NSCLC	797	NCI-H596	456	7.556662	1.124	1.076	0.92	0.9992	0.9285	0.936	0.911	1.0276	0.8862
026_790_00306231	Lung: NSCLC	790	NCI-H1573	456	7.606756	1.049	1	1.054	1.0146	1.0291	0.99	1.0304	1.0221	1.0512
026_752_00306191	Lung: NSCLC	752	A-427	456	7.608444	1.109	0.988	1.054	1.0224	0.9429	1.084	1.0956	1.0273	1.0528
026_845_00306271	Lung: NSCLC	845	NCI-H1838	456	7.666847	1.074	1.08	1.064	1.0779	1.0805	1.046	1.0674	0.9941	1.02
026_8133_00306280	Lung: NSCLC	8133	NCI-H322M	456	7.713112	1.158	1.06	1.135	1.1499	1.1305	1.103	1.1464	1.1475	1.0913
026_8130_00306220	Lung: NSCLC	8130	NCI-H1355	456	7.765888	1.12	1.188	1.002	0.9001	0.8103	1.095	0.9608	0.9714	0.9997
026_683_00306241	Lung: NSCLC	683	NCI-H1581	456	7.774034	1.163	1.024	0.949	1.0959	1.0605	1.114	1.0118	0.9537	0.9212
026_792_00306140	Lung: NSCLC	792	NCI-H1666	456	7.825548	1.136	1.069	1.132	1.0901	1.0688	1.097	1.0684	1.0463	1.1115
026_840_00306151	Lung: NSCLC	840	NCI-H441	456	7.946249	1.088	1.059	1.052	1.0622	1.0476	1.049	1.0439	1.045	1.0714
026_8075_00306131	Lung: NSCLC	8075	IA-LM	456	7.984543	1.046	1.042	1.043	1.0424	1.0323	1.048	1.0441	1.0279	1.0694
026_61_00285570	Lymphoma	61	JSC-1	456	0.316646	0.313	0.329	0.341	0.3908	0.5654	0.63	0.724	0.8346	0.8527
026_8222_00291350	Lymphoma	8222	H9	456	0.402947	0.102	0.284	0.272	0.3996	0.5762	0.732	0.8412	0.8346	0.8529
026_140_00291320	Lymphoma	140	A3/KAW	456	0.717935	0.185	0.296	0.408	0.4762	0.5561	0.736	0.8297	0.8761	0.8425
026_237_00291380	Lymphoma	237	SU-DHL-16	456	0.982467	0.155	0.278	0.405	0.5737	0.6759	0.816	0.9129	0.9363	0.9318
026_220_00288720	Lymphoma	220	OCI-LY-19	456	1.28484	0.324	0.393	0.455	0.5338	0.6443	0.826	0.9343	0.9969	1.073
026_257_00285640	Lymphoma	257	WIL2 NS	456	1.523653	0.32	0.456	0.509	0.6199	0.6926	0.771	0.8518	0.9524	0.934
026_239_00288750	Lymphoma	239	SU-DHL-5	456	1.616577	0.174	0.577	0.461	0.7856	0.7368	0.845	0.9512	0.9535	1.2005
026_124_00287850	Lymphoma	124	BC-1	456	1.816766	0.239	0.53	0.6	0.6778	0.8612	0.946	0.9754	0.9846	1.0038
026_104_00287960	Lymphoma	104	TUR	456	2.217781	0.396	0.51	0.597	0.7468	0.9062	0.94	0.9822	0.9761	1.0165
026_8199_00291330	Lymphoma	8199	CTB-1	456	2.341488	0.445	0.509	0.654	0.6993	0.7792	0.767	0.8214	0.8543	0.9676
026_69_00283480	Lymphoma	69	CA46	456	2.43077	0.358	0.6	0.775	0.78	0.8817	0.896	0.9912	0.9446	0.9358
026_112_00285620	Lymphoma	112	SR	456	2.466522	0.224	0.573	0.653	0.7668	0.8482	0.866	0.9087	0.9409	0.9255
026_241_00288760	Lymphoma	241	SU-DHL-8	456	2.509783	0.398	0.583	0.743	0.8249	0.935	0.956	1.0439	0.9903	1.0527
026_255_00285610	Lymphoma	255	Sci-1	456	2.705483	0.445	0.61	0.788	0.9473	0.9153	1.003	0.9035	0.8642	0.8757

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_62_00293930	Lymphoma	62	IM-9	456	2.809638	0.572	0.562	0.594	0.6839	0.7773	1.18	0.876	1.0089	1.0329
026_93_00287880	Lymphoma	93	HH	456	2.828886	0.523	0.575	0.731	0.804	0.9283	0.94	80.9965	0.999	1.0069
026_216_00290710	Lymphoma	216	NU-DUL-1	456	2.880782	0.459	0.664	0.767	0.8093	0.7784	0.884	0.9338	0.9363	0.9519
026_123_00287860	Lymphoma	123	BC-3	456	2.893681	0.495	0.678	0.776	0.9051	1.0108	1.003	1.0056	0.9841	0.9941
026_113_00288520	Lymphoma	113	DB	456	2.901204	0.479	0.705	0.868	0.9097	0.9559	0.984	1.0104	0.992	1.0316
026_8035_00303290	Lymphoma	8035	DOHH-2	456	2.927461	0.508	0.78	0.831	0.8009	0.9998	0.997	1.0295	0.9393	1.0203
026_240_00300290	Lymphoma	240	SU-DHL-6	456	2.933827	0.208	0.663	0.733	0.7473	0.7814	0.839	0.8554	0.9327	1.029
026_248_00285630	Lymphoma	248	VAL	456	2.964017	0.528	0.639	0.739	0.9112	0.9265	0.96	1.0023	0.9827	0.9859
026_162_00290790	Lymphoma	162	HDLM-2	456	2.980685	0.56	0.811	0.678	0.7341	0.7627	0.782	0.7915	0.9638	0.7387
026_105_00287940	Lymphoma	105	RPMI 6666	456	3.064381	0.516	0.701	0.691	0.7257	0.8234	0.904	0.9883	1.0013	1.033
026_240_00302920	Lymphoma	240	SU-DHL-6	456	3.114948	0.326	0.629	0.741	0.7802	0.8119	0.831	0.9347	0.921	0.9838
026_163_00287730	Lymphoma	163	HD-MY-Z	456	3.123344	0.582	0.606	0.654	0.6825	0.785	0.896	0.9395	0.98	1.0207
026_139_00283530	Lymphoma	139	MC116	456	3.12577	0.085	0.686	0.917	0.9565	0.9611	0.99	0.9875	0.9789	0.9559
026_133_00293941	Lymphoma	133	NK-92M1	456	3.297366	0.637	0.637	0.757	0.8911	0.8633	1.136	1.0548	0.89	0.9001
026_282_00287750	Lymphoma	282	P32/ISH	456	3.328203	0.416	0.744	0.875	0.8947	0.8754	0.907	0.9959	0.9144	0.9277
026_80_00287950	Lymphoma	80	ST486	456	3.520498	0.263	0.688	0.699	0.7969	0.8071	0.904	0.8902	0.9142	1.017
026_73_00283500	Lymphoma	73	EB-3	456	3.528971	0.566	0.739	0.806	0.8214	0.8547	1.09	0.8321	0.8619	0.8548
026_60_00287891	Lymphoma	60	JM1	456	3.618767	0.577	0.678	0.734	0.7932	0.8209	0.833	0.8444	0.8567	0.902
026_185_00288820	Lymphoma	185	L-540	456	3.666174	0.626	0.88	0.936	1.0302	1.0245	1.037	1.0524	1.0175	1.0525
026_70_00283490	Lymphoma	70	Daudi	456	3.687192	0.603	0.789	0.925	0.8867	0.9929	0.987	0.8586	0.9555	0.8243
026_228_00291370	Lymphoma	228	RC-K8	456	3.710403	0.605	0.678	0.732	0.7776	0.8387	0.943	0.9437	0.9368	0.9149
026_74_00285600	Lymphoma	74	Raji	456	3.736373	0.639	0.768	0.89	0.8258	0.9671	0.97	0.9444	0.9665	1.046
026_173_00288920	Lymphoma	173	KARPAS-422	456	3.812903	0.638	0.787	0.876	0.8937	0.8652	0.959	0.9976	0.9896	1.005
026_125_00287910	Lymphoma	125	MC/CAR	456	3.860302	0.687	0.792	0.873	0.8871	1.009	1.011	0.9976	0.987	1.0162
026_280_00285420	Lymphoma	280	SCC-3	456	3.903427	0.648	0.86	0.895	0.9301	0.9335	0.934	1.0707	0.9	0.9445
026_242_00288770	Lymphoma	242	SUP-HD1	456	4.023177	0.671	0.815	0.875	0.8573	0.8914	0.965	1.0137	0.9754	1.1043
026_160_00285410	Lymphoma	160	GRANTA-519	456	4.112789	0.631	0.706	0.761	0.7798	0.7991	0.771	0.9167	0.9366	0.9971
026_144_00287710	Lymphoma	144	BL-41	456	4.441898	0.536	1.076	0.941	0.9045	0.8922	0.893	0.9542	0.9696	1.0289
026_184_00290800	Lymphoma	184	L-428	456	4.489131	0.614	0.705	0.723	0.7315	0.7351	0.721	1.0011	0.7501	0.8687
026_128_00290690	Lymphoma	128	Farage	456	4.585156	0.766	0.834	0.861	0.8151	0.9324	0.908	1.3723	1.1697	1.2229
026_250_00285660	Lymphoma	250	WSU-NHL	456	4.693667	0.719	0.765	0.866	0.8242	0.9178	0.947	0.9725	0.9585	0.9714
026_182_00290700	Lymphoma	182	L-1236	456	4.714251	0.76	0.859	0.875	0.8522	0.9702	0.962	1.0483	0.9432	1.3018
026_95_00283510	Lymphoma	95	HT	456	4.721481	0.719	0.842	0.88	0.8266	0.8534	0.902	1.0348	0.9564	0.966
026_264_00288840	Lymphoma	264	TK	456	4.750226	0.794	0.966	0.936	0.9709	1.0212	1.024	1.0348	1.0318	1.0681
026_266_00287760	Lymphoma	266	SLVL	456	4.90866	0.731	0.786	0.794	0.8012	0.8742	0.873	0.9435	0.9199	0.977
026_75_00282830	Lymphoma	75	Jiyoye	456	4.937844	0.801	0.99	0.974	1.0523	1.196	1.107	1.0641	1.1044	1.0749
026_111_00291360	Lymphoma	111	Hs 445	456	5.022248	0.704	0.734	0.703	0.794	0.7451	0.779	0.8243	0.8675	0.946
026_8151_00288540	Lymphoma	8151	Ramos-2G6-4C10	456	5.147746	0.242	0.868	0.954	0.9827	1.022	0.974	0.9967	0.9674	1.0529
026_156_00287720	Lymphoma	156	DG-75	456	5.222394	0.834	1.001	1.03	1.0349	0.9848	0.996	1.012	0.9965	0.9857
026_243_00296620	Lymphoma	243	SUP-M2	456	5.25553	0.648	0.88	0.96	0.9351	0.9518	0.968	0.9742	0.9627	0.9659
026_86_00287870	Lymphoma	86	EB2	456	5.287284	0.86	1.017	1.01	1.0356	1.0217	1.05	1.0267	1.0118	1.0227
026_162_00288790	Lymphoma	162	HDLM-2	456	5.425219	0.877	0.903	0.797	0.9228	1.0293	1.043	1.0157	1.0517	1.0837
026_172_00287740	Lymphoma	172	KARPAS-299	456	5.433867	0.832	0.891	0.95	0.9494	0.955	0.954	0.9499	0.9633	0.9487
026_235_00285430	Lymphoma	235	SU-DHL-1	456	6.401484	0.885	0.997	0.987	0.9424	0.9387	0.884	0.8642	0.9464	0.9439
026_143_00288690	Lymphoma	143	AMO-1	456	6.692908	0.924	1.02	51.129	1.034	1.1112	1.034	1.0278	1.0136	1.0255
026_193_00288830	Lymphoma	193	MHH-PREB-1	456	6.799634	0.622	0.958	1.012	1.0149	1.0368	1.025	1.0064	0.9803	0.989
026_236_00288730	Lymphoma	236	SU-DHL-10	456	6.99662	0.175	0.993	1.05	1.0763	1.0476	1.029	1.0509	1.0397	1.0494
026_81_00288530	Lymphoma	81	GA-10	456	7.031749	0.608	1.003	1.009	1.1031	1.0252	1.021	1.0113	1.0077	1.0848
026_251_00287840	Lymphoma	251	YT	456	7.411746	0.64	0.986	1.008	1.0201	1.0204	1.022	1.0267	0.9848	1.0079

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_178_00288810	Lymphoma	178	KM-H2	456	7.739504	1.008	1.009	0.976	1.0197	1.0404	1.036	1.0412	1.0156	1.0276
026_249_00285650	Lymphoma	249	WSU-DLCL2	456	8.212885	1.047	1.226	1.172	1.1142	1.0869	1.071	0.9837	1.0247	1.0207
026_238_00288740	Lymphoma	238	SU-DHL-4	456	8.647656	1.061	1.077	1.045	1.0257	1.0384	1.029	1.0236	1.018	1.0204
026_131_00287930	Lymphoma	131	RL	456	8.679308	1.124	1.094	1.048	1.024	1.0293	1.012	1.0293	0.9824	1.0061
026_915_00269070	Miscellaneous	915	Hs 633T	456	1.797943	0.344	0.532	0.607	0.6061	0.6357	0.736	0.8936	1.0346	1.1375
026_911_00269060	Miscellaneous	911	GCT	456	2.424125	0.433	0.617	0.642	0.6508	0.655	0.804	0.7763	0.9066	0.9967
026_8172_00269460_	Miscellaneous	8172	SW872	456	3.196748	0.511	0.716	0.719	0.7459	0.8264	0.881	0.9107	0.9313	1.0224
026_913_00271970	Miscellaneous	913	JAR	456	3.876744	0.685	0.695	0.794	0.851	0.9936	1.011	0.9013	1.0881	1.0491
026_8194_00271980	Miscellaneous	8194	JEG-3	456	3.901223	0.623	0.808	0.876	0.9097	0.9037	0.874	0.9014	0.943	1.1354
026_8171_00269120	Miscellaneous	8171	SW684	456	3.978538	0.693	0.91	0.98	1.1114	1.0275	1.032	0.9881	0.9218	1.0725
026_8112_00269450	Miscellaneous	8112	MFH-ino	456	4.013788	0.691	0.674	0.795	0.8068	0.8378	0.91	0.9824	1.0389	1.0625
026_916_00271320	Miscellaneous	916	HT 1080	456	4.254215	0.695	0.804	0.766	0.7943	0.8276	0.873	1.1135	1.1006	1.1093
026_8004_00271280	Miscellaneous	8004	A388	456	4.494172	0.743	0.793	0.841	0.8441	0.8899	0.888	1.1408	0.925	1.1327
026_8112_00271340	Miscellaneous	8112	MFH-ino	456	4.624376	0.721	0.732	0.741	0.7501	0.7753	0.799	1.017	0.9044	1.0866
026_8004_00269400	Miscellaneous	8004	A388	456	4.778414	0.747	0.764	0.776	0.8164	0.8628	0.861	0.9217	0.8924	1.0697
026_8192_00269470	Miscellaneous	8192	VA-ES-BJ	456	4.956405	0.78	0.867	0.874	0.984	0.9192	0.889	0.9737	1.0227	1.0186
026_8194_00269440	Miscellaneous	8194	JEG-3	456	5.058221	0.786	0.87	1.048	0.908	0.8876	0.984	0.8804	1.0294	1.0609
026_913_00269430	Miscellaneous	913	JAR	456	5.170211	0.816	0.841	0.849	0.8709	0.8661	0.88	1.0502	1.0585	1.0591
026_916_00269420	Miscellaneous	916	HT 1080	456	5.302771	0.831	0.891	0.904	0.9053	0.9327	0.978	0.9465	1.1023	1.1108
026_8175_00269140	Miscellaneous	8175	SW982	456	5.586364	0.832	0.968	0.988	1.1946	1.0638	1.017	1.0728	1.1006	1.2781
026_1225_00269660	Muscle	1225	RD	456	2.694207	0.612	0.595	0.602	0.575	0.6051	0.678	0.8404	0.9183	0.947
26_135_00271680	Muscle	135	SJCRH30	456	2.740947	0.247	0.61	0.713	0.8654	0.8633	0.854	0.9433	0.9991	1.105
026_924_00269640	Muscle	924	A673	456	2.779569	0.563	0.554	0.607	0.6884	0.7085	0.808	0.8122	0.8796	0.9437
26_562_00271660	Muscle	562	KYM-1	456	2.818237	0.433	0.665	0.727	0.7663	0.7943	0.835	0.9132	0.9948	0.9596
026_135_00271410	Muscle	135	SJCRH30	456	3.059385	0.345	0.672	0.79	0.8395	0.8741	0.957	0.9768	1.032	1.1796
026_923_00269680	Muscle	923	RH-41	456	3.133389	0.309	0.65	0.731	0.7895	0.6971	0.795	0.7303	0.9458	0.9325
026_562_00270060	Muscle	562	KYM-1	456	3.396905	0.586	0.748	0.78	0.8707	0.8698	0.955	1.0372	1.0323	1.0217
026_920_00269670	Muscle	920	RH-1	456	3.433085	0.581	0.772	0.846	0.9032	0.9238	0.951	0.9496	0.9615	0.9852
026_135_00270070	Muscle	135	SJCRH30	456	3.759361	0.326	0.727	0.825	0.8737	0.9084	0.931	0.9701	0.9946	0.9435
026_919_00269630	Muscle	919	A-204	456	5.25605	0.778	0.798	0.868	0.8744	0.861	0.89	0.9735	0.9392	0.9765
026_921_00285151	Muscle	921	RH-18	456	5.863422	0.84	0.987	0.961	0.9653	0.9811	0.903	0.8875	0.9228	0.9815
026_8182_00293791	Muscle	8182	TE-441-T	456	6.133177	0.848	1.001	1.103	1.0954	1.1007	0.855	0.8882	1.0698	0.8069
026_369_00258500	Nervous System	369	CHP-212	456	−4.151196	0.165	0.184	0.183	0.1873	0.1985	0.219	0.2948	0.3285	0.4946
026_390_00262920	Nervous System	390	NB69	456	−1.3827	0.056	0.074	0.068	0.0948	0.096	0.163	0.4343	0.6938	0.8833
026_629_00316570	Nervous System	629	NB(TU)1-10	456	−0.654294	0.322	0.361	0.388	0.398	0.4347	0.594	0.7533	0.6321	0.6782
026_366_00257090	Nervous System	366	BE(2)-M17	456	−0.258429	0.204	0.352	0.333	0.3872	0.4128	0.547	0.6415	0.7687	0.9298
026_384_00314240	Nervous System	384	MHH-NB-11	456	1.316182	0.368	0.42	0.48	0.6318	0.5903	0.783	0.7802	0.9243	0.5317
026_385_00314290	Nervous System	385	SIMA	456	1.359572	0.402	0.496	0.488	0.5135	0.6006	0.629	0.8787	0.8808	1.0864
026_630_00264810	Nervous System	630	NH-12	456	1.516245	0.143	0.443	0.537	0.5763	0.6816	0.684	0.7263	0.9504	0.791
026_8124_00308720	Nervous System	8124	NB14	456	1.784337	0.802	0.401	0.6	0.6379	0.6871	0.943	0.8827	0.8247	0.9343
026_639_00271120	Nervous System	639	GOTO	456	1.784838	0.174	0.52	0.54	0.6353	0.6485	0.726	0.9341	0.8908	1.1295
026_8094_00314230	Nervous System	8094	LAN-6	456	1.824343	0.55	0.565	0.476	0.5734	0.6862	0.656	0.7893	0.9264	0.7016
026_8076_00260401	Nervous System	8076	IMR-5	456	1.864038	0.346	0.489	0.575	1.2246	0.8619	0.823	1.0781	0.7607	0.8894
026_8127_00258950	Nervous System	8127	NB5	456	2.106125	0.202	0.628	0.611	0.6823	0.725	0.845	0.9541	0.9703	1.0012
026_8124_00311130	Nervous System	8124	NB14	456	2.216808	0.544	0.563	0.516	0.5711	0.5857	0.776	0.9014	0.9091	1.0395
026_8126_00264800	Nervous System	8126	NB17	456	2.289546	0.347	0.54	0.684	0.7567	0.8851	0.929	0.8729	0.9752	0.9196
026_641_00308180	Nervous System	641	TGW	456	2.326645	0.456	0.502	0.593	0.7234	0.8006	0.88	0.9296	0.9651	0.9821
026_8121_00256290	Nervous System	8121	NB10	456	2.356578	0.646	0.568	0.562	0.5835	0.6642	0.613	0.5487	0.6035	1.0005
026_8220_00308810	Nervous System	8220	KP-N-YN	456	2.470465	0.366	0.619	0.752	0.7815	0.7642	0.87	0.8457	0.8335	0.8942

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_8090_00263920	Nervous System	8090	KP-N-YS	456	2.547617	0.267	0.583	0.69	0.9135	0.905	0.924	0.9505	0.9232	1.012
026_363_00252730	Nervous System	363	SK-N-FI	456	2.667265	0.519	0.583	0.574	0.6332	0.5059	0.571	0.7766	0.6898	0.9188
026_382_00311110	Nervous System	382	KELLY	456	3.39659	0.518	0.757	0.767	0.7123	0.7538	0.883	0.8718	0.8733	0.9755
026_8064_00259120	Nervous System	8064	GI-ME-N	456	3.426922	0.582	0.763	0.78	0.8295	0.8371	0.955	1.0539	1.0652	1.104
026_8195_00318640	Nervous System	8195	CHP-134	456	3.519288	0.6	0.8	0.86	0.909	0.9931	0.919	0.9533	0.941	1.0273
026_382_00308690	Nervous System	382	KELLY	456	3.678148	0.59	0.706	0.666	0.7413	0.8277	0.814	0.8335	0.8742	0.9843
026_8129_00314250	Nervous System	8129	NB7	456	3.824042	0.644	0.861	0.945	0.972	0.9655	0.998	1.0941	1.0771	1.0471
026_8126_00280241	Nervous System	8126	NB17	456	3.845261	0.611	0.771	0.746	1.0569	0.8567	0.864	0.9408	0.9041	0.972
026_8007_00252850	Nervous System	8007	ACN	456	3.989797	0.411	0.72	0.821	0.7359	0.7717	0.797	0.8528	1.0702	0.9564
026_8122_00273460	Nervous System	8122	NB12	456	4.358809	0.15	0.809	0.911	0.9912	0.9113	1.021	0.9055	0.8723	1.0083
026_8226_00252530	Nervous System	8226	NBsusSR	456	4.365592	1.14	0.81	0.878	0.6567	0.6737	0.94	0.7615	0.8399	1.1136
026_8064_00256670	Nervous System	8064	GI-ME-N	456	4.809816	0.398	0.871	0.839	0.9402	0.8757	0.96	0.9284	0.9838	1.0451
026_8128_00257200	Nervous System	8128	NB6	456	4.886145	0.836	0.93	0.956	1.0121	0.9926	1.008	0.9893	0.9944	0.9472
026_8123_00256300	Nervous System	8123	NB13	456	5.775254	0.837	1.028	1.034	0.9756	1.0272	0.974	0.9893	0.9781	0.9486
026_396_00261020	Nervous System	396	NB-1	456	5.873385	0.813	1.039	0.892	0.8527	0.9085	0.934	0.9583	0.9709	1.0441
026_370_00252740	Nervous System	370	SK-N-SH	456	6.176056	0.926	0.811	0.891	1.0803	2.0427	1.01	0.892	0.9269	0.9864
026_364_00252720	Nervous System	364	SK-N-DZ	456	6.251974	0.895	1.012	0.958	1.0963	0.9642	0.976	1.0005	0.9787	0.9774
026_370_00258530	Nervous System	370	SK-N-SH	456	6.266144	0.36	0.933	1.052	1.0961	1.0754	0.948	0.9798	1.0134	0.9668
026_362_00252710	Nervous System	362	SK-N-AS	456	6.874316	0.911	1.075	0.916	1.0354	0.9179	0.939	1.178	0.9451	0.9362
026_368_00252700	Nervous System	368	MC-IXC	456	6.982443	0.084	0.616	1.087	1.1559	1.0678	1.11	1.0784	0.9917	0.9902
026_8122_00262490	Nervous System	8122	NB12	456	7.149853	0.063	0.973	1.019	1.3067	1.0528	0.999	1.4063	0.9955	0.9632
026_934_00287430	Ovary	934	A2780	456	−0.227264	0.302	0.3	0.342	0.3503	0.3758	0.467	0.7239	0.7489	0.9268
026_1126_00293760	Ovary	1126	OV-90	456	0.856076	0.323	0.361	0.384	0.4703	0.5785	0.701	0.8275	0.885	0.873
026_1129_00290660	Ovary	1129	TOV-112D	456	2.270257	0.47	0.481	0.592	0.7498	0.7692	0.925	0.9217	0.9942	1.1258
026_1220_00291150	Ovary	1220	ES-2	456	2.397868	0.584	0.504	0.584	0.5655	0.9851	0.957	1.1602	1.1706	1.0966
026_949_00290350	Ovary	949	TYK-nu	456	2.489488	0.511	0.577	0.587	0.5768	0.6153	0.686	0.7718	1.0687	1.0378
026_925_00290850	Ovary	925	IGROV-1	456	2.753994	0.494	0.608	0.578	0.7594	0.7462	0.857	0.9169	0.8966	0.8943
026_8244_00314220	Ovary	8244	JHOS-4	456	2.779507	0.63	0.601	0.597	0.6381	0.7711	0.88	0.955	0.9128	0.9028
026_8279_00293400	Ovary	8279	UWB1.289	456	2.893774	0.764	0.625	0.723	0.7182	0.783	1.079	0.9597	1.044	1.0467
026_940_00290340	Ovary	940	RMG-I	456	3.11591	0.587	0.604	0.66	0.6995	0.6871	0.846	0.8531	0.9424	1.0257
26_8238_00304370	Ovary	8238	IOSE-364-	456	3.149354	0.505	0.763	0.761	0.7451	0.8102	0.848	1.0558	1.0226	1.0295
026_8237_00295840	Ovary	8237	Hey	456	3.317969	0.551	0.783	0.688	0.776	0.8484	0.917	1.1038	1.0681	1.1892
026_8260_00292720	Ovary	8260	PEO1	456	3.508406	0.648	0.61	0.642	0.7269	0.6891	0.74	1.0027	0.9408	0.9148
026_8230_00303100	Ovary	8230	DOV13	456	3.68994	0.636	0.73	0.886	0.851	0.9406	0.961	0.9388	0.9681	1.0998
026_8230_00292650	Ovary	8230	DOV13	456	3.809459	0.641	0.685	0.768	0.9488	0.8764	0.863	0.9076	0.9226	1.0565
026_8092_00295850	Ovary	8092	KURAMOCHI	456	3.819916	0.757	0.729	0.642	0.6589	0.7541	0.914	0.9211	1.0035	1.0531
026_8240_00291160	Ovary	8240	IOSE-523-	456	3.834885	0.676	0.747	0.827	0.9249	0.9868	1	0.9181	0.9742	1.0197
026_932_00291140	Ovary	932	EFO-27	456	3.943589	0.65	0.668	0.65	0.7216	0.7753	0.887	0.9104	0.9136	0.9152
026_8084_00292670	Ovary	8084	KGN	456	4.00968	0.776	0.686	0.68	0.804	0.816	0.93	0.911	0.9826	0.9092
026_1125_00290571	Ovary	1125	Caov-3	456	4.050855	0.676	0.787	0.855	0.951	0.9041	1.029	0.9092	0.8992	1.0107
026_8256_00292920	Ovary	8256	OV-7	456	4.064163	0.666	0.844	0.821	0.9099	0.9293	0.961	1.0098	0.9638	0.9379
026_8241_00292900	Ovary	8241	IOSE-75-16SV40	456	4.094216	0.698	0.804	0.834	0.8672	0.894	1.02	1.0443	1.0711	1.107
026_938_00287450	Ovary	938	OAW42	456	4.158942	0.689	0.707	0.728	0.8613	0.7453	0.912	0.7815	1.0258	1.0515
026_1235_00298501	Ovary	1235	Caov-4	456	4.19878	0.673	0.815	0.851	0.7794	0.8482	0.895	1.0046	1.0048	0.9449
026_1221_00293780	Ovary	1221	SW 626	456	4.261643	0.636	0.704	0.69	0.6894	0.7014	0.755	0.8172	0.8859	1.0281
026_933_00295510	Ovary	933	FU-OV-1	456	4.35795	0.921	0.786	0.66	0.785	0.7855	0.932	1.0797	1.0643	1.0563
026_8259_00292710	Ovary	8259	OVK-18	456	4.419332	0.714	0.849	0.926	0.7816	0.8328	1.11	1.0158	0.9241	1.1619
026_8242_00295400	Ovary	8242	JHOS-2	456	4.46038	0.744	0.845	0.843	0.8069	0.9687	1.09	0.9491	1.0683	1.0333
026_1128_00292620	Ovary	1128	PA-1	456	4.524728	0.741	0.875	0.809	0.8925	0.9409	1.005	1.0033	1.0111	1.0682

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_938_00290330	Ovary	938	OAW42	456	4.600882	0.772	0.772	0.843	0.9103	0.8456	1.001	1.0305	1.0314	1.0721
026_8148_00292700	Ovary	8148	OVCAR-4	456	4.649732	0.715	0.824	0.723	0.6704	0.8391	0.855	0.9034	1.0922	1.0169
026_8243_00295410	Ovary	8243	JHOS-3	456	4.699022	0.801	0.758	0.691	0.7427	0.8184	0.86	1.0104	0.9653	1.0478
026_1130_00308501	Ovary	1130	TOV-21G	456	4.743414	0.744	0.838	0.882	0.8952	0.9369	0.922	0.9212	0.9456	0.9683
026_931_00252940	Ovary	931	EFO-21	456	4.786052	0.749	0.962	0.957	1.0202	1.0143	0.983	0.9976	0.9688	0.9523
026_931_00290820	Ovary	931	EFO-21	456	4.852802	0.791	0.924	0.954	0.9827	1.0247	0.961	0.9353	0.9274	0.9237
026_932_00288450	Ovary	932	EFO-27	456	4.890908	0.759	0.729	0.783	0.7813	0.828	0.851	0.9362	1.0032	1.0515
026_8258_00291180	Ovary	8258	OVCA433	456	4.901177	0.703	0.713	0.753	0.7366	0.79	0.864	0.9468	0.9244	0.9669
026_928_00290870	Ovary	928	OVCAR-5	456	4.903025	0.791	0.718	0.699	0.6913	0.7147	0.8	0.831	0.8925	0.9149
026_8257_00293650	Ovary	8257	OVCA420	456	4.98883	0.716	0.738	0.79	0.8055	0.8238	0.819	0.8677	0.8812	1.0222
026_8257_00292690	Ovary	8257	OVCA420	456	5.050268	0.789	0.822	0.798	0.9932	0.8382	0.876	0.928	0.9213	1.1024
026_8239_00292890	Ovary	8239	IOSE-397	456	5.092878	0.842	0.8	0.866	0.8796	0.8926	0.921	1.2015	0.9976	1.2125
026_941_00288490	Ovary	941	RKN	456	5.095259	0.777	0.883	0.798	0.796	0.8682	1.049	1.195	1.0697	1.0119
026_929_00290880	Ovary	929	OVCAR-8	456	5.147098	0.763	0.805	0.822	0.8457	0.8675	0.888	0.9211	0.9687	1.0047
026_8215_00287660	Ovary	8215	OC-314	456	5.38803	0.869	0.99	0.986	1.0451	1.0092	1.01	1.0495	0.9963	1.0021
026_939_00287460	Ovary	939	SK-OV-3	456	5.430154	0.806	0.848	0.834	0.8094	0.8719	0.891	0.9424	0.903	1.1026
026_945_00288480	Ovary	945	OVMIU	456	5.797932	0.75	0.737	0.748	0.7949	0.7921	0.844	0.8857	0.9368	0.9866
026_948_00291230	Ovary	948	OVTOKO	456	5.89738	0.829	0.912	0.942	0.9105	0.938	0.909	0.9025	0.9329	0.9575
026_8255_00293640	Ovary	8255	OV-56	456	5.989644	0.874	0.894	0.904	0.9159	0.9189	0.911	0.9267	0.9453	0.9277
026_937_00288460	Ovary	937	OAW28	456	6.027686	0.859	0.878	0.802	0.8512	0.7724	0.814	1.0447	0.8649	1.0363
026_1127_00296460	Ovary	1127	NIH:OVCAR-3	456	6.109694	0.886	0.95	0.992	0.9785	0.8788	0.986	0.9619	1.0732	0.8745
026_947_00263500	Ovary	947	OVKATE	456	6.266319	0.819	0.823	0.875	0.8874	0.9093	0.906	0.9175	0.9563	0.9507
026_938_00292910	Ovary	938	OAW42	456	6.299032	0.918	0.963	0.958	0.9614	0.9778	1.041	1.0213	0.9899	1.0087
026_945_00256180	Ovary	945	OVMIU	456	6.360298	0.891	0.987	1.001	0.9225	0.8452	0.776	0.8273	0.9233	1.0102
026_946_00291190	Ovary	946	OVISE	456	6.600815	0.805	0.739	0.737	0.7358	0.7593	0.759	0.8539	0.8664	0.8624
026_8254_00295890	Ovary	8254	OV-17R	456	6.877329	0.913	1.041	0.974	1.0282	1.0077	1.015	1.0376	0.9484	1.0604
026_973_00295540	Pancreas	973	HUP-T4	456	0.866739	0.321	0.315	0.362	0.4721	0.5603	0.814	1.0984	0.8938	1.1407
026_983_00295450	Pancreas	983	SUIT-2	456	1.197889	0.397	0.339	0.382	0.581	0.6565	0.942	0.9937	1.019	1.1926
026_982_00292940	Pancreas	982	QGP-1	456	1.430625	0.538	0.437	0.492	0.5682	0.6307	0.8	0.8372	0.9601	1.0476
026_8118_00295430	Pancreas	8118	MZ1-PC	456	1.48113	0.363	0.489	0.495	0.5335	0.6471	0.671	0.9118	1.008	0.9838
026_8149_00293771	Pancreas	8149	PSN1	456	1.829333	0.531	0.553	0.5	0.5231	0.6104	0.71	0.8375	0.909	0.9509
026_953_00295470	Pancreas	953	AsPC-1	456	1.847893	0.476	0.515	0.508	0.4987	0.5741	0.746	0.8281	1.0377	1.0843
026_1256_00260300	Pancreas	1256	950-MP5	456	1.902786	0.332	0.473	0.515	0.7193	0.8035	0.916	0.9125	1.0441	0.9009
026_976_00298480	Pancreas	976	Panc 04.03	456	2.685969	0.592	0.594	0.57	0.562	0.6645	0.706	0.8319	0.9296	1.0176
026_954_00292870	Pancreas	954	BxPC-3	456	2.90077	0.574	0.607	0.558	0.6572	0.7404	0.813	1.0541	1.0916	0.9092
026_967_00292570	Pancreas	967	Capan-1	456	3.140577	0.522	0.69	0.758	0.8527	0.6713	0.874	0.9506	0.894	0.958
026_975_00295591	Pancreas	975	YAPC	456	3.507979	0.613	0.705	0.797	0.9196	0.8833	0.921	1.0616	1.0323	1.0675
026_1135_00292930	Pancreas	1135	PL18	456	3.513426	0.636	0.623	0.694	0.6978	0.7917	0.832	0.9096	0.9334	0.9721
026_977_00308210	Pancreas	977	KP-1N	456	3.657778	0.607	0.764	0.684	0.7525	0.7655	0.908	0.9944	0.9837	0.9553
026_969_00295580	Pancreas	969	PA-TU-8988T	456	3.657963	0.664	0.653	0.725	0.7145	0.7879	0.992	1.0299	1.0048	1.0863
026_1491_00273490	Pancreas	1491	SNU-324	456	3.732679	0.387	0.683	0.791	0.7879	0.8486	0.832	0.9455	0.9813	0.9695
026_961_00295570	Pancreas	961	Panc 02.03	456	4.088522	0.702	0.699	0.633	0.701	0.7003	0.795	0.8748	0.9019	1.1113
026_974_00292601	Pancreas	974	HUP-T3	456	4.280085	0.684	0.754	0.793	0.909	0.7596	0.88	0.9895	0.9696	1.0099
026_963_00293710	Pancreas	963	Hs 766T	456	4.34359	0.709	0.746	0.833	0.7623	0.8169	1.052	0.9605	0.9551	1.0544
026_959_00292630	Pancreas	959	Panc 03.27	456	4.482408	0.701	0.682	0.805	0.8272	0.7565	0.838	0.9087	0.9434	1.0258
026_981_00293750	Pancreas	981	KP-4	456	4.755774	0.733	0.9	0.784	0.9218	0.8875	1.007	0.9325	1.0003	0.8788
026_968_00292580	Pancreas	968	CFPAC-1	456	4.814885	0.772	0.822	0.87	0.9195	0.9082	0.935	0.8889	1.0106	1.1286
026_1134_00300280	Pancreas	1134	PL4	456	4.852316	0.738	0.739	0.727	0.7443	0.7816	0.797	0.9521	0.9663	1.0376
026_979_00293740	Pancreas	979	KP-3	456	4.900084	0.956	0.777	0.839	0.8825	0.8836	0.909	0.9593	0.9092	0.9686

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_956_00292591	Pancreas	956	HPAF-II	456	5.005523	0.734	0.786	0.762	0.6523	0.7269	0.755	0.9185	0.979	1.0195
026_953_00257150	Pancreas	953	AsPC-1	456	5.141432	0.761	0.708	0.731	0.7295	0.7369	0.79	0.8534	0.8911	0.9577
26_968_00304350	Pancreas	968	CFPAC-1	456	5.151366	0.817	0.828	0.864	0.8724	0.8715	1.008	1.007	0.9779	1.001
026_957_00296350	Pancreas	957	SW 1990	456	5.575766	0.849	0.911	0.906	0.8954	0.9494	0.957	0.977	0.9769	1.1173
026_960_00296311	Pancreas	960	Panc 08.13	456	5.65459	0.875	0.894	0.924	0.9669	0.9243	0.96	1.1005	1.065	1.0309
026_951_00256230	Pancreas	951	HPAC	456	5.736336	0.862	1.024	0.931	0.8532	0.9386	1.035	1.0328	1.0507	1.0612
026_964_00295480	Pancreas	964	Capan-2	456	5.74256	0.877	0.928	0.759	0.8346	0.9905	0.925	1.0364	1.027	0.9499
026_1134_00298560	Pancreas	1134	PL4	456	5.771259	0.844	0.812	0.91	0.8479	0.7738	0.977	0.9068	1.059	0.9774
026_970_00293370	Pancreas	970	PA-TU-8902	456	5.772043	0.841	0.97	0.919	0.8896	0.9177	0.966	0.9181	1.322	0.9871
026_952_00292610	Pancreas	952	MIA PaCa-2	456	5.946631	0.923	0.885	0.718	0.8919	0.8505	1.058	1.0586	0.8995	1.1403
026_972_00296250	Pancreas	972	DAN-G	456	5.955955	0.897	0.924	0.945	0.9646	0.9703	0.978	1.0074	1.032	1.0585
026_951_00295520	Pancreas	951	HPAC	456	5.962773	0.923	0.889	0.787	0.9719	0.9562	1.118	0.986	0.9708	1.1145
026_975_00252910	Pancreas	975	YAPC	456	5.989883	1.015	0.914	0.897	0.8713	0.8903	1.037	0.9777	1.1409	0.981
026_963_00252950	Pancreas	963	Hs 766T	456	6.264463	0.496	0.974	0.953	1.0445	0.9118	1.028	0.9324	1.0245	1.0186
026_958_00296320	Pancreas	958	Panc 10.05	456	6.318194	0.851	0.835	0.851	0.824	0.8929	0.879	0.9003	1.0065	1.0291
026_955_00292640	Pancreas	955	SU.86.86	456	6.593699	1.017	0.82	0.986	0.9378	1.1258	1.072	1.0873	1.0381	0.9789
026_759_00300240	Pleura	759	MSTO-211H	456	3.066599	0.666	0.637	0.664	0.6954	0.8026	0.901	1.0485	1.0165	1.0436
026_1213_00303050	Pleura	1213	H2818	456	3.157415	0.577	0.674	0.728	0.8558	0.9032	0.962	0.9285	1.0744	1.1008
026_8116_00303080	Pleura	8116	MPP-89	456	3.723631	0.416	0.808	0.823	0.9733	0.9887	0.968	1.0012	0.9912	1.0294
026_1206_00302600	Pleura	1206	H2722	456	3.764667	0.604	0.768	0.801	0.8049	0.8692	0.937	0.9073	0.9842	0.9698
026_1210_00302610	Pleura	1210	H2803	456	4.117283	0.686	0.723	0.669	0.7081	0.719	0.892	0.9533	1.0129	0.9547
026_1215_00311260	Pleura	1215	H290	456	4.122283	0.629	0.753	0.69	0.7652	0.7781	0.737	0.8199	0.9853	0.9812
026_1206_00308200	Pleura	1206	H2722	456	4.184817	0.699	0.769	0.85	0.8838	0.889	0.906	1.0135	0.9948	1.0129
026_1212_00300580	Pleura	1212	H2810	456	4.445211	0.69	0.929	0.942	0.9243	0.9927	0.884	0.9289	0.9051	0.9626
026_682_00304600	Pleura	682	NCI-H2452	456	4.452468	0.722	0.847	0.891	0.906	0.9407	0.899	0.9567	1.0786	1.1287
026_1200_00300690	Pleura	1200	H2373	456	4.612295	0.695	0.911	0.887	0.9257	0.9258	0.849	0.9218	0.9772	0.9399
026_1214_00308460	Pleura	1214	H2869	456	4.934927	0.775	0.881	0.878	0.926	0.9241	0.914	0.9475	0.9536	1.0138
026_1214_00308790	Pleura	1214	H2869	456	4.961713	0.802	0.879	0.908	0.9132	0.9528	0.991	0.9959	1.0132	1.0202
026_1202_00303040	Pleura	1202	H2591	456	5.067997	0.82	0.918	0.945	1.0327	0.9338	0.983	0.9541	1.0755	1.1707
026_1209_00300210	Pleura	1209	H28	456	5.341766	0.817	0.821	0.827	0.8331	0.8999	0.927	0.9491	1.0072	0.9857
026_8078_00303060	Pleura	8078	IST-MES1	456	5.358253	0.782	0.897	0.859	0.8822	0.8445	0.907	0.9752	0.926	1.0513
026_1199_00300560	Pleura	1199	H2369	456	5.439636	0.82	0.91	0.99	0.8596	0.9181	0.984	0.9172	0.9896	1.1394
026_8078_00304970	Pleura	8078	IST-MES1	456	5.505825	0.847	0.88	0.853	0.8587	0.8938	0.89	0.9416	0.9423	1.0968
026_1207_00298510	Pleura	1207	H2731	456	5.56988	0.819	1.018	1.003	0.8986	0.9778	0.921	0.9543	0.9856	0.9695
026_1198_00302580	Pleura	1198	H2052	456	5.579483	0.859	0.966	0.995	0.9551	0.9651	1.01	1.0265	1.0233	1.0095
026_1201_00302590	Pleura	1201	H2461	456	5.654117	0.856	0.868	0.914	0.904	0.8852	0.908	0.9343	1.0239	1.1079
026_1213_00300720	Pleura	1213	H2818	456	5.828097	0.843	0.946	0.86	0.9682	0.9236	0.942	0.9493	0.9688	0.9576
026_1211_00300570	Pleura	1211	H2804	456	5.890027	0.881	0.886	0.907	0.8753	0.9153	0.955	0.969	0.9857	1.0448
026_1218_00300730	Pleura	1218	H513	456	5.953268	0.9	0.905	0.905	1.0722	1.0284	0.976	0.9507	1.0341	1.2023
026_1208_00300710	Pleura	1208	H2795	456	6.063798	0.3	0.943	0.961	0.8752	0.9823	0.905	0.9466	0.9643	0.975
026_1203_00300850	Pleura	1203	H2595	456	6.184806	0.92	0.909	0.899	1.0357	1.0632	0.905	0.974	1.018	0.9037
026_8245_00282710	pleural effusion	8245	KMS-11	456	0.702427	0.356	0.381	0.404	0.4804	0.491	0.652	0.7128	1.0645	1.1048
026_996_00298490	Prostate	996	22RV1	456	2.346887	0.542	0.521	0.592	0.6234	0.6635	0.707	0.7764	0.8517	0.9168
026_985_00303070	Prostate	985	LNCaP clone FGC	456	4.018762	0.727	0.863	0.923	1.1164	1.0922	0.984	1.0179	1.1749	1.0533
026_987_00298550	Prostate	987	PC-3	456	4.097696	0.698	0.761	0.871	0.9338	0.9109	0.914	0.9938	1.2109	0.991
026_1001_00300200	Prostate	1001	DU 145	456	5.044916	0.768	0.832	0.867	0.8699	0.8879	0.906	0.9933	0.9168	1.1136
026_988_00308270	Prostate	988	PWR-1E	456	5.228199	0.804	0.854	0.877	0.8566	0.8621	0.923	0.9727	0.9516	0.9806
026_997_00300660	Prostate	997	BPH-1	456	5.448713	0.479	0.868	1.201	1.1209	1.1016	0.674	0.9562	1.1603	0.8983
026_1000_00300740	Prostate	1000	VCaP	456	5.968581	0.692	1.071	1.005	1.0988	0.9203	0.91	0.9225	0.9154	1.1301

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_1009_00264700	Skin	1009	WM35	456	−2.372512	0.112	0.201	0.203	0.2168	0.2138	0.242	0.3676	0.463	0.7025
026_8212_00264590	Skin	8212	CP50-MEL-B	456	−1.651586	0.151	0.398	0.392	0.3817	0.3556	0.35	0.4631	0.5633	0.8209
026_1039_00265170	Skin	1039	SK-MEL-30	456	−1.476493	0.263	0.352	0.317	0.3236	0.3515	0.424	0.5534	0.8565	0.8549
026_1023_00269690	Skin	1023	SK-MEL-2	456	−1.357658	0.147	0.207	0.235	0.2621	0.2935	0.343	0.5053	0.6866	0.8936
026_1034_00264680	Skin	1034	MEL-HO	456	−0.964561	0.144	0.372	0.375	0.3139	0.3537	0.327	0.4189	0.6188	0.8613
026_8073_00263480	Skin	8073	HT-144	456	−0.641233	0.154	0.241	0.236	0.3036	0.3695	0.397	0.6432	0.7444	0.9033
026_8114_00259970	Skin	8114	MMAC-SF	456	−0.613008	0.211	0.399	0.492	0.3813	0.4238	0.662	0.5683	0.6942	1.0563
026_8209_00266540	Skin	8209	A4-Fuk	456	−0.557176	0.179	0.476	0.467	0.4234	0.4176	0.498	0.6644	0.7338	0.7609
026_1046_00263470	Skin	1046	HMVII	456	−0.454742	0.389	0.419	0.403	0.3903	0.4097	0.503	0.6117	0.8285	1.0625
026_8120_00262840	Skin	8120	MZ7-mel	456	−0.254795	0.073	0.323	0.41	0.4001	0.4106	0.468	0.6687	0.6311	0.8761
026_8191_00260580	Skin	8191	UACC-257	456	−0.10266	0.456	0.468	0.426	0.404	0.4006	0.534	0.6654	0.7954	0.894
026_1176_00266430	Skin	1176	451Lu	456	−0.00066	0.26	0.428	0.38	0.386	0.4254	0.499	0.6795	0.8423	0.9729
026_1149_00263460	Skin	1149	G-MEL	456	0.018696	0.065	0.23	0.181	0.1928	0.2465	0.404	0.7707	0.8991	0.9576
026_1147_00263750	Skin	1147	SK-MEL-28	456	0.142676	0.187	0.48	0.376	0.4566	0.4611	0.565	0.6083	0.8116	0.9418
026_1037_00260080	Skin	1037	SK-MEL-1	456	0.168848	0.176	0.417	0.368	0.3716	0.3919	0.613	0.6978	0.9091	0.966
026_1190_00266570	Skin	1190	Hs 939.T	456	0.185332	0.283	0.631	0.615	0.5802	0.5603	0.559	0.5576	0.7187	0.8082
026_1024_00265150	Skin	1024	M-14	456	0.192152	0.418	0.433	0.383	0.391	0.4651	0.618	0.742	0.7678	0.9177
026_1025_00269710	Skin	1025	COLO-679	456	0.228168	0.267	0.288	0.296	0.3664	0.4611	0.681	0.8141	0.9334	1.1196
026_8161_00263740	Skin	8161	SH-4	456	0.433257	0.203	0.383	0.33	0.3147	0.3323	0.488	0.7539	0.8959	0.983
026_8097_00262820	Skin	8097	LB2518-MEL	456	0.437866	0.076	0.501	0.37	0.3843	0.4237	0.706	0.7414	0.8914	0.9396
026_8120_00260550	Skin	8120	MZ7-mel	456	0.447706	0.299	0.428	0.435	0.4782	0.4839	0.498	0.6521	0.7326	0.8788
026_1033_00262470	Skin	1033	IPC-298	456	0.460127	0.363	0.36	0.404	0.4297	0.5245	0.562	0.7868	0.9191	0.8529
026_1031_00264030	Skin	1031	IGR-37	456	0.57267	0.159	0.498	0.512	0.4794	0.5367	0.602	0.8381	0.9754	1.0032
026_1006_00260110	Skin	1006	WM-115	456	0.616077	0.079	0.437	0.583	0.4912	0.4928	0.627	0.6176	0.6485	0.9586
026_8023_00265291	Skin	8023	COLO-829	456	0.740747	0.164	0.659	0.533	0.5534	0.5976	0.709	0.8699	0.9148	0.9877
026_1036_00264690	Skin	1036	RVH-421	456	0.784255	0.099	0.511	0.489	0.5329	0.5785	0.531	0.5954	0.5867	0.7408
026_1011_00269770	Skin	1011	WM278	456	0.944573	0.289	0.463	0.457	0.4545	0.4605	0.568	0.7513	0.8836	0.9597
026_1003_00269650	Skin	1003	G-361	456	0.948854	0.099	0.326	0.434	0.5233	0.6155	0.705	0.83	0.8998	1.0756
026_8002_00263700	Skin	8002	A101D	456	0.960267	0.088	0.468	0.524	0.5105	0.5276	0.55	0.5835	0.7643	0.8791
026_8104_00260540	Skin	8104	LOXIMVI	456	1.072404	0.278	0.403	0.39	0.4769	0.6158	0.839	0.877	0.864	0.9209
026_1005_00268780	Skin	1005	A-375	456	1.191442	0.45	0.499	0.485	0.4604	0.5149	0.506	0.6624	0.892	0.928
026_1004_00260870	Skin	1004	C32	456	1.195832	0.288	0.331	0.256	0.265	0.3055	0.504	0.8497	0.9278	0.9753
026_1030_00264020	Skin	1030	IGR-1	456	1.307792	0.075	0.388	0.556	0.5173	0.6922	0.688	0.8911	0.7819	0.8658
026_1035_00265160	Skin	1035	MEL-JUSO	456	1.414781	0.305	0.481	0.494	0.5153	0.7013	0.739	0.9127	0.9597	1.0093
026_8119_00259980	Skin	8119	MZ2-MEL.	456	1.446447	0.402	0.467	0.438	0.4246	0.4152	0.679	0.7345	0.8985	0.9484
026_8097_00260530	Skin	8097	LB2518-MEL	456	1.447504	0.439	0.438	0.44	0.3578	0.3688	0.635	0.8111	0.8622	0.8731
026_8225_00264640	Skin	8225	SK-MEL-5	456	1.574212	0.07	0.432	0.581	0.5597	0.6534	0.603	0.7648	0.9285	1.0194
026_8104_00262830	Skin	8104	LOXIMVI	456	1.676415	0.172	0.565	0.594	0.5546	0.7085	0.865	1.2098	1.0454	1.1061
026_1042_00274340	Skin	1042	COLO 792	456	1.75025	0.329	0.514	0.573	0.6166	0.6518	0.787	0.8993	0.9066	0.9485
026_1026_00269720	Skin	1026	COLO-783	456	1.791757	0.479	0.599	0.603	0.6144	0.5728	0.634	0.6979	0.8575	0.9077
026_1010_00262530	Skin	1010	WM1552C	456	2.109919	0.364	0.794	0.685	0.6806	0.6737	0.881	0.8586	0.9992	0.9359
026_1041_00263450	Skin	1041	A431	456	2.481335	0.436	0.563	0.633	0.821	0.8517	0.858	1.0792	0.8962	0.9346
026_8098_00269090	Skin	8098	LB373-MEL-D	456	2.623655	0.496	0.615	0.627	0.6225	0.6708	0.815	0.8109	0.9711	1.0201
026_1022_00262940	Skin	1022	RPMI-7951	456	2.647594	0.249	0.552	0.678	0.6664	0.7181	0.824	0.8966	0.8605	0.908
026_1181_00269080	Skin	1181	Hs 944.T	456	2.824283	0.206	0.612	0.779	0.8499	0.8608	0.892	0.9924	1.1546	1.1214
026_1008_00262540	Skin	1008	WM793B	456	2.933974	0.371	0.744	0.693	0.6962	0.7393	0.731	0.8508	0.9586	0.8942
026_1027_00265280	Skin	1027	COLO-800	456	3.132083	0.537	0.717	0.804	0.8959	0.9417	0.926	0.9678	0.954	1.0136
026_8034_00265300	Skin	8034	DJM-1	456	3.234358	0.554	0.778	0.806	0.9452	0.9331	1.005	0.9966	1.0061	1.0084
026_1181_00264620	Skin	1181	Hs 944.T	456	3.491747	0.094	0.698	0.822	0.9152	0.8448	0.9	0.9921	0.9743	0.9841

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_8225_00263510	Skin	8225	SK-MEL-5	456	3.505326	0.234	0.653	0.694	0.7331	0.7681	0.79	0.9216	0.9437	0.9528
026_1145_00263720	Skin	1145	CHL-1	456	3.811805	0.609	0.895	0.833	0.8778	0.9025	0.855	0.9286	0.9316	1.0458
026_8060_00265311	Skin	8060	GAK	456	4.2621	0.37	0.758	0.827	0.7891	0.8733	0.894	0.9899	0.9692	0.9911
026_1047_00265320	Skin	1047	MEWO	456	4.342961	0.779	0.931	0.98	0.9757	0.9449	0.991	1.0008	0.9996	1
026_1022_00260910	Skin	1022	RPMI-7951	456	4.58823	0.257	0.748	0.801	0.8703	0.8751	0.884	0.9495	0.9173	0.9542
026_1038_00260090	Skin	1038	SK-MEL-3	456	4.834702	0.151	0.731	0.777	0.7955	0.7955	0.827	0.8793	0.913	0.9361
026_1002_00260861	Skin	1002	A2058	456	5.928358	0.795	0.897	0.85	0.894	0.8474	0.885	1.0053	0.8902	0.984
026_8025_00306491	Skin	8025	CP66-MEL	456	6.278644	0.914	0.888	1.059	0.9053	1.0334	0.961	0.8798	1.0258	0.9475
026_1120_00264061	Skin	1120	UACC-62	456	6.317961	0.417	0.99	0.941	0.9531	0.9635	1.005	1.0535	1.0033	0.9903
026_1049_00269761	Skin	1049	VMRC-MELG	456	6.363031	0.904	0.991	0.949	0.974	0.9849	1.004	1.032	1.0282	1.0264
026_8077_00311281	Skin	8077	IST-MEL1	456	6.486215	0.817	0.849	0.783	0.8212	0.8361	0.894	0.8282	0.9342	0.9134
026_1002_00262871	Skin	1002	A2058	456	6.768535	0.494	1.023	0.918	0.9957	0.9334	0.899	0.9223	0.931	0.9502
026_1191_00266580	Skin	1191	Hs 940.T	456	7.017835	0.562	0.98	1.123	1.1931	0.9727	1.159	1.1334	1.0446	1.0643
026_8211_00306531	Skin	8211	SK-MEL-24	456	7.240348	0.995	1.062	1.047	0.9379	1.0364	1.075	1.0521	1.0504	1.0137
026_1004_00262880	Skin	1004	C32	456	7.407136	1.327	0.196	1.169	0.1356	1.1547	0.213	1.1935	0.7281	1.1468
026_8077_00263490	Skin	8077	IST-MEL1	456	8.189893	1.25	1.21	1.184	1.1565	0.9453	0.931	1.1642	1.0861	1.0387
026_1076_00260350	Stomach	1076	OCUM-1	456	−1.975727	0.138	0.299	0.203	0.1441	0.1472	0.137	0.1598	0.2644	0.5747
026_1050_00262790	Stomach	1050	AGS	456	0.402284	0.198	0.304	0.337	0.4411	0.6201	0.452	0.6355	0.7729	1.0239
026_1070_00258920	Stomach	1070	HSC-39	456	1.218484	0.163	0.38	0.469	0.5806	0.7048	0.892	1.16	0.922	1.1787
026_8193_00311240	Stomach	8193	ECC10	456	1.328742	0.306	0.42	0.445	0.5445	0.7218	0.758	0.8813	0.9883	0.9993
026_1052_00255810	Stomach	1052	SNU-1	456	1.425654	0.369	0.469	0.497	0.5342	0.5814	0.77	0.7984	0.8285	0.947
026_1056_00316590	Stomach	1056	KATO III	456	1.949149	0.309	0.531	0.622	0.6777	0.7504	0.912	0.9052	1.0407	1.0158
026_1060_00256830	Stomach	1060	MKN45	456	2.285447	0.504	0.586	0.532	0.5224	0.5043	0.577	0.7757	0.8156	0.9028
026_1072_00258880	Stomach	1072	23132/87	456	2.907608	0.473	0.717	0.911	0.8748	1.0846	1.055	1.07	0.981	1.001
026_1060_00262910	Stomach	1060	MKN45	456	2.913103	0.498	0.498	0.474	0.9422	0.5296	0.623	1.0575	0.9958	0.8867
026_1078_00263960	Stomach	1078	IM-95	456	3.209661	0.348	0.625	0.723	1.042	0.7453	0.866	0.8746	0.9835	0.9734
026_1054_00308870	Stomach	1054	SNU-16	456	3.34225	0.574	0.78	0.883	0.9578	0.9599	0.973	0.9861	1.0293	1.027
026_1064_00258960	Stomach	1064	NUGC-3	456	3.516892	0.253	0.754	0.947	0.9636	0.9596	1.019	1.0426	1.0278	1.0027
026_1075_00308260	Stomach	1075	NUGC-4	456	3.652276	0.617	0.827	0.703	0.9984	1.0102	1.068	1.1379	0.9929	1.1512
026_1065_00273570	Stomach	1065	MKN7	456	3.792655	0.621	0.777	0.872	0.891	0.9122	0.904	0.9197	0.9359	0.9547
026_1067_00311560	Stomach	1067	RERF-GC-1B	456	4.166168	0.732	0.677	0.761	0.8438	0.781	0.877	0.8716	0.958	1.0772
26_1067_00314080	Stomach	1067	RERF-GC-1B	456	4.402339	0.708	0.833	0.831	0.8383	0.8843	0.854	0.9212	0.9276	1.1227
026_1068_00258930	Stomach	1068	MKN28	456	4.480011	0.554	0.885	0.897	0.9579	0.9774	1.009	1.0156	1.0042	1.0326
026_1057_00271310	Stomach	1057	Hs 746T	456	4.481195	0.745	0.743	0.677	0.6977	0.6882	0.86	0.875	0.9503	1.0984
026_1060_00260890	Stomach	1060	MKN45	456	4.604315	0.753	0.738	0.731	0.6895	0.6891	0.836	1.0727	1.0008	0.9928
026_1051_00269200	Stomach	1051	FU97	456	4.755599	0.738	0.851	0.914	0.8985	0.8947	0.955	0.9241	0.9866	1.0457
026_8187_00316461	Stomach	8187	TGBC11TKB	456	4.931222	0.775	0.953	0.925	0.9227	0.9488	0.988	0.9649	0.9982	0.9763
026_1058_00263730	Stomach	1058	NCI-N87	456	5.400356	0.754	0.824	0.808	0.8382	0.8486	0.868	0.9105	0.9132	0.9828
026_1064_00264040	Stomach	1064	NUGC-3	456	6.53754	0.915	1.021	1.007	1.0316	0.9966	1.014	1.0431	0.9819	1.0068
026_1077_00264820	Stomach	1077	SCH	456	6.77844	0.466	1.271	1.195	1.2103	1.1255	0.977	0.9179	1.1315	1.1153
026_1051_00265140	Stomach	1051	FU97	456	6.812551	0.149	0.752	0.783	0.8562	0.833	0.758	0.8748	0.8287	0.8438
026_8067_00258320	Stomach	8067	GT3TKB	456	7.007727	0.623	0.977	1.004	1.0575	1.0443	1.026	1.0598	1.0143	1.0267
026_1053_00258360	Stomach	1053	SNU-5	456	7.265878	1	0.967	0.868	0.95	0.958	1.018	1.0763	1.0284	1.0105
026_1073_00258910	Stomach	1073	HGC-27	456	7.474785	0.055	1.003	1.012	1.0288	1.0225	1.013	1.0331	0.9845	0.9972
026_8062_00266170	Stomach	8062	GCIY	456	7.70033	1.076	1.218	0.962	1.0422	0.9155	1.202	0.9466	0.9302	1.1001

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_1059_00256820	Stomach	1059	MKN1	456	7.84127	1.023	1.223	1.097	1.1806	1.0334	0.924	1.0209	0.9691	0.9885
026_8216_00258330	Stomach	8216	RF-48	456	8.041101	0.627	1.056	1.075	1.0873	1.0084	1.031	1.0144	1.008	0.9914
026_8143_00302630	Testes	8143	NTERA-S-cl-D1	456	4.238289	0.709	0.74	0.781	0.8439	0.8942	0.971	0.9553	0.9264	1.0878
026_1081_00299690	Testes	1081	NCC-IT-A3	456	4.69755	0.834	0.925	0.99	1.0022	1.0753	0.959	1.0664	0.9907	0.9674
026_1082_00300430	Testes	1082	NEC8	456	5.794775	0.518	0.919	1.026	1.1263	1.0267	0.882	1.2293	0.8206	0.9481
026_1087_00311210	Thyroid	1087	BHT-101	456	0.094631	0.409	0.442	0.405	0.4025	0.4677	0.606	0.749	0.9156	0.9734
026_1098_00252970	Thyroid	1098	IHH-4	456	0.734299	0.193	0.418	0.365	0.5027	0.4309	0.608	0.6796	0.9903	0.9333
026_1093_00253040	Thyroid	1093	TT2609-C02	456	1.438563	0.33	0.462	0.489	0.4674	0.6027	0.719	0.8623	0.9552	1.0031
026_1100_00252990	Thyroid	1100	KMH-2	456	1.898194	0.142	0.5	0.577	0.6566	0.6074	0.682	0.7694	0.8888	0.9822
026_1085_00252920	Thyroid	1085	8505C	456	2.3348	0.536	0.498	0.605	0.5369	0.584	0.788	0.7985	1.0523	0.937
026_1088_00252930	Thyroid	1088	CAL-62	456	2.495611	0.451	0.785	0.606	0.8114	0.6653	0.836	1.0285	1.0053	0.944
026_1089_00261010	Thyroid	1089	HTC-C3	456	2.538171	0.577	0.55	0.623	0.7757	0.5886	0.616	0.7161	0.7476	0.9625
026_1090_00311330	Thyroid	1090	ML-1	456	2.64388	0.368	0.64	0.793	0.8005	0.8127	0.931	0.9783	0.9389	1.0355
026_1090_00253010	Thyroid	1090	ML-1	456	3.121258	0.165	0.778	0.787	0.6376	0.6432	0.975	1.0524	0.7737	1.0765
026_1090_00308850	Thyroid	1090	ML-1	456	3.18393	0.308	0.673	0.724	0.8112	0.8338	0.925	0.9016	0.8988	1.0407
026_1086_00255730	Thyroid	1086	B-CPAP	456	3.682081	0.171	0.695	0.763	0.7585	0.7239	0.856	0.9452	0.9473	1.0079
026_8020_00314210	Thyroid	8020	CGTH-W-1	456	4.407018	0.694	0.874	0.871	0.8186	0.9478	0.965	0.9497	1.0206	1.0176
026_1084_00266520	Thyroid	1084	8305C	456	4.442179	0.592	0.739	0.746	0.7517	0.73	0.793	0.8273	0.8894	0.8901
026_8213_00259200	Thyroid	8213	TT	456	4.648028	0.769	0.966	0.965	0.9831	0.9968	0.984	0.9765	0.9632	0.942
026_8082_00252980	Thyroid	8082	K5	456	6.244906	0.27	0.935	0.007	0.9319	0.951	0.93	0.997	0.9506	0.9691
026_1099_00306470	Thyroid	1099	ASH-3	456	6.262224	0.912	0.905	0.964	0.9293	0.932	0.965	0.9777	0.9947	1.0629
026_1094_00259110	Thyroid	1094	FTC-133	456	6.573461	0.084	0.958	0.978	1.0951	1.0879	1.057	1.063	1.0254	0.8654
026_1092_00259170	Thyroid	1092	S-117	456	6.767861	0.271	0.973	0.988	1.0669	1.039	1.047	1.018	1.0563	1.0542
026_1097_00259160	Thyroid	1097	RO82-W-1	456	7.698514	0.685	1.079	1.053	1.0554	1.0411	1.049	1.0682	1.0349	1.0563
26_8036_00304360	UrinaryTrack	8036	DSH1	456	1.200178	0.377	0.348	0.397	0.5545	0.7402	0.871	0.9778	0.9884	1.0288
026_24_00298840	UrinaryTrack	24	RT4	456	2.281802	0.504	0.543	0.577	0.6272	0.7473	0.889	1.0564	1.0628	1.0768
026_18_00299720	UrinaryTrack	18	RT-112	456	2.448355	0.479	0.581	0.587	0.6728	0.7768	0.797	0.8705	1.106	1.03
026_24_00252540	UrinaryTrack	24	RT4	456	2.668527	0.216	0.59	0.634	0.6994	0.7144	0.855	0.9368	0.9696	1.0194
026_8036_00257170	UrinaryTrack	8036	DSH1	456	2.728478	0.679	0.605	0.639	0.6941	0.7355	0.829	0.9411	1.0033	1.0113
026_9_00298850	UrinaryTrack	9	SW 780	456	2.896276	0.523	0.587	0.676	0.7538	0.7859	0.866	0.9594	0.9717	1.0348
026_15_00316530	UrinaryTrack	15	BFTC-905	456	3.218144	0.607	0.59	0.688	0.6971	0.8338	0.848	0.8978	1.0448	1.0799
026_8_00298880	UrinaryTrack	8	UM-UC-3	456	3.221517	0.557	0.72	0.789	0.8471	0.8599	0.995	1.0484	1.045	1.0264
026_6_00303090	UrinaryTrack	6	5637	456	3.348554	0.553	0.725	0.744	0.7649	0.9313	0.918	0.9221	0.9563	1.0354
026_6_00256650	UrinaryTrack	6	5637	456	3.837233	0.726	0.703	0.715	0.7187	0.7189	0.755	0.9193	0.965	1.0004
026_8101_00256280	UrinaryTrack	8101	LB831-BLC	456	3.939929	0.504	0.835	0.952	1.0143	1.0014	1.01	0.9848	0.9739	0.9713
026_11_00298870	UrinaryTrack	11	T24	456	4.120815	0.697	0.744	0.763	0.8533	0.8788	0.941	0.9969	1.0222	1.1105
026_19_00298860	UrinaryTrack	19	SW-1710	456	4.713264	0.758	0.847	0.828	0.8254	0.8943	0.979	0.9968	1.0264	1.0955
026_7_00302400	UrinaryTrack	7	SCaBER	456	4.780909	0.779	0.775	0.708	0.7824	0.8163	0.882	1.0463	0.9494	1.0621
026_8101_00302620	UrinaryTrack	8101	LB831-BLC	456	4.856105	0.76	0.882	0.929	0.9235	0.9393	0.926	0.9386	0.9281	1.0507
026_22_00298810	UrinaryTrack	22	HT 1376	456	4.888331	0.823	0.879	1.047	0.8692	1.0283	0.988	1.0731	1.1432	1.097
026_20_00299740	UrinaryTrack	20	VM-CUB1	456	4.987745	0.751	0.753	0.758	0.8989	0.8726	0.877	0.9581	0.9471	0.9762
026_14_00298780	UrinaryTrack	14	647-V	456	5.049696	0.854	0.851	0.873	0.8859	0.9584	1.097	1.1389	1.2074	1.0083
026_12_00299730	UrinaryTrack	12	TCCSUP	456	5.306108	0.821	0.876	0.897	0.9178	0.9315	0.962	0.9176	1.0469	1.0217
026_13_00298770	UrinaryTrack	13	639-V	456	5.658711	0.867	0.933	0.849	0.9317	0.8466	1.046	1.0223	1.1266	1.2765
026_16_00298800	UrinaryTrack	16	CAL-29	456	5.956916	0.811	0.834	0.909	0.8884	0.9073	0.924	0.956	0.9709	0.9841

TABLE 22-continued

Barcode	Organ	Cell ID	Cell Line	Compound No	Fitted MGH_IC50	Viability ratio 20 uM	10 uM	5 uM	2.5 uM	1.25 uM	0.625 uM	0.3125 uM	0.15625 uM	0.078125 uM
026_3_00308800	UrinaryTrack	3	HT-1197	456	6.060787	0.877	0.935	0.984	0.8762	0.9541	0.87	1.0393	1.0266	1.0429
026_17_00300420	UrinaryTrack	17	KU-19-19	456	6.388593	0.216	0.953	0.975	0.9996	0.9834	0.744	0.9959	0.9777	1.0473
026_10_00298820	UrinaryTrack	10	J82	456	6.755266	0.951	0.965	0.925	0.9536	1.0393	1.06	1.0882	1.0657	1.037
026_8154_00262510	Uterus	8154	RL95-2	456	0.033885	0.116	0.241	0.307	0.315	0.5516	0.413	0.6863	0.814	0.8778
026_1116_00268860	Uterus	1116	SNG-M	456	2.236003	0.377	0.605	0.635	0.4653	0.7155	0.805	0.9708	1.0702	1.1724
026_8154_00280250	Uterus	8154	RL95-2	456	2.655708	0.475	0.611	0.69	0.5902	0.6865	0.677	0.826	0.8426	0.9723
026_8166_00269750	Uterus	8166	SK-UT-1	456	2.769805	0.399	0.642	0.861	0.9305	0.8691	0.946	0.8217	0.867	0.9308
026_1115_00268850	Uterus	1115	SKN	456	3.232484	0.402	0.724	0.819	0.8345	0.9291	0.941	1.0001	0.9878	0.9814
026_1112_00268820	Uterus	1112	Ishikawa (Heraklio) 02 ER-	456	3.572844	0.62	0.659	0.62	0.6814	0.702	0.72	0.9036	0.8807	1.0744
026_1107_00311310	Uterus	1107	MFE-296	456	3.590101	0.601	0.697	0.647	0.7074	0.7773	0.802	0.8186	0.9166	1.0105
026_1108_00308840	Uterus	1108	MFE-319	456	3.953038	0.7	0.723	0.698	0.8033	0.8993	0.819	0.9773	1.1189	1.0369
026_1109_00269701	Uterus	1109	COLO 684	456	4.059524	0.645	0.818	0.925	0.873	0.8541	0.934	0.9505	0.9782	1.0023
026_1102_00268790	Uterus	1102	AN3CA	456	4.238238	0.395	0.808	0.815	0.8203	0.9291	0.817	0.9786	0.9815	0.9877
026_1108_00314330	Uterus	1108	MFE-319	456	4.375739	0.745	0.784	0.794	0.8526	0.9259	0.907	1.0498	1.0643	1.1339
026_1113_00268840	Uterus	1113	MES-SA	456	4.83984	0.832	0.962	1.003	0.9833	0.9906	0.984	0.9981	1.0121	0.9684
026_1117_00268810	Uterus	1117	HEC-1	456	5.215029	0.824	0.904	0.885	0.8856	0.9834	0.972	0.9217	1.0697	1.0963
026_1113_00318661	Uterus	1113	MES-SA	456	5.307659	0.807	0.995	0.947	0.9632	1.0122	1.033	1.0384	1.0103	0.9636
026_8206_00264270	Uterus	8206	KLE	456	5.888467	0.885	1	1.029	1.0338	1.0454	1.029	0.9964	1.0291	0.9684
026_1105_00308190	Uterus	1105	ESS-1	456	6.082924	0.887	0.915	0.911	0.9349	0.8927	0.94	0.9007	0.9407	0.9198
026_1104_00306500	Uterus	1104	EN	456	7.302741	1.047	0.983	0.999	0.9204	1.0053	1.011	1.0162	1.0749	1.0308
026_1106_00306510	Uterus	1106	MFE-280	456	7.686964	1.124	0.983	1	0.9683	1.0601	1.156	1.0799	1.0206	0.9018
026_8163_00302640	Vulva	8163	SK-LMS-1	456	2.432701	0.479	0.526	0.621	0.7198	0.8786	0.991	1.0278	1.0369	1.1613
026_8173_00302660	Vulva	8173	SW954	456	2.875791	0.539	0.622	0.644	0.6956	0.8294	0.866	1.072	1.0089	1.087
26_8174_00304380	Vulva	8174	SW962	456	4.641057	0.756	0.704	0.824	0.7868	0.8056	0.875	0.851	0.96	1.0607
026_481_00302570	Vulva	481	CAL-39	456	5.164144	0.803	0.856	0.841	0.8864	0.9389	0.924	0.983	0.9909	1.1127
026_8174_00306540	Vulva	8174	SW962	456	6.896884	0.97	0.963	1.002	0.9267	1.0771	0.973	1.0027	1.0435	1.0588

Example 12

BVD-523 Demonstrates In Vivo Antitumor Activity in BRAF^{V600E}-Mutant Cancer Cell Line Xenograft Models

[0292] Based on our in vitro findings that BVD-523 reduced proliferation and induced apoptosis in a concentration-dependent manner, BVD-523 was administered by oral gavage to demonstrate its in vivo anti-tumor activity in models with MAPK/ERK-pathway dependency. Xenograft models of melanoma (cell line A375), and colorectal cancer (cell line Colo205), were utilized, both of which harbor a BRAF^{V600E} mutation.

[0293] In A375 cell line xenografts, BVD-523 efficacy was compared with the control cytotoxic alkylating agent temozolomide following 14 days of treatment. BVD-523 demonstrated significant dose-dependent antitumor activity starting at 50 mg/kg twice daily (BID) (FIG. **31**A). Doses of 50 and 100 mg/kg BID significantly attenuated tumor growth, with tumor growth inhibition (TGI) of 71% (P=0.004) and 99% (P<0.001), respectively. Seven partial regressions (PRs) were noted in the 100 mg/kg BID group; no regression responses were noted in any other group. The efficacy observed compared favorably with that of temozolomide, which when administered at 75 and 175 mg/kg resulted in modest dose-dependent TGI of 34% (P>0.05) and 78% (P=0.005), respectively.

[0294] Additionally, BVD-523 demonstrated antitumor efficacy in a Colo205 human colorectal cancer cell line xenograft model (FIG. **31**B). BVD-523 again showed significant dose-dependent tumor regressions at doses of 50, 75, and 100 mg/kg BID, yielding mean tumor regressions T/T_i (T=End of treatment, T_i=Treatment initiation) of −48.2%, −77.2%, and −92.3%, respectively (all P<0.0001). Regression was not observed at the lowest dose of BVD-523 (25 mg/kg BID); however, significant tumor growth inhibition, with a T/C (T=Treatment, C=Control) of 25.2% (P<0.0001), was observed. Although not well tolerated, the positive control chemotherapeutic agent irinotecan (CPT-11) showed significant antitumor activity, inhibiting Colo205 tumor growth with a T/C of 6.4% (P<0.0001). However, even at its maximum tolerated dose in mice, CPT-11 was not as effective as BVD-523 at doses of 50, 75, or 100 mg/kg BID.

[0295] To establish the relationship between pharmacokinetics and pharmacodynamics, BVD-523 plasma concentrations were compared with pERK1/2 levels measured in the tumor by immunohistochemistry and isotope-tagged internal standard mass spectrometry over a 24-hour period following a single 100 mg/kg oral dose of BVD-523 (FIG. **31**C). Phosphorylation of ERK1/2 was low in untreated tumors (0 hours). Following treatment with BVD-523, ERK1/2 phosphorylation steadily increased from 1 hour post-dose to maximal levels at 8 hours post-dose, then returned to predose levels by 24 hours. This increase in pERK1/2 correlated with BVD-523 drug plasma concentrations. The in vivo observation of increased pERK1/2 with BVD-523 treatment is consistent with earlier in vitro findings (FIG. **30**D).

Example 13

BVD-523 Results in ERK1/2 Substrate Inhibition Despite Increased ERK1/2 Phosphorylation

[0296] To examine the effects of BVD-523 on signaling relative to other known ERK1/2 inhibitors (SCH772984, GDC-0994, and Vx-11e) (Morris et al. 2013 and Liu et al. 2015), a large-scale reverse phase protein array (RPPA) of approximately 40 proteins was employed in a variety of cell lines with sensitivity to ERK inhibition. Cell lines with common alterations in BRAF and RAS were assayed: BRAF^{V600E} mutant lines A375, Colo205, and HT29; KRAS^{G12C}-mutant cell line MIAPACa-2; KRAS^{G13D}-mutant cell line HCT116; and AN3Ca with atypical HRAS^{F82L} mutation. Changes in protein levels are shown as a percentage change from dimethyl sulfoxide (DMSO)-treated parental control (FIG. **32**A and Table 23). All ERK inhibitors elicited qualitatively similar protein effects, with the exception of phosphorylation of ERK1/2 (pERK1/2 [ERK1/2-T202, -Y204]); SCH7722984 inhibited pERK1/2 in all cell lines, while BVD-523, GDC-0994, and Vx-11e markedly increased pERK1/2. Phospho-p90 RSK (pRSK1) and cyclin D1, which are proximal and distal targets of pERK1/2, respectively, were similarly inhibited by all inhibitors tested regardless of the degree of ERK1/2 phosphorylation (FIG. **32**B). These independent findings for BVD-523 are consistent with studies showing that phosphorylation of ERK1/2 substrates RSK1/2 remained inhibited despite dramatically elevated pERK1/2 by Western blots in A375 cells (FIG. **32**D), in addition to protein-binding studies demonstrating BVD-523 binding and stabilization of pERK1/2 and inactive ERK1/2 (FIG. **29**E and FIG. **29**F). Therefore, measuring increased pERK1/2 levels could be considered as a clinical pharmacodynamic biomarker for BVD-523, while quantifying inhibition of ERK1/2 targets such as pRSK1 and DUSP6 as well could serve a similar purpose.

[0297] Additional protein changes are of note in this RPPA dataset (FIG. **32**A). Decreased pS6-ribosomal protein appears to be another pharmacodynamic marker of ERK1/2 inhibition, as evidenced in all cell lines with all compounds (FIG. **32**B). Furthermore, prominent induction of pAKT appears to be a cell line-dependent observation, where each ERK1/2 inhibitor induced pAKT in cell lines A375 and AN3CA cells (FIG. **33**). Interestingly, the degree of inhibition of survival marker pBAD appears to differ between compounds, with only modest inhibition of pBAD by GDC-0994 compared with the other ERK1/2 inhibitors tested (FIG. **32**A).

[0298] Next, how BVD-523 affects cellular localization of ERK1/2 and downstream target pRSK in a BRAF^{V600E}-mutant RKO colorectal cell line (FIG. **32**C) was investigated. In resting cells, ERK1/2 localizes to the cytoplasm, and once stimulated pERK1/2 migrates to target organelles, particularly the nucleus where transcriptional targets are activated (Wainstein et al. 2016). In DMSO-treated control cells, pERK1/2 is evident in both nuclear and cytoplasmic fractions, which is likely reflective of MAPK pathway activity due to the presence of BRAF^{V600E} in this cell line. Treatment with BVD-523 resulted in elevated pERK1/2 in the nucleus and cytoplasm as well as a modest increase in nuclear total ERK1/2 compared with DMSO-treated cells, suggesting that compound-induced stabilization of pERK1/2 stimulates some nuclear translocation. Despite increased pERK1/2 in both compartments, pRSK levels are lower in

the cytoplasmic and nuclear compartments compared with DMSO control. Comparator MAPK signaling inhibitors (i.e., trametinib, SCH7722984, dabrafenib) inhibited phosphorylation of ERK1/2 and RSK, as reflected by lower levels in the nuclear and cytoplasmic compartments. These data again suggest that BVD-523-associated increases in pERK1/2 are evident in both the cytoplasm and nucleus; however, this does not translate to activation of target substrates. This is consistent with data presented in FIG. **30**D and FIG. **32**A.

TABLE 23

		% change from DMSO (matched cell line)					
Cell Line	Treatment	Avg(S6 Ribo Prot S235 236)	Avg(S6 Ribo Prot S240 244)	Avg(Cyclin D1)	Avg(p90 RSK S380)	Avg(bad S112)	Avg(4ebp1 T70)
A375	BVD	−95.3	−91.98	−81.45	−71	−72.37	−31.82
A375	Vx	(Empty)	(Empty)	−85.46	−65.25	−69.29	23.33
A375	GDC	−87.61	−80.3	−81.65	−60.74	−55.32	−29.47
A375	SCH	−94.71	−91.78	−84.05	−72.44	−71.44	−31.75
AN3Ca	BVD	−43.41	−22.2	−0.69	−28.11	−54.1	32.17
AN3Ca	Vx	−18.54	−12.55	−9.59	−28.41	−45.63	16.67
AN3Ca	GDC	−30.74	−23.47	0.34	−29.44	2.53	11.28
AN3Ca	SCH	−61.99	−35.88	−11.33	−40.26	−39.14	61.57
COLO205	BVD	−96.15	−97.33	−23.65	−50.84	−31.51	−36.35
COLO205	Vx	−93.04	−94.89	−39.79	−58.6	−30.28	−43.71
COLO205	GDC	−91.19	−91.59	−28.02	−57.5	−6.12	−36.69
COLO205	SCH	−94.67	−95.09	−36.7	−62.31	−29.4	−27.51
HCT116	BVD	−96.31	−96.26	−69.62	−31.81	−34.27	4.03
HCT116	Vx	−90.03	−86.06	−72.72	−33.05	−23.88	10.35
HCT116	GDC	−94.82	−95.1	−63.59	−22.25	−12.36	20.5
HCT116	SCH	−93.86	−91.07	−73.21	−33.7	−31.29	5.6
HT29	BVD	−44.68	−25.67	−37.21	−60.5	−20.66	−41.47
HT29	Vx	−32.8	−24.35	−35.2	−43.41	−35.62	−2.89
HT29	GDC	−41.45	−21.74	−35.69	−30.59	−12.98	1.95
HT29	SCH	−44.9	−25.73	−36.66	−53.88	−33.9	−40.58
MIAPaca2	BVD	−79.46	−88.03	−37.9	−35	−30.29	−9.42
MIAPaca2	Vx	−63.36	−74.82	−33.96	−39.91	−20.85	−15.72
MIAPaca2	GDC	−67.9	−75.59	−31.92	−39.09	−10.08	−34.01
MIAPaca2	SCH	−77.57	−86.61	−39.88	−38.58	−33.07	19.27

		% change from DMSO (matched cell line)					
Cell Line	Treatment	Avg(p70 S6 Kinase T389 T412)	Avg(p70 S6 Kinase S371 S394)	Avg(ERK 1 2)	Avg(Akt)	Avg(Raptor)	Avg(Caspase 3 CL D175)
A375	BVD	−23.79	−8.58	−22.91	−14.03	−7.77	−8.06
A375	Vx	−25.54	−17.32	−5.39	−30.34	−12.7	−9.27
A375	GDC	−31.9	−17.34	31.55	−20.7	−14.32	−16.74
A375	SCH	−42.73	−28.72	−21.65	−23.26	−11.66	−9.87
AN3Ca	BVD	−14.78	32.26	−9.05	−22.43	−13.82	−10.8
AN3Ca	Vx	0.56	44.04	−11.27	−24.62	−2.47	−12.7
AN3Ca	GDC	26.01	29.09	−2.87	−26.04	−8.05	1.55
AN3Ca	SCH	−16.63	24.56	−9.27	−16.35	−11.09	1.25
COLO205	BVD	−36.4	−18.11	−18.83	−3.85	−7.14	−3.18
COLO205	Vx	−28	−13.64	−12.32	−12.51	−0.05	−2.67
COLO205	GDC	−32.2	−13.02	−3.33	−11.83	−5.48	23.06
COLO205	SCH	−30.4	−14.59	−31.87	−10.31	−2.2	14.08
HCT116	BVD	−28.11	−16.9	−29.42	4.41	−7.06	−10.11
HCT116	Vx	−20.99	−9.89	−24.01	−18.15	−4.32	−5.19
HCT116	GDC	−24.73	−11.47	−1.9	−6.13	−6.2	−8.36
HCT116	SCH	−24.63	−12.3	−10.22	−9.86	−9.66	−4.63
HT29	BVD	−24.58	−35.94	−44.3	−13.41	−8.53	−7.03
HT29	Vx	−12.31	−22.86	0.24	−17.84	−6.53	−2.86
HT29	GDC	−20.86	−25.73	4.66	−10.01	−6.85	−3.44
HT29	SCH	−9.55	−20.52	−37	−16.93	−12.18	−7.9
MIAPaca2	BVD	−39.23	−28.27	−40.33	23.63	21.15	22.35
MIAPaca2	Vx	−30.66	−30.35	−14.85	−0.15	5.4	6.17
MIAPaca2	GDC	−40.99	−14.4	−6.88	4.33	22.43	10.47
MIAPaca2	SCH	−50.97	−40.47	−23.09	13.47	17.66	21.05

		% change from DMSO (matched cell line)						
Cell Line	Treatment	Avg(mTOR S2448)	Avg(Bad S155)	Avg(c Fos)	Avg(Rictor)	Avg(p70 S6 Kinase)	Avg(Raptor S792)	Avg(Bcl 2 T56)
A375	BVD	−27.87	−21.9	4.39	−20.11	−7.6	−10.33	−8.54
A375	Vx	−21.66	−6.3	−13.65	−8.16	−6.42	−0.86	−7.53
A375	GDC	−23.61	−13.31	−12.46	−23.29	−18.11	−15.93	−4.1
A375	SCH	−26.17	−13.86	−12.51	−22.13	−17.66	−6.89	−19.55
AN3Ca	BVD	−10.79	0.66	−5.15	−4.52	−10.27	−8.47	−12.85

TABLE 23-continued

AN3Ca	Vx	−2.37	4.59	−5.52	0.02	−2.33	0.37	−11.73
AN3Ca	GDC	−2.96	17.31	−0.63	−9.21	−3.67	4.85	1.23
AN3Ca	SCH	−4.84	12.92	−9.18	−10.89	−7.71	−4.03	−10.73
COLO205	BVD	−23.51	−18.18	−12.25	−5.21	0.14	0.41	−11.84
COLO205	Vx	−8.52	−9.72	−19.34	1.65	−3.42	0.2	−12.02
COLO205	GDC	−7.36	−9.11	−21.33	−5.04	5.83	−9.04	−4.6
COLO205	SCH	−9.44	−10.96	−15.17	−19.07	−2.85	−4.17	−6.73
HCT116	BVD	−12.78	−30.72	−14.08	−13.05	−12.86	−22.04	−8.36
HCT116	Vx	−10.12	−15.59	−13.89	1.78	−4.45	−11.21	−25
HCT116	GDC	−19.33	−19.71	−10.36	−10.98	−9.9	−15.77	−11.96
HCT116	SCH	−16.05	−22.96	−15.27	−18.5	−14.12	−18.18	−15.89
HT29	BVD	−20.68	−25.9	−13.48	−18.76	−10.64	−10.48	−8.18
HT29	Vx	−13.94	−11.26	−8.23	−2.6	−1.72	−2.13	−25.01
HT29	GDC	−11.44	−6.7	−12.92	−10.62	−2.83	−1.75	1.61
HT29	SCH	−22.65	−7.98	−9.26	−13.03	−2.36	−6.38	−17.9
MIAPaca2	BVD	−11.73	−5.65	−18.44	−11.11	−3.59	5.95	−1.78
MIAPaca2	Vx	−5.38	7.38	−4.43	−13.24	−9.27	−3.74	−9.86
MIAPaca2	GDC	11.84	8.18	−16.12	−11.25	−3.25	2.18	−2.12
MIAPaca2	SCH	−11.48	−1.71	−8.99	−15.15	−7.51	4.43	−1.98

		% change from DMSO (matched cell line)						
Cell Line	Treat-ment	Avg(Bcl2 S70)	Avg(Bcl 2)	Avg(Bax)	Avg(mTOR S2481)	Avg(Tuberin TSC2 Y1571)	Avg(Chk1 S345)	Avg(CREB S133)
A375	BVD	−7.91	−12.55	−6.98	−3.36	−6.32	−7.43	−12.65
A375	Vx	−4.02	−9.93	−5.05	−2.9	−3.55	0.56	−15.8
A375	GDC	6.3	−3.13	3.97	−19.37	−16.74	−18.35	−1.18
A375	SCH	−12.91	−18.53	−17.32	−15.82	−13.7	−10.59	−1.55
AN3Ca	BVD	−14.81	−16.83	−10.47	2.75	2.86	−13.34	1.03
AN3Ca	Vx	−14.39	−18.77	−7.89	7.22	3.8	−9.54	0.16
AN3Ca	GDC	−0.65	7.8	23.83	25.42	25.18	15.46	5.03
AN3Ca	SCH	−12.42	−5.14	0.15	11.24	13.44	14.56	3.64
COLO205	BVD	−10.2	−0.13	0.28	−1.33	−3.48	−4.63	−2.67
COLO205	Vx	−20.82	−14.09	−9.16	−9.43	−9.45	13.12	−10.64
COLO205	GDC	−9	17.95	8.2	0.96	0.66	6.08	−11.85
COLO205	SCH	−18.52	−14.56	−6.44	−6.68	−1.38	1	−14.56
HCT116	BVD	−8.23	−3.59	−0.8	−34.09	−29.89	−39.65	−30.64
HCT116	Vx	−17.79	−17.3	−20.46	−17.82	−16.51	−16.49	−9.17
HCT116	GDC	−12.53	−4.56	−20.11	−18.34	−9.4	−18.77	−8.56
HCT116	SCH	−18.34	−10.58	−13.86	−22.53	−16.17	−18.51	−24.18
HT29	BVD	2.83	10.68	8.39	−8.64	0.66	−13.48	−3.46
HT29	Vx	−12.55	−16.73	−18.47	0.52	2.85	6.44	14.16
HT29	GDC	10.59	18.16	1.1	3.23	11.86	6.88	9.54
HT29	SCH	−11.45	−10.01	−20.59	13.93	13.25	19.05	9.87
MIAPaca2	BVD	0.89	5.86	23.44	−0.24	1.7	1.2	−19.26
MIAPaca2	Vx	−7.83	−2.3	4.33	−3.12	−0.01	2.09	−13.28
MIAPaca2	GDC	−6.78	−7.8	3.48	3.65	5.71	32.96	−21.37
MIAPaca2	SCH	−4.23	4.96	15.67	2.43	8.86	13.39	−6.63

		% change from DMSO (matched cell line)							
Cell LIne	Treat-ment	Avg(Caspase 7 Cl D198)	Avg(Stat3)	Avg(Bak)	Avg(MSK1 S360)	Avg(mTOR)	Avg(c Myc)	Avg(Stat1)	Avg(Mcl1)
A375	BVD	3.18	6.02	−3.26	3.35	0.2	2.56	1.32	10.67
A375	Vx	−7.62	1.71	0.65	−7.63	−3.31	−0.97	0.23	1.6
A375	GDC	−5.53	14.24	2.76	−5.21	−6.2	−9.11	−5.67	−9.09
A375	SCH	−6	−1.42	−2.37	0.97	−5.18	1.86	−6.01	2.11
AN3Ca	BVD	−12.35	−4.97	3.38	0.49	5.58	−0.58	−5.65	−4.9
AN3Ca	Vx	−8.09	−7.67	−1.6	6.83	−6.27	−5.47	−0.83	−4.24
AN3Ca	GDC	−15.56	−13.05	7.33	6.84	−2.85	3.99	9.15	−4.16
AN3Ca	SCH	−24.17	−6.01	9.73	−5.02	−5.33	0.88	5.52	−7.15
COLO205	BVD	6.76	−2.58	3.79	14.69	12.77	−1.11	0.53	−2.7
COLO205	Vx	0.03	−7.96	−2.79	6.22	3.62	−7.42	−6.1	−10.64
COLO205	GDC	1.37	−0.86	6.58	0.82	3.39	−6.22	7.26	2.5
COLO205	SCH	12.36	−6.1	4.59	7.54	−5.62	−0.64	−4.31	−0.14
HCT116	BVD	−21.09	−5.52	−13.16	−13.45	−11.96	−11.15	−13.76	−8.72
HCT116	Vx	−11.41	−7.76	−3.07	−13.73	−0.59	−18.56	−14.06	−7.79
HCT116	GDC	−13.99	−0.25	−1.74	−12.93	−4.85	−12.03	−6.32	−4.77
HCT116	SCH	−16.35	−7.67	−4.66	−15.32	−12.56	−12.86	−10.74	−6.55
HT29	BVD	−6.93	−6.46	−1.42	1.49	5.02	17.85	4.74	−2.83
HT29	Vx	8.28	−4.28	2.69	5.64	16.94	10.71	4.29	1.36
HT29	GDC	−0.88	−3.69	3.56	−0.04	10.45	7.56	2.58	3.71
HT29	SCH	7.02	−2.15	2.78	1.25	9.31	13.55	5.79	14.05
MIAPaca2	BVD	−6.44	−1.23	−15.15	−10.72	−3.27	−8.77	8.62	−7.27
MIAPaca2	Vx	−0.32	0.61	−1.93	−0.87	−1.58	−5.94	−1.64	−6.58

TABLE 23-continued

MIAPaca2	GDC	−4.92	−9.44	−8.11	−5.25	−9.8	−7.84	7.4	−1.79
MIAPaca2	SCH	8.35	−9.19	−10.88	2.74	1.64	2.11	7.17	−1.88

		% change from DMSO (matched cell line)				
Cell Line	Treat-ment	Avg(Bad S136)	Avg(Chk1)	Avg(Bim)	Avg(Akt S473)	Avg(ERK 1 2 T202 Y204)
A375	BVD	12.31	16.94	14.57	73.07	43.34
A375	Vx	5.06	−0.86	12.32	93.85	128.93
A375	GDC	−6.21	−7.72	9.8	53.66	142.37
A375	SCH	5.32	2.83	17.52	58.13	−90.63
AN3Ca	BVD	−1.02	−8.45	−12.57	52.11	733.27
AN3Ca	Vx	−3.81	−0.46	−1.46	56.17	718.94
AN3Ca	GDC	0.71	9.43	−11.63	82.37	645.51
AN3Ca	SCH	5.26	1.35	−14.09	66.17	19.75
COLO205	BVD	5.05	−2.86	41.73	−5.78	14.39
COLO205	Vx	−1.01	−9.16	34.1	−10.96	98.48
COLO205	GDC	4	5.06	20.59	4.45	20.01
COLO205	SCH	1.88	7.49	29.22	−1.74	−91.43
HCT116	BVD	−11.49	−11.26	12.44	−6.14	849.12
HCT116	Vx	−5.39	−8.63	4.82	−16.94	873.33
HCT116	GDC	−1.24	2.28	6.2	4.69	526.64
HCT116	SCH	−10.55	−5.58	1.95	−8.76	−75.21
HT29	BVD	10.73	7.4	2.81	−3.06	54.82
HT29	Vx	5.53	4.68	3.12	−20.5	435.68
HT29	GDC	2	5.68	7.74	−10.5	268.99
HT29	SCH	9.67	14.64	0.69	−22.14	−74.84
MIAPaca2	BVD	−4.12	−3.51	−12.51	9.9	209.14
MIAPaca2	Vx	0.36	−1.8	2.1	0.48	729.27
MIAPaca2	GDC	2.25	6.56	5.07	2.24	199.59
MIAPaca2	SCH	8.62	12.07	2.08	2.84	−76.71

Example 14

BVD-523 Exhibited Activity in In Vitro Models of BRAF and MEK Inhibitor Resistance

[0299] Emergence of resistance to BRAF and MEK inhibitors limits their clinical efficacy. Here, the experiments sought to model and compare the development of resistance to BRAF (dabrafenib), MEK (trametinib), and ERK1/2 (BVD-523) inhibition in vitro. Over several months, $BRAF^{V600E}$-mutant A375 cells were cultured in progressively increasing concentrations of each inhibitor. Drug-resistant A375 cell lines were readily obtained following growth in high concentrations of trametinib or dabrafenib, while developing cell lines with resistance to BVD-523 proved challenging (FIG. **34**A). Overall, these in vitro data suggest that at concentrations yielding similar target inhibition, resistance to BVD-523 is delayed compared with dabrafenib or trametinib, and may translate to durable responses in the clinic.

[0300] Reactivation and dependence on ERK1/2 signaling is a common feature of acquired resistance to BRAF/MEK inhibition (Morris et al. 2013 and Hatzivassiliou et al. 2012); therefore, the activity of BVD-523 in in vitro models of acquired resistance was evaluated. First, a dabrafenib and trametinib combination-resistant A375 population was obtained using the increased concentration method described. The IC_{50} and IC_{50}-fold change from parental A375 for dabrafenib, trametinib, and BVD-523 in the BRAF/MEK combination-resistant population is shown in Table 24. BVD-523 IC_{50} was modestly shifted (2.5-fold), while dabrafenib and trametinib were more significantly shifted (8.5-fold and 13.5-fold, respectively) (Table 24). The cytotoxic agent paclitaxel was tested as a control with only a modest shift in potency observed. These data support the investigation of BVD-523 in the setting of BRAF/MEK therapy resistance, although the mechanism of resistance in this cell population remains to be characterized.

TABLE 24

BVD-523 activity in models of BRAF/MEK inhibition

Cell Line	Dabrafenib	Trametinib	BVD-523	Paclitaxel
Parental (IC_{50} nM)	2.1	0.2	129	1.9
BRAFi- + MEKi-resistant (IC_{50} nM)	17.9	2.7	323	3.5
Fold Change	+8.5	+13.5	+2.5	+1.8

[0301] To further investigate the tractability of ERK1/2 inhibition in a model with a known mechanism of BRAF inhibitor resistance, AAV-mediated gene targeting was used to generate a pair of RKO $BRAF^{V600E}$-mutant cell lines isogenic for the presence or absence of an engineered heterozygous knock-in of $MEK1^{Q56P}$-activating mutation (Trunzer et al. 2013 and Emery et al. 2009). MEK1/2 mutations, including $MEK1^{Q56P}$, have been implicated in both single-agent BRAF and combination BRAF/MEK therapy-acquired resistance in patients (Wagle et al. 2011, Wagle et al. 2014, Emery et al. 2009 and Johnson et al. 2015). Single-agent assays demonstrated that relative to the parental $BRAF^{V600E}$::MEK1 wt cells, the double-mutant $BRAF^{V600E}$::$MEK1^{Q56P}$ cells displayed a markedly reduced sensitivity to the BRAF inhibitors vemurafenib and dabrafenib and the MEK inhibitor trametinib (FIG. **34**B). In contrast, response to BVD-523 was essentially identical in both the parental and MEK^{Q56P}-mutant cells, indicating that

BVD-523 is not susceptible to this mechanism of acquired resistance. These results were confirmed in 2 independently derived double-mutant $BRAF^{V600E}$::$MEK1^{Q56P}$ cell line clones, thus validating that results were specifically related to the presence of the $MEK1^{Q56P}$ mutation rather than an unrelated clonal artifact (data not shown). Similar results were also observed with a second mechanistically distinct ERK1/2 inhibitor (SCH772984), supporting the expectation that these observations are specifically related to mechanistic inhibition of ERK1/2 and not due to an off-target compound effect.

[0302] To further characterize the mechanistic effects of BVD-523 on MAPK pathway signaling in $BRAF^{V600E}$::$MEK1^{Q56P}$ cell lines, protein levels were assessed by Western blot (FIG. **34**C). In the parental $BRAF^{V600E}$ RKO cells, a reduced level of pRSK1/2 was observed following 4-hour treatment with BRAF (vemurafenib), MEK (trametinib), or ERK1/2 (BVD-523) inhibitors at pharmacologically active concentrations. In contrast, isogenic double-mutant $BRAF^{V600E}$::$MEK1^{Q56P}$ cells did not exhibit reduced RSK phosphorylation following BRAF or MEK inhibitor treatment, while BVD-523 remained effective in inhibiting pRSK1/2 to a level comparable to parental RKO. Similarly, pRB is reduced, indicating G0/G1 arrest, by 24 hours of BVD-523 treatment in both parental RKO and $BRAF^{V600E}$::$MEK1^{Q56P}$.

[0303] Acquired KRAS mutations are also known drivers of resistance to MAPK pathway inhibitors. To understand the susceptibility of BVD-523 to this mechanism of resistance, an isogenic panel of clinically relevant KRAS mutations in colorectal cell line SW48 was used. Sensitivity to BVD-523 was compared with MEK inhibitors selumetinib and trametinib (FIG. **34**D). Sensitivity to paclitaxel was unaltered (FIG. **37**A). While several mutant KRAS alleles conferred robust to intermediate levels of resistance to MEK inhibition, sensitivity to BVD-523 was unaltered by the majority of alleles, and where a shift in sensitivity was observed, it was not to the extent observed with trametinib or selumetinib. Overall, these data suggest that BVD-523 is more efficacious in this context than MEK inhibitors.

Example 15

BVD-523 Demonstrates In Vivo Activity in a BRAF Inhibitor-Resistant Patient-Derived Melanoma Xenograft Model

[0304] To confirm and extend the antitumor effects of BVD-523 observed in in vitro models of BRAF-/MEK-acquired resistance, a BRAF-resistant xenograft model derived from a patient with resistance to vemurafenib was utilized. BVD-523 was dosed by oral gavage at 100 mg/kg BID for 28 days, both alone and in combination with dabrafenib at 50 mg/kg BID (FIG. **35**). As expected, minimal antitumor activity was demonstrated for single-agent dabrafenib (22% TGI). BVD-523 activity was significant compared with vehicle control ($P \leq 0.05$), with a TGI of 78%. In this model, combining BVD-523 with dabrafenib resulted in a TGI of 76% ($P \leq 0.05$); therefore, further benefit was not gained for the combination compared with single-agent BVD-523 in this model of BRAF-acquired resistance.

Example 16

Combination Therapy with BVD-523 and a BRAF Inhibitor Provides Promising Antitumor Activity

[0305] Patients with BRAF-mutant cancer may acquire resistance to combined BRAF/MEK therapy (Wagle et al. 2014), warranting consideration of other combination approaches within the MAPK pathway. The anti-proliferative effects of combining BVD-523 with the BRAF inhibitor vemurafenib was assessed in the $BRAF^{V600E}$-mutant melanoma cell line G-361. As anticipated, single agents BVD-523 and vemurafenib were both active, and modest synergy was observed when combined (FIG. **37**B). This indicates that BVD-523 combined with BRAF inhibitors are at least additive and potentially synergistic in melanoma cell lines carrying a $BRAF^{V600E}$ mutation. Furthermore, generating acquired resistance in vitro following continuous culturing of $BRAF^{V600E}$ mutant cell line (A375) in BRAF inhibitor plus BVD-523 was challenging. In contrast generating resistance to dabrafenib alone occurred relatively rapidly (FIG. **37**C). Even resistance to combined dabrafenib and trametinib emerged before dabrafenib plus trametinib.

[0306] The benefit of combined BRAF and ERK inhibition may not be fully realized in in vitro combination studies where concentrations are not limited by tolerability. To understand the benefit of the combination, efficacy was assessed in vivo utilizing xenografts of the $BRAF^{V600E}$-mutant human melanoma cell line A375. Due to the noteworthy response to combination treatment, dosing in the combination groups was stopped on Day 20 to monitor for tumor regrowth, and was reinitiated on Day 42 (FIG. **36**A). Tumors were measured twice weekly until the study was terminated on Day 45. The median time to endpoint (TTE) for controls was 9.2 days, and the maximum possible tumor growth delay (TGD) of 35.8 days was defined as 100%. Temozolomide treatment resulted in a TGD of 1.3 days (4%) and no regressions. The 50- and 100-mg/kg dabrafenib monotherapies produced TGDs of 6.9 days (19%) and 19.3 days (54%), respectively, a significant survival benefit ($P<0.001$), and 1 PR in the 100-mg/kg group. The 100-mg/kg BVD-523 monotherapy resulted in a TGD of 9.3 days (26%), a significant survival benefit ($P<0.001$), and 2 durable complete responses. The combinations of dabrafenib with BVD-523 each produced the maximum possible 100% TGD with noteworthy regression responses, and statistically superior overall survival compared with their corresponding monotherapies ($P<0.001$). The lowest dose combination produced a noteworthy 7/15 tumor-free survivors (TFS), and the 3 higher-dosage combinations produced a total of 43/44 TFS, consistent with curative or near-curative activity (FIG. **36**B). In summary, the combination of dabrafenib with BVD-523 produced a greater number of TFS and superior efficacy to either single agent.

[0307] Based on the activity of BVD-523 plus dabrafenib in A375 xenograft models with a starting tumor volume of approximately 75-144 mm^3, a follow-up experiment was conducted to determine the efficacy of combination therapy in "upstaged" A375 xenografts (average tumor start volume, 700-800 mm^3) (FIG. **36**C). The median TTE for controls was 6.2 days, establishing a maximum possible TGD of 53.8 days, which was defined as 100% TGD for the 60-day study. BVD-523 100-mg/kg monotherapy produced a negligible TGD (0.7 day, 1%) and no significant survival difference from controls ($P>0.05$). The distribution of TTEs and 2 PRs

suggested there may have been a subset of responders to treatment with BVD-523 alone. Dabrafenib 50-mg/kg monotherapy was efficacious, yielding a TGD of 46.2 days (86%) and a significant survival benefit compared with controls (P<0.001). This group had 5 PRs and 5 CRs, including 3 TFS, among the 11 evaluable mice (FIG. **36**D). Both combinations of dabrafenib with BVD-523 produced the maximum 100% TGD and a significant survival benefit compared with controls (P<0.001). Each combination produced 100% regression responses among evaluable mice, though there were distinctions in regression activity. The 25-mg/kg dabrafenib and 50-mg/kg BVD-523 combination had 2 PRs and 8 CRs, with 6/10 TFS, whereas the 50-mg/kg dabrafenib and 100-mg/kg BVD-523 combination had 11/11 TFS on Day 60 (FIG. **36**D). Overall, these data support the rationale for frontline combination of BVD-523 with BRAF-targeted therapy in $BRAF^{V600}$-mutant melanoma, and this is likely to extend to other tumor types harboring this alteration.

Discussion

[0308] BVD-523 is a potent, highly selective, reversible, small molecule ATP-competitive inhibitor of ERK1/2 with activity in in vivo and in vitro cancer models. In vitro, BVD-523 demonstrated potent inhibition against several human tumor cell lines, particularly those harboring activating mutations in the MAPK signaling pathway, consistent with its mechanism of action. BVD-523 elicited changes in downstream target and effector proteins, including inhibition of direct substrate of ERK1/2, pRSK, and total DUSP6 protein levels. These findings are in line with those of previous studies of other ERK1/2 inhibitors, which demonstrated effective suppression of pRSK with ERK1/2 inhibition (Morris et al. 2013 and Hatzivassiliou et al. 2012). Interestingly, BVD-523 treatment resulted in a marked increase in ERK1/2 phosphorylation in vitro and in vivo. Similar to our findings, an increase in pERK1/2 has been reported with the ERK1/2 inhibitor Vx11e; conversely, pERK1/2 inhibition occurs with SCH772984 (Morris et al. 2013). Although differences in pERK1/2 levels were observed among the various ERK1/2 inhibitors tested, downstream effectors (i.e., pRSK1 and total DUSP6) were similarly inhibited. These findings suggest quantifying ERK1/2 target substrates, such as pRSK1, may serve as reliable pharmacodynamic biomarkers for BVD-523-mediated inhibition of ERK1/2 activity.

[0309] While BRAF (dabrafenib, vemurafenib) and MEK (trametinib, cobimetinib) inhibitors validate the MAPK pathway as a therapeutic target, particularly in patients with $BRAF^{V600}$ mutations, the antitumor response is limited by the emergence of acquired resistance and subsequent disease progression. Resistance has been attributed to the upregulation and activation of compensatory signaling molecules (Nazarian et al. 2010, Villanueva et al. 2010, Johannessen et al. 2010 and Wang et al. 2011), amplification of the target genes (Corcoran et al. 2010), and activating mutations of pathway components (e.g., RAS, MEK) (Wagle et al. 2011, Emery et al. 2009 and Wang et al. 2011). Reactivation of the ERK1/2 pathway is one common consequence of acquired resistance mechanism. When introduced into the $BRAF^{V600E}$-mutant melanoma cell line A375, MEK^{Q56P} conferred resistance to MEK and BRAF inhibition (Wagle et al. 2011). By contrast, BVD-523 retained its potent inhibitory activity in the engineered MEK^{Q56P} cell line, indicating that ERK1/2 inhibition is effective in the setting of upstream activating alterations which can arise in response to BRAF/MEK treatment. As further evidence of a role for BVD-523 in the context of acquired resistance, efficacy of BVD-523 was evident in a xenograft model derived from a tumor sample from a patient whose disease progressed on vemurafenib; the BRAF inhibitor dabrafenib was not effective in this model. These data support a role for targeting ERK1/2 in the setting of BRAF/MEK resistance, and complement previously published findings (Morris et al. 2013 and Hatzivassiliou et al. 2012). To further characterize resistance to inhibitors of the MAPK pathway, the emergence of resistance to BVD-523 itself was investigated. It was found that single-agent treatment of cancer cells with BVD-523 was durable and more challenging to develop resistance compared with other agents targeting upstream MAPK signaling components (i.e., dabrafenib, trametinib). This may suggest that acquiring resistance to ERK1/2-targeting agents is harder to achieve than acquiring resistance to BRAF or MEK therapy, potentially due to the fact that BVD-523 preferentially targets the more conserved active confirmation of the ATP binding site. However, in vitro studies with other ERK1/2 inhibitors have identified specific mutants in ERK1/2 that drive resistance (Jha et al. 2016 and Goetz et al. 2014); these specific mutations have yet to be identified in clinical samples from ERK1/2 inhibitor-relapsed patients.

[0310] The potential clinical benefit of ERK1/2 inhibition with BVD-523 extends beyond the setting of BRAF/MEK therapy-resistant patients. As ERK1/2 is a downstream master node within this MAPK pathway, its inhibition is attractive in numerous cancer settings where tumor growth depends on MAPK signaling. Approximately 30% of all cancers harbor RAS mutations; therefore, targeting downstream ERK1/2 with BVD-523 is a rational treatment approach for these cancers. Furthermore, results from a study by Hayes et al. indicate that prolonged ERK1/2 inhibition in KRAS-mutant pancreatic cancer is associated with senescent-like growth suppression (Hayes et al. 2016). However, a combination approach may be required for maximal and durable attenuation of MAPK signaling in the setting of RAS mutations. For example, MEK inhibition in KRAS-mutant colorectal cancer cell results in an adaptive response of ErbB family activation, which dampens the response to MEK inhibition (Sun et al. 2014). Similar context-specific adaptive responses may occur following ERK1/2 inhibition with BVD-523. The optimal treatment combinations for various genetic profiles and cancer histologies are the subject of ongoing research. In addition to $BRAF^{V600}$ and RAS mutations, other alterations which drive MAPK are emerging. For example, novel RAF fusions and atypical non-V600 BRAF mutations which promote RAF dimerization activate the MAPK pathway (Yao et al. 2015). BRAF inhibitors such as vemurafenib and dabrafenib which inhibit BRAFV600-mutant monomer proteins have been shown to be inactive in atypical RAF alterations which drive MAPK signaling in a dimerization-dependent manner (Yao et al. 2015). However, treatment with BVD-523 to target downstream ERK1/2 in these tumors may be a novel approach to addressing this unmet medical need.

[0311] In the setting of $BRAF^{V600}$-mutant melanoma tumors, combined BRAF and MEK inhibition exemplifies how agents targeting different nodes of the same pathway can improve treatment response and duration. Our combination studies in $BRAF^{V600E}$-mutant xenografts of human

melanoma cell line A375 provides support for combination therapy with BVD-523 and BRAF inhibitors. The combination demonstrated superior benefit relative to single-agent treatments, including results consistent with curative responses. The clinical efficacy and tolerability of combined BRAF/BVD-523 therapy remains to be determined. It would not be unreasonable to expect that a BRAF/ERK1/2 combination will at least be comparable in efficacy to a targeted BRAF/MEK combination. Furthermore, the in vitro observation that acquired resistance to BVD-523 is more challenging to achieve compared with other MAPK pathway inhibitors suggests that the BRAF/BVD-523 inhibitor combination has the potential to provide a more durable response.

[0312] Significant progress has also been made using immunotherapy for melanoma. The US FDA has approved various immune checkpoint inhibitors for the treatment of advanced melanoma, including the cytotoxic T-lymphocyte antigen-4 targeted agent ipilimumab and the programmed death-1 inhibitors pembrolizumab and nivolumab. Combining BVD-523 with such immunotherapies is an attractive therapeutic option; further investigation is warranted to explore dosing schedules and to assess whether synergistic response can be achieved.

[0313] Based on the preclinical data, BVD-523 may hold promise for treatment of patients with malignancies dependent on MAPK signaling, including those whose tumors have acquired resistance to other treatments. The clinical development of BVD-523 is described below. See, Examples 17-24

Example 17

Phase I Dose-Escalation Study of the First-in-Class Novel Oral ERK1/2 Kinase Inhibitor BVD-523 (Ulixertinib) in Patients with Advanced Solid Tumors

[0314] The present invention describes the first-in-human dose escalation study of an ERK1/2 inhibitor for the treatment of patients with advanced solid tumors. BVD-523 has an acceptable safety profile with favorable pharmacokinetics and early evidence of clinical activity.

[0315] Mitogen-activated protein kinase (MAPK) signaling via the RAS-RAF-MEK-ERK cascade plays a critical role in oncogenesis; thus attracting significant interest as a therapeutic target. This ubiquitous pathway is composed of RAS upstream of a cascade of the protein kinases RAF, MEK1/2, and ERK1/2. RAS is activated by GTP binding, which in turn results in activation of each protein kinase sequentially. Although they appear to be the only physiologic substrates for MEK1/2, ERK1/2 have many targets in the cytoplasm and nucleus, including the transcription factors Elk1, c-Fos, p53, Ets1/2, and c-Jun (Shaul et al. 2007). ERK1/2 activation and kinase activity influences cellular proliferation, differentiation, and survival through a variety of mechanisms (Rasola et al. 2010), including activation of the ribosomal S6 kinase (RSK) family members (Romeo et al. 2012).

[0316] Constitutive, aberrant activation of the RAS-RAF-MEK1/2-ERK1/2 signaling pathway has been identified and implicated in the development or maintenance of many cancers (Schubbert et al. 2007 and Gollob et al. 2006). Mutations in RAS family genes, such as KRAS, NRAS, and HRAS are the most common, with activating RAS mutations occurring in ≈30% of human cancers (Schubbert et al. 2007). KRAS mutations are prevalent in pancreatic (>90%) (Kanda et al. 2012), biliary tract (3%-50%) (Hezel et al. 2014), colorectal (30%-50%) (Arrington et al. 2012), lung (27%) (Pennycuick et al. 2012), ovarian (15%-39%) (Dobrzycka et al. 2009), and endometrioid endometrial (18%) (O'Hara and Bell 2012) cancers; NRAS mutations are prevalent in melanoma (20%) (Khattak et al. 2013) and myeloid leukemia (8%-13%) (Yohe 2015); and HRAS mutations are prevalent in bladder (12%) cancer (Fernandez-Medarde and Santos 2011). Mutations in RAF family genes, most notably BRAF, are frequent, particularly in melanoma. BRAF mutations have been identified in 66% of malignant melanomas and in ~7% of a wide range of other cancers (Davies et al. 2002), while MEK mutations are rarer, occurring at an overall frequency of 8% in melanomas (Nikolaev et al. 2012). In contrast, ERK mutations resulting in tumorigenesis have been reported only rarely to date (Deschenes-Simard et al. 2014).

[0317] The US Food and Drug Administration (FDA) has approved two selective BRAF inhibitors, vemurafenib and dabrafenib, as monotherapies for patients with $BRAF^{V600}$-mutant metastatic melanoma (Taflinar [package insert] and Zelboraf [package insert]). Though response rates for these targeted therapies can be as high as 50% in in patients with $BRAF^{V600}$ mutations, duration of response is often measured in months, not years (Hauschild et al. 2012 and McArthur et al. 2014). The MEK1/2 inhibitor trametinib is also approved as a monotherapy in this setting (Mekinist [package insert]), but is more commonly used in combination with the BRAF inhibitor dabrafenib. First-line use of trametinib administered in combination with dabrafenib offers an even greater improvement in overall survival compared with vemurafenib monotherapy without increased overall toxicity (Robert et al. 2015), highlighting the potential utility of simultaneously targeting multiple proteins of this MAPK signaling pathway. This therapeutic combination was also associated with a lower incidence of MEK inhibitor-associated rash and BRAF inhibitor-induced hyperproliferative skin lesions compared with each single agent alone (Flaherty et al. 2012). Recently, a phase III trial also demonstrated significant improvements in overall survival (25.1 vs. 18.7 months, hazard ratio [HR]0.71, P=0.0107), progression-free survival (PFS) (11.0 vs. 8.8 months, HR 0.67, P=0.0004), and overall response (69% vs. 53%; P=0.0014) with dabrafenib plus trametinib versus dabrafenib alone in patients with $BRAF^{V600E/K}$ mutation-positive melanoma (Long et al. 2015). Similarly, significant improvements in PFS (9.9 vs. 6.2 months, HR 0.51, P<0.001) and the rate of complete response (CR) or partial response (PR) (68% vs. 45%; P<0.001) have been demonstrated with the combination of cobimetinib plus vemurafenib compared with vemurafenib alone (Larkin et al. 2014). To this end, FDA approval was recently granted for the combination of vemurafenib and cobemetinib for $BRAF^{V600E/K}$-mutated melanoma. Based on these and related findings, the combination of a BRAF inhibitor plus a MEK inhibitor has become a standard targeted treatment option for patients with metastatic melanoma containing $BRAF^{V600E/K}$ mutations.

[0318] Though BRAF/MEK-targeted combination therapy has been demonstrated to provide significant additional benefit beyond single-agent options, most patients eventually develop resistance and disease progression after ~12 months (Robert et al. 2015, Flaherty et al. 2012 and Long et al. 2015). Several mechanisms of acquired resistance following either single-agent or combination therapies have been identified, including the generation of BRAF splicing variants, BRAF amplification, development of NRAS or MEK mutations, and upregulation of bypass pathways (Poulikakos et al. 2011, Corcoran et al. 2010, Nazarian et al. 2010, Shi et al. 2014, Johannessen et al. 2010, Wagle et al. 2011, Wagle et al. 2014 and Ahronian et al. 2015). Central to many of these mechanisms of resistance is the reactivation of ERK signaling, which enables the rapid recovery of MAPK pathway signaling and escape of tumor cells from single-agent BRAF or combination BRAF/MEK inhibitor therapies (Paraiso et al. 2010). ERK inhibition may provide the opportunity to avoid or overcome resistance from upstream mechanisms, as it is the most distal master kinase of this MAPK signaling pathway. This is supported by preclinical evidence that inhibition of ERK by small molecule inhibitors acted to both inhibit the emergence of resistance and overcome acquired resistance to BRAF and MEK inhibitors (Morris et al. 2013 and Hatzivassiliou et al. 2012).

[0319] BVD-523 is a highly potent, selective, reversible, ATP-competitive ERK1/2 inhibitor which has been shown to reduce tumor growth and induce tumor regression in BRAF and RAS mutant xenograft models. Furthermore, single-agent BVD-523 inhibited human xenograft models that were cross-resistant to both BRAF and MEK inhibitors. See, Examples 9-16. Therefore, an open-label, first-in-human study (Clinicaltrials.gov identifier, NCT01781429) of oral BVD-523 to identify both the maximum tolerated dose and the recommended dose for further study was undertaken. The present study also aimed to assess pharmacokinetic and pharmacodynamic properties as well as preliminary efficacy in patients with advanced cancers.

Example 18

Patient Characteristics

[0320] A total of 27 patients were enrolled and received at least one dose of study drug from Apr. 4, 2013 to Dec. 1, 2015. Baseline demographics and disease characteristics are shown in Table 25. The median patient age was 61 years (range, 33-86 years). Fifty-two percent (14/27) of patients were male and 63% (17/27) had an Eastern Cooperative Oncology Group (ECOG) performance status of 1. Melanoma was the most common cancer (30%; BRAF mutation present in 7/8 of these patients). The remaining patients had colorectal (19%; 5/27), papillary thyroid (15%; 4/27), or non-small cell lung cancer (NSCLC) (7%; 2/27), and 8 (30%) were classified as having other cancers (2 pancreatic, 1 appendiceal, 1 nonseminomatous germ cell, 1 ovarian and 3 with unknown primary). The majority of patients had received 2 or more prior lines of systemic therapy, with 41% (11/27) receiving 2 to 3 and 48% (13/27) receiving >3 prior lines of systemic therapy.

TABLE 25

Baseline demographics and clinical characteristics of patients

Parameter	N = 27
Median age, years (range)	61 (33-86)
Sex, n (%)	
Female	13 (48)
Male	14 (52)
Ethnicity, n (%)	
Not Hispanic/Latino	27 (100)
ECOG performance status	
0	10 (37)
1	17 (63)
Cancer type, n (%)	
Melanoma[a]	8 (30)
Colorectal	5 (19)
Papillary thyroid	4 (15)
Non-small cell lung	2 (7)
Other[b]	8 (30)
Molecular abnormalities, n (%)[c]	
BRAF mutant	13 (48)
KRAS mutant	6 (22)
NRAS mutant	2 (7)
Other[d]	7 (26)
Unknown	4 (15)
Number of prior systemic anticancer regimens, n (%)	
0	1 (4)
1	2 (7)
2-3	11 (41)
>3	13 (48)
Prior BRAF/MEK-targeted therapy[e], n (%)	11 (41)
BRAF	5 (19)
MEK	6 (22)
BRAF/MEK	2 (7)

[a]Seven were BRAF mutant and 1 was unknown.

[b]Two pancreatic, 1 appendiceal, 1 non-seminomatous germ cell, 1 ovarian, 3 unknown primary.

[c]Patients may have more than 1 molecular abnormality.

[d]Other molecular abnormalities included ERCC1, RRM1, thymidylate synthetase, GNAS, MEK1, TP53, CREBBP, ROS1, PTEN, AKT3, and PIK3CA.

[e]Some patients were treated with more than one BRAF inhibitor.

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Example 19

Ex Vivo Effects of BVD-523 on RSK1/2 Phosphorylation

[0321] An ex vivo biomarker assay that could be used to support clinical studies was developed to demonstrate the inhibitory effects of BVD-523 on ERK activity. The assay extends preclinical cellular data where inhibitors of MAPK signaling, such as BVD-523, dabrafenib, trametinib, and vemurafenib, have been shown to inhibit RSK phosphorylation as a function of inhibitor concentration in BRAF mutant cancer cell lines. See, Examples 9-16. Specifically, ERK inhibitor-dependent inhibition of phorbol 12-myristate 13-acetate (PMA)-stimulated phosphorylation of the ERK substrate RSK1 in whole blood was used as a target marker. When BVD-523 was added directly to whole blood from healthy volunteers, PMA-stimulated RSK phosphorylation decreased with increasing concentrations of BVD-523 (FIG. **38**). The mean IC_{50} for the cumulative data was 461±20 nM for BVD-523, with a maximum inhibition of 75.8±2.7% at 10 μM BVD-523. Maximum inhibition was defined as the RSK phosphorylation measured in the presence of 10 μM

BVD-523. Patient-derived whole blood samples, collected just prior to dosing or at defined timepoints following dosing with BVD-523, were similarly treated and RSK phosphorylation levels quantitated.

Example 20

Dose Escalation, Dose-Limiting Toxicities (DLTs), Maximum Tolerated Dose (MTD), and Recommended Phase II Dose (RP2D)

[0322] As per protocol, 5 single-patient cohorts (from 10 to 150 mg twice-daily [BID]) proceeded without evidence of a DLT. The 300-mg BID cohort was expanded to more fully characterize BVD-523 exposures. One of 6 patients given 600 mg BID experienced a DLT of Grade 3 rash. The 900-mg BID dose exceeded the MTD, with one patient experiencing Grade 3 pruritus and elevated aspartate aminotransferase (AST) and another patient experiencing Grade 3 diarrhea, vomiting, dehydration, and elevated creatinine (Table 26). The subsequent intermediate dose of 750 mg BID also exceeded the MTD, with DLTs of Grade 3 rash and Grade 2 diarrhea in 1 patient and Grade 2 hypotension, elevated creatinine, and anemia in another patient. Therefore, the MTD and RP2D were determined to be 600 mg BID.

TABLE 26

Dose-limiting toxicities in Cycle 1 (21 days)

Dose, mg (BID)	DLT Frequency	DLT Description
10	0/1	N/A
20	0/1	N/A
40	0/1	N/A
75	0/1	N/A
150	0/1	N/A
300	0/4	N/A
600	1/8	Rash (Grade 3)
750[a]	2/4	Rash (Grade 3), diarrhea (Grade 2) Hypotension (Grade 2), elevated creatinine (Grade 2), anemia (Grade 2), delay to cycle 2 dosing
900	2/7	Pruritus (Grade 3), elevated AST (Grade 3) Diarrhea (Grade 3), vomiting (Grade 3), dehydration (Grade 3), elevated creatinine (Grade 3)

[a]Intermediate dose.

Abbreviations: AST, aspartate transaminase, BID, twice daily; DLT, dose-limiting toxicity; N/A, not applicable.

Example 21

Adverse Events (AEs)

[0323] Investigator-assessed treatment-related AEs of any grade were noted in 26 of 27 patients (96%). The most common treatment-related AEs (>30%) were rash (predominately acneiform) (70%), fatigue (59%), diarrhea (52%), and nausea (52%) (Table 27). No patients experienced a Grade 4 or 5 treatment-related AE or discontinued treatment due to a treatment-related AE. Most events were Grade 1 to 2, with treatment-related Grade 3 events noted in 13 of 27 patients (48%). The only Grade 3 treatment-related events present in >10% of patients were diarrhea (15%) and increased liver function tests (11%), all of which occurred above the 600-mg BID dose.

TABLE 27

Adverse events possibly/definitely related to BVD-523 in ≥10% of patients

	N = 27		
Event	Any grade, n (%)	Grade 1 or 2, n (%)	Grade 3[a], n (%)
Rash	20 (74)	18 (67)	2[b] (7)
Fatigue	17 (63)	16 (59)	1 (4)
Diarrhea	16 (59)	12 (44)	4 (15)
Nausea	14 (52)	14 (52)	0
Vomiting	8 (30)	7 (26)	1 (4)
Anorexia	6 (22)	6 (22)	0
Pruritus	6 (22)	6 (22)	0
Anemia	5 (19)	3 (11)	2 (7)
Increased creatinine	5 (19)	4 (15)	1 (4)
Dehydration	5 (19)	3 (11)	2 (7)
Peripheral edema	4 (15)	4 (15)	0
Increased LFTs (ALT and AST)	4 (14)	1 (4)	3 (11)
Blurry/dimmed vision[c]	3 (11)	3 (11)	0
Constipation	3 (11)	3 (11)	0
Fever	3 (11)	3 (11)	0

[a]No patients experienced Grade 4 or 5 AEs that were possibly or definitely related to BVD-523 treatment.
[b]Acneiform and maculo-papular rash.
[c]One Grade 1 event of related central serous retinopathy.

Analysis cut-off date: Dec. 1, 2015.

Abbreviations: AEs, adverse events; ALT, alanine transaminase; AST, aspartate transaminase; LFTs, liver function tests.

[0324] Fourteen patients experienced a total of 28 serious AEs (SAEs). Nine of these were considered to be related or possibly related to BVD-523 by the investigator, which included dehydration, diarrhea, or elevated creatinine (2 patients each), vomiting, nausea, and fever (1 patient each). All other SAEs were considered to be unrelated to treatment with BVD-523. Dose reductions resulting from AEs occurred in 3 patients during the study: 1 patient reduced from 600 mg BID to 300 mg BID and 2 patients reduced from 900 mg BID to 600 mg BID.

Example 22

Pharmacokinetics

[0325] Single-dose and steady-state pharmacokinetics of BVD-523 are summarized in FIG. **39**A and Table 28. Generally, orally administered BVD-523 was slowly absorbed in patients with advanced malignancies. After reaching the maximum concentration (C_{max}), plasma BVD-523 levels remained sustained for approximately 2 to 4 hours. Subsequently, plasma drug concentrations slowly declined. Since plasma drug concentrations were measured only up to 12 hours after the morning dose, it was not possible to calculate an effective or terminal phase elimination rate. BVD-523 pharmacokinetics were linear and dose proportional in terms of both C_{max} and area under the curve (AUC) when administered up to 600 mg BID. A further increase in exposure was not observed as the dose increased from 600 to 900 mg BID. The C_{max} reached the level of the EC_{50} based on the ex vivo whole blood assay (≈200 ng/mL) for all doses above 20 mg BID. Additionally, steady-state exposures remained at or above the target EC_{50} for dose levels of ≥150 mg BID throughout the dosing period. Minimal plasma accumulation of BVD-523 and its metabolites were observed on Day 15 at the lower (<75 mg BID) dose levels, whereas accumulation ranged from approximately 1.3- to 4.0-fold for the higher dose levels. Predose

concentrations on Day 22 were generally similar to those on Day 15, indicating that steady state had already been attained by Day 15 (data not shown). The degree of inter-patient variability in plasma exposure to BVD-523 and its metabolites was considered moderate and not problematic.

TABLE 28

Steady-state BVD-523 pharmacokinetics (Cycle 1, Day 15)

		C_{max}, ng/mL ± SD		AUC_{0-22}, ng · hr/mL ± SD	
Dose, mg[a]	n∞	Day 1	Day 15	Day 1	Day 15
10	1	48.2	45.7	220	234
20	1	14.9	15.8	91.7	98.7
40	1	100	191	614	999
150	1	133	326	817	2770
300	4[b]	765 ± 234	586 ± 257	4110 ± 1140	4460 ± 2460
600[c]	7[d]	1110 ± 589	2750 ± 1740	2750 ± 1740	24400 ± 16200
750	4[b]	1450 ± 539	2290 ± 1790[f]	10700 ± 1120[g]	23300 ± 19800[f]
900	7[e]	1430 ± 1010	1720 ± 328	10800 ± 6320[h]	15900 ± 1300[g]

[a]Dose level administered twice daily;

[b]n = 3 on Day 15;

[c]Number of subjects for Day 15 at the 600 mg dose level includes two subjects who started Day 1 dosing at 900 mg and were later reduced to 600 mg;

[d]n = 8 on Day 15;

[e]n = 4 on Day 15;

[f]One subject started on Day 1 dosing at 750 mg and was later reduced to 450 mg. Day 15 parameters for this subject reflect at least 10 consecutive doses at 450 mg/dose. Individual Day 15 parameters were 1300 ng/mL for C_{max} and 10700 ng · hr/mL for AU_{max};

[g]n = 3;

[h]n = 5.

[0326] The urinary excretion after first dose and at steady state of BVD-523 was negligible (<0.2% of the dose) at all dose levels within 12 hours postdose, and not dose-related within this very low percentage range. Renal clearance appeared to be dose-independent. Individual renal clearance values ranged from 0.128 to 0.0895 L/hr (where n=1 per dose level) and mean values ranged from 0.0149 to 0.0300 L/hr (where n≥3).

Example 23

Pharmacodynamic Confirmation of Target Inhibition by BVD-523

[0327] To confirm on-target and pathway inhibition by BVD-523, RSK-1 phosphorylation was examined as a target biomarker in human whole blood samples from patients with solid tumors who received BVD-523. Steady state whole blood samples collected just prior to Day 15 dosing from BVD-523-treated patients displayed concentration-dependent inhibition of PMA stimulated ERK activity (FIG. **39**B), ranging from 0% ERK inhibition with BVD-523 dosing at 10 mg BID to 93±8% ERK inhibition with dosing at 900 mg BID. The plasma concentrations of BVD-523 that yielded 50% inhibition of ERK phosphorylation were similar whether BVD-523 was spiked directly into healthy volunteer plasma or was present following oral dosing of patients.

Example 24

Antitumor Effects

[0328] Tumor response to BVD-523 was assessed in 25 evaluable patients using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1); 2 patients did not receive both scans of target lesions and were thus not evaluated using RECIST v1.1. No patients achieved a complete response, but 3 patients (all patients with melanoma with $BRAF^{V600}$ mutations) achieved a partial response (129 days [BRAF/MEK-inhibitor naïve], 294 days ongoing at [refractory to prior BRAF/MEK inhibitors], 313 days ongoing by the data cutoff date [intolerant to other BRAF/MEK inhibitors]) (FIG. **40**A). Interestingly, all 3 partial responders had BRAF-mutant melanoma. One partial responder, who was receiving BVD-523 at a dose of 450 mg BID, had an approximate 70% reduction in the sum of target lesions from baseline, while the other partial responders showed reductions of 47.0% and 33.6%. Stable disease was demonstrated in 18 patients, with 6 having stable disease for more than 6 months, and 6 additional patients having stable disease for more than 3 months. In this study, 4 patients displayed progressive disease at first evaluation.

[0329] FIG. **40**B shows computed tomography (CT) scans of 1 of the 3 partial responders (RECIST v1.1) who had progressed on prior vemurafenib and subsequent dabrafenib/trametinib treatment; a durable partial response was observed following dosing of BVD-523 600 mg BID for >300 days. BVD-523 was associated with a metabolic response using fluorodeoxyglucose-positive emission tomography (^{18}F-FDG-PET) in 5 of 16 evaluable patients.

[0330] FIG. **41** depicts the time to response and the duration of response in the study population. The two patients who demonstrated responses to BVD-523 remained on study and continued with BVD-523 treatment as of the study cutoff date (>500 days); additionally, one patient with bronchoalveolar NSCLC (not enough tissue for molecular profiling) had been on treatment for >700 days with stable disease. Twenty-four of 27 patients (90%) discontinued treatment due to progressive disease (22/27, 82%) or other reasons (2/27, 7%). The mean duration of BVD-523 treatment before discontinuation was 4.7 months.

Discussion

[0331] The present invention presents results from a first-in-human study evaluating the safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of BVD-523 in 27 patients with advanced solid tumors. In this dose-esca-

lation study, oral treatment with BVD-523 resulted in both radiographic responses by RECIST v1.1 (3 partial responses) and prolonged disease stabilization in some patients, the majority of whom had been treated with 22 prior systemic therapies. Evidence of BVD-523-dependent inhibition of metabolic response in tumors was established in a subset of patients by imaging tumor uptake of ^{18}F-glucose. Drug exposures increased linearly with increasing doses up to 600 mg BID, with exposures at 600 mg BID providing near complete 24/7 inhibition of ERK-dependent substrate (RSK-1) phosphorylation in an ex vivo whole blood assay. Furthermore, tolerability to BVD-523 was manageable when administered up to its MTD and RP2D, determined to be 600 mg BID.

[0332] BVD-523 was generally well tolerated, with manageable and reversible toxicity. The most common AEs were rash (usually acneiform), fatigue, and gastrointestinal side effects, including nausea, vomiting, and diarrhea. The safety profile of BVD-523 is consistent with its selective inhibition of the MAPK pathway; the AE profile shows considerable overlap with MEK inhibitor experience. However, toxicities associated with any targeted therapy may include dependence on both the specific mechanism and the degree of target inhibition as well as any off-target effects (Zelboraf [package insert] and Hauschild et al. 2012). Ongoing and future investigations will extend both the efficacy and safety profile demonstrated in this dose-escalation study, and will guide how the unique profile of the ERK inhibitor BVD-523 might be used as a single agent or in combination with other agents.

[0333] Durable responses by RAF and MEK inhibitors are often limited by intrinsic and eventual acquired resistance, with a common feature often involving reactivation of the ERK pathway (Poulikakos et al. 2011, Corcoran et al. 2010, Nazarian et al. 2010, Shi et al. 2014, Johannessen et al. 2010, Wagle et al. 2011, Wagle et al. 2014, Ahronian et al. 2015 and Paraiso et al. 2010). Thus, ERK inhibition with BVD-523 alone or in combination with other MAPK signaling pathway inhibitors may have the potential to delay the development of resistance to existing therapies and to benefit a broader patient population. That ERK inhibitors, including BVD-523, retain their potency in BRAF- and MEK-resistant cell lines provide preclinical evidence for the use of ERK inhibitors in patients with acquired resistance to standard of care (BRAF/MEK combination therapy) See, e.g., Examples 9-16. Importantly, in this study, a patient whose cancer had progressed after experiencing stable disease when treated initially with a BRAF inhibitor (vemurafenib) and subsequently with a combination of BRAF and MEK inhibitors (dabrafenib/trametinib) had a partial response when receiving single-agent BVD-523. This patient has remained on-study for a total of 708 days, as of the cutoff date of the study reported herein. Based in part on the antitumor effects observed in this patient, the FDA has designated as a Fast Track development program the investigation of BVD-523 for the treatment of patients with unresectable or metastatic $BRAF^{V600}$ mutation-positive melanoma that is refractory to or has progressed following treatment with a BRAF and/or MEK inhibitor(s). Precise definition of exactly how BVD-523 might best support patient care (eg, as a single agent or in various combinations) requires additional clinical studies.

[0334] In summary, the present examples present data from an initial data from the dose escalation portion of a phase I study evaluating BVD-523, a novel first-in-class ERK inhibitor, as a treatment for patients with advanced cancers. Continuous, twice-daily oral treatment with BVD-523 resulted in antitumor effects in several patients, including patients either naïve to or having progressed on available MAPK pathway-targeted therapies. BVD-523 was generally well tolerated in this advanced cancer patient population and toxicities were manageable; the MTD and RP2D were 600 mg BID. BVD-523 exposures increased linearly up to the RP2D and robust pharmacodynamics effects were evident at this dose level. An expansion of this phase I clinical study is currently underway to confirm and extend the observations made in the dose-escalation phase. Specifically, patients are being enrolled into molecularly classified expansion cohorts (e.g., NRAS, BRAF, MEK or ERK alterations) across various tumor histologies. Furthermore, expansion cohorts are evaluating the use of BVD-523 in patients with cancer who are either naïve to available MAPK pathway therapies or those whose disease has progressed on such treatments.

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[0417] All documents cited in this application are hereby incorporated by reference as if recited in full herein.

[0418] Although illustrative embodiments of the present invention have been described herein, it should be understood that the invention is not limited to those described, and that various other changes or modifications may be made by one skilled in the art without departing from the scope or spirit of the invention.

SEQUENCE LISTING

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

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cggggacatg gagcccgagg ccggcgccgg cgccggcgcc gcggcctctt cggctgcgga 180

ccctgccatt ccggaggagg tgtggaatat caaacaaatg attaagttga cacaggaaca 240

tatagaggcc ctattggaca aatttggtgg ggagcataat ccaccatcaa tatatctgga 300

ggcctatgaa gaatacacca gcaagctaga tgcactccaa caaagagaac aacagttatt 360

ggaatctctg gggaacggaa ctgatttttc tgtttctagc tctgcatcaa tggataccgt 420

tacatcttct tcctcttcta gcctttcagt gctaccttca tctctttcag tttttcaaaa 480

tcccacagat gtggcacgga gcaaccccaa gtcaccacaa aaacctatcg ttagagtctt 540

cctgcccaac aaacagagga cagtggtacc tgcaaggtgt ggagttacag tccgagacag 600

tctaaagaaa gcactgatga tgagaggtct aatcccagag tgctgtgctg tttacagaat 660

tcaggatgga gagaagaaac caattggttg ggacactgat atttcctggc ttactggaga 720

agaattgcat gtggaagtgt tggagaatgt tccacttaca acacacaact ttgtacgaaa 780

aacgtttttc accttagcat tttgtgactt ttgtcgaaag ctgcttttcc agggtttccg 840

ctgtcaaaca tgtggttata aatttcacca gcgttgtagt acagaagttc cactgatgtg 900

tgttaattat gaccaacttg atttgctgtt tgtctccaag ttctttgaac accacccaat 960

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cacaaagcca caactggcta ttgttaccca gtggtgtgag ggctccagct tgtatcacca 1680

tctccatatc attgagacca aatttgagat gatcaaactt atagatattg cacgacagac 1740

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gaaatctcga tggagtgggt cccatcagtt tgaacagttg tctggatcca ttttgtggat 1920

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caacagggac cagataattt ttatggtggg acgaggatac ctgtctccag atctcagtaa 2100

ggtacggagt aactgtccaa aagccatgaa gagattaatg gcagagtgcc tcaaaaagaa 2160

aagagatgag agaccactct ttccccaaat tctcgcctct attgagctgc tggcccgctc 2220

attgccaaaa attcaccgca gtgcatcaga accctccttg aatcgggctg gtttccaaac 2280

agaggatttt agtctatatg cttgtgcttc tccaaaaaca cccatccagg caggggata 2340

tggtgcgttt cctgtccact gaaacaaatg agtgagagag ttcaggagag tagcaacaaa 2400

aggaaaataa atgaacatat gtttgcttat atgttaaatt gaataaaata ctctcttttt 2460

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ctaaaattta tacttaacat tggattttta acatccaagg gttaaaatac atagacattg 2580

ctaaaaattg gcagagcctc ttctagaggc tttactttct gttccgggtt tgtatcattc 2640

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catgtccact agggactcca gaagaagacc ctacctatgc ctgtgtttgc aggtgagaag 2760

ttggcagtcg gttagcctgg gttagataag gcaaactgaa cagatctaat ttaggaagtc 2820

agtagaattt aataattcta ttattattct taataatttt tctataacta tttctttta 2880

taacaatttg gaaaatgtgg atgtctttta tttccttgaa gcaataaact aagtttcttt 2940

ttataaaaa 2949

<210> SEQ ID NO 2
<211> LENGTH: 765
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

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Leu Phe Asn Gly Asp Met Glu Pro Glu Ala Gly Ala Gly Ala Gly Ala
20 25 30

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Ala Ala Ser Ser Ala Ala Asp Pro Ala Ile Pro Glu Glu Val Trp Asn
        35                  40                  45

Ile Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu
    50                  55                  60

Asp Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala
65                  70                  75                  80

Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln
                85                  90                  95

Gln Leu Leu Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser
            100                 105                 110

Ser Ala Ser Met Asp Thr Val Thr Ser Ser Ser Ser Ser Ser Leu Ser
        115                 120                 125

Val Leu Pro Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val Ala
    130                 135                 140

Arg Ser Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu
145                 150                 155                 160

Pro Asn Lys Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr Val
                165                 170                 175

Arg Asp Ser Leu Lys Lys Ala Leu Met Met Arg Gly Leu Ile Pro Glu
            180                 185                 190

Cys Cys Ala Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly
        195                 200                 205

Trp Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu
    210                 215                 220

Val Leu Glu Asn Val Pro Leu Thr Thr His Asn Phe Val Arg Lys Thr
225                 230                 235                 240

Phe Phe Thr Leu Ala Phe Cys Asp Phe Cys Arg Lys Leu Leu Phe Gln
                245                 250                 255

Gly Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys Ser
            260                 265                 270

Thr Glu Val Pro Leu Met Cys Val Asn Tyr Asp Gln Leu Asp Leu Leu
        275                 280                 285

Phe Val Ser Lys Phe Phe Glu His His Pro Ile Pro Gln Glu Glu Ala
    290                 295                 300

Ser Leu Ala Glu Thr Ala Leu Thr Ser Gly Ser Ser Pro Ser Ala Pro
305                 310                 315                 320

Ala Ser Asp Ser Ile Gly Pro Gln Ile Leu Thr Ser Pro Ser Pro Ser
                325                 330                 335

Lys Ser Ile Pro Ile Pro Gln Pro Phe Arg Pro Ala Asp Glu Asp His
            340                 345                 350

Arg Asn Gln Phe Gly Gln Arg Asp Arg Ser Ser Ser Ala Pro Asn Val
        355                 360                 365

His Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Asp Leu Ile Arg Asp
    370                 375                 380

Gln Gly Phe Arg Gly Asp Gly Gly Ser Thr Thr Gly Leu Ser Ala Thr
385                 390                 395                 400

Pro Pro Ala Ser Leu Pro Gly Ser Leu Thr Asn Val Lys Ala Leu Gln
                405                 410                 415

Lys Ser Pro Gly Pro Gln Arg Glu Arg Lys Ser Ser Ser Ser Ser Glu
            420                 425                 430

Asp Arg Asn Arg Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp Asp
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        435                 440                 445

Trp Glu Ile Pro Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly Ser
    450                 455                 460

Gly Ser Phe Gly Thr Val Tyr Lys Gly Lys Trp His Gly Asp Val Ala
465                 470                 475                 480

Val Lys Met Leu Asn Val Thr Ala Pro Thr Pro Gln Gln Leu Gln Ala
                485                 490                 495

Phe Lys Asn Glu Val Gly Val Leu Arg Lys Thr Arg His Val Asn Ile
            500                 505                 510

Leu Leu Phe Met Gly Tyr Ser Thr Lys Pro Gln Leu Ala Ile Val Thr
        515                 520                 525

Gln Trp Cys Glu Gly Ser Ser Leu Tyr His His Leu His Ile Ile Glu
    530                 535                 540

Thr Lys Phe Glu Met Ile Lys Leu Ile Asp Ile Ala Arg Gln Thr Ala
545                 550                 555                 560

Gln Gly Met Asp Tyr Leu His Ala Lys Ser Ile Ile His Arg Asp Leu
                565                 570                 575

Lys Ser Asn Asn Ile Phe Leu His Glu Asp Leu Thr Val Lys Ile Gly
            580                 585                 590

Asp Phe Gly Leu Ala Thr Val Lys Ser Arg Trp Ser Gly Ser His Gln
        595                 600                 605

Phe Glu Gln Leu Ser Gly Ser Ile Leu Trp Met Ala Pro Glu Val Ile
    610                 615                 620

Arg Met Gln Asp Lys Asn Pro Tyr Ser Phe Gln Ser Asp Val Tyr Ala
625                 630                 635                 640

Phe Gly Ile Val Leu Tyr Glu Leu Met Thr Gly Gln Leu Pro Tyr Ser
                645                 650                 655

Asn Ile Asn Asn Arg Asp Gln Ile Ile Phe Met Val Gly Arg Gly Tyr
            660                 665                 670

Leu Ser Pro Asp Leu Ser Lys Val Arg Ser Asn Cys Pro Lys Ala Met
        675                 680                 685

Lys Arg Leu Met Ala Glu Cys Leu Lys Lys Lys Arg Asp Glu Arg Pro
    690                 695                 700

Leu Phe Pro Gln Ile Leu Ala Ser Ile Glu Leu Leu Ala Arg Ser Leu
705                 710                 715                 720

Pro Lys Ile His Arg Ser Ala Ser Glu Pro Ser Leu Asn Arg Ala Gly
                725                 730                 735

Phe Gln Thr Glu Asp Phe Ser Leu Tyr Ala Cys Ala Ser Pro Lys Thr
            740                 745                 750

Pro Ile Gln Ala Gly Gly Tyr Gly Ala Phe Pro Val His
        755                 760                 765


<210> SEQ ID NO 3
<211> LENGTH: 3906
<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 3

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ggcggtggtg gcggcggcgg cggcggcgcc gaacagggac aggctctgtt caatggcgac    120

atggagccgg aggccggcgc tggcgccgcg gcctcttcgg ccgcggaccc ggccattcct    180
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ttggacaagt ttggtgggga gcataaccca ccgtcaatat acctggaggc ctatgaagag 300

tacaccagca agctagatgc ccttcagcag agagagcagc agctgttgga atccctggtt 360

tttcaaactc ccacagatgt atcacggaac aaccccaagt caccacagaa acctatcgtt 420

cgtgtcttcc tgcccaacaa acagaggaca gtggtgcccg caagatgtgg tgtaacggtc 480

cgagacagtc taaagaaagc actaatgatg aggggtctca tcccagagtg ctgtgctgtt 540

tacagaattc aggacggaga gaagaaacca attggctggg acactgacat ttcctggctt 600

actggagagg agctacatgt tgaagtacta gagaatgttc ctctgacaac ccacaacttc 660

gtacggaaaa ctttttttcac cttagcattt tgtgactttt gccgaaagct gcttttccag 720

ggtttccgct gtcaaacatg tggttataag tttcaccagc gttgtagtac agaggttcca 780

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tccattccaa ttccacagcc cttccggcca gcagatgaag atcatcgcaa tcagtttggg 1020

caacgagacc gctcctcctc cgctcccaat gttcatataa acacaatcga acctgtcaat 1080

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gggtttcgtg gggatggagc ccctttgaac cagctgatgc gctgtcttcg gaaataccaa 1200

tcccggactc ccagcccccc cctccattct gtccccagtg aaatagtgtt tgattttgag 1260

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atggattact tacacgccaa gtcaatcatc cacagagacc tcaagagtaa taatatattt 1860

cttcatgaag acctcacggt aaaaataggt gactttggtt tagccacagt gaagtcccga 1920

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gtaatcagaa tgcaagataa aaacccatat agctttcagt cagacgtgta tgcatttggg 2040

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cagataattt ttatggtggg acgaggatac ctatctccag atctcagtaa ggtacggagt 2160

aactgtccaa aagccatgaa gagattaatg gcagagtgcc tcaaaaagaa aagagacgag 2220

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gcagccttca agtagccact ccatcatggc agcatctact ctttatttct taagtcttgt 2460

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ctgatggggc gatttcaatc accaagcatc gttcttgcct gttgtgggat tatgtcgtgg 2880

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gttctt 3906

<210> SEQ ID NO 4
<211> LENGTH: 804
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 4

Met Ala Ala Leu Ser Gly Gly Gly Gly Ser Ser Ser Gly Gly Gly Gly
1 5 10 15

Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Ala Glu Gln
20 25 30

Gly Gln Ala Leu Phe Asn Gly Asp Met Glu Pro Glu Ala Gly Ala Gly
35 40 45

Ala Ala Ala Ser Ser Ala Ala Asp Pro Ala Ile Pro Glu Glu Val Trp
50 55 60

Asn Ile Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu
65 70 75 80

Leu Asp Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu
85 90 95

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Ala Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu
            100                 105                 110

Gln Gln Leu Leu Glu Ser Leu Val Phe Gln Thr Pro Thr Asp Val Ser
        115                 120                 125

Arg Asn Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu
    130                 135                 140

Pro Asn Lys Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr Val
145                 150                 155                 160

Arg Asp Ser Leu Lys Lys Ala Leu Met Met Arg Gly Leu Ile Pro Glu
                165                 170                 175

Cys Cys Ala Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly
            180                 185                 190

Trp Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu
        195                 200                 205

Val Leu Glu Asn Val Pro Leu Thr Thr His Asn Phe Val Arg Lys Thr
    210                 215                 220

Phe Phe Thr Leu Ala Phe Cys Asp Phe Cys Arg Lys Leu Leu Phe Gln
225                 230                 235                 240

Gly Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys Ser
                245                 250                 255

Thr Glu Val Pro Leu Met Cys Val Asn Tyr Asp Gln Leu Asp Leu Leu
            260                 265                 270

Phe Val Ser Lys Phe Phe Glu His His Pro Val Pro Gln Glu Glu Ala
        275                 280                 285

Phe Ser Ala Glu Thr Thr Leu Pro Ser Gly Cys Ser Ser Ala Pro Pro
    290                 295                 300

Ser Asp Ser Ile Gly Pro Gln Ile Leu Thr Ser Pro Ser Pro Ser Lys
305                 310                 315                 320

Ser Ile Pro Ile Pro Gln Pro Phe Arg Pro Ala Asp Glu Asp His Arg
                325                 330                 335

Asn Gln Phe Gly Gln Arg Asp Arg Ser Ser Ser Ala Pro Asn Val His
            340                 345                 350

Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Glu Lys Phe Pro Glu Val
        355                 360                 365

Glu Leu Gln Asp Gln Arg Asp Leu Ile Arg Asp Gln Gly Phe Arg Gly
    370                 375                 380

Asp Gly Ala Pro Leu Asn Gln Leu Met Arg Cys Leu Arg Lys Tyr Gln
385                 390                 395                 400

Ser Arg Thr Pro Ser Pro Leu Leu His Ser Val Pro Ser Glu Ile Val
                405                 410                 415

Phe Asp Phe Glu Pro Gly Pro Val Phe Arg Gly Ser Thr Thr Gly Leu
            420                 425                 430

Ser Ala Thr Pro Pro Ala Ser Leu Pro Gly Ser Leu Thr Asn Val Lys
        435                 440                 445

Ala Leu Gln Lys Ser Pro Gly Pro Gln Arg Glu Arg Lys Ser Ser Ser
    450                 455                 460

Ser Ser Ser Ser Thr Glu Asp Arg Ser Arg Met Lys Thr Leu Gly Arg
465                 470                 475                 480

Arg Asp Ser Ser Asp Asp Trp Glu Ile Pro Asp Gly Gln Ile Thr Val
                485                 490                 495

Gly Gln Arg Ile Gly Ser Gly Ser Phe Gly Thr Val Tyr Lys Gly Lys
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            500                 505                 510

Trp His Gly Asp Val Ala Val Lys Met Leu Asn Val Thr Ala Pro Thr
        515                 520                 525

Pro Gln Gln Leu Gln Ala Phe Lys Asn Glu Val Gly Val Leu Arg Lys
    530                 535                 540

Thr Arg His Val Asn Ile Leu Leu Phe Met Gly Tyr Ser Thr Lys Pro
545                 550                 555                 560

Gln Leu Ala Ile Val Thr Gln Trp Cys Glu Gly Ser Ser Leu Tyr His
                565                 570                 575

His Leu His Ile Ile Glu Thr Lys Phe Glu Met Ile Lys Leu Ile Asp
            580                 585                 590

Ile Ala Arg Gln Thr Ala Gln Gly Met Asp Tyr Leu His Ala Lys Ser
        595                 600                 605

Ile Ile His Arg Asp Leu Lys Ser Asn Asn Ile Phe Leu His Glu Asp
    610                 615                 620

Leu Thr Val Lys Ile Gly Asp Phe Gly Leu Ala Thr Val Lys Ser Arg
625                 630                 635                 640

Trp Ser Gly Ser His Gln Phe Glu Gln Leu Ser Gly Ser Ile Leu Trp
                645                 650                 655

Met Ala Pro Glu Val Ile Arg Met Gln Asp Lys Asn Pro Tyr Ser Phe
            660                 665                 670

Gln Ser Asp Val Tyr Ala Phe Gly Ile Val Leu Tyr Glu Leu Met Thr
        675                 680                 685

Gly Gln Leu Pro Tyr Ser Asn Ile Asn Asn Arg Asp Gln Ile Ile Phe
    690                 695                 700

Met Val Gly Arg Gly Tyr Leu Ser Pro Asp Leu Ser Lys Val Arg Ser
705                 710                 715                 720

Asn Cys Pro Lys Ala Met Lys Arg Leu Met Ala Glu Cys Leu Lys Lys
                725                 730                 735

Lys Arg Asp Glu Arg Pro Leu Phe Pro Gln Ile Leu Ala Ser Ile Glu
            740                 745                 750

Leu Leu Ala Arg Ser Leu Pro Lys Ile His Arg Ser Ala Ser Glu Pro
        755                 760                 765

Ser Leu Asn Arg Ala Gly Phe Gln Thr Glu Asp Phe Ser Leu Tyr Ala
    770                 775                 780

Cys Ala Ser Pro Lys Thr Pro Ile Gln Ala Gly Gly Tyr Gly Glu Phe
785                 790                 795                 800

Ala Ala Phe Lys
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<210> SEQ ID NO 5
<211> LENGTH: 9728
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 5

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cccctccccg ccccgcggcg gccgctcggc ccggctcgcg cttcgaagat ggcggcgctg    180

agtggcggcg gtggcagcag cagcggtggc ggcggcggcg gtggcggcgg cggtggcggt    240

ggcgacggcg gcggcggcgc cgagcagggc caggctctgt tcaatggcga catggagccg    300
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gaggccggcg ctggcgccgc ggcctcttcg gctgcggacc cggccattcc tgaagaggta 360

tggaatatca agcaaatgat taagttgaca caggaacata tagaggccct attggacaaa 420

tttggtggag agcataaccc accatcaata tacctggagg cctatgaaga gtacaccagc 480

aagctagatg cccttcagca aagagaacag cagcttttgg aatccctggt ttttcaaact 540

cccacagatg catcacggaa caaccccaag tcaccacaga aacctatcgt tagagtcttc 600

ctgcccaaca aacagaggac agtggtaccc gcaagatgtg gtgttacagt tcgagacagt 660

ctaaagaaag cactgatgat gagaggtctc atcccagaat gctgtgctgt ttacagaatt 720

caggatggag agaagaaacc aattggctgg gacacggaca tttcctggct tactggagag 780

gagttacatg ttgaagtact ggagaatgtc ccacttacaa cacacaactt tgtacggaaa 840

actttttca ccttagcatt ttgtgacttt tgccgaaagc tgcttttcca gggtttccgt 900

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<210> SEQ ID NO 6
<211> LENGTH: 804
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 6

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Gln Gly Gln Ala Leu Phe Asn Gly Asp Met Glu Pro Glu Ala Gly Ala
35 40 45

Gly Ala Ala Ala Ser Ser Ala Ala Asp Pro Ala Ile Pro Glu Glu Val
50 55 60

Trp Asn Ile Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala
65 70 75 80

Leu Leu Asp Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu
85 90 95

Glu Ala Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg
100 105 110

Glu Gln Gln Leu Leu Glu Ser Leu Val Phe Gln Thr Pro Thr Asp Ala
115 120 125

Ser Arg Asn Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe
130 135 140

Leu Pro Asn Lys Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr
145 150 155 160

Val Arg Asp Ser Leu Lys Lys Ala Leu Met Met Arg Gly Leu Ile Pro
165 170 175

Glu Cys Cys Ala Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile
180 185 190

Gly Trp Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val
195 200 205

Glu Val Leu Glu Asn Val Pro Leu Thr Thr His Asn Phe Val Arg Lys
210 215 220

Thr Phe Phe Thr Leu Ala Phe Cys Asp Phe Cys Arg Lys Leu Leu Phe
225 230 235 240

Gln Gly Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys
245 250 255

Ser Thr Glu Val Pro Leu Met Cys Val Asn Tyr Asp Gln Leu Asp Leu
260 265 270

Leu Phe Val Ser Lys Phe Phe Glu His His Pro Val Pro Gln Glu Glu
275 280 285

Ala Ser Phe Pro Glu Thr Ala Leu Pro Ser Gly Ser Ser Ser Ala Pro
290 295 300

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Lys Ser Ile Pro Ile Pro Gln Pro Phe Arg Pro Ala Asp Glu Asp His
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Arg Asn Gln Phe Gly Gln Arg Asp Arg Ser Ser Ser Ala Pro Asn Val
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His Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Glu Lys Phe Pro Glu
        355                 360                 365

Val Glu Leu Gln Asp Gln Arg Asp Leu Ile Arg Asp Gln Gly Phe Arg
    370                 375                 380

Gly Asp Gly Ala Pro Leu Asn Gln Leu Met Arg Cys Leu Arg Lys Tyr
385                 390                 395                 400

Gln Ser Arg Thr Pro Ser Pro Leu Leu His Ser Val Pro Ser Glu Ile
                405                 410                 415

Val Phe Asp Phe Glu Pro Gly Pro Val Phe Arg Gly Ser Thr Thr Gly
            420                 425                 430

Leu Ser Ala Thr Pro Pro Ala Ser Leu Pro Gly Ser Leu Thr Asn Val
        435                 440                 445

Lys Ala Leu Gln Lys Ser Pro Gly Pro Gln Arg Glu Arg Lys Ser Ser
    450                 455                 460

Ser Ser Ser Ser Ser Glu Asp Arg Ser Arg Met Lys Thr Leu Gly Arg
465                 470                 475                 480

Arg Asp Ser Ser Asp Asp Trp Glu Ile Pro Asp Gly Gln Ile Thr Val
                485                 490                 495

Gly Gln Arg Ile Gly Ser Gly Ser Phe Gly Thr Val Tyr Lys Gly Lys
            500                 505                 510

Trp His Gly Asp Val Ala Val Lys Met Leu Asn Val Thr Ala Pro Thr
        515                 520                 525

Pro Gln Gln Leu Gln Ala Phe Lys Asn Glu Val Gly Val Leu Arg Lys
    530                 535                 540

Thr Arg His Val Asn Ile Leu Leu Phe Met Gly Tyr Ser Thr Lys Pro
545                 550                 555                 560

Gln Leu Ala Ile Val Thr Gln Trp Cys Glu Gly Ser Ser Leu Tyr His
                565                 570                 575

His Leu His Ile Ile Glu Thr Lys Phe Glu Met Ile Lys Leu Ile Asp
            580                 585                 590

Ile Ala Arg Gln Thr Ala Gln Gly Met Asp Tyr Leu His Ala Lys Ser
        595                 600                 605

Ile Ile His Arg Asp Leu Lys Ser Asn Asn Ile Phe Leu His Glu Asp
    610                 615                 620

Leu Thr Val Lys Ile Gly Asp Phe Gly Leu Ala Thr Val Lys Ser Arg
625                 630                 635                 640

Trp Ser Gly Ser His Gln Phe Glu Gln Leu Ser Gly Ser Ile Leu Trp
                645                 650                 655

Met Ala Pro Glu Val Ile Arg Met Gln Asp Lys Asn Pro Tyr Ser Phe
            660                 665                 670

Gln Ser Asp Val Tyr Ala Phe Gly Ile Val Leu Tyr Glu Leu Met Thr
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Gly Gln Leu Pro Tyr Ser Asn Ile Asn Asn Arg Asp Gln Ile Ile Phe
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Met Val Gly Arg Gly Tyr Leu Ser Pro Asp Leu Ser Lys Val Arg Ser
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Asn Cys Pro Lys Ala Met Lys Arg Leu Met Ala Glu Cys Leu Lys Lys
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Lys Arg Asp Glu Arg Pro Leu Phe Pro Gln Ile Leu Ala Ser Ile Glu
            740                 745                 750

Leu Leu Ala Arg Ser Leu Pro Lys Ile His Arg Ser Ala Ser Glu Pro
        755                 760                 765

Ser Leu Asn Arg Ala Gly Phe Gln Thr Glu Asp Phe Ser Leu Tyr Ala
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Cys Ala Ser Pro Lys Thr Pro Ile Gln Ala Gly Gly Tyr Gly Glu Phe
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Ala Ala Phe Lys
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<210> SEQ ID NO 7
<211> LENGTH: 2232
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 7

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<210> SEQ ID NO 8
<211> LENGTH: 743
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 8

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His Ile Glu Ala Leu Leu Asp Lys Phe Gly Gly Glu His Asn Pro Pro
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Ser Ile Tyr Leu Glu Ala Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala
35 40 45

Leu Gln Gln Arg Glu Gln Gln Leu Leu Glu Ser Leu Val Phe Gln Asn
50 55 60

Pro Thr Asp Val Ser Arg Ser Asn Pro Lys Ser Pro Gln Lys Pro Ile
65 70 75 80

Val Arg Val Phe Leu Pro Asn Lys Gln Arg Thr Val Val Pro Ala Arg
85 90 95

Cys Gly Val Thr Val Arg Asp Ser Leu Lys Lys Ala Leu Met Met Arg
100 105 110

Gly Leu Ile Pro Glu Cys Cys Ala Val Tyr Arg Ile Gln Asp Gly Glu
115 120 125

Lys Lys Pro Ile Gly Trp Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu
130 135 140

Glu Leu His Val Glu Val Leu Glu Asn Val Pro Leu Thr Thr His Asn
145 150 155 160

Phe Val Arg Lys Thr Phe Phe Thr Leu Ala Phe Cys Asp Phe Cys Arg
165 170 175

Lys Leu Leu Phe Gln Gly Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe
180 185 190

His Gln Arg Cys Ser Thr Glu Val Pro Leu Met Cys Val Asn Tyr Asp
195 200 205

Gln Leu Asp Leu Leu Phe Val Ser Lys Phe Phe Glu His His Pro Val

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    210                 215                 220

Pro Gln Glu Glu Ala Ser Leu Ala Glu Thr Ala Leu Thr Ser Gly Ser
225                 230                 235                 240

Ser Pro Ser Ala Pro Pro Ser Asp Ser Ile Gly His Gln Ile Leu Thr
                245                 250                 255

Ser Pro Ser Pro Ser Lys Ser Ile Pro Ile Pro Gln Ser Phe Arg Pro
            260                 265                 270

Ala Asp Glu Asp His Arg Asn Gln Phe Gly Gln Arg Asp Arg Ser Ser
        275                 280                 285

Ser Ala Pro Asn Val His Ile Asn Thr Ile Glu Pro Val Asn Ile Asp
    290                 295                 300

Glu Lys Phe Pro Glu Val Glu Leu Gln Asp Gln Arg Asp Leu Ile Arg
305                 310                 315                 320

Asp Gln Gly Phe Arg Gly Asp Gly Ala Pro Leu Asn Gln Leu Met Arg
                325                 330                 335

Cys Leu Arg Lys Tyr Gln Ser Arg Thr Pro Ser Pro Leu Leu Pro Ser
            340                 345                 350

Val Pro Ser Asp Ile Val Phe Asp Phe Glu Pro Gly Pro Val Phe Arg
        355                 360                 365

Gly Ser Thr Thr Gly Leu Ser Ala Thr Pro Pro Ala Ser Leu Pro Gly
    370                 375                 380

Ser Leu Thr Ser Val Lys Ala Val Gln Arg Ser Pro Gly Pro Gln Arg
385                 390                 395                 400

Glu Arg Lys Ser Ser Ser Ser Ser Glu Asp Arg Asn Arg Met Lys Thr
                405                 410                 415

Leu Gly Arg Arg Asp Ser Ser Asp Asp Trp Glu Ile Pro Asp Gly Gln
            420                 425                 430

Ile Thr Val Gly Gln Arg Ile Gly Ser Gly Ser Phe Gly Thr Val Tyr
        435                 440                 445

Lys Gly Lys Trp His Gly Asp Val Ala Val Lys Met Leu Asn Val Thr
    450                 455                 460

Ala Pro Thr Pro Gln Gln Leu Gln Ala Phe Lys Asn Glu Val Gly Val
465                 470                 475                 480

Leu Arg Lys Thr Arg His Val Asn Ile Leu Leu Phe Met Gly Tyr Ser
                485                 490                 495

Thr Lys Pro Gln Leu Ala Ile Val Thr Gln Trp Cys Glu Gly Ser Ser
            500                 505                 510

Leu Tyr His His Leu His Ile Ile Glu Thr Lys Phe Glu Met Ile Lys
        515                 520                 525

Leu Ile Asp Ile Ala Arg Gln Thr Ala Gln Gly Met Asp Tyr Leu His
    530                 535                 540

Ala Lys Ser Ile Ile His Arg Asp Leu Lys Ser Asn Asn Ile Phe Leu
545                 550                 555                 560

His Glu Asp Leu Thr Val Lys Ile Gly Asp Phe Gly Leu Ala Thr Val
                565                 570                 575

Lys Ser Arg Trp Ser Gly Ser His Gln Phe Glu Gln Leu Ser Gly Ser
            580                 585                 590

Ile Leu Trp Met Ala Pro Glu Val Ile Arg Met Gln Asp Lys Asn Pro
        595                 600                 605

Tyr Ser Phe Gln Ser Asp Val Tyr Ala Phe Gly Ile Val Leu Tyr Glu
    610                 615                 620
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Leu Met Thr Gly Gln Leu Pro Tyr Ser Asn Ile Asn Asn Arg Asp Gln
625                 630                 635                 640

Ile Ile Phe Met Val Gly Arg Gly Tyr Leu Ser Pro Asp Leu Ser Lys
                645                 650                 655

Val Arg Ser Asn Cys Pro Lys Ala Met Lys Arg Leu Met Ala Glu Cys
            660                 665                 670

Leu Lys Lys Lys Arg Asp Glu Arg Pro Leu Phe Pro Gln Ile Leu Ala
        675                 680                 685

Ser Ile Glu Leu Leu Ala Arg Ser Leu Pro Lys Ile His Arg Ser Ala
    690                 695                 700

Ser Glu Pro Ser Leu Asn Arg Ala Gly Phe Gln Thr Glu Asp Phe Ser
705                 710                 715                 720

Leu Tyr Ala Cys Ala Ser Pro Lys Thr Pro Ile Gln Ala Gly Gly Tyr
                725                 730                 735

Gly Glu Phe Ala Ala Phe Lys
            740
```

<210> SEQ ID NO 9
<211> LENGTH: 2186
<212> TYPE: DNA
<213> ORGANISM: Cavia porcellus

<400> SEQUENCE: 9

```
atggcggcgc tcagcggcgg cggtggcgcg gagcagggcc aggctctgtt caacggggac     60

atggagctcg aggccggcgc cggcgccgca gcctcttcgg ctgcagaccc tgccattccc    120

gaggaggtat ggaatatcaa acaaatgatt aagttgacgc aggaacacat agaggcccta    180

ttggacaaat ttggtggaga gcataatcca ccatcaatat acctggaggc ctatgaagaa    240

tacaccagca aactagatgc cctccaacaa agagaacagc agttactgga atccctcggg    300

aatggaactg atttttctgt ttctagctct gcatcactgg acaccgttac atcttcttct    360

tcttctagcc tttcagtact accttcatct ctttcagttt ttcaaaatcc tacagatgtg    420

tcacggagca accccaaatc accacaaaaa cctattgtta gagtcttcct gcccaacaaa    480

cagaggacag tggtacctgc aaggtgtgga gttacagtcc gagacagtct gaagaaagca    540

ctcatgatga gaggtcttat cccagagtgc tgtgctgtgt acagaattca ggatggagaa    600

aagaaaccaa ttggctggga cactgacatt tcctggctta ctggggaaga attacatgta    660

gaagtattgg agaatgttcc acttacaaca cacaattttg tatgtatctt tatatttttt    720

ttgctgtttg tctccaagtt ctttgaacac cacccaatac cacaggagga ggcttcctta    780

gcagagacca cccttacatc tggatcatcc ccttctgcac ccccctcaga gtccattggg    840

cccccaattc tcaccagccc atctccttca aaatccattc caattccaca gcctttccgg    900

ccaggagagg aagatcatcg aaatcaattt gggcagcgag accggtcctc atctgctccc    960

aatgtgcata taaacacaat agaacctgtc aatattgatg atttgattag agaccaaggg   1020

tttcgtagtg atggaggatc aactacaggt ttgtctgcca ccccacctgc ctcattacct   1080

ggctcactca ctaatgtgaa agccttacag aaatctccag gacctcagcg agaaaggaag   1140

tcatcttcat cctcagaaga cagaaatcga atgaaaacgc ttggtagacg ggactcaagt   1200

gatgattggg agattcctga tgggcagatt acagtgggac aaagaattgg atctgggtca   1260

tttggaacag tctacaaggg gaagtggcat ggtgacgtgg cagtgaaaat gttgaatgtg   1320
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acagcaccca cacctcaaca gttacaggcc ttcaaaaatg aagtaggagt actcaggaaa   1380

acacgacatg tgaatatcct actcttcatg ggctattcca caaagccaca gctagctatt   1440

gttacccagt ggtgtgaggg ctccagctta taccaccatc tccacatcat cgagaccaaa   1500

tttgagatga tcaaacttat agatattgca cgacagactg cccagggcat ggattactta   1560

cacgccaagt caatcatcca cagagacctc aagagtaata atatatttct tcacgaagac   1620

ctcacggtta aaataggtga ttttggtcta gccacagtga aatctcgatg gagtgggtcc   1680

catcagtttg aacagttgtc tggatccatt ttgtggatgg caccagaagt aatcagaatg   1740

cgagataaaa acccatacag ttttcagtcc gatgtatatg catttgggat tgttctatat   1800

gaattgatga ctgggcagtt accctattca aatatcaaca acagggacca gataattttt   1860

atggtgggac gaggatatct atctccagat ctcagcaagg tacggagtaa ctgtccaaaa   1920

gccatgaaga ggttaatggc ggagtgcctc aaaaagaaaa gagatgagag accactcttt   1980

ccccaaattc tcgcctctat tgagctgctg gcccgctcat tgccaaaaat tcaccgcagt   2040

gcatcagaac cctccttgaa tcgggctggt ttccaaacag aggattttag tctctatgct   2100

tgtgcttctc caaaaacacc catccaggca gggggatatg gtgcgtttcc tgtccactga   2160

tgcaaattaa atgagtgaga aataaa                                        2186
```

<210> SEQ ID NO 10
<211> LENGTH: 719
<212> TYPE: PRT
<213> ORGANISM: Cavia porcellus

<400> SEQUENCE: 10

```
Met Ala Ala Leu Ser Gly Gly Gly Gly Ala Glu Gln Gly Gln Ala Leu
1               5                   10                  15

Phe Asn Gly Asp Met Glu Leu Glu Ala Gly Ala Gly Ala Ala Ala Ser
            20                  25                  30

Ser Ala Ala Asp Pro Ala Ile Pro Glu Glu Val Trp Asn Ile Lys Gln
        35                  40                  45

Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu Asp Lys Phe
    50                  55                  60

Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala Tyr Glu Glu
65                  70                  75                  80

Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln Gln Leu Leu
                85                  90                  95

Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser Ser Ala Ser
            100                 105                 110

Leu Asp Thr Val Thr Ser Ser Ser Ser Ser Ser Leu Ser Val Leu Pro
        115                 120                 125

Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val Ser Arg Ser Asn
    130                 135                 140

Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu Pro Asn Lys
145                 150                 155                 160

Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr Val Arg Asp Ser
                165                 170                 175

Leu Lys Lys Ala Leu Met Met Arg Gly Leu Ile Pro Glu Cys Cys Ala
            180                 185                 190

Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly Trp Asp Thr
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        195                 200                 205

Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu Val Leu Glu
    210                 215                 220

Asn Val Pro Leu Thr Thr His Asn Phe Val Cys Ile Phe Ile Phe Phe
225                 230                 235                 240

Leu Leu Phe Val Ser Lys Phe Phe Glu His His Pro Ile Pro Gln Glu
                245                 250                 255

Glu Ala Ser Leu Ala Glu Thr Thr Leu Thr Ser Gly Ser Ser Pro Ser
            260                 265                 270

Ala Pro Pro Ser Glu Ser Ile Gly Pro Pro Ile Leu Thr Ser Pro Ser
        275                 280                 285

Pro Ser Lys Ser Ile Pro Ile Pro Gln Pro Phe Arg Pro Gly Glu Glu
    290                 295                 300

Asp His Arg Asn Gln Phe Gly Gln Arg Asp Arg Ser Ser Ser Ala Pro
305                 310                 315                 320

Asn Val His Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Asp Leu Ile
                325                 330                 335

Arg Asp Gln Gly Phe Arg Ser Asp Gly Gly Ser Thr Thr Gly Leu Ser
            340                 345                 350

Ala Thr Pro Pro Ala Ser Leu Pro Gly Ser Leu Thr Asn Val Lys Ala
        355                 360                 365

Leu Gln Lys Ser Pro Gly Pro Gln Arg Glu Arg Lys Ser Ser Ser Ser
    370                 375                 380

Ser Glu Asp Arg Asn Arg Met Lys Thr Leu Gly Arg Arg Asp Ser Ser
385                 390                 395                 400

Asp Asp Trp Glu Ile Pro Asp Gly Gln Ile Thr Val Gly Gln Arg Ile
                405                 410                 415

Gly Ser Gly Ser Phe Gly Thr Val Tyr Lys Gly Lys Trp His Gly Asp
            420                 425                 430

Val Ala Val Lys Met Leu Asn Val Thr Ala Pro Thr Pro Gln Gln Leu
        435                 440                 445

Gln Ala Phe Lys Asn Glu Val Gly Val Leu Arg Lys Thr Arg His Val
    450                 455                 460

Asn Ile Leu Leu Phe Met Gly Tyr Ser Thr Lys Pro Gln Leu Ala Ile
465                 470                 475                 480

Val Thr Gln Trp Cys Glu Gly Ser Ser Leu Tyr His His Leu His Ile
                485                 490                 495

Ile Glu Thr Lys Phe Glu Met Ile Lys Leu Ile Asp Ile Ala Arg Gln
            500                 505                 510

Thr Ala Gln Gly Met Asp Tyr Leu His Ala Lys Ser Ile Ile His Arg
        515                 520                 525

Asp Leu Lys Ser Asn Asn Ile Phe Leu His Glu Asp Leu Thr Val Lys
    530                 535                 540

Ile Gly Asp Phe Gly Leu Ala Thr Val Lys Ser Arg Trp Ser Gly Ser
545                 550                 555                 560

His Gln Phe Glu Gln Leu Ser Gly Ser Ile Leu Trp Met Ala Pro Glu
                565                 570                 575

Val Ile Arg Met Arg Asp Lys Asn Pro Tyr Ser Phe Gln Ser Asp Val
            580                 585                 590

Tyr Ala Phe Gly Ile Val Leu Tyr Glu Leu Met Thr Gly Gln Leu Pro
        595                 600                 605
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Tyr Ser Asn Ile Asn Asn Arg Asp Gln Ile Ile Phe Met Val Gly Arg
    610                 615                 620

Gly Tyr Leu Ser Pro Asp Leu Ser Lys Val Arg Ser Asn Cys Pro Lys
625                 630                 635                 640

Ala Met Lys Arg Leu Met Ala Glu Cys Leu Lys Lys Lys Arg Asp Glu
                645                 650                 655

Arg Pro Leu Phe Pro Gln Ile Leu Ala Ser Ile Glu Leu Leu Ala Arg
            660                 665                 670

Ser Leu Pro Lys Ile His Arg Ser Ala Ser Glu Pro Ser Leu Asn Arg
        675                 680                 685

Ala Gly Phe Gln Thr Glu Asp Phe Ser Leu Tyr Ala Cys Ala Ser Pro
    690                 695                 700

Lys Thr Pro Ile Gln Ala Gly Gly Tyr Gly Ala Phe Pro Val His
705                 710                 715


<210> SEQ ID NO 11
<211> LENGTH: 3229
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 11

gtaatgctgg attttcatgg aataagtttg acctgtgctg cagtggcctc cagcaaggta     60

cccgcaagat gtggagttac agtccgggac agtctaaaga aagctctgat gatgagaggt    120

ctaatcccag agtgctgtgc tgtttacaga attcaggatg gagagaagaa accgattggc    180

tgggacactg atatttcctg gctcactgga gaggaattgc atgtagaagt gttggaaaat    240

gttccgctta ccacacacaa ctttgtacgg aaaacttttt tcaccttagc attttgtgac    300

ttttgtcgaa agctgctttt ccagggtttt cgctgtcaaa catgtggtta taaatttcac    360

cagcgttgta gtacagaggt tccactgatg tgtgttaatt atgaccaact tgatttgctg    420

tttgtctcca agttctttga acaccaccca ataccacagg aggaggcctc catagcagag    480

actgcccttа cgtctggatc atccccttct gctcccccct ccgattctcc tgggccccca    540

attctgacca gtccgtctcc ttcaaaatcc attccaattc cacagccttt ccgaccagca    600

gatgaagatc atcgaaatca gtttggacaa cgagaccggt cctcatcagc tccaaatgtg    660

catataaaca caatagaacc cgtcaacatt gatgacttga ttagagacca agggtttcgt    720

agtgatggag gatcaaccac aggtttgtct gccacccccc ctgcctcatt gcctggctca    780

ctcactaatg taaaagcatt acagaaatct ccaggacctc agcgggaaag aaaatcatct    840

tcatcctcag aagataggaa tcgaatgaaa acacttggta gacgggattc aagtgatgat    900

tgggagatac ctgatgggca gatcacagtg ggacagagaa ttggatccgg gtcatttggg    960

acagtctaca agggaaagtg gcatggtgac gtggcagtga aaatgttgaa tgtgacagca   1020

cccacacctc agcagttaca ggccttcaaa aatgaagtag gagtactcag gaaaactcga   1080

catgtgaata tcctactctt tatgggctat tcaacaaagc cccaactggc tattgttacc   1140

cagtggtgtg agggctccag cttatatcac catctccaca tcattgagac caaatttgag   1200

atgataaagc ttatagatat tgcacggcag actgcacagg gcatggatta cttacacgcc   1260

aagtcaatca tccacagaga cctcaagagt aataatattt ttcttcatga agacctcaca   1320

gtaaaaatag gtgattttgg tctagccaca gtgaaatctc gatggagtgg gtcccatcag   1380
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tttgaacagt tgtctggatc cattttgtgg atggcaccag aagtgatccg aatgcaagac 1440

aaaaacccat atagcttcca gtcagatgta tacgcatttg ggattgttct atatgaattg 1500

atgacagggc agttaccttа ttcaaacatc aacaacaggg accagataat ttttatggtg 1560

ggacgaggat atctttctcc agatctcagt aaggtacgga gtaactgtcc aaaagccatg 1620

aagagattga tggcagagtg cctaaaaaag aaaagagatg agaggccact ctttccccaa 1680

attctcgcct ctattgagct gctggcccgc tcattgccaa aaattcaccg cagtgcatca 1740

gaaccctcct tgaatcgggc tggcttccaa acagaggatt ttagtctcta tgcttgcgct 1800

tctccaaaaa cacccatcca ggcaggggga tacggagaat ttgcagcctt caagtagcca 1860

caccatcatg gcaacaacta ctcttatttc ttaagtcttg tgttcgtaca atttgttaac 1920

atcaaaacac agttctgttc ctcaaatctt tttttaaaga tacagaattt tcaatgcata 1980

agctggtgtg gaacagaatg gaatttccca tccaacaaaa gagggaagaa tgttttagga 2040

accagaattc tctgctgcca gtgtttcttc ttcaacacaa ataccacgtg catacaagtc 2100

tgcccactcc caggaaggaa gaggagagcc tgagttctga ccttttgatg gtcaggcatg 2160

atggaaagaa actgctgcta cagcttggga gattggctgt ggagagcctg cccgtcagct 2220

ctgcccttct aaccgccaga tgagtgtgtg gctggtcacc tgacagggca gctgcaatcg 2280

ccaagcatcg ttctctttcc tgtcctggga ttttgtcgtg gagctctttc cccctagtca 2340

ccaccggttc atttctgagg gatggaacaa aaatgcagca tggcctttct gtgtggtgca 2400

tgtccggtct ttgacaaatt tttatcaagt gaagctcttg tatttaaatg gagaatgaga 2460

ggcgaggggg ggggatcacg ttttggtgta ggggcaaagg gaatgctgca tctttttcct 2520

gacccactgg gtttctggcc tttgtttcct tgctcactga gggtgtctgc ctataaccac 2580

gcaggctgga aagtgctggc acacattgcc ttctcttctc actgggtcca gcaatgaaga 2640

caagtgttgg ggatttttt ttttgccctc cacaatgtag caagttctca ggaaaatаca 2700

gttaatatct tcctcctaag ctcttccagt catcaagtac ttatgtggct actttgtcca 2760

gggcacaaaa tgccatggcg gtatccaatt aaaagcctac aaaactgctt gataacagtt 2820

ttgaatgtgt gagacattta tgtaatttaa atgtaaggta caagttttaa tttctgagtt 2880

tctctattat atttttatta aaaagaaaat aattttcaga tttaattgaa ttggaataaa 2940

ataatacttc ccaccagaat tatatatcct ggaaaattgt atttttgtta tataaacaac 3000

ttttaaagaa agatcattat ccttttctct acctaaatat ggggagtctt agcataatga 3060

cagatattta taatttttaa attaatggta cttgctggat ccacactaac atctttgcta 3120

atatctcatg ttttcctcca acttactcct acactacatc ctccatcctc tttccagtct 3180

tttatctaga atatgcaacc taaaataaaa atggtggtgt ctccattca 3229

<210> SEQ ID NO 12
<211> LENGTH: 617
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 12

Met Leu Asp Phe His Gly Ile Ser Leu Thr Cys Ala Ala Val Ala Ser
1 5 10 15

Ser Lys Val Pro Ala Arg Cys Gly Val Thr Val Arg Asp Ser Leu Lys
20 25 30

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Lys Ala Leu Met Met Arg Gly Leu Ile Pro Glu Cys Cys Ala Val Tyr
        35                  40                  45

Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly Trp Asp Thr Asp Ile
    50                  55                  60

Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu Val Leu Glu Asn Val
65                  70                  75                  80

Pro Leu Thr Thr His Asn Phe Val Arg Lys Thr Phe Phe Thr Leu Ala
                85                  90                  95

Phe Cys Asp Phe Cys Arg Lys Leu Leu Phe Gln Gly Phe Arg Cys Gln
            100                 105                 110

Thr Cys Gly Tyr Lys Phe His Gln Arg Cys Ser Thr Glu Val Pro Leu
        115                 120                 125

Met Cys Val Asn Tyr Asp Gln Leu Asp Leu Leu Phe Val Ser Lys Phe
    130                 135                 140

Phe Glu His His Pro Ile Pro Gln Glu Glu Ala Ser Ile Ala Glu Thr
145                 150                 155                 160

Ala Leu Thr Ser Gly Ser Ser Pro Ser Ala Pro Pro Ser Asp Ser Pro
                165                 170                 175

Gly Pro Pro Ile Leu Thr Ser Pro Ser Pro Ser Lys Ser Ile Pro Ile
            180                 185                 190

Pro Gln Pro Phe Arg Pro Ala Asp Glu Asp His Arg Asn Gln Phe Gly
        195                 200                 205

Gln Arg Asp Arg Ser Ser Ser Ala Pro Asn Val His Ile Asn Thr Ile
    210                 215                 220

Glu Pro Val Asn Ile Asp Asp Leu Ile Arg Asp Gln Gly Phe Arg Ser
225                 230                 235                 240

Asp Gly Gly Ser Thr Thr Gly Leu Ser Ala Thr Pro Pro Ala Ser Leu
                245                 250                 255

Pro Gly Ser Leu Thr Asn Val Lys Ala Leu Gln Lys Ser Pro Gly Pro
            260                 265                 270

Gln Arg Glu Arg Lys Ser Ser Ser Ser Ser Glu Asp Arg Asn Arg Met
        275                 280                 285

Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp Asp Trp Glu Ile Pro Asp
    290                 295                 300

Gly Gln Ile Thr Val Gly Gln Arg Ile Gly Ser Gly Ser Phe Gly Thr
305                 310                 315                 320

Val Tyr Lys Gly Lys Trp His Gly Asp Val Ala Val Lys Met Leu Asn
                325                 330                 335

Val Thr Ala Pro Thr Pro Gln Gln Leu Gln Ala Phe Lys Asn Glu Val
            340                 345                 350

Gly Val Leu Arg Lys Thr Arg His Val Asn Ile Leu Leu Phe Met Gly
        355                 360                 365

Tyr Ser Thr Lys Pro Gln Leu Ala Ile Val Thr Gln Trp Cys Glu Gly
    370                 375                 380

Ser Ser Leu Tyr His His Leu His Ile Ile Glu Thr Lys Phe Glu Met
385                 390                 395                 400

Ile Lys Leu Ile Asp Ile Ala Arg Gln Thr Ala Gln Gly Met Asp Tyr
                405                 410                 415

Leu His Ala Lys Ser Ile Ile His Arg Asp Leu Lys Ser Asn Asn Ile
            420                 425                 430

Phe Leu His Glu Asp Leu Thr Val Lys Ile Gly Asp Phe Gly Leu Ala
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        435                 440                 445

Thr Val Lys Ser Arg Trp Ser Gly Ser His Gln Phe Glu Gln Leu Ser
    450                 455                 460

Gly Ser Ile Leu Trp Met Ala Pro Glu Val Ile Arg Met Gln Asp Lys
465                 470                 475                 480

Asn Pro Tyr Ser Phe Gln Ser Asp Val Tyr Ala Phe Gly Ile Val Leu
                485                 490                 495

Tyr Glu Leu Met Thr Gly Gln Leu Pro Tyr Ser Asn Ile Asn Asn Arg
            500                 505                 510

Asp Gln Ile Ile Phe Met Val Gly Arg Gly Tyr Leu Ser Pro Asp Leu
        515                 520                 525

Ser Lys Val Arg Ser Asn Cys Pro Lys Ala Met Lys Arg Leu Met Ala
    530                 535                 540

Glu Cys Leu Lys Lys Lys Arg Asp Glu Arg Pro Leu Phe Pro Gln Ile
545                 550                 555                 560

Leu Ala Ser Ile Glu Leu Leu Ala Arg Ser Leu Pro Lys Ile His Arg
                565                 570                 575

Ser Ala Ser Glu Pro Ser Leu Asn Arg Ala Gly Phe Gln Thr Glu Asp
            580                 585                 590

Phe Ser Leu Tyr Ala Cys Ala Ser Pro Lys Thr Pro Ile Gln Ala Gly
        595                 600                 605

Gly Tyr Gly Glu Phe Ala Ala Phe Lys
    610                 615


<210> SEQ ID NO 13
<211> LENGTH: 1889
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 13

ggaatatcaa acaaatgatt aagttgacac aggaacatat agaagcccta ttggacaagt     60

ttggtgggga gcataatcca ccatcaatat atctggaggc ctatgaagaa tacaccagca    120

aactagatgc cctccaacag cgagaacaac agttattgga atccctgggg aatggaactg    180

atttttctgt ttctagctct gcatcaacgg acaccgttac atcttcttcc tcttctagcc    240

tttcagtgct accttcatct ctttcagttt ttcaaaatcc cacagatata tcacggagca    300

atcccaagtc accacaaaaa cctatcgtta gagtcttcct gcccaataaa cagaggacgg    360

tggtacccgc aagatgtgga gttacagtcc gggacagtct aaagaaagct ctgatgatga    420

gaggtctaat cccagagtgc tgtgctgttt acagaattca ggatggagag aagaaaccga    480

ttggctggga cactgatatt tcctggctca ctggagagga attgcatgta gaagtgttgg    540

aaaatgttcc gcttaccaca cacaactttg tacggaaaac ttttttcacc ttagcatttt    600

gtgacttttg tcgaaagctg cttttccagg gttttcgctg tcaaacatgt ggttataaat    660

ttcaccagcg ttgtagtaca gaggttccac tgatgtgtgt taattatgac caacttgatt    720

tgctgtttgt ctccaagttc tttgaacacc acccaatacc acaggaggag gcctccatag    780

cagagactgc ccttacgtct ggatcatccc cttctgctcc cccctccgat tctcctgggc    840

ccccaattct gaccagtccg tctccttcaa aatccattcc aattccacag cctttccgac    900

cagcagatga agatcatcga aatcagtttg gacaacgaga ccggtcctca tcagctccaa    960

atgtgcatat aaacacaata gaacccgtca acattgatga cttgattaga gaccaagggt   1020
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ttcgtagtga tggaggatca accacaggtt tgtctgccac ccccctgcc tcattgcctg   1080

gctcactcac taatgtaaaa gcattacaga aatctccagg acctcagcgg gaaagaaaat   1140

catcttcatc ctcagaagat aggaatcgaa tgaaaacact tggtagacgg gattcaagtg   1200

atgattggga gatacctgat gggcagatca cagtgggaca gagaattgga tccgggtcat   1260

ttgggacagt ctacaaggga aagtggcatg gtgacgtggc agtgaaaatg ttgaatgtga   1320

cagcacccac acctcagcag ttacaggcct tcaaaaatga agtaggagta ctcaggaaaa   1380

ctcgacatgt gaatatccta ctctttatgg gctattcaac aaagccccaa ctggctattg   1440

ttacccagtg gtgtgagggc tccagcttat atcaccatct ccacatcatt gagaccaaat   1500

ttgagatgat aaagcttata gatattgcac ggcagactgc acagggcatg gattacttac   1560

acgccaagtc aatcatccac agagacctca agagtaataa tatttttctt catgaagacc   1620

tcacagtaaa aataggtgat tttggtctag ccacagtgaa atctcgatgg agtgggtccc   1680

atcagtttga acagttgtct ggatccattt tgtggatggc accagaagtg atccgaatgc   1740

aagacaaaaa cccatatagc ttccagtcag atgtatacgc atttgggatt gttctatatg   1800

aattgatgac agggcagtta ccttattcaa acatcaacaa cagggaccag ctcagatcat   1860

gatcacggtg tcatgagatc aagccccac                                     1889
```

<210> SEQ ID NO 14
<211> LENGTH: 615
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 14

```
Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu Asp Lys Phe
1               5                   10                  15

Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala Tyr Glu Glu
            20                  25                  30

Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln Gln Leu Leu
        35                  40                  45

Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser Ser Ala Ser
    50                  55                  60

Thr Asp Thr Val Thr Ser Ser Ser Ser Ser Ser Leu Ser Val Leu Pro
65                  70                  75                  80

Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Ile Ser Arg Ser Asn
                85                  90                  95

Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu Pro Asn Lys
            100                 105                 110

Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr Val Arg Asp Ser
        115                 120                 125

Leu Lys Lys Ala Leu Met Met Arg Gly Leu Ile Pro Glu Cys Cys Ala
    130                 135                 140

Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly Trp Asp Thr
145                 150                 155                 160

Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu Val Leu Glu
                165                 170                 175

Asn Val Pro Leu Thr Thr His Asn Phe Val Arg Lys Thr Phe Phe Thr
            180                 185                 190

Leu Ala Phe Cys Asp Phe Cys Arg Lys Leu Leu Phe Gln Gly Phe Arg
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        195                 200                 205

Cys Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys Ser Thr Glu Val
    210                 215                 220

Pro Leu Met Cys Val Asn Tyr Asp Gln Leu Asp Leu Leu Phe Val Ser
225                 230                 235                 240

Lys Phe Phe Glu His His Pro Ile Pro Gln Glu Glu Ala Ser Ile Ala
                245                 250                 255

Glu Thr Ala Leu Thr Ser Gly Ser Ser Pro Ser Ala Pro Pro Ser Asp
            260                 265                 270

Ser Pro Gly Pro Pro Ile Leu Thr Ser Pro Ser Pro Ser Lys Ser Ile
        275                 280                 285

Pro Ile Pro Gln Pro Phe Arg Pro Ala Asp Glu Asp His Arg Asn Gln
    290                 295                 300

Phe Gly Gln Arg Asp Arg Ser Ser Ser Ala Pro Asn Val His Ile Asn
305                 310                 315                 320

Thr Ile Glu Pro Val Asn Ile Asp Asp Leu Ile Arg Asp Gln Gly Phe
                325                 330                 335

Arg Ser Asp Gly Gly Ser Thr Thr Gly Leu Ser Ala Thr Pro Pro Ala
            340                 345                 350

Ser Leu Pro Gly Ser Leu Thr Asn Val Lys Ala Leu Gln Lys Ser Pro
        355                 360                 365

Gly Pro Gln Arg Glu Arg Lys Ser Ser Ser Ser Ser Glu Asp Arg Asn
    370                 375                 380

Arg Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp Asp Trp Glu Ile
385                 390                 395                 400

Pro Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly Ser Gly Ser Phe
                405                 410                 415

Gly Thr Val Tyr Lys Gly Lys Trp His Gly Asp Val Ala Val Lys Met
            420                 425                 430

Leu Asn Val Thr Ala Pro Thr Pro Gln Gln Leu Gln Ala Phe Lys Asn
        435                 440                 445

Glu Val Gly Val Leu Arg Lys Thr Arg His Val Asn Ile Leu Leu Phe
    450                 455                 460

Met Gly Tyr Ser Thr Lys Pro Gln Leu Ala Ile Val Thr Gln Trp Cys
465                 470                 475                 480

Glu Gly Ser Ser Leu Tyr His His Leu His Ile Ile Glu Thr Lys Phe
                485                 490                 495

Glu Met Ile Lys Leu Ile Asp Ile Ala Arg Gln Thr Ala Gln Gly Met
            500                 505                 510

Asp Tyr Leu His Ala Lys Ser Ile Ile His Arg Asp Leu Lys Ser Asn
        515                 520                 525

Asn Ile Phe Leu His Glu Asp Leu Thr Val Lys Ile Gly Asp Phe Gly
    530                 535                 540

Leu Ala Thr Val Lys Ser Arg Trp Ser Gly Ser His Gln Phe Glu Gln
545                 550                 555                 560

Leu Ser Gly Ser Ile Leu Trp Met Ala Pro Glu Val Ile Arg Met Gln
                565                 570                 575

Asp Lys Asn Pro Tyr Ser Phe Gln Ser Asp Val Tyr Ala Phe Gly Ile
            580                 585                 590

Val Leu Tyr Glu Leu Met Thr Gly Gln Leu Pro Tyr Ser Asn Ile Asn
        595                 600                 605
```

-continued

Asn Arg Asp Gln Leu Arg Ser
610 615

<210> SEQ ID NO 15
<211> LENGTH: 3521
<212> TYPE: DNA
<213> ORGANISM: Felis catus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (630)..(649)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 15

atgcctaacc tcagtctctg ccaccacggc caatttgctc atgtgcccac tgtgtcggca 60

ctgggatatt ttgtgatttg ccttggccat tgtccactgt ccttgacatt gcctgaagga 120

gaaccactga tgctaatgtt gaaggtgacc tttgcaggct ctccactact cataccaaag 180

atgcggcccc ctgataatcc cagagccact gtctgcacat gggcaaaaca ggctacattc 240

tgtgcagact ggggagaaag gttccaagaa cacagtgcca tagttttggg cagagagttt 300

caacacagca tagtgtctat ggcagtatct ggatttggcc gggggaagtg cccaagagga 360

gacagtcagg ctgtgtccta cggccaagga cctgcactta tttttgcatg cagtggttta 420

gcacagggaa gagaacgaag taggaaatcg gagccatgga aacggcagag cggaggaaac 480

gtgcacgcgc gagggtgggc acgaaaggaa agaaccctcc ccagaagact gcgcgagggc 540

gctcctagga ttacgtcacg caccccgcga aaactgaaat gtactgtgtg tggtctttta 600

attgaactat cttccttatg tgcacttaan nnnnnnnnnn nnnnnnnnng cggcggcggc 660

ggtggcgcgg agcagggcca ggctctgttc aacggggaca tggagcccga agccggcgcc 720

gcggcctctt cggctgcgga ccctgccatt cccgaggagg tgtggaatat caaacaaatg 780

attaagttga cacaggaaca tatagaggcc ctattggaca aatttggtgg ggagcataat 840

ccaccatcaa tatatctaga ggcctatgaa gaatacacca gcaagctaga tgccctccaa 900

cagagagaac aacagttatt ggaatccctg gggaatggaa ctgatttttc tgtttctagc 960

tctgcatcaa cagacaccgt tacatcttcc tcctcttcta gcctttcagt gctaccttca 1020

tctctttcag tttttcaaaa ccccacagat gtgtcacgga gcaatcccaa gtcaccacag 1080

aaacctatcg ttagagtctt cctgcctaat aaacagagga cagtggtacc tgcaagatgt 1140

ggagttacag tccgggacag tctaaagaaa gctctgatga tgagaggtct aatccctgag 1200

tgctgtgctg tttacagaat tcaggatgga gagaagaaac caattggctg ggacactgat 1260

atctcctggc tcaccggaga ggaattgcat gtagaagtgt tggaaaatgt tccacttaca 1320

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agtacagagg ttccactgat gtgtgttaat tatgaccaac ttgatttgct gtttgtctcc 1500

aagttctttg aacaccaccc aataccacag gaggaggcct ccatagcaga gactgcccta 1560

acgtctggat cgtccccttc tgccccccgc tccgattcta ctgggcccca aattctcacc 1620

agtccgtctc cttcaaaatc cattccaatt ccacagcctt tccgaccagc agatgaagat 1680

catcgaaatc aatttggaca gcgagaccgg tcctcatcag ctccaaatgt gcatataaat 1740

acaatagaac ctgtcaatat tgatgacttg attagagacc aggggtttcg tagtgatgga 1800

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ggatcaacca caggcttgtc tgccaccccc cctgcctcat tgccgggctc tctcactaat   1860

gtaaaagcat tacagaaatc tccagggcct cagcgggaaa ggaaatcttc ttcatcctca   1920

gaagatagga atcgaatgaa aacacttggt agaagggatt caagtgatga ttgggagatt   1980

cctgatgggc agatcacagt gggacagaga attggatccg ggtcatttgg gacagtctac   2040

aagggaaagt ggcatggtga tgtggcagtg aaaatgttga atgtgacagc acccacacct   2100

cagcagttac aggccttcaa aaatgaagta ggagtactca ggaaaactcg gcatgtgaac   2160

atcctgctct tcatgggcta ttcaacaaag ccccagctgg ctattgtcac ccagtggtgt   2220

gagggctcca gcttatacca ccatctccac atcatcgaga ccaaattcga gatgatcaag   2280

ctgatagata ttgctcggca gactgcgcag ggcatggatt acttacacgc caagtcaatc   2340

atccacagag acctcaagag taataatatt tttcttcacg aagacctcac agtaaaaata   2400

ggtgattttg gtctagccac agtgaaatct cgatggagtg ggtcccatca gtttgaacag   2460

ttgtctggat ccattttgtg gatggcacca gaagtaattc gaatgcaaga taaaaaccca   2520

tatagctttc agtcagatgt atatgcattt gggattgttc tatatgaatt gatgactgga   2580

cagttacctt attcaaacat caacaacagg gaccagataa tttttatggt gggacgagga   2640

tatctttctc cagatctcag taaggtacga agtaactgtc caaaagccat gaagagattg   2700

atggcagagt gcctaaaaaa gaaaagagat gagaggccac tgtttcccca aattcttgcc   2760

tctattgagc tgctggcccg ctcattgcca aaaattcacc gcagtgcatc agaaccctcc   2820

ttgaatcggg ctggcttcca gacagaggat tttagtctct atgcttgtgc ttctccaaaa   2880

acacccatcc aggcaggggg atatggtgcg tttcccgtcc actgagataa gttagatgag   2940

tgcgcgagtg caggggggccg gggccaagga ggtggaaatg tgcgtgcttc tgtactaagt   3000

tggatagcat cttctttttt aaaaaaagat gaaccaaaga atgtgtatgt ttttaaagac   3060

tagatataat tatttcctga tctaaaatgt atacttagct ttggattttc aatatccaag   3120

ggttttcaaa atgcacagac attgctgaac atttgcagta cctcttctgg aggctttact   3180

tcctgttaca aattggtttt gtttactggc ttatcctaat tattaaactt caattaaact   3240

tttctcctgc acctttttgtt atgagctatc acatgtccct tagggactcg caagagcagt   3300

actgcccccg tgtacgggct tgcaggtaga aaggggatga cgggttttaa cacctgtgtg   3360

aggcaaggca gtccgaacag atctcattta ggaagccacg agagttgaat aagttatttt   3420

tattcttagt atttttctg taactacttt ttattataac ttggaaaata tggatgtcct   3480

ttatacacct tagcaataga ctgaatttct ttttataaat t                      3521


<210> SEQ ID NO 16
<211> LENGTH: 974
<212> TYPE: PRT
<213> ORGANISM: Felis catus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (210)..(217)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 16

Met Pro Asn Leu Ser Leu Cys His His Gly Gln Phe Ala His Val Pro
1               5                  10                  15

Thr Val Ser Ala Leu Gly Tyr Phe Val Ile Cys Leu Gly His Cys Pro
            20                  25                  30
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Leu Ser Leu Thr Leu Pro Glu Gly Glu Pro Leu Met Leu Met Leu Lys
        35                  40                  45

Val Thr Phe Ala Gly Ser Pro Leu Leu Ile Pro Lys Met Arg Pro Pro
    50                  55                  60

Asp Asn Pro Arg Ala Thr Val Cys Thr Trp Ala Lys Gln Ala Thr Phe
65                  70                  75                  80

Cys Ala Asp Trp Gly Glu Arg Phe Gln Glu His Ser Ala Ile Val Leu
                85                  90                  95

Gly Arg Glu Phe Gln His Ser Ile Val Ser Met Ala Val Ser Gly Phe
            100                 105                 110

Gly Arg Gly Lys Cys Pro Arg Gly Asp Ser Gln Ala Val Ser Tyr Gly
        115                 120                 125

Gln Gly Pro Ala Leu Ile Phe Ala Cys Ser Gly Leu Ala Gln Gly Arg
    130                 135                 140

Glu Arg Ser Arg Lys Ser Glu Pro Trp Lys Arg Gln Ser Gly Gly Asn
145                 150                 155                 160

Val His Ala Arg Gly Trp Ala Arg Lys Glu Arg Thr Leu Pro Arg Arg
                165                 170                 175

Leu Arg Glu Gly Ala Pro Arg Ile Thr Ser Arg Thr Pro Arg Lys Leu
            180                 185                 190

Lys Cys Thr Val Cys Gly Leu Leu Ile Glu Leu Ser Ser Leu Cys Ala
        195                 200                 205

Leu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gly Gly Gly Gly Gly Ala Glu
    210                 215                 220

Gln Gly Gln Ala Leu Phe Asn Gly Asp Met Glu Pro Glu Ala Gly Ala
225                 230                 235                 240

Ala Ala Ser Ser Ala Ala Asp Pro Ala Ile Pro Glu Glu Val Trp Asn
                245                 250                 255

Ile Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu
            260                 265                 270

Asp Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala
        275                 280                 285

Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln
    290                 295                 300

Gln Leu Leu Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser
305                 310                 315                 320

Ser Ala Ser Thr Asp Thr Val Thr Ser Ser Ser Ser Ser Ser Leu Ser
                325                 330                 335

Val Leu Pro Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val Ser
            340                 345                 350

Arg Ser Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu
        355                 360                 365

Pro Asn Lys Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr Val
    370                 375                 380

Arg Asp Ser Leu Lys Lys Ala Leu Met Met Arg Gly Leu Ile Pro Glu
385                 390                 395                 400

Cys Cys Ala Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly
                405                 410                 415

Trp Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu
            420                 425                 430

Val Leu Glu Asn Val Pro Leu Thr Thr His Asn Phe Val Cys Thr Glu
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        435                 440                 445

Asn Val Phe Thr Leu Ala Phe Cys Asp Phe Cys Arg Lys Leu Leu Phe
    450                 455                 460

Gln Gly Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys
465                 470                 475                 480

Ser Thr Glu Val Pro Leu Met Cys Val Asn Tyr Asp Gln Leu Asp Leu
                485                 490                 495

Leu Phe Val Ser Lys Phe Phe Glu His His Pro Ile Pro Gln Glu Glu
            500                 505                 510

Ala Ser Ile Ala Glu Thr Ala Leu Thr Ser Gly Ser Ser Pro Ser Ala
        515                 520                 525

Pro Pro Ser Asp Ser Thr Gly Pro Gln Ile Leu Thr Ser Pro Ser Pro
    530                 535                 540

Ser Lys Ser Ile Pro Ile Pro Gln Pro Phe Arg Pro Ala Asp Glu Asp
545                 550                 555                 560

His Arg Asn Gln Phe Gly Gln Arg Asp Arg Ser Ser Ser Ala Pro Asn
                565                 570                 575

Val His Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Asp Leu Ile Arg
            580                 585                 590

Asp Gln Gly Phe Arg Ser Asp Gly Gly Ser Thr Thr Gly Leu Ser Ala
        595                 600                 605

Thr Pro Pro Ala Ser Leu Pro Gly Ser Leu Thr Asn Val Lys Ala Leu
    610                 615                 620

Gln Lys Ser Pro Gly Pro Gln Arg Glu Arg Lys Ser Ser Ser Ser Ser
625                 630                 635                 640

Glu Asp Arg Asn Arg Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp
                645                 650                 655

Asp Trp Glu Ile Pro Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly
            660                 665                 670

Ser Gly Ser Phe Gly Thr Val Tyr Lys Gly Lys Trp His Gly Asp Val
        675                 680                 685

Ala Val Lys Met Leu Asn Val Thr Ala Pro Thr Pro Gln Gln Leu Gln
    690                 695                 700

Ala Phe Lys Asn Glu Val Gly Val Leu Arg Lys Thr Arg His Val Asn
705                 710                 715                 720

Ile Leu Leu Phe Met Gly Tyr Ser Thr Lys Pro Gln Leu Ala Ile Val
                725                 730                 735

Thr Gln Trp Cys Glu Gly Ser Ser Leu Tyr His His Leu His Ile Ile
            740                 745                 750

Glu Thr Lys Phe Glu Met Ile Lys Leu Ile Asp Ile Ala Arg Gln Thr
        755                 760                 765

Ala Gln Gly Met Asp Tyr Leu His Ala Lys Ser Ile Ile His Arg Asp
    770                 775                 780

Leu Lys Ser Asn Asn Ile Phe Leu His Glu Asp Leu Thr Val Lys Ile
785                 790                 795                 800

Gly Asp Phe Gly Leu Ala Thr Val Lys Ser Arg Trp Ser Gly Ser His
                805                 810                 815

Gln Phe Glu Gln Leu Ser Gly Ser Ile Leu Trp Met Ala Pro Glu Val
            820                 825                 830

Ile Arg Met Gln Asp Lys Asn Pro Tyr Ser Phe Gln Ser Asp Val Tyr
        835                 840                 845
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Ala Phe Gly Ile Val Leu Tyr Glu Leu Met Thr Gly Gln Leu Pro Tyr
    850                 855                 860

Ser Asn Ile Asn Asn Arg Asp Gln Ile Ile Phe Met Val Gly Arg Gly
865                 870                 875                 880

Tyr Leu Ser Pro Asp Leu Ser Lys Val Arg Ser Asn Cys Pro Lys Ala
                885                 890                 895

Met Lys Arg Leu Met Ala Glu Cys Leu Lys Lys Lys Arg Asp Glu Arg
            900                 905                 910

Pro Leu Phe Pro Gln Ile Leu Ala Ser Ile Glu Leu Leu Ala Arg Ser
        915                 920                 925

Leu Pro Lys Ile His Arg Ser Ala Ser Glu Pro Ser Leu Asn Arg Ala
    930                 935                 940

Gly Phe Gln Thr Glu Asp Phe Ser Leu Tyr Ala Cys Ala Ser Pro Lys
945                 950                 955                 960

Thr Pro Ile Gln Ala Gly Gly Tyr Gly Ala Phe Pro Val His
                965                 970


<210> SEQ ID NO 17
<211> LENGTH: 3853
<212> TYPE: DNA
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 17

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cgacgccgcc cgggccgccc gggccgtccc tccccgctgc cccccgtcct ccgcctccgc    120

ctccccccgc cctcagcctc ccttcccccc ccccgcccag cagcggtcgc tcgggcccgg    180

ctctcggtta taagatggcg gcgctgagtg gcggcggcgg cggcggcggc ggtggcgcgg    240

agcagggcca ggctctgttc aacggggaca tggagcccga ggccggcgcc gcggcctctt    300

cggctgcgga ccccgccatt cccgaggagg tgtggaatat caaacaaatg attaagttga    360

cacaggagca tatagaggcc ctattggaca aatttggtgg ggagcataat ccaccatcaa    420

tatatctgga ggcctatgaa gaatacacca gcaagctaga tgccctccaa caaagagaac    480

aacagttatt ggaatccctg gggaatggaa ctgatttttc tgtttctagc tctgcatcaa    540

cggacaccgt tacatcttct tcctcttcta gcctttcagt gctgccttca tctctttcag    600

tttttcaaaa tcccacagat gtgtcacgga gcaaccccaa gtcaccacaa aaacctatcg    660

ttagagtctt cctgcccaat aaacagagga cagtggtacc tgcacggtgt ggagtcacag    720

tccgggacag cctgaagaag gcactgatga tgagaggtct aatcccagag tgctgtgctg    780

tttacagaat tcaggatggg gagaagaaac caattggctg ggacactgat atttcctggc    840

ttactggaga ggagttgcat gtagaagtgt tggagaatgt tccacttaca acacacaact    900

ttgtacggaa aacttttttc accttagcat tttgtgactt ctgtagaaag ctgcttttcc    960

agggattccg ctgtcaaaca tgtggttata aatttcacca gcgttgtagt acagaggttc   1020

cactgatgtg tgttaattat gaccaactag atttgctgtt tgtctccaag ttctttgaac   1080

accacccaat accacaggag gaggcctcct tagcagagac taccttcca tgtggctcat   1140

ccccttctgc acccccctcc gattctattg ggcccccaat tctcaccagt ccatctcctt   1200

caaaatccat tccaattcca cagcctttcc gaccagcaga tgaagatcat cgaaatcagt   1260

ttggacaacg agaccggtcc tcatcagctc caaatgtgca tataaacaca atagaacccg   1320
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tcaatattga tgacttgatt agagaccaag ggtttcgtag tgatggagga tcaaccacag 1380

gtttatccgc cacacccccc gcctcattac ctggctcact ctctaatgtg aaagcattgc 1440

agaaatctcc aggacctcag cgagaaagaa agtcctcttc atcctcagaa gacaggaatc 1500

gaatgaaaac gcttggtaga cgggattcaa gtgacgattg ggagattcct gatggacaga 1560

tcacagtggg acaaagaatt ggatcagggt catttgggac agtctacaag ggaaagtggc 1620

atggtgatgt ggcagtgaaa atgttgaatg tgacagcacc cacacctcag cagttacagg 1680

ccttcaaaaa tgaagtagga gtactcagga aaacgcgaca tgtgaatatc ctcctcttca 1740

tgggttattc aacaaagcca caactggcta ttgttaccca gtggtgtgag ggctccagtt 1800

tatatcatca tctccacatc attgagacca aattcgagat gatcaaactt atagatattg 1860

cacggcagac tgcacagggc atggattact tacacgccaa gtcaatcatc cacagagacc 1920

tcaagagtaa taatattttt cttcatgaag acctcacagt aaaaataggt gattttggtc 1980

tagccacagt gaaatctcga tggagtgggt cccatcagtt tgaacagttg tctggatcca 2040

ttttgtggat ggcaccagaa gtaatcagaa tgcaagataa aaacccatat agctttcagt 2100

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atctcagtaa ggtacggagt aactgtccaa aagccatgaa gagattaatg gcagagtgcc 2280

taaaaaagaa aagagatgaa agaccactct ttccccaaat tctcgcctct attgagctgc 2340

tggcccgctc attgccaaaa attcaccgca gtgcatcaga accctccttg aatcgggctg 2400

gcttccaaac agaggatttt agtctatatg cttgtgcttc tccaaaaaca cccattcagg 2460

caggggata tggtacgttt cctgttcact gaaacaaacc gagtgagtga cagcatgtag 2520

gagggtaggg acaaaagaaa gtgaacaaat gtttgcttat atatttgtta aattgaatag 2580

gattttcttt ttctttaaag gtgaacaaga gaacatgtgt gtttttaaag tttggatata 2640

gttttcttcc cagtctaaaa cccatagtta gcattacatt ttcaacatcg aatttttttt 2700

taattcatag acattgctga aaatttataa tacctttcc agaggcttta cttcccattc 2760

caagtttgtt ttgtttactt ggttagtcta atcattaaac tttaaacttt ccccacctac 2820

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caggtctaat taggagtcac tagaattgaa taagcttatt tttattaata ttttttctta 3000

taactatttc tttttgtaat aatttagaaa atataattgt tctttattcc cttacagcag 3060

tataaattat tggtgcaggt aaccaaagat attactgagg agtggcatgt ttgacatgag 3120

tgacatggtt taactttgga tttttagtta atatttcttt atatattaag gatgtcttac 3180

acattataga agtcaaattt actgacaaag gtattgcctc ctcttcctcc ccaaaaacac 3240

agcaaaattc tctgggaact cgtagcattg ttggttttct tttggatgac tatggttgcc 3300

aaacaaccaa gtaattgatt ttttttaaat tattattgct ttagattata ctcacctctc 3360

atgatgcctg ttagcaatca cctttatcca tgtgtcttgt aaaatatctt tcctccttat 3420

attctttgcc caacaagagt ctacttgtta tgaatgagta ctattttctt tttttgattc 3480

cccagtataa ttagtatgtt tagtgctttc taggacttcc actttcttat gttaaaaaaa 3540

aaaacaaact aatgtggcag tcagtatatt cttactgtga atcagagtct ttactgggaa 3600

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tcaaagtgaa agaagcagct gttctgactt cagagtcagc ctagggacca aaaccagcct 3660

cttaaataca ccttcattta ttcagtttgg atttgtgatg attttcatta tagctgacag 3720

ttcaaggtta ttcagtggca cacagatagc atctgcataa atgcctttct tcttgaaaat 3780

aaaggagaaa attgggaaga ctttacacca atagtttagt ctttaagtac cacagataac 3840

acacaccata aat 3853

<210> SEQ ID NO 18
<211> LENGTH: 764
<212> TYPE: PRT
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 18

Ala Ala Leu Ser Gly Gly Gly Gly Gly Gly Gly Gly Gly Ala Glu Gln
1 5 10 15

Gly Gln Ala Leu Phe Asn Gly Asp Met Glu Pro Glu Ala Gly Ala Ala
20 25 30

Ala Ser Ser Ala Ala Asp Pro Ala Ile Pro Glu Glu Val Trp Asn Ile
35 40 45

Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu Asp
50 55 60

Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala Tyr
65 70 75 80

Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln Gln
85 90 95

Leu Leu Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser Ser
100 105 110

Ala Ser Thr Asp Thr Val Thr Ser Ser Ser Ser Ser Ser Leu Ser Val
115 120 125

Leu Pro Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val Ser Arg
130 135 140

Ser Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu Pro
145 150 155 160

Asn Lys Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr Val Arg
165 170 175

Asp Ser Leu Lys Lys Ala Leu Met Met Arg Gly Leu Ile Pro Glu Cys
180 185 190

Cys Ala Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly Trp
195 200 205

Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu Val
210 215 220

Leu Glu Asn Val Pro Leu Thr Thr His Asn Phe Val Arg Lys Thr Phe
225 230 235 240

Phe Thr Leu Ala Phe Cys Asp Phe Cys Arg Lys Leu Leu Phe Gln Gly
245 250 255

Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys Ser Thr
260 265 270

Glu Val Pro Leu Met Cys Val Asn Tyr Asp Gln Leu Asp Leu Leu Phe
275 280 285

Val Ser Lys Phe Phe Glu His His Pro Ile Pro Gln Glu Glu Ala Ser
290 295 300

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Leu Ala Glu Thr Thr Leu Pro Cys Gly Ser Ser Pro Ser Ala Pro Pro
305                 310                 315                 320

Ser Asp Ser Ile Gly Pro Pro Ile Leu Thr Ser Pro Ser Pro Ser Lys
                325                 330                 335

Ser Ile Pro Ile Pro Gln Pro Phe Arg Pro Ala Asp Glu Asp His Arg
            340                 345                 350

Asn Gln Phe Gly Gln Arg Asp Arg Ser Ser Ser Ala Pro Asn Val His
        355                 360                 365

Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Asp Leu Ile Arg Asp Gln
    370                 375                 380

Gly Phe Arg Ser Asp Gly Gly Ser Thr Thr Gly Leu Ser Ala Thr Pro
385                 390                 395                 400

Pro Ala Ser Leu Pro Gly Ser Leu Ser Asn Val Lys Ala Leu Gln Lys
                405                 410                 415

Ser Pro Gly Pro Gln Arg Glu Arg Lys Ser Ser Ser Ser Ser Glu Asp
            420                 425                 430

Arg Asn Arg Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp Asp Trp
        435                 440                 445

Glu Ile Pro Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly Ser Gly
    450                 455                 460

Ser Phe Gly Thr Val Tyr Lys Gly Lys Trp His Gly Asp Val Ala Val
465                 470                 475                 480

Lys Met Leu Asn Val Thr Ala Pro Thr Pro Gln Gln Leu Gln Ala Phe
                485                 490                 495

Lys Asn Glu Val Gly Val Leu Arg Lys Thr Arg His Val Asn Ile Leu
            500                 505                 510

Leu Phe Met Gly Tyr Ser Thr Lys Pro Gln Leu Ala Ile Val Thr Gln
        515                 520                 525

Trp Cys Glu Gly Ser Ser Leu Tyr His His Leu His Ile Ile Glu Thr
    530                 535                 540

Lys Phe Glu Met Ile Lys Leu Ile Asp Ile Ala Arg Gln Thr Ala Gln
545                 550                 555                 560

Gly Met Asp Tyr Leu His Ala Lys Ser Ile Ile His Arg Asp Leu Lys
                565                 570                 575

Ser Asn Asn Ile Phe Leu His Glu Asp Leu Thr Val Lys Ile Gly Asp
            580                 585                 590

Phe Gly Leu Ala Thr Val Lys Ser Arg Trp Ser Gly Ser His Gln Phe
        595                 600                 605

Glu Gln Leu Ser Gly Ser Ile Leu Trp Met Ala Pro Glu Val Ile Arg
    610                 615                 620

Met Gln Asp Lys Asn Pro Tyr Ser Phe Gln Ser Asp Val Tyr Ala Phe
625                 630                 635                 640

Gly Ile Val Leu Tyr Glu Leu Met Thr Gly Gln Leu Pro Tyr Ser Asn
                645                 650                 655

Ile Asn Asn Arg Asp Gln Ile Ile Phe Met Val Gly Arg Gly Tyr Leu
            660                 665                 670

Ser Pro Asp Leu Ser Lys Val Arg Ser Asn Cys Pro Lys Ala Met Lys
        675                 680                 685

Arg Leu Met Ala Glu Cys Leu Lys Lys Lys Arg Asp Glu Arg Pro Leu
    690                 695                 700

Phe Pro Gln Ile Leu Ala Ser Ile Glu Leu Leu Ala Arg Ser Leu Pro
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705 710 715 720

Lys Ile His Arg Ser Ala Ser Glu Pro Ser Leu Asn Arg Ala Gly Phe
725 730 735

Gln Thr Glu Asp Phe Ser Leu Tyr Ala Cys Ala Ser Pro Lys Thr Pro
740 745 750

Ile Gln Ala Gly Gly Tyr Gly Thr Phe Pro Val His
755 760

<210> SEQ ID NO 19
<211> LENGTH: 4936
<212> TYPE: DNA
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 19

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ctctcggtta taagatggcg gcgctgagtg gcggcggcgg cggcggcggc ggtggcgcgg 240

agcagggcca ggctctgttc aacggggaca tggagcccga ggccggcgcc gcggcctctt 300

cggctgcgga ccccgccatt cccgaggagg tgtggaatat caaacaaatg attaagttga 360

cacaggagca tatagaggcc ctattggaca aatttggtgg ggagcataat ccaccatcaa 420

tatatctgga ggcctatgaa gaatacacca gcaagctaga tgccctccaa caaagagaac 480

aacagttatt ggaatccctg gggaatggaa ctgatttttc tgtttctagc tctgcatcaa 540

cggacaccgt tacatcttct tcctcttcta gcctttcagt gctgccttca tctctttcag 600

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cactgatgtg tgttaattat gaccaactag atttgctgtt tgtctccaag ttctttgaac 1080

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cacggcagac tgcacagggc atggattact tacacgccaa gtcaatcatc cacagagacc 1920

tcaagagtaa taatattttt cttcatgaag acctcacagt aaaaataggt gattttggtc 1980

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tgctggcccg ctcattgcca aaaattcacc gcagtgcatc agaaccctcc ttgaatcggg 2460

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gaccttggac tttggagtca gtgcctagct atgcattcca ggtctgccat tttctggctg 3840

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ccagtaaatt aagaagtaat agcagccact tcgtagagtt gttatgaggc tcagatgcag 3960

tgcaaatgtg tataaagtat tcagggagtc acctggtata ctataataga cactagaata 4020

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aatgagttga taatttgggg ggaaagtatt ctacaaatca accttattat tttaccattg 4680

gtttctgaga aattttgttc atttgaaccg tttatagctt gattagaatc atagcatgta 4740

aaacccaact gagggattat ctgcagactt aatgtagtat tatgtaagtt gtcttctttc 4800

atttcgacct tttttgcttt tgttgttgct agatctgtag tatgtagcta gtcacctttc 4860

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ttagctcttg tcctcc 4936

<210> SEQ ID NO 20
<211> LENGTH: 797
<212> TYPE: PRT
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 20

Met Ala Ala Leu Ser Gly Gly Gly Gly Gly Gly Gly Gly Gly Ala Glu
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Gln Gly Gln Ala Leu Phe Asn Gly Asp Met Glu Pro Glu Ala Gly Ala
20 25 30

Ala Ala Ser Ser Ala Ala Asp Pro Ala Ile Pro Glu Glu Val Trp Asn
35 40 45

Ile Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu
50 55 60

Asp Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala
65 70 75 80

Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln
85 90 95

Gln Leu Leu Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser
100 105 110

Ser Ala Ser Thr Asp Thr Val Thr Ser Ser Ser Ser Ser Ser Leu Ser
115 120 125

Val Leu Pro Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val Ser
130 135 140

Arg Ser Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu
145 150 155 160

Pro Asn Lys Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr Val
165 170 175

Arg Asp Ser Leu Lys Lys Ala Leu Met Met Arg Gly Leu Ile Pro Glu
180 185 190

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Cys Cys Ala Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly
        195                 200                 205

Trp Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu
    210                 215                 220

Val Leu Glu Asn Val Pro Leu Thr Thr His Asn Phe Val Arg Lys Thr
225                 230                 235                 240

Phe Phe Thr Leu Ala Phe Cys Asp Phe Cys Arg Lys Leu Leu Phe Gln
                245                 250                 255

Gly Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys Ser
            260                 265                 270

Thr Glu Val Pro Leu Met Cys Val Asn Tyr Asp Gln Leu Asp Leu Leu
        275                 280                 285

Phe Val Ser Lys Phe Phe Glu His His Pro Ile Pro Gln Glu Glu Ala
    290                 295                 300

Ser Leu Ala Glu Thr Thr Leu Pro Cys Gly Ser Ser Pro Ser Ala Pro
305                 310                 315                 320

Pro Ser Asp Ser Ile Gly Pro Pro Ile Leu Thr Ser Pro Ser Pro Ser
                325                 330                 335

Lys Ser Ile Pro Ile Pro Gln Pro Phe Arg Pro Ala Asp Glu Asp His
            340                 345                 350

Arg Asn Gln Phe Gly Gln Arg Asp Arg Ser Ser Ser Ala Pro Asn Val
        355                 360                 365

His Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Asp Leu Ile Arg Asp
    370                 375                 380

Gln Gly Phe Arg Ser Asp Gly Gly Ser Thr Thr Gly Leu Ser Ala Thr
385                 390                 395                 400

Pro Pro Ala Ser Leu Pro Gly Ser Leu Ser Asn Val Lys Ala Leu Gln
                405                 410                 415

Lys Ser Pro Gly Pro Gln Arg Glu Arg Lys Ser Ser Ser Ser Ser Glu
            420                 425                 430

Asp Arg Asn Arg Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp Asp
        435                 440                 445

Trp Glu Ile Pro Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly Ser
    450                 455                 460

Gly Ser Phe Gly Thr Val Tyr Lys Gly Lys Trp His Gly Asp Val Ala
465                 470                 475                 480

Val Lys Met Leu Asn Val Thr Ala Pro Thr Pro Gln Gln Leu Gln Ala
                485                 490                 495

Phe Lys Asn Glu Val Gly Val Leu Arg Lys Thr Arg His Val Asn Ile
            500                 505                 510

Leu Leu Phe Met Gly Tyr Ser Thr Lys Pro Gln Leu Ala Ile Val Thr
        515                 520                 525

Gln Trp Cys Glu Gly Ser Ser Leu Tyr His His Leu His Ile Ile Glu
    530                 535                 540

Thr Lys Phe Glu Met Ile Lys Leu Ile Asp Ile Ala Arg Gln Thr Ala
545                 550                 555                 560

Gln Gly Met Asp Tyr Leu His Ala Lys Ser Ile Ile His Arg Asp Leu
                565                 570                 575

Lys Ser Asn Asn Ile Phe Leu His Glu Asp Leu Thr Val Lys Ile Gly
            580                 585                 590
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Asp Phe Gly Leu Ala Thr Val Lys Ser Arg Trp Ser Gly Ser His Gln
        595                 600                 605

Phe Glu Gln Leu Ser Gly Ser Ile Leu Trp Met Ala Pro Glu Val Ile
    610                 615                 620

Arg Met Gln Asp Lys Asn Pro Tyr Ser Phe Gln Ser Asp Val Tyr Ala
625                 630                 635                 640

Phe Gly Ile Val Leu Tyr Glu Leu Met Thr Gly Gln Leu Pro Tyr Ser
                645                 650                 655

Asn Ile Asn Asn Arg Asp Gln Ile Ile Phe Met Val Gly Arg Gly Tyr
            660                 665                 670

Leu Ser Pro Asp Leu Ser Lys Val Arg Ser Asn Cys Pro Lys Ala Met
        675                 680                 685

Lys Arg Leu Met Ala Glu Cys Leu Lys Lys Lys Arg Asp Glu Arg Pro
    690                 695                 700

Leu Phe Pro Gln Val Gly Lys Thr Leu Leu Ser Lys Arg Gln Asn Ser
705                 710                 715                 720

Glu Val Ile Arg Glu Lys Asp Lys Gln Ile Leu Ala Ser Ile Glu Leu
                725                 730                 735

Leu Ala Arg Ser Leu Pro Lys Ile His Arg Ser Ala Ser Glu Pro Ser
            740                 745                 750

Leu Asn Arg Ala Gly Phe Gln Thr Glu Asp Phe Ser Leu Tyr Ala Cys
        755                 760                 765

Ala Ser Pro Lys Thr Pro Ile Gln Ala Gly Gly Tyr Glu Ala Asp Leu
    770                 775                 780

Ala Leu Thr Ser Asn Lys Asn Arg Val Glu Val Gly Ile
785                 790                 795
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<210> SEQ ID NO 21
<211> LENGTH: 4154
<212> TYPE: DNA
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 21

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ctccccccgc cctcagcctc ccttcccccc ccccgcccag cagcggtcgc tcgggcccgg    180

ctctcggtta taagatggcg gcgctgagtg gcggcggcgg cggcggcggc ggtggcgcgg    240

agcagggcca ggctctgttc aacggggaca tggagcccga ggccggcgcc gcggcctctt    300

cggctgcgga ccccgccatt cccgaggagg tgtggaatat caaacaaatg attaagttga    360

cacaggagca tatagaggcc ctattggaca aatttggtgg ggagcataat ccaccatcaa    420

tatatctgga ggcctatgaa gaatacacca gcaagctaga tgccctccaa caaagagaac    480

aacagttatt ggaatccctg gggaatggaa ctgatttttc tgtttctagc tctgcatcaa    540

cggacaccgt tacatcttct tcctcttcta gcctttcagt gctgccttca tctctttcag    600

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ttagagtctt cctgcccaat aaacagagga cagtggtacc tgcacggtgt ggagtcacag    720

tccgggacag cctgaagaag gcactgatga tgagaggtct aatcccagag tgctgtgctg    780

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cacggcagac tgcacagggc atggattact tacacgccaa gtcaatcatc cacagagacc 1920

tcaagagtaa taatattttt cttcatgaag acctcacagt aaaaataggt gattttggtc 1980

tagccacagt gaaatctcga tggagtgggt cccatcagtt tgaacagttg tctggatcca 2040

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attgactgca tgga 4154

<210> SEQ ID NO 22
<211> LENGTH: 781
<212> TYPE: PRT
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 22

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Ala Ala Ser Ser Ala Ala Asp Pro Ala Ile Pro Glu Glu Val Trp Asn
35 40 45

Ile Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu
50 55 60

Asp Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala
65 70 75 80

Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln
85 90 95

Gln Leu Leu Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser
100 105 110

Ser Ala Ser Thr Asp Thr Val Thr Ser Ser Ser Ser Ser Ser Leu Ser
115 120 125

Val Leu Pro Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val Ser
130 135 140

Arg Ser Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu
145 150 155 160

Pro Asn Lys Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr Val
165 170 175

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Arg Asp Ser Leu Lys Lys Ala Leu Met Met Arg Gly Leu Ile Pro Glu
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Cys Cys Ala Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly
        195                 200                 205

Trp Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu
    210                 215                 220

Val Leu Glu Asn Val Pro Leu Thr Thr His Asn Phe Val Arg Lys Thr
225                 230                 235                 240

Phe Phe Thr Leu Ala Phe Cys Asp Phe Cys Arg Lys Leu Leu Phe Gln
                245                 250                 255

Gly Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys Ser
            260                 265                 270

Thr Glu Val Pro Leu Met Cys Val Asn Tyr Asp Gln Leu Asp Leu Leu
        275                 280                 285

Phe Val Ser Lys Phe Phe Glu His His Pro Ile Pro Gln Glu Glu Ala
    290                 295                 300

Ser Leu Ala Glu Thr Thr Leu Pro Cys Gly Ser Ser Pro Ser Ala Pro
305                 310                 315                 320

Pro Ser Asp Ser Ile Gly Pro Pro Ile Leu Thr Ser Pro Ser Pro Ser
                325                 330                 335

Lys Ser Ile Pro Ile Pro Gln Pro Phe Arg Pro Ala Asp Glu Asp His
            340                 345                 350

Arg Asn Gln Phe Gly Gln Arg Asp Arg Ser Ser Ser Ala Pro Asn Val
        355                 360                 365

His Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Asp Leu Ile Arg Asp
    370                 375                 380

Gln Gly Phe Arg Ser Asp Gly Gly Ser Thr Thr Gly Leu Ser Ala Thr
385                 390                 395                 400

Pro Pro Ala Ser Leu Pro Gly Ser Leu Ser Asn Val Lys Ala Leu Gln
                405                 410                 415

Lys Ser Pro Gly Pro Gln Arg Glu Arg Lys Ser Ser Ser Ser Ser Glu
            420                 425                 430

Asp Arg Asn Arg Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp Asp
        435                 440                 445

Trp Glu Ile Pro Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly Ser
    450                 455                 460

Gly Ser Phe Gly Thr Val Tyr Lys Gly Lys Trp His Gly Asp Val Ala
465                 470                 475                 480

Val Lys Met Leu Asn Val Thr Ala Pro Thr Pro Gln Gln Leu Gln Ala
                485                 490                 495

Phe Lys Asn Glu Val Gly Val Leu Arg Lys Thr Arg His Val Asn Ile
            500                 505                 510

Leu Leu Phe Met Gly Tyr Ser Thr Lys Pro Gln Leu Ala Ile Val Thr
        515                 520                 525

Gln Trp Cys Glu Gly Ser Ser Leu Tyr His His Leu His Ile Ile Glu
    530                 535                 540

Thr Lys Phe Glu Met Ile Lys Leu Ile Asp Ile Ala Arg Gln Thr Ala
545                 550                 555                 560

Gln Gly Met Asp Tyr Leu His Ala Lys Ser Ile Ile His Arg Asp Leu
                565                 570                 575

Lys Ser Asn Asn Ile Phe Leu His Glu Asp Leu Thr Val Lys Ile Gly
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           580                 585                 590

Asp Phe Gly Leu Ala Thr Val Lys Ser Arg Trp Ser Gly Ser His Gln
        595                 600                 605

Phe Glu Gln Leu Ser Gly Ser Ile Leu Trp Met Ala Pro Glu Val Ile
    610                 615                 620

Arg Met Gln Asp Lys Asn Pro Tyr Ser Phe Gln Ser Asp Val Tyr Ala
625                 630                 635                 640

Phe Gly Ile Val Leu Tyr Glu Leu Met Thr Gly Gln Leu Pro Tyr Ser
                645                 650                 655

Asn Ile Asn Asn Arg Asp Gln Ile Ile Phe Met Val Gly Arg Gly Tyr
            660                 665                 670

Leu Ser Pro Asp Leu Ser Lys Val Arg Ser Asn Cys Pro Lys Ala Met
        675                 680                 685

Lys Arg Leu Met Ala Glu Cys Leu Lys Lys Lys Arg Asp Glu Arg Pro
    690                 695                 700

Leu Phe Pro Gln Val Gly Lys Thr Leu Leu Ser Lys Arg Gln Asn Ser
705                 710                 715                 720

Glu Val Ile Arg Glu Lys Asp Lys Gln Ile Leu Ala Ser Ile Glu Leu
                725                 730                 735

Leu Ala Arg Ser Leu Pro Lys Ile His Arg Ser Ala Ser Glu Pro Ser
            740                 745                 750

Leu Asn Arg Ala Gly Phe Gln Thr Glu Asp Phe Ser Leu Tyr Ala Cys
        755                 760                 765

Ala Ser Pro Lys Thr Pro Ile Gln Ala Gly Gly Tyr Gly
    770                 775                 780


<210> SEQ ID NO 23
<211> LENGTH: 7914
<212> TYPE: DNA
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 23

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ctctcggtta taagatggcg gcgctgagtg gcggcggcgg cggcggcggc ggtggcgcgg    240

agcagggcca ggctctgttc aacggggaca tggagcccga ggccggcgcc gcggcctctt    300

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tatatctgga ggcctatgaa gaatacacca gcaagctaga tgccctccaa caaagagaac    480

aacagttatt ggaatccctg gggaatggaa ctgatttttc tgtttctagc tctgcatcaa    540

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<210> SEQ ID NO 24
<211> LENGTH: 766
<212> TYPE: PRT
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 24

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20 25 30

Ala Ala Ser Ser Ala Ala Asp Pro Ala Ile Pro Glu Glu Val Trp Asn
35 40 45

Ile Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu
50 55 60

Asp Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala
65 70 75 80

Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln
85 90 95

Gln Leu Leu Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser
100 105 110

Ser Ala Ser Thr Asp Thr Val Thr Ser Ser Ser Ser Ser Ser Leu Ser
115 120 125

Val Leu Pro Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val Ser
130 135 140

Arg Ser Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu
145 150 155 160

Pro Asn Lys Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr Val
165 170 175

Arg Asp Ser Leu Lys Lys Ala Leu Met Met Arg Gly Leu Ile Pro Glu
180 185 190

Cys Cys Ala Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly
195 200 205

Trp Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu
210 215 220

Val Leu Glu Asn Val Pro Leu Thr Thr His Asn Phe Val Arg Lys Thr
225 230 235 240

Phe Phe Thr Leu Ala Phe Cys Asp Phe Cys Arg Lys Leu Leu Phe Gln
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Gly Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys Ser
260 265 270

Thr Glu Val Pro Leu Met Cys Val Asn Tyr Asp Gln Leu Asp Leu Leu
275 280 285

Phe Val Ser Lys Phe Phe Glu His His Pro Ile Pro Gln Glu Glu Ala
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Ser Leu Ala Glu Thr Thr Leu Pro Cys Gly Ser Ser Pro Ser Ala Pro
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Pro Ser Asp Ser Ile Gly Pro Pro Ile Leu Thr Ser Pro Ser Pro Ser
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Arg Asn Gln Phe Gly Gln Arg Asp Arg Ser Ser Ser Ala Pro Asn Val
        355                 360                 365

His Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Asp Leu Ile Arg Asp
    370                 375                 380

Gln Gly Phe Arg Ser Asp Gly Gly Ser Thr Thr Gly Leu Ser Ala Thr
385                 390                 395                 400

Pro Pro Ala Ser Leu Pro Gly Ser Leu Ser Asn Val Lys Ala Leu Gln
                405                 410                 415

Lys Ser Pro Gly Pro Gln Arg Glu Arg Lys Ser Ser Ser Ser Ser Glu
            420                 425                 430

Asp Arg Asn Arg Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp Asp
        435                 440                 445

Trp Glu Ile Pro Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly Ser
    450                 455                 460

Gly Ser Phe Gly Thr Val Tyr Lys Gly Lys Trp His Gly Asp Val Ala
465                 470                 475                 480

Val Lys Met Leu Asn Val Thr Ala Pro Thr Pro Gln Gln Leu Gln Ala
                485                 490                 495

Phe Lys Asn Glu Val Gly Val Leu Arg Lys Thr Arg His Val Asn Ile
            500                 505                 510

Leu Leu Phe Met Gly Tyr Ser Thr Lys Pro Gln Leu Ala Ile Val Thr
        515                 520                 525

Gln Trp Cys Glu Gly Ser Ser Leu Tyr His His Leu His Ile Ile Glu
    530                 535                 540

Thr Lys Phe Glu Met Ile Lys Leu Ile Asp Ile Ala Arg Gln Thr Ala
545                 550                 555                 560

Gln Gly Met Asp Tyr Leu His Ala Lys Ser Ile Ile His Arg Asp Leu
                565                 570                 575

Lys Ser Asn Asn Ile Phe Leu His Glu Asp Leu Thr Val Lys Ile Gly
            580                 585                 590

Asp Phe Gly Leu Ala Thr Val Lys Ser Arg Trp Ser Gly Ser His Gln
        595                 600                 605

Phe Glu Gln Leu Ser Gly Ser Ile Leu Trp Met Ala Pro Glu Val Ile
    610                 615                 620

Arg Met Gln Asp Lys Asn Pro Tyr Ser Phe Gln Ser Asp Val Tyr Ala
625                 630                 635                 640

Phe Gly Ile Val Leu Tyr Glu Leu Met Thr Gly Gln Leu Pro Tyr Ser
                645                 650                 655

Asn Ile Asn Asn Arg Asp Gln Ile Ile Phe Met Val Gly Arg Gly Tyr
            660                 665                 670

Leu Ser Pro Asp Leu Ser Lys Val Arg Ser Asn Cys Pro Lys Ala Met
        675                 680                 685

Lys Arg Leu Met Ala Glu Cys Leu Lys Lys Lys Arg Asp Glu Arg Pro
    690                 695                 700

Leu Phe Pro Gln Ile Leu Ala Ser Ile Glu Leu Leu Ala Arg Ser Leu
705                 710                 715                 720

Pro Lys Ile His Arg Ser Ala Ser Glu Pro Ser Leu Asn Arg Ala Gly
                725                 730                 735
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Phe Gln Thr Glu Asp Phe Ser Leu Tyr Ala Cys Ala Ser Pro Lys Thr
740 745 750

Pro Ile Gln Ala Gly Gly Tyr Gly Glu Phe Ala Ala Phe Lys
755 760 765

<210> SEQ ID NO 25
<211> LENGTH: 4670
<212> TYPE: DNA
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 25

ggtgtgtcat agtgcagcag attgaatgca gaagatatga aaattcagat gtcttctgtt 60

aaggtgtgga atatcaaaca aatgattaag ttgacacagg agcatataga ggccctattg 120

gacaaatttg gtggggagca taatccacca tcaatatatc tggaggccta tgaagaatac 180

accagcaagc tagatgccct ccaacaaaga gaacaacagt tattggaatc cctggggaat 240

ggaactgatt tttctgtttc tagctctgca tcaacggaca ccgttacatc ttcttcctct 300

tctagccttt cagtgctgcc ttcatctctt tcagtttttc aaaatcccac agatgtgtca 360

cggagcaacc ccaagtcacc acaaaaacct atcgttagag tcttcctgcc caataaacag 420

aggacagtgg tacctgcacg gtgtggagtc acagtccggg acagcctgaa gaaggcactg 480

atgatgagag gtctaatccc agagtgctgt gctgtttaca gaattcagga tggggagaag 540

aaaccaattg gctgggacac tgatatttcc tggcttactg gagaggagtt gcatgtagaa 600

gtgttggaga atgttccact tacaacacac aactttgtac ggaaaacttt tttcacctta 660

gcattttgtg acttctgtag aaagctgctt ttccagggat tccgctgtca aacatgtggt 720

tataaatttc accagcgttg tagtacagag gttccactga tgtgtgttaa ttatgaccaa 780

ctagatttgc tgtttgtctc caagttcttt gaacaccacc caataccaca ggaggaggcc 840

tccttagcag agactaccct tccatgtggc tcatcccctt ctgcaccccc ctccgattct 900

attgggcccc caattctcac cagtccatct ccttcaaaat ccattccaat tccacagcct 960

ttccgaccag cagatgaaga tcatcgaaat cagtttggac aacgagaccg gtcctcatca 1020

gctccaaatg tgcatataaa cacaatagaa cccgtcaata ttgatgactt gattagagac 1080

caagggtttc gtagtgatgg aggatcaacc acaggtttat ccgccacacc ccctgcctca 1140

ttacctggct cactctctaa tgtgaaagca ttgcagaaat ctccaggacc tcagcgagaa 1200

agaaagtcct cttcatcctc agaagacagg aatcgaatga aaacgcttgg tagacgggat 1260

tcaagtgacg attgggagat tcctgatgga cagatcacag tgggacaaag aattggatca 1320

gggtcatttg ggacagtcta caagggaaag tggcatggtg atgtggcagt gaaaatgttg 1380

aatgtgacag cacccacacc tcagcagtta caggccttca aaaatgaagt aggagtactc 1440

aggaaaacgc gacatgtgaa tatcctcctc ttcatgggtt attcaacaaa gccacaactg 1500

gctattgtta cccagtggtg tgagggctcc agtttatatc atcatctcca catcattgag 1560

accaaattcg agatgatcaa acttatagat attgcacggc agactgcaca gggcatggat 1620

tacttacacg ccaagtcaat catccacaga gacctcaaga gtaataatat ttttcttcat 1680

gaagacctca cagtaaaaat aggtgatttt ggtctagcca cagtgaaatc tcgatggagt 1740

gggtcccatc agtttgaaca gttgtctgga tccattttgt ggatggcacc agaagtaatc 1800

agaatgcaag ataaaaaccc atatagcttt cagtcagatg tatatgcatt tgggattgtt 1860

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ctgtatgaat tgatgaccgg acagttacct tattcaaata tcaacaacag ggaccagata 1920

atttttatgg tgggacgagg atatctgtct ccagatctca gtaaggtacg gagtaactgt 1980

ccaaaagcca tgaagagatt aatggcagag tgcctaaaaa agaaaagaga tgaaagacca 2040

ctctttcccc aagtaggaaa gactctccta agcaagagac aaaattcaga agttatcagg 2100

gaaaaagata agcagattct cgcctctatt gagctgctgg cccgctcatt gccaaaaatt 2160

caccgcagtg catcagaacc ctccttgaat cgggctggct tccaaacaga ggattttagt 2220

ctatatgctt gtgcttctcc aaaaacaccc attcaggcag ggggatatga agcagatttg 2280

gctcttacat caaataaaaa tagagtagaa gttgggattt agagatttcc tgacatgcaa 2340

gaaggaataa gcaagaaaaa aaggtttgtt ttccccaaat catatctatt gtcttttact 2400

tctatttttt cttaaatttt ttgtgatttc agagacatgt agagttttat tgatacctaa 2460

actatgagtt ctttttttttt ttttttttte attattttga ttttttggc caagaggcat 2520

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aggtgaagtc ttaaacactg gaccagcaga gaaattccta ctctatgagt tctttttgtc 2700

atcccctccc cgcaccctcc acccccaacc taaagtctga tgatgaaatc aacaactatt 2760

ccattagaag cagtagattc tggtagcatg atctttagtt tgttagtaag attttgtgct 2820

ttgtggggtt gtgtcgtttt aaggctaata tttaagtttg tcaaatagaa tgctgttcag 2880

attgtaaaaa tgagtaataa acatctgaag tttttttttaa gttattttta acatggtata 2940

tacagttgag cttagagttt atcatttttct gatattctct tacttagtag atgaattcta 3000

gccatttttt ataaagattt ctgttaagca aatcctgttt tcacatgggc ttcctttaag 3060

ggattttaga ttctgctgga tatggtgact gctcataaga ctgttgaaaa ttacttttaa 3120

gatgtattag aatacttctg aaaaaaaata gcaaccttaa aaccataagc aaaagtagta 3180

agggtgttta tacatttcta gagtccctgt ttaggtaata gcctcctatg attgtacttt 3240

aaatgttttg ctctccaagg ttttagtaac ttggcttttt ttctaatcag tgccaaactc 3300

ccccagtttt tttaacttta aatatgaggt aataaatctt ttacccttcc ttgatctttt 3360

gacttataat accttggtca gttgtttctt aaaaggaatc cttaaatgga aagagacaat 3420

atcactgtct gcagttctga ttagtagttt tattcagaat ggaaaaacag attattcatt 3480

tttgaaaatt gttcaggggt atgttcattg ttaggacctt ggactttgga gtcagtgcct 3540

agctatgcat tccaggtctg ccattttctg gctgtgaaat tttggacaag ttacttaacc 3600

actttaaacc ccagctttaa gaagtaaatt aaccccagta aattaagaag taatagcagc 3660

cacttcgtag agttgttatg aggctcagat gcagtgcaaa tgtgtataaa gtattcaggg 3720

agtcacctgg tatactataa tagacactag aatagttgcc aatattatca gcatacaatc 3780

tgaggattct gtcagccaat cattagcaat ctgttgtttg ttgggacatg ccagtgttct 3840

ccagttgaaa tcagtagcaa tctaaaaatg gatagattat tcctcattta aatagtgtgt 3900

tcatataagt gattgcttgg atccttatca gaagttgctg ttactgaaaa atgataaggc 3960

tgactaaatt gtgatagttg tcagttacta accaactccc agaaatgaat aagaggaacc 4020

tatctctagt tcctagtaga aggtatggac aaaatagtag gtgaaaaata atgtcttgaa 4080

cccccaaatt aagtaagctt taaagagtac aatacctcaa agggtctttg cggtttaaaa 4140

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tttgtatgct gagaatgatg ttcattgaca tgtgcctata tgtaattttt tgatagttta   4200

aaaggtgaaa tgaactacag atgggagagg tctgaatttt cttgccttca gtcaaatgtg   4260

taatgtggac atattatttg acctgtgaat tttatctttt aaaaaagatt aattcctgct   4320

tcttccttcc taatagttgc attataataa tgaaaatgag ttgataattt ggggggaaag   4380

tattctacaa atcaacctta ttattttacc attggtttct gagaaatttt gttcatttga   4440

accgtttata gcttgattag aatcatagca tgtaaaaccc aactgaggga ttatctgcag   4500

acttaatgta gtattatgta agttgtcttc tttcatttcg accttttttg cttttgttgt   4560

tgctagatct gtagtatgta gctagtcacc tttcagcgag gtttcagcga ggcttttctg   4620

tgtctctagg ttatttgaga taacttttt aaaattagct cttgtcctcc               4670


<210> SEQ ID NO 26
<211> LENGTH: 761
<212> TYPE: PRT
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 26

Met Lys Ile Gln Met Ser Ser Val Lys Val Trp Asn Ile Lys Gln Met
1               5                   10                  15

Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu Asp Lys Phe Gly
            20                  25                  30

Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala Tyr Glu Glu Tyr
        35                  40                  45

Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln Gln Leu Leu Glu
    50                  55                  60

Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser Ser Ala Ser Thr
65                  70                  75                  80

Asp Thr Val Thr Ser Ser Ser Ser Ser Ser Leu Ser Val Leu Pro Ser
                85                  90                  95

Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val Ser Arg Ser Asn Pro
            100                 105                 110

Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu Pro Asn Lys Gln
        115                 120                 125

Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr Val Arg Asp Ser Leu
    130                 135                 140

Lys Lys Ala Leu Met Met Arg Gly Leu Ile Pro Glu Cys Cys Ala Val
145                 150                 155                 160

Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly Trp Asp Thr Asp
                165                 170                 175

Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu Val Leu Glu Asn
            180                 185                 190

Val Pro Leu Thr Thr His Asn Phe Val Arg Lys Thr Phe Phe Thr Leu
        195                 200                 205

Ala Phe Cys Asp Phe Cys Arg Lys Leu Leu Phe Gln Gly Phe Arg Cys
    210                 215                 220

Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys Ser Thr Glu Val Pro
225                 230                 235                 240

Leu Met Cys Val Asn Tyr Asp Gln Leu Asp Leu Leu Phe Val Ser Lys
                245                 250                 255

Phe Phe Glu His His Pro Ile Pro Gln Glu Glu Ala Ser Leu Ala Glu
            260                 265                 270
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Thr Thr Leu Pro Cys Gly Ser Ser Pro Ser Ala Pro Pro Ser Asp Ser
        275                 280                 285

Ile Gly Pro Pro Ile Leu Thr Ser Pro Ser Pro Ser Lys Ser Ile Pro
    290                 295                 300

Ile Pro Gln Pro Phe Arg Pro Ala Asp Glu Asp His Arg Asn Gln Phe
305                 310                 315                 320

Gly Gln Arg Asp Arg Ser Ser Ser Ala Pro Asn Val His Ile Asn Thr
                325                 330                 335

Ile Glu Pro Val Asn Ile Asp Asp Leu Ile Arg Asp Gln Gly Phe Arg
            340                 345                 350

Ser Asp Gly Gly Ser Thr Thr Gly Leu Ser Ala Thr Pro Pro Ala Ser
        355                 360                 365

Leu Pro Gly Ser Leu Ser Asn Val Lys Ala Leu Gln Lys Ser Pro Gly
    370                 375                 380

Pro Gln Arg Glu Arg Lys Ser Ser Ser Ser Ser Glu Asp Arg Asn Arg
385                 390                 395                 400

Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp Asp Trp Glu Ile Pro
                405                 410                 415

Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly Ser Gly Ser Phe Gly
            420                 425                 430

Thr Val Tyr Lys Gly Lys Trp His Gly Asp Val Ala Val Lys Met Leu
        435                 440                 445

Asn Val Thr Ala Pro Thr Pro Gln Gln Leu Gln Ala Phe Lys Asn Glu
    450                 455                 460

Val Gly Val Leu Arg Lys Thr Arg His Val Asn Ile Leu Leu Phe Met
465                 470                 475                 480

Gly Tyr Ser Thr Lys Pro Gln Leu Ala Ile Val Thr Gln Trp Cys Glu
                485                 490                 495

Gly Ser Ser Leu Tyr His His Leu His Ile Ile Glu Thr Lys Phe Glu
            500                 505                 510

Met Ile Lys Leu Ile Asp Ile Ala Arg Gln Thr Ala Gln Gly Met Asp
        515                 520                 525

Tyr Leu His Ala Lys Ser Ile Ile His Arg Asp Leu Lys Ser Asn Asn
    530                 535                 540

Ile Phe Leu His Glu Asp Leu Thr Val Lys Ile Gly Asp Phe Gly Leu
545                 550                 555                 560

Ala Thr Val Lys Ser Arg Trp Ser Gly Ser His Gln Phe Glu Gln Leu
                565                 570                 575

Ser Gly Ser Ile Leu Trp Met Ala Pro Glu Val Ile Arg Met Gln Asp
            580                 585                 590

Lys Asn Pro Tyr Ser Phe Gln Ser Asp Val Tyr Ala Phe Gly Ile Val
        595                 600                 605

Leu Tyr Glu Leu Met Thr Gly Gln Leu Pro Tyr Ser Asn Ile Asn Asn
    610                 615                 620

Arg Asp Gln Ile Ile Phe Met Val Gly Arg Gly Tyr Leu Ser Pro Asp
625                 630                 635                 640

Leu Ser Lys Val Arg Ser Asn Cys Pro Lys Ala Met Lys Arg Leu Met
                645                 650                 655

Ala Glu Cys Leu Lys Lys Lys Arg Asp Glu Arg Pro Leu Phe Pro Gln
            660                 665                 670
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Val Gly Lys Thr Leu Leu Ser Lys Arg Gln Asn Ser Glu Val Ile Arg
        675                 680                 685

Glu Lys Asp Lys Gln Ile Leu Ala Ser Ile Glu Leu Leu Ala Arg Ser
    690                 695                 700

Leu Pro Lys Ile His Arg Ser Ala Ser Glu Pro Ser Leu Asn Arg Ala
705                 710                 715                 720

Gly Phe Gln Thr Glu Asp Phe Ser Leu Tyr Ala Cys Ala Ser Pro Lys
                725                 730                 735

Thr Pro Ile Gln Ala Gly Gly Tyr Glu Ala Asp Leu Ala Leu Thr Ser
            740                 745                 750

Asn Lys Asn Arg Val Glu Val Gly Ile
        755                 760


<210> SEQ ID NO 27
<211> LENGTH: 4816
<212> TYPE: DNA
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 27

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cgacgccgcc cgggccgccc gggccgtccc tccccgctgc cccccgtcct ccgcctccgc    120

ctccccccgc cctcagcctc ccttcccccc ccccgcccag cagcggtcgc tcgggcccgg    180

ctctcggtta taagatggcg gcgctgagtg gcggcggcgg cggcggcggc ggtggcgcgg    240

agcagggcca ggctctgttc aacggggaca tggagcccga ggccggcgcc gcggcctctt    300

cggctgcgga ccccgccatt cccgaggagg tgtggaatat caaacaaatg attaagttga    360

cacaggagca tatagaggcc ctattggaca aatttggtgg ggagcataat ccaccatcaa    420

tatatctgga ggcctatgaa gaatacacca gcaagctaga tgccctccaa caaagagaac    480

aacagttatt ggaatccctg gggaatggaa ctgatttttc tgtttctagc tctgcatcaa    540

cggacaccgt tacatcttct tcctcttcta gcctttcagt gctgccttca tctctttcag    600

tttttcaaaa tcccacagat gtgtcacgga gcaaccccaa gtcaccacaa aaacctatcg    660

ttagagtctt cctgcccaat aaacagagga cagtggtacc tgcacggtgt ggagtcacag    720

tccgggacag cctgaagaag gcactgatga tgagaggtct aatcccagag tgctgtgctg    780

tttacagaat tcaggatggg gagaagaaac caattggctg ggacactgat atttcctggc    840

ttactggaga ggagttgcat gtagaagtgt tggagaatgt tccacttaca acacacaact    900

ttgtacggaa aacttttttc accttagcat tttgtgactt ctgtagaaag ctgcttttcc    960

agggattccg ctgtcaaaca tgtggttata aatttcacca gcgttgtagt acagaggttc   1020

cactgatgtg tgttaattat gaccaactag agcccccaat tctcaccagt ccatctcctt   1080

caaaatccat tccaattcca cagcctttcc gaccagcaga tgaagatcat cgaaatcagt   1140

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tcaatattga tgacttgatt agagaccaag ggtttcgtag tgatggagga tcaaccacag   1260

gtttatccgc cacacccccc gcctcattac ctggctcact ctctaatgtg aaagcattgc   1320

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gaatgaaaac gcttggtaga cgggattcaa gtgacgattg ggagattcct gatggacaga   1440

tcacagtggg acaaagaatt ggatcagggt catttgggac agtctacaag ggaaagtggc   1500
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atggtgatgt ggcagtgaaa atgttgaatg tgacagcacc cacacctcag cagttacagg 1560

ccttcaaaaa tgaagtagga gtactcagga aaacgcgaca tgtgaatatc ctcctcttca 1620

tgggttattc aacaaagcca caactggcta ttgttaccca gtggtgtgag ggctccagtt 1680

tatatcatca tctccacatc attgagacca aattcgagat gatcaaactt atagatattg 1740

cacggcagac tgcacagggc atggattact tacacgccaa gtcaatcatc cacagagacc 1800

tcaagagtaa taatattttt cttcatgaag acctcacagt aaaaataggt gattttggtc 1860

tagccacagt gaaatctcga tggagtgggt cccatcagtt tgaacagttg tctggatcca 1920

ttttgtggat ggcaccagaa gtaatcagaa tgcaagataa aaacccatat agctttcagt 1980

cagatgtata tgcatttggg attgttctgt atgaattgat gaccggacag ttaccttatt 2040

caaatatcaa caacagggac cagataattt ttatggtggg acgaggatat ctgtctccag 2100

atctcagtaa ggtacggagt aactgtccaa aagccatgaa gagattaatg gcagagtgcc 2160

taaaaaagaa aagagatgaa agaccactct ttccccaagt aggaaagact ctcctaagca 2220

agagacaaaa ttcagaagtt atcagggaaa aagataagca gattctcgcc tctattgagc 2280

tgctggcccg ctcattgcca aaaattcacc gcagtgcatc agaaccctcc ttgaatcggg 2340

ctggcttcca aacagaggat tttagtctat atgcttgtgc ttctccaaaa acacccattc 2400

aggcaggggg atatgaagca gatttggctc ttacatcaaa taaaaataga gtagaagttg 2460

ggatttagag atttcctgac atgcaagaag gaataagcaa gaaaaaaagg tttgttttcc 2520

ccaaatcata tctattgtct tttacttcta ttttttctta aatttttttgt gatttcagag 2580

acatgtagag ttttattgat acctaaacta tgagttcttt ttttttttt tttttcatta 2640

ttttgatttt tttggccaag aggcatatgg gatcttagct tgagaaagca acaattttct 2700

tgatgtcatt ttgggtgagg gcacatattg ctgtgaacag tgtggtgata gccaccaggg 2760

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ctgttttcac atgggcttcc tttaagggat tttagattct gctggatatg gtgactgctc 3240

ataagactgt tgaaaattac ttttaagatg tattagaata cttctgaaaa aaaatagcaa 3300

ccttaaaacc ataagcaaaa gtagtaaggg tgtttataca tttctagagt ccctgtttag 3360

gtaatagcct cctatgattg tactttaaat gttttgctct ccaaggtttt agtaacttgg 3420

ctttttttct aatcagtgcc aaactccccc agtttttttа actttaaata tgaggtaata 3480

aatcttttac ccttccttga tcttttgact tataatacct tggtcagttg tttcttaaaa 3540

ggaatcctta aatggaaaga gacaatatca ctgtctgcag ttctgattag tagttttatt 3600

cagaatggaa aaacagatta ttcatttttg aaaattgttc aggggtatgt tcattgttag 3660

gaccttggac tttggagtca gtgcctagct atgcattcca ggtctgccat tttctggctg 3720

tgaaattttg gacaagttac ttaaccactt taaaccccag ctttaagaag taaattaacc 3780

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ccagtaaatt aagaagtaat agcagccact tcgtagagtt gttatgaggc tcagatgcag   3840

tgcaaatgtg tataaagtat tcagggagtc acctggtata ctataataga cactagaata   3900

gttgccaata ttatcagcat acaatctgag gattctgtca gccaatcatt agcaatctgt   3960

tgtttgttgg gacatgccag tgttctccag ttgaaatcag tagcaatcta aaaatggata   4020

gattattcct catttaaata gtgtgttcat ataagtgatt gcttggatcc ttatcagaag   4080

ttgctgttac tgaaaaatga taaggctgac taaattgtga tagttgtcag ttactaacca   4140

actcccagaa atgaataaga ggaacctatc tctagttcct agtagaaggt atggacaaaa   4200

tagtaggtga aaaataatgt cttgaacccc caaattaagt aagctttaaa gagtacaata   4260

cctcaaaggg tctttgcggt ttaaaatttg tatgctgaga atgatgttca ttgacatgtg   4320

cctatatgta attttttgat agtttaaaag gtgaaatgaa ctacagatgg gagaggtctg   4380

aattttcttg ccttcagtca aatgtgtaat gtggacatat tatttgacct gtgaatttta   4440

tcttttaaaa aagattaatt cctgcttctt ccttcctaat agttgcatta taataatgaa   4500

aatgagttga taatttgggg ggaaagtatt ctacaaatca accttattat tttaccattg   4560

gtttctgaga aattttgttc atttgaaccg tttatagctt gattagaatc atagcatgta   4620

aaacccaact gagggattat ctgcagactt aatgtagtat tatgtaagtt gtcttctttc   4680

atttcgacct tttttgcttt tgttgttgct agatctgtag tatgtagcta gtcacctttc   4740

agcgaggttt cagcgaggct tttctgtgtc tctaggttat ttgagataac ttttttaaaa   4800

ttagctcttg tcctcc                                                   4816
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<210> SEQ ID NO 28
<211> LENGTH: 757
<212> TYPE: PRT
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 28

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Met Ala Ala Leu Ser Gly Gly Gly Gly Gly Gly Gly Gly Gly Ala Glu
1               5                   10                  15

Gln Gly Gln Ala Leu Phe Asn Gly Asp Met Glu Pro Glu Ala Gly Ala
            20                  25                  30

Ala Ala Ser Ser Ala Ala Asp Pro Ala Ile Pro Glu Glu Val Trp Asn
        35                  40                  45

Ile Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu
    50                  55                  60

Asp Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala
65                  70                  75                  80

Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln
                85                  90                  95

Gln Leu Leu Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser
            100                 105                 110

Ser Ala Ser Thr Asp Thr Val Thr Ser Ser Ser Ser Ser Ser Leu Ser
        115                 120                 125

Val Leu Pro Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val Ser
    130                 135                 140

Arg Ser Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu
145                 150                 155                 160

Pro Asn Lys Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr Val
                165                 170                 175
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Arg Asp Ser Leu Lys Lys Ala Leu Met Met Arg Gly Leu Ile Pro Glu
            180                 185                 190

Cys Cys Ala Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly
        195                 200                 205

Trp Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu
    210                 215                 220

Val Leu Glu Asn Val Pro Leu Thr Thr His Asn Phe Val Arg Lys Thr
225                 230                 235                 240

Phe Phe Thr Leu Ala Phe Cys Asp Phe Cys Arg Lys Leu Leu Phe Gln
                245                 250                 255

Gly Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys Ser
            260                 265                 270

Thr Glu Val Pro Leu Met Cys Val Asn Tyr Asp Gln Leu Glu Pro Pro
        275                 280                 285

Ile Leu Thr Ser Pro Ser Pro Ser Lys Ser Ile Pro Ile Pro Gln Pro
    290                 295                 300

Phe Arg Pro Ala Asp Glu Asp His Arg Asn Gln Phe Gly Gln Arg Asp
305                 310                 315                 320

Arg Ser Ser Ser Ala Pro Asn Val His Ile Asn Thr Ile Glu Pro Val
                325                 330                 335

Asn Ile Asp Asp Leu Ile Arg Asp Gln Gly Phe Arg Ser Asp Gly Gly
            340                 345                 350

Ser Thr Thr Gly Leu Ser Ala Thr Pro Pro Ala Ser Leu Pro Gly Ser
        355                 360                 365

Leu Ser Asn Val Lys Ala Leu Gln Lys Ser Pro Gly Pro Gln Arg Glu
    370                 375                 380

Arg Lys Ser Ser Ser Ser Ser Glu Asp Arg Asn Arg Met Lys Thr Leu
385                 390                 395                 400

Gly Arg Arg Asp Ser Ser Asp Asp Trp Glu Ile Pro Asp Gly Gln Ile
                405                 410                 415

Thr Val Gly Gln Arg Ile Gly Ser Gly Ser Phe Gly Thr Val Tyr Lys
            420                 425                 430

Gly Lys Trp His Gly Asp Val Ala Val Lys Met Leu Asn Val Thr Ala
        435                 440                 445

Pro Thr Pro Gln Gln Leu Gln Ala Phe Lys Asn Glu Val Gly Val Leu
    450                 455                 460

Arg Lys Thr Arg His Val Asn Ile Leu Leu Phe Met Gly Tyr Ser Thr
465                 470                 475                 480

Lys Pro Gln Leu Ala Ile Val Thr Gln Trp Cys Glu Gly Ser Ser Leu
                485                 490                 495

Tyr His His Leu His Ile Ile Glu Thr Lys Phe Glu Met Ile Lys Leu
            500                 505                 510

Ile Asp Ile Ala Arg Gln Thr Ala Gln Gly Met Asp Tyr Leu His Ala
        515                 520                 525

Lys Ser Ile Ile His Arg Asp Leu Lys Ser Asn Asn Ile Phe Leu His
    530                 535                 540

Glu Asp Leu Thr Val Lys Ile Gly Asp Phe Gly Leu Ala Thr Val Lys
545                 550                 555                 560

Ser Arg Trp Ser Gly Ser His Gln Phe Glu Gln Leu Ser Gly Ser Ile
                565                 570                 575
```

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```
Leu Trp Met Ala Pro Glu Val Ile Arg Met Gln Asp Lys Asn Pro Tyr
            580                 585                 590

Ser Phe Gln Ser Asp Val Tyr Ala Phe Gly Ile Val Leu Tyr Glu Leu
        595                 600                 605

Met Thr Gly Gln Leu Pro Tyr Ser Asn Ile Asn Asn Arg Asp Gln Ile
    610                 615                 620

Ile Phe Met Val Gly Arg Gly Tyr Leu Ser Pro Asp Leu Ser Lys Val
625                 630                 635                 640

Arg Ser Asn Cys Pro Lys Ala Met Lys Arg Leu Met Ala Glu Cys Leu
                645                 650                 655

Lys Lys Lys Arg Asp Glu Arg Pro Leu Phe Pro Gln Val Gly Lys Thr
            660                 665                 670

Leu Leu Ser Lys Arg Gln Asn Ser Glu Val Ile Arg Glu Lys Asp Lys
        675                 680                 685

Gln Ile Leu Ala Ser Ile Glu Leu Leu Ala Arg Ser Leu Pro Lys Ile
    690                 695                 700

His Arg Ser Ala Ser Glu Pro Ser Leu Asn Arg Ala Gly Phe Gln Thr
705                 710                 715                 720

Glu Asp Phe Ser Leu Tyr Ala Cys Ala Ser Pro Lys Thr Pro Ile Gln
                725                 730                 735

Ala Gly Gly Tyr Glu Ala Asp Leu Ala Leu Thr Ser Asn Lys Asn Arg
            740                 745                 750

Val Glu Val Gly Ile
        755
```

<210> SEQ ID NO 29
<211> LENGTH: 2499
<212> TYPE: DNA
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 29

```
ctcagctgcg ccgggtctca caagacggtt cccgaggtgg cccaggcgcc gtcccaccgc     60

cgacgccgcc cgggccgccc gggccgtccc tccccgctgc cccccgtcct ccgcctccgc    120

ctccccccgc cctcagcctc ccttcccccc ccccgcccag cagcggtcgc tcgggcccgg    180

ctctcggtta taagatggcg gcgctgagtg gcggcggcgg cggcggcggc ggtggcgcgg    240

agcagggcca ggctctgttc aacggggaca tggagcccga ggccggcgcc gcggcctctt    300

cggctgcgga ccccgccatt cccgaggagg tgtggaatat caaacaaatg attaagttga    360

cacaggagca tatagaggcc ctattggaca aatttggtgg ggagcataat ccaccatcaa    420

tatatctgga ggcctatgaa gaatacacca gcaagctaga tgccctccaa caaagagaac    480

aacagttatt ggaatccctg gggaatggaa ctgatttttc tgtttctagc tctgcatcaa    540

cggacaccgt tacatcttct tcctcttcta gcctttcagt gctgccttca tctctttcag    600

tttttcaaaa tcccacagat gtgtcacgga gcaaccccaa gtcaccacaa aaacctatcg    660

ttagagtctt cctgcccaat aaacagagga cagtggtacc tgcacggtgt ggagtcacag    720

tccgggacag cctgaagaag gcactgatga tgagaggtct aatcccagag tgctgtgctg    780

tttacagaat tcaggatggg gagaagaaac caattggctg ggacactgat atttcctggc    840

ttactggaga ggagttgcat gtagaagtgt tggagaatgt tccacttaca acacacaact    900

ttgtacggaa aacttttttc accttagcat tttgtgactt ctgtagaaag ctgcttttcc    960
```

-continued

```
agggattccg ctgtcaaaca tgtggttata aatttcacca gcgttgtagt acagaggttc   1020

cactgatgtg tgttaattat gaccaactag atttgctgtt tgtctccaag ttctttgaac   1080

accacccaat accacaggag gaggcctcct tagcagagac tacccttcca tgtggctcat   1140

ccccttctgc acccccctcc gattctattg ggcccccaat tctcaccagt ccatctcctt   1200

caaaatccat tccaattcca cagcctttcc gaccagcaga tgaagatcat cgaaatcagt   1260

ttggacaacg agaccggtcc tcatcagctc caaatgtgca tataaacaca atagaacccg   1320

tcaatattga tgacttgatt agagaccaag ggtttcgtag tgatggagga tcaaccacag   1380

gtttatccgc cacacccccc gcctcattac ctggctcact ctctaatgtg aaagcattgc   1440

agaaatctcc aggacctcag cgagaaagaa agtcctcttc atcctcagaa gacaggaatc   1500

gaatgaaaac gcttggtaga cgggattcaa gtgacgattg ggagattcct gatggacaga   1560

tcacagtggg acaaagaatt ggatcagggt catttgggac agtctacaag ggaaagtggc   1620

atggtgatgt ggcagtgaaa atgttgaatg tgacagcacc cacacctcag cagttacagg   1680

ccttcaaaaa tgaagtagga gtactcagga aaacgcgaca tgtgaatatc ctcctcttca   1740

tgggttattc aacaaagcca caactggcta ttgttaccca gtggtgtgag ggctccagtt   1800

tatatcatca tctccacatc attgagacca aattcgagat gatcaaactt atagatattg   1860

cacggcagac tgcacagggc atggattact tacacgccaa gtcaatcatc cacagagacc   1920

tcaagagtaa taatattttt cttcatgaag acctcacagt aaaaataggt gattttggtc   1980

tagccacagt gaaatctcga tggagtgggt cccatcagtt tgaacagttg tctggatcca   2040

ttttgtggat ggcaccagaa gtaatcagaa tgcaagataa aaacccatat agctttcagt   2100

cagatgtata tgcatttggg attgttctgt atgaattgat gaccggacag ttaccttatt   2160

caaatatcaa caacagggac cagataattt ttatggtggg acgaggatat ctgtctccag   2220

atctcagtaa ggtacggagt aactgtccaa aagccatgaa gagattaatg gcagagtgcc   2280

taaaaaagaa aagagatgaa agaccactct ttccccaagt aggaaagact ctcctaagca   2340

agagacaaaa ttcagaagtt atcagggaaa aagataagca ggaaaagtat gtttctttag   2400

tacattccag gcatttggga ttacagtaaa aacaatattc tcgcctctat tgagctgctg   2460

gcccgctcat tgccaaaaat tcaccgcagt gcatcagaa                          2499
```

<210> SEQ ID NO 30
<211> LENGTH: 744
<212> TYPE: PRT
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 30

```
Met Ala Ala Leu Ser Gly Gly Gly Gly Gly Gly Gly Gly Gly Ala Glu
1               5                  10                  15

Gln Gly Gln Ala Leu Phe Asn Gly Asp Met Glu Pro Glu Ala Gly Ala
            20                  25                  30

Ala Ala Ser Ser Ala Ala Asp Pro Ala Ile Pro Glu Glu Val Trp Asn
        35                  40                  45

Ile Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu
    50                  55                  60

Asp Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala
65                  70                  75                  80

Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln
```

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```
               85                  90                  95

Gln Leu Leu Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser
            100                 105                 110

Ser Ala Ser Thr Asp Thr Val Thr Ser Ser Ser Ser Ser Ser Leu Ser
        115                 120                 125

Val Leu Pro Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val Ser
    130                 135                 140

Arg Ser Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu
145                 150                 155                 160

Pro Asn Lys Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr Val
                165                 170                 175

Arg Asp Ser Leu Lys Lys Ala Leu Met Met Arg Gly Leu Ile Pro Glu
            180                 185                 190

Cys Cys Ala Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly
        195                 200                 205

Trp Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu
    210                 215                 220

Val Leu Glu Asn Val Pro Leu Thr Thr His Asn Phe Val Arg Lys Thr
225                 230                 235                 240

Phe Phe Thr Leu Ala Phe Cys Asp Phe Cys Arg Lys Leu Leu Phe Gln
                245                 250                 255

Gly Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys Ser
            260                 265                 270

Thr Glu Val Pro Leu Met Cys Val Asn Tyr Asp Gln Leu Asp Leu Leu
        275                 280                 285

Phe Val Ser Lys Phe Phe Glu His His Pro Ile Pro Gln Glu Glu Ala
    290                 295                 300

Ser Leu Ala Glu Thr Thr Leu Pro Cys Gly Ser Ser Pro Ser Ala Pro
305                 310                 315                 320

Pro Ser Asp Ser Ile Gly Pro Pro Ile Leu Thr Ser Pro Ser Pro Ser
                325                 330                 335

Lys Ser Ile Pro Ile Pro Gln Pro Phe Arg Pro Ala Asp Glu Asp His
            340                 345                 350

Arg Asn Gln Phe Gly Gln Arg Asp Arg Ser Ser Ser Ala Pro Asn Val
        355                 360                 365

His Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Asp Leu Ile Arg Asp
    370                 375                 380

Gln Gly Phe Arg Ser Asp Gly Gly Ser Thr Thr Gly Leu Ser Ala Thr
385                 390                 395                 400

Pro Pro Ala Ser Leu Pro Gly Ser Leu Ser Asn Val Lys Ala Leu Gln
                405                 410                 415

Lys Ser Pro Gly Pro Gln Arg Glu Arg Lys Ser Ser Ser Ser Ser Glu
            420                 425                 430

Asp Arg Asn Arg Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp Asp
        435                 440                 445

Trp Glu Ile Pro Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly Ser
    450                 455                 460

Gly Ser Phe Gly Thr Val Tyr Lys Gly Lys Trp His Gly Asp Val Ala
465                 470                 475                 480

Val Lys Met Leu Asn Val Thr Ala Pro Thr Pro Gln Gln Leu Gln Ala
                485                 490                 495
```

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```
Phe Lys Asn Glu Val Gly Val Leu Arg Lys Thr Arg His Val Asn Ile
            500                 505                 510

Leu Leu Phe Met Gly Tyr Ser Thr Lys Pro Gln Leu Ala Ile Val Thr
        515                 520                 525

Gln Trp Cys Glu Gly Ser Ser Leu Tyr His His Leu His Ile Ile Glu
    530                 535                 540

Thr Lys Phe Glu Met Ile Lys Leu Ile Asp Ile Ala Arg Gln Thr Ala
545                 550                 555                 560

Gln Gly Met Asp Tyr Leu His Ala Lys Ser Ile Ile His Arg Asp Leu
                565                 570                 575

Lys Ser Asn Asn Ile Phe Leu His Glu Asp Leu Thr Val Lys Ile Gly
            580                 585                 590

Asp Phe Gly Leu Ala Thr Val Lys Ser Arg Trp Ser Gly Ser His Gln
        595                 600                 605

Phe Glu Gln Leu Ser Gly Ser Ile Leu Trp Met Ala Pro Glu Val Ile
    610                 615                 620

Arg Met Gln Asp Lys Asn Pro Tyr Ser Phe Gln Ser Asp Val Tyr Ala
625                 630                 635                 640

Phe Gly Ile Val Leu Tyr Glu Leu Met Thr Gly Gln Leu Pro Tyr Ser
                645                 650                 655

Asn Ile Asn Asn Arg Asp Gln Ile Ile Phe Met Val Gly Arg Gly Tyr
            660                 665                 670

Leu Ser Pro Asp Leu Ser Lys Val Arg Ser Asn Cys Pro Lys Ala Met
        675                 680                 685

Lys Arg Leu Met Ala Glu Cys Leu Lys Lys Lys Arg Asp Glu Arg Pro
    690                 695                 700

Leu Phe Pro Gln Val Gly Lys Thr Leu Leu Ser Lys Arg Gln Asn Ser
705                 710                 715                 720

Glu Val Ile Arg Glu Lys Asp Lys Gln Glu Lys Tyr Val Ser Leu Val
                725                 730                 735

His Ser Arg His Leu Gly Leu Gln
            740
```

<210> SEQ ID NO 31
<211> LENGTH: 2404
<212> TYPE: DNA
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 31

```
ctcagctgcg ccgggtctca caagacggtt cccgaggtgg cccaggcgcc gtcccaccgc     60

cgacgccgcc cgggccgccc gggccgtccc tccccgctgc cccccgtcct ccgcctccgc    120

ctccccccgc cctcagcctc ccttcccctt ccccgcccag cagcggtcgc tcgggcccgg    180

ctctcggtta taagatggcg gcgctgagtg gcggcggcgg cggcggcggc ggtggcgcgg    240

agcagggcca ggctctgttc aacggggaca tggagcccga ggccggcgcc gcggcctctt    300

cggctgcgga ccccgccatt cccgaggagg tgtggaatat caaacaaatg attaagttga    360

cacaggagca tatagaggcc ctattggaca aatttggtgg ggagcataat ccaccatcaa    420

tatatctgga ggcctatgaa gaatacacca gcaagctaga tgccctccaa caaagagaac    480

aacagttatt ggaatccctg gggaatggaa ctgatttttc tgtttctagc tctgcatcaa    540

cggacaccgt tacatcttct tcctcttcta gcctttcagt gctgccttca tctctttcag    600
```

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```
tttttcaaaa tcccacagat gtgtcacgga gcaaccccaa gtcaccacaa aaacctatcg    660

ttagagtctt cctgcccaat aaacagagga cagtggtacc tgcacggtgt ggagtcacag    720

tccgggacag cctgaagaag gcactgatga tgagaggtct aatcccagag tgctgtgctg    780

tttacagaat tcaggatggg gagaagaaac caattggctg ggacactgat atttcctggc    840

ttactggaga ggagttgcat gtagaagtgt tggagaatgt tccacttaca acacacaact    900

ttgtacggaa aacttttttc accttagcat tttgtgactt ctgtagaaag ctgcttttcc    960

agggattccg ctgtcaaaca tgtggttata aatttcacca gcgttgtagt acagaggttc   1020

cactgatgtg tgttaattat gaccaactag atttgctgtt tgtctccaag ttctttgaac   1080

accacccaat accacaggag gaggcctcct tagcagagac tacccttcca tgtggctcat   1140

ccccttctgc acccccctcc gattctattg ggcccccaat tctcaccagt ccatctcctt   1200

caaaatccat tccaattcca cagcctttcc gaccagcaga tgaagatcat cgaaatcagt   1260

ttggacaacg agaccggtcc tcatcagctc caaatgtgca tataaacaca atagaacccg   1320

tcaatattga tgacttgatt agagaccaag ggtttcgtag tgatggagga tcaaccacag   1380

gtttatccgc cacacccccc gcctcattac ctggctcact ctctaatgtg aaagcattgc   1440

agaaatctcc aggacctcag cgagaaagaa agtcctcttc atcctcagaa gacaggaatc   1500

gaatgaaaac gcttggtaga cgggattcaa gtgacgattg ggagattcct gatggacaga   1560

tcacagtggg acaaagaatt ggatcagggt catttgggac agtctacaag ggaaagtggc   1620

atggtgatgt ggcagtgaaa atgttgaatg tgacagcacc cacacctcag cagttacagg   1680

ccttcaaaaa tgaagtagga gtactcagga aaacgcgaca tgtgaatatc ctcctcttca   1740

tgggttattc aacaaagcca caactggcta ttgttaccca gtggtgtgag ggctccagtt   1800

tatatcatca tctccacatc attgagacca aattcgagat gatcaaactt atagatattg   1860

cacggcagac tgcacagggc atggattact tacacgccaa gtcaatcatc cacagagacc   1920

tcaagagtaa taatattttt cttcatgaag acctcacagt aaaaataggt gattttggtc   1980

tagccacagt gaaatctcga tggagtgggt cccatcagtt tgaacagttg tctggatcca   2040

ttttgtggat ggcaccagaa gtaatcagaa tgcaagataa aaacccatat agctttcagt   2100

cagatgtata tgcatttggg attgttctgt atgaattgat gaccggacag ttaccttatt   2160

caaatatcaa caacagggac cagataattt ttatggtggg acgaggatat ctgtctccag   2220

atctcagtaa ggtacggagt aactgtccaa aagccatgaa gagattaatg gcagagtgcc   2280

taaaaaagaa aagagatgaa agaccactct ttccccaaga tctctcttcc caccatagac   2340

acaaaaattt cagatggcta caggtttaca tgtaaaaaac agaattataa caaatgattt   2400

ttat                                                               2404
```

<210> SEQ ID NO 32
<211> LENGTH: 726
<212> TYPE: PRT
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 32

```
Met Ala Ala Leu Ser Gly Gly Gly Gly Gly Gly Gly Gly Gly Ala Glu
1               5                  10                  15

Gln Gly Gln Ala Leu Phe Asn Gly Asp Met Glu Pro Glu Ala Gly Ala
            20                  25                  30
```

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```
Ala Ala Ser Ser Ala Ala Asp Pro Ala Ile Pro Glu Glu Val Trp Asn
        35                  40                  45

Ile Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu
    50                  55                  60

Asp Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala
65                  70                  75                  80

Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln
                85                  90                  95

Gln Leu Leu Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser
            100                 105                 110

Ser Ala Ser Thr Asp Thr Val Thr Ser Ser Ser Ser Ser Ser Leu Ser
        115                 120                 125

Val Leu Pro Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val Ser
    130                 135                 140

Arg Ser Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu
145                 150                 155                 160

Pro Asn Lys Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr Val
                165                 170                 175

Arg Asp Ser Leu Lys Lys Ala Leu Met Met Arg Gly Leu Ile Pro Glu
            180                 185                 190

Cys Cys Ala Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly
        195                 200                 205

Trp Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu
    210                 215                 220

Val Leu Glu Asn Val Pro Leu Thr Thr His Asn Phe Val Arg Lys Thr
225                 230                 235                 240

Phe Phe Thr Leu Ala Phe Cys Asp Phe Cys Arg Lys Leu Leu Phe Gln
                245                 250                 255

Gly Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys Ser
            260                 265                 270

Thr Glu Val Pro Leu Met Cys Val Asn Tyr Asp Gln Leu Asp Leu Leu
        275                 280                 285

Phe Val Ser Lys Phe Phe Glu His His Pro Ile Pro Gln Glu Glu Ala
    290                 295                 300

Ser Leu Ala Glu Thr Thr Leu Pro Cys Gly Ser Ser Pro Ser Ala Pro
305                 310                 315                 320

Pro Ser Asp Ser Ile Gly Pro Pro Ile Leu Thr Ser Pro Ser Pro Ser
                325                 330                 335

Lys Ser Ile Pro Ile Pro Gln Pro Phe Arg Pro Ala Asp Glu Asp His
            340                 345                 350

Arg Asn Gln Phe Gly Gln Arg Asp Arg Ser Ser Ser Ala Pro Asn Val
        355                 360                 365

His Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Asp Leu Ile Arg Asp
    370                 375                 380

Gln Gly Phe Arg Ser Asp Gly Gly Ser Thr Thr Gly Leu Ser Ala Thr
385                 390                 395                 400

Pro Pro Ala Ser Leu Pro Gly Ser Leu Ser Asn Val Lys Ala Leu Gln
                405                 410                 415

Lys Ser Pro Gly Pro Gln Arg Glu Arg Lys Ser Ser Ser Ser Ser Glu
            420                 425                 430
```

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```
Asp Arg Asn Arg Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp Asp
        435                 440                 445

Trp Glu Ile Pro Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly Ser
    450                 455                 460

Gly Ser Phe Gly Thr Val Tyr Lys Gly Lys Trp His Gly Asp Val Ala
465                 470                 475                 480

Val Lys Met Leu Asn Val Thr Ala Pro Thr Pro Gln Gln Leu Gln Ala
                485                 490                 495

Phe Lys Asn Glu Val Gly Val Leu Arg Lys Thr Arg His Val Asn Ile
            500                 505                 510

Leu Leu Phe Met Gly Tyr Ser Thr Lys Pro Gln Leu Ala Ile Val Thr
        515                 520                 525

Gln Trp Cys Glu Gly Ser Ser Leu Tyr His His Leu His Ile Ile Glu
    530                 535                 540

Thr Lys Phe Glu Met Ile Lys Leu Ile Asp Ile Ala Arg Gln Thr Ala
545                 550                 555                 560

Gln Gly Met Asp Tyr Leu His Ala Lys Ser Ile Ile His Arg Asp Leu
                565                 570                 575

Lys Ser Asn Asn Ile Phe Leu His Glu Asp Leu Thr Val Lys Ile Gly
            580                 585                 590

Asp Phe Gly Leu Ala Thr Val Lys Ser Arg Trp Ser Gly Ser His Gln
        595                 600                 605

Phe Glu Gln Leu Ser Gly Ser Ile Leu Trp Met Ala Pro Glu Val Ile
    610                 615                 620

Arg Met Gln Asp Lys Asn Pro Tyr Ser Phe Gln Ser Asp Val Tyr Ala
625                 630                 635                 640

Phe Gly Ile Val Leu Tyr Glu Leu Met Thr Gly Gln Leu Pro Tyr Ser
                645                 650                 655

Asn Ile Asn Asn Arg Asp Gln Ile Ile Phe Met Val Gly Arg Gly Tyr
            660                 665                 670

Leu Ser Pro Asp Leu Ser Lys Val Arg Ser Asn Cys Pro Lys Ala Met
        675                 680                 685

Lys Arg Leu Met Ala Glu Cys Leu Lys Lys Lys Arg Asp Glu Arg Pro
    690                 695                 700

Leu Phe Pro Gln Asp Leu Ser Ser His His Arg His Lys Asn Phe Arg
705                 710                 715                 720

Trp Leu Gln Val Tyr Met
                725


<210> SEQ ID NO 33
<211> LENGTH: 2331
<212> TYPE: DNA
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 33

ctcagctgcg ccgggtctca caagacggtt cccgaggtgg cccaggcgcc gtcccaccgc     60

cgacgccgcc cgggccgccc gggccgtccc tccccgctgc cccccgtcct ccgcctccgc    120

ctccccccgc cctcagcctc ccttcccccc ccccgcccag cagcggtcgc tcgggcccgg    180

ctctcggtta taagatggcg gcgctgagtg gcggcggcgg cggcggcggc ggtggcgcgg    240

agcagggcca ggctctgttc aacggggaca tggagcccga ggccggcgcc gcggcctctt    300

cggctgcgga ccccgccatt cccgaggagg tgtggaatat caaacaaatg attaagttga    360
```

-continued

cacaggagca tatagaggcc ctattggaca aatttggtgg ggagcataat ccaccatcaa 420

tatatctgga ggcctatgaa gaatacacca gcaagctaga tgccctccaa caaagagaac 480

aacagttatt ggaatccctg gggaatggaa ctgatttttc tgtttctagc tctgcatcaa 540

cggacaccgt tacatcttct tcctcttcta gcctttcagt gctgccttca tctctttcag 600

tttttcaaaa tcccacagat gtgtcacgga gcaaccccaa gtcaccacaa aaacctatcg 660

ttagagtctt cctgcccaat aaacagagga cagtggtacc tgcacggtgt ggagtcacag 720

tccgggacag cctgaagaag gcactgatga tgagaggtct aatcccagag tgctgtgctg 780

tttacagaat tcaggatggg gagaagaaac caattggctg ggacactgat atttcctggc 840

ttactggaga ggagttgcat gtagaagtgt tggagaatgt tccacttaca acacacaact 900

ttgtacggaa aacttttttc accttagcat tttgtgactt ctgtagaaag ctgcttttcc 960

agggattccg ctgtcaaaca tgtggttata aatttcacca gcgttgtagt acagaggttc 1020

cactgatgtg tgttaattat gaccaactag atttgctgtt tgtctccaag ttctttgaac 1080

accacccaat accacaggag gaggcctcct tagcagagac tacccttcca tgtggctcat 1140

ccccttctgc acccccctcc gattctattg ggcccccaat tctcaccagt ccatctcctt 1200

caaaatccat tccaattcca cagcctttcc gaccagcaga tgaagatcat cgaaatcagt 1260

ttggacaacg agaccggtcc tcatcagctc caaatgtgca tataaacaca atagaacccg 1320

tcaatattga tgacttgatt agagaccaag ggtttcgtag tgatggagga tcaaccacag 1380

gtttatccgc cacacccccc gcctcattac ctggctcact ctctaatgtg aaagcattgc 1440

agaaatctcc aggacctcag cgagaaagaa agtcctcttc atcctcagaa gacaggaatc 1500

gaatgaaaac gcttggtaga cgggattcaa gtgacgattg ggagattcct gatggacaga 1560

tcacagtggg acaaagaatt ggatcagggt catttgggac agtctacaag ggaaagtggc 1620

atggtgatgt ggcagtgaaa atgttgaatg tgacagcacc cacacctcag cagttacagg 1680

ccttcaaaaa tgaagtagga gtactcagga aaacgcgaca tgtgaatatc ctcctcttca 1740

tgggttattc aacaaagcca caactggcta ttgttaccca gtggtgtgag ggctccagtt 1800

tatatcatca tctccacatc attgagacca aattcgagat gatcaaactt atagatattg 1860

cacggcagac tgcacagggc atggattact tacacgccaa gtcaatcatc cacagagacc 1920

tcaagagtaa taatattttt cttcatgaag acctcacagt aaaaataggt gattttggtc 1980

tagccacagt gaaatctcga tggagtgggt cccatcagtt tgaacagttg tctggatcca 2040

ttttgtggat ggcaccagaa gtaatcagaa tgcaagataa aaacccatat agctttcagt 2100

cagatgtata tgcatttggg attgttctgt atgaattgat gaccggacag ttaccttatt 2160

caaatatcaa caacagggac caggtgcttt gtcctccatg ggagtgtaat aaatgctgtg 2220

caagggctta cttcccatga gagaagtgag tgaccaacag aaggataatt tttatggtgg 2280

gacgaggata tctgtctcca gatctcagta aggtacggag taactgtcca a 2331

<210> SEQ ID NO 34
<211> LENGTH: 681
<212> TYPE: PRT
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 34

Met Ala Ala Leu Ser Gly Gly Gly Gly Gly Gly Gly Gly Gly Ala Glu

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```
1               5                   10                  15

Gln Gly Gln Ala Leu Phe Asn Gly Asp Met Glu Pro Glu Ala Gly Ala
            20                  25                  30

Ala Ala Ser Ser Ala Ala Asp Pro Ala Ile Pro Glu Glu Val Trp Asn
        35                  40                  45

Ile Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu
    50                  55                  60

Asp Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala
65                  70                  75                  80

Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln
                85                  90                  95

Gln Leu Leu Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser
            100                 105                 110

Ser Ala Ser Thr Asp Thr Val Thr Ser Ser Ser Ser Ser Ser Leu Ser
        115                 120                 125

Val Leu Pro Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val Ser
    130                 135                 140

Arg Ser Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu
145                 150                 155                 160

Pro Asn Lys Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr Val
                165                 170                 175

Arg Asp Ser Leu Lys Lys Ala Leu Met Met Arg Gly Leu Ile Pro Glu
            180                 185                 190

Cys Cys Ala Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly
        195                 200                 205

Trp Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu
    210                 215                 220

Val Leu Glu Asn Val Pro Leu Thr Thr His Asn Phe Val Arg Lys Thr
225                 230                 235                 240

Phe Phe Thr Leu Ala Phe Cys Asp Phe Cys Arg Lys Leu Leu Phe Gln
                245                 250                 255

Gly Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys Ser
            260                 265                 270

Thr Glu Val Pro Leu Met Cys Val Asn Tyr Asp Gln Leu Asp Leu Leu
        275                 280                 285

Phe Val Ser Lys Phe Phe Glu His His Pro Ile Pro Gln Glu Glu Ala
    290                 295                 300

Ser Leu Ala Glu Thr Thr Leu Pro Cys Gly Ser Ser Pro Ser Ala Pro
305                 310                 315                 320

Pro Ser Asp Ser Ile Gly Pro Pro Ile Leu Thr Ser Pro Ser Pro Ser
                325                 330                 335

Lys Ser Ile Pro Ile Pro Gln Pro Phe Arg Pro Ala Asp Glu Asp His
            340                 345                 350

Arg Asn Gln Phe Gly Gln Arg Asp Arg Ser Ser Ser Ala Pro Asn Val
        355                 360                 365

His Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Asp Leu Ile Arg Asp
    370                 375                 380

Gln Gly Phe Arg Ser Asp Gly Gly Ser Thr Thr Gly Leu Ser Ala Thr
385                 390                 395                 400

Pro Pro Ala Ser Leu Pro Gly Ser Leu Ser Asn Val Lys Ala Leu Gln
                405                 410                 415
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```
Lys Ser Pro Gly Pro Gln Arg Glu Arg Lys Ser Ser Ser Ser Ser Glu
            420                 425                 430

Asp Arg Asn Arg Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp Asp
        435                 440                 445

Trp Glu Ile Pro Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly Ser
    450                 455                 460

Gly Ser Phe Gly Thr Val Tyr Lys Gly Lys Trp His Gly Asp Val Ala
465                 470                 475                 480

Val Lys Met Leu Asn Val Thr Ala Pro Thr Pro Gln Gln Leu Gln Ala
                485                 490                 495

Phe Lys Asn Glu Val Gly Val Leu Arg Lys Thr Arg His Val Asn Ile
            500                 505                 510

Leu Leu Phe Met Gly Tyr Ser Thr Lys Pro Gln Leu Ala Ile Val Thr
        515                 520                 525

Gln Trp Cys Glu Gly Ser Ser Leu Tyr His His Leu His Ile Ile Glu
    530                 535                 540

Thr Lys Phe Glu Met Ile Lys Leu Ile Asp Ile Ala Arg Gln Thr Ala
545                 550                 555                 560

Gln Gly Met Asp Tyr Leu His Ala Lys Ser Ile Ile His Arg Asp Leu
                565                 570                 575

Lys Ser Asn Asn Ile Phe Leu His Glu Asp Leu Thr Val Lys Ile Gly
            580                 585                 590

Asp Phe Gly Leu Ala Thr Val Lys Ser Arg Trp Ser Gly Ser His Gln
        595                 600                 605

Phe Glu Gln Leu Ser Gly Ser Ile Leu Trp Met Ala Pro Glu Val Ile
    610                 615                 620

Arg Met Gln Asp Lys Asn Pro Tyr Ser Phe Gln Ser Asp Val Tyr Ala
625                 630                 635                 640

Phe Gly Ile Val Leu Tyr Glu Leu Met Thr Gly Gln Leu Pro Tyr Ser
                645                 650                 655

Asn Ile Asn Asn Arg Asp Gln Val Leu Cys Pro Pro Trp Glu Cys Asn
            660                 665                 670

Lys Cys Cys Ala Arg Ala Tyr Phe Pro
        675                 680


<210> SEQ ID NO 35
<211> LENGTH: 2319
<212> TYPE: DNA
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 35

ctcagctgcg ccgggtctca caagacggtt cccgaggtgg cccaggcgcc gtcccaccgc     60

cgacgccgcc cgggccgccc gggccgtccc tccccgctgc cccccgtcct ccgcctccgc    120

ctccccccgc cctcagcctc ccttcccccc ccccgcccag cagcggtcgc tcgggcccgg    180

ctctcggtta taagatggcg gcgctgagtg gcggcggcgg cggcggcggc ggtggcgcgg    240

agcagggcca ggctctgttc aacggggaca tggagcccga ggccggcgcc gcggcctctt    300

cggctgcgga ccccgccatt cccgaggagg tgtggaatat caaacaaatg attaagttga    360

cacaggagca tatagaggcc ctattggaca aatttggtgg ggagcataat ccaccatcaa    420

tatatctgga ggcctatgaa gaatacacca gcaagctaga tgccctccaa caaagagaac    480
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aacagttatt ggaatccctg gggaatggaa ctgatttttc tgtttctagc tctgcatcaa 540

cggacaccgt tacatcttct tcctcttcta gcctttcagt gctgccttca tctctttcag 600

tttttcaaaa tcccacagat gtgtcacgga gcaaccccaa gtcaccacaa aaacctatcg 660

ttagagtctt cctgcccaat aaacagagga cagtggtacc tgcacggtgt ggagtcacag 720

tccgggacag cctgaagaag gcactgatga tgagaggtct aatcccagag tgctgtgctg 780

tttacagaat tcaggatggg gagaagaaac caattggctg ggacactgat atttcctggc 840

ttactggaga ggagttgcat gtagaagtgt tggagaatgt tccacttaca acacacaact 900

ttgtacggaa aacttttttc accttagcat tttgtgactt ctgtagaaag ctgcttttcc 960

agggattccg ctgtcaaaca tgtggttata aatttcacca gcgttgtagt acagaggttc 1020

cactgatgtg tgttaattat gaccaactag atttgctgtt tgtctccaag ttctttgaac 1080

accacccaat accacaggag gaggcctcct tagcagagac tacccttcca tgtggctcat 1140

ccccttctgc acccccctcc gattctattg ggcccccaat tctcaccagt ccatctcctt 1200

caaaatccat tccaattcca cagcctttcc gaccagcaga tgaagatcat cgaaatcagt 1260

ttggacaacg agaccggtcc tcatcagctc caaatgtgca tataaacaca atagaacccg 1320

tcaatattga tgacttgatt agagaccaag ggtttcgtag tgatggagga tcaaccacag 1380

gtttatccgc cacacccccc gcctcattac ctggctcact ctctaatgtg aaagcattgc 1440

agaaatctcc aggacctcag cgagaaagaa agtcctcttc atcctcagaa gacaggaatc 1500

gaatgaaaac gcttggtaga cgggattcaa gtgacgattg ggagattcct gatggacaga 1560

tcacagtggg acaaagaatt ggatcagggt catttgggac agtctacaag ggaaagtggc 1620

atggtgatgt ggcagtgaaa atgttgaatg tgacagcacc cacacctcag cagttacagg 1680

ccttcaaaaa tgaagtagga gtactcagga aaacgcgaca tgtgaatatc ctcctcttca 1740

tgggttattc aacaaagcca caactggcta ttgttaccca gtggtgtgag ggctccagtt 1800

tatatcatca tctccacatc attgagacca aattcgagat gatcaaactt atagatattg 1860

cacggcagac tgcacagggc atggattact tacacgccaa gtcaatcatc cacagagacc 1920

tcaagagtaa taatattttt cttcatgaag acctcacagt aaaaataggt gattttggtc 1980

tagccacagt gaaatctcga tggagtgggt cccatcagtt tgaacagttg tctggatcca 2040

ttttgtggat ggcaccagaa gtaatcagaa tgcaagataa aaacccatat agctttcagt 2100

cagatgtata tgcatttggg attgttctgt atgaattgat gaccggacag ttaccttatt 2160

caaatatcaa caacagggac caggtgcttt gtcctccatg ggagtgtaat aaatgctgtg 2220

caagggctta cttcccatga gagaagtgag tgaccaacag aaggtctgtg caaggaaaag 2280

agacaaagcc acggatcaga agcacatggc cataactga 2319

<210> SEQ ID NO 36
<211> LENGTH: 681
<212> TYPE: PRT
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 36

Met Ala Ala Leu Ser Gly Gly Gly Gly Gly Gly Gly Gly Gly Ala Glu
1 5 10 15

Gln Gly Gln Ala Leu Phe Asn Gly Asp Met Glu Pro Glu Ala Gly Ala
20 25 30

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```
Ala Ala Ser Ser Ala Ala Asp Pro Ala Ile Pro Glu Glu Val Trp Asn
        35                  40                  45

Ile Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu
    50                  55                  60

Asp Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala
65                  70                  75                  80

Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln
                85                  90                  95

Gln Leu Leu Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser
            100                 105                 110

Ser Ala Ser Thr Asp Thr Val Thr Ser Ser Ser Ser Ser Ser Leu Ser
        115                 120                 125

Val Leu Pro Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val Ser
    130                 135                 140

Arg Ser Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu
145                 150                 155                 160

Pro Asn Lys Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr Val
                165                 170                 175

Arg Asp Ser Leu Lys Lys Ala Leu Met Met Arg Gly Leu Ile Pro Glu
            180                 185                 190

Cys Cys Ala Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly
        195                 200                 205

Trp Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu
    210                 215                 220

Val Leu Glu Asn Val Pro Leu Thr Thr His Asn Phe Val Arg Lys Thr
225                 230                 235                 240

Phe Phe Thr Leu Ala Phe Cys Asp Phe Cys Arg Lys Leu Leu Phe Gln
                245                 250                 255

Gly Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys Ser
            260                 265                 270

Thr Glu Val Pro Leu Met Cys Val Asn Tyr Asp Gln Leu Asp Leu Leu
        275                 280                 285

Phe Val Ser Lys Phe Phe Glu His His Pro Ile Pro Gln Glu Glu Ala
    290                 295                 300

Ser Leu Ala Glu Thr Thr Leu Pro Cys Gly Ser Ser Pro Ser Ala Pro
305                 310                 315                 320

Pro Ser Asp Ser Ile Gly Pro Pro Ile Leu Thr Ser Pro Ser Pro Ser
                325                 330                 335

Lys Ser Ile Pro Ile Pro Gln Pro Phe Arg Pro Ala Asp Glu Asp His
            340                 345                 350

Arg Asn Gln Phe Gly Gln Arg Asp Arg Ser Ser Ser Ala Pro Asn Val
        355                 360                 365

His Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Asp Leu Ile Arg Asp
    370                 375                 380

Gln Gly Phe Arg Ser Asp Gly Gly Ser Thr Thr Gly Leu Ser Ala Thr
385                 390                 395                 400

Pro Pro Ala Ser Leu Pro Gly Ser Leu Ser Asn Val Lys Ala Leu Gln
                405                 410                 415

Lys Ser Pro Gly Pro Gln Arg Glu Arg Lys Ser Ser Ser Ser Ser Glu
            420                 425                 430

Asp Arg Asn Arg Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp Asp
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        435                 440                 445

Trp Glu Ile Pro Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly Ser
    450                 455                 460

Gly Ser Phe Gly Thr Val Tyr Lys Gly Lys Trp His Gly Asp Val Ala
465                 470                 475                 480

Val Lys Met Leu Asn Val Thr Ala Pro Thr Pro Gln Gln Leu Gln Ala
                485                 490                 495

Phe Lys Asn Glu Val Gly Val Leu Arg Lys Thr Arg His Val Asn Ile
            500                 505                 510

Leu Leu Phe Met Gly Tyr Ser Thr Lys Pro Gln Leu Ala Ile Val Thr
        515                 520                 525

Gln Trp Cys Glu Gly Ser Ser Leu Tyr His His Leu His Ile Ile Glu
    530                 535                 540

Thr Lys Phe Glu Met Ile Lys Leu Ile Asp Ile Ala Arg Gln Thr Ala
545                 550                 555                 560

Gln Gly Met Asp Tyr Leu His Ala Lys Ser Ile Ile His Arg Asp Leu
                565                 570                 575

Lys Ser Asn Asn Ile Phe Leu His Glu Asp Leu Thr Val Lys Ile Gly
            580                 585                 590

Asp Phe Gly Leu Ala Thr Val Lys Ser Arg Trp Ser Gly Ser His Gln
        595                 600                 605

Phe Glu Gln Leu Ser Gly Ser Ile Leu Trp Met Ala Pro Glu Val Ile
    610                 615                 620

Arg Met Gln Asp Lys Asn Pro Tyr Ser Phe Gln Ser Asp Val Tyr Ala
625                 630                 635                 640

Phe Gly Ile Val Leu Tyr Glu Leu Met Thr Gly Gln Leu Pro Tyr Ser
                645                 650                 655

Asn Ile Asn Asn Arg Asp Gln Val Leu Cys Pro Pro Trp Glu Cys Asn
            660                 665                 670

Lys Cys Cys Ala Arg Ala Tyr Phe Pro
        675                 680


<210> SEQ ID NO 37
<211> LENGTH: 2661
<212> TYPE: DNA
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 37

tcagctgcgc cgggtctcac aagacggttc ccgaggtggc ccaggcgccg tcccaccgcc     60

gacgccgccc gggccgcccg ggccgtccct ccccgctgcc ccccgtcctc cgcctccgcc    120

tccccccgcc ctcagcctcc cttccccctc cccgcccagc agcggtcgct cgggcccggc    180

tctcggttat aagatggcgg cgctgagtgg cggcggcggc ggcggcggcg gtggcgcgga    240

gcagggccag gctctgttca acggggacat ggagcccgag gccggcgccg cggcctcttc    300

ggctgcggac cccgccattc ccgaggaggt gtggaatatc aaacaaatga ttaagttgac    360

acaggagcat atagaggccc tattggacaa atttggtggg gagcataatc caccatcaat    420

atatctggag gcctatgaag aatacaccag caagctagat gccctccaac aaagagaaca    480

acagttattg gaatccctgg ggaatggaac tgatttttct gtttctagct ctgcatcaac    540

ggacaccgtt acatcttctt cctcttctag cctttcagtg ctgccttcat ctctttcagt    600

ttttcaaaat cccacagatg tgtcacggag caaccccaag tcaccacaaa aacctatcgt    660
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-continued

tagagtcttc ctgcccaata aacagaggac agtggtacct gcacggtgtg gagtcacagt 720

ccgggacagc ctgaagaagg cactgatgat gagaggtcta atcccagagt gctgtgctgt 780

ttacagaatt caggatgggg agaagaaacc aattggctgg gacactgata tttcctggct 840

tactggagag gagttgcatg tagaagtgtt ggagaatgtt ccacttacaa cacacaactt 900

tgtacggaaa actttttca ccttagcatt ttgtgacttc tgtagaaagc tgcttttcca 960

gggattccgc tgtcaaacat gtggttataa atttcaccag cgttgtagta cagaggttcc 1020

actgatgtgt gttaattatg accaactaga tttgctgttt gtctccaagt tctttgaaca 1080

ccacccaata ccacaggagg aggcctcctt agcagagact acccttccat gtggctcatc 1140

cccttctgca ccccctccg attctattgg gcccccaatt ctcaccagtc catctccttc 1200

aaaatccatt ccaattccac agcctttccg accagcagat gaagatcatc gaaatcagtt 1260

tggacaacga gaccggtcct catcagctcc aaatgtgcat ataaacacaa tagaacccgt 1320

caatattgat gacttgatta gagaccaagg gtttcgtagt gatggaggat caaccacagg 1380

tttatccgcc acacccccctg cctcattacc tggctcactc tctaatgtga aagcattgca 1440

gaaatctcca ggacctcagc gagaaagaaa gtcctcttca tcctcagaag acaggaatcg 1500

aatgaaaacg cttggtagac gggattcaag tgacgattgg gagattcctg atggacagat 1560

cacagtggga caaagaattg gatcagggtc atttgggaca gtctacaagg gaaagtggca 1620

tggtgatgtg gcagtgaaaa tgttgaatgt gacagcaccc acacctcagc agttacaggc 1680

cttcaaaaat gaagtaggag tactcaggaa aacgcgacat gtgaatatcc tcctcttcat 1740

gggttattca acaaagccac aactggctat tgttacccag tggtgtgagg gctccagttt 1800

atatcatcat ctccacatca ttgagaccaa attcgagatg atcaaactta tagatattgc 1860

acggcagact gcacagggca tggattactt acacgccaag tcaatcatcc acagagacct 1920

caagagtaat aatatttttc ttcatgaaga cctcacagta aaaataggtg attttggtct 1980

agccacagtg aaatctcgat ggagtgggtc ccatcagttt gaacagttgt ctggatccat 2040

tttgtggatg gcaccagaag taatcagaat gcaagataaa aacccatata gctttcagtc 2100

agatgtatat gcatttggga ttgttctgta tgaattgatg accggacagt taccttattc 2160

aaatatcaac aacagggacc agtctgtgca aggaaaagag acaaagccac ggatcagaag 2220

cacatggcca taactgaaga ttttgtgaac tctcacaagg aaaaaatttg ctctttgaac 2280

aataagaagg aactcactaa aatgtaactg agaactgttc aacaggttga aagctgaaag 2340

atgccattgg aactgacaaa atgtttctta aacataaatg atgaaacagt gaaactacat 2400

aatatctcct ctggctgaaa cattcaagaa gtttaaaatg cttaagttaa aaataaaatc 2460

ctagtaaaca atggacttac tgtgcaacat agagaatatc ttacgataac ctgtaatgga 2520

aaagaatctg aaaaagaatg tatataactg aatcactttg ctgtaaacta gaatctgaca 2580

caacactgta aatcactaca cttttctgtt gcatgccaaa gattatttaa taacgtcatt 2640

aaaaaattat tttaataatt a 2661

<210> SEQ ID NO 38
<211> LENGTH: 679
<212> TYPE: PRT
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 38

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```
Met Ala Ala Leu Ser Gly Gly Gly Gly Gly Gly Gly Gly Gly Ala Glu
1               5                  10                  15

Gln Gly Gln Ala Leu Phe Asn Gly Asp Met Glu Pro Glu Ala Gly Ala
            20                  25                  30

Ala Ala Ser Ser Ala Ala Asp Pro Ala Ile Pro Glu Glu Val Trp Asn
        35                  40                  45

Ile Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu
    50                  55                  60

Asp Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala
65                  70                  75                  80

Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln
                85                  90                  95

Gln Leu Leu Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser
            100                 105                 110

Ser Ala Ser Thr Asp Thr Val Thr Ser Ser Ser Ser Ser Ser Leu Ser
        115                 120                 125

Val Leu Pro Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val Ser
    130                 135                 140

Arg Ser Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu
145                 150                 155                 160

Pro Asn Lys Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr Val
                165                 170                 175

Arg Asp Ser Leu Lys Lys Ala Leu Met Met Arg Gly Leu Ile Pro Glu
            180                 185                 190

Cys Cys Ala Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly
        195                 200                 205

Trp Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu
    210                 215                 220

Val Leu Glu Asn Val Pro Leu Thr Thr His Asn Phe Val Arg Lys Thr
225                 230                 235                 240

Phe Phe Thr Leu Ala Phe Cys Asp Phe Cys Arg Lys Leu Leu Phe Gln
                245                 250                 255

Gly Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys Ser
            260                 265                 270

Thr Glu Val Pro Leu Met Cys Val Asn Tyr Asp Gln Leu Asp Leu Leu
        275                 280                 285

Phe Val Ser Lys Phe Phe Glu His His Pro Ile Pro Gln Glu Glu Ala
    290                 295                 300

Ser Leu Ala Glu Thr Thr Leu Pro Cys Gly Ser Ser Pro Ser Ala Pro
305                 310                 315                 320

Pro Ser Asp Ser Ile Gly Pro Pro Ile Leu Thr Ser Pro Ser Pro Ser
                325                 330                 335

Lys Ser Ile Pro Ile Pro Gln Pro Phe Arg Pro Ala Asp Glu Asp His
            340                 345                 350

Arg Asn Gln Phe Gly Gln Arg Asp Arg Ser Ser Ser Ala Pro Asn Val
        355                 360                 365

His Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Asp Leu Ile Arg Asp
    370                 375                 380

Gln Gly Phe Arg Ser Asp Gly Gly Ser Thr Thr Gly Leu Ser Ala Thr
385                 390                 395                 400
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```
Pro Pro Ala Ser Leu Pro Gly Ser Leu Ser Asn Val Lys Ala Leu Gln
                405                 410                 415

Lys Ser Pro Gly Pro Gln Arg Glu Arg Lys Ser Ser Ser Ser Ser Glu
            420                 425                 430

Asp Arg Asn Arg Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp Asp
        435                 440                 445

Trp Glu Ile Pro Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly Ser
    450                 455                 460

Gly Ser Phe Gly Thr Val Tyr Lys Gly Lys Trp His Gly Asp Val Ala
465                 470                 475                 480

Val Lys Met Leu Asn Val Thr Ala Pro Thr Pro Gln Gln Leu Gln Ala
                485                 490                 495

Phe Lys Asn Glu Val Gly Val Leu Arg Lys Thr Arg His Val Asn Ile
            500                 505                 510

Leu Leu Phe Met Gly Tyr Ser Thr Lys Pro Gln Leu Ala Ile Val Thr
        515                 520                 525

Gln Trp Cys Glu Gly Ser Ser Leu Tyr His His Leu His Ile Ile Glu
    530                 535                 540

Thr Lys Phe Glu Met Ile Lys Leu Ile Asp Ile Ala Arg Gln Thr Ala
545                 550                 555                 560

Gln Gly Met Asp Tyr Leu His Ala Lys Ser Ile Ile His Arg Asp Leu
                565                 570                 575

Lys Ser Asn Asn Ile Phe Leu His Glu Asp Leu Thr Val Lys Ile Gly
            580                 585                 590

Asp Phe Gly Leu Ala Thr Val Lys Ser Arg Trp Ser Gly Ser His Gln
        595                 600                 605

Phe Glu Gln Leu Ser Gly Ser Ile Leu Trp Met Ala Pro Glu Val Ile
    610                 615                 620

Arg Met Gln Asp Lys Asn Pro Tyr Ser Phe Gln Ser Asp Val Tyr Ala
625                 630                 635                 640

Phe Gly Ile Val Leu Tyr Glu Leu Met Thr Gly Gln Leu Pro Tyr Ser
                645                 650                 655

Asn Ile Asn Asn Arg Asp Gln Ser Val Gln Gly Lys Glu Thr Lys Pro
            660                 665                 670

Arg Ile Arg Ser Thr Trp Pro
        675
```

<210> SEQ ID NO 39
<211> LENGTH: 7434
<212> TYPE: DNA
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 39

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acaccgttac atcttcttcc tcttctagcc tttcagtgct gccttcatct ctttcagttt     60

ttcaaaatcc cacagatgtg tcacggagca accccaagtc accacaaaaa cctatcgtta    120

gagtcttcct gcccaataaa cagaggacag tggtacctgc acggtgtgga gtcacagtcc    180

gggacagcct gaagaaggca ctgatgatga gaggtctaat cccagagtgc tgtgctgttt    240

acagaattca ggatggggag aagaaaccaa ttggctggga cactgatatt tcctggctta    300

ctggagagga gttgcatgta gaagtgttgg agaatgttcc acttacaaca cacaactttg    360

tacggaaaac ttttttcacc ttagcatttt gtgacttctg tagaaagctg cttttccagg    420
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gattccgctg tcaaacatgt ggttataaat ttcaccagcg ttgtagtaca gaggttccac 480

tgatgtgtgt taattatgac caactagatt tgctgtttgt ctccaagttc tttgaacacc 540

acccaatacc acaggaggag gcctccttag cagagactac ccttccatgt ggctcatccc 600

cttctgcacc cccctccgat tctattgggc ccccaattct caccagtcca tctccttcaa 660

aatccattcc aattccacag cctttccgac cagcagatga agatcatcga aatcagtttg 720

gacaacgaga ccggtcctca tcagctccaa atgtgcatat aaacacaata gaacccgtca 780

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gacaaaattc agaagttatc agggaaaaag ataagcagat tctcgcctct attgagctgc 1860

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caggggata tggagaattt gcagccttca agtagccaca ccatcatgac agcatctact 2040

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gctgcacacc cctcctcaga tctcacctgc ccctcctgta cattcacctc tccagccttg 5220

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<210> SEQ ID NO 40
<211> LENGTH: 603
<212> TYPE: PRT
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 40

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Asp Gly Glu Lys Lys Pro Ile Gly Trp Asp Thr Asp Ile Ser Trp Leu
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Thr Gly Glu Glu Leu His Val Glu Val Leu Glu Asn Val Pro Leu Thr
35 40 45

Thr His Asn Phe Val Arg Lys Thr Phe Phe Thr Leu Ala Phe Cys Asp
50 55 60

Phe Cys Arg Lys Leu Leu Phe Gln Gly Phe Arg Cys Gln Thr Cys Gly
65 70 75 80

Tyr Lys Phe His Gln Arg Cys Ser Thr Glu Val Pro Leu Met Cys Val
85 90 95

Asn Tyr Asp Gln Leu Asp Leu Leu Phe Val Ser Lys Phe Phe Glu His
100 105 110

His Pro Ile Pro Gln Glu Glu Ala Ser Leu Ala Glu Thr Thr Leu Pro
115 120 125

Cys Gly Ser Ser Pro Ser Ala Pro Pro Ser Asp Ser Ile Gly Pro Pro
130 135 140

Ile Leu Thr Ser Pro Ser Pro Ser Lys Ser Ile Pro Ile Pro Gln Pro
145 150 155 160

Phe Arg Pro Ala Asp Glu Asp His Arg Asn Gln Phe Gly Gln Arg Asp
165 170 175

Arg Ser Ser Ser Ala Pro Asn Val His Ile Asn Thr Ile Glu Pro Val
180 185 190

Asn Ile Asp Asp Leu Ile Arg Asp Gln Gly Phe Arg Ser Asp Gly Gly
195 200 205

Ser Thr Thr Gly Leu Ser Ala Thr Pro Pro Ala Ser Leu Pro Gly Ser
210 215 220

Leu Ser Asn Val Lys Ala Leu Gln Lys Ser Pro Gly Pro Gln Arg Glu
225 230 235 240

Arg Lys Ser Ser Ser Ser Ser Glu Asp Arg Asn Arg Met Lys Thr Leu
245 250 255

Gly Arg Arg Asp Ser Ser Asp Asp Trp Glu Ile Pro Asp Gly Gln Ile
260 265 270

Thr Val Gly Gln Arg Ile Gly Ser Gly Ser Phe Gly Thr Val Tyr Lys
275 280 285

Gly Lys Trp His Gly Asp Val Ala Val Lys Met Leu Asn Val Thr Ala
290 295 300

Pro Thr Pro Gln Gln Leu Gln Ala Phe Lys Asn Glu Val Gly Val Leu
305 310 315 320

Arg Lys Thr Arg His Val Asn Ile Leu Leu Phe Met Gly Tyr Ser Thr
325 330 335

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Lys Pro Gln Leu Ala Ile Val Thr Gln Trp Cys Glu Gly Ser Ser Leu
            340                 345                 350

Tyr His His Leu His Ile Ile Glu Thr Lys Phe Glu Met Ile Lys Leu
        355                 360                 365

Ile Asp Ile Ala Arg Gln Thr Ala Gln Gly Met Asp Tyr Leu His Ala
    370                 375                 380

Lys Ser Ile Ile His Arg Asp Leu Lys Ser Asn Asn Ile Phe Leu His
385                 390                 395                 400

Glu Asp Leu Thr Val Lys Ile Gly Asp Phe Gly Leu Ala Thr Val Lys
                405                 410                 415

Ser Arg Trp Ser Gly Ser His Gln Phe Glu Gln Leu Ser Gly Ser Ile
            420                 425                 430

Leu Trp Met Ala Pro Glu Val Ile Arg Met Gln Asp Lys Asn Pro Tyr
        435                 440                 445

Ser Phe Gln Ser Asp Val Tyr Ala Phe Gly Ile Val Leu Tyr Glu Leu
    450                 455                 460

Met Thr Gly Gln Leu Pro Tyr Ser Asn Ile Asn Asn Arg Asp Gln Ile
465                 470                 475                 480

Ile Phe Met Val Gly Arg Gly Tyr Leu Ser Pro Asp Leu Ser Lys Val
                485                 490                 495

Arg Ser Asn Cys Pro Lys Ala Met Lys Arg Leu Met Ala Glu Cys Leu
            500                 505                 510

Lys Lys Lys Arg Asp Glu Arg Pro Leu Phe Pro Gln Val Gly Lys Thr
        515                 520                 525

Leu Leu Ser Lys Arg Gln Asn Ser Glu Val Ile Arg Glu Lys Asp Lys
    530                 535                 540

Gln Ile Leu Ala Ser Ile Glu Leu Leu Ala Arg Ser Leu Pro Lys Ile
545                 550                 555                 560

His Arg Ser Ala Ser Glu Pro Ser Leu Asn Arg Ala Gly Phe Gln Thr
                565                 570                 575

Glu Asp Phe Ser Leu Tyr Ala Cys Ala Ser Pro Lys Thr Pro Ile Gln
            580                 585                 590

Ala Gly Gly Tyr Gly Glu Phe Ala Ala Phe Lys
        595                 600


<210> SEQ ID NO 41
<211> LENGTH: 2295
<212> TYPE: DNA
<213> ORGANISM: Equus caballus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (79)..(79)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 41

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attcccgagg aggtatggaa tatcaaacaa atgattaaat tgacacagga acatatagag    180

gccctattgg acaaatttgg tggggagcat aatccaccat caatatatct ggaggcctat    240

gaagaataca ccagcaagct agatgccctc caacaaagag aacaacagtt attggaatcc    300

ctggggaatg gaactgattt ttctgtttct agttctgcat caacggacac cgttacatct    360
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acatgtggtt ataaatttca ccagcgttgt agtacagagg ttccactgat gtgtgttaat 840

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cctgcctcat tacctggctc actcactaat gtgaaggcat tacagaaatc tccaggacct 1260

caacgggaaa ggaaatcatc ttcatcctca gaagacagga atcgaatgaa aactcttggt 1320

agacgggatt caagtgacga ttgggagatt cctgatgggc agatcacagt gggacaaaga 1380

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ggagtactca ggaaaactcg acatgtgaat atcctactct tcatgggcta ttcaacaaag 1560

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gagagaccac tcttccccca aattctcgcc tctattgagc tgctggcccg ctcattgcca 2160

aaaattcacc gcagtgcatc agagccctcc ttgaatcggg ctggcttcca gacagaggat 2220

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tttcctgtcc actga 2295

<210> SEQ ID NO 42
<211> LENGTH: 764
<212> TYPE: PRT
<213> ORGANISM: Equus caballus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (27)..(27)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

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<400> SEQUENCE: 42

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            20                  25                  30

Ala Ser Ser Ala Ala Asp Pro Ala Ile Pro Glu Glu Val Trp Asn Ile
        35                  40                  45

Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu Asp
    50                  55                  60

Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala Tyr
65                  70                  75                  80

Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln Gln
                85                  90                  95

Leu Leu Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser Ser
            100                 105                 110

Ala Ser Thr Asp Thr Val Thr Ser Ser Ser Ser Ser Ser Leu Ser Val
        115                 120                 125

Leu Pro Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val Ser Arg
    130                 135                 140

Ser Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu Pro
145                 150                 155                 160

Asn Lys Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr Val Arg
                165                 170                 175

Asp Ser Leu Lys Lys Ala Leu Met Met Arg Gly Leu Ile Pro Glu Cys
            180                 185                 190

Cys Ala Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly Trp
        195                 200                 205

Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu Val
    210                 215                 220

Leu Glu Asn Val Pro Leu Thr Thr His Asn Phe Val Arg Lys Thr Phe
225                 230                 235                 240

Phe Thr Leu Ala Phe Cys Asp Phe Cys Arg Lys Leu Leu Phe Gln Gly
                245                 250                 255

Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys Ser Thr
            260                 265                 270

Glu Val Pro Leu Met Cys Val Asn Tyr Asp Gln Leu Asp Leu Leu Phe
        275                 280                 285

Val Ser Lys Phe Phe Glu His His Pro Val Ser Gln Glu Glu Ala Ser
    290                 295                 300

Leu Ala Glu Thr Ala Leu Thr Ser Gly Ser Ser Pro Ser Ala Pro Pro
305                 310                 315                 320

Ser Asp Ser Ile Gly Pro Gln Ile Leu Thr Ser Pro Ser Pro Ser Lys
                325                 330                 335

Ser Ile Pro Ile Pro Gln Pro Phe Arg Pro Ala Asp Glu Asp His Arg
            340                 345                 350

Asn Gln Phe Gly Gln Arg Asp Arg Ser Ser Ser Ala Pro Asn Val His
        355                 360                 365

Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Asp Leu Ile Arg Asp Gln
    370                 375                 380

Gly Phe Arg Ser Asp Gly Gly Ser Thr Thr Gly Leu Ser Ala Thr Pro
385                 390                 395                 400
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Pro Ala Ser Leu Pro Gly Ser Leu Thr Asn Val Lys Ala Leu Gln Lys
               405                 410                 415

Ser Pro Gly Pro Gln Arg Glu Arg Lys Ser Ser Ser Ser Ser Glu Asp
           420                 425                 430

Arg Asn Arg Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp Asp Trp
       435                 440                 445

Glu Ile Pro Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly Ser Gly
   450                 455                 460

Ser Phe Gly Thr Val Tyr Lys Gly Lys Trp His Gly Asp Val Ala Val
465                 470                 475                 480

Lys Met Leu Asn Val Thr Ala Pro Thr Pro Gln Gln Leu Gln Ala Phe
               485                 490                 495

Lys Asn Glu Val Gly Val Leu Arg Lys Thr Arg His Val Asn Ile Leu
           500                 505                 510

Leu Phe Met Gly Tyr Ser Thr Lys Pro Gln Leu Ala Ile Val Thr Gln
       515                 520                 525

Trp Cys Glu Gly Ser Ser Leu Tyr His His Leu His Ile Ile Glu Thr
   530                 535                 540

Lys Phe Glu Met Ile Lys Leu Ile Asp Ile Ala Arg Gln Thr Ala Gln
545                 550                 555                 560

Gly Met Asp Tyr Leu His Ala Lys Ser Ile Ile His Arg Asp Leu Lys
               565                 570                 575

Ser Asn Asn Ile Phe Leu His Glu Asp Leu Thr Val Lys Ile Gly Asp
           580                 585                 590

Phe Gly Leu Ala Thr Val Lys Ser Arg Trp Ser Gly Ser His Gln Phe
       595                 600                 605

Glu Gln Leu Ser Gly Ser Ile Leu Trp Met Ala Pro Glu Val Ile Arg
   610                 615                 620

Met Gln Asp Lys Asn Pro Tyr Ser Phe Gln Ser Asp Val Tyr Ala Phe
625                 630                 635                 640

Gly Ile Val Leu Tyr Glu Leu Met Thr Gly Gln Leu Pro Tyr Ser Asn
               645                 650                 655

Ile Asn Asn Arg Asp Gln Ile Ile Phe Met Val Gly Arg Gly Tyr Leu
           660                 665                 670

Ser Pro Asp Leu Ser Lys Val Arg Ser Asn Cys Pro Lys Ala Met Lys
       675                 680                 685

Arg Leu Met Ala Glu Cys Leu Lys Lys Lys Arg Asp Glu Arg Pro Leu
   690                 695                 700

Phe Pro Gln Ile Leu Ala Ser Ile Glu Leu Leu Ala Arg Ser Leu Pro
705                 710                 715                 720

Lys Ile His Arg Ser Ala Ser Glu Pro Ser Leu Asn Arg Ala Gly Phe
               725                 730                 735

Gln Thr Glu Asp Phe Ser Leu Tyr Ala Cys Ala Ser Pro Lys Thr Pro
           740                 745                 750

Ile Gln Ala Gly Gly Tyr Gly Ala Phe Pro Val His
       755                 760


<210> SEQ ID NO 43
<211> LENGTH: 2678
<212> TYPE: DNA
<213> ORGANISM: Gallus gallus
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<400> SEQUENCE: 43

tccccctccc tcgccccagc gcttcgatcc aagatggcgg cgctgagcag cggcagcagc 60

gccgaggggg cctcgctctt caacggggac atggagcccg agccgccgcc gcccgtgctg 120

ggcgcctgct acgccgggag cggcggcggc gacccggcca tcccggagga ggtgtggaat 180

atcaaacaga tgattaaatt aacacaagaa catatagaag cgctgttaga caagtttgga 240

ggagagcata acccaccatc aatatattta gaggcctatg aggagtacac cagcaaacta 300

gatgctctac agcagagaga acagcagtta ttggaatcca tgggaaatgg aactgatttc 360

tctgtttcca gttcagcttc aacggacaca gttgcatcat cttcctcctc tagcctctct 420

gtagcacctt catccctttc agtttatcaa aatcctactg atatgtcgcg gaataaccct 480

aagtctccac agaagcctat tgttagagtc ttcctgccca acaagcaaag gactgtggtt 540

ccggcaagat gtggggtgac agtccgagac agcctgaaga aagctctgat gatgagaggt 600

cttattccag aatgctgtgc tgtttacaga atacaggatg gagagaagaa gccaattggc 660

tgggacactg acatttcctg gctaaccgga gaggagttac acgtggaggt cttggagaat 720

gtgccactca caacacacaa ttttgtacga aaaacattct tcacgttagc gttctgcgac 780

ttctgtcgaa agctgctttt ccagggattc cgatgccaga catgtggcta caaatttcac 840

cagcgctgta gcacagaagt gccactgatg tgtgttaact acgaccaact cgatttgctg 900

tttgtctcca agttctttga acatcacccc atatcgcagg aggagaccac cttaggagag 960

accaccccgg catcgggatc gtacccctca gtgcccccat cagattctgt tggaccacca 1020

attctcccta gtccttctcc ttcaaaatcc attccaatcc cacagccctt ccgaccagca 1080

gatgaagacc atcggaatca gtttgggcaa cgcgaccgat cctcttcagc tcccaatgtt 1140

cacatcaata caattgagcc agtcaatatt gatgacttga ttagagacca gggtgtacga 1200

ggagagggag ccccctttgaa ccagctgatg cgctgtcttc ggaaatacca atcccggact 1260

cccagtcccc tccttcattc tgtccccagt gaaatagtgt ttgattttga gcctggccca 1320

gtgttcagag gttcaactgc aggtttgtct gcaacacctc ctgcatcttt gcctgggtca 1380

cttaccaatg tgaaagcatt acagaaatca ccaggccccc aacgggaaag gaaatcatcc 1440

tcatcctcag aagacagaaa taggatgaaa acccttggtc gacgagattc aagtgatgat 1500

tgggaaatac cagatgggca gatcacagtt ggacaaagga taggatctgg atcatttgga 1560

acagtctaca aaggaaagtg gcatggtgac gtggcagtga aaatgttgaa tgttacagca 1620

cccacacctc aacagttaca ggctttcaaa aatgaagtag gagtgctcag gaaaacacgg 1680

catgtgaata tcctactttt tatgggttat tcaacaaaac ctcagttggc tattgttaca 1740

cagtggtgtg aggggtccag cttatatcac catctgcaca taattgagac caagtttgaa 1800

atgatcaaac taattgatat tgcacgacag actgcacaag gcatggatta tttgcatgcc 1860

aagtcaatca tccacagaga cctcaagagt aataatattt ttcttcatga agacctcaca 1920

gtaaaaatag gtgacttcgg tctggctaca gtgaaatcac gatggagtgg atctcatcaa 1980

tttgaacagt tatctggatc aattctatgg atggcaccgg aagtgatcag gatgcaagac 2040

aaaaacccat atagctttca gtcagatgtg tatgcattcg ggattgtgct ttatgaactg 2100

atgactggac agttaccata ctcaaacatc aacaacaggg accagataat ttttatggtg 2160

ggacgaggat atctatctcc agacctcagt aaagtaagaa gtaactgtcc aaaagctatg 2220

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aagagactaa tggcagaatg cttgaaaaag aaaagagatg agagacctct ttttccacag 2280

attcttgcct ccattgagct tctggcccgg tcgttgccaa aaattcaccg cagtgcatct 2340

gagccgtcac taaaccgggc tggcttccag accgaggatt tcagtctgta tgcttgtgct 2400

tctccaaaaa cgcccatcca agcaggggga tacggtgggt ttccagtaca ctgaaaagaa 2460

atgtgaaagc gtgtgcctgt ttgctcatgt gctggtgtgt tcctgtgtgt gcaacgcata 2520

cgtacgttct cagttcctac cagcgacttt ttaaggttta ctgagggaat gaagactcat 2580

ttcctaacat ggggcattga acgtcctgag cacaagtcag tgctggtaag gaatgtcttg 2640

ggaacagctg gcaagaagaa ttagaaggta cttaaagg 2678

<210> SEQ ID NO 44
<211> LENGTH: 806
<212> TYPE: PRT
<213> ORGANISM: Gallus gallus

<400> SEQUENCE: 44

Met Ala Ala Leu Ser Ser Gly Ser Ser Ala Glu Gly Ala Ser Leu Phe
1 5 10 15

Asn Gly Asp Met Glu Pro Glu Pro Pro Pro Pro Val Leu Gly Ala Cys
20 25 30

Tyr Ala Gly Ser Gly Gly Gly Asp Pro Ala Ile Pro Glu Glu Val Trp
35 40 45

Asn Ile Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu
50 55 60

Leu Asp Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu
65 70 75 80

Ala Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu
85 90 95

Gln Gln Leu Leu Glu Ser Met Gly Asn Gly Thr Asp Phe Ser Val Ser
100 105 110

Ser Ser Ala Ser Thr Asp Thr Val Ala Ser Ser Ser Ser Ser Ser Leu
115 120 125

Ser Val Ala Pro Ser Ser Leu Ser Val Tyr Gln Asn Pro Thr Asp Met
130 135 140

Ser Arg Asn Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe
145 150 155 160

Leu Pro Asn Lys Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr
165 170 175

Val Arg Asp Ser Leu Lys Lys Ala Leu Met Met Arg Gly Leu Ile Pro
180 185 190

Glu Cys Cys Ala Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile
195 200 205

Gly Trp Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val
210 215 220

Glu Val Leu Glu Asn Val Pro Leu Thr Thr His Asn Phe Val Arg Lys
225 230 235 240

Thr Phe Phe Thr Leu Ala Phe Cys Asp Phe Cys Arg Lys Leu Leu Phe
245 250 255

Gln Gly Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys
260 265 270

Ser Thr Glu Val Pro Leu Met Cys Val Asn Tyr Asp Gln Leu Asp Leu

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        275                 280                 285

Leu Phe Val Ser Lys Phe Phe Glu His His Pro Ile Ser Gln Glu Glu
    290                 295                 300

Thr Thr Leu Gly Glu Thr Thr Pro Ala Ser Gly Ser Tyr Pro Ser Val
305                 310                 315                 320

Pro Pro Ser Asp Ser Val Gly Pro Pro Ile Leu Pro Ser Pro Ser Pro
                325                 330                 335

Ser Lys Ser Ile Pro Ile Pro Gln Pro Phe Arg Pro Ala Asp Glu Asp
            340                 345                 350

His Arg Asn Gln Phe Gly Gln Arg Asp Arg Ser Ser Ser Ala Pro Asn
        355                 360                 365

Val His Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Asp Leu Ile Arg
    370                 375                 380

Asp Gln Gly Val Arg Gly Glu Gly Ala Pro Leu Asn Gln Leu Met Arg
385                 390                 395                 400

Cys Leu Arg Lys Tyr Gln Ser Arg Thr Pro Ser Pro Leu Leu His Ser
                405                 410                 415

Val Pro Ser Glu Ile Val Phe Asp Phe Glu Pro Gly Pro Val Phe Arg
            420                 425                 430

Gly Ser Thr Ala Gly Leu Ser Ala Thr Pro Pro Ala Ser Leu Pro Gly
        435                 440                 445

Ser Leu Thr Asn Val Lys Ala Leu Gln Lys Ser Pro Gly Pro Gln Arg
    450                 455                 460

Glu Arg Lys Ser Ser Ser Ser Ser Glu Asp Arg Asn Arg Met Lys Thr
465                 470                 475                 480

Leu Gly Arg Arg Asp Ser Ser Asp Asp Trp Glu Ile Pro Asp Gly Gln
                485                 490                 495

Ile Thr Val Gly Gln Arg Ile Gly Ser Gly Ser Phe Gly Thr Val Tyr
            500                 505                 510

Lys Gly Lys Trp His Gly Asp Val Ala Val Lys Met Leu Asn Val Thr
        515                 520                 525

Ala Pro Thr Pro Gln Gln Leu Gln Ala Phe Lys Asn Glu Val Gly Val
    530                 535                 540

Leu Arg Lys Thr Arg His Val Asn Ile Leu Leu Phe Met Gly Tyr Ser
545                 550                 555                 560

Thr Lys Pro Gln Leu Ala Ile Val Thr Gln Trp Cys Glu Gly Ser Ser
                565                 570                 575

Leu Tyr His His Leu His Ile Ile Glu Thr Lys Phe Glu Met Ile Lys
            580                 585                 590

Leu Ile Asp Ile Ala Arg Gln Thr Ala Gln Gly Met Asp Tyr Leu His
        595                 600                 605

Ala Lys Ser Ile Ile His Arg Asp Leu Lys Ser Asn Asn Ile Phe Leu
    610                 615                 620

His Glu Asp Leu Thr Val Lys Ile Gly Asp Phe Gly Leu Ala Thr Val
625                 630                 635                 640

Lys Ser Arg Trp Ser Gly Ser His Gln Phe Glu Gln Leu Ser Gly Ser
                645                 650                 655

Ile Leu Trp Met Ala Pro Glu Val Ile Arg Met Gln Asp Lys Asn Pro
            660                 665                 670

Tyr Ser Phe Gln Ser Asp Val Tyr Ala Phe Gly Ile Val Leu Tyr Glu
        675                 680                 685
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Leu Met Thr Gly Gln Leu Pro Tyr Ser Asn Ile Asn Asn Arg Asp Gln
    690                 695                 700

Ile Ile Phe Met Val Gly Arg Gly Tyr Leu Ser Pro Asp Leu Ser Lys
705                 710                 715                 720

Val Arg Ser Asn Cys Pro Lys Ala Met Lys Arg Leu Met Ala Glu Cys
                725                 730                 735

Leu Lys Lys Lys Arg Asp Glu Arg Pro Leu Phe Pro Gln Ile Leu Ala
            740                 745                 750

Ser Ile Glu Leu Leu Ala Arg Ser Leu Pro Lys Ile His Arg Ser Ala
        755                 760                 765

Ser Glu Pro Ser Leu Asn Arg Ala Gly Phe Gln Thr Glu Asp Phe Ser
    770                 775                 780

Leu Tyr Ala Cys Ala Ser Pro Lys Thr Pro Ile Gln Ala Gly Gly Tyr
785                 790                 795                 800

Gly Gly Phe Pro Val His
                805


<210> SEQ ID NO 45
<211> LENGTH: 4454
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

gaaacgtccc gtgtgggagg ggcgggtctg ggtgcggcct gccgcatgac tcgtggttcg     60

gaggcccacg tggccggggc ggggactcag gcgcctgggg cgccgactga ttacgtagcg    120

ggcggggccg gaagtgccgc tccttggtgg gggctgttca tggcggttcc ggggtctcca    180

acatttttcc cggctgtggt cctaaatctg tccaaagcag aggcagtgga gcttgaggtt    240

cttgctggtg tgaaatgact gagtacaaac tggtggtggt tggagcaggt ggtgttggga    300

aaagcgcact gacaatccag ctaatccaga accactttgt agatgaatat gatcccacca    360

tagaggattc ttacagaaaa caagtggtta tagatggtga aacctgtttg ttggacatac    420

tggatacagc tggacaagaa gagtacagtg ccatgagaga ccaatacatg aggacaggcg    480

aaggcttcct ctgtgtattt gccatcaata atagcaagtc atttgcggat attaacctct    540

acagggagca gattaagcga gtaaaagact cggatgatgt acctatggtg ctagtgggaa    600

acaagtgtga tttgccaaca aggacagttg atacaaaaca agcccacgaa ctggccaaga    660

gttacgggat tccattcatt gaaacctcag ccaagaccag acagggtgtt gaagatgctt    720

tttacacact ggtaagagaa atacgccagt accgaatgaa aaaactcaac agcagtgatg    780

atgggactca gggttgtatg ggattgccat gtgtggtgat gtaacaagat acttttaaag    840

ttttgtcaga aaagagccac tttcaagctg cactgacacc ctggtcctga cttccctgga    900

ggagaagtat tcctgttgct gtcttcagtc tcacagagaa gctcctgcta cttccccagc    960

tctcagtagt ttagtacaat aatctctatt tgagaagttc tcagaataac tacctcctca   1020

cttggctgtc tgaccagaga atgcacctct tgttactccc tgttatttttt ctgccctggg   1080

ttcttccaca gcacaaacac acctctgcca ccccaggttt ttcatctgaa aagcagttca   1140

tgtctgaaac agagaaccaa accgcaaacg tgaaattcta ttgaaaacag tgtcttgagc   1200

tctaaagtag caactgctgg tgatttttttt tttctttttta ctgttgaact tagaactatg   1260

ctaatttttg gagaaatgtc ataaattact gttttgccaa gaatatagtt attattgctg   1320
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tttggtttgt ttataatgtt atcggctcta ttctctaaac tggcatctgc tctagattca 1380

taaatacaaa aatgaatact gaattttgag tctatcctag tcttcacaac tttgacgtaa 1440

ttaaatccaa ctttcacagt gaagtgcctt tttcctagaa gtggtttgta gacttccttt 1500

ataatatttc agtggaatag atgtctcaaa aatccttatg catgaaatga atgtctgaga 1560

tacgtctgtg acttatctac cattgaagga aagctatatc tatttgagag cagatgccat 1620

tttgtacatg tatgaaattg gttttccaga ggcctgtttt ggggctttcc caggagaaag 1680

atgaaactga aagcacatga ataatttcac ttaataattt ttacctaatc tccacttttt 1740

tcataggtta ctacctatac aatgtatgta atttgtttcc cctagcttac tgataaacct 1800

aatattcaat gaacttccat ttgtattcaa atttgtgtca taccagaaag ctctacattt 1860

gcagatgttc aaatattgta aaactttggt gcattgttat ttaatagctg tgatcagtga 1920

ttttcaaacc tcaaatatag tatattaaca aattacattt tcactgtata tcatggtatc 1980

ttaatgatgt atataattgc cttcaatccc cttctcaccc caccctctac agcttccccc 2040

acagcaatag gggcttgatt atttcagttg agtaaagcat ggtgctaatg gaccagggtc 2100

acagtttcaa aacttgaaca atccagttag catcacagag aaagaaattc ttctgcattt 2160

gctcattgca ccagtaactc cagctagtaa ttttgctagg tagctgcagt tagccctgca 2220

aggaaagaag aggtcagtta gcacaaaccc tttaccatga ctggaaaact cagtatcacg 2280

tatttaaaca ttttttttc ttttagccat gtagaaactc taaattaagc caatattctc 2340

atttgagaat gaggatgtct cagctgagaa acgttttaaa ttctctttat tcataatgtt 2400

ctttgaaggg tttaaaacaa gatgttgata aatctaagct gatgagtttg ctcaaaacag 2460

gaagttgaaa ttgttgagac aggaatggaa aatataatta attgatacct atgaggattt 2520

ggaggcttgg cattttaatt tgcagataat accctggtaa ttctcatgaa aaatagactt 2580

ggataacttt tgataaaaga ctaattccaa aatggccact ttgttcctgt ctttaatatc 2640

taaatactta ctgaggtcct ccatcttcta tattatgaat tttcatttat taagcaaatg 2700

tcatattacc ttgaaattca gaagagaaga aacatatact gtgtccagag tataatgaac 2760

ctgcagagtt gtgcttctta ctgctaattc tgggagcttt cacagtactg tcatcatttg 2820

taaatggaaa ttctgctttt ctgtttctgc tccttctgga gcagtgctac tctgtaattt 2880

tcctgaggct tatcacctca gtcatttctt ttttaaatgt ctgtgactgg cagtgattct 2940

ttttcttaaa aatctattaa atttgatgtc aaattaggga gaaagatagt tactcatctt 3000

gggctcttgt gccaatagcc cttgtatgta tgtacttaga gttttccaag tatgttctaa 3060

gcacagaagt ttctaaatgg ggccaaaatt cagacttgag tatgttcttt gaatacctta 3120

agaagttaca attagccggg catggtggcc cgtgcctgta gtcccagcta cttgagaggc 3180

tgaggcagga gaatcacttc aacccaggag gtggaggtta cagtgagcag agatcgtgcc 3240

actgcactcc agcctgggtg acaagagaga cttgtctcca aaaaaaaagt tacacctagg 3300

tgtgaatttt ggcacaaagg agtgacaaac ttatagttaa aagctgaata acttcagtgt 3360

ggtataaaac gtggttttta ggctatgttt gtgattgctg aaaagaattc tagtttacct 3420

caaaatcctt ctctttcccc aaattaagtg cctggccagc tgtcataaat tacatattcc 3480

ttttggtttt tttaaaggtt acatgttcaa gagtgaaaat aagatgttct gtctgaaggc 3540

taccatgccg gatctgtaaa tgaacctgtt aaatgctgta tttgctccaa cggcttacta 3600

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tagaatgtta cttaatacaa tatcatactt attacaattt ttactatagg agtgtaatag 3660

gtaaaattaa tctctatttt agtgggccca tgtttagtct ttcaccatcc tttaaactgc 3720

tgtgaatttt tttgtcatga cttgaaagca aggatagaga aacactttag agatatgtgg 3780

ggtttttta ccattccaga gcttgtgagc ataatcatat ttgctttata tttatagtca 3840

tgaactccta agttggcagc tacaaccaag aaccaaaaaa tggtgcgttc tgcttcttgt 3900

aattcatctc tgctaataaa ttataagaag caaggaaaat tagggaaaat attttatttg 3960

gatggtttct ataaacaagg gactataatt cttgtacatt atttttcatc tttgctgttt 4020

ctttgagcag tctaatgtgc cacacaatta tctaaggtat ttgttttcta taagaattgt 4080

tttaaaagta ttcttgttac cagagtagtt gtattatatt tcaaaacgta agatgatttt 4140

taaaagcctg agtactgacc taagatggaa ttgtatgaac tctgctctgg agggagggga 4200

ggatgtccgt ggaagttgta agacttttat ttttttgtgc catcaaatat aggtaaaaat 4260

aattgtgcaa ttctgctgtt taaacaggaa ctattggcct ccttggccct aaatggaagg 4320

gccgatattt taagttgatt attttattgt aaattaatcc aacctagttc tttttaattt 4380

ggttgaatgt tttttcttgt taaatgatgt ttaaaaaata aaaactggaa gttcttggct 4440

tagtcataat tctt 4454

<210> SEQ ID NO 46
<211> LENGTH: 189
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly Lys
1 5 10 15

Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr
20 25 30

Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly
35 40 45

Glu Thr Cys Leu Leu Asp Ile Leu Asp Thr Ala Gly Gln Glu Glu Tyr
50 55 60

Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys
65 70 75 80

Val Phe Ala Ile Asn Asn Ser Lys Ser Phe Ala Asp Ile Asn Leu Tyr
85 90 95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Asp Asp Val Pro Met Val
100 105 110

Leu Val Gly Asn Lys Cys Asp Leu Pro Thr Arg Thr Val Asp Thr Lys
115 120 125

Gln Ala His Glu Leu Ala Lys Ser Tyr Gly Ile Pro Phe Ile Glu Thr
130 135 140

Ser Ala Lys Thr Arg Gln Gly Val Glu Asp Ala Phe Tyr Thr Leu Val
145 150 155 160

Arg Glu Ile Arg Gln Tyr Arg Met Lys Lys Leu Asn Ser Ser Asp Asp
165 170 175

Gly Thr Gln Gly Cys Met Gly Leu Pro Cys Val Val Met
180 185

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<210> SEQ ID NO 47
<211> LENGTH: 1326
<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 47

gccgttcatg gcggtttcgg ggtctccaac agcttctcag gttgaaatcc aaaagcctcc 60

cgaggcgggg tctgcggagt ttgagatttt tgcaggtgtg aaatgactga gtacaaactg 120

gtggtggttg gagcaggtgg cgttgggaaa agtgctttga caatccagct aatccagaac 180

cactttgtgg atgaatatga tcccaccata gaggattctt accgaaaaca agtggtgatt 240

gacggtgaga cctgtctact ggacatactg gacacagctg gacaagagga gtacagtgcc 300

atgagagacc aatacatgag gacaggcgaa gggttcctct gtgtgtttgc catcaataat 360

agcaaatcct ttgcagatat taacctctac agggagcaaa ttaagcgcgt gaaagactct 420

gatgatgtac ccatggtgct ggtagggaac aagtgtgact tgccaacaag gacagttgac 480

acaaagcaag cccacgagct ggccaagagt tatggaattc cattcattga aacctcagcc 540

aagacccgac agggtgtgga ggatgccttt tacacgcttg taagggagat acgccagtac 600

cggatgaaga agctcaacag cagtgaggat ggcactcaag gctgtatggg gctgccctgt 660

gtggtgatgt agtaagaccc tttaaaagtt ctgtcatcag aaacgagcca ctttcaagcc 720

tcactgatgc cctggttctg acatccctgg aggagacgtg tttctgctgc tctctgcatc 780

tcagagaagc tcctgcttcc tgcttcccca acttagttac tgagcacagc catctaacct 840

gagacctctt cagaataact acctcctcac tcggctgtcc gaccagagaa atgaacctgt 900

ttctccccag tagttctctg ccctgggttt cccctagaaa caaacacacc tgccagctgg 960

ctttgtcctc cgaaaagcag tttacattga tgcagagaac caaactatag acaagcaatt 1020

ctgttgtcaa cagtttctta agctctaagg taacaattgc tggtgatttc ccccttgcc 1080

cccaactgtt gaacttggcc ttgttagttt tgggggaaat gtcaaaaatt aatctcttcc 1140

cgagaataga attagtgttg ctgattgcct gatttgcaat gtgatcagct atattctata 1200

agctggcgtc tgctctgtat tcataaatgc aaacatgagt actgacgtaa gtgcatccct 1260

agtcttctca gctgcatgca attaaatcca acgttcacaa caaaaaaaaa aaaaaaaaaa 1320

aaaaaa 1326

<210> SEQ ID NO 48
<211> LENGTH: 189
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 48

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly Lys
1 5 10 15

Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr
20 25 30

Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly
35 40 45

Glu Thr Cys Leu Leu Asp Ile Leu Asp Thr Ala Gly Gln Glu Glu Tyr
50 55 60

Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys
65 70 75 80

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Val Phe Ala Ile Asn Asn Ser Lys Ser Phe Ala Asp Ile Asn Leu Tyr
                85                  90                  95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Asp Asp Val Pro Met Val
            100                 105                 110

Leu Val Gly Asn Lys Cys Asp Leu Pro Thr Arg Thr Val Asp Thr Lys
        115                 120                 125

Gln Ala His Glu Leu Ala Lys Ser Tyr Gly Ile Pro Phe Ile Glu Thr
    130                 135                 140

Ser Ala Lys Thr Arg Gln Gly Val Glu Asp Ala Phe Tyr Thr Leu Val
145                 150                 155                 160

Arg Glu Ile Arg Gln Tyr Arg Met Lys Lys Leu Asn Ser Ser Glu Asp
                165                 170                 175

Gly Thr Gln Gly Cys Met Gly Leu Pro Cys Val Val Met
            180                 185


<210> SEQ ID NO 49
<211> LENGTH: 4470
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 49

gggactgggg cgccttgggc gcctagtgat tacgtagcgg gtggggccgg aagtgccgct     60

ccctggcggg ggctgttcat ggcggtttcg gggtctccaa cagcttctca ggttgaagtc    120

caaaagcctc ccgaggcggg gtctgcggag tttgaggttt ttgctggtgt gaaatgactg    180

agtacaaact ggtggtggtt ggagcaggtg gtgttgggaa aagcgccttg acgatccagc    240

taatccagaa ccactttgtg gatgaatatg atcccaccat agaggattct taccgaaagc    300

aagtggtgat tgatggtgag acctgcctgc tggacatact ggacacagct ggacaagagg    360

agtacagtgc catgagagac cagtacatga ggacaggcga agggttcctc tgtgtatttg    420

ccatcaataa tagcaaatca tttgcagata ttaacctcta cagggagcaa attaagcgtg    480

tgaaagattc tgatgatgtc cccatggtgc tggtaggcaa caagtgtgac ttgccaacaa    540

ggacagttga cacaaagcaa gcccacgaac tggccaagag ttacggaatt ccattcattg    600

agacctcagc caagacccga cagggtgtgg aggatgcctt ttacacactg gtaagggaga    660

tacgccagta ccgaatgaaa aagctcaaca gcagtgacga tggcactcaa ggttgtatgg    720

ggctgccctg tgtgctgatg tagtaagaca ctttgaaagt tctgtcatca gaaaagagcc    780

actttgaagc tgcactgatg ccctggttct gacatccctg gaggagacct gttcctgctg    840

ctctctgcat ctcagagaag ctcctgcttc ctgcttcccc gactcagtta ctgagcacag    900

ccatctaacc tgagacctct tcagaataac tacctcctca ctcggctgtc tgaccagaga    960

aatagacctg tctctcccgg tcgttctctg ccctgggttc ccctagaaac agacacagcc   1020

tccagctggc tttgtcctct gaaaagcagt ttacattgat gcagagaacc aaactagaca   1080

tgccattctg ttgacaacag tttcttatac tctaaggtaa caactgctgg tgattttccc   1140

ctgcccccaa ctgttgaact tggccttgtt ggtttggggg gaaaatgtca taaattactt   1200

tcttcccaaa atataattag tgttgctgat tgatttgtaa tgtgatcagc tatattccat   1260

aaactggcat ctgctctgta ttcataaatg caaacacgaa tactctcaac tgcatgcaat   1320

taaatccaac attcacaaca aagtgccttt ttcctaaaag tgctctgtag gctccattac   1380

agtttgtaat tggaatagat gtgtcaagaa ccattgtata ggaaagtgac tctgagccat   1440
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ctacctttga gggaaaggtg tatgtacctg atggcagatg ctttgtgtat gcacatgaag 1500

atagtttccc tgtctgggat tctcccagga gaaagatgga actgaaacaa ttacaagtaa 1560

tttcatttaa ttctagctaa tctttttttt ttttttttt ttttttggta gactatcacc 1620

tataaatatt tggaatatct tctagcttac tgataatcta ataattaatg agcttccatt 1680

ataatgaatt ggttcatacc aggaagccct ccatttatag tatagatact gtaaaaattg 1740

gcatgttgtt actttatagc tgtgattaat gattcctcag accttgctga gatatagtta 1800

ttagcagaca ggttatatct ttgctgcata gtttcttcat ggaatatata tctatctgta 1860

tgtggagaga acgtggccct cagttccctt ctcagcatcc ctcatctctc agcctagaga 1920

agttcgagca tcctagaggg gcttgaacag ttatctcggt taaaccatgg tgctaatgga 1980

ccgggtcatg gtttcaaaac ttgaacaagc cagttagcat cacagagaaa cagtccatcc 2040

atatttgctc cctgcctatt attcctgctt acagactttt gcctgatgcc tgctgttagt 2100

gctacaagga taaagcttgt gtggttctca ccaggactgg aagtacctgg tgagctctgg 2160

ggtaagccta gatatcttta cattttcaga cccttattct tagccacgtg gaaactgaag 2220

ccagagtcca tacctccatc tccttccccc cccaaaaaaa ttagattaat gttctttata 2280

tagctttttt aaagtattta aaacatgtct ataagttagg ctgccaacta acaaaagctg 2340

atgtgtttgt tcaaataaag aggtatcctt cgctactcga gagaagaatg taaaatgcca 2400

ttgattgttg tcacttggag gcttgatgtt tgccctgata attcattagt gggttttgtt 2460

tgtcacatga tacctaagat gtaactcagc tcagtaattc taatgaaaac ataaattgga 2520

taccttaatt gaaaaaagca aacctaattc caaaatggcc attttctctt ctgatcttgt 2580

aatacctaaa attctgaggt ccttgggatt cttttgttta taacaggatc ttgctgtgta 2640

gtcctagctg gcctcaaact cacaatactc ttcctggatc aatctcccaa gtgctgggat 2700

tacaggcaca ttccaccaca cacacctgac tgagctcgtt cctaatgagt tttcattaag 2760

caaattcccc atcaccttga aactaatcag aaggggggaag aaacatttgc tatgctcctg 2820

agtgctaaca ctgggatcat tcacatgggg tttgcattcc taggcaaact aaactgctgc 2880

cttttacaac aaggctcagt catcttcctg aagctgctga gaccagcact tggtcttgtt 2940

ttgttttaat atgtctatat gactggtggt ggatccctaa atagtttatt aattaaactc 3000

cagttaagga gaaagttact caccttgacc cgtttgacca tatcccgtgt gtgtgtgtgt 3060

gtgtgtgtgt gtgtgtgtgt gtgtgtgtgt gtgcacgcgt atgtacgtac gtatgtatgt 3120

aggtatgtag gtggtttcca gtataaacac agaaacaaat ggagccaatt caggtttcag 3180

atgcccttac taacatatat tcccacgggg tgtgggtttt ggcacaacag tgacaaactt 3240

aaaagccaag taagagccgg gcgtggtggc gcacgccttt aatcccagca cttgggaggc 3300

agaggcaggc ggatttctga gttctaggcc atcctggtct acagtgagtt ccaggacagc 3360

cagtgctaca cagagaaacc ctgtctcgaa aagccaaaaa aaaaaaaaaa aaaaaaaaaa 3420

aaaagccaag taggtccagt tggtatagta tcaaagtgtt tttagagtaa ttagtgaagg 3480

tctgctttac ctcaaagttg cagagcctct cttcctgagt ttaagtgcct ggccggcagt 3540

cacaaattaa catgttgctg taaggcagtt agttgaagct ttgttcacac attggagagt 3600

atgaaaataa agtgttctaa gagcgctgat actggatctg tgtaaacctg gtaaatgccg 3660

tttgtccagg acttagcgtg tgtgagttgg tagctcagta cgagtttact agttccgcag 3720

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tgtgtacaat ggaggcgggt ttgttttagc tggccacctg tagaatcagc ctttaaactg 3780

ctgtgaactt tgtcatgact tgaatatgaa gatagacaaa aactctgtaa agacaaatgt 3840

ttgttttccc ccttacagaa cgtgtgagct tggttttatc ttcctttgta tttagtcata 3900

acctctcaag ctggcagctc cgaccaagga tcagaagctg tgtgcgttcc acctggtgga 3960

attagctcag ctctatatga gaagtggagt taatggaaaa cgtgttgact gggtggtttc 4020

tatttaaaag agtgatgata attcttgaac agtagttttt attttgctat ttctttaagc 4080

tgactgatgt gccacaaaat tattttaagg tatttgtgtt ttaagagtgt tctcatgaga 4140

ttagttgtag atatttttta aaatacaact ggtttttaaa atctgagtat tgctctaagc 4200

aagtgtttag actcttacgg gaaggtgggt ggaagttgtt tggcttccgt atttccatgc 4260

gtgccgtcag acataggtca gaacgccaac tgtgcatcct gctgtttaaa gacctcttgg 4320

cctctgtgac cctcatgaag gggctgatat tttaagttga ctgtttgatt gtaaattaat 4380

cctttctaat ttttaaagac ttgcttgact gttttccttg ttaaataatt ttaaaaaaat 4440

aaaaaactgg aagttctttg cttaactgta 4470

<210> SEQ ID NO 50
<211> LENGTH: 189
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 50

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly Lys
1 5 10 15

Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr
20 25 30

Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly
35 40 45

Glu Thr Cys Leu Leu Asp Ile Leu Asp Thr Ala Gly Gln Glu Glu Tyr
50 55 60

Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys
65 70 75 80

Val Phe Ala Ile Asn Asn Ser Lys Ser Phe Ala Asp Ile Asn Leu Tyr
85 90 95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Asp Asp Val Pro Met Val
100 105 110

Leu Val Gly Asn Lys Cys Asp Leu Pro Thr Arg Thr Val Asp Thr Lys
115 120 125

Gln Ala His Glu Leu Ala Lys Ser Tyr Gly Ile Pro Phe Ile Glu Thr
130 135 140

Ser Ala Lys Thr Arg Gln Gly Val Glu Asp Ala Phe Tyr Thr Leu Val
145 150 155 160

Arg Glu Ile Arg Gln Tyr Arg Met Lys Lys Leu Asn Ser Ser Asp Asp
165 170 175

Gly Thr Gln Gly Cys Met Gly Leu Pro Cys Val Leu Met
180 185

<210> SEQ ID NO 51
<211> LENGTH: 570
<212> TYPE: DNA
<213> ORGANISM: Cavia porcellus

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<400> SEQUENCE: 51

atgactgagt ataaactggt ggtggttgga gcaggtggtg tcgggaaaag tgcactgacc 60

atccagctaa ttcagaacca ctttgtcgat gaatatgatc ccaccataga ggattcttac 120

cgaaaacagg tggttataga tggtgaaact tgtctgttgg atattctgga tacagctgga 180

caagaggagt acagtgccat gagagaccaa tacatgagga caggcgaagg cttcctctgt 240

gtgtttgcca tcaataatag caaatcattt gcagatatta acctctacag ggagcagatt 300

aaacgagtaa aagactcaga tgatgtacct atggtgctgg tagggaacaa gtgtgatttg 360

ccaacaagga ctgttgacac aaaacaagcc catgaactgg ccaagagtta cgggattcca 420

ttcattgaaa cctcagccaa gaccagacag ggtgttgaag atgcatttta cacactcgta 480

agagaaatac gccagtacag aatgaaaaaa ctcaacagca atgatgatgg gactcaaggt 540

tgtatggggt tgccatgtgt ggtgatgtaa 570

<210> SEQ ID NO 52
<211> LENGTH: 189
<212> TYPE: PRT
<213> ORGANISM: Cavia porcellus

<400> SEQUENCE: 52

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly Lys
1 5 10 15

Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr
20 25 30

Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly
35 40 45

Glu Thr Cys Leu Leu Asp Ile Leu Asp Thr Ala Gly Gln Glu Glu Tyr
50 55 60

Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys
65 70 75 80

Val Phe Ala Ile Asn Asn Ser Lys Ser Phe Ala Asp Ile Asn Leu Tyr
85 90 95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Asp Asp Val Pro Met Val
100 105 110

Leu Val Gly Asn Lys Cys Asp Leu Pro Thr Arg Thr Val Asp Thr Lys
115 120 125

Gln Ala His Glu Leu Ala Lys Ser Tyr Gly Ile Pro Phe Ile Glu Thr
130 135 140

Ser Ala Lys Thr Arg Gln Gly Val Glu Asp Ala Phe Tyr Thr Leu Val
145 150 155 160

Arg Glu Ile Arg Gln Tyr Arg Met Lys Lys Leu Asn Ser Asn Asp Asp
165 170 175

Gly Thr Gln Gly Cys Met Gly Leu Pro Cys Val Val Met
180 185

<210> SEQ ID NO 53
<211> LENGTH: 1220
<212> TYPE: DNA
<213> ORGANISM: Cavia porcellus

<400> SEQUENCE: 53

gttccggggt cctcaacgtt tctcagggtt gagattctat atccttttga agctggggcg 60

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gcagagcttg aggttcttgc tggtgtgaaa tgactgagta taaactggtg gtggttggag 120

caggtggtgt cgggaaaagt gcactgacca tccagctaat tcagaaccac tttgtcgatg 180

aatatgatcc caccatagag gattcttacc gaaaacaggt ggttatagat ggtgaaactt 240

gtctgttgga tattctggat acagctggac aagaggagta cagtgccatg agagaccaat 300

acatgaggac aggcgaaggc ttcctctgtg tgtttgccat caataatagc aaatcatttg 360

cagatattaa cctctacagg gagcagatta aacgagtaaa agactcagat gatgtaccta 420

tggtgctggt agggaacaag tgtgatttgc caacaaggac tgttgacaca aaacaagccc 480

atgaactggc caagagttac gggattccat tcattgaaac ctcagccaag accagacagg 540

gtgttgaaga tgcattttac acactcgtaa gagaaatacg ccagtacaga atgaaaaaac 600

tcaacagcaa tgatgatggg actcaaggtt gtatggggtt gccatgtgtg gtgatgtaac 660

aagatattta acaaagttct atcagaaaag agccactttc aagctgcact gataccctgg 720

tcctgacttc cctggaggag aagtatccct gttgctctct tcatctcaga gaagctcctg 780

ctgtttgtcc acctctcagt gtatgagcac agtctctgct tgagaacttc tcagaataac 840

tacctcctca cttggttgtc tgaccagaga aatgcacctc ttgttaattc cccaataatt 900

ttctgccctg ggctctcccc aacaaaaaac aaacacttct gccatccaaa aagcaacttg 960

gtctgaaaca gaaccaaact gtagattgaa attctcttaa aaagtcttga gctctaaagt 1020

tagcaaccgc tggtgatttt tattttcctt tttatttttg aacttggaac tgacctatgt 1080

tagattttgg agaaatgtca taaagtactg ttgtgccaag aagataatta tgttgctgaa 1140

tggttgattt atagtgttat cagctatatt ttacaaactg gcatctgctc tgtattcata 1200

aatacaaaaa tgaagccagg 1220

<210> SEQ ID NO 54
<211> LENGTH: 189
<212> TYPE: PRT
<213> ORGANISM: Cavia porcellus

<400> SEQUENCE: 54

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly Lys
1 5 10 15

Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr
20 25 30

Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly
35 40 45

Glu Thr Cys Leu Leu Asp Ile Leu Asp Thr Ala Gly Gln Glu Glu Tyr
50 55 60

Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys
65 70 75 80

Val Phe Ala Ile Asn Asn Ser Lys Ser Phe Ala Asp Ile Asn Leu Tyr
85 90 95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Asp Asp Val Pro Met Val
100 105 110

Leu Val Gly Asn Lys Cys Asp Leu Pro Thr Arg Thr Val Asp Thr Lys
115 120 125

Gln Ala His Glu Leu Ala Lys Ser Tyr Gly Ile Pro Phe Ile Glu Thr
130 135 140

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Ser Ala Lys Thr Arg Gln Gly Val Glu Asp Ala Phe Tyr Thr Leu Val
145                 150                 155                 160

Arg Glu Ile Arg Gln Tyr Arg Met Lys Lys Leu Asn Ser Asn Asp Asp
                165                 170                 175

Gly Thr Gln Gly Cys Met Gly Leu Pro Cys Val Val Met
            180                 185


<210> SEQ ID NO 55
<211> LENGTH: 1307
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 55

tgattacgta gcgggcgggg ccggaagtgc cgctccctag tgggggctgt tcatggcggt     60

tccggggtct ccaacctttc tcctagttgt ggtcctaaat acgtcggaag cggaggcggc    120

gaagcttgag gttcttgctg gtgtgaaatg actgagtaca aactggtggt ggttggagca    180

ggtggtgttg ggaaaagcgc actgacaatc cagctaatcc agaaccactt tgtagatgaa    240

tatgatccca ccatagagga ttcttaccga aaacaggtgg ttatagacgg tgaaacctgt    300

ctgttggata tactggatac agctggtcaa gaagagtaca gtgccatgag agaccaatac    360

atgaggacag gcgaaggctt cctctgtgta tttgccatca ataatagcaa atcatttgca    420

gacattaacc tctacaggga acagattaag cgagtaaaag attcagatga tgtacctatg    480

gtgctagtag gaaacaagtg tgatttgcca acaaggacag ttgacacaaa acaagcccat    540

gaactggcca agagttatgg gattccattc attgaaacct cagccaagac cagacagggt    600

gtcgaggatg ccttttacac actggtaaga gaaatacgtc agtaccgaat gaagaaactc    660

aacagcagtg atgatgggac tcaaggttgt atggggttac catgtgtggt gatgtaacaa    720

gacacttta aagttctagc atcagaaaag agccactgtc aagctgcact gacaccctgg    780

tcctgacttc cctggaggag aagtattcct gttgctatct tcagtctcac aaagaagctc    840

ctgctacttc cccaactctc agtagatcag tacaatgttc tctatttgag aagttctccg    900

aacaactacc tcctcacttg gttgtctgac cagagaaatg aacctcttgt tccttcccgc    960

tgtttttcca ccctgaattc tcccccaaca cacataaaca aacctctgcc atcccaggtt   1020

tttcatctga aaaataattc atgctctgaa acagagaaca aaactgtaga catgaaattc   1080

tgtaggaaac aaggtcttga gctcaaaagt agcaactgct ggtgaccttt ttttcccccc   1140

tttttactgt tgaacttgga actatgttgg tttttggaga aatgtcataa gttactgttt   1200

tgctgagaat atagttaagt tgacatttgg tttgtttgta atatcattag ctattttcta   1260

taaattggca tctgctctgc attcataaat acacgagtga attctga                1307


<210> SEQ ID NO 56
<211> LENGTH: 189
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 56

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly Lys
1               5                   10                  15

Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr
            20                  25                  30

Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly
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        35                  40                  45

Glu Thr Cys Leu Leu Asp Ile Leu Asp Thr Ala Gly Gln Glu Glu Tyr
    50                  55                  60

Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys
65                  70                  75                  80

Val Phe Ala Ile Asn Asn Ser Lys Ser Phe Ala Asp Ile Asn Leu Tyr
                85                  90                  95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Asp Asp Val Pro Met Val
            100                 105                 110

Leu Val Gly Asn Lys Cys Asp Leu Pro Thr Arg Thr Val Asp Thr Lys
        115                 120                 125

Gln Ala His Glu Leu Ala Lys Ser Tyr Gly Ile Pro Phe Ile Glu Thr
    130                 135                 140

Ser Ala Lys Thr Arg Gln Gly Val Glu Asp Ala Phe Tyr Thr Leu Val
145                 150                 155                 160

Arg Glu Ile Arg Gln Tyr Arg Met Lys Lys Leu Asn Ser Ser Asp Asp
                165                 170                 175

Gly Thr Gln Gly Cys Met Gly Leu Pro Cys Val Val Met
            180                 185


<210> SEQ ID NO 57
<211> LENGTH: 3104
<212> TYPE: DNA
<213> ORGANISM: Felis catus

<400> SEQUENCE: 57

aaaaaataaa taaatttaag aaaccatttt aaaattatgc acagttgcag cctggaaaac     60

ttaaggtggc gccttatagt atcaatctta ggagctttat ttggtgcatt taacgcaact    120

ggtaattgca aaatccactt cgcctgtgta agtgaaaaat atagactgtt atcttgttgg    180

ccctatgaaa ttctgcactt ggtatttagc atatactcta ccttcattac tatctggcaa    240

gatgttctgc cttagcactc agttgcattc ttttcctttt ctttcctgtt cattatgctt    300

taattctgag gaccatatga gggtagaata tattaaaaat tacaaaaatt ataaaaattt    360

gtataggcaa accatttcct taagttgatg gccaaatgtt aaaatgttat ttttcatatc    420

atttataatc ttgtcacagt ccacttaacg aagtttggtt agatttcagt gaaaattatc    480

ttccagagta gttttttttt ttttttcctg ggattaggga ggggggtaac tttactgcaa    540

ttagtatgta tggtgcagaa tttcatgcaa atgaggtgtg ccagcagtgt ggtaatttaa    600

tcgtatttaa acaaaaacaa acaaaaaaaa aacgaatgca caaacttgct gctgcttaga    660

tcactgcagc ttctaggacc cagtttcttt tactgatttc aaaacaaaac aaaacaaaaa    720

aataaaaaaa gttgtgcctg aaatgaatct tgtttttttt ataagtagcc gcctggttcc    780

tgtgtcctgt gaaatacagg cacttgaccc ttggtgtagc ttctgttcga ctttatatca    840

cgggaatgga ttggtctgat ttcttggccc tcatcttgaa ttggccacat ccagggtccc    900

tggccagtgg actgaaggct ttgtctaaga ggacaagggc agctcagggg atgtgggggа    960

gggcgctttt atcttccccg ttgtcgtttg aggttttgat cttctctggg taaagaggcc   1020

gtttatcttt gtaaacacaa aacatttttg ctttctccag ttttctgtta atggcgaaag   1080

aatggaagcg aataaagttt tactgatttt tgagactcta gcacctagcg ctttcatttt   1140

tgaaacgtcc tgtgtgggag gggcgggtct gggtgcggcc cgccgcgtga ctcctgagtc   1200
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ggggggcccac gtggctgggg cggggactcg gacgccccgg gcgccgactg attacgtagc 1260

gggcggggcc ggaagtgccg ctccctagtg ggggctgttc atggcggttc cggggtctcc 1320

atccttttc ccagttgttc taaatcagtc ggaagcggag gcagcgaagt ttgaggttct 1380

cgctggtgtg aaatgactga gtacaaactg gtggtggttg gagcaggtgg tgttgggaaa 1440

agcgcactga caatccagct aatccagaac cactttgtag atgaatatga tcccaccata 1500

gaggattctt accgaaaaca ggtggttata gacggtgaaa cctgtctgtt ggacatactg 1560

gatacagctg gtcaagaaga gtacagtgcc atgagagacc aatacatgag gacaggcgaa 1620

ggcttcctct gtgtatttgc catcaacaat agcaaatcat ttgcagatat taacctttac 1680

agggaacaga ttaagcgagt aaaagactcc gatgatgtac ctatggtgct agtaggaaac 1740

aagtgtgatt tgccaacaag gaccgtcgac acaaaacaag cccacgaact ggccaagagt 1800

tatgggattc cattcattga aacctcagcc aagaccagac agggtgttga agatgccttt 1860

tacacactgg taagagaaat acgtcagtac cgaatgaaga aactcaacag cagtgatgac 1920

gggactcaag gttgtatggg gttaccgtgt gtggtgatgt aacaagatac ttttaaagtt 1980

ctagcatcag aaaagagcca ctgtcaagct gcactgacac cctggtcctg acttccctgg 2040

aggagaagcg ttcctgttgc tattttcagt ttcacaaaga agctcctgct atttccccaa 2100

ctctccgtag atcagtacat tattctctgt ttgagaagtt ctccgaataa ctacctcctc 2160

acttggttgt ctgaccagag aaatgaacct cttgttactc cccactgttt ttccaccctg 2220

gttctccccc agcacatata aacaaacctc ccaggttttt catctgaaaa gtaattcatg 2280

ctctgaaaca gagaaccaaa ctgtagacat gaaattctgt aggaaacaat gtcttgagct 2340

ctaaagtagc aactgctggt gacttttttt ttttttttt ccttttact gttgaacttg 2400

gaactatgtt ggtttttgga gaaatgtcgt aagttactgt tttgctgagt atatagttaa 2460

gtttaccatt cggtttgttt gtaatgtcat tggctatact ctgtacctgg catctgctct 2520

gcattcataa atacaaaagt gaattctgac ttttgagtct atcctagtgt tctcaacttc 2580

cacataatta aatctaactt ttgcagcaaa gtgccttttt cctagaagtg gtttgtagat 2640

ttgctttata atactttggt ggaatagatg tctcaaaaac cattatacat gaaaatgaat 2700

gtctgagata cgtctatgat ctgtctacct ttgagggaaa aatataccga cataatagca 2760

gatgccatgt cttacgtgta tgaagttgga tttccagaga cctgatttgg gtctcttcca 2820

agagaaagat gaaactggaa acaattatga ataacttcac ttaatttta cctaatctct 2880

acttcggggt gggagggcag ggagtaggtt accacttaca aaatatatgc aatttgtttc 2940

ttctagctta ctgataatga acttccattc ttatttaaat ttaggtcata tcctaaagct 3000

ttacatttgc aggtgttcga aattgtaagt ttaatgcagt tttatttaat agctatgatc 3060

aatgattttc aagcctcaga tgtattaacg gacacatttt cact 3104

<210> SEQ ID NO 58
<211> LENGTH: 189
<212> TYPE: PRT
<213> ORGANISM: Felis catus

<400> SEQUENCE: 58

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly Lys
1 5 10 15

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Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr
            20                  25                  30

Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly
        35                  40                  45

Glu Thr Cys Leu Leu Asp Ile Leu Asp Thr Ala Gly Gln Glu Glu Tyr
    50                  55                  60

Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys
65                  70                  75                  80

Val Phe Ala Ile Asn Asn Ser Lys Ser Phe Ala Asp Ile Asn Leu Tyr
                85                  90                  95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Asp Asp Val Pro Met Val
            100                 105                 110

Leu Val Gly Asn Lys Cys Asp Leu Pro Thr Arg Thr Val Asp Thr Lys
        115                 120                 125

Gln Ala His Glu Leu Ala Lys Ser Tyr Gly Ile Pro Phe Ile Glu Thr
    130                 135                 140

Ser Ala Lys Thr Arg Gln Gly Val Glu Asp Ala Phe Tyr Thr Leu Val
145                 150                 155                 160

Arg Glu Ile Arg Gln Tyr Arg Met Lys Lys Leu Asn Ser Ser Asp Asp
                165                 170                 175

Gly Thr Gln Gly Cys Met Gly Leu Pro Cys Val Val Met
            180                 185


<210> SEQ ID NO 59
<211> LENGTH: 4283
<212> TYPE: DNA
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 59

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atgactgagt acaaactggt ggtggttgga gcaggtggtg ttgggaaaag tgcactgaca    180

atccagctaa tccagaacca ctttgtagat gaatatgatc ccaccataga ggattcctac    240

cgaaaacagg tggttataga tggtgaaacc tgtctgttgg acatactgga tacagctgga    300

caagaggagt acagtgccat gagagaccaa tacatgagga caggcgaagg cttcctttgt    360

gtgtttgcca tcaataatag caaatcattt gcagatatta acctctacag ggaacagata    420

aagcgtgtaa aggactcgga tgatgtacct atggtgctag taggaaacaa gtgtgatttg    480

ccaacaagga cagttgacac aaaacaagcc catgaactgg ccaaaagtta tgggattcca    540

ttcattgaaa cctcagccaa gaccagacag ggtgttgaag atgcctttta cacactggta    600

agagaaatac gtcagtaccg aatgaaaaag ctcaacagca gtgatgatgg cactcaaggc    660

tgtatggggt tgccgtgtgt ggtgatgtaa caagatactt ttaaagttct cacatcagaa    720

aagagccact gtcaagctgc actgacaccc tggtcctgac ttccctggag gagaagtatt    780

cctgttgcta tcttcagttt caaaaagaag ctcctgctat ttccccaact ctcagtagat    840

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gcacacacaa acgcacctct gccacccagg tttttcatct gaaaagcaat taatactctg   1020

aaacagagaa ccaaactgta gaaacatgaa attctgtaga aaacaatgtc ttgagctcta   1080
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tcaaaacttc agtgagccag taagcatcac agagaaagaa attctttcac atttgctcac 2040

cattaactcc agctaatagt tttgccagat gtgtgtggtt agtcctgcaa ggaaaggaga 2100

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gtctgaaagc taccatgcct gtctgtaaat gaatccactg agtgctgtac ttgttccaac 3360

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tcctttaaac tgctgtgaat ttttgtcttg acttgaaagc aaggatagag aaacacttta 3540

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acatttacag tcatgaactc ttaagctggc agctacaacc aagaaccaaa agagggtgca 3660

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agaaactatt ttatttgggt ggtttctata aacaagggac tataattctt aaacattatt 3780

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cttaaaagaa ttgtttttaa aagtgttctc attttcagag taattgtaga tatatttcaa 3900

aatataactg ataatttta aaggcctgag tactgaccta agaagcagtt gtatgaattc 3960

tctgggggga agggaggagc tcagtgaaag ttgtatgact tttatatttc tgtgccatca 4020

aataaaggta aaaatgtctt ttgtgcagtt ttgctgttca aacagaaact attggcctcc 4080

ttggccctaa atgaaagggc tggtatttta agttgactat tttattgtaa attaatccat 4140

cttaattttt ttaaatttgg ttgaatgttc tcttgttaaa tgtttaaaaa ataaaaactg 4200

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aaaaaaataa aaaaaaaaaa aaa 4283

<210> SEQ ID NO 60
<211> LENGTH: 189
<212> TYPE: PRT
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 60

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly Lys
1 5 10 15

Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr
20 25 30

Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly
35 40 45

Glu Thr Cys Leu Leu Asp Ile Leu Asp Thr Ala Gly Gln Glu Glu Tyr
50 55 60

Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys
65 70 75 80

Val Phe Ala Ile Asn Asn Ser Lys Ser Phe Ala Asp Ile Asn Leu Tyr
85 90 95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Asp Asp Val Pro Met Val
100 105 110

Leu Val Gly Asn Lys Cys Asp Leu Pro Thr Arg Thr Val Asp Thr Lys
115 120 125

Gln Ala His Glu Leu Ala Lys Ser Tyr Gly Ile Pro Phe Ile Glu Thr
130 135 140

Ser Ala Lys Thr Arg Gln Gly Val Glu Asp Ala Phe Tyr Thr Leu Val
145 150 155 160

Arg Glu Ile Arg Gln Tyr Arg Met Lys Lys Leu Asn Ser Ser Asp Asp
165 170 175

Gly Thr Gln Gly Cys Met Gly Leu Pro Cys Val Val Met
180 185

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<210> SEQ ID NO 61
<211> LENGTH: 4825
<212> TYPE: DNA
<213> ORGANISM: Gallus gallus

<400> SEQUENCE: 61

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gggccgctgg gagggcgatg actgaataca agctggtggt ggtgggagct ggcggcgtcg 180

ggaagagcgc gttgaccatc cagctcatcc agaaccactt cgtggacgag tacgacccca 240

ccatcgagga ttcgtacaga aagcaggttg tcatcgatgg agagacgtgc ttgttggaca 300

ttctggacac tgcaggacag gaagaataca gtgctatgcg tgatcagtac atgagaactg 360

gggaaggatt cctttgtgtg tttgccatta acaacagtaa atcattcgct gatattaacc 420

tttacagaga gcaaatcaag agagtgaaag attcagacga tgtgccaatg gtgctggtgg 480

ggaataagtg cgatttgcca acaaggacag tagacaccaa acaggctcaa gagttagcaa 540

aaagctacgg cattcccttc atagagacat cagccaaaac gagacagggt gtggaagatg 600

cgttttacac actggtgagg gagattcggc agtaccggat gaaaaagctc aacagcaacg 660

aagatgggaa tcagggctgt atggggttgt cctgcattgt gatgtgataa gatgccaggt 720

tcagatgtag ctgctggaca agtctcgatg ctactgtatt gtgtctcatg ctgatgccct 780

gcagtatttt ggtgccagcg accagactct tggtaccagt taattagctc aggatccttt 840

cctgtgctcc atctgaagaa aacatctctg gtatctacct ccttgctcag ctcacagagc 900

agtcatatct cttggtgtac tgggattctt ttctagctgt gttgtctggg tttgttcaag 960

aagaaaacca gtcacaagaa aagtgaatta cagagactaa atgctgtgaa aaagatcaca 1020

ctttacctcc agagtaaaag ctagaagtgg cgtttgaccc ctttgcattg gattcagatt 1080

tgcggtgttg tcagaggagt ggcagaagta attttgccat tacaaaggtt tctgtcacca 1140

gtcggattgg tatctgctgt ctgtgcaccc acacagtgta tctgcaacat ctgcattgtg 1200

ccagaagtat cacttaactg atgaactgat cctttatttt tctgtaataa aaaggagata 1260

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ggctgaggag aaccccaagg atgaatttct tgggtgctca ttgtcttgag caggcaagtt 1380

ttgtgtgggt gatctctttt catggcagga tattaaaatg ggaatttgta gtctggaaga 1440

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tcaatggttg tcacagactt aaggtgtcca ggctgattgg aggaggcact gagccctaac 1860

agagcactga gctgacttct aattgcagca tccttgcaaa atgaggaagg gagttcagtg 1920

atgtctgcac tgaagatgta tgatacactg atagcagttc tgggtatgtt gtaacagctt 1980

caaagtagaa ccgcagtact gcgtgagctg tgtgacttct tcctagaaca cagcactgtc 2040

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ggtttgggtt tatataggca gtatttttaa acagaatatc cgaagcactt tctggagttc 3660

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ctttggtggg agctgcactg cagaaggacc aaaccccaac aagatttggc acatttgttt 4200

agaagataag cacagatggt tttgcacaag gcagctcctc ataatggtgg ctttgtagat 4260

ttagtccaaa tgttcttatt tagatctagc agcacatcac tgtgtccgtg cccatctaac 4320

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cttgttaatg tgagtgcccc aactctatgg tcttattaaa gaaacccaaa cattgctcag 4500

attttgttct tattgtcatc ataagacttg aatagtgatg gtaatgctta cgtagacgtg 4560

tcttgtgagt gcacttcagt gatttagaaa gaactggatt tcaagcaact ttggacctgt 4620

ggggggaggg agattaatga aggtttgaat cacattctaa ttctatgtac agtccttcat 4680

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actttttttt tttaatccaa gggctaactt gttgtaactt ggtataatta tctgctttcg 4800

gaaatgcatc tctgttggtt tgaaa 4825

<210> SEQ ID NO 62
<211> LENGTH: 189
<212> TYPE: PRT
<213> ORGANISM: Gallus gallus

<400> SEQUENCE: 62

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly Lys
1 5 10 15

Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr
20 25 30

Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly
35 40 45

Glu Thr Cys Leu Leu Asp Ile Leu Asp Thr Ala Gly Gln Glu Glu Tyr
50 55 60

Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys
65 70 75 80

Val Phe Ala Ile Asn Asn Ser Lys Ser Phe Ala Asp Ile Asn Leu Tyr
85 90 95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Asp Asp Val Pro Met Val
100 105 110

Leu Val Gly Asn Lys Cys Asp Leu Pro Thr Arg Thr Val Asp Thr Lys
115 120 125

Gln Ala Gln Glu Leu Ala Lys Ser Tyr Gly Ile Pro Phe Ile Glu Thr
130 135 140

Ser Ala Lys Thr Arg Gln Gly Val Glu Asp Ala Phe Tyr Thr Leu Val
145 150 155 160

Arg Glu Ile Arg Gln Tyr Arg Met Lys Lys Leu Asn Ser Asn Glu Asp
165 170 175

Gly Asn Gln Gly Cys Met Gly Leu Ser Cys Ile Val Met
180 185

<210> SEQ ID NO 63
<211> LENGTH: 2603
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

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tctggtgcgc gcgcggctgt gccgcccgag ccggagggac tggttggttg agagagagag 180

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ccggggcccg cggcccggac ttggtcctgc gcagcgggcg cggggcagcg cagcgggagg 420

aagcgagagg tgctgccctc cccccggagt tggaagcgcg ttacccgggt ccaaaatgcc 480

caagaagaag ccgacgccca tccagctgaa cccggccccc gacggctctg cagttaacgg 540

gaccagctct gcggagacca acttggaggc cttgcagaag aagctggagg agctagagct 600

tgatgagcag cagcgaaagc gccttgaggc ctttcttacc cagaagcaga aggtgggaga 660

actgaaggat gacgactttg agaagatcag tgagctgggg gctggcaatg gcggtgtggt 720

gttcaaggtc tcccacaagc cttctggcct ggtcatggcc agaaagctaa ttcatctgga 780

gatcaaaccc gcaatccgga accagatcat aagggagctg caggttctgc atgagtgcaa 840

ctctccgtac atcgtgggct tctatggtgc gttctacagc gatggcgaga tcagtatctg 900

catggagcac atggatggag gttctctgga tcaagtcctg aagaaagctg gaagaattcc 960

tgaacaaatt ttaggaaaag ttagcattgc tgtaataaaa ggcctgacat atctgaggga 1020

gaagcacaag atcatgcaca gagatgtcaa gccctccaac atcctagtca actcccgtgg 1080

ggagatcaag ctctgtgact ttggggtcag cgggcagctc atcgactcca tggccaactc 1140

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ccagcccagc acaccaaccc atgctgctgg cgtctaagtg tttgggaagc aacaaagagc 1680

gagtcccctg cccggtggtt tgccatgtcg cttttgggcc tccttcccat gcctgtctct 1740

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agacttctgg ttgtatttct atatttattt tcagtatact gtgtgggata cttagtggta 2340

tgtctcttta agttttgatt aatgtttctt aaatggaatt attttgaatg tcacaaattg 2400

atcaagatat taaaatgtcg gatttatctt tccccatatc caagtaccaa tgctgttgta 2460

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tttaacaaat ctaatctctt attctaataa atatactatg aaataaaaaa aaaaggatga 2580

aagctaaaaa aaaaaaaaaa aaa 2603

<210> SEQ ID NO 64
<211> LENGTH: 393
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

Met Pro Lys Lys Lys Pro Thr Pro Ile Gln Leu Asn Pro Ala Pro Asp
1 5 10 15

Gly Ser Ala Val Asn Gly Thr Ser Ser Ala Glu Thr Asn Leu Glu Ala
20 25 30

Leu Gln Lys Lys Leu Glu Glu Leu Glu Leu Asp Glu Gln Gln Arg Lys
35 40 45

Arg Leu Glu Ala Phe Leu Thr Gln Lys Gln Lys Val Gly Glu Leu Lys
50 55 60

Asp Asp Asp Phe Glu Lys Ile Ser Glu Leu Gly Ala Gly Asn Gly Gly
65 70 75 80

Val Val Phe Lys Val Ser His Lys Pro Ser Gly Leu Val Met Ala Arg
85 90 95

Lys Leu Ile His Leu Glu Ile Lys Pro Ala Ile Arg Asn Gln Ile Ile
100 105 110

Arg Glu Leu Gln Val Leu His Glu Cys Asn Ser Pro Tyr Ile Val Gly
115 120 125

Phe Tyr Gly Ala Phe Tyr Ser Asp Gly Glu Ile Ser Ile Cys Met Glu
130 135 140

His Met Asp Gly Gly Ser Leu Asp Gln Val Leu Lys Lys Ala Gly Arg
145 150 155 160

Ile Pro Glu Gln Ile Leu Gly Lys Val Ser Ile Ala Val Ile Lys Gly
165 170 175

Leu Thr Tyr Leu Arg Glu Lys His Lys Ile Met His Arg Asp Val Lys
180 185 190

Pro Ser Asn Ile Leu Val Asn Ser Arg Gly Glu Ile Lys Leu Cys Asp
195 200 205

Phe Gly Val Ser Gly Gln Leu Ile Asp Ser Met Ala Asn Ser Phe Val
210 215 220

Gly Thr Arg Ser Tyr Met Ser Pro Glu Arg Leu Gln Gly Thr His Tyr
225 230 235 240

Ser Val Gln Ser Asp Ile Trp Ser Met Gly Leu Ser Leu Val Glu Met
245 250 255

Ala Val Gly Arg Tyr Pro Ile Pro Pro Pro Asp Ala Lys Glu Leu Glu
260 265 270

Leu Met Phe Gly Cys Gln Val Glu Gly Asp Ala Ala Glu Thr Pro Pro
275 280 285

Arg Pro Arg Thr Pro Gly Arg Pro Leu Ser Ser Tyr Gly Met Asp Ser
290 295 300

Arg Pro Pro Met Ala Ile Phe Glu Leu Leu Asp Tyr Ile Val Asn Glu
305 310 315 320

Pro Pro Pro Lys Leu Pro Ser Gly Val Phe Ser Leu Glu Phe Gln Asp

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               325                 330                 335

Phe Val Asn Lys Cys Leu Ile Lys Asn Pro Ala Glu Arg Ala Asp Leu
            340                 345                 350

Lys Gln Leu Met Val His Ala Phe Ile Lys Arg Ser Asp Ala Glu Glu
        355                 360                 365

Val Asp Phe Ala Gly Trp Leu Cys Ser Thr Ile Gly Leu Asn Gln Pro
    370                 375                 380

Ser Thr Pro Thr His Ala Ala Gly Val
385                 390


<210> SEQ ID NO 65
<211> LENGTH: 2151
<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 65

cggccgcgcg ctccctgctg agttgcaggc tgtttcccgg ctgcaagatg cccaagaaga     60

agccgacgcc catccagctg aacccggccc ccgatggctc cgcggttaac gggaccagct    120

cggccgagac caacctggag gccttgcaga agaagctgga ggagctggag ctggacgagc    180

agcagcggaa gcgccttgag gcctttctga cgcagaagca gaaggtggga gagttgaagg    240

atgatgactt tgagaagatc agtgaactgg gggctggcaa tggtggagtg gtgttcaagg    300

tctcccacaa gccatctggc ctggttatgg ctaggaagct aattcacctg gagatcaaac    360

ccgcaatccg gaaccagatc atccgggagc tgcaggtgct gcatgagtgc aactccccgt    420

acatagtggg cttctacggg gccttctaca gtgacggcga gatcagcatc tgcatggagc    480

acatggatgg tgggtccttg gatcaagtgc tgaagaaagc tggaagaatt cctgagcaaa    540

ttttaggaaa agtcagcatc gctgtgataa aaggcctgac atatctacga gagaagcaca    600

agattatgca cagagatgtc aagccttcca acattctagt gaactcacgt ggggagatca    660

aactctgcga ttttggggtc agcgggcagc taattgactc catggccaac tccttcgtgg    720

gaacaaggtc ctacatgtcg cctgagagac tccaggggac tcactactct gtgcagtcgg    780

acatctggag catggggctc tctctggtgg agatggcagt tggaagatac cccattcctc    840

ctcctgatgc caaggagctg gagctgctgt ttggatgcca ggtggaagga gacgcggccg    900

aaacgccacc caggccaagg acccctggga ggcccctcag ctcatatgga atggatagcc    960

gacctcccat ggcaattttt gagttgttgg attacatcgt caatgagcct cctccaaaac   1020

tgcccagtgg agtattcagt ctggaatttc aggattttgt gaataagtgc ttaataaaga   1080

accctgcaga gagagcagat ctgaagcagc tcatggtaca tgctttcatc aagagatctg   1140

atgccgagga ggtagacttc gcaggctggc tctgctccac cattgggctt aaccagccca   1200

gcacaccaac ccacgctgcc agcatctgag cctttgggaa gcagcagaga ggaatcctct   1260

gcccagtggc atgccatgtt gctttcaggc ctctcccatg cttgtctatg ttcagatgtg   1320

catctcatct gtgacaaagg atgaagaaca cagcatgtgc caaatcgtac ttgtgtcatt   1380

tttaatattg tctttatcgc tatggttact cccctaagtg gattggcttt gtgcttgggg   1440

ctatttgtct gttcatcaaa tacatgccag gttgaactac agtgaaaccc tggtgacctg   1500

ggtggtcttc ttactgatgt ttgcgctgct gttcatcgtg actcactagc tggctgcctg   1560

tattgtcagg attctcggac ccttggtact tcactcttgc tggtgacctc tcagtctgag   1620
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gagaggggggc cttctgagac ccttcacagg cagtgcatgc atgaaaagca tgctttgctg 1680

ctactgaaat gagcaccaga acgtgtacat catggtattt tatttttgct tttggtatag 1740

aactcagcag ttcccattta aaaaaaaaat ctaaccagag cccatcactg ccatgatagc 1800

tggggcttca gtctgtctac tgtggtgatt tttagacttc tggttgtatt tctatattta 1860

tttttaaata tactgtgtgg gatacttagt ggtatatgtc tctgagtttg gattagtgtt 1920

tctaaattgg tagttatttt gaatgtcaca aatggattaa ggaatcaacg tatcaagagt 1980

tctatctttc ttccagtcta agtaccaatg ctattgtaaa cgtgtatagt gcctacaaat 2040

tgtatgaaaa ccctttttaac cactttactc aagatgttta tcaaatctaa tctcttattc 2100

taataaaaat actatcaagt taaagtaaaa aaaaaaaaaa aaaaaaaaaa a 2151

<210> SEQ ID NO 66
<211> LENGTH: 393
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 66

Met Pro Lys Lys Lys Pro Thr Pro Ile Gln Leu Asn Pro Ala Pro Asp
1 5 10 15

Gly Ser Ala Val Asn Gly Thr Ser Ser Ala Glu Thr Asn Leu Glu Ala
20 25 30

Leu Gln Lys Lys Leu Glu Glu Leu Glu Leu Asp Glu Gln Gln Arg Lys
35 40 45

Arg Leu Glu Ala Phe Leu Thr Gln Lys Gln Lys Val Gly Glu Leu Lys
50 55 60

Asp Asp Asp Phe Glu Lys Ile Ser Glu Leu Gly Ala Gly Asn Gly Gly
65 70 75 80

Val Val Phe Lys Val Ser His Lys Pro Ser Gly Leu Val Met Ala Arg
85 90 95

Lys Leu Ile His Leu Glu Ile Lys Pro Ala Ile Arg Asn Gln Ile Ile
100 105 110

Arg Glu Leu Gln Val Leu His Glu Cys Asn Ser Pro Tyr Ile Val Gly
115 120 125

Phe Tyr Gly Ala Phe Tyr Ser Asp Gly Glu Ile Ser Ile Cys Met Glu
130 135 140

His Met Asp Gly Gly Ser Leu Asp Gln Val Leu Lys Lys Ala Gly Arg
145 150 155 160

Ile Pro Glu Gln Ile Leu Gly Lys Val Ser Ile Ala Val Ile Lys Gly
165 170 175

Leu Thr Tyr Leu Arg Glu Lys His Lys Ile Met His Arg Asp Val Lys
180 185 190

Pro Ser Asn Ile Leu Val Asn Ser Arg Gly Glu Ile Lys Leu Cys Asp
195 200 205

Phe Gly Val Ser Gly Gln Leu Ile Asp Ser Met Ala Asn Ser Phe Val
210 215 220

Gly Thr Arg Ser Tyr Met Ser Pro Glu Arg Leu Gln Gly Thr His Tyr
225 230 235 240

Ser Val Gln Ser Asp Ile Trp Ser Met Gly Leu Ser Leu Val Glu Met
245 250 255

Ala Val Gly Arg Tyr Pro Ile Pro Pro Pro Asp Ala Lys Glu Leu Glu
260 265 270

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Leu Leu Phe Gly Cys Gln Val Glu Gly Asp Ala Ala Glu Thr Pro Pro
275 280 285

Arg Pro Arg Thr Pro Gly Arg Pro Leu Ser Ser Tyr Gly Met Asp Ser
290 295 300

Arg Pro Pro Met Ala Ile Phe Glu Leu Leu Asp Tyr Ile Val Asn Glu
305 310 315 320

Pro Pro Pro Lys Leu Pro Ser Gly Val Phe Ser Leu Glu Phe Gln Asp
325 330 335

Phe Val Asn Lys Cys Leu Ile Lys Asn Pro Ala Glu Arg Ala Asp Leu
340 345 350

Lys Gln Leu Met Val His Ala Phe Ile Lys Arg Ser Asp Ala Glu Glu
355 360 365

Val Asp Phe Ala Gly Trp Leu Cys Ser Thr Ile Gly Leu Asn Gln Pro
370 375 380

Ser Thr Pro Thr His Ala Ala Ser Ile
385 390

<210> SEQ ID NO 67
<211> LENGTH: 2387
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 67

agtccctcac tgggacgtct gtgcgcggcg tctcggagcg ccggagcagc ggtggccgca 60

ctttctccaa gctggggctg tagctgagct gtgggtagtg cgcagggagc cgtccgagcc 120

cgaggaaccg gtgtgctgag gcgagagttc ccggccggcg agcgcgcgca gctggttctc 180

cgcgtgggtt gggcggaggg tcccaggagc gcggcgttga tcgagccgcc ccgactctgg 240

gcagagccga gggaggaagc gagaagcggc cgcgcgctcc ctgctgagtt gcaggctctt 300

tcccggctgc aagatgccca agaagaagcc gacgcccatc cagctgaacc cggcccccga 360

tggctcggcg gttaacggga ccagctcggc cgagaccaac ctggaggcct tgcagaagaa 420

gctggaggag ctggagcttg acgagcagca gcggaagcgg ctcgaggcct ttctgacgca 480

gaagcagaag gtgggggaac tgaaggatga tgactttgag aagatcagcg aactgggagc 540

tggcaacggt ggagtggtct tcaaggtctc ccacaagcca tctggcctgg ttatggctag 600

aaagctgatc cacctggaga tcaaacccgc aatccggaac cagatcatcc gggagctgca 660

ggtactgcac gagtgcaact ccccgtacat cgtgggcttc tacggggcct tctacagcga 720

cggcgagatc agcatctgca tggagcacat ggatggtggg tccttggatc aagttctgaa 780

gaaagctgga agaattcctg agcaaatttt aggaaaagtt agcattgctg tgataaaagg 840

cctgacctat cttcgggaga agcacaagat tatgcacaga gatgtcaagc catccaacat 900

tctagtgaac tcacgtgggg agatcaaact ctgtgatttt ggggtcagcg ggcagctaat 960

tgactctatg gccaactcct tcgtgggcac gagatcctac atgtcgcctg agagactcca 1020

ggggactcac tactctgtgc agtcggacat ctggagcatg gggctctctc tggtggagat 1080

ggcagttggg agatacccca ttcctcctcc tgatgccaag gagctggagc tactgtttgg 1140

atgccatgtg gaaggagacg cagccgaaac accacccagg ccaaggaccc ctgggaggcc 1200

tctcagctca tatggaatgg acagccgacc tcccatggca atttttgagt tgttggatta 1260

cattgtcaat gagcctcctc caaaactgcc cagtggagta ttcagtctgg agtttcagga 1320

-continued

ttttgtgaat aaatgcttaa taaagaaccc tgcagagaga gcagatctga agcagctcat 1380

ggtacatgct ttcatcaaaa gatctgacgc cgaggaggta gacttcgcag gctggctctg 1440

ctccaccatt gggcttaacc agcccagcac accaacccac gctgccagca tctgagcctt 1500

taggaagcag caaagaggaa ttctctgccc agtggcatgc catgttgctt tcaggcctct 1560

cccatgcttg tctatgttca gacgtgcatc tcatctgtga caaaggatga agaacacagc 1620

atgtgccaaa ttgtacttgt gtcatttta atatcattgt ctttatcact atggttactc 1680

ccctaagtgg attggctttg tgcttggggc tatttgtctg ttcatcaaac acatgccagg 1740

ctgaactaca gtgaaaccct agtgacctgg gtggtcgttc ttactgatgt ttgcactgct 1800

gttcatcgtg actcactagc tggctgcctg tattgtcagg attctcggac cttggtactt 1860

cactcttgct ggtgacctct cagtctgaga gggagccttg tgagaccctt cacaggcagt 1920

gcatgcatgg aaagcatgct ttgctgctac tgaaatgagc atcagaacgt gtacgtcatg 1980

gtatttttat tttttgcttt tggtatagaa ctcagcaatt cccatcaaaa aaacctaagc 2040

agagcccatc actgccatga tagctgggct tcagtctgtc tactgtggtg atttttagac 2100

ttctggttgt atttctatat ttatttttaa atatacagtg tgggatactt agtggtgtgt 2160

gtctctaagt ttggattagt gtttctaaat tggtggttat tttgaatgtc acaaatggat 2220

taaagcatca atgtatcaag agttctatct ttcttccagt ctaagtacca atgctattgt 2280

aaacaacgtg tatagtgcct acaaattgta tgaaacccct tttaaccact ttaatcaaga 2340

tgtttatcaa atctaatctc ttattctaat aaaaatacta tcaagtt 2387

<210> SEQ ID NO 68
<211> LENGTH: 393
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 68

Met Pro Lys Lys Lys Pro Thr Pro Ile Gln Leu Asn Pro Ala Pro Asp
1 5 10 15

Gly Ser Ala Val Asn Gly Thr Ser Ser Ala Glu Thr Asn Leu Glu Ala
20 25 30

Leu Gln Lys Lys Leu Glu Glu Leu Glu Leu Asp Glu Gln Gln Arg Lys
35 40 45

Arg Leu Glu Ala Phe Leu Thr Gln Lys Gln Lys Val Gly Glu Leu Lys
50 55 60

Asp Asp Asp Phe Glu Lys Ile Ser Glu Leu Gly Ala Gly Asn Gly Gly
65 70 75 80

Val Val Phe Lys Val Ser His Lys Pro Ser Gly Leu Val Met Ala Arg
85 90 95

Lys Leu Ile His Leu Glu Ile Lys Pro Ala Ile Arg Asn Gln Ile Ile
100 105 110

Arg Glu Leu Gln Val Leu His Glu Cys Asn Ser Pro Tyr Ile Val Gly
115 120 125

Phe Tyr Gly Ala Phe Tyr Ser Asp Gly Glu Ile Ser Ile Cys Met Glu
130 135 140

His Met Asp Gly Gly Ser Leu Asp Gln Val Leu Lys Lys Ala Gly Arg
145 150 155 160

Ile Pro Glu Gln Ile Leu Gly Lys Val Ser Ile Ala Val Ile Lys Gly

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               165                 170                 175

Leu Thr Tyr Leu Arg Glu Lys His Lys Ile Met His Arg Asp Val Lys
            180                 185                 190

Pro Ser Asn Ile Leu Val Asn Ser Arg Gly Glu Ile Lys Leu Cys Asp
        195                 200                 205

Phe Gly Val Ser Gly Gln Leu Ile Asp Ser Met Ala Asn Ser Phe Val
    210                 215                 220

Gly Thr Arg Ser Tyr Met Ser Pro Glu Arg Leu Gln Gly Thr His Tyr
225                 230                 235                 240

Ser Val Gln Ser Asp Ile Trp Ser Met Gly Leu Ser Leu Val Glu Met
                245                 250                 255

Ala Val Gly Arg Tyr Pro Ile Pro Pro Pro Asp Ala Lys Glu Leu Glu
            260                 265                 270

Leu Leu Phe Gly Cys His Val Glu Gly Asp Ala Ala Glu Thr Pro Pro
        275                 280                 285

Arg Pro Arg Thr Pro Gly Arg Pro Leu Ser Ser Tyr Gly Met Asp Ser
    290                 295                 300

Arg Pro Pro Met Ala Ile Phe Glu Leu Leu Asp Tyr Ile Val Asn Glu
305                 310                 315                 320

Pro Pro Pro Lys Leu Pro Ser Gly Val Phe Ser Leu Glu Phe Gln Asp
                325                 330                 335

Phe Val Asn Lys Cys Leu Ile Lys Asn Pro Ala Glu Arg Ala Asp Leu
            340                 345                 350

Lys Gln Leu Met Val His Ala Phe Ile Lys Arg Ser Asp Ala Glu Glu
        355                 360                 365

Val Asp Phe Ala Gly Trp Leu Cys Ser Thr Ile Gly Leu Asn Gln Pro
    370                 375                 380

Ser Thr Pro Thr His Ala Ala Ser Ile
385                 390


<210> SEQ ID NO 69
<211> LENGTH: 1182
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 69

atgccaaaga agaagcccac ccccatccag ctgaatcctg cccctgacgg ctcggcggtg     60

aatggtacca gctcggcgga gaccaacctg gaggccttgc agaagaagct ggaggagctg    120

gagcttgacg agcagcagcg gaagcgcctg gaggccttcc tcacccagaa gcagaaagtg    180

ggagagctga aggacgatga cttcgagaag atcagtgagc tgggagccgg caacggcggc    240

gtggtgttca aggtctccca caagcccagt ggcctggtga tggccagaaa gcttattcac    300

ctggagatca aacctgctat ccggaaccag atcataaggg agctgcaggt tctgcacgag    360

tgcaactccc cgtacatcgt gggcttctac ggggcattct acagcgatgg cgagatcagc    420

atctgcatgg agcacatgga cgggggttcc ttggatcaag tcctgaagaa agctggacgg    480

attcccgagc aaattttggg gaaagttagc attgctgtga tcaagggcct gacgtatctg    540

agggagaagc acaagatcat gcacagagat gtgaagccct ccaacatcct ggtcaactcc    600

cgcgggggaga tcaagctctg tgacttcggg gtcagtgggc agctcatcga ctccatggcc    660

aactccttcg tgggcaccag gtcttatatg tcgcccgaga gactccaggg gacacactac    720
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tctgtgcagt cggacatctg gagcatgggg ctgtccctgg tggagatggc ggtggggcgg 780

taccccatcc cgccccccga cgccaaggag ctggagctga tgtttgggtg ccaggtggag 840

ggcgatgcgg ccgagactcc gcccaggccc aggacccctg ggcggcccct cagctcgtat 900

ggaatggata gccggcctcc catggcgatt tttgagctgc tggattacat cgtcaatgag 960

cctcctccga aactccccag cgcagtcttc agcctggagt ttcaagattt tgtgaataaa 1020

tgcttaataa aaaaccccgc cgagagagca gacttgaagc agctcatggt tcatgctttt 1080

atcaagaggt ctgatgccga ggaggtggat tttgctggtt ggctgtgctc caccatcggc 1140

cttaaccagc ccagcacgcc gacgcacgcg gccggtgtgt ga 1182

<210> SEQ ID NO 70
<211> LENGTH: 393
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 70

Met Pro Lys Lys Lys Pro Thr Pro Ile Gln Leu Asn Pro Ala Pro Asp
1 5 10 15

Gly Ser Ala Val Asn Gly Thr Ser Ser Ala Glu Thr Asn Leu Glu Ala
20 25 30

Leu Gln Lys Lys Leu Glu Glu Leu Glu Leu Asp Glu Gln Gln Arg Lys
35 40 45

Arg Leu Glu Ala Phe Leu Thr Gln Lys Gln Lys Val Gly Glu Leu Lys
50 55 60

Asp Asp Asp Phe Glu Lys Ile Ser Glu Leu Gly Ala Gly Asn Gly Gly
65 70 75 80

Val Val Phe Lys Val Ser His Lys Pro Ser Gly Leu Val Met Ala Arg
85 90 95

Lys Leu Ile His Leu Glu Ile Lys Pro Ala Ile Arg Asn Gln Ile Ile
100 105 110

Arg Glu Leu Gln Val Leu His Glu Cys Asn Ser Pro Tyr Ile Val Gly
115 120 125

Phe Tyr Gly Ala Phe Tyr Ser Asp Gly Glu Ile Ser Ile Cys Met Glu
130 135 140

His Met Asp Gly Gly Ser Leu Asp Gln Val Leu Lys Lys Ala Gly Arg
145 150 155 160

Ile Pro Glu Gln Ile Leu Gly Lys Val Ser Ile Ala Val Ile Lys Gly
165 170 175

Leu Thr Tyr Leu Arg Glu Lys His Lys Ile Met His Arg Asp Val Lys
180 185 190

Pro Ser Asn Ile Leu Val Asn Ser Arg Gly Glu Ile Lys Leu Cys Asp
195 200 205

Phe Gly Val Ser Gly Gln Leu Ile Asp Ser Met Ala Asn Ser Phe Val
210 215 220

Gly Thr Arg Ser Tyr Met Ser Pro Glu Arg Leu Gln Gly Thr His Tyr
225 230 235 240

Ser Val Gln Ser Asp Ile Trp Ser Met Gly Leu Ser Leu Val Glu Met
245 250 255

Ala Val Gly Arg Tyr Pro Ile Pro Pro Pro Asp Ala Lys Glu Leu Glu
260 265 270

Leu Met Phe Gly Cys Gln Val Glu Gly Asp Ala Ala Glu Thr Pro Pro

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        275                 280                 285

Arg Pro Arg Thr Pro Gly Arg Pro Leu Ser Ser Tyr Gly Met Asp Ser
    290                 295                 300

Arg Pro Pro Met Ala Ile Phe Glu Leu Leu Asp Tyr Ile Val Asn Glu
305                 310                 315                 320

Pro Pro Pro Lys Leu Pro Ser Ala Val Phe Ser Leu Glu Phe Gln Asp
                325                 330                 335

Phe Val Asn Lys Cys Leu Ile Lys Asn Pro Ala Glu Arg Ala Asp Leu
            340                 345                 350

Lys Gln Leu Met Val His Ala Phe Ile Lys Arg Ser Asp Ala Glu Glu
        355                 360                 365

Val Asp Phe Ala Gly Trp Leu Cys Ser Thr Ile Gly Leu Asn Gln Pro
    370                 375                 380

Ser Thr Pro Thr His Ala Ala Gly Val
385                 390


<210> SEQ ID NO 71
<211> LENGTH: 1872
<212> TYPE: DNA
<213> ORGANISM: Cavia porcellus

<400> SEQUENCE: 71

cgtgtcttcg tcgggaccgc cctcctcctt gagtcctccc cccaccggga cggccgagtg     60

gagaggccgg acgaaggcgg cggccccggc ggcggctttt cctcggcttc gctgtgcagc    120

gtgcgcggcg aggttgaccg cccgcgagcg cccgtgactg agggaacagg gagagagctc    180

gggcggccga gcgcgcagcc ctccgtgggc attgccgcct ggacctcccg gaaggcaccc    240

cgggccgcgg ccgccacccg tcccgccctc gttcggagct gagacgccgt cgccgcgcaa    300

gatgcccaag aagaagccga cgcccatcca gctgaacccg gcccccgacg gctcggcggt    360

gaacgggacc agctcggccg agaccaacct agaggctttg cagaagaagc tggaggagct    420

ggagctggat gagcagcagc ggaagcgcct cgaagctttc ctgacacaga agcagaaggt    480

gggcgagctg aaggacgatg actttgagaa gatcagtgag ctgggtgccg gcaatggcgg    540

tgtggtgttc aaggtctccc acaagccatc tggcctggtc atggcccgaa agcttatcca    600

cctggagatc aagccagcca tccgcaatca gatcatccgt gagctgcagg ttctgcacga    660

gtgcaactcg ccctacattg tgggcttcta tggggccttc tacagtgatg gcgagatcag    720

catctgcatg gagcacatgg atggaggttc cttggatcaa gtcctgaaga aagctggaag    780

aattcctgag caaattttag gaaaagttag cattgctgtg atcaaaggcc tgacatacct    840

gagggagaag cacaagatta tgcacagaga tgtcaagccc tccaacatcc tggtcaactc    900

ccgcggggag atcaagctct gtgactttgg ggtcagcggg cagctcatcg attccatggc    960

caactccttc gtgggcaccc ggtcctacat gtcgccagag agactgcagg gcacacacta   1020

ctcagtgcag tcggacatct ggagcatggg actgtcactg gtggagatgg cggttgggag   1080

gtaccccatc ccccctccag atgccaagga gctggagctg gtgttcgggt gccaggtgga   1140

aggagatgca gctgagatgc cgcccaggcc caggaccccc ggaagacccc tgagctcata   1200

tggaatggac agccggcctc ccatggcgat tttcgagctg ttggattaca tagtcaacga   1260

gccacctccc aaactgccca gtggagtctt cagtctggaa ttccaggact ttgtaaataa   1320

atgcttaata aagaaccctg cggagagagc agacttgaag cagctcatgg ttcatgcctt   1380
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catcaagcgc tctgatgctg aggaggtgga cttcgcaggt tggctctgtg ccaccatcgg 1440

ccttaaccag cccagtaccc cgacccacgt ggccagcatc tgagctgcgg cccggcccag 1500

acgtgctctg ccagcagccg ctatgctctg gcctctccct cgcttctctt cagacgtgcg 1560

tttcacctcc gaccagggtg cagacacagc atgtgccaag ctgtatttgt gttccttttc 1620

agtctttatt gccaccgtgt cacccgagtg gatttgcttt gtgcttaggg ctgtttgtgc 1680

tgatgatcac acacacgctg agctgaacag tgacacttgg tgatgtggtt gtcactgttc 1740

tcactccatg tggctggcct gttgcctcca gtgtctccag acttggggat gtctggtggc 1800

acttcccctg ccagggcatc tcctcagcag agagggaggc ctctgggccc ttgtccttgg 1860

cagtgcaagt ga 1872

<210> SEQ ID NO 72
<211> LENGTH: 393
<212> TYPE: PRT
<213> ORGANISM: Cavia porcellus

<400> SEQUENCE: 72

Met Pro Lys Lys Lys Pro Thr Pro Ile Gln Leu Asn Pro Ala Pro Asp
1 5 10 15

Gly Ser Ala Val Asn Gly Thr Ser Ser Ala Glu Thr Asn Leu Glu Ala
20 25 30

Leu Gln Lys Lys Leu Glu Glu Leu Glu Leu Asp Glu Gln Gln Arg Lys
35 40 45

Arg Leu Glu Ala Phe Leu Thr Gln Lys Gln Lys Val Gly Glu Leu Lys
50 55 60

Asp Asp Asp Phe Glu Lys Ile Ser Glu Leu Gly Ala Gly Asn Gly Gly
65 70 75 80

Val Val Phe Lys Val Ser His Lys Pro Ser Gly Leu Val Met Ala Arg
85 90 95

Lys Leu Ile His Leu Glu Ile Lys Pro Ala Ile Arg Asn Gln Ile Ile
100 105 110

Arg Glu Leu Gln Val Leu His Glu Cys Asn Ser Pro Tyr Ile Val Gly
115 120 125

Phe Tyr Gly Ala Phe Tyr Ser Asp Gly Glu Ile Ser Ile Cys Met Glu
130 135 140

His Met Asp Gly Gly Ser Leu Asp Gln Val Leu Lys Lys Ala Gly Arg
145 150 155 160

Ile Pro Glu Gln Ile Leu Gly Lys Val Ser Ile Ala Val Ile Lys Gly
165 170 175

Leu Thr Tyr Leu Arg Glu Lys His Lys Ile Met His Arg Asp Val Lys
180 185 190

Pro Ser Asn Ile Leu Val Asn Ser Arg Gly Glu Ile Lys Leu Cys Asp
195 200 205

Phe Gly Val Ser Gly Gln Leu Ile Asp Ser Met Ala Asn Ser Phe Val
210 215 220

Gly Thr Arg Ser Tyr Met Ser Pro Glu Arg Leu Gln Gly Thr His Tyr
225 230 235 240

Ser Val Gln Ser Asp Ile Trp Ser Met Gly Leu Ser Leu Val Glu Met
245 250 255

Ala Val Gly Arg Tyr Pro Ile Pro Pro Pro Asp Ala Lys Glu Leu Glu

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            260                 265                 270

Leu Val Phe Gly Cys Gln Val Glu Gly Asp Ala Ala Glu Met Pro Pro
        275                 280                 285

Arg Pro Arg Thr Pro Gly Arg Pro Leu Ser Ser Tyr Gly Met Asp Ser
    290                 295                 300

Arg Pro Pro Met Ala Ile Phe Glu Leu Leu Asp Tyr Ile Val Asn Glu
305                 310                 315                 320

Pro Pro Pro Lys Leu Pro Ser Gly Val Phe Ser Leu Glu Phe Gln Asp
                325                 330                 335

Phe Val Asn Lys Cys Leu Ile Lys Asn Pro Ala Glu Arg Ala Asp Leu
            340                 345                 350

Lys Gln Leu Met Val His Ala Phe Ile Lys Arg Ser Asp Ala Glu Glu
        355                 360                 365

Val Asp Phe Ala Gly Trp Leu Cys Ala Thr Ile Gly Leu Asn Gln Pro
    370                 375                 380

Ser Thr Pro Thr His Val Ala Ser Ile
385                 390


<210> SEQ ID NO 73
<211> LENGTH: 1257
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 73

ggagagcgag acacgggccg ctctccgctc ggagccggac gcgccttccc gcgtccaaaa     60

tgcccaagaa gaagccgacg cccatccagc tgaacccggc ccccgacggc tcggcggtga    120

acgggaccag ctcggcggag accaacctgg aggccttgca gaagaagctg gaggagctgg    180

agcttgatga gcagcagcgg aagcgccttg aggcctttct cacccagaag cagaaggtcg    240

gggaactgaa ggatgacgac ttcgagaaga tcagtgagct gggtgctggc aacggtggcg    300

tggtgttcaa ggtctcccac aagccgtccg gcctagtcat ggccagaaag ctaattcacc    360

tggagatcaa acctgcaatc cggaaccaga tcataaggga gctacaggtt ctacatgagt    420

gcaactcccc gtacatcgtg ggcttctatg gtgcattcta cagcgatggc gagatcagta    480

tctgcatgga gcacatggat gggggttcct tggatcaagt cctgaagaaa gctggaagaa    540

ttcctgaaca aattctagga aaagttagca tcgctgtaat aaaaggtctg acatacctga    600

gagagaagca caagattatg cacagagatg tcaagccttc caacatcctc gtgaactccc    660

gtggggagat caagctctgt gactttgggg tcagcgggca gctcattgac tccatggcca    720

actccttcgt gggcacaagg tcctacatgt cgccagaaag actccagggg actcattact    780

ccgtgcagtc ggacatctgg agcatggggc tctctctggt ggagatggca gttgggaggt    840

atcccatccc tcctccggat gccaaggagc tggagctgat gtttgggtgc caagtggagg    900

gagacgtggc tgagacccca cccagaccaa ggaccccggg aagacccctt agctcttatg    960

gaatggacag ccgaccgccc atggcaattt ttgagctgtt ggattacata gtcaacgagc   1020

cccctccaaa actgcccagt ggagtattca gtctggaatt tcaagatttt gtgaataaat   1080

gcttaataaa aaacccagca gagagagcag atctgaagca actcatggtt catgccttca   1140

tcaagagatc tgacggtgaa gaagtggatt ttgcaggttg gctctgctcc ccccattggc   1200

cttaaccagc ccagcacgcc gacccacgca gctggcgtct aactcgagtc tagagat      1257
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<210> SEQ ID NO 74
<211> LENGTH: 381
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 74

Met Pro Lys Lys Lys Pro Thr Pro Ile Gln Leu Asn Pro Ala Pro Asp
1 5 10 15

Gly Ser Ala Val Asn Gly Thr Ser Ser Ala Glu Thr Asn Leu Glu Ala
20 25 30

Leu Gln Lys Lys Leu Glu Glu Leu Glu Leu Asp Glu Gln Gln Arg Lys
35 40 45

Arg Leu Glu Ala Phe Leu Thr Gln Lys Gln Lys Val Gly Glu Leu Lys
50 55 60

Asp Asp Asp Phe Glu Lys Ile Ser Glu Leu Gly Ala Gly Asn Gly Gly
65 70 75 80

Val Val Phe Lys Val Ser His Lys Pro Ser Gly Leu Val Met Ala Arg
85 90 95

Lys Leu Ile His Leu Glu Ile Lys Pro Ala Ile Arg Asn Gln Ile Ile
100 105 110

Arg Glu Leu Gln Val Leu His Glu Cys Asn Ser Pro Tyr Ile Val Gly
115 120 125

Phe Tyr Gly Ala Phe Tyr Ser Asp Gly Glu Ile Ser Ile Cys Met Glu
130 135 140

His Met Asp Gly Gly Ser Leu Asp Gln Val Leu Lys Lys Ala Gly Arg
145 150 155 160

Ile Pro Glu Gln Ile Leu Gly Lys Val Ser Ile Ala Val Ile Lys Gly
165 170 175

Leu Thr Tyr Leu Arg Glu Lys His Lys Ile Met His Arg Asp Val Lys
180 185 190

Pro Ser Asn Ile Leu Val Asn Ser Arg Gly Glu Ile Lys Leu Cys Asp
195 200 205

Phe Gly Val Ser Gly Gln Leu Ile Asp Ser Met Ala Asn Ser Phe Val
210 215 220

Gly Thr Arg Ser Tyr Met Ser Pro Glu Arg Leu Gln Gly Thr His Tyr
225 230 235 240

Ser Val Gln Ser Asp Ile Trp Ser Met Gly Leu Ser Leu Val Glu Met
245 250 255

Ala Val Gly Arg Tyr Pro Ile Pro Pro Pro Asp Ala Lys Glu Leu Glu
260 265 270

Leu Met Phe Gly Cys Gln Val Glu Gly Asp Val Ala Glu Thr Pro Pro
275 280 285

Arg Pro Arg Thr Pro Gly Arg Pro Leu Ser Ser Tyr Gly Met Asp Ser
290 295 300

Arg Pro Pro Met Ala Ile Phe Glu Leu Leu Asp Tyr Ile Val Asn Glu
305 310 315 320

Pro Pro Pro Lys Leu Pro Ser Gly Val Phe Ser Leu Glu Phe Gln Asp
325 330 335

Phe Val Asn Lys Cys Leu Ile Lys Asn Pro Ala Glu Arg Ala Asp Leu
340 345 350

Lys Gln Leu Met Val His Ala Phe Ile Lys Arg Ser Asp Gly Glu Glu
355 360 365

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Val Asp Phe Ala Gly Trp Leu Cys Ser Pro His Trp Pro
370 375 380

<210> SEQ ID NO 75
<211> LENGTH: 2095
<212> TYPE: DNA
<213> ORGANISM: Felis catus

<400> SEQUENCE: 75

agccggcaag gagttgagcg tgcggggtgc ataggcgcgg gtcgtgggag atgaagctgg 60

agaggaccaa cctggaggcc ttgcagaaga agctggagga gctggagctc gatgagcagc 120

aacggaagcg cctggaggcc tttcttaccc agaagcagaa ggtcggggaa ttgaaggatg 180

acgacttcga gaagatcagc gagctgggcg ctggcaacgg tggtgtggtg ttcaaggtct 240

cccataagcc gtctggcctg gtcatggcca gaaagctaat tcacctggag atcaaacctg 300

caatccggaa ccagatcata agggagctgc aggttctaca tgagtgcaac tccccataca 360

tcgtgggctt ctatggcgcg ttctacagcg acggcgagat cagtatctgt atggagcaca 420

tggatggggg ttccttggat caagtcctga agaaagctgg aagaattcct gaacaaattt 480

taggaaaagt tagcattgct gtaataaaag gtctgacata cctgagggag aagcacaaga 540

ttatgcacag agatgtcaag ccttccaaca tcctagtgaa ctctcgtggg gagatcaagc 600

tctgtgactt tggggtcagc gggcagctca tcgactccat ggccaactcc ttcgtgggca 660

caaggtccta catgtcgcca gaaagactcc aggggactca ttactccgtg cagtcggaca 720

tctggagcat ggggctatct ctggttgaga tggcagtcgg gaggtatccc atccctcctc 780

ccgatgccaa ggagctggag ctgatgtttg ggtgccaagt ggagggagat gcggctgaga 840

cgccacccag gccgaggacc cccggaaggc ccctcagctc gtatggaatg gacagccgac 900

ctcccatggc aatttttgag ttgttggatt acatagtcaa cgagcctcct ccaaagctgc 960

ccagtggagt attcagtctg gaatttcaag attttgtgaa taaatgcctc ataaaaaacc 1020

cagcagagag agcagatctg aaacaactca tggttcatgc ctttatcaag agatctgatg 1080

gtgaggaagt ggattttgca ggttggctct gctccaccat cggccttaac cagcccagca 1140

caccgaccca cgcggccggc gtctaagtat ctgggaagca gcaaagagcg agtcccctgc 1200

ccagtggtgt gccattgtcg ctttcaggcc tctttgccat gcctgtctcc gttcagacgt 1260

gcatttcgcc tacgacaaag gatgaagaac acagcatgtg ccaaaattct atttgtgtct 1320

tttttaatat tactgtcatt tattctgtta tttccctaag tggattggct ttgtgcttgg 1380

ggctattttt gtgtatgttg atccaaacat gcgcaacgtt cagttacagt gaaaccttgg 1440

tgactgtggg tagtcattct tactgaaaat tgcactgctc ttcccccacc gtgactggct 1500

agctgcctgt agttttggga ttcttttgac acttggtggt actgcattct tgccgggcgc 1560

accttccttc tgttggggta ggagccttgt aagatccttc acaggcactg catgtgaagc 1620

atgctttgct gctatgaaaa agaacatcag aaagtataga tcttgttatt ttattatatt 1680

tttgcttttg gtgtagaatg aagcaatttc tgtcaaaatc tagccagagc ccttcactgc 1740

cacgatagct ggggcttcac cagtctgtct actgtgatga tttgtagact tctggttgta 1800

tttctatatt tattttaaaa tatattatgt gggatattta gtggtatgtg tctctttaag 1860

tttgaattag tgtttctaaa atgatggtta ctttgaatgt tacaaatgga tcaaggcatt 1920

-continued

aaaatgtatg agatttatct ttccccaaat ccaagtaccg atgctattgt aaacaacagt 1980

gtgtatagtg cctaagaatt gtatgaaaat ccttttaacc atttcaaccc agatgtttaa 2040

caaatctaat ctcttattct aataaatata ctatcaagtt aaaaggatga aaaaa 2095

<210> SEQ ID NO 76
<211> LENGTH: 371
<212> TYPE: PRT
<213> ORGANISM: Felis catus

<400> SEQUENCE: 76

Met Lys Leu Glu Arg Thr Asn Leu Glu Ala Leu Gln Lys Lys Leu Glu
1 5 10 15

Glu Leu Glu Leu Asp Glu Gln Gln Arg Lys Arg Leu Glu Ala Phe Leu
20 25 30

Thr Gln Lys Gln Lys Val Gly Glu Leu Lys Asp Asp Asp Phe Glu Lys
35 40 45

Ile Ser Glu Leu Gly Ala Gly Asn Gly Gly Val Val Phe Lys Val Ser
50 55 60

His Lys Pro Ser Gly Leu Val Met Ala Arg Lys Leu Ile His Leu Glu
65 70 75 80

Ile Lys Pro Ala Ile Arg Asn Gln Ile Ile Arg Glu Leu Gln Val Leu
85 90 95

His Glu Cys Asn Ser Pro Tyr Ile Val Gly Phe Tyr Gly Ala Phe Tyr
100 105 110

Ser Asp Gly Glu Ile Ser Ile Cys Met Glu His Met Asp Gly Gly Ser
115 120 125

Leu Asp Gln Val Leu Lys Lys Ala Gly Arg Ile Pro Glu Gln Ile Leu
130 135 140

Gly Lys Val Ser Ile Ala Val Ile Lys Gly Leu Thr Tyr Leu Arg Glu
145 150 155 160

Lys His Lys Ile Met His Arg Asp Val Lys Pro Ser Asn Ile Leu Val
165 170 175

Asn Ser Arg Gly Glu Ile Lys Leu Cys Asp Phe Gly Val Ser Gly Gln
180 185 190

Leu Ile Asp Ser Met Ala Asn Ser Phe Val Gly Thr Arg Ser Tyr Met
195 200 205

Ser Pro Glu Arg Leu Gln Gly Thr His Tyr Ser Val Gln Ser Asp Ile
210 215 220

Trp Ser Met Gly Leu Ser Leu Val Glu Met Ala Val Gly Arg Tyr Pro
225 230 235 240

Ile Pro Pro Pro Asp Ala Lys Glu Leu Glu Leu Met Phe Gly Cys Gln
245 250 255

Val Glu Gly Asp Ala Ala Glu Thr Pro Pro Arg Pro Arg Thr Pro Gly
260 265 270

Arg Pro Leu Ser Ser Tyr Gly Met Asp Ser Arg Pro Pro Met Ala Ile
275 280 285

Phe Glu Leu Leu Asp Tyr Ile Val Asn Glu Pro Pro Pro Lys Leu Pro
290 295 300

Ser Gly Val Phe Ser Leu Glu Phe Gln Asp Phe Val Asn Lys Cys Leu
305 310 315 320

Ile Lys Asn Pro Ala Glu Arg Ala Asp Leu Lys Gln Leu Met Val His
325 330 335

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Ala Phe Ile Lys Arg Ser Asp Gly Glu Glu Val Asp Phe Ala Gly Trp
            340                 345                 350

Leu Cys Ser Thr Ile Gly Leu Asn Gln Pro Ser Thr Pro Thr His Ala
        355                 360                 365

Ala Gly Val
    370


<210> SEQ ID NO 77
<211> LENGTH: 2405
<212> TYPE: DNA
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 77

ccggttgact gagggagagt gggagggaat cccgggctgc cgagctgcgc cggcggggaa     60

gcccttcggt tccctgtgca ctgagcaagt gggccggggg gttcccccag accgccactg    120

gccctttggc cctgacggga ccgcgcaggg cgcgcccccc gaaggcagcc ttcgggcttg    180

cggcccagac ttggccccgc gaggccggcg cggggcagct cagagggagg aagctagagg    240

ggccgccctc agagttggga gcgcctttcc tgggtccaaa atgcccaaga agaagccgac    300

gcccatccag ctgaacccgg ccccggacgg ctccgcggtt aacgggacca gctcggcgga    360

gaccaacctg gaggccttgc agaagaagct ggaggagctg gagctcgatg aacagcagcg    420

gaagcgcctc gaggcctttc tgacccagaa gcagaaggtg ggggaactga aggatgatga    480

ctttgagaag atcagtgagc tgggtgccgg caatggaggt gtggtgttca aggtctccca    540

caagccgtcc ggacttgtta tggccagaaa gctaattcac ctggagatca aacctgccat    600

ccggaaccag atcataaggg agctgcaggt tctccatgag tgcaactcgc cttatatcgt    660

gggcttctac ggggcgttct acagcgacgg cgagatcagc atctgcatgg agcacatgga    720

tgggggttcc ttggatcaag ttctgaagaa agctggaaga attcctgaac aaattttagg    780

aaaagttagc attgctgtaa taaaaggcct gacatacctg agggagaagc acaagattat    840

gcacagagat gtcaagccgt ccaacatcct agtgaacagc cgtggagaga tcaagctctg    900

tgactttggg gtcagcgggc agctcatcga ctccatggcc aactccttcg tgggcaccag    960

gtcctacatg tcgccagagc gactccaggg gacccattac tccgtgcagt cggacatctg   1020

gagcatgggg ctctctctgg ttgagatggc tgtcgggagg tatcccatcc ctcctccaga   1080

tgccaaggag ctggagctga tgtttgggtg ccaggtggag ggagatgcgg ctgagacccc   1140

gcccaggcca aggacccccg ggaggcccct cagctcttat ggaatggaca gccgacctcc   1200

aatggcaatt tttgagttgt tggattacat agtcaatgag cctcctccaa aactgcccag   1260

tggagtattc agtctggaat ttcaagattt tgtgaataaa tgcttaataa aaaaccccgc   1320

agagagagca gatttgaagc aactcatggt tcatgctttt atcaagagat ctgatgctga   1380

ggaagtggat tttgcaggtt ggctctgctc caccatcggc cttaaccaac ccagcacacc   1440

cacccatgcg gctggcgtct aagtggttgg gaagcagcag tccctgccca agggcatgca   1500

ctgttgcttc cgggcagcct tcccatgcct gtctctgttc agacgtgcat ttcacctatg   1560

acaaaggatg aagaacacag catgtgccaa aattctattt gtgtcatttt caatattatc   1620

atctttactc ttattactat tgttattccc ctaagtggat tggctttgtg cttggggcta   1680

tttttgtgta tattgatgat gaagacatgt gcaatgtaga attacagtga aactctggtg   1740
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actgtgggta gtcattctta ctgaaaactg cactgctttc ccacaccatg aactggctgg 1800

tcgcctctat tttcgggatt ctttgacact tggtggtact tcattcttgc caggcatacc 1860

ttctaactga gtaggaagga gccttgtaag atccttcaca ggcagtgcat gtgaagcatg 1920

ctttgctgct ataaaaatga gcatcagaaa gtgtgtatca tgttatttta ttatgttctt 1980

gcttttggtg tagaattcag caaattttca tcaaaatcta gccagagccc ttcactgcca 2040

tgatagctgg ggcttcacca gtctgtctac tgtgatgatt tgtagacttc tggttgtatt 2100

tctgtattta tttttaaatc taccgtgtgg atatttagtg ctatgtctct ttaagtttgg 2160

attagtgttt ctaaaatggt ggagttgctc tgaatgttac aaatggatca aggcattaaa 2220

atgaatgaga tctacctttc accaagtact gatgctattg taaacaacag tgtgtatagt 2280

gcctaacaac tgtatgaaaa tccttttacc attttaatcc agatgtttaa caagcctaat 2340

ctcttactct aataaatata ctatcaaatt caaaggaaaa aaaaaaaaaa aaaaaaaaaa 2400

aaaaa 2405

<210> SEQ ID NO 78
<211> LENGTH: 393
<212> TYPE: PRT
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 78

Met Pro Lys Lys Lys Pro Thr Pro Ile Gln Leu Asn Pro Ala Pro Asp
1 5 10 15

Gly Ser Ala Val Asn Gly Thr Ser Ser Ala Glu Thr Asn Leu Glu Ala
20 25 30

Leu Gln Lys Lys Leu Glu Glu Leu Glu Leu Asp Glu Gln Gln Arg Lys
35 40 45

Arg Leu Glu Ala Phe Leu Thr Gln Lys Gln Lys Val Gly Glu Leu Lys
50 55 60

Asp Asp Asp Phe Glu Lys Ile Ser Glu Leu Gly Ala Gly Asn Gly Gly
65 70 75 80

Val Val Phe Lys Val Ser His Lys Pro Ser Gly Leu Val Met Ala Arg
85 90 95

Lys Leu Ile His Leu Glu Ile Lys Pro Ala Ile Arg Asn Gln Ile Ile
100 105 110

Arg Glu Leu Gln Val Leu His Glu Cys Asn Ser Pro Tyr Ile Val Gly
115 120 125

Phe Tyr Gly Ala Phe Tyr Ser Asp Gly Glu Ile Ser Ile Cys Met Glu
130 135 140

His Met Asp Gly Gly Ser Leu Asp Gln Val Leu Lys Lys Ala Gly Arg
145 150 155 160

Ile Pro Glu Gln Ile Leu Gly Lys Val Ser Ile Ala Val Ile Lys Gly
165 170 175

Leu Thr Tyr Leu Arg Glu Lys His Lys Ile Met His Arg Asp Val Lys
180 185 190

Pro Ser Asn Ile Leu Val Asn Ser Arg Gly Glu Ile Lys Leu Cys Asp
195 200 205

Phe Gly Val Ser Gly Gln Leu Ile Asp Ser Met Ala Asn Ser Phe Val
210 215 220

Gly Thr Arg Ser Tyr Met Ser Pro Glu Arg Leu Gln Gly Thr His Tyr
225 230 235 240

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Ser Val Gln Ser Asp Ile Trp Ser Met Gly Leu Ser Leu Val Glu Met
                245                 250                 255

Ala Val Gly Arg Tyr Pro Ile Pro Pro Pro Asp Ala Lys Glu Leu Glu
            260                 265                 270

Leu Met Phe Gly Cys Gln Val Glu Gly Asp Ala Ala Glu Thr Pro Pro
        275                 280                 285

Arg Pro Arg Thr Pro Gly Arg Pro Leu Ser Ser Tyr Gly Met Asp Ser
    290                 295                 300

Arg Pro Pro Met Ala Ile Phe Glu Leu Leu Asp Tyr Ile Val Asn Glu
305                 310                 315                 320

Pro Pro Pro Lys Leu Pro Ser Gly Val Phe Ser Leu Glu Phe Gln Asp
                325                 330                 335

Phe Val Asn Lys Cys Leu Ile Lys Asn Pro Ala Glu Arg Ala Asp Leu
            340                 345                 350

Lys Gln Leu Met Val His Ala Phe Ile Lys Arg Ser Asp Ala Glu Glu
        355                 360                 365

Val Asp Phe Ala Gly Trp Leu Cys Ser Thr Ile Gly Leu Asn Gln Pro
    370                 375                 380

Ser Thr Pro Thr His Ala Ala Gly Val
385                 390


<210> SEQ ID NO 79
<211> LENGTH: 2146
<212> TYPE: DNA
<213> ORGANISM: Equus caballus

<400> SEQUENCE: 79

caagtgggaa agcttgggat gcgtggagga gccagctact agtttagtgt gctgggtgcg     60

tcggtgcagg tcgcaggaga tgaagccgga gaggaccaac ctggaggcct tgcagaagaa    120

gctggaggag ctggagctcg atgaacagca gcgaaagcgc cttgaggcct ttcttactca    180

gaagcagaag gttggggaac tgaaggatga tgactttgag aagatcagtg agctgggtgc    240

tggcaatggt ggtgtggtat tcaaggttgc ccacaaaccg tctggtttgg tcatggccag    300

aaagctaatt cacctggaga tcaagcctgc aatccggaac cagatcataa gggagctgca    360

ggttctacat gagtgcaact ccccatatat tgtgggcttc tatggcgcat tctacagcga    420

tggtgagatc agcatctgca tggagcacat ggatgggggt tccttggatc aagtcctaaa    480

gaaagctgga agaattcctg agcaaatttt aggaaaagtt agcattgctg taataaaagg    540

cctgacgtat ctgagggaga agcacaagat tatgcacaga gatgtcaagc cctccaacat    600

cctagtgaac tcccgtgggg agatcaagct gtgtgatttt ggggtcagcg ggcagctcat    660

cgactccatg gccaactcct tcgtgggcac aaggtcttac atgtcgccgg aaagactcca    720

ggggactcat tattcagtgc agtcggacat ctggagcatg gggctctctc tggttgagat    780

ggcggtcggg aggtatccca tccctcctcc agatgccaag gagctggagc tgatgtttgg    840

gtgccaagtg gagggagatg cggctgagac tccgcctagg ccaaggaccc ctggaagacc    900

cctcagctct tatggaatgg acagccgacc tcctatggca atttttgagt tactggatta    960

catagtcaac gagcctcctc ccaagctgcc cagtggagta ttcagtctgg aatttcagga   1020

ttttgtgaat aaatgcttaa tcaaaaaccc tgcagagaga gcagatttga agcaactcat   1080

ggttcacgct tttatcaaga gatctgatgc cgaggaagtg gattttgcag gttggctctg   1140
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ctccaccatt ggccttaacc agcccagcac accaacccac gcggctggcg tctaagcgtt   1200

tgggaagcag caaaaagcga gccccctgcc gcgtggtgtg ccatgttgct ttcgggcctc   1260

cttcccatgc ctgtctgttc acacgtgcat ttcacctgtg acaaaggatg aagaacacag   1320

catgtgccaa aattctattt gtgtcatttt taatagtact gtctttattc ttattactat   1380

tgttattccc ctaagtggat tggctttgtg cttgggacta ttttgtgtat gttgatgatc   1440

aaaacatgcg caatgttgaa ttaccgtgaa actggtgact gtgggtagtc cttcttattg   1500

aaaattgcac tgctcttccc tccctgtcac tggctggctg cctgtatttc tggggttctt   1560

tgacacttgg tggtacttca ttcttgcagg gcatacctcc tattcgagta ggaaggagcc   1620

tttaagatcc ttcacaggca gtgcatgtga agcatgcttt gctgctatga aaatgagcat   1680

cagaaagtgt atatcatgtt attttattat tattatgttt ttgcttttgg tgtagaattc   1740

agcaatttcc atcaagatct agccagagcc cttcactgcc atgatagctg gggcttcacc   1800

agtctgccta ctgtgatgat ttgtagactt ctggttgtat ttctatattt atttttaaat   1860

atactgtgtg ggatatttag tggtatatgt ctctctaagt ttggagtggt gtttctaaaa   1920

tggagttact ttgaatgtta tagatggatc aaggcataaa atgtatgaga tttatttttc   1980

cccaaatcca aatactgatg ctattgtaaa caacaaacag tgtgtatagt gcctaaaaat   2040

tgtatgaaag tccttttaac cattttaatc cagatgttta acaaatctaa tctcttattc   2100

taataaatat actatcaagt taaacggaca aaagatttct actttc                  2146
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<210> SEQ ID NO 80
<211> LENGTH: 371
<212> TYPE: PRT
<213> ORGANISM: Equus caballus

<400> SEQUENCE: 80

```
Met Lys Pro Glu Arg Thr Asn Leu Glu Ala Leu Gln Lys Lys Leu Glu
1               5                   10                  15

Glu Leu Glu Leu Asp Glu Gln Gln Arg Lys Arg Leu Glu Ala Phe Leu
            20                  25                  30

Thr Gln Lys Gln Lys Val Gly Glu Leu Lys Asp Asp Asp Phe Glu Lys
        35                  40                  45

Ile Ser Glu Leu Gly Ala Gly Asn Gly Gly Val Val Phe Lys Val Ala
    50                  55                  60

His Lys Pro Ser Gly Leu Val Met Ala Arg Lys Leu Ile His Leu Glu
65                  70                  75                  80

Ile Lys Pro Ala Ile Arg Asn Gln Ile Ile Arg Glu Leu Gln Val Leu
                85                  90                  95

His Glu Cys Asn Ser Pro Tyr Ile Val Gly Phe Tyr Gly Ala Phe Tyr
            100                 105                 110

Ser Asp Gly Glu Ile Ser Ile Cys Met Glu His Met Asp Gly Gly Ser
        115                 120                 125

Leu Asp Gln Val Leu Lys Lys Ala Gly Arg Ile Pro Glu Gln Ile Leu
    130                 135                 140

Gly Lys Val Ser Ile Ala Val Ile Lys Gly Leu Thr Tyr Leu Arg Glu
145                 150                 155                 160

Lys His Lys Ile Met His Arg Asp Val Lys Pro Ser Asn Ile Leu Val
                165                 170                 175
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Asn Ser Arg Gly Glu Ile Lys Leu Cys Asp Phe Gly Val Ser Gly Gln
            180                 185                 190

Leu Ile Asp Ser Met Ala Asn Ser Phe Val Gly Thr Arg Ser Tyr Met
        195                 200                 205

Ser Pro Glu Arg Leu Gln Gly Thr His Tyr Ser Val Gln Ser Asp Ile
    210                 215                 220

Trp Ser Met Gly Leu Ser Leu Val Glu Met Ala Val Gly Arg Tyr Pro
225                 230                 235                 240

Ile Pro Pro Pro Asp Ala Lys Glu Leu Glu Leu Met Phe Gly Cys Gln
                245                 250                 255

Val Glu Gly Asp Ala Ala Glu Thr Pro Pro Arg Pro Arg Thr Pro Gly
            260                 265                 270

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385                 390                 395
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What is claimed is:

1. A method for treating or ameliorating the effects of a cancer in a subject, which cancer is refractory or resistant to non-ERK MAPK pathway inhibitor therapy, the method comprising administering to the subject an effective amount of BVD-523 or a pharmaceutically acceptable salt thereof.

2. The method according to claim **1**, wherein the non-ERK MAPK pathway inhibitor therapy is selected from the group consisting of a RAS inhibitor, a RAF inhibitor, a MEK inhibitor, and combinations thereof.

3. The method according to claim **1**, wherein the non-ERK MAPK pathway inhibitor therapy is selected from the group consisting of a BRAF inhibitor, a MEK inhibitor, and combinations thereof.

4. The method according to claim **1**, wherein substantially all phosphorylation of RSK is inhibited after administration of BVD-523 or a pharmaceutically acceptable salt thereof.

5. The method according to claim **1**, wherein the subject is a mammal.

6. The method according to claim **5**, wherein the mammal is selected from the group consisting of humans, primates, farm animals, and domestic animals.

7. The method according to claim **5**, wherein the mammal is a human.

8. The method according to claim **1**, wherein the cancer has MAPK activity.

9. The method according to claim **8**, wherein the cancer is a solid tumor cancer or a hematologic cancer.

10. The method according to claim **8**, wherein the cancer is selected from the group consisting of a cancer of the large intestine, breast cancer, pancreatic cancer, skin cancer, and endometrial cancers.

11. The method according to claim **8**, wherein the cancer is melanoma.

12. The method according to claim **1** further comprising administering to the subject at least one additional therapeutic agent selected from the group consisting of an antibody or fragment thereof, a cytotoxic agent, a toxin, a radionuclide, an immunomodulator, a photoactive therapeutic agent, a radiosensitizing agent, a hormone, an anti-angiogenesis agent, and combinations thereof.

13. The method according to claim **12**, wherein the additional therapeutic agent is an inhibitor of the PI3K/Akt pathway.

14. The method according to claim **13**, wherein the inhibitor of the PI3K/Akt pathway is selected from the group consisting of A-674563 (CAS #552325-73-2), AGL 2263, AMG-319 (Amgen, Thousand Oaks, Calif.), AS-041164 (5-benzo[1,3]dioxol-5-ylmethylene-thiazolidine-2,4-dione), AS-604850 (5-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethylene)-thiazolidine-2,4-dione), AS-605240 (5-quinoxilin-6-methylene-1,3-thiazolidine-2,4-dione), AT7867 (CAS #857531-00-1), benzimidazole series, Genentech (Roche Holdings Inc., South San Francisco, Calif.), BML-257 (CAS #32387-96-5), CAL-120 (Gilead Sciences, Foster City, Calif.), CAL-129 (Gilead Sciences), CAL-130 (Gilead Sciences), CAL-253 (Gilead Sciences), CAL-263 (Gilead Sciences), CAS #612847-09-3, CAS #681281-88-9, CAS #75747-14-7, CAS #925681-41-0, CAS #98510-80-6, CCT128930 (CAS #885499-61-6), CH5132799 (CAS #1007207-67-1), CHR-4432 (Chroma Therapeutics, Ltd., Abingdon, UK), FPA 124 (CAS #902779-59-3), GS-1101 (CAL-101) (Gilead Sciences), GSK 690693 (CAS #937174-76-0), H-89 (CAS #127243-85-0), Honokiol, IC87114 (Gilead Science), IPI-145 (Intellikine Inc.), KAR-4139 (Karus Therapeutics, Chilworth, UK), KAR-4141 (Karus Therapeutics), KIN-1 (Karus Therapeutics), KT 5720 (CAS #108068-98-0), Miltefosine, MK-2206 dihydrochloride (CAS #1032350-13-2), ML-9 (CAS #105637-50-1), Naltrindole Hydrochloride, OXY-111A (NormOxys Inc., Brighton, Mass.), perifosine, PHT-427 (CAS #1191951-57-1), PI3 kinase delta inhibitor, Merck KGaA (Merck & Co., Whitehouse Station, N.J.), PI3 kinase delta inhibitors, Genentech (Roche Holdings Inc.), PI3 kinase delta inhibitors, Incozen (Incozen Therapeutics, Pvt. Ltd., Hydrabad, India), PI3 kinase delta inhibitors-2, Incozen (Incozen Therapeutics), PI3 kinase inhibitor, Roche-4 (Roche Holdings Inc.), PI3 kinase inhibitors, Roche (Roche Holdings Inc.), PI3 kinase inhibitors, Roche-5 (Roche Holdings Inc.), PI3-alpha/delta inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd., South San Francisco, Calif.), PI3-delta inhibitors, Cellzome (Cellzome AG, Heidelberg, Germany), PI3-delta inhibitors, Intellikine (Intellikine Inc., La Jolla, Calif.), PI3-delta inhibitors, Pathway Therapeutics-1 (Pathway Therapeutics Ltd.), PI3-delta inhibitors, Pathway Therapeutics-2 (Pathway Therapeutics Ltd.), PI3-delta/gamma inhibitors, Cellzome (Cellzome AG), PI3-delta/gamma inhibitors, Cellzome (Cellzome AG), PI3-delta/gamma inhibitors, Intellikine (Intellikine Inc.), PI3-delta/gamma inhibitors, Intellikine (Intellikine Inc.), PI3-delta/gamma inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd.), PI3-delta/gamma inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd.), PI3-gamma inhibitor Evotec (Evotec), PI3-gamma inhibitor, Cellzome (Cellzome AG), PI3-gamma inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd.), PI3K delta/gamma inhibitors, Intellikine-1 (Intellikine Inc.), PI3K delta/gamma inhibitors, Intellikine-1 (Intellikine Inc.), pictilisib (Roche Holdings Inc.), PIK-90 (CAS #677338-12-4), SC-103980 (Pfizer, New York, N.Y.), SF-1126 (Semafore Pharmaceuticals, Indianapolis, Ind.), SH-5, SH-6, Tetrahydro Curcumin, TG100-115 (Targegen Inc., San Diego, Calif.), Triciribine, X-339 (Xcovery, West Palm Beach, Fla.), XL-499 (Evotech, Hamburg, Germany), pharmaceutically acceptable salts thereof, and combinations thereof.

15. A method for treating or ameliorating the effects of a cancer in a subject comprising:

(a) identifying a subject with cancer that has become refractory or resistant to BRAF inhibitor therapy, MEK inhibitor therapy, or BRAF and MEK inhibitor therapy; and

(b) administering to the subject with said refractory or resistant cancer an effective amount of an ERK inhibitor, which is BVD-523 or a pharmaceutically acceptable salt thereof.

16. The method according to claim **15**, wherein the subject is a mammal.

17. The method according to claim **16**, wherein the mammal is selected from the group consisting of humans, primates, farm animals, and domestic animals.

18. The method according to claim **16**, wherein the mammal is a human.

19. The method according to claim **15**, wherein the cancer has MAPK activity.

20. The method according to claim **19**, wherein the cancer is a solid tumor cancer or a hematologic cancer.

21. The method according to claim **19**, wherein the cancer is selected from the group consisting of a cancer of the large intestine, breast cancer, pancreatic cancer, skin cancer, and endometrial cancers.

22. The method according to claim **19**, wherein the cancer is melanoma.

23. The method according to claim **15**, wherein identifying a subject with cancer that is refractory or resistant to BRAF and/or MEK inhibitor therapy comprises:

(a) obtaining a biological sample from the subject; and

(b) screening the sample to determine whether the subject has become resistant to an inhibitor therapy selected from the group consisting of BRAF inhibitor therapy, MEK inhibitor therapy, and combinations thereof.

24. The method according to claim **23**, wherein the screening for a cancer that is refractory or resistant to BRAF inhibitor therapy comprises identifying (i) a switch between RAF isoforms, (ii) upregulation of RTK or NRAS signaling, (iii) reactivation of mitogen activated protein kinase (MAPK) signaling, (iv) the presence of a MEK activating mutation, and combinations thereof.

25. The method according to claim **23**, wherein the screening for a cancer that is refractory or resistant to MEK inhibitor therapy comprises identifying (i) amplification of mutant BRAF, (ii) STAT3 upregulation, (iii) mutations in the allosteric pocket of MEK that directly block binding of inhibitors to MEK or lead to constitutive MEK activity, and combinations thereof.

26. The method according to claim **15** further comprising administering at least one additional therapeutic agent selected from the group consisting of an antibody or fragment thereof, a cytotoxic agent, a toxin, a radionuclide, an immunomodulator, a photoactive therapeutic agent, a radiosensitizing agent, a hormone, an anti-angiogenesis agent, and combinations thereof.

27. The method according to claim **26**, wherein the additional therapeutic agent is an inhibitor of the PI3K/Akt pathway.

28. The method according to claim **27**, wherein the inhibitor of the PI3K/Akt pathway is selected from the group consisting of A-674563 (CAS #552325-73-2), AGL 2263, AMG-319 (Amgen, Thousand Oaks, Calif.), AS-041164 (5-benzo[1,3]dioxol-5-ylmethylene-thiazolidine-2,4-dione), AS-604850 (5-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethylene)-thiazolidine-2,4-dione), AS-605240 (5-quinoxilin-6-methylene-1,3-thiazolidine-2,4-dione), AT7867 (CAS #857531-00-1), benzimidazole series, Genentech (Roche Holdings Inc., South San Francisco, Calif.), BML-257 (CAS #32387-96-5), CAL-120 (Gilead Sciences, Foster City, Calif.), CAL-129 (Gilead Sciences), CAL-130 (Gilead Sciences), CAL-253 (Gilead Sciences), CAL-263 (Gilead Sciences), CAS #612847-09-3, CAS #681281-88-9, CAS #75747-14-7, CAS #925681-41-0, CAS #98510-80-6, CCT128930 (CAS #885499-61-6), CH5132799 (CAS #1007207-67-1), CHR-4432 (Chroma Therapeutics, Ltd., Abingdon, UK), FPA 124 (CAS #902779-59-3), GS-1101 (CAL-101) (Gilead Sciences), GSK 690693 (CAS #937174-76-0), H-89 (CAS #127243-85-0), Honokiol, IC87114 (Gilead Science), IPI-145 (Intellikine Inc.), KAR-4139 (Karus Therapeutics, Chilworth, UK), KAR-4141 (Karus Therapeutics), KIN-1 (Karus Therapeutics), KT 5720 (CAS #108068-98-0), Miltefosine, MK-2206 dihydrochloride (CAS #1032350-13-2), ML-9 (CAS #105637-50-1), Naltrindole Hydrochloride, OXY-111A (NormOxys Inc., Brighton, Mass.), perifosine, PHT-427 (CAS #1191951-57-1), PI3 kinase delta inhibitor, Merck KGaA (Merck & Co., Whitehouse Station, N.J.), PI3 kinase delta inhibitors, Genentech (Roche Holdings Inc.), PI3 kinase delta inhibitors, Incozen (Incozen Therapeutics, Pvt. Ltd., Hydrabad, India), PI3 kinase delta inhibitors-2, Incozen (Incozen Therapeutics), PI3 kinase inhibitor, Roche-4 (Roche Holdings Inc.), PI3 kinase inhibitors, Roche (Roche Holdings Inc.), PI3 kinase inhibitors, Roche-5 (Roche Holdings Inc.), PI3-alpha/delta inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd., South San Francisco, Calif.), PI3-delta inhibitors, Cellzome (Cellzome AG, Heidelberg, Germany), PI3-delta inhibitors, Intellikine (Intellikine Inc., La Jolla, Calif.), PI3-delta inhibitors, Pathway Therapeutics-1 (Pathway Therapeutics Ltd.), PI3-delta inhibitors, Pathway Therapeutics-2 (Pathway Therapeutics Ltd.), PI3-delta/gamma inhibitors, Cellzome (Cellzome AG), PI3-delta/gamma inhibitors, Cellzome (Cellzome AG), PI3-delta/gamma inhibitors, Intellikine (Intellikine Inc.), PI3-delta/gamma inhibitors, Intellikine (Intellikine Inc.), PI3-delta/gamma inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd.), PI3-delta/gamma inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd.), PI3-gamma inhibitor Evotec (Evotec), PI3-gamma inhibitor, Cellzome (Cellzome AG), PI3-gamma inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd.), PI3K delta/gamma inhibitors, Intellikine-1 (Intellikine Inc.), PI3K delta/gamma inhibitors, Intellikine-1 (Intellikine Inc.), pictilisib (Roche Holdings Inc.), PIK-90 (CAS #677338-12-4), SC-103980 (Pfizer, New York, N.Y.), SF-1126 (Semafore Pharmaceuticals, Indianapolis, Ind.), SH-5, SH-6, Tetrahydro Curcumin, TG100-115 (Targegen Inc., San Diego, Calif.), Triciribine, X-339 (Xcovery, West Palm Beach, Fla.), XL-499 (Evotech, Hamburg, Germany), pharmaceutically acceptable salts thereof, and combinations thereof.

29. A method for treating or ameliorating the effects of cancer in a subject, which cancer is refractory or resistant to BRAF inhibitor therapy, MEK inhibitor therapy, or both, the method comprising administering to the subject an effective amount of BVD-523 or a pharmaceutically acceptable salt thereof.

30. The method according to claim **29**, wherein the subject is a mammal.

31. The method according to claim **30**, wherein the mammal is selected from the group consisting of humans, primates, farm animals, and domestic animals.

32. The method according to claim **30**, wherein the mammal is a human.

33. The method according to claim **29**, wherein the cancer has MAPK activity.

34. The method according to claim **33**, wherein the cancer is a solid tumor cancer or a hematologic cancer.

35. The method according to claim **33**, wherein the cancer is selected from the group consisting of a cancer of the large intestine, breast cancer, pancreatic cancer, skin cancer, and endometrial cancers.

36. The method according to claim **33**, wherein the cancer is melanoma.

37. The method according to claim **29**, wherein the cancer is determined to be refractory or resistant to BRAF inhibitor therapy based on one or more of the following: (i) a switch between RAF isoforms, (ii) upregulation of RTK or NRAS signaling, (iii) reactivation of mitogen activated protein kinase (MAPK) signaling, (iv) the presence of a MEK activating mutation.

38. The method according to claim **29**, wherein the cancer is determined to be refractory or resistant to MEK inhibitor therapy based on one or more of the following: (i) amplification of mutant BRAF, (ii) STAT3 upregulation, (iii) mutations in the allosteric pocket of MEK that directly block binding of inhibitors to MEK or lead to constitutive MEK activity.

39. The method according to claim **29** further comprising administering to the subject at least one additional therapeutic agent selected from the group consisting of an antibody or fragment thereof, a cytotoxic agent, a toxin, a radionuclide, an immunomodulator, a photoactive therapeutic agent, a radiosensitizing agent, a hormone, an anti-angiogenesis agent, and combinations thereof.

40. The method according to claim **39**, wherein the additional therapeutic agent is an inhibitor of the PI3K/Akt pathway.

41. The method according to claim **40**, wherein the inhibitor of the PI3K/Akt pathway is selected from the group consisting of A-674563 (CAS #552325-73-2), AGL 2263, AMG-319 (Amgen, Thousand Oaks, Calif.), AS-041164 (5-benzo[1,3]dioxol-5-ylmethylene-thiazolidine-2,4-dione), AS-604850 (5-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethylene)-thiazolidine-2,4-dione), AS-605240 (5-quinoxilin-6-methylene-1,3-thiazolidine-2,4-dione), AT7867 (CAS #857531-00-1), benzimidazole series, Genentech (Roche Holdings Inc., South San Francisco, Calif.), BML-257 (CAS #32387-96-5), CAL-120 (Gilead Sciences, Foster City, Calif.), CAL-129 (Gilead Sciences), CAL-130 (Gilead Sciences), CAL-253 (Gilead Sciences), CAL-263 (Gilead Sciences), CAS #612847-09-3, CAS #681281-88-9, CAS #75747-14-7, CAS #925681-41-0, CAS #98510-80-6, CCT128930 (CAS #885499-61-6), CH5132799 (CAS #1007207-67-1), CHR-4432 (Chroma Therapeutics, Ltd.,

Abingdon, UK), FPA 124 (CAS #902779-59-3), GS-1101 (CAL-101) (Gilead Sciences), GSK 690693 (CAS #937174-76-0), H-89 (CAS #127243-85-0), Honokiol, IC87114 (Gilead Science), IPI-145 (Intellikine Inc.), KAR-4139 (Karus Therapeutics, Chilworth, UK), KAR-4141 (Karus Therapeutics), KIN-1 (Karus Therapeutics), KT 5720 (CAS #108068-98-0), Miltefosine, MK-2206 dihydrochloride (CAS #1032350-13-2), ML-9 (CAS #105637-50-1), Naltrindole Hydrochloride, OXY-111A (NormOxys Inc., Brighton, Mass.), perifosine, PHT-427 (CAS #1191951-57-1), PI3 kinase delta inhibitor, Merck KGaA (Merck & Co., Whitehouse Station, N.J.), PI3 kinase delta inhibitors, Genentech (Roche Holdings Inc.), PI3 kinase delta inhibitors, Incozen (Incozen Therapeutics, Pvt. Ltd., Hydrabad, India), PI3 kinase delta inhibitors-2, Incozen (Incozen Therapeutics), PI3 kinase inhibitor, Roche-4 (Roche Holdings Inc.), PI3 kinase inhibitors, Roche (Roche Holdings Inc.), PI3 kinase inhibitors, Roche-5 (Roche Holdings Inc.), PI3-alpha/delta inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd., South San Francisco, Calif.), PI3-delta inhibitors, Cellzome (Cellzome AG, Heidelberg, Germany), PI3-delta inhibitors, Intellikine (Intellikine Inc., La Jolla, Calif.), PI3-delta inhibitors, Pathway Therapeutics-1 (Pathway Therapeutics Ltd.), PI3-delta inhibitors, Pathway Therapeutics-2 (Pathway Therapeutics Ltd.), PI3-delta/gamma inhibitors, Cellzome (Cellzome AG), PI3-delta/gamma inhibitors, Cellzome (Cellzome AG), PI3-delta/gamma inhibitors, Intellikine (Intellikine Inc.), PI3-delta/gamma inhibitors, Intellikine (Intellikine Inc.), PI3-delta/gamma inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd.), PI3-delta/gamma inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd.), PI3-gamma inhibitor Evotec (Evotec), PI3-gamma inhibitor, Cellzome (Cellzome AG), PI3-gamma inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd.), PI3K delta/gamma inhibitors, Intellikine-1 (Intellikine Inc.), PI3K delta/gamma inhibitors, Intellikine-1 (Intellikine Inc.), pictilisib (Roche Holdings Inc.), PIK-90 (CAS #677338-12-4), SC-103980 (Pfizer, New York, N.Y.), SF-1126 (Semafore Pharmaceuticals, Indianapolis, Ind.), SH-5, SH-6, Tetrahydro Curcumin, TG100-115 (Targegen Inc., San Diego, Calif.), Triciribine, X-339 (Xcovery, West Palm Beach, Fla.), XL-499 (Evotech, Hamburg, Germany), pharmaceutically acceptable salts thereof, and combinations thereof.

42. A method for identifying a subject having cancer who would benefit from therapy with an ERK inhibitor, the method comprising:

(a) obtaining a biological sample from the subject; and

(b) screening the sample to determine whether the subject has one or more of the following markers:

(i) a switch between RAF isoforms,

(ii) upregulation of receptor tyrosine kinase (RTK) or NRAS signaling,

(iii) reactivation of mitogen activated protein kinase (MAPK) signaling,

(iv) the presence of a MEK activating mutation,

(v) amplification of mutant BRAF,

(vi) STAT3 upregulation,

(vii) mutations in the allosteric pocket of MEK that directly block binding of inhibitors to MEK or lead to constitutive MEK activity,

wherein the presence of one or more of the markers confirms that the subject's cancer is refractory or resistant to BRAF and/or MEK inhibitor therapy and that the subject would benefit from therapy with an ERK inhibitor, which is BVD-523 or a pharmaceutically acceptable salt thereof.

43. The method according to claim **42**, wherein the subject is a mammal.

44. The method according to claim **43**, wherein the mammal is selected from the group consisting of humans, primates, farm animals, and domestic animals.

45. The method according to claim **43**, wherein the mammal is a human.

46. The method according to claim **42**, wherein the cancer has MAPK activity.

47. The method according to claim **46**, wherein the cancer is a solid tumor cancer or a hematologic cancer.

48. The method according to claim **46**, wherein the cancer is selected from the group consisting of a cancer of the large intestine, breast cancer, pancreatic cancer, skin cancer, and endometrial cancers.

49. The method according to claim **46**, wherein the cancer is melanoma.

50. The method according to claim **42** further comprising administering BVD-523 or a pharmaceutically acceptable salt thereof to a subject having one or more of the markers.

51. The method according to claim **50** further comprising administering to the subject having one or more of the markers at least one additional therapeutic agent selected from the group consisting of an antibody or fragment thereof, a cytotoxic agent, a toxin, a radionuclide, an immunomodulator, a photoactive therapeutic agent, a radiosensitizing agent, a hormone, an anti-angiogenesis agent, and combinations thereof.

52. The method according to claim **51**, wherein the additional therapeutic agent is an inhibitor of the PI3K/Akt pathway.

53. The method according to claim **52**, wherein the inhibitor of the PI3K/Akt pathway is selected from the group consisting of A-674563 (CAS #552325-73-2), AGL 2263, AMG-319 (Amgen, Thousand Oaks, Calif.), AS-041164 (5-benzo[1,3]dioxol-5-ylmethylene-thiazolidine-2,4-dione), AS-604850 (5-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethylene)-thiazolidine-2,4-dione), AS-605240 (5-quinoxilin-6-methylene-1,3-thiazolidine-2,4-dione), AT7867 (CAS #857531-00-1), benzimidazole series, Genentech (Roche Holdings Inc., South San Francisco, Calif.), BML-257 (CAS #32387-96-5), CAL-120 (Gilead Sciences, Foster City, Calif.), CAL-129 (Gilead Sciences), CAL-130 (Gilead Sciences), CAL-253 (Gilead Sciences), CAL-263 (Gilead Sciences), CAS #612847-09-3, CAS #681281-88-9, CAS #75747-14-7, CAS #925681-41-0, CAS #98510-80-6, CCT128930 (CAS #885499-61-6), CH5132799 (CAS #1007207-67-1), CHR-4432 (Chroma Therapeutics, Ltd., Abingdon, UK), FPA 124 (CAS #902779-59-3), GS-1101 (CAL-101) (Gilead Sciences), GSK 690693 (CAS #937174-76-0), H-89 (CAS #127243-85-0), Honokiol, IC87114 (Gilead Science), IPI-145 (Intellikine Inc.), KAR-4139 (Karus Therapeutics, Chilworth, UK), KAR-4141 (Karus Therapeutics), KIN-1 (Karus Therapeutics), KT 5720 (CAS #108068-98-0), Miltefosine, MK-2206 dihydrochloride (CAS #1032350-13-2), ML-9 (CAS #105637-50-1), Naltrindole Hydrochloride, OXY-111A (NormOxys Inc., Brighton, Mass.), perifosine, PHT-427 (CAS #1191951-57-1), PI3 kinase delta inhibitor, Merck KGaA (Merck & Co., Whitehouse Station, N.J.), PI3 kinase delta inhibitors, Genentech (Roche Holdings Inc.), PI3 kinase delta inhibitors, Incozen (Incozen Therapeutics, Pvt. Ltd., Hydrabad, India), PI3

kinase delta inhibitors-2, Incozen (Incozen Therapeutics), PI3 kinase inhibitor, Roche-4 (Roche Holdings Inc.), PI3 kinase inhibitors, Roche (Roche Holdings Inc.), PI3 kinase inhibitors, Roche-5 (Roche Holdings Inc.), PI3-alpha/delta inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd., South San Francisco, Calif.), PI3-delta inhibitors, Cellzome (Cellzome AG, Heidelberg, Germany), PI3-delta inhibitors, Intellikine (Intellikine Inc., La Jolla, Calif.), PI3-delta inhibitors, Pathway Therapeutics-1 (Pathway Therapeutics Ltd.), PI3-delta inhibitors, Pathway Therapeutics-2 (Pathway Therapeutics Ltd.), PI3-delta/gamma inhibitors, Cellzome (Cellzome AG), PI3-delta/gamma inhibitors, Cellzome (Cellzome AG), PI3-delta/gamma inhibitors, Intellikine (Intellikine Inc.), PI3-delta/gamma inhibitors, Intellikine (Intellikine Inc.), PI3-delta/gamma inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd.), PI3-delta/gamma inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd.), PI3-gamma inhibitor Evotec (Evotec), PI3-gamma inhibitor, Cellzome (Cellzome AG), PI3-gamma inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd.), PI3K delta/gamma inhibitors, Intellikine-1 (Intellikine Inc.), PI3K delta/gamma inhibitors, Intellikine-1 (Intellikine Inc.), pictilisib (Roche Holdings Inc.), PIK-90 (CAS #677338-12-4), SC-103980 (Pfizer, New York, N.Y.), SF-1126 (Semafore Pharmaceuticals, Indianapolis, Ind.), SH-5, SH-6, Tetrahydro Curcumin, TG100-115 (Targegen Inc., San Diego, Calif.), Triciribine, X-339 (Xcovery, West Palm Beach, Fla.), XL-499 (Evotech, Hamburg, Germany), pharmaceutically acceptable salts thereof, and combinations thereof.

54. A pharmaceutical composition for treating or ameliorating the effects of a cancer in a subject, which cancer is refractory or resistant to non-ERK MAPK pathway therapy, the composition comprising a pharmaceutically acceptable carrier or diluent and an effective amount of BVD-523 or a pharmaceutically acceptable salt thereof.

55. The pharmaceutical composition according to claim **54**, wherein the non-ERK MAPK pathway inhibitor therapy is selected from the group consisting of a RAS inhibitor, a RAF inhibitor, a MEK inhibitor, and combinations thereof.

56. The pharmaceutical composition according to claim **54**, wherein the non-ERK MAPK pathway inhibitor therapy is selected from the group consisting of a BRAF inhibitor, a MEK inhibitor, and combinations thereof.

57. The pharmaceutical composition according to claim **54**, wherein the subject is a mammal.

58. The pharmaceutical composition according to claim **57**, wherein the mammal is selected from the group consisting of humans, primates, farm animals, and domestic animals.

59. The pharmaceutical composition according to claim **57**, wherein the mammal is a human.

60. The pharmaceutical composition according to claim **54**, wherein the cancer has MAPK activity.

61. The pharmaceutical composition according to claim **60**, wherein the cancer is a solid tumor cancer or a hematologic cancer.

62. The pharmaceutical composition according to claim **60**, wherein the cancer is selected from the group consisting of a cancer of the large intestine, breast cancer, pancreatic cancer, skin cancer, and endometrial cancers.

63. The pharmaceutical composition according to claim **60**, wherein the cancer is melanoma.

64. The pharmaceutical composition according to claim **54** further comprising at least one additional therapeutic agent selected from the group consisting of an antibody or fragment thereof, a cytotoxic agent, a toxin, a radionuclide, an immunomodulator, a photoactive therapeutic agent, a radiosensitizing agent, a hormone, an anti-angiogenesis agent, and combinations thereof.

65. The pharmaceutical composition according to claim **64**, wherein the additional therapeutic agent is an inhibitor of the PI3K/Akt pathway.

66. The pharmaceutical composition according to claim **65**, wherein the inhibitor of the PI3K/Akt pathway is selected from the group consisting of A-674563 (CAS #552325-73-2), AGL 2263, AMG-319 (Amgen, Thousand Oaks, Calif.), AS-041164 (5-benzo[1,3]dioxol-5-ylmethylene-thiazolidine-2,4-dione), AS-604850 (5-(2,2-Difluorobenzo[1,3]dioxol-5-ylmethylene)-thiazolidine-2,4-dione), AS-605240 (5-quinoxilin-6-methylene-1,3-thiazolidine-2,4-dione), AT7867 (CAS #857531-00-1), benzimidazole series, Genentech (Roche Holdings Inc., South San Francisco, Calif.), BML-257 (CAS #32387-96-5), CAL-120 (Gilead Sciences, Foster City, Calif.), CAL-129 (Gilead Sciences), CAL-130 (Gilead Sciences), CAL-253 (Gilead Sciences), CAL-263 (Gilead Sciences), CAS #612847-09-3, CAS #681281-88-9, CAS #75747-14-7, CAS #925681-41-0, CAS #98510-80-6, CCT128930 (CAS #885499-61-6), CH5132799 (CAS #1007207-67-1), CHR-4432 (Chroma Therapeutics, Ltd., Abingdon, UK), FPA 124 (CAS #902779-59-3), GS-1101 (CAL-101) (Gilead Sciences), GSK 690693 (CAS #937174-76-0), H-89 (CAS #127243-85-0), Honokiol, IC87114 (Gilead Science), IPI-145 (Intellikine Inc.), KAR-4139 (Karus Therapeutics, Chilworth, UK), KAR-4141 (Karus Therapeutics), KIN-1 (Karus Therapeutics), KT 5720 (CAS #108068-98-0), Miltefosine, MK-2206 dihydrochloride (CAS #1032350-13-2), ML-9 (CAS #105637-50-1), Naltrindole Hydrochloride, OXY-111A (NormOxys Inc., Brighton, Mass.), perifosine, PHT-427 (CAS #1191951-57-1), PI3 kinase delta inhibitor, Merck KGaA (Merck & Co., Whitehouse Station, N.J.), PI3 kinase delta inhibitors, Genentech (Roche Holdings Inc.), PI3 kinase delta inhibitors, Incozen (Incozen Therapeutics, Pvt. Ltd., Hydrabad, India), PI3 kinase delta inhibitors-2, Incozen (Incozen Therapeutics), PI3 kinase inhibitor, Roche-4 (Roche Holdings Inc.), PI3 kinase inhibitors, Roche (Roche Holdings Inc.), PI3 kinase inhibitors, Roche-5 (Roche Holdings Inc.), PI3-alpha/delta inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd., South San Francisco, Calif.), PI3-delta inhibitors, Cellzome (Cellzome AG, Heidelberg, Germany), PI3-delta inhibitors, Intellikine (Intellikine Inc., La Jolla, Calif.), PI3-delta inhibitors, Pathway Therapeutics-1 (Pathway Therapeutics Ltd.), PI3-delta inhibitors, Pathway Therapeutics-2 (Pathway Therapeutics Ltd.), PI3-delta/gamma inhibitors, Cellzome (Cellzome AG), PI3-delta/gamma inhibitors, Cellzome (Cellzome AG), PI3-delta/gamma inhibitors, Intellikine (Intellikine Inc.), PI3-delta/gamma inhibitors, Intellikine (Intellikine Inc.), PI3-delta/gamma inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd.), PI3-delta/gamma inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd.), PI3-gamma inhibitor Evotec (Evotec), PI3-gamma inhibitor, Cellzome (Cellzome AG), PI3-gamma inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd.), PI3K delta/gamma inhibitors, Intellikine-1 (Intellikine Inc.), PI3K delta/gamma inhibitors, Intellikine-1 (Intellikine Inc.), pic-

tilisib (Roche Holdings Inc.), PIK-90 (CAS #677338-12-4), SC-103980 (Pfizer, New York, N.Y.), SF-1126 (Semafore Pharmaceuticals, Indianapolis, Ind.), SH-5, SH-6, Tetrahydro Curcumin, TG100-115 (Targegen Inc., San Diego, Calif.), Triciribine, X-339 (Xcovery, West Palm Beach, Fla.), XL-499 (Evotech, Hamburg, Germany), pharmaceutically acceptable salts thereof, and combinations thereof.

67. A kit for treating or ameliorating the effects of a cancer in a subject, which cancer is refractory or resistant to non-ERK MAPK pathway therapy, the kit comprising a pharmaceutical composition according to any one of claims **54**, **55**, or **56** packaged together with instructions for its use.

68. A method for inhibiting phosphorylation of RSK in a cancer cell that is refractory or resistant to a non-ERK MAPK pathway inhibitor, the method comprising contacting the cancer cell with an effective amount of BVD-523 or a pharmaceutically acceptable salt thereof for a period of time sufficient for phosphorylation of RSK in the cancer cell to be inhibited.

69. The method according to claim **68**, wherein greater than 50% of RSK phosphorylation is inhibited.

70. The method according to claim **68**, wherein greater than 75% of RSK phosphorylation is inhibited.

71. The method according to claim **68**, wherein greater than 90% of RSK phosphorylation is inhibited.

72. The method according to claim **68**, wherein greater than 95% of RSK phosphorylation is inhibited.

73. The method according to claim **68**, wherein greater than 99% of RSK phosphorylation is inhibited.

74. The method according to claim **68**, wherein 100% of RSK phosphorylation is inhibited.

75. The method according to claim **68**, which is carried out in vitro, ex vivo, or in vivo.

76. The method according to claim **68**, wherein the contacting step comprises administering BVD-523 or a pharmaceutically acceptable salt to a subject from whom the cancer cell was obtained.

77. The method according to claim **68**, wherein the non-ERK MAPK pathway inhibitor is selected from the group consisting of a RAS inhibitor, a RAF inhibitor, a MEK inhibitor, and combinations thereof.

78. The method according to claim **68**, wherein the non-ERK MAPK pathway inhibitor is selected from the group consisting of BRAF inhibitors, MEK inhibitors, and combinations thereof.

79. The method according to claim **68**, wherein the cancer is from a mammal.

80. The method according to claim **79**, wherein the mammal is selected from the group consisting of humans, primates, farm animals, and domestic animals.

81. The method according to claim **79**, wherein the mammal is a human.

82. The method according to claim **68**, wherein the cancer has MAPK activity.

83. The method according to claim **82**, wherein the cancer is a solid tumor cancer or a hematologic cancer.

84. The method according to claim **82**, wherein the cancer is selected from the group consisting of a cancer of the large intestine, breast cancer, pancreatic cancer, skin cancer, and endometrial cancers.

85. The method according to claim **82**, wherein the cancer is melanoma.

86. A method of treating a subject having an unresectable or metastatic BRAF600 mutation-positive melanoma comprising administering to the subject 600 mg BID of BVD-523 or a pharmaceutically acceptable salt thereof.

87. The method according to claim **86**, wherein the mutation is a $BRAF^{V600E}$ mutation.

88. The method according to claim **86**, wherein the mammal is selected from the group consisting of humans, primates, farm animals, and domestic animals.

89. The method according to claim **86**, wherein the mammal is a human.

90. The method according to claim **86**, wherein the melanoma has MAPK activity.

91. A composition for treating a subject having an unresectable or metastatic BRAF600 mutation-positive melanoma, the composition comprising 600 mg of BVD-523 or a pharmaceutically acceptable salt thereof and optionally a pharmaceutically acceptable carrier, adjuvant, or vehicle.

92. The composition according to claim **91**, wherein the subject is a mammal.

93. The composition according to claim **91**, wherein the mammal is selected from the group consisting of humans, primates, farm animals, and domestic animals.

94. The composition according to claim **91**, wherein the mammal is a human.

95. The composition according to claim **91**, wherein the melanoma has MAPK activity.

96. The composition of claim **91** wherein the mutation is a $BRAF^{V600E}$ mutation.

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