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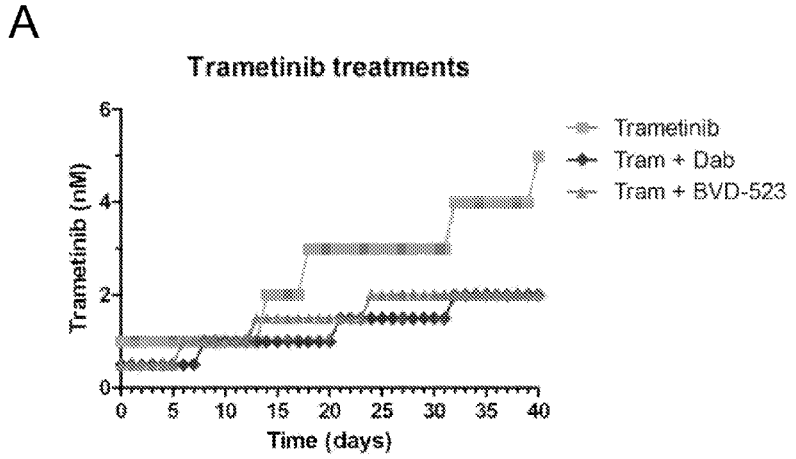
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(54) Title: CANCER TREATMENTS USING COMBINATIONS OF TYPE 2 MEK AND ERK INHIBITORS



(57) Abstract: The present invention provides, *inter alia,* methods, kits, and pharmaceutical compositions for treating or ameliorating the effects of a cancer in a subject in need thereof. The method includes administering to the subject an effective amount of (i) a first anti-cancer agent, which is BVD 523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a type 2 MEK inhibitor, or other MEK inhibitors, or pharmaceutically acceptable salts thereof, to treat or ameliorate the effects of the cancer. Additional methods for effecting cancer cell death are also provided.

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CANCER TREATMENTS USING COMBINATIONS OF TYPE 2 MEK AND ERK INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit of U.S. Patent Application Serial No. 61/919,625, filed on December 20, 2013 which application is incorporated by reference herein in its entirety.

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 using a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and a second anti-cancer agent, which is a type 2 MEK inhibitor or a pharmaceutically acceptable salt thereof.

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 "0375603.txt", file size of 474 KB, created on December 19, 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] Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

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[0004A] Within cellular signaling networks, Ras and Raf play significant roles in the regulation of various biological processes, including cell growth, proliferation, differentiation, inflammatory responses, and programmed cell death. Notably, mutations in ras genes were the first genetic alterations identified in human cancer. Activating mutations of HRAS, NRAS, and KRAS ('RAS'), as well as BRAF are found frequently in several types of cancer.

[0005] A MEK inhibitor is an agent that inhibits the mitogen – activated protein kinase enzymes, MEK1 and/or MEK2. Depending on their target and effect, *i.e.* MEK1, MEK2 or both, MEK inhibitors may be classified as type 1 MEK inhibitors, type 2 MEK inhibitors or pan MEK inhibitors. MEK inhibitors are known to modulate, *e.g.*, the MAPK pathway, which is often over-active in many cancers, and, therefore, have been used in cancer therapy. Unfortunately, many cancers become resistant to MEK inhibitor treatment over time.

[0006] Extracellular-signal-regulated kinases (ERKs) are protein kinases that are involved in cell cycle regulation, including the regulation of meiosis, mitosis, and postmitotic functions in differentiated cells. Disruption of the ERK pathway is common in cancers. However, to date, little progress has been made developing effective ERK inhibitors for the treatment of cancer.

[0007] As the understanding of the molecular basis of cancer grows, there is an increased emphasis on developing drugs that specifically target particular nodes in pathways that lead to cancer. In view of the deficiencies noted above, there is, *inter alia*, a need for effective molecularly targeted cancer treatments, including combination therapies. The present application is directed to meeting these and other needs.

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SUMMARY OF THE INVENTION

[0008] Unless the context clearly requires otherwise, throughout the description and the claims, the words 'comprise', 'comprising' and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say in the sense of "including but not limited to".

[0008A] One embodiment of the present invention is a method of treating or ameliorating the effects of a cancer in a subject in need thereof. The method comprises administering to the subject an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a type 2 MEK inhibitor or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer.

[0008B] In a particular aspect, the present invention provides a method of treating or ameliorating the effects of a cancer in a subject in need thereof comprising administering to the subject an effective amount of (i) a first anti-cancer agent, which is BVD 523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a type 2 MEK inhibitor or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer, wherein the type 2 MEK inhibitor is selected from the group consisting of GDC-0623, MEK162, trametinib, pharmaceutically acceptable salts thereof, and combinations thereof, and wherein administration of the first and second anti-cancer agents provides a synergistic effect compared to administration of either anti-cancer agent alone.

[0009] Another embodiment of the present invention is a method of treating or ameliorating the effects of a cancer in a subject in need thereof.

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The method comprises administering to the subject an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is trametinib or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer.

[0009A] In a particular aspect, the present invention provides a method of treating or ameliorating the effects of a cancer in a subject in need thereof comprising administering to the subject an effective amount of (i) a first anti-cancer agent, which is BVD 523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is trametinib or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer, wherein administration of the first and second anti-cancer agents provides a synergistic effect compared to administration of either anti-cancer agent alone.

[0010] A further embodiment of the present invention is a method of effecting cancer cell death. The method comprises contacting the cancer cell with an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a type 2 MEK inhibitor or a pharmaceutically acceptable salt thereof.

[0010A] In a particular aspect, the present invention provides a method of effecting cancer cell death comprising contacting the cancer cell with an effective amount of (i) a first anti-cancer agent, which is BVD 523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a type 2 MEK inhibitor or a pharmaceutically acceptable salt thereof,

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wherein the type 2 MEK inhibitor is selected from the group consisting of GDC-0623, MEK162, trametinib, pharmaceutically acceptable salts thereof, and combinations thereof, and wherein administration of the first and second anti-cancer agents provides a synergistic effect compared to administration of either anti-cancer agent alone.

[0011] An additional embodiment of the present invention is a kit for treating or ameliorating the effects of a cancer in a subject in need thereof. The kit comprises an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a type 2 MEK inhibitor or a pharmaceutically acceptable salt thereof, packaged together with instructions for their use.

[0011A] In a particular aspect, the present invention provides a kit when used to treat or ameliorate the effects of a cancer in a subject in need thereof comprising an effective amount of (i) a first anti-cancer agent, which is BVD 523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a type 2 MEK inhibitor or a pharmaceutically acceptable salt thereof, packaged together with instructions for their use, wherein the type 2 MEK inhibitor is selected from the group consisting of GDC-0623, MEK162, trametinib, pharmaceutically acceptable salts thereof, and combinations thereof, and wherein administration of the first and second anti-cancer agents provides a synergistic effect compared to administration of either anti-cancer agent alone.

[0012] Another embodiment of the present invention is a pharmaceutical composition for treating or ameliorating the effects of cancer

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in a subject in need thereof. The pharmaceutical composition comprises a pharmaceutically acceptable diluent or carrier and an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a type 2 MEK inhibitor or a pharmaceutically acceptable salt thereof, wherein administration of the first and second anti-cancer agents provides a synergistic effect compared to administration of either anti-cancer agent alone.

[0012A] In a particular aspect, the present invention provides a pharmaceutical composition when used to treat or ameliorate the effects of a cancer in a subject in need thereof, the pharmaceutical composition comprising a pharmaceutically acceptable diluent or carrier and an effective amount of (i) a first anti-cancer agent, which is BVD 523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a type 2 MEK inhibitor or a pharmaceutically acceptable salt thereof, wherein the type 2 MEK inhibitor is selected from the group consisting of GDC-0623, MEK162, trametinib, pharmaceutically acceptable salts thereof, and combinations thereof, and wherein administration of the first and second anti-cancer agents provides a synergistic effect compared to administration of either anti-cancer agent alone.

[0013] A further embodiment of the present invention is a method of treating or ameliorating the effects of a cancer in a subject in need thereof. The method comprises administering to the subject an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a MEK inhibitor selected from the group consisting of antroquinonol (Golden Biotechnology),

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AS-1940477 (Astellas), AS-703988 (Merck KGaA), BI-847325 (Boehringer Ingelheim), E-6201 (Eisai), GDC-0623 (Hoffmann-La Roche), GDC-0973 (Hoffmann-La Roche), RG422 (Chugai Pharmaceutical Co.), RO4987655 (Hoffmann-La Roche), RO5126766 (Hoffmann-La Roche), SL327 (Sigma), WX-554 (Wilex), YopJ polypeptide (Mittal *et al.*, 2010), pharmaceutically acceptable salts thereof, and combinations thereof, to treat or ameliorate the effects of the cancer.

[FOLLOWED BY PAGE 5]

[0014] An additional embodiment of the present invention is a method of effecting cancer cell death. The method comprises contacting the cancer cell with an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a MEK inhibitor selected from the group consisting of antroquinonol (Golden Biotechnology), AS-1940477 (Astellas), AS-703988 (Merck KGaA), BI-847325 (Boehringer Ingelheim), E-6201 (Eisai), GDC-0623 (Hoffmann-La Roche), GDC-0973, RG422, RO4987655, RO5126766, SL327, WX-554 (Wilex), YopJ polypeptide, pharmaceutically acceptable salts thereof, and combinations thereof.

[0015] Another embodiment of the present invention is a kit for treating or ameliorating the effects of a cancer in a subject in need thereof. The kit comprises an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a MEK inhibitor selected from the group consisting of antroquinonol (Golden Biotechnology), AS-1940477 (Astellas), AS-703988 (Merck KGaA), BI-847325 (Boehringer Ingelheim), E-6201 (Eisai), GDC-0623 (Hoffmann-La Roche), GDC-0973, RG422, RO4987655, RO5126766, SL327, WX-554 (Wilex), YopJ polypeptide, pharmaceutically acceptable salts thereof, and combinations thereof, packaged together with instructions for their use.

[0016] A further embodiment of the present invention is a pharmaceutical composition for treating or ameliorating the effects of a cancer in a subject in need thereof. The pharmaceutical composition comprises a pharmaceutically acceptable diluent or carrier and an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable

salt thereof and (ii) a second anti-cancer agent, which is a MEK inhibitor selected from the group consisting of antroquinonol (Golden Biotechnology), AS-1940477 (Astellas), AS-703988 (Merck KGaA), BI-847325 (Boehringer Ingelheim), E-6201 (Eisai), GDC-0623 (Hoffmann-La Roche), GDC-0973, RG422, RO4987655, RO5126766, SL327, WX-554 (Wilex), YopJ polypeptide, pharmaceutically acceptable salts thereof, and combinations thereof, wherein administration of the first and second anti-cancer agents provides a synergistic effect compared to administration of either anti-cancer agent alone.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] 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.

[0018] FIGS. 1A-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.

[0019] FIGS. 2A-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. FIGS. 2A-2C and 2G are normalized to control, whereas FIGS. 2D-2F and 2H show the raw data.

[0020] FIGS. 3A-3D show the progress of a dose escalation study in A375 cells for month 2. Various treatments (trametinib, dabrafenib, and BVD-523) are as labeled.

[0021] FIGS. 4A-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. FIGS. 4A-4C and 4G are normalized to control, whereas FIGS. 4D-4F and 4H show the raw data.

[0022] FIGS. 5A-H show only the parental and BVD-523 cell line data from FIG. 4. Various treatments (trametinib, dabrafenib, BVD-523, and pacitaxel) are as labeled. FIGS. 5A-5C and 5G are normalized to control, whereas FIGS. 5D-5F and 5H show the raw data.

[0023] FIGS. 6A-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.

[0024] 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.

[0025] FIGS. 8A-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.

[0026] FIGS. 9A-D show only the parental, dabrafenib, and BVD-523 cell line data from FIG. 8.

[0027] FIG. 10A is a dose matrix showing % inhibition of the trametinib/dabrafenib combination in A375 cells using the Alamar Blue cell viability assay. FIG. 10B is a dose matrix showing excess over Bliss for the trametinib/dabrafenib combination. FIGS. 10C and 10D 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. 10E shows % viability relative to DMSO only treated controls for dabrafenib and trametinib combination treatments in A375 cells using the Alamar Blue cell viability assay.

[0028] FIG. 11A is a dose matrix showing % inhibition of the trametinib/dabrafenib combination in A375 cells using the CellTiter-Glo cell viability assay. FIG. 11B is a dose matrix showing excess over Bliss for the trametinib/dabrafenib combination. FIGS. 11C and 11D 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. 11E shows % viability relative to DMSO only treated controls for dabrafenib and trametinib combination treatments in A375 cells using the CellTiter-Glo cell viability assay.

[0029] FIG. 12A is a dose matrix showing % inhibition of the BVD-523/dabrafenib combination in A375 cells using the Alamar Blue cell viability assay. FIG. 12B is a dose matrix showing excess over Bliss for the BVD-523/dabrafenib combination. FIGS. 12C and 12D 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. 12E 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.

[0030] FIG. 13A is a dose matrix showing % inhibition of the BVD-523/dabrafenib combination in A375 cells using the CellTiter-Glo cell viability assay. FIG. 13B is a dose matrix showing excess over Bliss for the BVD-523/dabrafenib combination. FIGS. 13C and 13D 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. 13E 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.

[0031] FIG. 14A is a dose matrix showing % inhibition of the trametinib/BVD-523 combination in A375 cells using the Alamar Blue cell viability assay. FIG. 14B is a dose matrix showing excess over Bliss for the trametinib/BVD-523 combination. FIGS. 14C and 14D 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. 14E 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.

[0032] FIG. 15A is a dose matrix showing % inhibition of the trametinib/BVD-523 combination in A375 cells using the CellTiter-Glo cell viability assay. FIG. 15B is a dose matrix showing excess over Bliss for the trametinib/BVD-523 combination. FIGS. 15C and 15D 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. 15E 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.

[0033] FIGS. 16A-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. FIGS. 16A and 16B show results from duplicate samples. Similarly, FIGS. 16C and 16D also show results from duplicate samples. In FIGS. 16A and 16B, 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 FIGS. 16C and 16D, pCRAF-338 gave a minimal signal.

[0034] FIGS. 17A-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. FIGS. 17A and 17B show results from duplicate samples. Similarly, FIGS. 17C and 17D also show results from duplicate samples. In FIGS. 17A-17B, pRSK1 levels appear to be very low in HCT116 cells, and in FIGS. 17C and 17D, pCRAF-338 signal was also very weak.

[0035] FIGS. 18A-D are a set of images showing Western blot analysis of cell cycle and apoptosis signalling 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. FIGS. 18A and 18B show results from duplicate samples. Similarly, FIGS. 18C and 18D also show results from duplicate samples. In FIGS. 18A and 18B, no band of a size corresponding to cleaved PARP (89 kDa) was apparent.

[0036] FIG. 19 is a flowchart showing the dose escalation protocol used herein.

[0037] FIG. 20 shows the results of single agent proliferation assays in parental A375 and A375 NRAS (Q61K/+) cells. Proliferation results are shown for treatment with BVD-523 (FIG. 20A), SCH772984 (FIG. 20B), Trametinib (FIG. 20C), MEK-162 (FIG. 20D), GDC-0623 (FIG. 20E), GDC-0973 (FIG. 20F), and Paclitaxel (FIG. 20G).

[0038] FIG. 21 shows the results of single agent proliferation assays in parental HCT116 and A375 KRAS KO (-/+) cells. Proliferation results are shown for treatment with BVD-523 (FIG. 21A), SCH772984 (FIG. 21B), Trametinib (FIG. 21C), MEK-162 (FIG. 21D), GDC-0623 (FIG. 21E), GDC-0973 (FIG. 21F), and Paclitaxel (FIG. 21G).

[0039] FIG. 22 shows the results of single agent proliferation assays in parental RKO and RKO BRAF V600E KO (+/-/-) cells. Proliferation results are shown for treatment with BVD-523 (FIG. 22A), SCH772984 (FIG. 22B), Trametinib (FIG. 22C), MEK-162 (FIG. 22D), GDC-0623 (FIG. 22E), GDC-0973 (FIG. 22F), and Paclitaxel (FIG. 22G).

[0040] FIG. 23 shows the results of the combination of BVD-523 and Trametinib in parental A375 and A375 NRAS (Q61K/+) cells. FIG. 23A shows a dose matrix showing inhibition (%) for the combination in parental A375 cells. FIG. 23B shows Loewe excess for the combination in 23A and FIG. 23C shows Bliss excess for the combination in 23A. FIG. 23D shows a dose matrix showing inhibition (%) for the combination in A375 NRAS (Q61K/+) cells. FIG. 23E shows Loewe excess for the combination in 23D and FIG. 23F shows Bliss excess for the combination in 23D. FIG. 23G – FIG. 23H show the results of single agent proliferation assays for the combination in 23A. FIG. 23I – FIG. 23J show the results of single agent proliferation assays for the combination in 23D.

[0041] FIG. 24 shows the results of the combination of SCH772984 and Trametinib in parental A375 and A375 NRAS (Q61K/+) cells. FIG. 24A shows a dose matrix showing inhibition (%) for the combination in parental A375 cells. FIG. 24B shows Loewe excess for the combination in 24A and FIG.

24C shows Bliss excess for the combination in 24A. FIG. 24D shows a dose matrix showing inhibition (%) for the combination in A375 NRAS (Q61K/+) cells. FIG. 24E shows Loewe excess for the combination in 24D and FIG. 24F shows Bliss excess for the combination in 24D. FIG. 24G – FIG. 24H show the results of single agent proliferation assays for the combination in 24A. FIG. 24I – FIG. 24J show the results of single agent proliferation assays for the combination in 24D.

[0042] FIG. 25 shows the results of the combination of BVD-523 and MEK-162 in parental A375 and A375 NRAS (Q61K/+) cells. FIG. 25A shows a dose matrix showing inhibition (%) for the combination in parental A375 cells. FIG. 25B shows Loewe excess for the combination in 25A and FIG. 25C shows Bliss excess for the combination in 25A. FIG. 25D shows a dose matrix showing inhibition (%) for the combination in A375 NRAS (Q61K/+) cells. FIG. 25E shows Loewe excess for the combination in 25D and FIG. 25F shows Bliss excess for the combination in 25D. FIG. 25G – FIG. 25H show the results of single agent proliferation assays for the combination in 25A. FIG. 25I – FIG. 25J show the results of single agent proliferation assays for the combination in 25D.

[0043] FIG. 26 shows the results of the combination of SCH772984 and MEK-162 in parental A375 and A375 NRAS (Q61K/+) cells. FIG. 26A shows a dose matrix showing inhibition (%) for the combination in parental A375 cells. FIG. 26B shows Loewe excess for the combination in 26A and FIG. 26C shows Bliss excess for the combination in 26A. FIG. 26D shows a dose matrix showing inhibition (%) for the combination in A375 NRAS (Q61K/+) cells. FIG. 26E shows Loewe excess for the combination in 26D and FIG.

26F shows Bliss excess for the combination in 26D. FIG. 26G – FIG. 26H show the results of single agent proliferation assays for the combination in 26A. FIG. 26I – FIG. 26J show the results of single agent proliferation assays for the combination in 26D.

[0044] FIG. 27 shows the results of the combination of BVD-523 and GDC-0623 in parental A375 and A375 NRAS (Q61K/+) cells. FIG. 27A shows a dose matrix showing inhibition (%) for the combination in parental A375 cells. FIG. 27B shows Loewe excess for the combination in 27A and FIG. 27C shows Bliss excess for the combination in 27A. FIG. 27D shows a dose matrix showing inhibition (%) for the combination in A375 NRAS (Q61K/+) cells. FIG. 27E shows Loewe excess for the combination in 27D and FIG. 27F shows Bliss excess for the combination in 27D. FIG. 27G – FIG. 27H show the results of single agent proliferation assays for the combination in 27A. FIG. 27I – FIG. 27J show the results of single agent proliferation assays for the combination in 27D.

[0045] FIG. 28 shows the results of the combination of SCH772984 and GDC-0623 in parental A375 and A375 NRAS (Q61K/+) cells. FIG. 28A shows a dose matrix showing inhibition (%) for the combination in parental A375 cells. FIG. 28B shows Loewe excess for the combination in 28A and FIG. 28C shows Bliss excess for the combination in 28A. FIG. 28D shows a dose matrix showing inhibition (%) for the combination in A375 NRAS (Q61K/+) cells. FIG. 28E shows Loewe excess for the combination in 28D and FIG. 28F shows Bliss excess for the combination in 28D. FIG. 28G – FIG. 28H show the results of single agent proliferation assays for the combination in

28A. FIG. 28I – FIG. 28J show the results of single agent proliferation assays for the combination in 28D.

[0046] FIG. 29 shows the results of the combination of BVD-523 and Trametinib in parental HCT116 and HCT116 KRAS KO (+/-) cells. FIG. 29A shows a dose matrix showing inhibition (%) for the combination in parental HCT116 cells. FIG. 29B shows Loewe excess for the combination in 29A and FIG. 29C shows Bliss excess for the combination in 29A. FIG. 29D shows a dose matrix showing inhibition (%) for the combination in HCT116 KRAS KO (+/-) cells. FIG. 29E shows Loewe excess for the combination in 29D and FIG. 29F shows Bliss excess for the combination in 29D. FIG. 29G – FIG. 29H show the results of single agent proliferation assays for the combination in 29A. FIG. 29I – FIG. 29J show the results of single agent proliferation assays for the combination in 29D.

[0047] FIG. 30 shows the results of the combination of SCH772984 and Trametinib in parental HCT116 and HCT116 KRAS KO (+/-) cells. FIG. 30A shows a dose matrix showing inhibition (%) for the combination in parental HCT116 cells. FIG. 30B shows Loewe excess for the combination in 30A and FIG. 30C shows Bliss excess for the combination in 30A. FIG. 30D shows a dose matrix showing inhibition (%) for the combination in HCT116 KRAS KO (+/-) cells. FIG. 30E shows Loewe excess for the combination in 30D and FIG. 30F shows Bliss excess for the combination in 30D. FIG. 30G – FIG. 30H show the results of single agent proliferation assays for the combination in 30A. FIG. 30I – FIG. 30J show the results of single agent proliferation assays for the combination in 30D.

[0048] FIG. 31 shows the results of the combination of BVD-523 and MEK-162 in parental HCT116 and HCT116 KRAS KO (+/-) cells. FIG. 31A shows a dose matrix showing inhibition (%) for the combination in parental HCT116 cells. FIG. 31B shows Loewe excess for the combination in 31A and FIG. 31C shows Bliss excess for the combination in 31A. FIG. 31D shows a dose matrix showing inhibition (%) for the combination in HCT116 KRAS KO (+/-) cells. FIG. 31E shows Loewe excess for the combination in 31D and FIG. 31F shows Bliss excess for the combination in 31D. FIG. 31G – FIG. 31H show the results of single agent proliferation assays for the combination in 31A. FIG. 31I – FIG. 31J show the results of single agent proliferation assays for the combination in 31D.

[0049] FIG. 32 shows the results of the combination of SCH772984 and MEK-162 in parental HCT116 and HCT116 KRAS KO (+/-) cells. FIG. 32A shows a dose matrix showing inhibition (%) for the combination in parental HCT116 cells. FIG. 32B shows Loewe excess for the combination in 32A and FIG. 32C shows Bliss excess for the combination in 32A. FIG. 32D shows a dose matrix showing inhibition (%) for the combination in HCT116 KRAS KO (+/-) cells. FIG. 32E shows Loewe excess for the combination in 32D and FIG. 32F shows Bliss excess for the combination in 32D. FIG. 32G – FIG. 32H show the results of single agent proliferation assays for the combination in 32A. FIG. 32I – FIG. 32J show the results of single agent proliferation assays for the combination in 32D.

[0050] FIG. 33 shows the results of the combination of BVD-523 and Trametinib in parental RKO and RKO BRAF V600E KO (+/-/-) cells. FIG. 33A shows a dose matrix showing inhibition (%) for the combination in parental

RKO cells. FIG. 33B shows Loewe excess for the combination in 33A and FIG. 33C shows Bliss excess for the combination in 33A. FIG. 33D shows a dose matrix showing inhibition (%) for the combination in RKO BRAF V600E KO (+/-/-) cells. FIG. 33E shows Loewe excess for the combination in 33D and FIG. 33F shows Bliss excess for the combination in 33D. FIG. 33G – FIG. 33H show the results of single agent proliferation assays for the combination in 33A. FIG. 33I – FIG. 33J show the results of single agent proliferation assays for the combination in 33D.

[0051] FIG. 34 shows the results of the combination of SCH772984 and Trametinib in parental RKO and RKO BRAF V600E KO (+/-/-) cells. FIG. 34A shows a dose matrix showing inhibition (%) for the combination in parental RKO cells. FIG. 34B shows Loewe excess for the combination in 34A and FIG. 34C shows Bliss excess for the combination in 34A. FIG. 34D shows a dose matrix showing inhibition (%) for the combination in RKO BRAF V600E KO (+/-/-) cells. FIG. 34E shows Loewe excess for the combination in 34D and FIG. 34F shows Bliss excess for the combination in 34D. FIG. 34G – FIG. 34H show the results of single agent proliferation assays for the combination in 34A. FIG. 34I – FIG. 34J show the results of single agent proliferation assays for the combination in 34D.

[0052] FIG. 35 shows the results of the combination of BVD-523 and MEK-162 in parental RKO and RKO BRAF V600E KO (+/-/-) cells. FIG. 35A shows a dose matrix showing inhibition (%) for the combination in parental RKO cells. FIG. 35B shows Loewe excess for the combination in 35A and FIG. 35C shows Bliss excess for the combination in 35A. FIG. 35D shows a dose matrix showing inhibition (%) for the combination in RKO BRAF V600E

KO (+/-/-) cells. FIG. 35E shows Loewe excess for the combination in 35D and FIG. 35F shows Bliss excess for the combination in 35D. FIG. 35G – FIG. 35H show the results of single agent proliferation assays for the combination in 35A. FIG. 35I – FIG. 35J show the results of single agent proliferation assays for the combination in 35D.

[0053] FIG. 36 shows the results of the combination of SCH772984 and MEK-162 in parental RKO and RKO BRAF V600E KO (+/-/-) cells. FIG. 36A shows a dose matrix showing inhibition (%) for the combination in parental RKO cells. FIG. 36B shows Loewe excess for the combination in 36A and FIG. 36C shows Bliss excess for the combination in 36A. FIG. 36D shows a dose matrix showing inhibition (%) for the combination in RKO BRAF V600E KO (+/-/-) cells. FIG. 36E shows Loewe excess for the combination in 36D and FIG. 36F shows Bliss excess for the combination in 36D. FIG. 36G – FIG. 36H show the results of single agent proliferation assays for the combination in 36A. FIG. 36I – FIG. 36J show the results of single agent proliferation assays for the combination in 36D.

[0054] FIG. 37 shows the results of the combination of BVD-523 and Trametinib in G-361 cells. FIG. 37A shows a dose matrix showing inhibition (%) for the combination. FIG. 37B shows Loewe excess for the combination in 37A and FIG. 37C shows Bliss excess for the combination in 37A. FIG. 37D – FIG. 37E show the results of single agent proliferation assays for the combination in 37A.

[0055] FIG. 38 shows the results of the combination of SCH772984 and Trametinib in G-361 cells. FIG. 38A shows a dose matrix showing inhibition (%) for the combination. FIG. 38B shows Loewe excess for the combination

in 38A and FIG. 38C shows Bliss excess for the combination in 38A. FIG. 38D – FIG. 38E show the results of single agent proliferation assays for the combination in 38A.

[0056] FIG. 39 shows the results of the combination of BVD-523 and MEK-162 in G-361 cells. FIG. 39A shows a dose matrix showing inhibition (%) for the combination. FIG. 39B shows Loewe excess for the combination in 39A and FIG. 39C shows Bliss excess for the combination in 39A. FIG. 39D – FIG. 39E show the results of single agent proliferation assays for the combination in 39A.

[0057] FIG. 40 shows the results of the combination of SCH772984 and MEK-162 in G-361 cells. FIG. 40A shows a dose matrix showing inhibition (%) for the combination. FIG. 40B shows Loewe excess for the combination in 40A and FIG. 40C shows Bliss excess for the combination in 40A. FIG. 40D – FIG. 40E show the results of single agent proliferation assays for the combination in 40A.

[0058] FIG. 41 shows the results of the combination of BVD-523 and GDC-0623 in G-361 cells. FIG. 41A shows a dose matrix showing inhibition (%) for the combination. FIG. 41B shows Loewe excess for the combination in 41A and FIG. 41C shows Bliss excess for the combination in 41A. FIG. 41D – FIG. 41E show the results of single agent proliferation assays for the combination in 41A.

[0059] FIG. 42 shows the results of the combination of SCH772984 and GDC-0623 in G-361 cells. FIG. 42A shows a dose matrix showing inhibition (%) for the combination. FIG. 42B shows Loewe excess for the combination in 42A and FIG. 42C shows Bliss excess for the combination in 42A. FIG.

42D – FIG. 42E show the results of single agent proliferation assays for the combination in 42A.

[0060] FIG. 43 shows the results of the combination of BVD-523 and Trametinib in A549 cells. FIG. 43A shows a dose matrix showing inhibition (%) for the combination. FIG. 43B – FIG. 43C show the results of single agent proliferation assays for the combination in 43A. FIG. 43D shows Loewe excess for the combination in 43A and FIG. 43E shows Bliss excess for the combination in 43A.

[0061] FIG. 44 shows the results of the combination of BVD-523 and Trametinib in H2122 cells. FIG. 44A shows a dose matrix showing inhibition (%) for the combination. FIG. 44B – FIG. 44C show the results of single agent proliferation assays for the combination in 44A. FIG. 44D shows Loewe excess for the combination in 44A and FIG. 44E shows Bliss excess for the combination in 44A.

[0062] FIG. 45 shows the results of the combination of BVD-523 and Trametinib in H1437 cells. FIG. 45A shows a dose matrix showing inhibition (%) for the combination. FIG. 45B – FIG. 45C show the results of single agent proliferation assays for the combination in 45A. FIG. 45D shows Loewe excess for the combination in 45A and FIG. 45E shows Bliss excess for the combination in 45A.

[0063] FIG. 46 shows the results of the combination of BVD-523 and Trametinib in H226 cells. FIG. 46A shows a dose matrix showing inhibition (%) for the combination. FIG. 46B – FIG. 46C show the results of single agent proliferation assays for the combination in 46A. FIG. 46D shows Loewe

excess for the combination in 46A and FIG. 46E shows Bliss excess for the combination in 46A.

[0064] FIG. 47 shows the results of the combination of SCH772984 and Trametinib in A549 cells. FIG. 47A shows a dose matrix showing inhibition (%) for the combination. FIG. 47B – FIG. 47C show the results of single agent proliferation assays for the combination in 47A. FIG. 47D shows Loewe excess for the combination in 47A and FIG. 47E shows Bliss excess for the combination in 47A.

[0065] FIG. 48 shows the results of the combination of SCH772984 and Trametinib in H2122 cells. FIG. 48A shows a dose matrix showing inhibition (%) for the combination. FIG. 48B – FIG. 48C show the results of single agent proliferation assays for the combination in 48A. FIG. 48D shows Loewe excess for the combination in 48A and FIG. 48E shows Bliss excess for the combination in 48A.

[0066] FIG. 49 shows the results of the combination of SCH772984 and Trametinib in H1437 cells. FIG. 49A shows a dose matrix showing inhibition (%) for the combination. FIG. 49B – FIG. 49C show the results of single agent proliferation assays for the combination in 49A. FIG. 49D shows Loewe excess for the combination in 49A and FIG. 49E shows Bliss excess for the combination in 49A.

[0067] FIG. 50 shows the results of the combination of SCH772984 and Trametinib in H226 cells. FIG. 50A shows a dose matrix showing inhibition (%) for the combination. FIG. 50B – FIG. 50C show the results of single agent proliferation assays for the combination in 50A. FIG. 50D shows Loewe

excess for the combination in 50A and FIG. 50E shows Bliss excess for the combination in 50A.

[0068] FIG. 51 shows the results of the combination of BVD-523 and GDC-0623 in H2122 cells. FIG. 51A shows a dose matrix showing inhibition (%) for the combination. FIG. 51B – FIG. 51C show the results of single agent proliferation assays for the combination in 51A. FIG. 51D shows Loewe excess for the combination in 51A and FIG. 51E shows Bliss excess for the combination in 51A.

[0069] FIG. 52 shows the results of the combination of BVD-523 and GDC-0623 in H1437 cells. FIG. 52A shows a dose matrix showing inhibition (%) for the combination. FIG. 52B – FIG. 52C show the results of single agent proliferation assays for the combination in 52A. FIG. 52D shows Loewe excess for the combination in 52A and FIG. 52E shows Bliss excess for the combination in 52A.

[0070] FIG. 53 shows the results of the combination of BVD-523 and GDC-0623 in H226 cells. FIG. 53A shows a dose matrix showing inhibition (%) for the combination. FIG. 53B – FIG. 53C show the results of single agent proliferation assays for the combination in 53A. FIG. 53D shows Loewe excess for the combination in 53A and FIG. 53E shows Bliss excess for the combination in 53A.

[0071] FIG. 54 shows the results of the combination of SCH772984 and GDC-0623 in A549 cells. FIG. 54A shows a dose matrix showing inhibition (%) for the combination. FIG. 54B – FIG. 54C show the results of single agent proliferation assays for the combination in 54A. FIG. 54D shows Loewe

excess for the combination in 54A and FIG. 54E shows Bliss excess for the combination in 54A.

[0072] FIG. 55 shows the results of the combination of SCH772984 and GDC-0623 in H2122 cells. FIG. 55A shows a dose matrix showing inhibition (%) for the combination. FIG. 55B – FIG. 55C show the results of single agent proliferation assays for the combination in 55A. FIG. 55D shows Loewe excess for the combination in 55A and FIG. 55E shows Bliss excess for the combination in 55A.

[0073] FIG. 56 shows the results of the combination of SCH772984 and GDC-0623 in H1437 cells. FIG. 56A shows a dose matrix showing inhibition (%) for the combination. FIG. 56B – FIG. 56C show the results of single agent proliferation assays for the combination in 56A. FIG. 56D shows Loewe excess for the combination in 56A and FIG. 56E shows Bliss excess for the combination in 56A.

[0074] FIG. 57 shows the results of the combination of SCH772984 and GDC-0623 in H226 cells. FIG. 57A shows a dose matrix showing inhibition (%) for the combination. FIG. 57B – FIG. 57C show the results of single agent proliferation assays for the combination in 57A. FIG. 57D shows Loewe excess for the combination in 57A and FIG. 57E shows Bliss excess for the combination in 57A.

[0075] FIG. 58 shows the results of the combination of BVD-523 and SCH772984. FIG. 58A shows a dose matrix showing inhibition (%) for the combination in A375 cells. FIG. 58B – FIG. 58C show the results of single agent proliferation assays for the combination in 58A. FIG. 58D shows Loewe

excess for the combination in 58A and FIG. 58E shows Bliss excess for the combination in 58A.

DETAILED DESCRIPTION OF THE INVENTION

[0076] One embodiment of the present invention is a method of treating or ameliorating the effects of a cancer in a subject in need thereof. The method comprises administering to the subject an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a type 2 MEK inhibitor or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer.

[0077] 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.

[0078] 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.

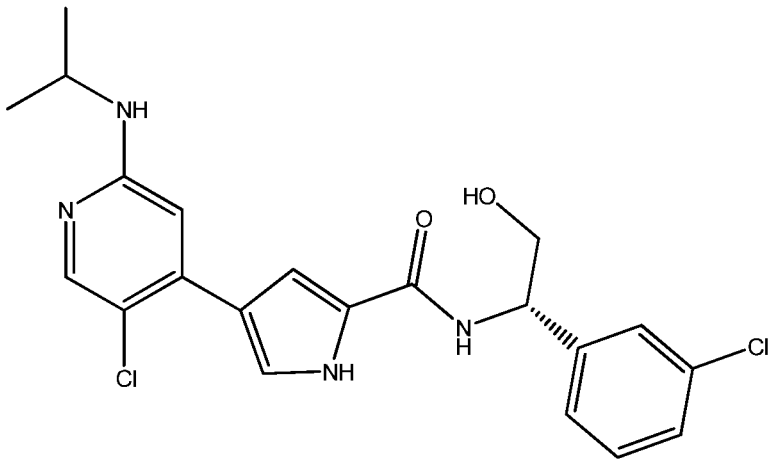
[0079] In the present invention, cancers include both solid and hemotologic cancers. Non-limiting examples of solid cancers include adrenocortical carcinoma, anal cancer, bladder cancer, bone cancer (such as osteosarcoma), brain cancer, breast cancer, carcinoid cancer, carcinoma, cervical cancer, colon 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, laryngeal 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.

[0080] 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, Sézary 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.

[0081] A preferred set of cancers that may be treated according to the present invention include a cancer of the large intestine, breast cancer, pancreatic cancer, skin cancer, endometrial cancer, neuroblastoma, leukemia, lymphoma, liver cancer, lung cancer, testicular cancer, and thyroid cancer. Preferably, the cancer is melanoma.

[0082] 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.

[0083] 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. Patent 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).

[0084] As used herein, a "MEK inhibitor", such as a type 2 MEK inhibitor means those substances that (i) directly interact with MEK (*i.e.* MEK2), *e.g.* by binding to MEK (*i.e.* MEK2) and (ii) decrease the expression or the activity of MEK (*i.e.* MEK2). Therefore, inhibitors that act upstream of MEK (*i.e.* MEK2), such as RAS inhibitors and RAF inhibitors, are not MEK

(*i.e.* MEK2) inhibitors according to the present invention. As noted above, MEK inhibitors may be classified into two types depending on whether the inhibitor competes with ATP. As used herein, "Type 1" MEK inhibitors mean those inhibitors that compete with ATP for binding to MEK. "Type 2" MEK inhibitors means those that do not compete with ATP for binding to MEK.

[0085] Non-limiting examples of type 2 MEK inhibitors according to the present invention include anthrax toxin, lethal factor portion of anthrax toxin, 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), MEK162 (Array BioPharma), PD 098059 (2-(2'-amino-3'-methoxyphenyl)-oxanaphthalen-4-one), PD 184352 (CI-1040), PD-0325901 (Pfizer), pimasertib (Santhera Pharmaceuticals), refametinib (AstraZeneca), selumetinib (AZD6244) (AstraZeneca), TAK-733 (Takeda), trametinib (Japan Tobacco), U0126 (1,4-diamino-2,3-dicyano-1,4-bis(2-aminophenylthio)butadiene) (Sigma), RDEA119 (Ardea Biosciences/Bayer), pharmaceutically acceptable salts thereof, and combinations thereof. Preferably, the type 2 MEK inhibitor is trametinib or a pharmaceutically acceptable salt thereof.

[0086] In an additional aspect of this embodiment, the subject with cancer has a somatic RAS or BRAF mutation. As used herein, "somatic mutation" means a change occurring in any cell that is not destined to become a germ cell. The mutation may be, *e.g.*, a substitution, deletion, insertion, or a fusion. Preferably, the RAS mutation is a mutation in H-RAS, N-RAS, or K-RAS. The following Tables 1, 2 and 3 show the SEQ ID Nos. of

representative nucleic acid and amino acid sequences of wild type H-RAS, K-RAS, and N-RAS from various animals, respectively. These sequences may be used in methods for identifying subjects with a mutant RAS genotype (such as in the methods set forth below).

Table 1 H-RAS sequences

SEQ ID No.	polypeptide or nucleic acid sequence	Organism	Other Information
1	nucleic acid	human	isoform 1
2	polypeptide	human	isoform 1
3	nucleic acid	human	isoform 2
4	polypeptide	human	isoform 2
5	nucleic acid	human	isoform 3
6	polypeptide	human	isoform 3
7	nucleic acid	rat (Rattus norvegicus)	variant 1
8	polypeptide	rat (Rattus norvegicus)	variant 1
9	nucleic acid	rat (Rattus norvegicus)	variant 2
10	polypeptide	rat (Rattus norvegicus)	variant 2
11	nucleic acid	mouse, Mus musculus	
12	polypeptide	mouse, Mus musculus	
13	nucleic acid	guinea pig, Cavia porcellus	variant 1
14	polypeptide	guinea pig, Cavia porcellus	variant 1
15	nucleic acid	guinea pig, Cavia porcellus	variant 2
16	polypeptide	guinea pig, Cavia porcellus	variant 2
17	nucleic acid	guinea pig, Cavia porcellus	variant 3
18	polypeptide	guinea pig, Cavia porcellus	variant 3
19	nucleic acid	guinea pig, Cavia porcellus	variant 4
20	polypeptide	guinea pig, Cavia porcellus	variant 4
21	nucleic acid	dog, Canis lupus familiaris	variant 1
22	polypeptide	dog, Canis lupus	variant 1

SEQ ID No.	polypeptide or nucleic acid sequence	Organism	Other Information
		familiaris	
23	nucleic acid	dog, Canis lupus familiaris	variant 2
24	polypeptide	dog, Canis lupus familiaris	variant 2
25	nucleic acid	cat, Felis catus	variant 1
26	polypeptide	cat, Felis catus	variant 1
27	nucleic acid	cat, Felis catus	variant 2
28	polypeptide	cat, Felis catus	variant 2
29	nucleic acid	cow, Bos taurus	variant 1
30	polypeptide	cow, Bos taurus	variant 1
31	nucleic acid	cow, Bos taurus	variant 2
32	polypeptide	cow, Bos taurus	variant 2
33	nucleic acid	cow, Bos taurus	variant X1
34	polypeptide	cow, Bos taurus	variant X1
35	nucleic acid	chicken, Gallus gallus	
36	polypeptide	chicken, Gallus gallus	

Table 2 K- RAS sequences

SEQ ID No.	polypeptide or nucleic acid sequence	Organism	Other Information
37	nucleic acid	human	isoform a
38	polypeptide	human	isoform a
39	nucleic acid	human	isoform b
40	polypeptide	human	isoform b
41	nucleic acid	rat (Rattus norvegicus)	
42	polypeptide	rat (Rattus norvegicus)	
43	nucleic acid	mouse, Mus musculus	
44	polypeptide	mouse, Mus musculus	
45	nucleic acid	rabbit, Oryctolagus cuniculus	
46	polypeptide	rabbit, Oryctolagus cuniculus	
47	nucleic acid	guinea pig, Cavia porcellus	variant 1
48	polypeptide	guinea pig, Cavia porcellus	variant 1
49	nucleic acid	guinea pig, Cavia porcellus	variant 2

SEQ ID No.	polypeptide or nucleic acid sequence	Organism	Other Information
50	polypeptide	guinea pig, Cavia porcellus	variant 2
51	nucleic acid	dog, Canis lupus familiaris	variant 1
52	polypeptide	dog, Canis lupus familiaris	variant 1
53	nucleic acid	dog, Canis lupus familiaris	variant 2
54	polypeptide	dog, Canis lupus familiaris	variant 2
55	nucleic acid	cat, Felis catus	variant 1
56	polypeptide	cat, Felis catus	variant 1
57	nucleic acid	cat, Felis catus	variant 2
58	polypeptide	cat, Felis catus	variant 2
59	nucleic acid	cow, Bos taurus	
60	polypeptide	cow, Bos taurus	
61	nucleic acid	cow, Bos taurus	variant X2
62	polypeptide	cow, Bos taurus	variant X2
63	nucleic acid	cow, Bos taurus	variant X3
64	polypeptide	cow, Bos taurus	variant X3
65	nucleic acid	chicken, Gallus gallus	
66	polypeptide	chicken, Gallus gallus	

Table 3 N-RAS sequences

SEQ ID No.	polypeptide or nucleic acid sequence	Organism	Other Information
67	nucleic acid	human	
68	polypeptide	human	
69	nucleic acid	rat (Rattus norvegicus)	
70	polypeptide	rat (Rattus norvegicus)	
71	nucleic acid	mouse, Mus musculus	
72	polypeptide	mouse, Mus musculus	
73	nucleic acid	guinea pig, Cavia porcellus	
74	polypeptide	guinea pig, Cavia porcellus	
75	nucleic acid	guinea pig, Cavia porcellus	variant X1

SEQ ID No.	polypeptide or nucleic acid sequence	Organism	Other Information
76	polypeptide	guinea pig, Cavia porcellus	variant X1
77	nucleic acid	dog, Canis lupus familiaris	
78	polypeptide	dog, Canis lupus familiaris	
79	nucleic acid	cat, Felis catus	
80	polypeptide	cat, Felis catus	
81	nucleic acid	cow, Bos taurus	
82	polypeptide	cow, Bos taurus	
83	nucleic acid	chicken, Gallus gallus	
84	polypeptide	chicken, Gallus gallus	

[0087] The following Table 4 shows the SEQ ID Nos. of representative nucleic acid and amino acid sequences of wild type BRAF from various animals. These wild type sequences may be used in methods (such as the methods set forth below) for identifying subjects with a mutant BRAF genotype.

Table 4 BRAF sequences

SEQ ID NO	Nucleic acid or polypeptide	Organism	Other information
85	nucleic acid	human	
86	polypeptide	human	
87	nucleic acid	rat (Rattus norvegicus)	
88	polypeptide	rat (Rattus norvegicus)	
89	nucleic acid	mouse, Mus musculus	
90	polypeptide	mouse, Mus musculus	
91	nucleic acid	rabbit, Oryctolagus cuniculus	
92	polypeptide	rabbit, Oryctolagus cuniculus	
93	nucleic acid	guinea pig, Cavia porcellus	
94	polypeptide	guinea pig, Cavia porcellus	
95	nucleic acid	dog, Canis lupus familiaris	variant x1

SEQ ID NO	Nucleic acid or polypeptide	Organism	Other information
96	polypeptide	dog, Canis lupus familiaris	variant x1
97	nucleic acid	dog, Canis lupus familiaris	variant x2
98	polypeptide	dog, Canis lupus familiaris	variant x2
99	nucleic acid	cat, Felis catus	
100	polypeptide	cat, Felis catus	
101	nucleic acid	cow, Bos taurus	variant X1
102	polypeptide	cow, Bos taurus	variant X1
103	nucleic acid	cow, Bos taurus	variant X2
104	polypeptide	cow, Bos taurus	variant X2
105	nucleic acid	cow, Bos taurus	variant X3
106	polypeptide	cow, Bos taurus	variant X3
107	nucleic acid	cow, Bos taurus	variant X4
108	polypeptide	cow, Bos taurus	variant X4
109	nucleic acid	cow, Bos taurus	variant X5
110	polypeptide	cow, Bos taurus	variant X5
111	nucleic acid	cow, Bos taurus	variant X6
112	polypeptide	cow, Bos taurus	variant X6
113	nucleic acid	cow, Bos taurus	variant X7
114	polypeptide	cow, Bos taurus	variant X7
115	nucleic acid	cow, Bos taurus	variant X8
116	polypeptide	cow, Bos taurus	variant X8
117	nucleic acid	cow, Bos taurus	variant X9
118	polypeptide	cow, Bos taurus	variant X9
119	nucleic acid	cow, Bos taurus	variant X10
120	polypeptide	cow, Bos taurus	variant X10
121	nucleic acid	cow, Bos taurus	variant X11
122	polypeptide	cow, Bos taurus	variant X11
123	nucleic acid	cow, Bos taurus	variant 2
124	polypeptide	cow, Bos taurus	variant 2
125	nucleic acid	horse, Equus caballus	
126	polypeptide	horse, Equus caballus	
127	nucleic acid	chicken, Gallus gallus	
128	polypeptide	chicken, Gallus gallus	

[0088] Methods for identifying mutations in nucleic acids, such as the above identified RAS and BRAF 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.

[0089] Non-limiting examples of methods for identifying mutations include PCR, sequencing, hybrid capture, in-solution capture, molecular inversion probes, fluorescent *in situ* hybridization (FISH) assay, and combinations thereof.

[0090] 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. Patent 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.

[0091] 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.

[0092] Hybrid capture methods are known in the art and are disclosed in *e.g.*, U.S. Patent Publication No. 20130203632 and U.S. Patent 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).

[0093] 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.

[0094] 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.

[0095] 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.

[0096] Examples of therapeutic antibodies that may be used in the present invention include rituximab (Rituxan), Cetuximab (Erbitux), bevacizumab (Avastin), and Ibritumomab (Zevalin).

[0097] 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.

[0098] 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 according to the present invention include A-674563 (CAS # 552325-73-2), AGL 2263, AMG-319 (Amgen, Thousand Oaks, CA), 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, CA), BML-257 (CAS # 32387-96-5), CAL-120 (Gilead Sciences, Foster City, CA), 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, MA), perifosine, PHT-427 (CAS # 1191951-57-1), PI3 kinase delta inhibitor, Merck KGaA (Merck & Co., Whitehouse Station, NJ), PI3 kinase delta inhibitors, Genentech (Roche Holdings Inc.), PI3 kinase delta inhibitors, Incozen (Incozen Therapeutics, Pvt. Ltd., Hyderabad, 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, CA), PI3-delta inhibitors, Cellzome (Cellzome AG, Heidelberg, Germany), PI3-delta inhibitors, Intellikine (Intellikine Inc., La Jolla, CA), 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, NY), SF-1126 (Semafore Pharmaceuticals, Indianapolis, IN), SH-5, SH-6, Tetrahydro Curcumin, TG100-115 (Targegen Inc., San Diego, CA), Triciribine, X-339 (Xcovery, West Palm Beach, FL), XL-499 (Evotech, Hamburg, Germany), pharmaceutically acceptable salts thereof, and combinations thereof.

[0099] 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.

[0100] 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.

[0101] 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).

[0102] 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."

[0103] 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.

[0104] 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.

[0105] 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.

[0106] 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.

[0107] In another aspect of this embodiment, administration of the first and second anti-cancer agents provides a synergistic effect compared to administration of either anti-cancer agent alone. As used herein, "synergistic" means more than additive. Synergistic effects may be measured by various assays known in the art, including but not limited to those disclosed herein, such as the excess over bliss assay.

[0108] Another embodiment of the present invention is a method of treating or ameliorating the effects of a cancer in a subject in need thereof. The method comprises administering to the subject an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is trametinib or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer.

[0109] Suitable and preferred subjects and various types of cancer 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 identified above. Methods of identifying such mutations are also as set forth above.

[0110] In one aspect of this embodiment, the BVD-523 or a pharmaceutically acceptable salt thereof is administered in the form of a pharmaceutical composition further comprising a pharmaceutically acceptable carrier or diluent.

[0111] In a further aspect of this embodiment, the trametinib or a pharmaceutically acceptable salt thereof is administered in the form of a pharmaceutical composition further comprising a pharmaceutically acceptable carrier or diluent.

[0112] In an additional 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.

[0113] In another aspect of this embodiment, administration of the first and second anti-cancer agents provides a synergistic effect compared to administration of either anti-cancer agent alone.

[0114] A further embodiment of the present invention is a method of effecting cancer cell death. The method comprises contacting the cancer cell with an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a type 2 MEK inhibitor or a pharmaceutically acceptable salt thereof.

[0115] Suitable and preferred type 2 MEK inhibitors are as disclosed herein. In this embodiment, effecting cancer cell death may be accomplished in cancer cells having various mutational backgrounds and/or that are characterized as disclosed above. Methods of identifying such mutations are also as set forth above.

[0116] In one 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.

[0117] The methods of this embodiment, which may be carried out *in vitro* 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.

[0118] In an additional aspect of this embodiment, the method further comprises contacting the cancer cell with at least one additional therapeutic agent, preferably an inhibitor of the PI3K/Akt pathway, as disclosed herein.

[0119] In another aspect of this embodiment, contacting the cancer cell with the first and second anti-cancer agents provides a synergistic effect compared to contacting the cancer cell with either anti-cancer agent alone. In this embodiment, "contacting" means bringing BVD-523 and the Type 2 MEK inhibitors, 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 and the Type 2 MEK inhibitors, and optionally other therapeutic agents to a culture media in which the cancer cells are located.

[0120] An additional embodiment of the present invention is a kit for treating or ameliorating the effects of a cancer in a subject in need thereof. The kit comprises an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a type 2 MEK inhibitor or a pharmaceutically acceptable salt thereof, packaged together with instructions for their use.

[0121] The kits may also include suitable storage containers, *e.g.*, ampules, vials, tubes, etc., for each anti-cancer agent of the present invention (which, *e.g.*, may be in the form of pharmaceutical compositions) and other reagents, *e.g.*, buffers, balanced salt solutions, etc., for use in administering the anti-cancer agents to subjects. The anti-cancer agents of the invention 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.

[0122] In this embodiment, suitable and preferred type 2 MEK inhibitors and subjects are as set forth above. In this embodiment, the kit may be used to treat the cancers disclosed above, including those cancers with the mutational backgrounds identified herein. Methods of identifying such mutations are as set forth above.

[0123] 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.

[0124] In another aspect of this embodiment, administration of the first and second anti-cancer agents provides a synergistic effect compared to administration of either anti-cancer agent alone.

[0125] Another embodiment of the present invention is a pharmaceutical composition for treating or ameliorating the effects of a cancer in a subject in need thereof. The pharmaceutical composition comprises a pharmaceutically acceptable diluent or carrier and an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a type 2 MEK inhibitor or a pharmaceutically acceptable salt thereof, wherein administration of the first and second anti-cancer agents provides a synergistic effect compared to administration of either anti-cancer agent alone.

[0126] Suitable and preferred subjects and type 2 MEK inhibitors are as disclosed herein. The pharmaceutical compositions of the invention may be used to treat the cancers disclosed above, including those cancers with the mutational backgrounds identified herein. Methods of identifying such mutations are also as set forth above.

[0127] In a further 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.

[0128] The pharmaceutical compositions according to the present invention may be in a unit dosage form comprising both anti-cancer agents. In another aspect of this embodiment, the first anti-cancer agent is in a first unit dosage form and the second anti-cancer agent is in a second unit dosage form, separate from the first.

[0129] The first and second anti-cancer agents may be co-administered to the subject, either simultaneously or at different times, as deemed most appropriate by a physician. If the first and second anti-cancer agents are administered at different times, for example, by serial administration, the first anti-cancer agent may be administered to the subject before the second anti-cancer agent. Alternatively, the second anti-cancer agent may be administered to the subject before the first anti-cancer agent.

[0130] A further embodiment of the present invention is a method of treating or ameliorating the effects of a cancer in a subject in need thereof. The method comprises administering to the subject an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a MEK inhibitor selected from the group consisting of antroquinonol (Golden Biotechnology), AS-1940477 (Astellas), AS-703988 (Merck KGaA), BI-847325 (Boehringer Ingelheim), E-6201 (Eisai), GDC-0623 (Hoffmann-La Roche), GDC-0973, RG422, RO4987655, RO5126766, SL327, WX-554 (Wilex), YopJ polypeptide, pharmaceutically acceptable salts thereof, and combinations thereof, to treat or ameliorate the effects of the cancer.

[0131] 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 identified above. Methods of identifying such mutations are also as set forth above.

[0132] In an additional 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.

[0133] In another aspect of this embodiment, administration of the first and second anti-cancer agents provides a synergistic effect compared to administration of either anti-cancer agent alone.

[0134] An additional embodiment of the present invention is a method of effecting cancer cell death. The method comprises contacting the cancer cell with an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a MEK inhibitor selected from the group consisting of antroquinonol (Golden Biotechnology), AS-1940477 (Astellas), AS-703988 (Merck KGaA), BI-847325 (Boehringer Ingelheim), E-6201 (Eisai), GDC-0623 (Hoffmann-La Roche), GDC-0973, RG422, RO4987655, RO5126766, SL327, WX-554 (Wilex), YopJ polypeptide, pharmaceutically acceptable salts thereof, and combinations thereof.

[0135] In this embodiment, the methods may be used to effect cell death in any of the cancers disclosed above, including those cancers with the mutational backgrounds identified herein. Methods of identifying such mutations are also as set forth above.

[0136] In one 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.

[0137] In another aspect of this embodiment, the method further comprises contacting the cancer cell with at least one additional therapeutic agent, preferably an inhibitor of the PI3K/Akt pathway, as disclosed herein.

[0138] In a further aspect of this embodiment, contacting the cancer with the first and second anti-cancer agents provides a synergistic effect compared to contacting the cancer cell with either anti-cancer agent alone. In this embodiment, "contacting" means bringing BVD-523 and the MEK inhibitors, 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 and the MEK inhibitors, and optionally other therapeutic agents to a culture media in which the cancer cells are located.

[0139] The methods of this embodiment, which may be carried out *in vitro* 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.

[0140] Another embodiment of the present invention is a kit for treating or ameliorating the effects of a cancer in a subject in need thereof. The kit comprises an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a MEK inhibitor selected from the group consisting of antroquinonol (Golden Biotechnology), AS-1940477 (Astellas), AS-703988 (Merck KGaA), BI-847325 (Boehringer Ingelheim), E-6201 (Eisai), GDC-0623 (Hoffmann-La Roche), GDC-0973, RG422, RO4987655, RO5126766, SL327, WX-554 (Wilex), YopJ polypeptide, pharmaceutically acceptable salts thereof, and combinations thereof, packaged together with instructions for their use.

[0141] Suitable and preferred subjects 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 identified herein. Methods of identifying such mutations are also as set forth above.

[0142] In another 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.

[0143] In a further aspect of this embodiment, administration of the first and second anti-cancer agents provides a synergistic effect compared to administration of either anti-cancer agent alone.

[0144] A further embodiment of the present invention is a pharmaceutical composition for treating or ameliorating the effects of a cancer in a subject in need thereof. The pharmaceutical composition comprises a pharmaceutically acceptable diluent or carrier and an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a MEK inhibitor selected from the group consisting of antroquinonol (Golden Biotechnology), AS-1940477 (Astellas), AS-703988 (Merck KGaA), BI-847325 (Boehringer Ingelheim), E-6201 (Eisai), GDC-0623 (Hoffmann-La Roche), GDC-0973, RG422, RO4987655, RO5126766, SL327, WX-554 (Wilex), YopJ polypeptide, pharmaceutically acceptable salts thereof, and combinations thereof, wherein administration of the first and second anti-cancer agents provides a synergistic effect compared to administration of either anti-cancer agent alone.

[0145] Suitable and preferred subjects 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 identified herein. Methods of identifying such mutations are also as set forth above.

[0146] In another 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.

[0147] The pharmaceutical compositions according to this embodiment may be in a unit dosage form comprising both anti-cancer agents. In another aspect of this embodiment, the first anti-cancer agent is in a first unit dosage form and the second anti-cancer agent is in a second unit dosage form, separate from the first.

[0148] The first and second anti-cancer agents may be co-administered to the subject, either simultaneously or at different times, as deemed most appropriate by a physician. If the first and second anti-cancer agents are administered at different times, for example, by serial administration, the first anti-cancer agent may be administered to the subject before the second anti-cancer agent. Alternatively, the second anti-cancer agent may be administered to the subject before the first anti-cancer agent.

[0149] 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 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.

[0150] A suitable, non-limiting example of a dosage of an anti-cancer agent 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 an anti-cancer agent disclosed herein, *e.g.*, BVD-523 and a MEK inhibitor, may be administered as two, three, four, five, six or more sub-doses, administered separately at appropriate intervals throughout the day.

[0151] The anti-cancer agents or the pharmaceutical compositions 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, the anti-cancer agents or the pharmaceutical compositions of the present invention may be administered in conjunction with other treatments. The anti-cancer agents or the pharmaceutical compositions of the present invention may be encapsulated or otherwise protected against gastric or other secretions, if desired.

[0152] The pharmaceutical compositions of the invention comprise one or more active ingredients, *e.g.* anti-cancer agents, 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.).

[0153] 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.

[0154] 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.

[0155] 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.

[0156] 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.

[0157] 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.

[0158] 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.

[0159] 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.

[0160] 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.

[0161] 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.

[0162] 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.

[0163] 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.

Nucleic Acid

[0164] “Nucleic acid" or "oligonucleotide" or "polynucleotide" used herein mean at least two nucleotides covalently linked together. Many variants of a nucleic acid may be used for the same purpose as a given nucleic acid. Thus, a nucleic acid also encompasses substantially identical nucleic acids and complements thereof.

[0165] Nucleic acids may be single stranded or double stranded, or may contain portions of both double stranded and single stranded sequences. The nucleic acid may be DNA, both genomic and cDNA, RNA, or a hybrid, where the nucleic acid may contain combinations of deoxyribo- and ribo-nucleotides, and combinations of bases including uracil, adenine, thymine, cytosine, guanine, inosine, xanthine hypoxanthine, isocytosine and isoguanine. Nucleic acids may be synthesized as a single stranded molecule or expressed in a cell (*in vitro* or *in vivo*) using a synthetic gene. Nucleic acids may be obtained by chemical synthesis methods or by recombinant methods.

[0166] A nucleic acid will generally contain phosphodiester bonds, although nucleic acid analogs may be included that may have at least one different linkage, *e.g.*, phosphoramidate, phosphorothioate, phosphorodithioate, or O-methylphosphoroamidite linkages and peptide

nucleic acid backbones and linkages. Other analog nucleic acids include those with positive backbones; non-ionic backbones, and non-ribose backbones, including those disclosed in U.S. Pat. Nos. 5,235,033 and 5,034,506. Nucleic acids containing one or more non-naturally occurring or modified nucleotides are also included within the definition of nucleic acid.

[0167] A nucleic acid molecule is "complementary" to another nucleic acid molecule if it hybridizes with the second nucleic acid molecule, although some level of mismatch is permitted. Hybridization may be under conditions of low stringency, moderate stringency or high stringency. Suitable stringency conditions are, in general, determined by the length of the nucleic acid molecules, the degree of complementation, and other factors readily understood by those of skill in the art. In some embodiments, for example, for preliminary screening, low stringency conditions, such as a temperature of about 48 to about 55°C, in a buffer including about 5x SSC, about 0.1 to about 0.5 % SDS, and about 0 to about 30% formamide. Moderate stringency hybridization conditions may be at a temperature of about 60°C in a buffer including about 5x to about 6x SSC, about 0.1 to about 0.5 % SDS, and about 40% formamide. High stringency hybridization conditions may be at a temperature of about 65°C in a buffer including about 5x to about 6x SSC, about 0.1 to about 0.5 % SDS, and about 50% formamide. In some embodiments, high stringency conditions are as described herein or are, for example, conditions that allow hybridization comparable with the hybridization that occurs using a DNA probe of at least 500 nucleotides in length, in a buffer containing 0.5 M $NaHP0_4$, pH 7.2, 7% SDS, 1 mM EDTA, and 1 % BSA (fraction V), at a temperature of 65°C, or a buffer containing 48% formamide,

4.8x SSC, 0.2 M Tris-Cl, pH 7.6, 1x Denhardt's solution, 10% dextran sulfate, and 0.1 % SDS, at a temperature of 42°C.

[0168] Hybridizations may be carried out over a period of about 20 to 30 minutes, or about 2 to 6 hours, or about 10 to 15 hours, or over 24 hours or more. High stringency hybridization is also relied upon for the success of numerous techniques routinely performed by molecular biologists, such as high stringency PCR, DNA sequencing, single strand conformational polymorphism analysis, and *in situ* hybridization. In contrast to northern and Southern hybridizations, these techniques are usually performed with relatively short probes (*e.g.*, usually about 15 nucleotides or longer for PCR or sequencing and about 40 nucleotides or longer for *in situ* hybridization).

[0169] A probe or primer is a single-stranded DNA or RNA molecule (*e.g.*, an oligonucleotide) of defined sequence that can base pair to a second DNA or RNA molecule that contains a complementary sequence (the target). The stability of the resulting hybrid molecule depends upon the extent of the base pairing that occurs, and is affected by parameters such as the degree of complementarity between the probe and target molecule, and the degree of stringency of the hybridization conditions. The degree of hybridization stringency is affected by parameters such as the temperature, salt concentration, and concentration of organic molecules, such as formamide, and is determined by methods that are known to those skilled in the art. Probes or primers specific for the nucleic acid sequences described herein, or portions thereof, may vary in length by any integer from at least 8 nucleotides to over 500 nucleotides, including any value in between, depending on the purpose for which, and conditions under which, the probe or primer is used.

For example, a probe or primer may be 8, 10, 15, 20, or 25 nucleotides in length, or may be at least 30, 40, 50, or 60 nucleotides in length, or may be over 100, 200, 500, or 1000 nucleotides in length. Probes or primers specific for the nucleic acid molecules described herein may have greater than 55-75% sequence identity, or at least 75-85% sequence identity, or at least 85-99% sequence identity, or 100% sequence identity to the nucleic acid sequences described herein.

[0170] Probes or primers may be derived from a gene, chromosomal segment, or chromosome that is used as a reference, for example, in variance detection to determine whether a test sample of the same gene, chromosomal segment, or chromosome derived from a particular individual contains the identical sequence or a different sequence at one or more nucleotide positions. Probes may be derived from genomic DNA or cDNA, for example, by amplification, or from cloned DNA segments, and may contain either genomic DNA or cDNA sequences representing all or a portion of a single gene from a single individual. Probes or primers may be chemically synthesized.

[0171] Probes or primers can be detectably-labeled, either radioactively or nonradioactive, by methods that are known to those skilled in the art.

[0172] The present invention provides 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.

[0173] 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

[0174] 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 5 shows a summary of drug treatments that were escalated.

Table 5 - 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)

[0175] Single agent dose escalations were performed based on Little *et al.*, 2011 and is outlined in FIG. 19. 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. 19).

[0176] 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.

[0177] 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 6 shows the projected dose increases using these schemes.

Table 6 - 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

				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)**
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

[0178] Clonal resistant cell populations were derived from resistant cell pools by limiting dilution.

[0179] 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 FIGS. 2A-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.

[0180] Proliferation assays for month 1 were initiated at day 28 using cells growing in the concentrations of each agent indicated in Table 7.

Table 7 - 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

[0181] Proliferation assays for month 2 were initiated at day 56 using cells growing in the concentrations of each agent indicated in Table 8.

Table 8 - 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

[0182] 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 9). For the BVD-523 treatment, where cells appeared to have almost completely stopped growing and looked particularly fragile at the top concentration (1.8μM), cultures were maintained at a lower concentration for the 2 week period.

Table 9 - 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 T: 30 nM	D: 80 nM T: 16 nM
5	Dab + BVD-523	D: 42 nM 523: 1.4 μM	D: 28 nM 523: 0.9 μM
6	Tram + BVD-523	T: 4 nM 523: 0.6 μM	T: 2.5 nM 523: 0.4 μM

[0183] Proliferation assays for month 3 used cells growing in the concentrations of each agent indicated in Table 10.

Table 10 - 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

[0184] 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 10x8 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 100μl of CellTiter-Glo/PBS (1:1) added and the plates processed as per the manufacturer's instructions (Promega). Media only background values were subtracted before the data was analysed. The Bliss additivity model was then applied.

[0185] In brief, predicted fractional inhibition values for combined inhibition were calculated using the equation C_{bliss} =A + B – (A x 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.

[0186] 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).

[0187] 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 800nM 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.

Example 2

Dose Escalation and Proliferation Assays – Month 1

Dose Escalation Progress – Month 1

[0188] 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. FIGS. 1A-C show month 1 progress for the dose escalation studies.

Proliferation Assay Results – Month 1

[0189] Proliferation assays were performed to assess the response of the escalated cells lines vs. parental cell line, to BVD-523, dabrafenib, and trametinib treatments.

[0190] FIGS. 2A-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 (FIGS. 2D-F, 2H) suggest differential growth rates between treatments. These differences may influence the responses of lines to inhibitors in the proliferation assays.

[0191] Table 11 shows IC_{50} data for month 1 of the studies.

Table 11 - IC_{50} Data - Month 1

Compound	Cell Line, Relative IC_{50} (nM)						
	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

[0192] 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.

[0193] 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

[0194] 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 100x parental cell IC_{50} (FIGS. 3A,B). The single agent escalation of BVD-523 progressed more slowly compared to dabrafenib and trametinib (FIG. 3C). See FIG. 3D 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.

[0195] 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

[0196] 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.

[0197] FIGS. 4A-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 (FIGS. 4D-F, 4H) suggest differential growth rates between treatments. These differences may influence the responses of lines to inhibitors in the proliferation assays.

[0198] FIGS. 5A-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.

[0199] Table 12 shows IC_{50} data for month 2 of the studies. Relative IC_{50}s were determined from 4-parameter curve fits in Prism.

Table 12 - IC_{50} Data - Month 2

Compound	Cell Line, Relative IC_{50} (nM)						
	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

[0200] FIGS. 6A-C show single and combination agent escalation for month 3 of the studies. FIG. 6D shows a comparison of single agent escalations.

Proliferation Assay Results – Month 3

[0201] FIG. 7 shows an assessment of growth during the proliferation assay in DMSO control wells. FIGS. 8A-D show results from month 3 of the studies. FIGS. 9A-D show results from month 3 of the studies with a focus on single treatment cell lines.

[0202] Table 13 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 13 - IC_{50} Data - Month 3

Compound	**Cell Line, Relative IC_{50} (nM)**						
	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

Example 5

Combination Study Results

[0203] As expected, A375 cells, which carry a BRAF (V600E) mutation, were sensitive to dabrafenib. Single agent IC_{50} values calculated using Alamar Blue (FIGS. 10, 12, 14) were generally slightly lower for Dabrafenib and BVD-523 compared to those derived using CellTiter-Glo (FIGS. 11, 13, 15). Published IC_{50} values for Dabrafenib and Trametinib in a 72 hour CellTiter-Glo assay were 28 ± 16nM and 5 ± 3nM 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.

[0204] 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.

[0205] HCT116 cells are human colorectal cancer cells with mutations in KRAS. Dabrafenib and Trametinib were antagonist at relevant on-target concentrations. In contrast, Trametinib exhibited synergy with AZ628 over a broad range of combinations, and with higher concentrations of Sorafenib. BVD-523 exhibited windows of synergy with both AZ628 and Sorafenib.

[0206] In A375 cells, trametinib exhibited pockets of synergy at lower concentrations of Dabrafenib and AZ628. BVD-523 exhibited a window of synergy with the lower concentrations of Sorafenib.

Example 6

BVD-523 altered markers of MAPK kinase activity and effector function

[0207] For Western blot studies, HCT116 cells (5 x 10^6) were seeded into 10 cm dishes in McCoy's 5A plus 10% FBS. A375 cells (2.5 x 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 14 (for the 4-hour treatment) and Table 15 (for the 24-hour treatment) below.

Table 14 – 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/S363	90	Millipore	04-419	1:40000	o/n 4˚C 5% BSA	anti-rabbit

Antigen	Size (kDa)	Supplier	Cat No	Dilution	Incubation / Block Conditions	Secondary
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
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 15 – Antibody details

Antigen	Size (kDa)	Supplier	Cat No	Dilution	Incubation / Block Conditions	Secondary
pRB (Ser780)	105	Cell Signalin	9307	1:2000	o/n 4˚C 5% BSA	anti-rabbit

Antigen	Size (kDa)	Supplier	Cat No	Dilution	Incubation / Block Conditions	Secondary
		g				
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/S363	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

[0208] FIGS. 16-18 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.

[0209] 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.

[0210] 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.

[0211] 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.

[0212] In sum, FIGS. 16-18 show that BVD-523 inhibits the MAPK signaling pathway and may be more favorable compared to RAF or MEK inhibition in this setting.

[0213] 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

Cell culture studies of MEK and ERK inhibitors

Single Agent Proliferation Assay

[0214] Cells were seeded in 96-well plates at the densities and media conditions indicated in Table 16 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 72h at 37°C, 5% CO2 in a humidified atmosphere. CellTiter-Glo® reagent (Promega, Madison, WI) 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, CA).

Combination Proliferation Assay

[0215] Cells were seeded in triplicate 96-well plates at the densities and media conditions indicated in Table 16 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 0.2%. Combinations were tested using a 10 x 8 dose matrix or a 10 x 6 dose matrix. Test compounds were incubated with the cells for 72h at 37°C, 5% CO2 in a humidified atmosphere. CellTiter-Glo® reagent (Promega, Madison, WI) 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.

[0216] 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, MA) 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 GraphPad Prism (GraphPad Software, La Jolla, CA) (plotted using percentage viability relative to DMSO only treated controls).

Table 16 - Cell Line Seeding Density and Growth Media

Cell Line	Seeding Density (cells/well)	Media
HCT116 Parental	1000	McCoy's 5A + 10% FBS
HCT116 KRAS KO (+/-)	2000	McCoy's 5A + 10% FBS
RKO Parental	2000	McCoy's 5A + 10% FBS
RKO BRAF KO (+/-/-)	2000	McCoy's 5A + 10% FBS
A375 Parental	2000	DMEM + 10% FBS
A375 NRAS (Q61K/+/+)	2000	DMEM + 10% FBS
G-361	5000	McCoy's 5A + 10% FBS
A549	750	RPMI 1640 + 10% FBS
H2212	4000	RPMI 1640 + 10% FBS
H1437	1500	RPMI 1640 + 10% FBS
H226	750	RPMI 1640 + 10% FBS

Results

[0217] The aim of this study was to assess the effects on cell viability of combining ERK inhibitors with MEK inhibitors in a panel of isogenic and non-isogenic cancer cell lines (Table 17).

Table 17 – Description of Cell Lines Studied

Cell Line	Cancer Type	Description
HCT116 Parental	CRC	Heterozygous parental cells containing one mutant KRAS allele (G13D) and one wild type allele
HCT116 KRAS KO (+/-)	CRC	Knock out of mutant KRAS allele in heterozygous parental cells
RKO Parental	CRC	Triploid parental cells containing two mutant BRAF alleles (V600E) and one wild type allele
RKO BRAF KO (+/-/-)	CRC	Knock out of both mutant BRAF alleles (V600E) in triploid parental cells
A375 Parental	Melanoma	Hypotriploid parental line carrying BRAF (V600E) mutation
A375 NRAS (Q61K/+/+)	Melanoma	Heterozygous knock-in of NRAS activating mutation (Q61K)

Cell Line	Cancer Type	Description
G-361	Melanoma	BRAF (V600E) mutant
A549	NSCLC	BRAF mutant
H2212	NSCLC	BRAF mutant
H1437	NSCLC	KRAS wild type
H226	NSCLC	KRAS wild type

[0218] An initial round of single agent assays was performed in the A375 (FIG. 20), HCT116 (FIG. 21) and RKO-isogenic (FIG. 22) cell line pairs. IC_{50} values are shown in Table 18. These revealed no differentials in response to ERK or MEK inhibition between the two cell lines within the A375 and HCT116 isogenic pair. This suggests that under the assay conditions tested 1) the knocked-in mutant NRAS allele does not drive resistance to MEK or ERK inhibition in A375 cells and 2) sensitivity of HCT116 to MEK/ERK inhibition is not coupled to the mutant KRAS allele.

Table 18 – Single Agent IC_{50} Values

Compound	A375		HCT116		RKO	
	Parental	NRAS (Q61K/+)	Parental	KRAS KO (+/-)	Parental	BRAF KO (+/-/-)
BVD-523	0.193	0.243	0.256	0.316	0.621	0.762
SCH772984	0.043	0.079	0.116	0.141	0.126	0.125
Trametinib	0.0003	0.0005	0.007	0.006	0.008	0.003
MEK-162	0.023	0.033	0.114	0.113	0.210	0.023
GDC-0623	0.008	0.010	0.031	0.029	0.032	0.005
GDC-0973	0.002	0.003	0.090	0.061	0.040	0.031
Paclitaxel	0.003	0.006	0.003	0.003	0.003	0.003

Table 19 – Bliss Volumes

	A549	H1437	H2122	H226	HCT116 KRAS KO (+/-)	HCT116 Parental	RKO BRAF V600E KO (+/-/-)	RKO Parental	A375 NRAS (Q61K/+)	A375 Parental	G-361
BVD-523 x GDC-0623	nt	0.29	0.633	-0.505	nt	nt	nt	nt	0.014	-0.963	4.62
BVD-523 x MEK-162	nt	nt	nt	nt	-0.221	1.09	-0.781	-0.748	-0.117	-0.488	1.29
BVD-523 x Trametinib	1.06	-0.324	0.361	0.364	0.811	0.606	1.88	2.16	0.188	1.83	0.774
SCH772984 x GDC-0623	-0.0669	0.525	0.244	-0.792	nt	nt	nt	nt	0.442	-0.444	3.25
SCH772984 x MEK-162	nt	nt	nt	nt	1.25	1.4	2.47	0.378	-0.697	-0.261	1.53
SCH772984 x Trametinib	-0.436	-1.44	-0.0333	-3.15	1.94	2.09	4.62	-1.59	0.0516	-0.256	2.42

Table 20 – Loewe Volumes

	A549	H1437	H2122	H226	HCT116 KRAS KO (+/-)	HCT116 Parental	RKO BRAF V600E KO (+/-/-)	RKO Parental	A375 NRAS (Q61K/+)	A375 Parental	G-361
BVD-523 x GDC-0623	nt	0.899	1.1	0.731	nt	nt	nt	nt	-0.0852	-0.217	4.39
BVD-523 x MEK-162	nt	nt	nt	nt	1.3	1.93	3.08	0.596	1.18	0.821	1.94
BVD-523 x Trametinib	1.69	2.35	1.61	2.77	3.1	2.05	2.99	1.43	2.2	0.294	1.65
SCH772984 x GDC-0623	0.846	1.52	1.1	1.22	nt	nt	nt	nt	0.0892	0.256	4.04
SCH772984 x MEK-162	nt	nt	nt	nt	3.27	3.08	2.56	1.96	0.685	1.34	1.95
SCH772984 x Trametinib	2.4	2.4	2	2.1	4.94	4.23	2.52	2.71	2.1	1.95	2.72

Table 21 – Synergy Scores

	A549	H1437	H2122	H226	HCT116 KRAS KO (+/-)	HCT116 Parental	RKO BRAF V600E KO (+/-/-)	RKO Parental	A375 NRAS (Q61K/+)	A375 Parental	G-361
BVD-523 x GDC-0623	nt	0.562	0.483	0.578	nt	nt	nt	nt	0.463	0.498	2.5
BVD-523 x MEK-162	nt	nt	nt	nt	1.68	2.28	2.53	0.777	1.43	1.49	1.88
BVD-523 x Trametinib	1.59	1.51	0.748	1.35	3.23	2.46	2.82	1.06	1.28	0.731	1.23
SCH772984 x GDC-0623	0.897	0.695	0.546	0.679	nt	nt	nt	nt	0.695	0.673	2.74
SCH772984 x MEK-162	nt	nt	nt	nt	3.2	3.4	2.06	1.26	1.22	1.54	2.08
SCH772984 x Trametinib	2	1.39	0.927	1.23	4.62	4.32	1.97	1.81	1.29	1.19	1.53

[0219] Surprisingly, deletion of the mutant BRAF (V600E) alleles in RKO cells increased the sensitivity to several of the MEK inhibitors, but did not markedly alter the response to ERK inhibition (FIG. 22). This is consistent with the general observation that upstream modulations of the MAPK pathway that alter sensitivity to MEK inhibitors do not markedly affect sensitivity to ERK inhibition.

[0220] Combination interactions between two compounds were assessed across a matrix of concentrations using the Loewe Additivity and Bliss Independence Models with Chalice™ Bioinformatics Software (Horizon Discovery Group, Cambridge, MA). 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.

[0221] Visualization of the Bliss 'excess inhibition' heat maps for the A375 parental and NRAS mutant (Q61K) cell lines revealed a small window of synergy between BVD-523 and all three MEK inhibitors tested (FIG. 23, FIG. 25, FIG. 27). These observations were confirmed in a second BRAF mutant cell line G-361 (FIG. 37, FIG. 39, FIG. 41) and using a second benchmark ERK inhibitor SCH772984 (FIG. 24, FIG. 26, FIG. 28 and FIG. 38, FIG. 40, FIG. 42, respectively). Although not as strong, these windows of synergy were also mostly detected when the data was analyzed using the Loewe model.

[0222] In summary, these results suggest that interactions between BVD-523 and MEK inhibitors may potentially be synergistic in melanoma cell lines mutated for BRAF.

[0223] In contrast, when assessed using the Bliss model, interactions between BVD-523 or SCH772984 and MEK inhibitors in HCT116 (FIG. 29 – FIG. 32) and the lung lines (FIG. 44 – FIG. 57) appeared to be mostly additive. In the RKO cells (FIG. 33 – FIG. 36) there were pockets of mild antagonism at higher concentrations. Excess scores were generally more positive, but still mainly additive, when the BVD-523 combinations were analyzed using the Loewe model. Similar results were also obtained for the SCH772984 combinations in these cell lines using the Bliss model, however, the Loewe model suggested the possible presence of regions of synergy in HCT116 and some of the lung lines that were not apparent from the Bliss model.

[0224] Synergistic interactions were scored in two ways. Excess activity over that predicted if a combination was additive can be calculated using a simple volume score, which calculates the volume between the measured and the predicted response surface. This volume score shows whether the overall response to a combination is synergistic (positive values), antagonistic (negative values) or additive (values ~ 0). Table 19 shows Bliss volumes and Table 20 shows Loewe volumes; nt = not tested. Additionally, a 'Synergy Score', a positive-gated inhibition-weighted volume over Loewe additivity, is calculated and results are shown in Table 21; nt = not tested. This provides an additional prioritization favoring combinations whose synergy occurs at high effect levels, ignoring antagonistic portions of the response surface.

Example 8

Combination Interactions Between ERK inhibitors

[0225] 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 7. Viability was determined using CellTiter-Glo® reagent (Promega, Madison, WI) according to manufacturer's instructions and luminescence was detected using the BMG FLUOstar plate reader (BMG Labtech, Ortenberg, Germany).

[0226] 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. 58).

[0227] In summary, these results suggest that interactions between BVD-523 and SCH772984 are at least additive, and in some cases synergistic.

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[0228] All documents cited in this application are hereby incorporated by reference as if recited in full herein.

[0229] 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.

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The claims defining the invention are as follows:

1. A method of treating or ameliorating the effects of a cancer in a subject in need thereof comprising administering to the subject an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a type 2 MEK inhibitor or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer,

wherein the type 2 MEK inhibitor is selected from the group consisting of GDC-0623, MEK162, trametinib, pharmaceutically acceptable salts thereof, and combinations thereof, and

wherein administration of the first and second anti-cancer agents provides a synergistic effect compared to administration of either anti-cancer agent alone.

2. The method according to claim 1, wherein the subject is a mammal.

3. The method according to claim 2, wherein the mammal is selected from the group consisting of humans, primates, farm animals, and domestic animals.

4. The method according to claim 2, wherein the mammal is a human.

5. The method according to claim 1, wherein the type 2 MEK inhibitor is trametinib or a pharmaceutically acceptable salt thereof.

6. The method according to claim 1, wherein the subject with cancer has a somatic RAS or BRAF mutation.

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7. The method according to claim 1, wherein the cancer is selected from the group consisting of a cancer of the large intestine, breast cancer, pancreatic cancer, skin cancer, endometrial cancer, neuroblastoma, leukemia, lymphoma, liver cancer, lung cancer, testicular cancer, and thyroid cancer.

8. The method according to claim 1, wherein the cancer is melanoma.

9. 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 drug, a toxin, a radionuclide, an immunomodulator, a photoactive therapeutic agent, a radiosensitizing agent, a hormone, an anti-angiogenesis agent, and combinations thereof.

10. The method according to claim 9, wherein the additional therapeutic agent is an inhibitor of the PI3K/Akt pathway.

11. The method according to claim 10, 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, CA), 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), BML-257 (CAS # 32387-96-5), CAL-120 (Gilead Sciences, Foster City, CA), 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),

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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, MA), perifosine, PHT-427 (CAS # 1191951-57-1), pictilisib (Roche Holdings Inc.), PIK-90 (CAS # 677338-12-4), SC-103980 (Pfizer, New York, NY), SF-1126 (Semafore Pharmaceuticals, Indianapolis, IN), SH-5, SH-6, Tetrahydro Curcumin, TG100-115 (Targegen Inc., San Diego, CA), Triciribine, X-339 (Xcovery, West Palm Beach, FL), XL-499 (Evotech, Hamburg, Germany), pharmaceutically acceptable salts thereof, and combinations thereof.

12. A method of treating or ameliorating the effects of a cancer in a subject in need thereof comprising administering to the subject an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is trametinib or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer,

wherein administration of the first and second anti-cancer agents provides a synergistic effect compared to administration of either anti-cancer agent alone.

13. The method according to claim 12, wherein the subject is a mammal.

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14. The method according to claim 13, wherein the mammal is selected from the group consisting of humans, primates, farm animals, and domestic animals.

15. The method according to claim 13, wherein the mammal is a human.

16. The method according to claim 12, wherein the BVD-523 or a pharmaceutically acceptable salt thereof is administered in the form of a pharmaceutical composition further comprising a pharmaceutically acceptable carrier or diluent.

17. The method according to claim 12, wherein the trametinib or a pharmaceutically acceptable salt thereof is administered in the form of a pharmaceutical composition further comprising a pharmaceutically acceptable carrier or diluent.

18. The method according to claim 12, wherein the subject with cancer has a somatic RAS mutation or BRAF mutation.

19. The method according to claim 12, wherein the cancer is selected from the group consisting of a cancer of the large intestine, breast cancer, pancreatic cancer, skin cancer, endometrial cancer, neuroblastoma, leukemia, lymphoma, liver cancer, lung cancer, testicular cancer, and thyroid cancer.

20. The method according to claim 12, wherein the cancer is melanoma.

21. The method according to claim 12 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 drug, a

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toxin, a radionuclide, an immunomodulator, a photoactive therapeutic agent, a radiosensitizing agent, a hormone, an anti-angiogenesis agent, and combinations thereof.

22. The method according to claim 21, wherein the additional therapeutic agent is an inhibitor of the PI3K/Akt pathway.

23. The method according to claim 22, 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, CA), 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), BML-257 (CAS # 32387-96-5), CAL-120 (Gilead Sciences, Foster City, CA), 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, MA), perifosine, PHT-427 (CAS # 1191951-57-1),

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pictilisib (Roche Holdings Inc.), PIK-90 (CAS # 677338-12-4), SC-103980 (Pfizer, New York, NY), SF-1126 (Semafore Pharmaceuticals, Indianapolis, IN), SH-5, SH-6, Tetrahydro Curcumin, TG100-115 (Targegen Inc., San Diego, CA), Triciribine, X-339 (Xcovery, West Palm Beach, FL), XL-499 (Evotech, Hamburg, Germany), pharmaceutically acceptable salts thereof, and combinations thereof.

24. A method of effecting cancer cell death comprising contacting the cancer cell with an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a type 2 MEK inhibitor or a pharmaceutically acceptable salt thereof,

wherein the type 2 MEK inhibitor is selected from the group consisting of GDC-0623, MEK162, trametinib, pharmaceutically acceptable salts thereof, and combinations thereof, and

wherein administration of the first and second anti-cancer agents provides a synergistic effect compared to administration of either anti-cancer agent alone.

25. The method according to claim 24, wherein the subject is a mammal.

26. The method according to claim 25, wherein the mammal is selected from the group consisting of humans, primates, farm animals, and domestic animals.

27. The method according to claim 25, wherein the mammal is a human.

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28. The method according to claim 24, wherein the type 2 MEK inhibitor is selected from the group consisting of trametinib or a pharmaceutically acceptable salt thereof.

29. The method according to claim 24, wherein the subject with cancer has a somatic RAS mutation or BRAF mutation.

30. The method according to claim 24, wherein the cancer is selected from the group consisting of a cancer of the large intestine, breast cancer, pancreatic cancer, skin cancer, endometrial cancer, neuroblastoma, leukemia, lymphoma, liver cancer, lung cancer, testicular cancer, and thyroid cancer.

31. The method according to claim 24, wherein the cancer is melanoma.

32. The method according to claim 24 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 drug, a toxin, a radionuclide, an immunomodulator, a photoactive therapeutic agent, a radiosensitizing agent, a hormone, an anti-angiogenesis agent, and combinations thereof.

33. The method according to claim 32, wherein the additional therapeutic agent is an inhibitor of the PI3K/Akt pathway.

34. The method according to claim 33, 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, CA), 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

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(5-quinoxilin-6-methylene-1,3-thiazolidine-2,4-dione), AT7867 (CAS # 857531-00-1), BML-257 (CAS # 32387-96-5), CAL-120 (Gilead Sciences, Foster City, CA), 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, MA), perifosine, PHT-427 (CAS # 1191951-57-1), pictilisib (Roche Holdings Inc.), PIK-90 (CAS # 677338-12-4), SC-103980 (Pfizer, New York, NY), SF-1126 (Semafore Pharmaceuticals, Indianapolis, IN), SH-5, SH-6, Tetrahydro Curcumin, TG100-115 (Targegen Inc., San Diego, CA), Triciribine, X-339 (Xcovery, West Palm Beach, FL), XL-499 (Evotech, Hamburg, Germany), pharmaceutically acceptable salts thereof, and combinations thereof.

35. A kit when used to treat or ameliorate the effects of a cancer in a subject in need thereof comprising an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a type 2 MEK inhibitor or a

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pharmaceutically acceptable salt thereof, packaged together with instructions for their use,

wherein the type 2 MEK inhibitor is selected from the group consisting of GDC-0623, MEK162, trametinib, pharmaceutically acceptable salts thereof, and combinations thereof, and

wherein administration of the first and second anti-cancer agents provides a synergistic effect compared to administration of either anti-cancer agent alone.

36. The kit according to claim 35, wherein the subject is a mammal.

37. The kit according to claim 35, wherein the mammal is selected from the group consisting of humans, primates, farm animals, and domestic animals.

38. The kit according to claim 35, wherein the mammal is a human.

39. The kit according to claim 35, wherein the type 2 MEK inhibitor is trametinib or a pharmaceutically acceptable salt thereof.

40. The kit according to claim 35, wherein the subject with cancer has a somatic RAS mutation or BRAF mutation.

41. The kit according to claim 35, wherein the cancer is selected from the group consisting of a cancer of the large intestine, breast cancer, pancreatic cancer, skin cancer, endometrial cancer, neuroblastoma, leukemia, lymphoma, liver cancer, lung cancer, testicular cancer, and thyroid cancer.

42. The kit according to claim 35, wherein the cancer is melanoma.

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43. The kit according to claim 35 further comprising at least one additional therapeutic agent selected from the group consisting of an antibody or fragment thereof, a cytotoxic agent, a drug, a toxin, a radionuclide, an immunomodulator, a photoactive therapeutic agent, a radiosensitizing agent, a hormone, an anti-angiogenesis agent, and combinations thereof.

44. The kit according to claim 43, wherein the additional therapeutic agent is an inhibitor of the PI3K/Akt pathway.

45. The kit according to claim 44, 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, CA), 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), BML-257 (CAS # 32387-96-5), CAL-120 (Gilead Sciences, Foster City, CA), 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-

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13-2), ML-9 (CAS # 105637-50-1), Naltrindole Hydrochloride, OXY-111A (NormOxys Inc., Brighton, MA), perifosine, PHT-427 (CAS # 1191951-57-1), pictilisib (Roche Holdings Inc.), PIK-90 (CAS # 677338-12-4), SC-103980 (Pfizer, New York, NY), SF-1126 (Semafore Pharmaceuticals, Indianapolis, IN), SH-5, SH-6, Tetrahydro Curcumin, TG100-115 (Targegen Inc., San Diego, CA), Triciribine, X-339 (Xcovery, West Palm Beach, FL), XL-499 (Evotech, Hamburg, Germany), pharmaceutically acceptable salts thereof, and combinations thereof.

46. A pharmaceutical composition when used to treat or ameliorate the effects of a cancer in a subject in need thereof, the pharmaceutical composition comprising a pharmaceutically acceptable diluent or carrier and an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a type 2 MEK inhibitor or a pharmaceutically acceptable salt thereof, wherein the type 2 MEK inhibitor is selected from the group consisting of GDC-0623, MEK162, trametinib, pharmaceutically acceptable salts thereof, and combinations thereof, and wherein administration of the first and second anti-cancer agents provides a synergistic effect compared to administration of either anti-cancer agent alone.

47. The pharmaceutical composition according to claim 46, wherein the subject is a mammal.

48. The pharmaceutical composition according to claim 47, wherein the mammal is selected from the group consisting of humans, primates, farm animals, and domestic animals.

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49. The pharmaceutical composition according to claim 47, wherein the mammal is a human.

50. The pharmaceutical composition according to claim 46, wherein the type 2 MEK inhibitor is trametinib or a pharmaceutically acceptable salt thereof.

51. The pharmaceutical composition according to claim 46, wherein the subject with cancer has a somatic RAS mutation or BRAF mutation

52. The pharmaceutical composition 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, endometrial cancer, neuroblastoma, leukemia, lymphoma, liver cancer, lung cancer, testicular cancer, and thyroid cancer.

53. The pharmaceutical composition according to claim 46, wherein the cancer is melanoma.

54. The pharmaceutical composition according to claim 46 further comprising at least one additional therapeutic agent selected from the group consisting of an antibody or fragment thereof, a cytotoxic agent, a drug, a toxin, a radionuclide, an immunomodulator, a photoactive therapeutic agent, a radiosensitizing agent, a hormone, an anti-angiogenesis agent, and combinations thereof.

55. The pharmaceutical composition according to claim 54, wherein the additional therapeutic agent is an inhibitor of the PI3K/Akt pathway.

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56. The pharmaceutical composition according to claim 55, 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, CA), 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), BML-257 (CAS # 32387-96-5), CAL-120 (Gilead Sciences, Foster City, CA), 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, MA), perifosine, PHT-427 (CAS # 1191951-57-1), pictilisib (Roche Holdings Inc.), PIK-90 (CAS # 677338-12-4), SC-103980 (Pfizer, New York, NY), SF-1126 (Semafore Pharmaceuticals, Indianapolis, IN), SH-5, SH-6, Tetrahydro Curcumin, TG100-115 (Targegen Inc., San Diego, CA), Triciribine, X-339 (Xcovery, West Palm Beach, FL), XL-499 (Evotech, Hamburg, Germany), pharmaceutically acceptable salts thereof, and combinations thereof.

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57. The pharmaceutical composition according to claim 46, which is in a unit dosage form comprising both anti-cancer agents.

58. The pharmaceutical composition according to claim 46 in which the first anti-cancer agent is in a first unit dosage form and the second anti-cancer agent is in a second unit dosage form, separate from the first.

59. The pharmaceutical composition according to claim 46, wherein the first and second anti-cancer agents are co-administered to the subject.

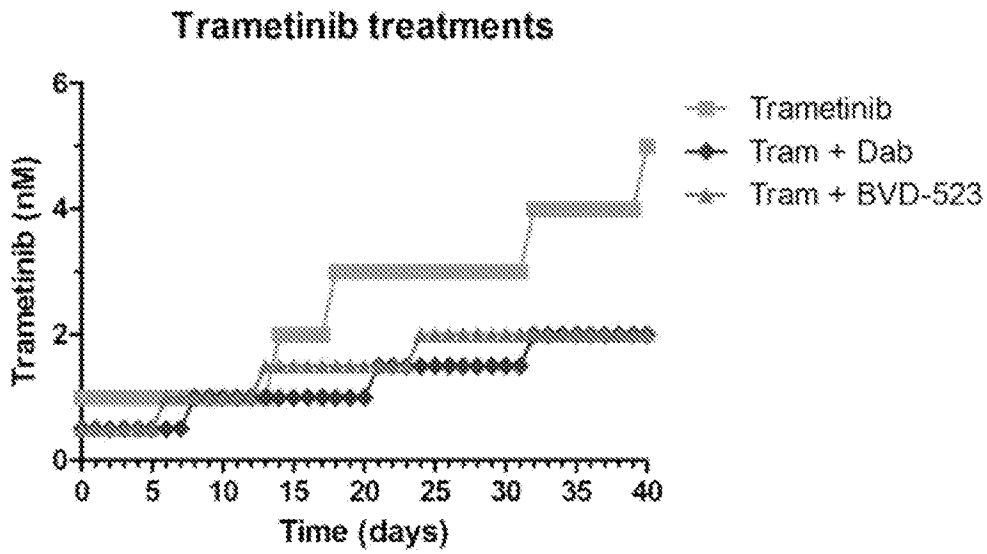
60. The pharmaceutical composition according to claim 46, wherein the first and second anti-cancer agents are administered to the subject serially.

61. The pharmaceutical composition according to claim 60, wherein the first anti-cancer agent is administered to the subject before the second anti-cancer agent.

62. The pharmaceutical composition according to claim 60, wherein the second anti-cancer agent is administered to the subject before the first anti-cancer agent.

FIG. 1

A


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

B

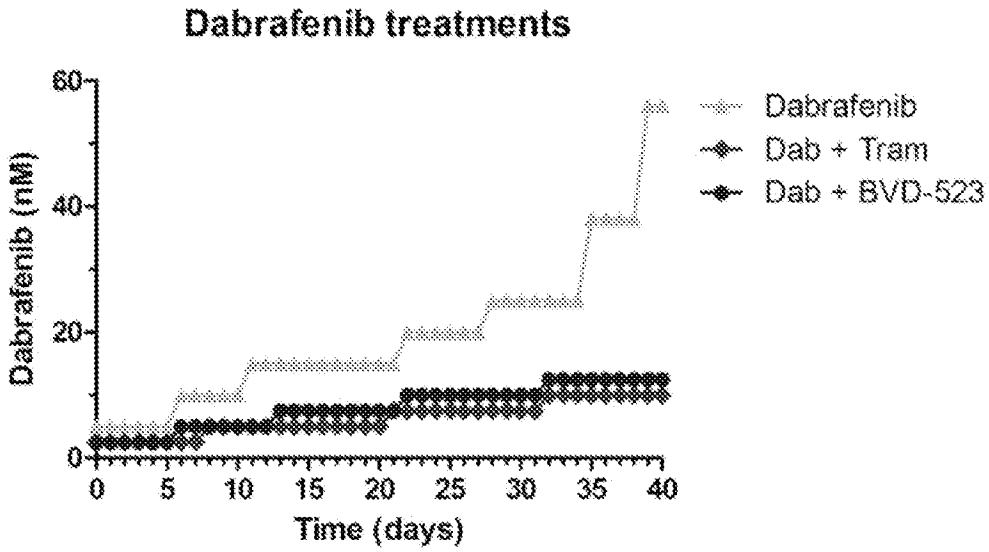

Dabrafenib treatments
Dabrafenib (nM)
0
20
40
60
0 5 10 15 20 25 30 35 40
Time (days)
Dabrafenib
Dab + Tram
Dab + BVD-523

FIG. 1, Con't

C

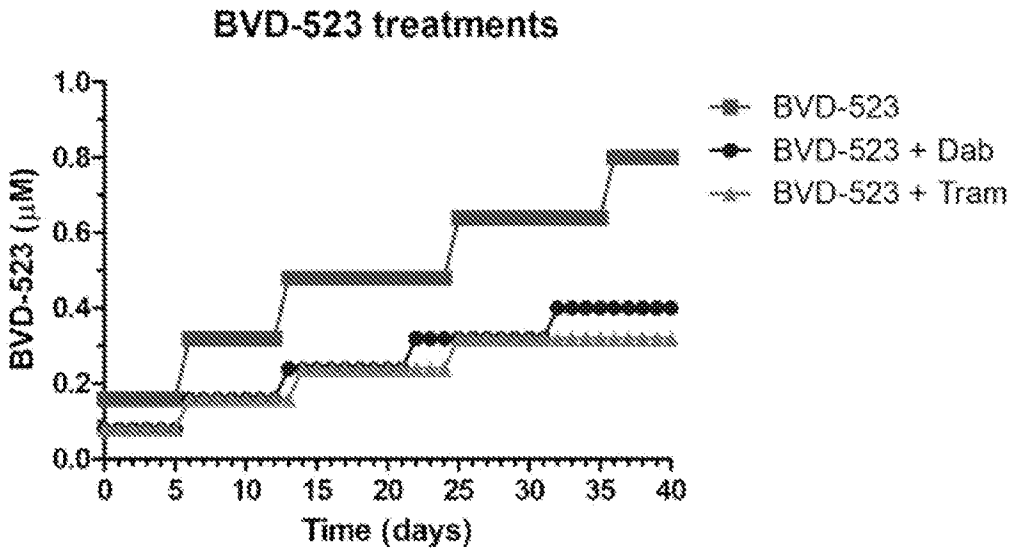

BVD-523 treatments
BVD-523 (μM)
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
30
35
40
Time (days)
BVD-523
BVD-523 + Dab
BVD-523 + Tram

FIG. 2

A

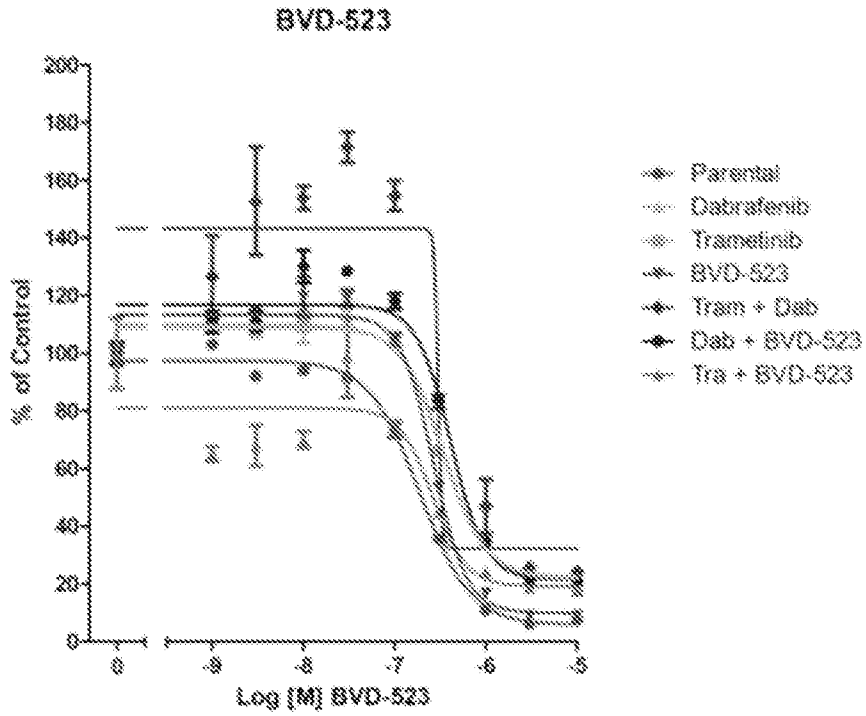

BVD-523
% of Control
200
180
160
140
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] BVD-523
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 2, Con't

B

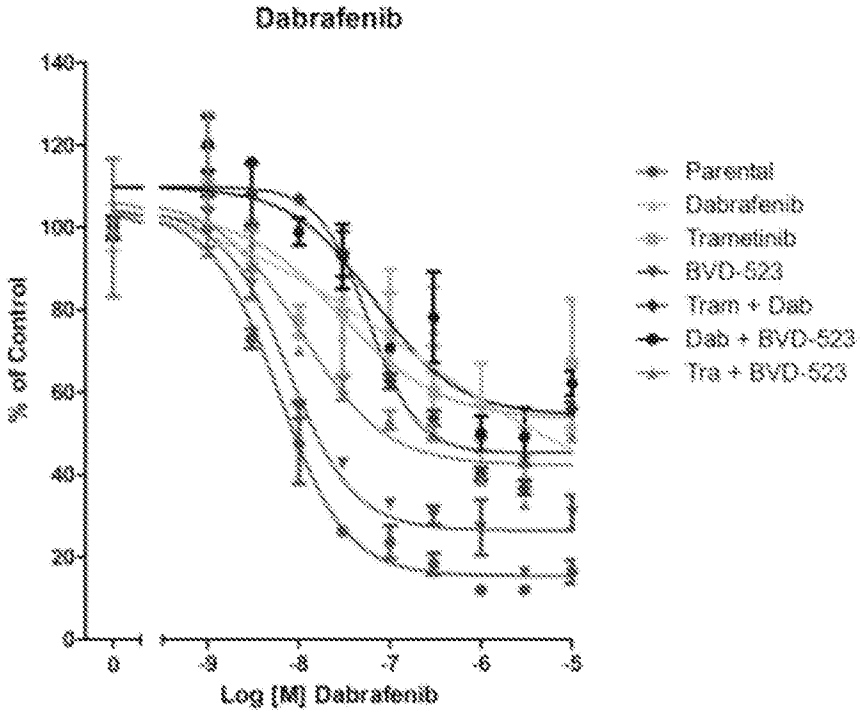

Dabrafenib
% of Control
140
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] Dabrafenib
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 2, Con't

C

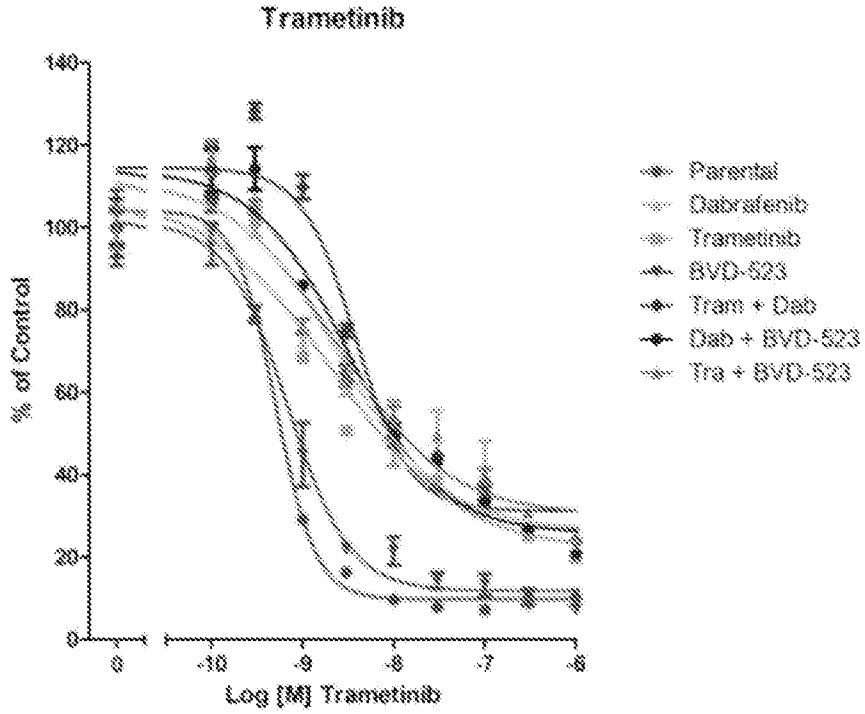

Trametinib
% of Control
140
120
100
80
60
40
20
0
0
-10
-9
-8
-7
-6
Log [M] Trametinib
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 2, Con't

D

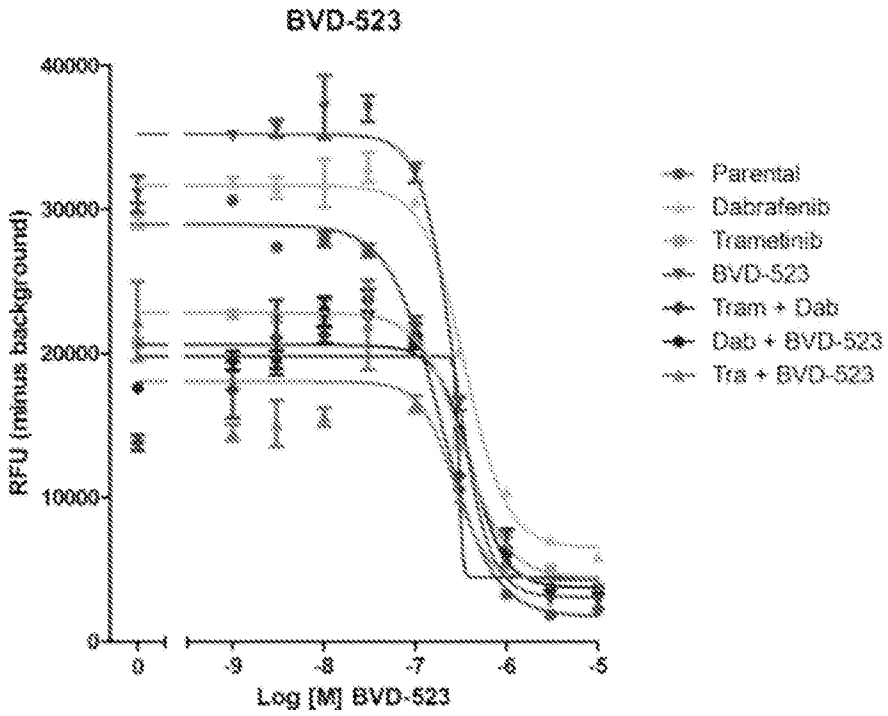

BVD-523
40000
30000
20000
10000
0
RFU (minus background)
0
-9
-8
-7
-6
-5
Log [M] BVD-523
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 2, Con't

E

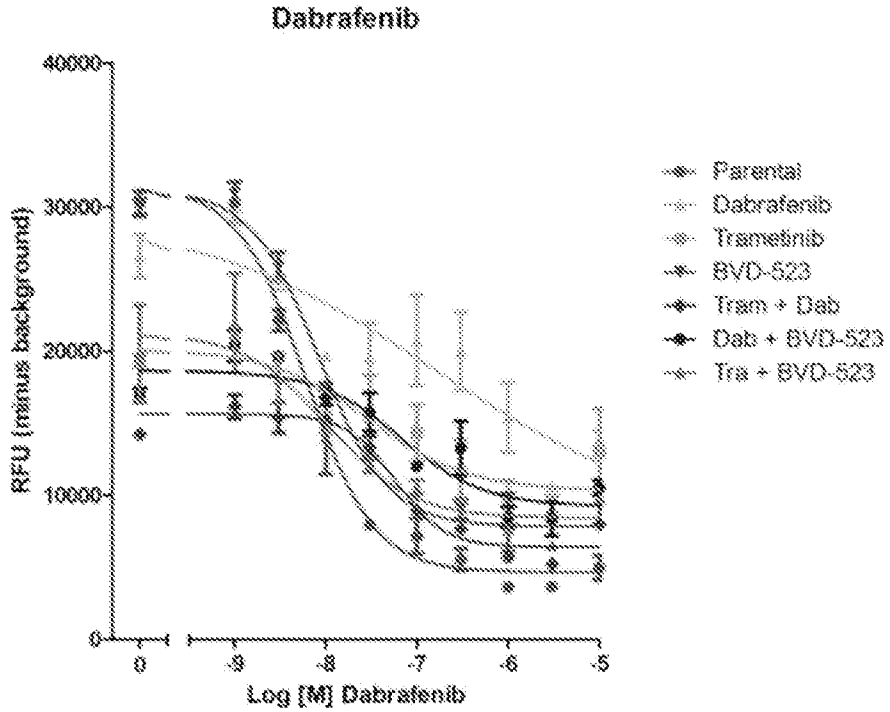

Dabrafenib
RFU (minus background)
40000
30000
20000
10000
0
0
-9
-8
-7
-6
-5
Log [M] Dabrafenib
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 2, Con't

F

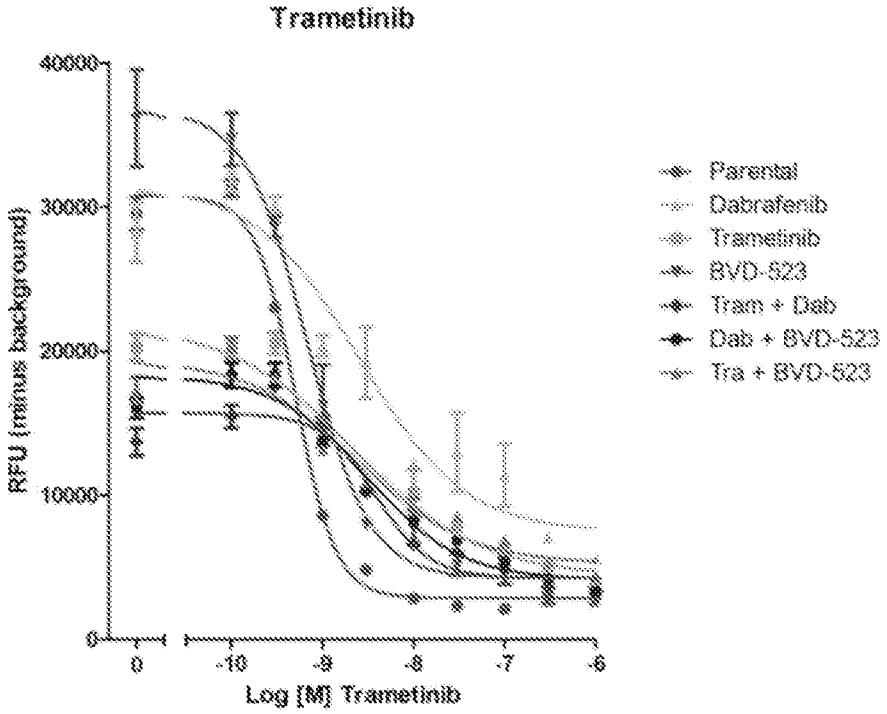

Trametinib
RFU (minus background)
40000
30000
20000
10000
0
0
-10
-9
-8
-7
-6
Log [M] Trametinib
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 2, Con't

G

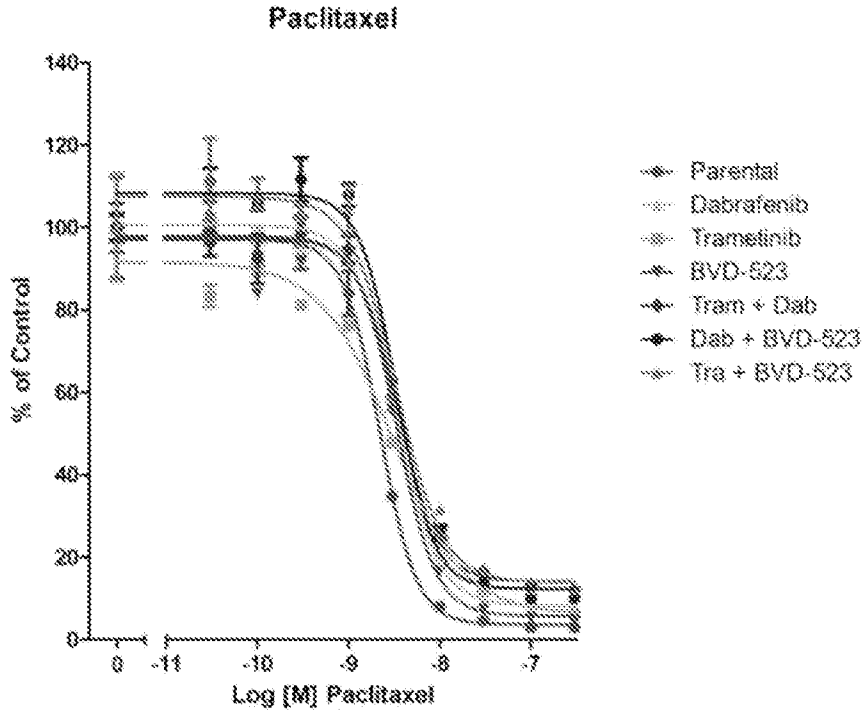

Paclitaxel
% of Control
140
120
100
80
60
40
20
0
0
-11
-10
-9
-8
-7
Log [M] Paclitaxel
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 2, Con't

H

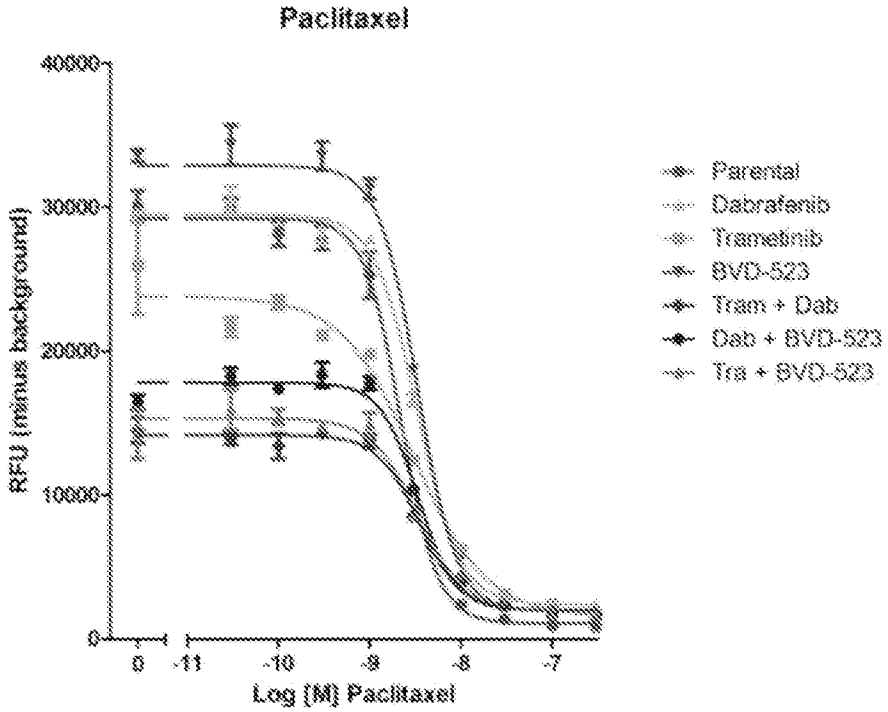
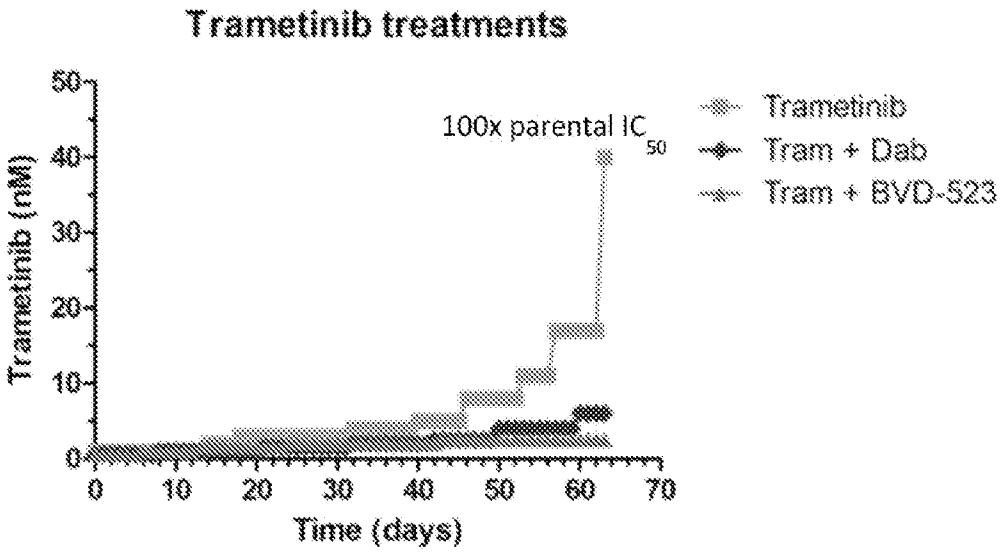

Paclitaxel
RFU (minus background)
40000
30000
20000
10000
0
0
-11
-10
-9
-8
-7
Log [M] Paclitaxel
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 3

A


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

B

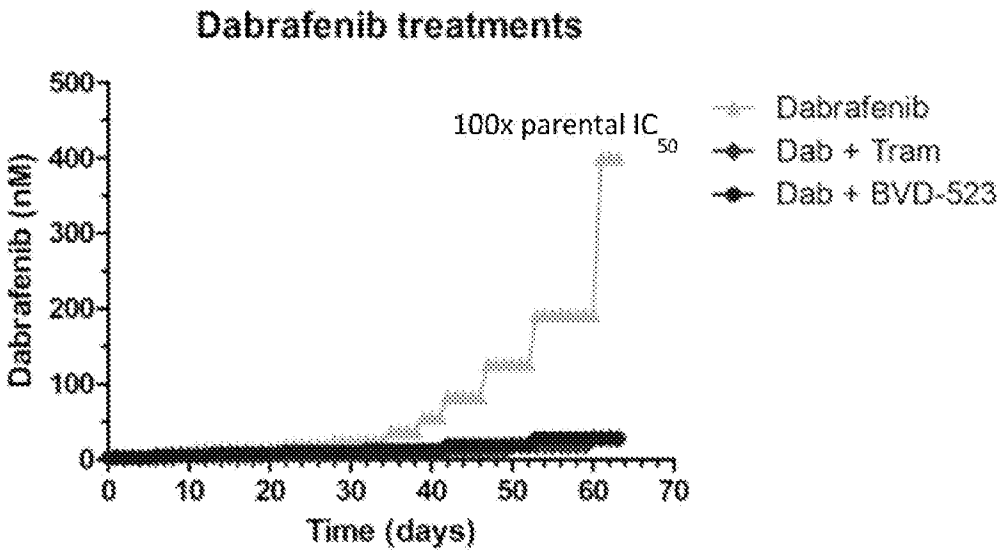
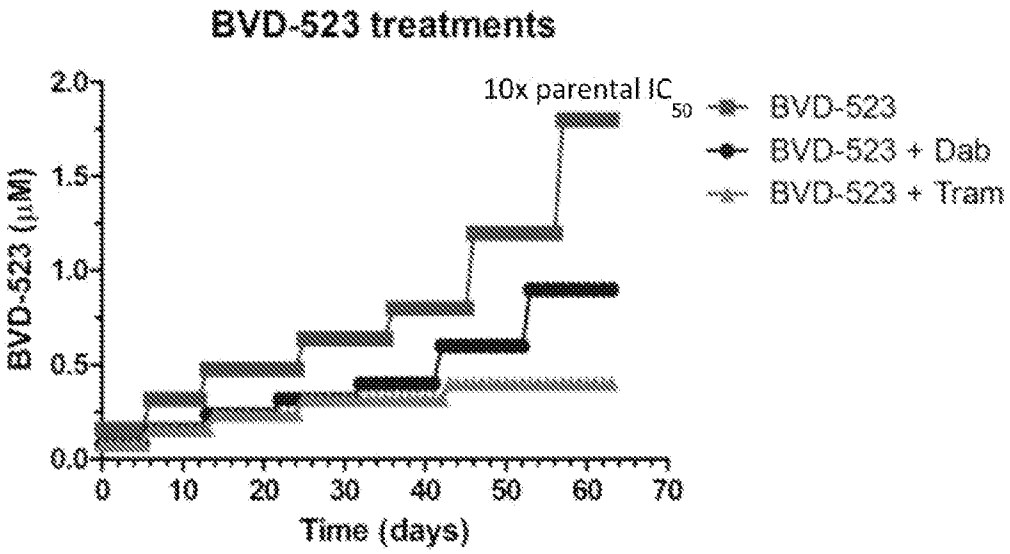

Dabrafenib treatments
Dabrafenib (nM)
500
400
300
200
100
0
0
10
20
30
40
50
60
70
Time (days)
100x parental IC50
Dabrafenib
Dab + Tram
Dab + BVD-523

FIG. 3, Con't

C


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)

D

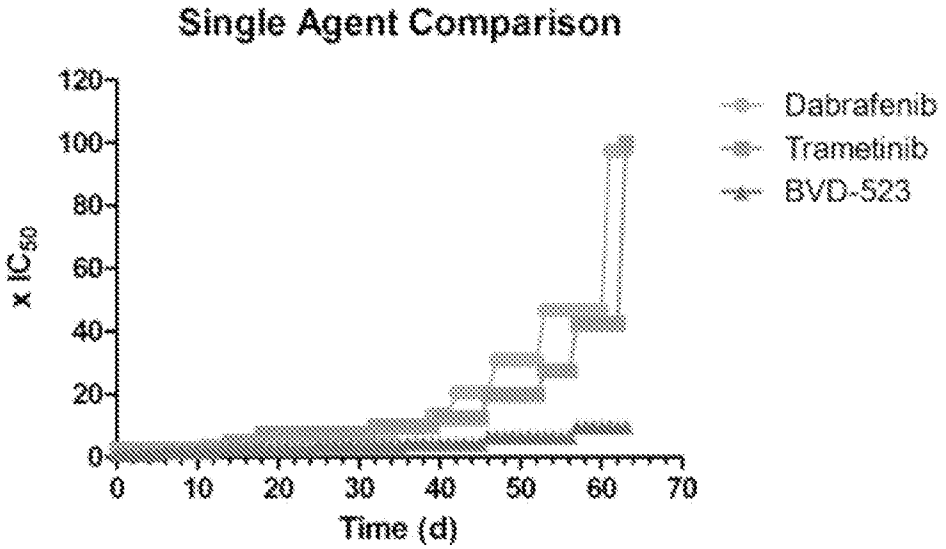

Single Agent Comparison
Dabrafenib
Trametinib
BVD-523
x IC50
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
Time (d)

FIG. 4

A

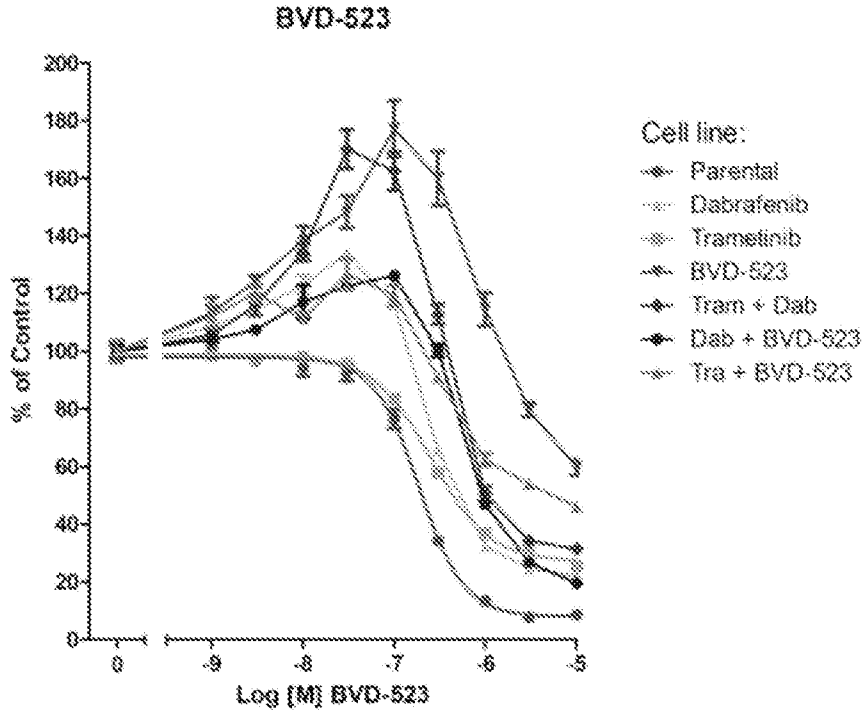

BVD-523
% of Control
200
180
160
140
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] BVD-523
Cell line:
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 4, Con't

B

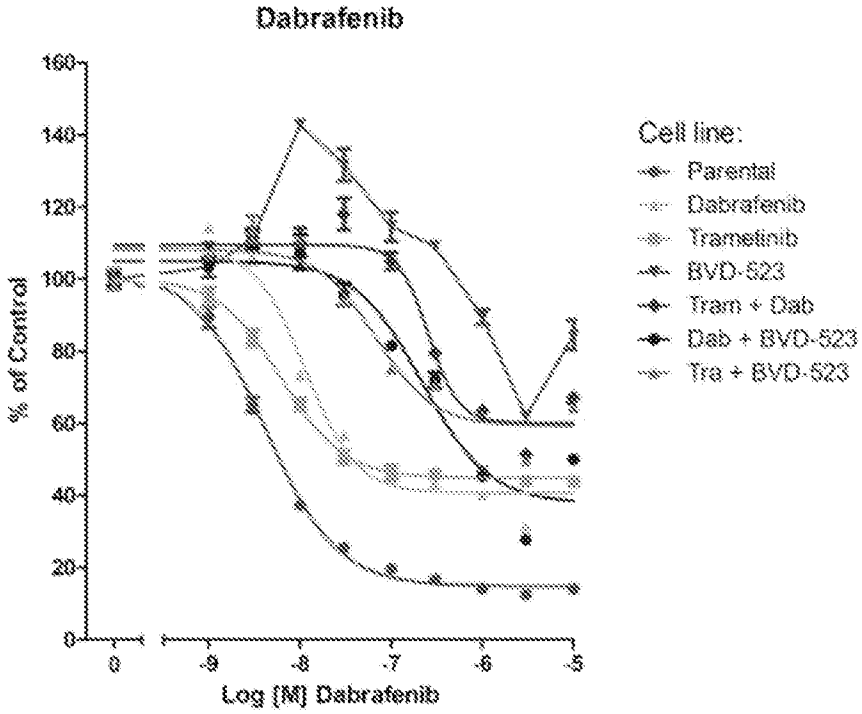

Dabrafenib
% of Control
160
140
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] Dabrafenib
Cell line:
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 4, Con't

C

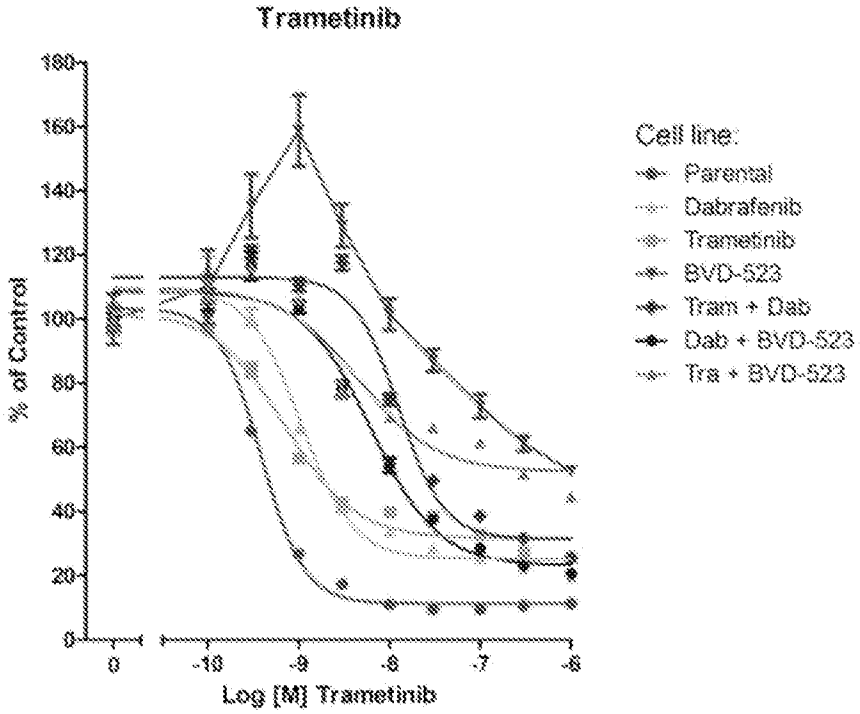

Trametinib
% of Control
180
160
140
120
100
80
60
40
20
0
0
-10
-9
-8
-7
-6
Log [M] Trametinib
Cell line:
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 4, Con't

D

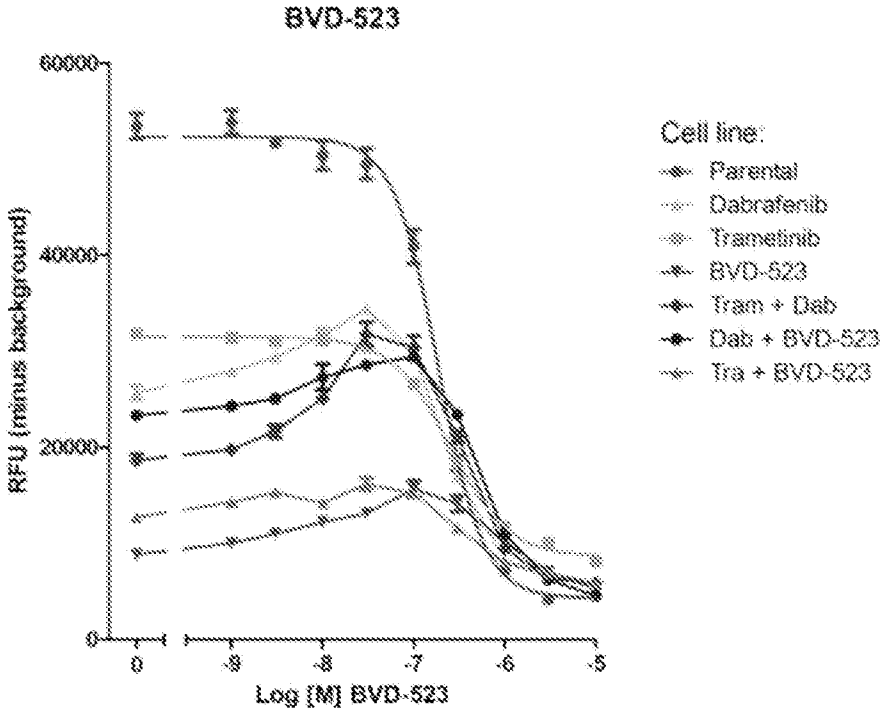

BVD-523
60000
40000
20000
0
RFU (minus background)
0
-9
-8
-7
-6
-5
Log [M] BVD-523
Cell line:
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 4, Con't

E

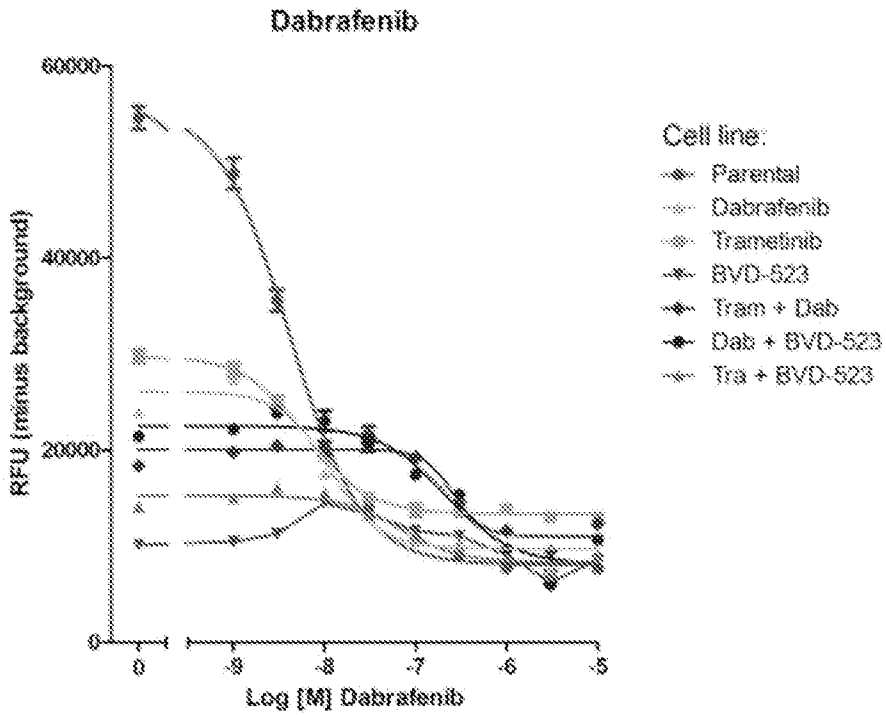

Dabrafenib
60000
40000
20000
0
RFU (minus background)
0
-9
-8
-7
-6
-5
Log [M] Dabrafenib
Cell line:
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 4, Con't

F

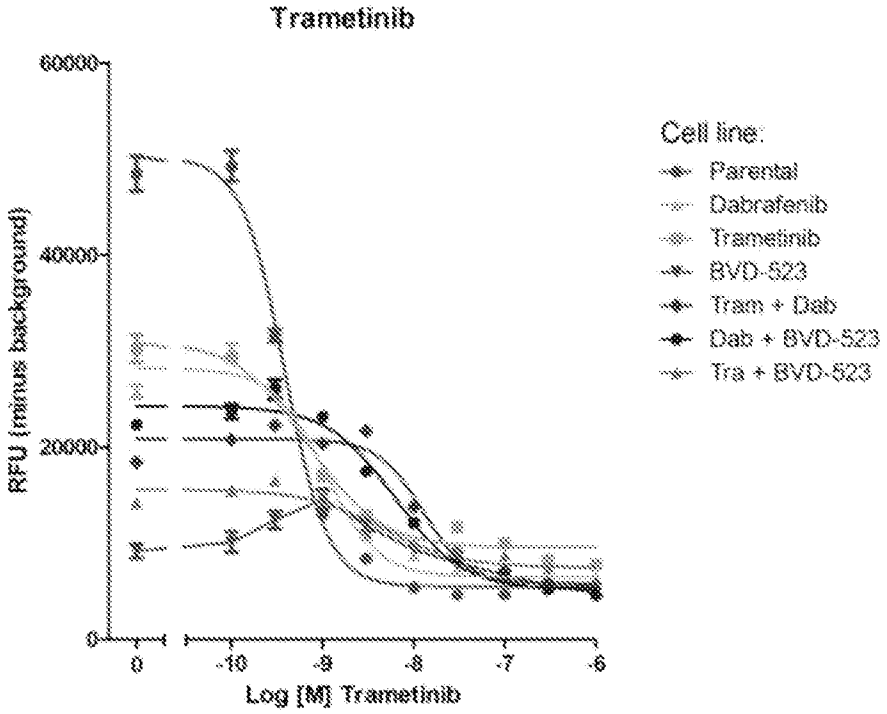

Trametinib
60000
40000
20000
0
RFU (minus background)
0
-10
-9
-8
-7
-6
Log [M] Trametinib
Cell line:
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 4, Con't

G

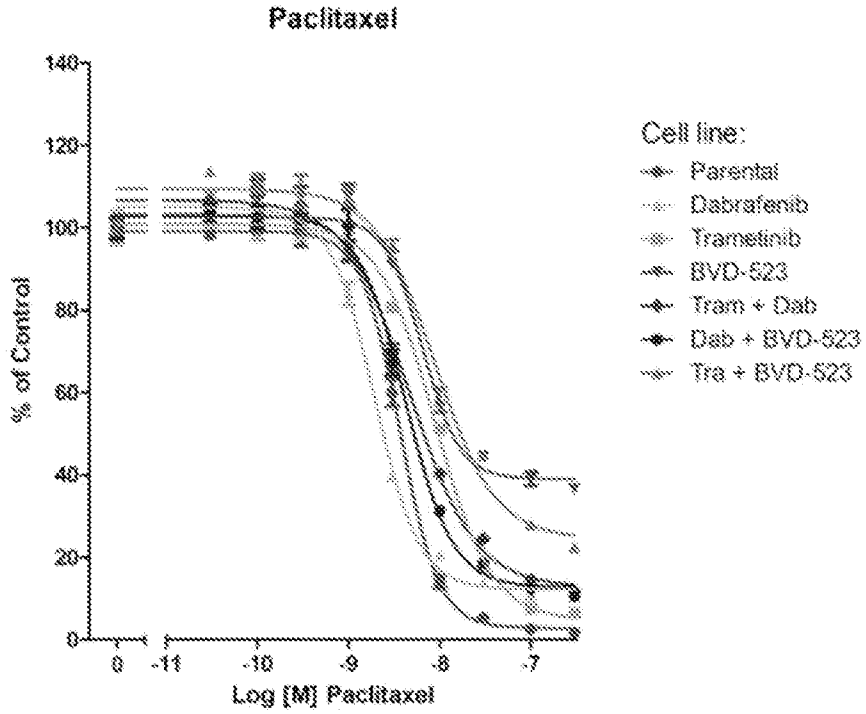

Paclitaxel
% of Control
140
120
100
80
60
40
20
0
0
-11
-10
-9
-8
-7
Log [M] Paclitaxel
Cell line:
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 4, Con't

H

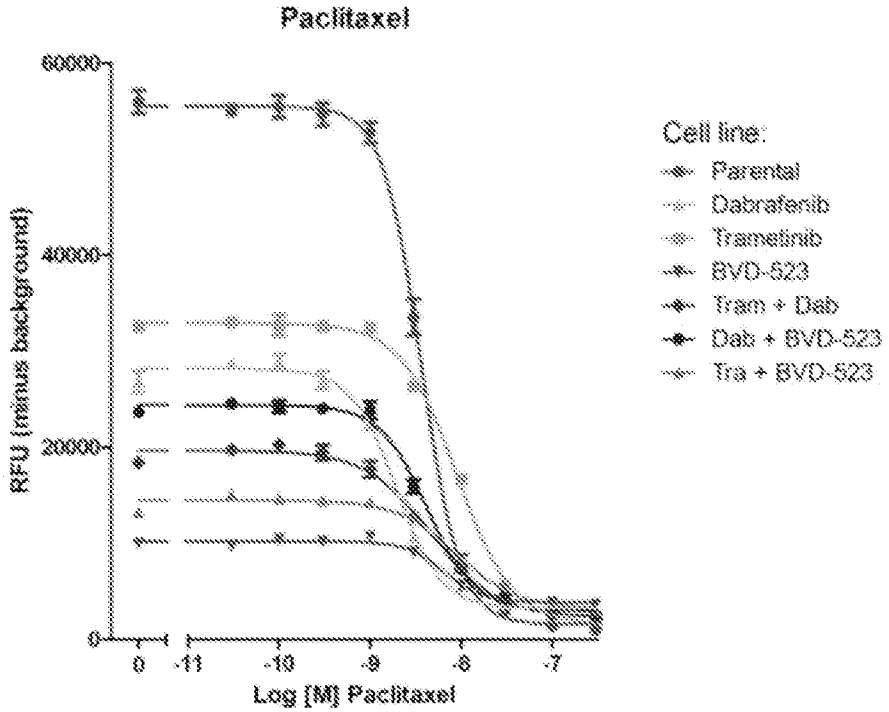

Paclitaxel
60000
40000
20000
0
RFU (minus background)
0
-11
-10
-9
-8
-7
Log [M] Paclitaxel
Cell line:
Parental
Dabrafenib
Trametinib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 5

A

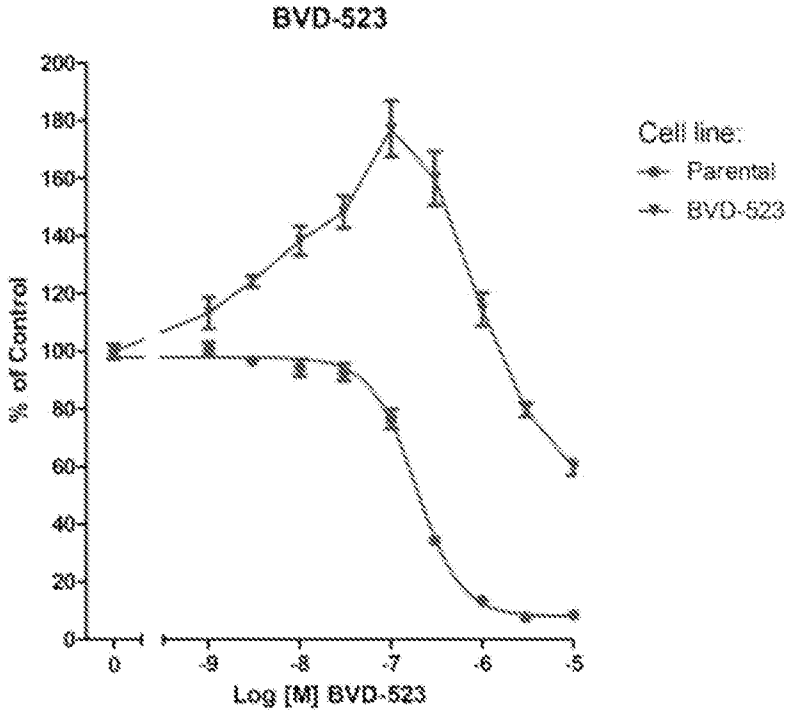

BVD-523
% of Control
200
180
160
140
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] BVD-523
Cell line:
Parental
BVD-523

FIG. 5, Con't

B

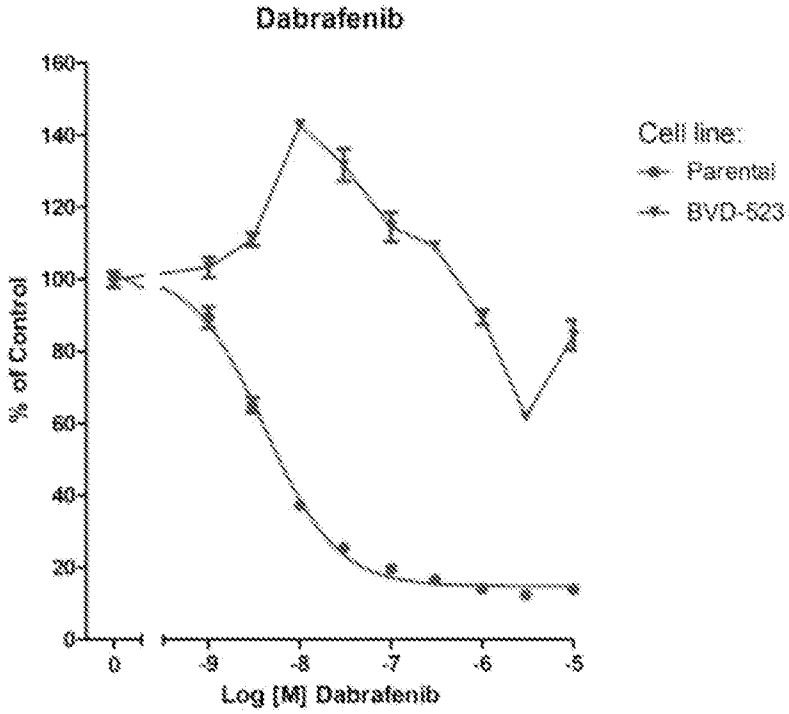

Dabrafenib
% of Control
160
140
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] Dabrafenib
Cell line:
Parental
BVD-523

FIG. 5, Con't

C

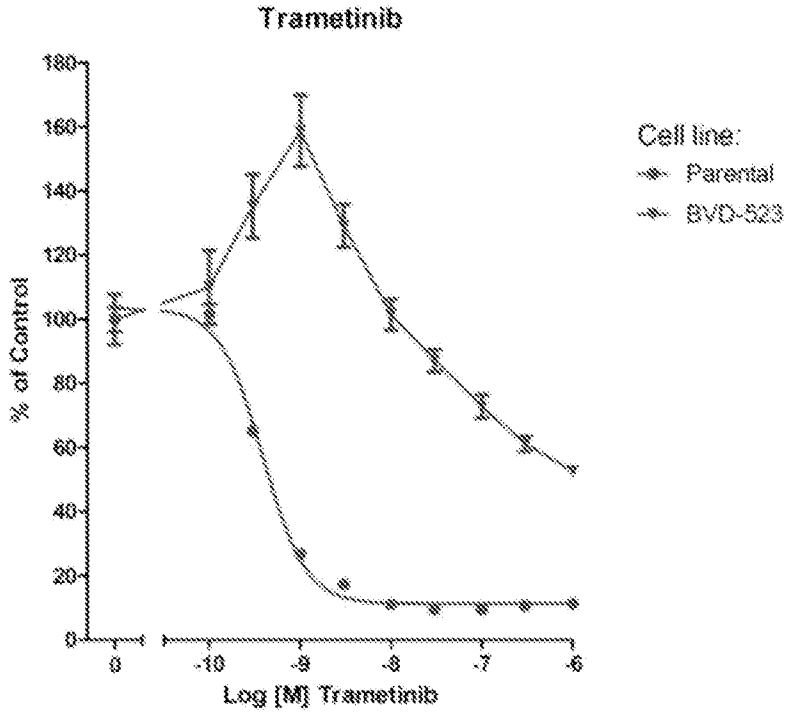

Trametinib
% of Control
180
160
140
120
100
80
60
40
20
0
0
-10
-9
-8
-7
-6
Log [M] Trametinib
Cell line:
Parental
BVD-523

FIG. 5, Con't

D

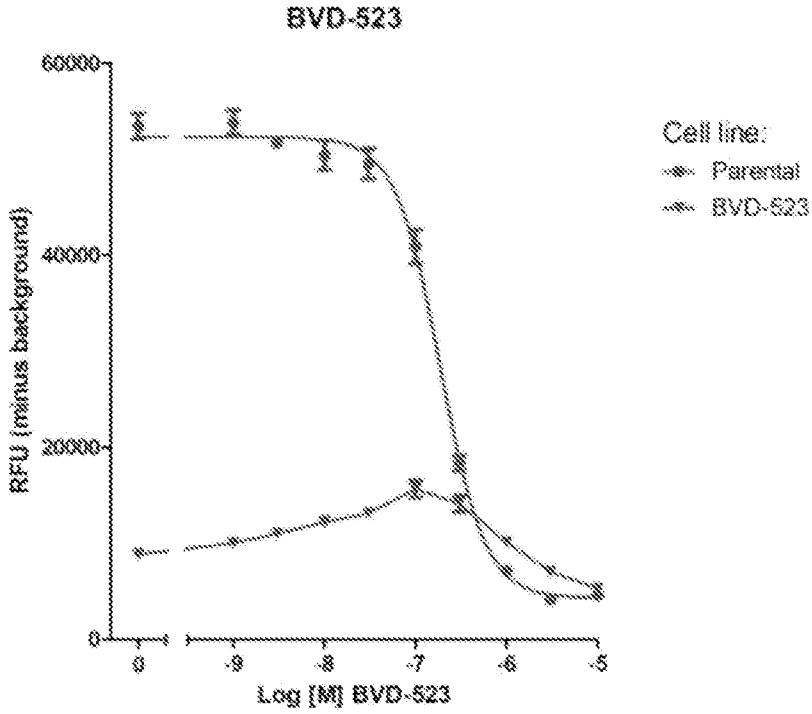

BVD-523
60000
40000
20000
0
RFU (minus background)
0
-9
-8
-7
-6
-5
Log [M] BVD-523
Cell line:
Parental
BVD-523

FIG. 5, Con't

E

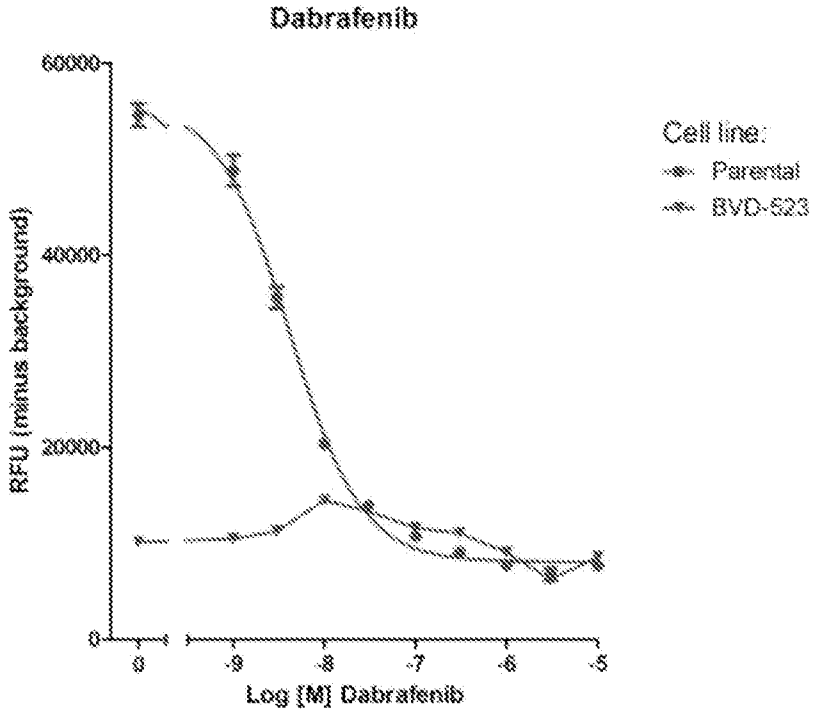

Dabrafenib
60000
40000
20000
0
RFU (minus background)
0
-9
-8
-7
-6
-5
Log [M] Dabrafenib
Cell line:
Parental
BVD-523

FIG. 5, Con't

F

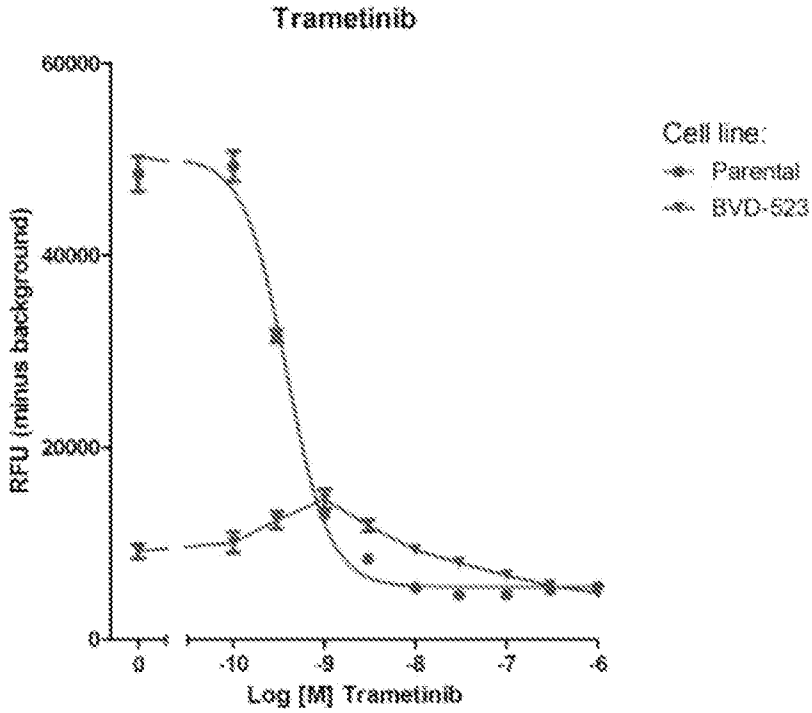

Trametinib
60000
40000
20000
0
RFU (minus background)
0
-10
-9
-8
-7
-6
Log [M] Trametinib
Cell line:
Parental
BVD-523

FIG. 5 Con't

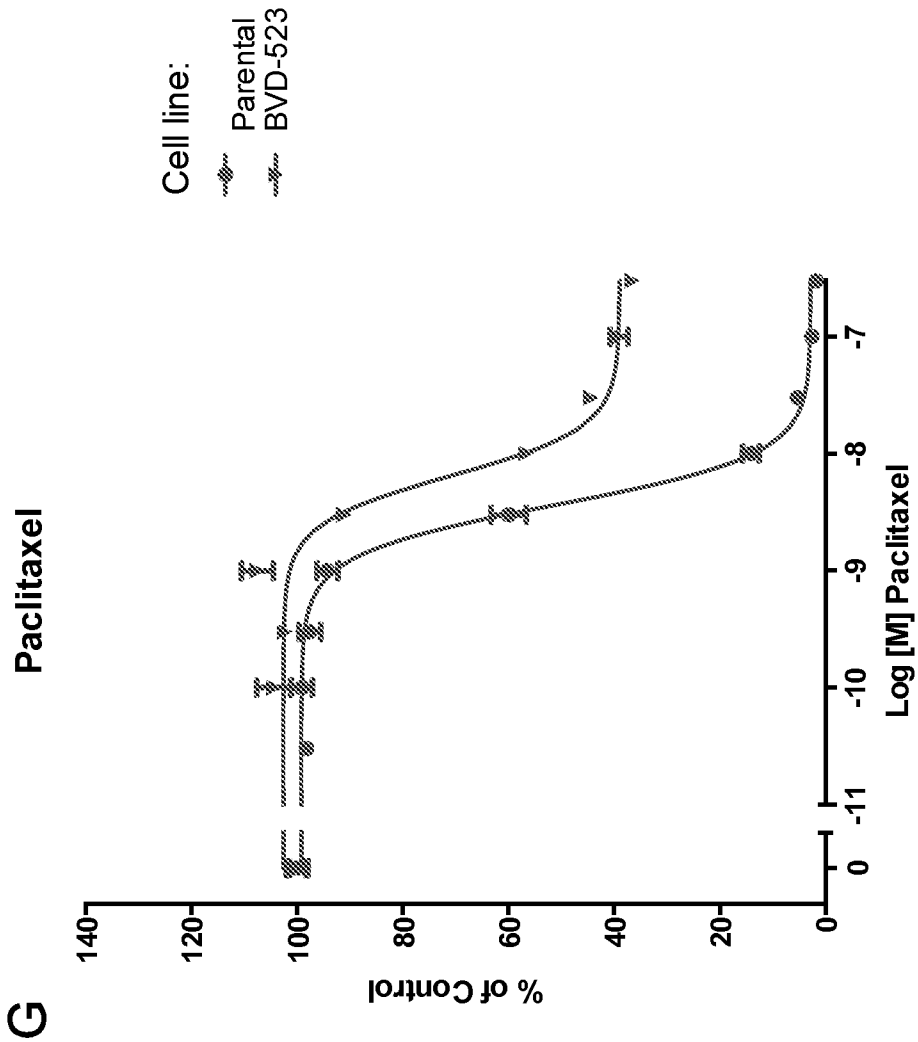

G
Paclitaxel
Cell line:
Parental
BVD-523
% of Control
140
120
100
80
60
40
20
0
0
-11
-10
-9
-8
-7
Log [M] Paclitaxel

FIG. 5 Con't

H

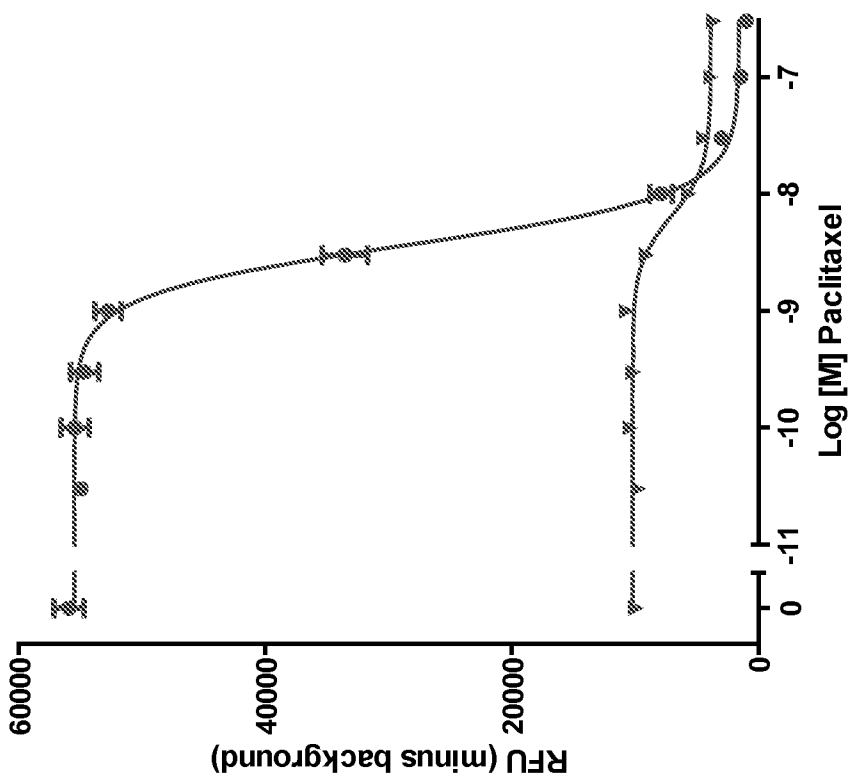

Paclitaxel
Cell line:
Parental
BVD-523
RFU (minus background)
60000
40000
20000
0
0
-11
-10
-9
-8
-7
Log [M] Paclitaxel

FIG. 6

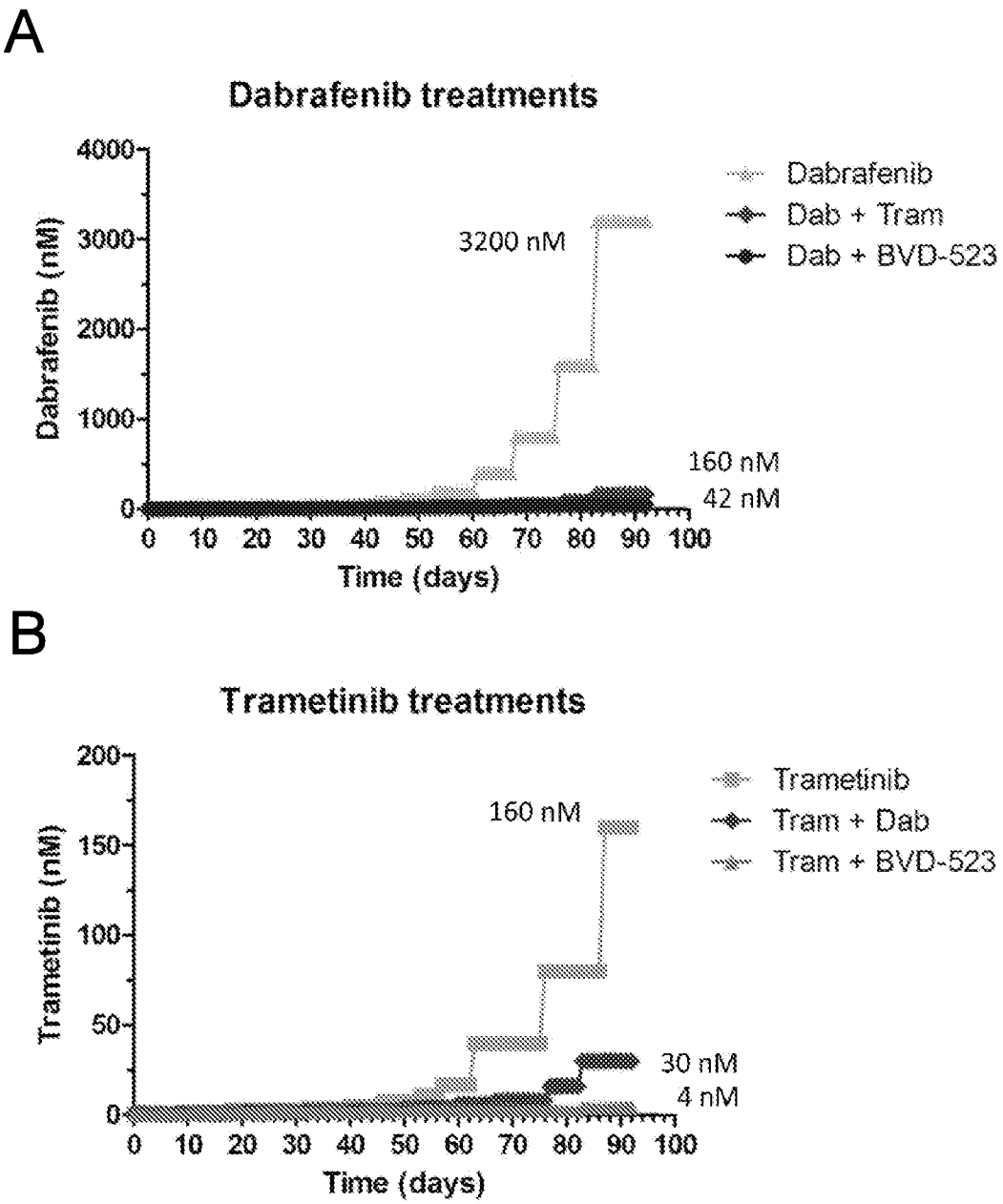
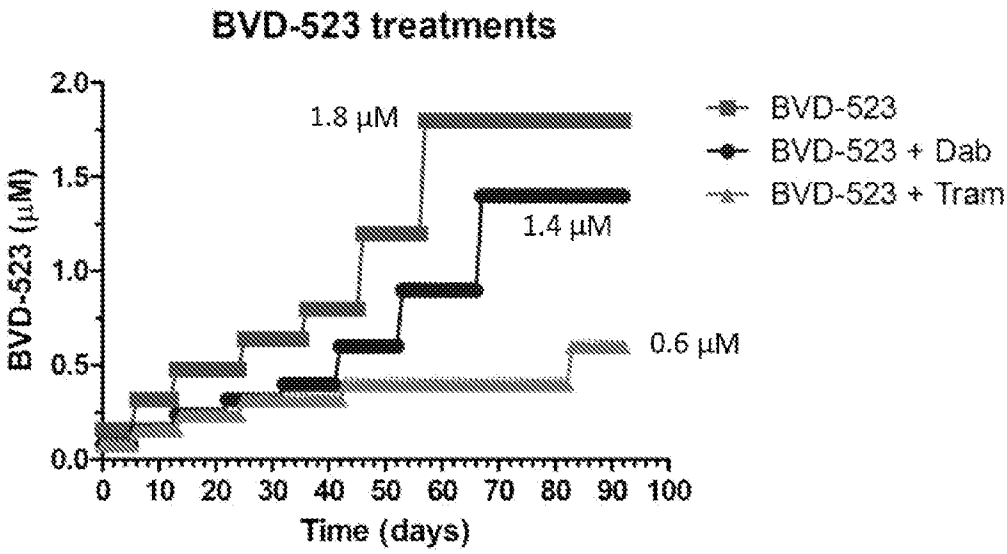

A
Dabrafenib treatments
Dabrafenib (nM)
4000
3000
2000
1000
0
3200 nM
160 nM
42 nM
Dabrafenib
Dab + Tram
Dab + BVD-523
0 10 20 30 40 50 60 70 80 90 100
Time (days)
B
Trametinib treatments
Trametinib (nM)
200
150
100
50
0
160 nM
30 nM
4 nM
Trametinib
Tram + Dab
Tram + BVD-523
0 10 20 30 40 50 60 70 80 90 100
Time (days)

FIG. 6, Con't

C


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

D

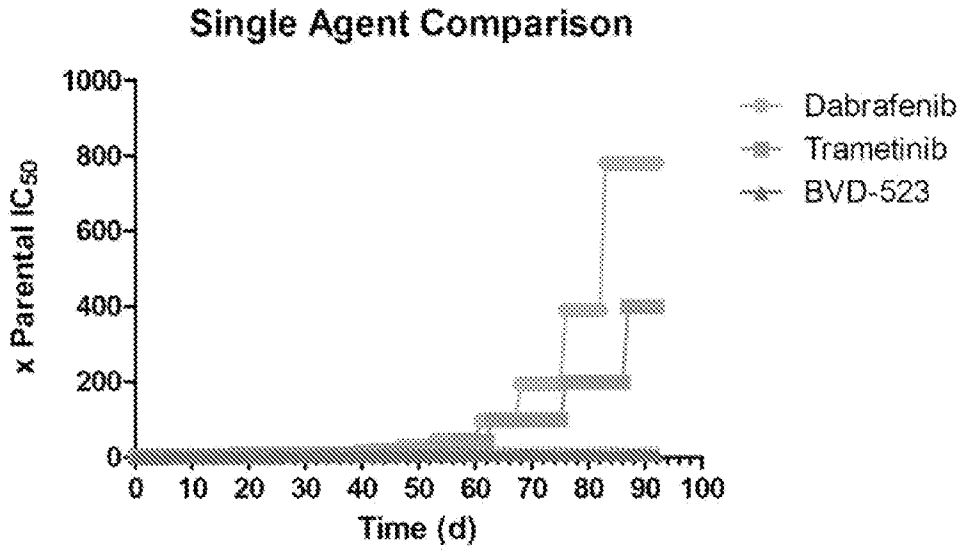

Single Agent Comparison
x Parental IC50
1000
800
600
400
200
0
Dabrafenib
Trametinib
BVD-523
0 10 20 30 40 50 60 70 80 90 100
Time (d)

FIG. 7

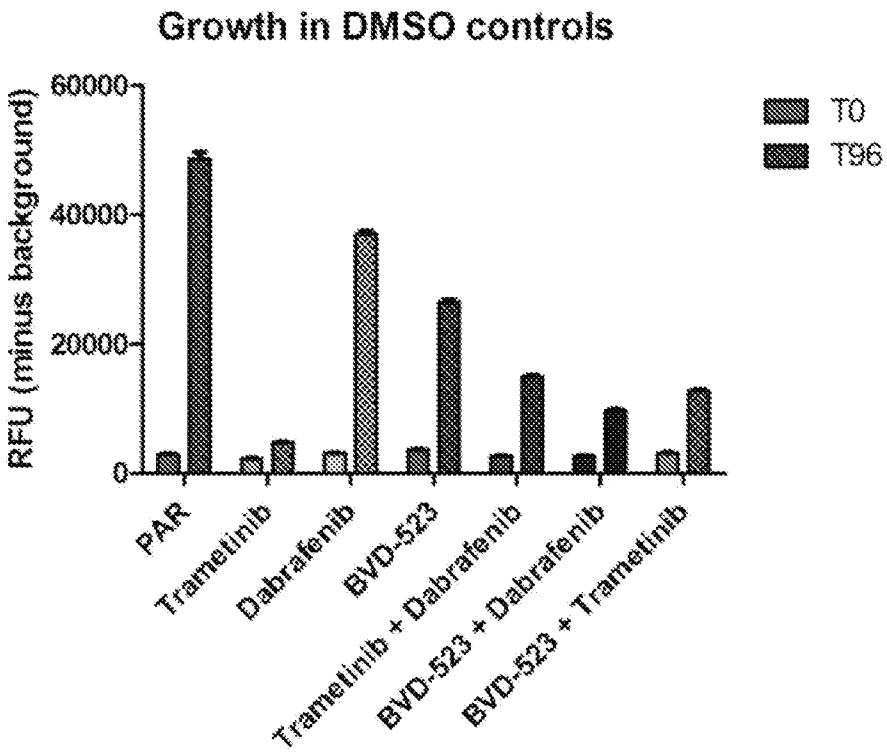

Growth in DMSO controls
RFU (minus background)
60000
40000
20000
0
T0
T96
PAR
Trametinib
Dabrafenib
BVD-523
Trametinib + Dabrafenib
BVD-523 + Dabrafenib
BVD-523 + Trametinib

FIG. 8

A

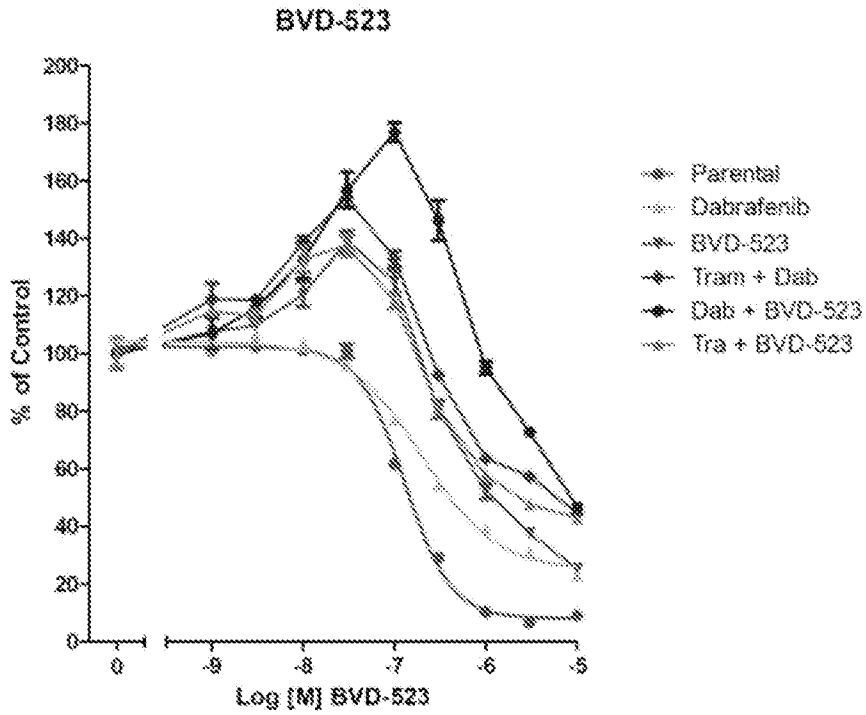

BVD-523
% of Control
200
180
160
140
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] BVD-523
Parental
Dabrafenib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 8, Con't

B

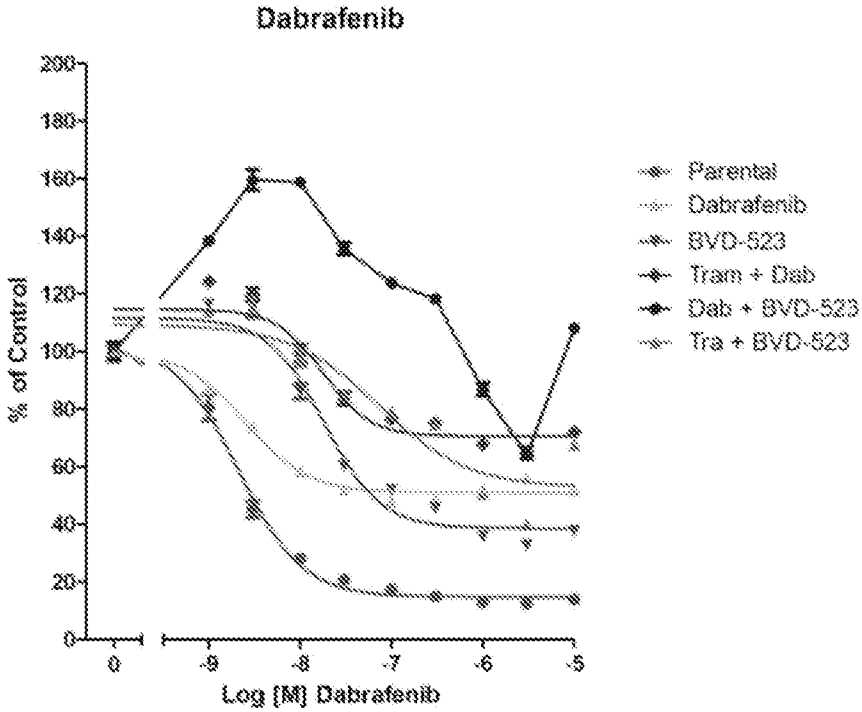

Dabrafenib
% of Control
200
180
160
140
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] Dabrafenib
Parental
Dabrafenib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 8, Con't

C

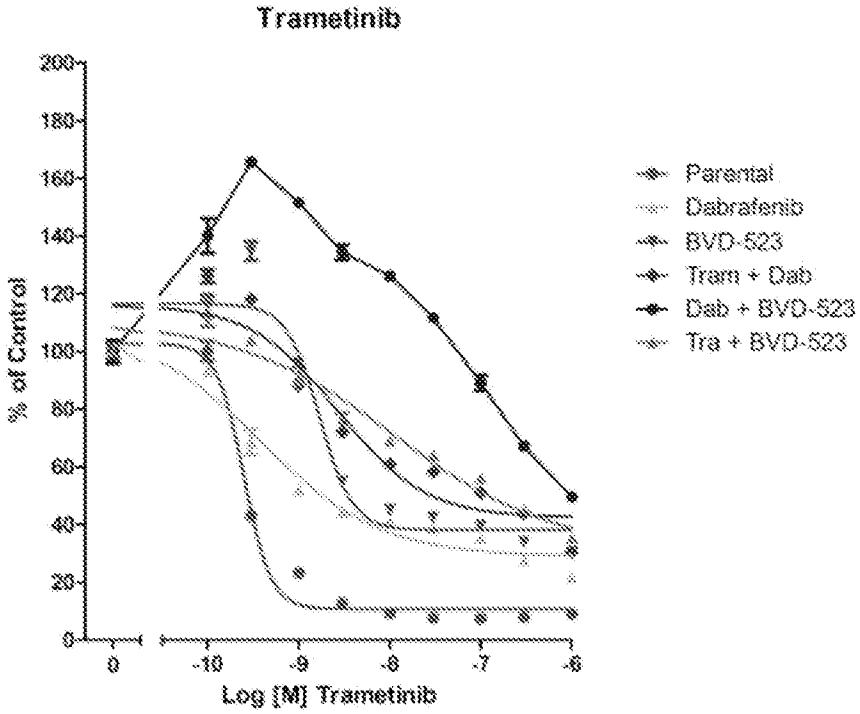

Trametinib
% of Control
200
180
160
140
120
100
80
60
40
20
0
0
-10
-9
-8
-7
-6
Log [M] Trametinib
Parental
Dabrafenib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 8, Con't

D

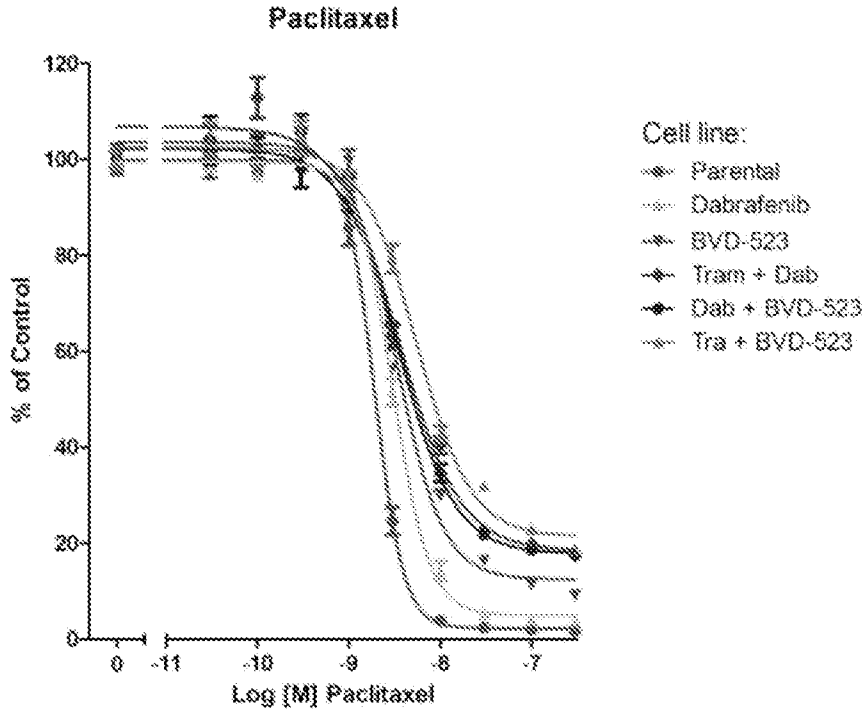

Paclitaxel
% of Control
120
100
80
60
40
20
0
0
-11
-10
-9
-8
-7
Log [M] Paclitaxel
Cell line:
Parental
Dabrafenib
BVD-523
Tram + Dab
Dab + BVD-523
Tra + BVD-523

FIG. 9

A

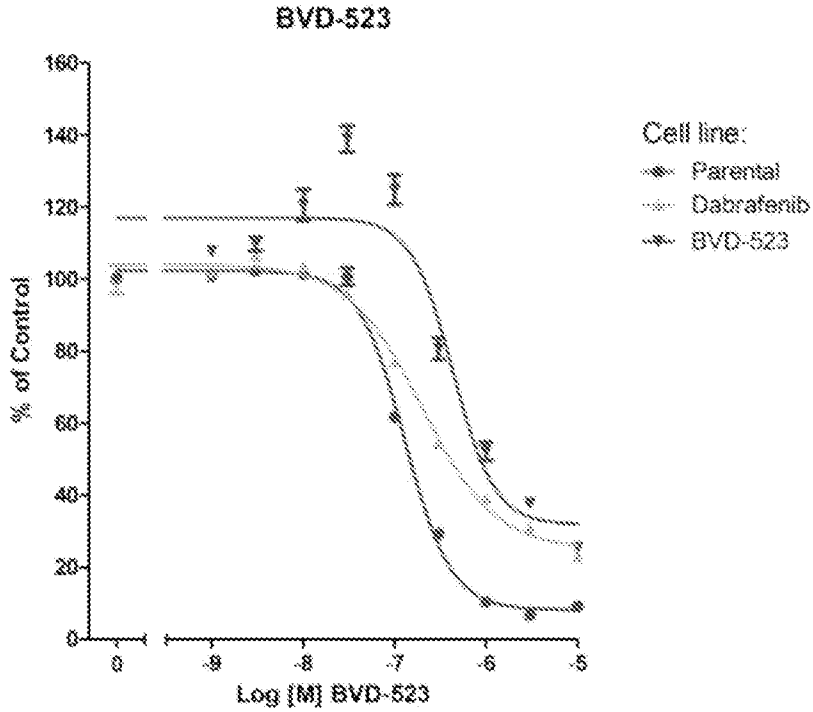

BVD-523
% of Control
160
140
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] BVD-523
Cell line:
Parental
Dabrafenib
BVD-523

FIG. 9, Con't

B

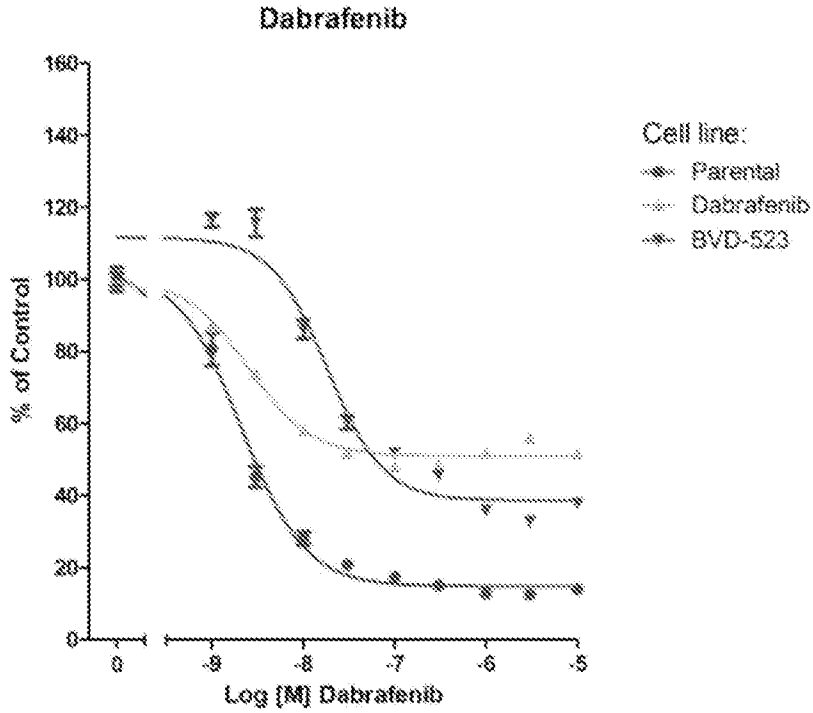

Dabrafenib
% of Control
Log [M] Dabrafenib
Cell line:
Parental
Dabrafenib
BVD-523

FIG. 9, Con't

C

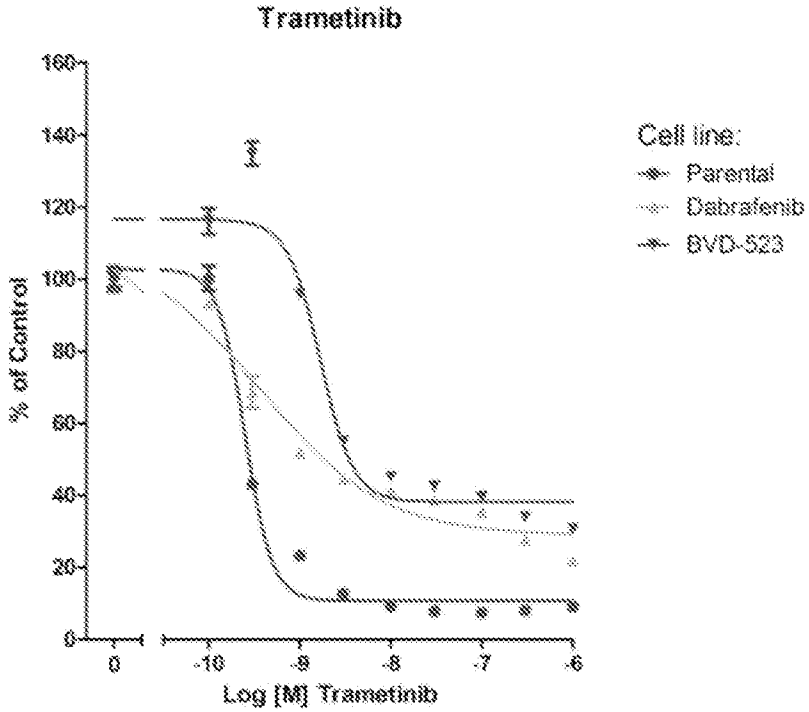

Trametinib
% of Control
160
140
120
100
80
60
40
20
0
0
-10
-9
-8
-7
-6
Log [M] Trametinib
Cell line:
Parental
Dabrafenib
BVD-523

FIG. 9, Con't

D

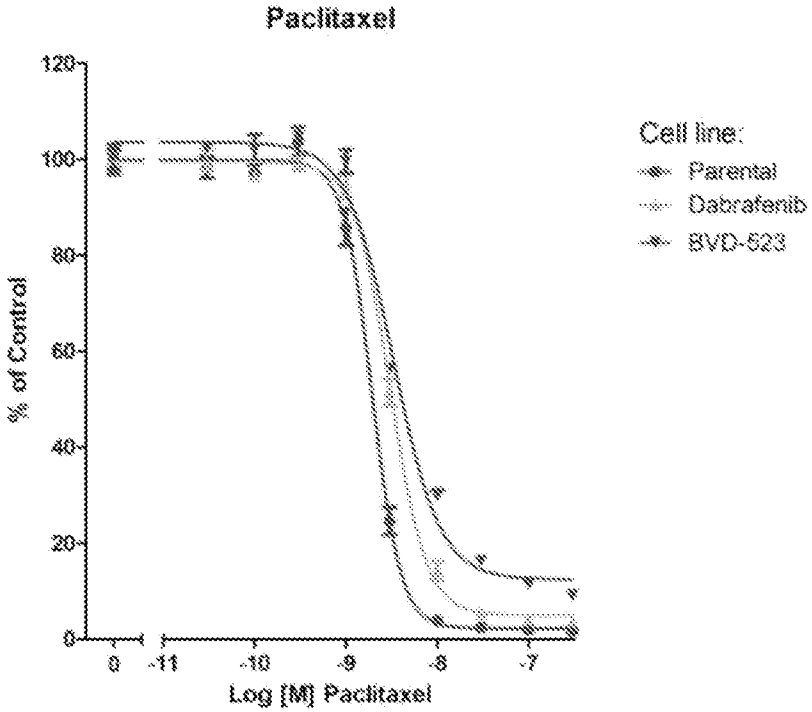

Paclitaxel
% of Control
120
100
80
60
40
20
0
0
-11
-10
-9
-8
-7
Log [M] Paclitaxel
Cell line:
Parental
Dabrafenib
SVD-623

FIG. 10

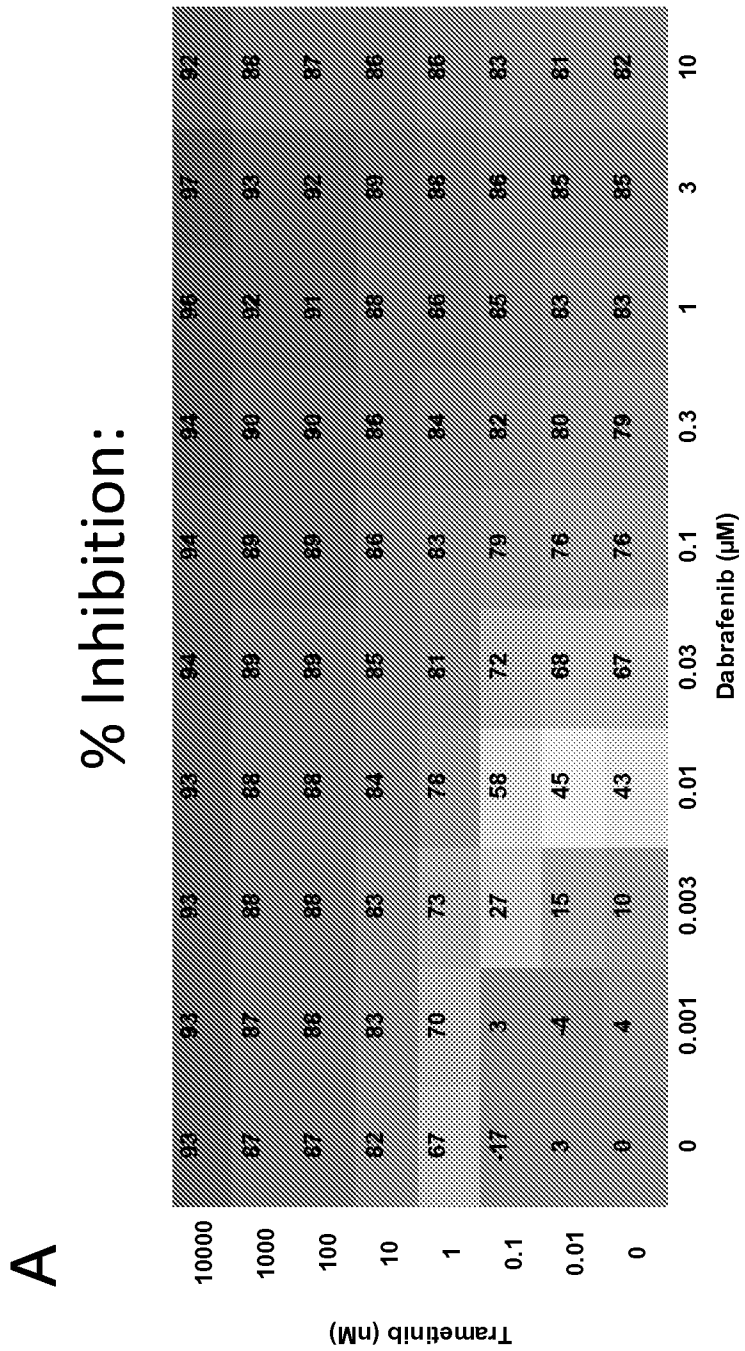

A
% Inhibition:
Trametinib (nM)
10000
1000
100
10
1
0.1
0.01
0
93 93 93 93 94 94 94 95 96 97 97
87 87 88 88 89 89 89 90 92 93 93
87 86 86 88 89 89 89 90 91 92 93
82 83 83 84 85 86 86 86 88 89 89
67 70 73 78 81 83 84 86 86 88 88
17 3 27 58 72 79 82 85 85 86 86
3 -4 15 45 68 76 80 83 85 85 81
0 4 10 43 67 76 79 83 85 85 82
0 0.001 0.003 0.01 0.03 0.1 0.3 1 3 10
Dabrafenib (μM)

FIG. 10, Con't

B

Excess over Bliss:

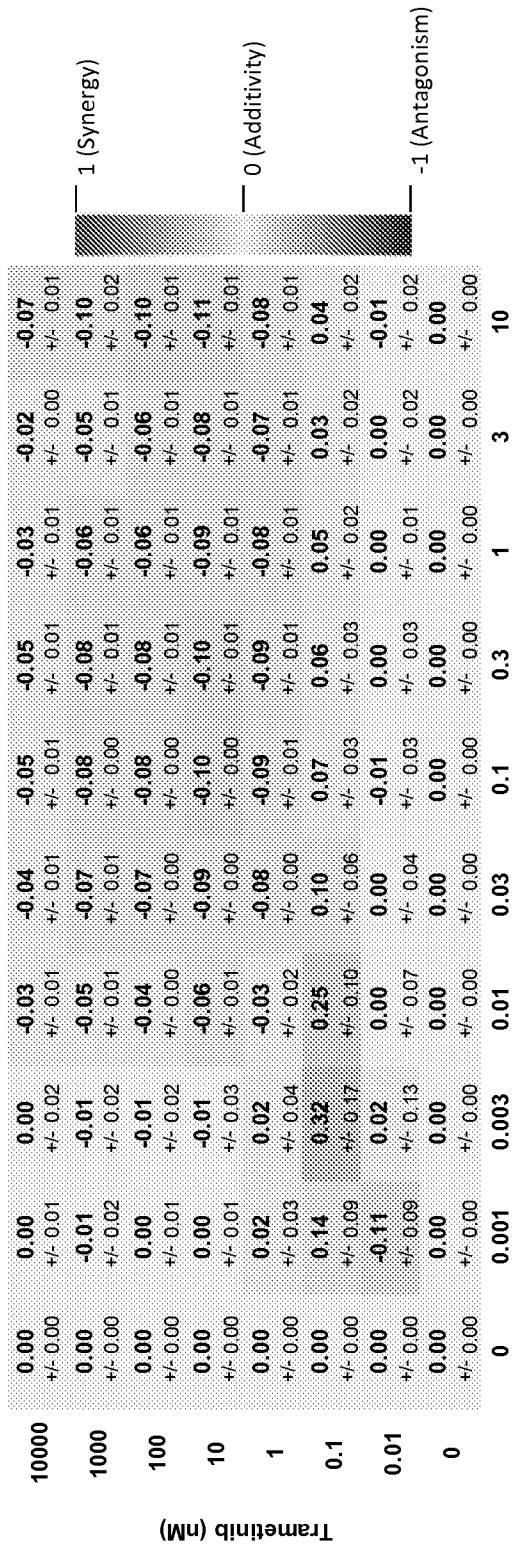


FIG. 10, Con't

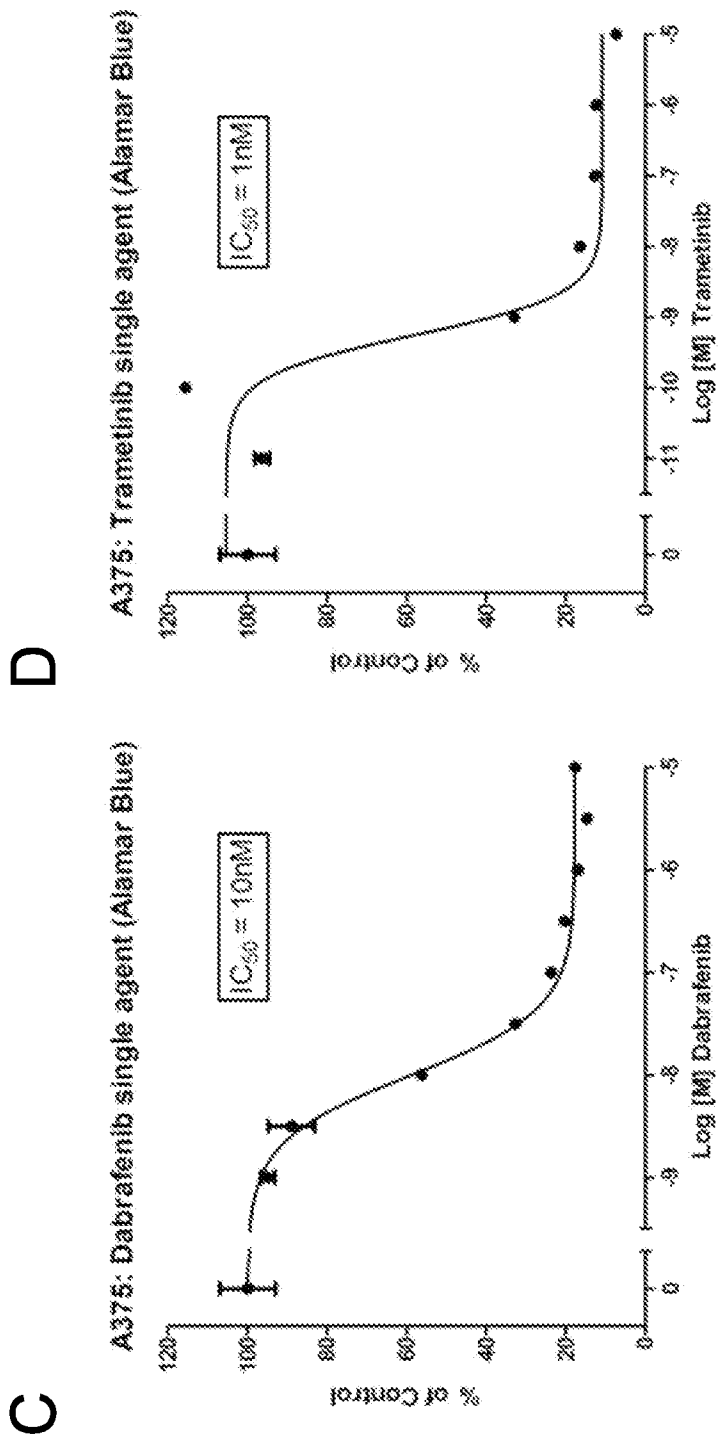

C
A375: Dabrafenib single agent (Alamar Blue)
IC50 = 10nM
% of Control
Log [M] Dabrafenib
D
A375: Trametinib single agent (Alamar Blue)
IC50 = 1nM
% of Control
Log [M] Trametinib

FIG. 10, Con't

E

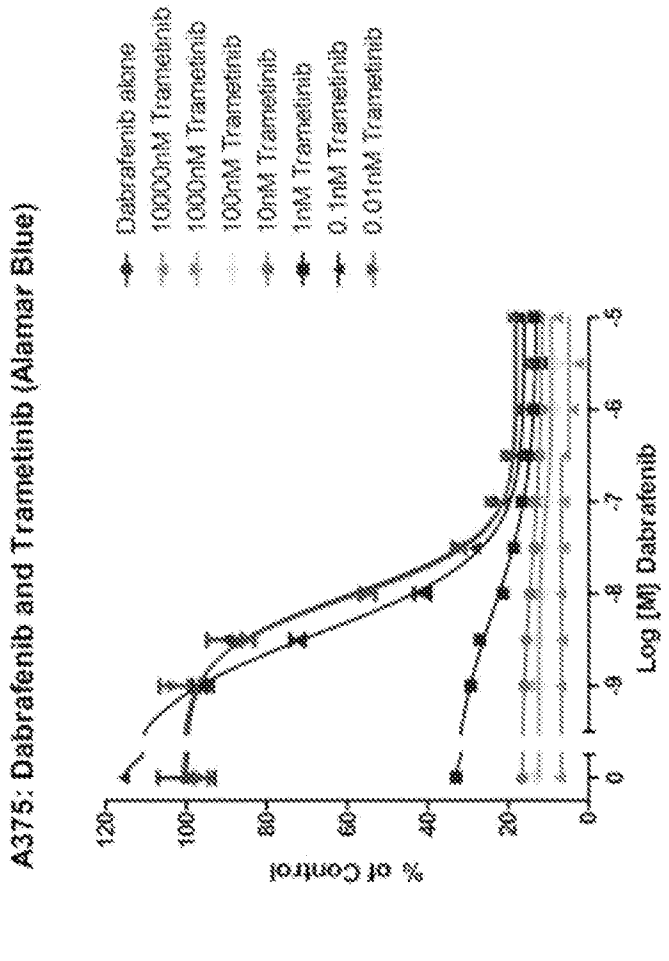

A375: Dabrafenib and Trametinib (Alamar Blue)
Dabrafenib alone
1000nM Trametinib
100nM Trametinib
10nM Trametinib
1nM Trametinib
0.1nM Trametinib
0.01nM Trametinib
% of Control
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] Dabrafenib

FIG. 11

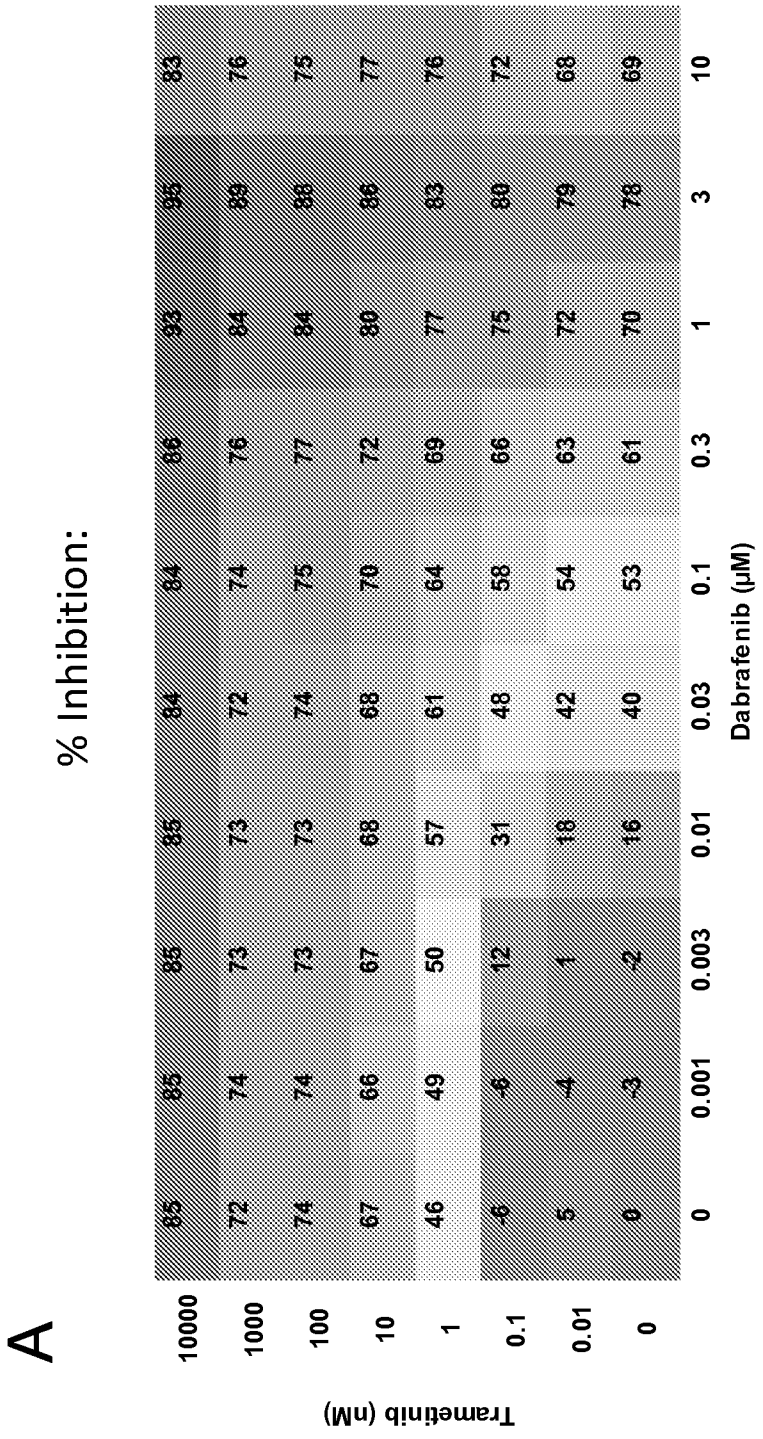

A
% Inhibition:
Trametinib (nM)
Dabrafenib (μM)
10000
1000
100
10
1
0.1
0.01
0
0
0.001
0.003
0.01
0.03
0.1
0.3
1
3
10
85 85 85 85 84 84 86 93 95 83
72 74 73 73 72 74 76 84 89 76
74 74 73 73 74 75 77 84 86 75
67 66 67 68 68 70 72 80 86 77
46 49 50 57 61 64 69 77 83 76
6 6 12 31 48 58 66 75 80 72
5 4 1 18 42 54 63 72 79 68
0 3 2 16 40 53 61 70 78 69

FIG. 11, Con't

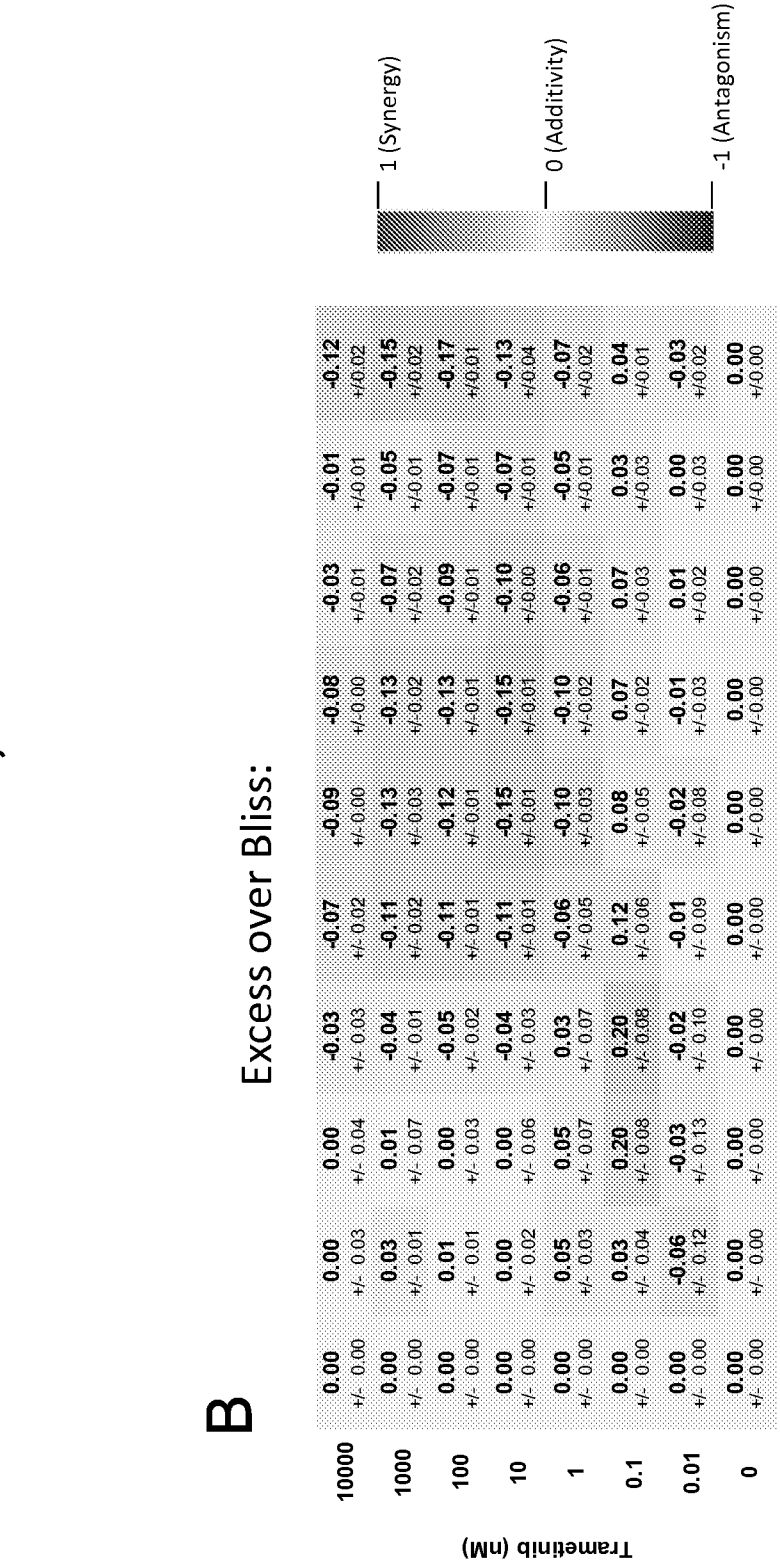

B
Excess over Bliss:
1 (Synergy)
0 (Additivity)
-1 (Antagonism)
Trametinib (nM)
Dabrafenib (μM)
10000
1000
100
10
1
0.1
0.01
0
0
0.001
0.003
0.01
0.03
0.1
0.3
1
3
10
0.00 +/- 0.00 | 0.00 +/- 0.03 | 0.00 +/- 0.04 | -0.03 +/- 0.03 | -0.07 +/- 0.02 | -0.09 +/- 0.00 | -0.08 +/- 0.00 | -0.03 +/- 0.01 | -0.01 +/- 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 | 0.00 +/- 0.00

FIG. 11, Con't

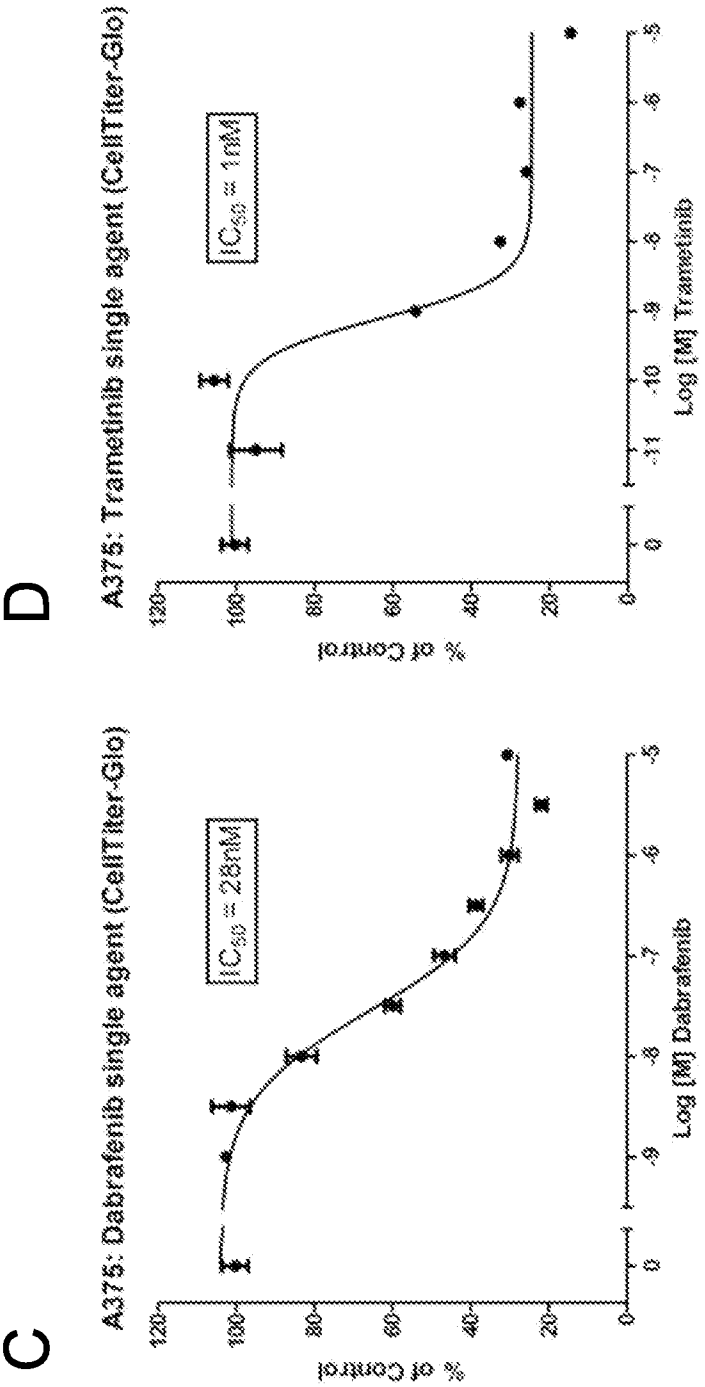

C
A375: Dabrafenib single agent (CellTiter-Glo)
IC50 = 28nM
% of Control
Log [M] Dabrafenib
D
A375: Trametinib single agent (CellTiter-Glo)
IC50 = 1nM
% of Control
Log [M] Trametinib

FIG. 11, Con't

E

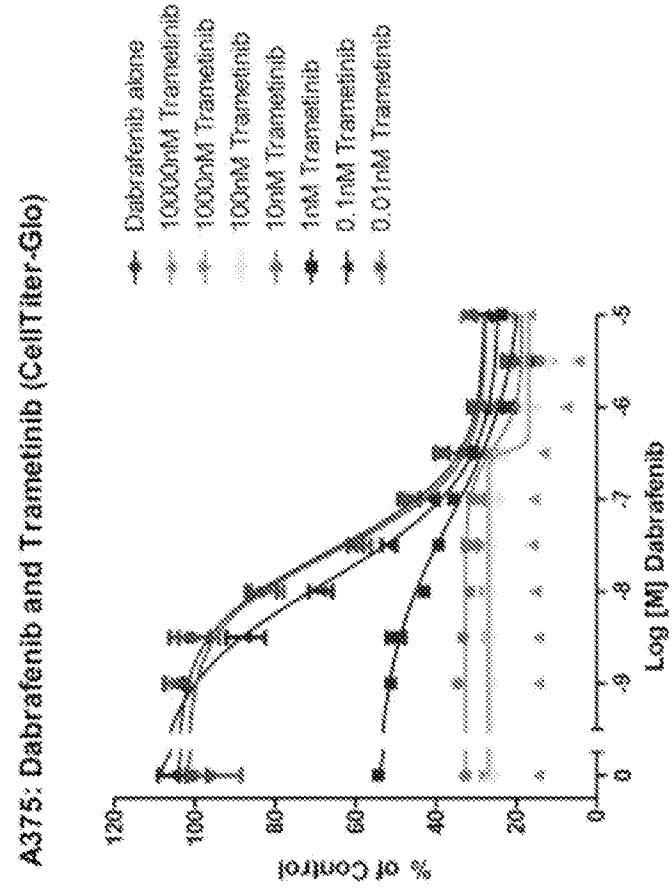

A375: Dabrafenib and Trametinib (CellTiter-Glo)
Dabrafenib alone
1000nM Trametinib
100nM Trametinib
10nM Trametinib
1nM Trametinib
0.1nM Trametinib
0.01nM Trametinib
% of Control
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] Dabrafenib

FIG. 12

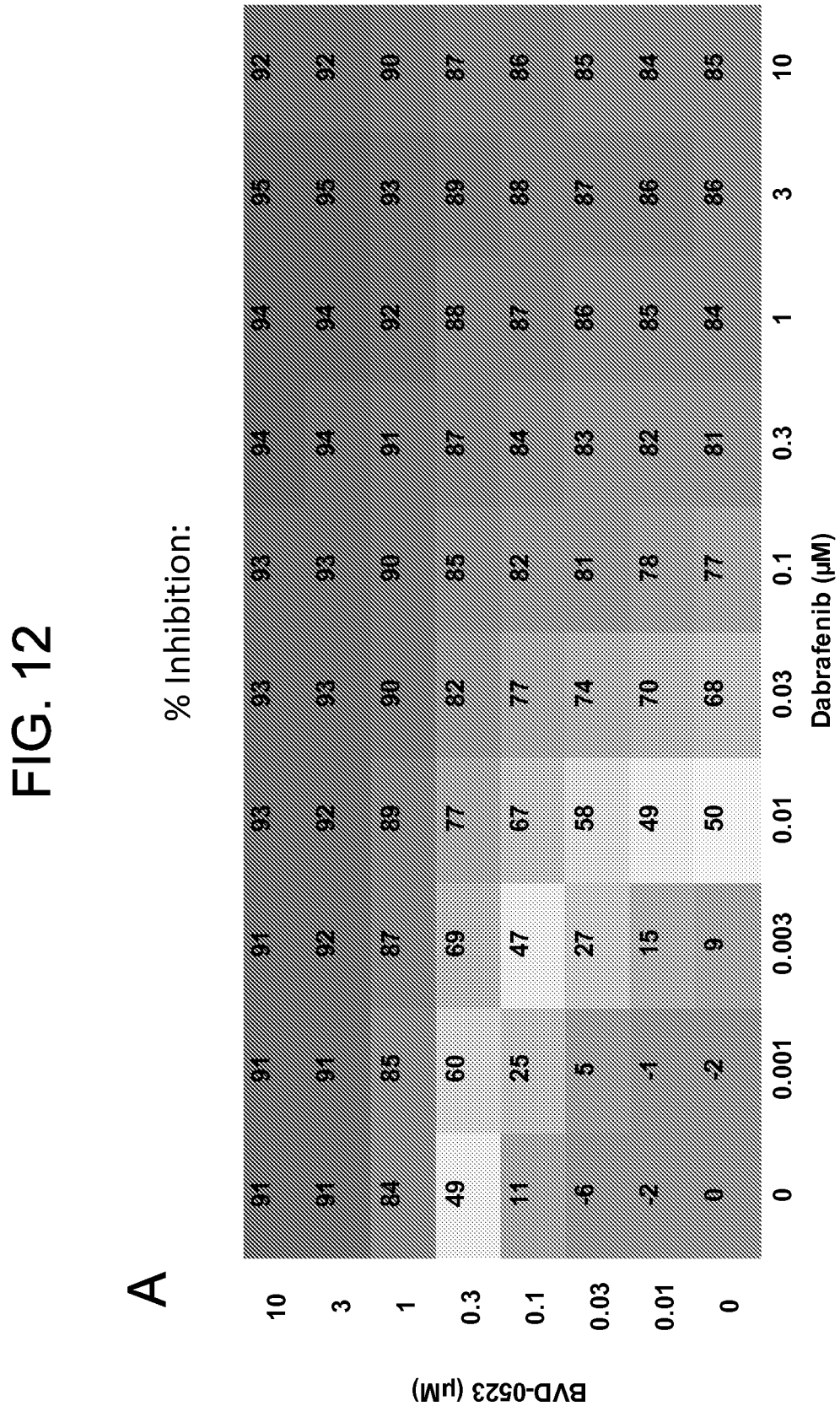

A
% Inhibition:
BVD-0523 (μM)
10
3
1
0.3
0.1
0.03
0.01
0
91 91 91 91 93 93 93 94 94 95 92
91 91 92 92 92 93 93 94 94 95 92
84 85 87 87 89 90 90 91 92 93 90
49 60 69 77 82 85 87 88 89 89 87
11 25 47 67 77 82 84 87 88 88 86
-6 5 27 58 74 81 83 86 87 87 85
-2 -1 15 49 70 78 82 85 86 86 84
0 -2 9 50 68 77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

FIG. 12, Con't

B

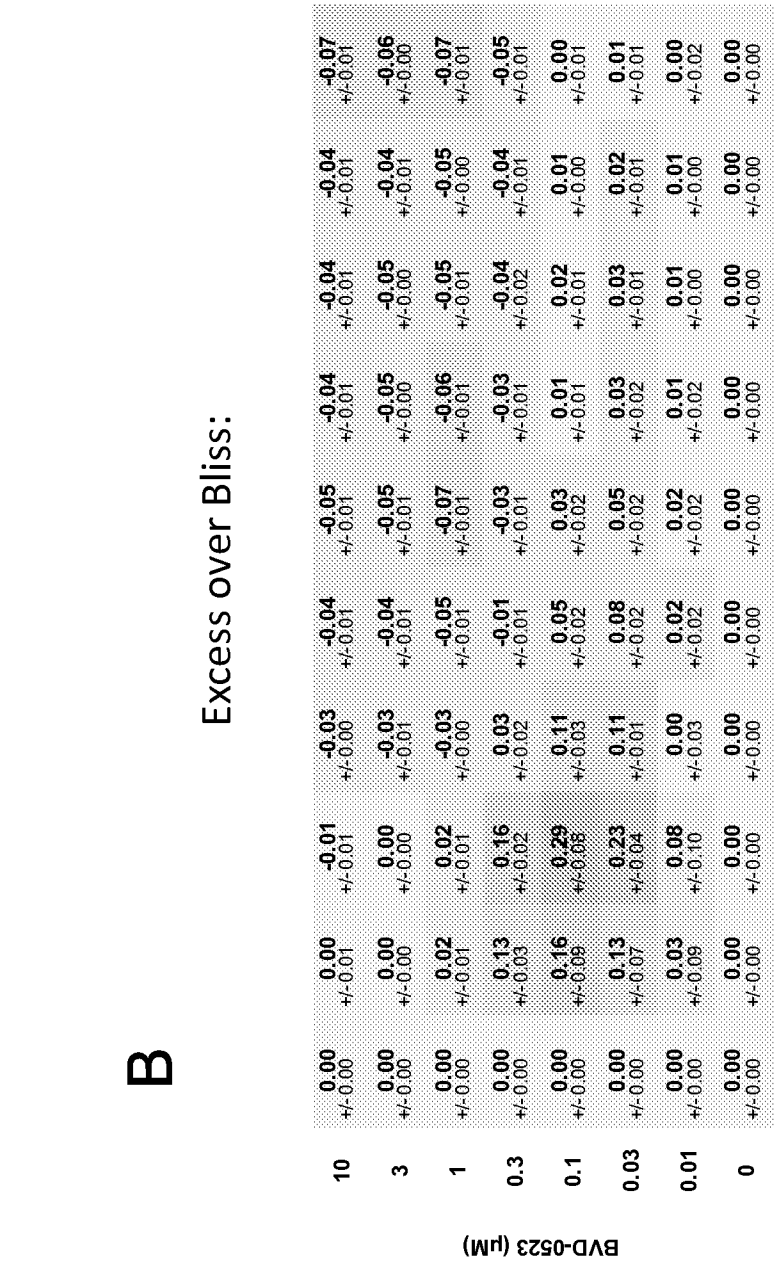

Excess over Bliss:
1 (Synergy)
0 (Additivity)
-1 (Antagonism)
BVD-0523 (μM)
10 3 1 0.3 0.1 0.03 0.01 0
0.00 +/-0.00 0.00 +/-0.01 -0.01 +/-0.01 -0.03 +/-0.00 -0.04 +/-0.01 -0.05 +/-0.01 -0.04 +/-0.01 -0.04 +/-0.01 -0.07 +/-0.01
0.00 +/-0.00 0.00 +/-0.00 0.00 +/-0.00 -0.03 +/-0.01 -0.04 +/-0.01 -0.05 +/-0.01 -0.05 +/-0.00 -0.04 +/-0.01 -0.06 +/-0.00
0.00 +/-0.00 0.02 +/-0.01 0.02 +/-0.01 -0.03 +/-0.00 -0.05 +/-0.01 -0.07 +/-0.01 -0.06 +/-0.01 -0.05 +/-0.00 -0.05 +/-0.00 -0.07 +/-0.01
0.00 +/-0.00 0.13 +/-0.03 0.16 +/-0.02 0.03 +/-0.02 -0.01 +/-0.01 -0.03 +/-0.01 -0.03 +/-0.01 -0.04 +/-0.02 -0.04 +/-0.01 -0.05 +/-0.01
0.00 +/-0.00 0.16 +/-0.09 0.29 +/-0.05 0.11 +/-0.03 0.05 +/-0.02 0.03 +/-0.02 0.01 +/-0.01 0.02 +/-0.01 0.01 +/-0.00 0.00 +/-0.01
0.00 +/-0.00 0.13 +/-0.07 0.23 +/-0.04 0.11 +/-0.01 0.08 +/-0.02 0.05 +/-0.02 0.03 +/-0.02 0.03 +/-0.01 0.02 +/-0.01 0.01 +/-0.01
0.00 +/-0.00 0.03 +/-0.09 0.08 +/-0.10 0.00 +/-0.03 0.02 +/-0.02 0.02 +/-0.02 0.01 +/-0.02 0.01 +/-0.00 0.01 +/-0.00 0.00 +/-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 0.00 +/-0.00
0 0.001 0.003 0.01 0.03 0.1 0.3 1 3 10
Dabrafenib (μM)

FIG. 12, Con't

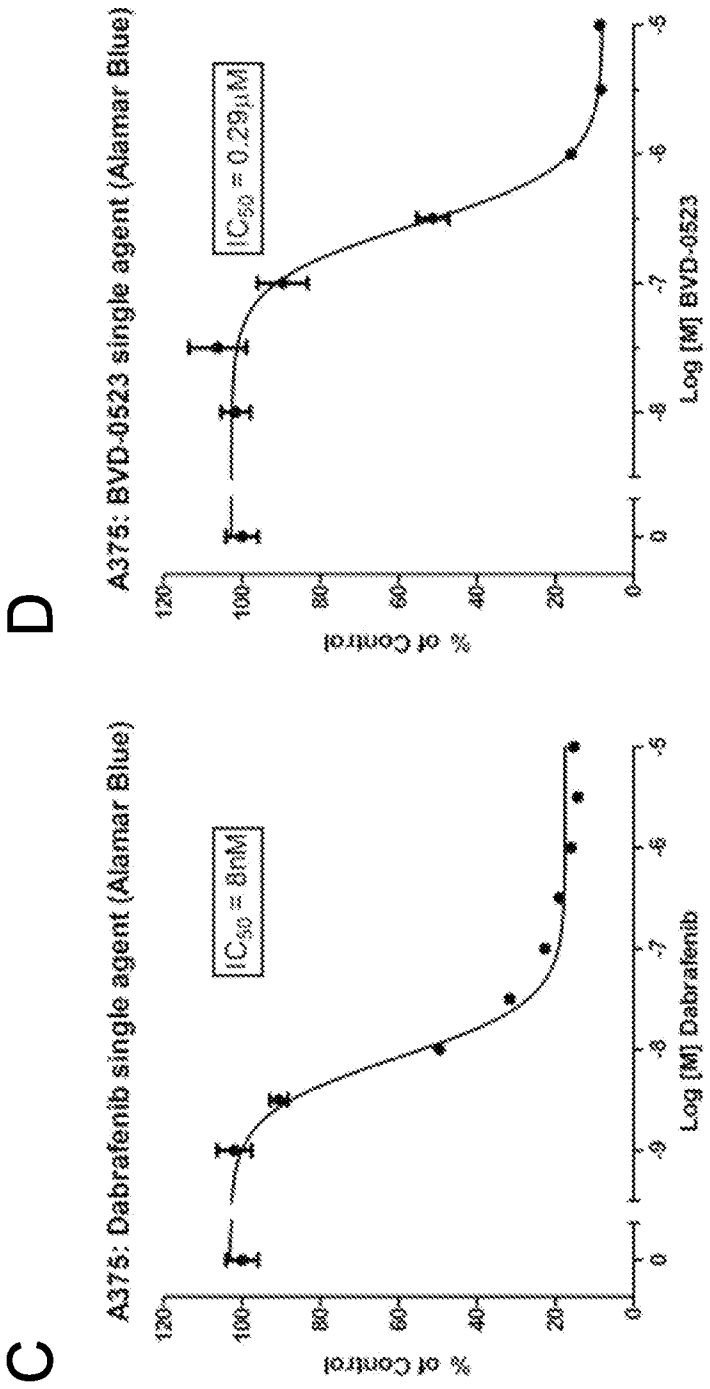

C
A375: Dabrafenib single agent (Alamar Blue)
IC50 = 8nM
% of Control
Log [M] Dabrafenib
D
A375: BVD-0523 single agent (Alamar Blue)
IC50 = 0.29μM
% of Control
Log [M] BVD-0523

FIG. 12, Con't

E

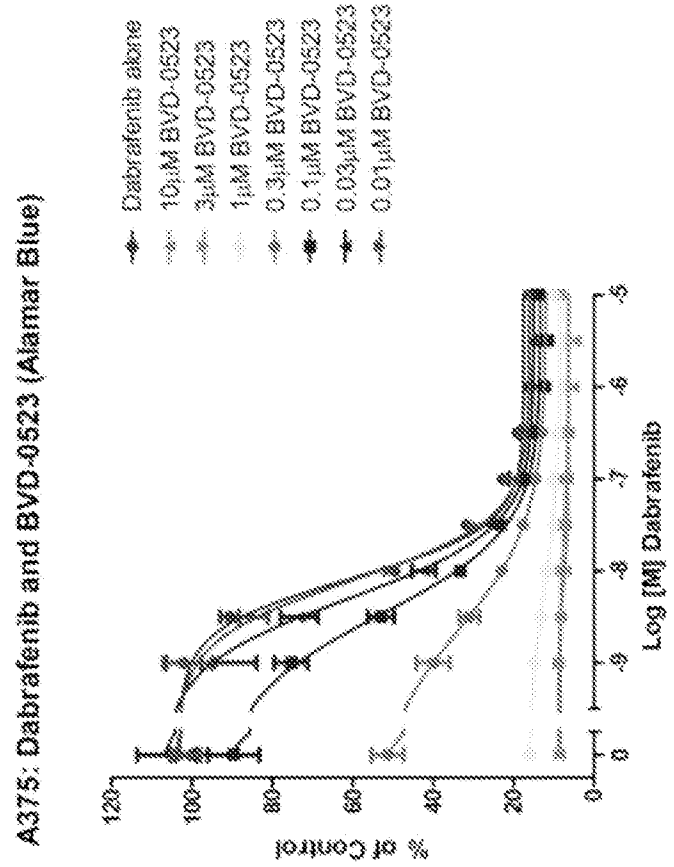

A375: Dabrafenib and BVD-0523 (Alamar Blue)
Dabrafenib alone
10μM BVD-0523
3μM BVD-0523
1μM BVD-0523
0.3μM BVD-0523
0.1μM BVD-0523
0.03μM BVD-0523
0.01μM BVD-0523
% of Control
120
100
80
60
40
20
0
0
-9
-8
-7
-6
-5
Log [M] Dabrafenib

FIG. 13

A

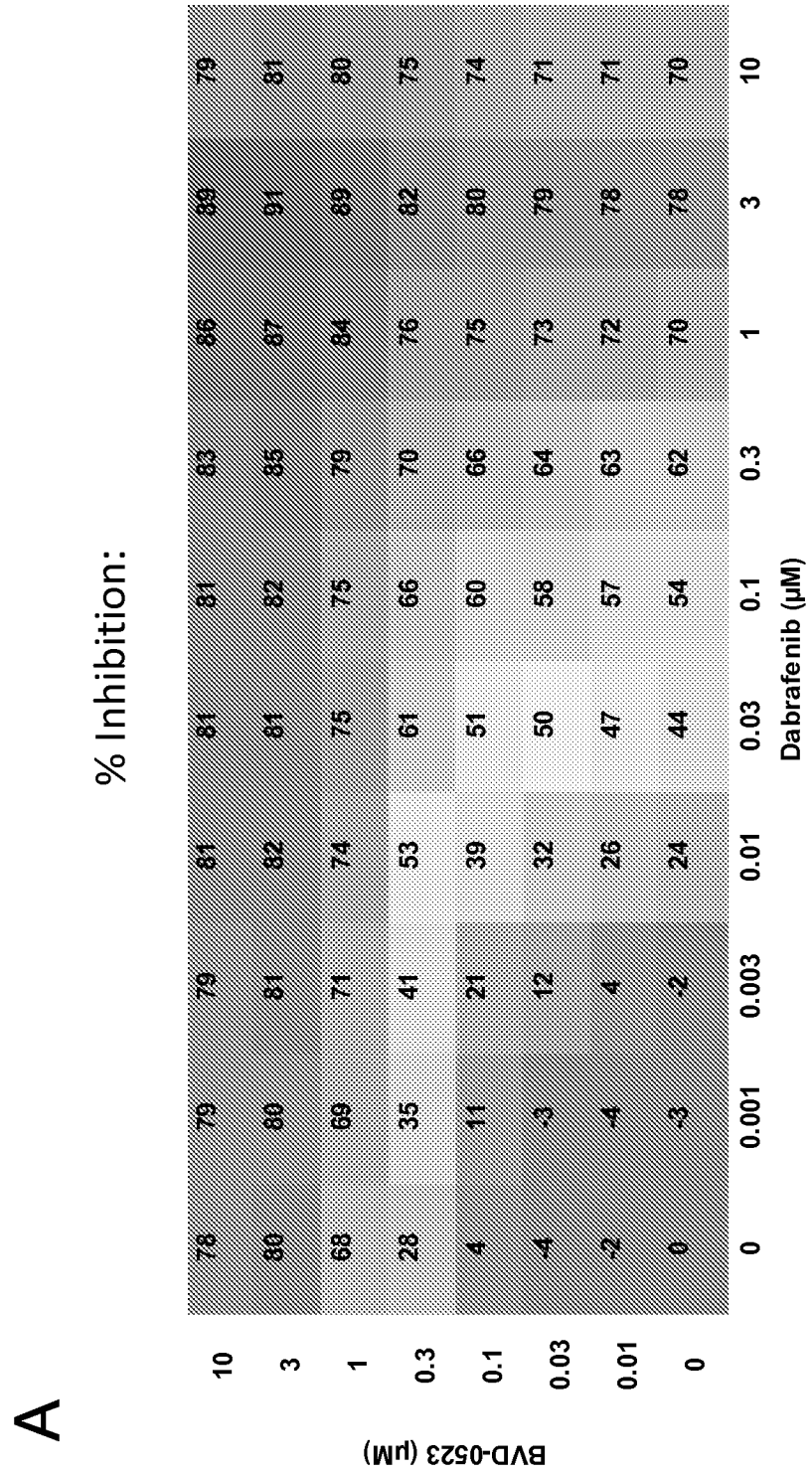

% Inhibition:
BVD-523 (μM)
Dabrafenib (μM)
10 78 79 79 81 81 81 81 83 86 89 79
3 80 80 81 82 81 82 85 87 91 81
1 68 69 71 74 75 75 79 84 89 80
0.3 28 35 41 53 61 66 70 76 82 75
0.1 4 11 21 39 51 60 66 75 80 74
0.03 -4 -3 12 32 50 58 64 73 79 71
0.01 -2 -4 4 26 47 57 63 72 78 71
0 0 -3 -2 24 44 54 62 70 78 70
0 0.001 0.003 0.01 0.03 0.1 0.3 1 3 10

FIG. 13, Con't

B

Excess over Bliss:

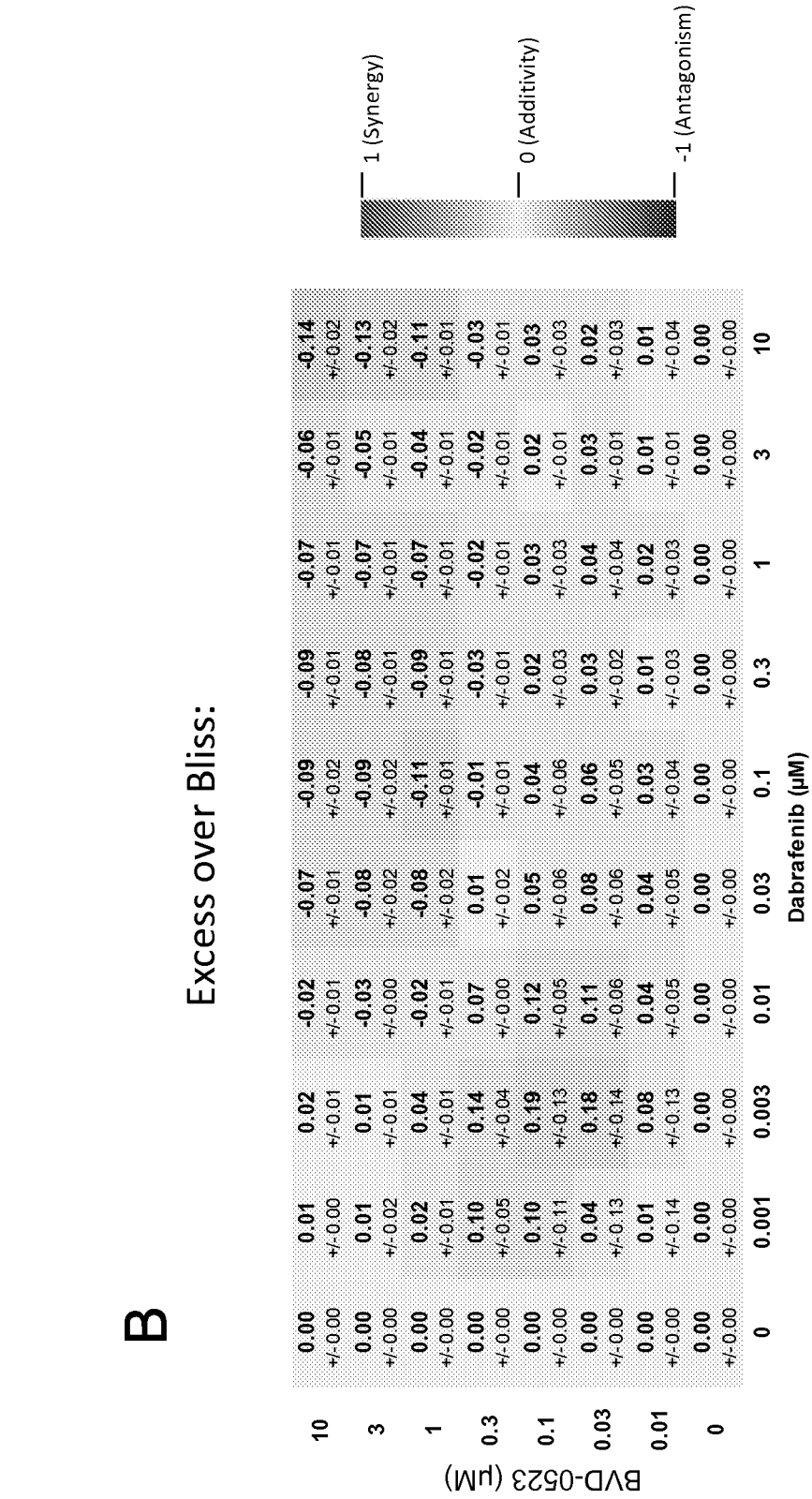


FIG. 13, Con't

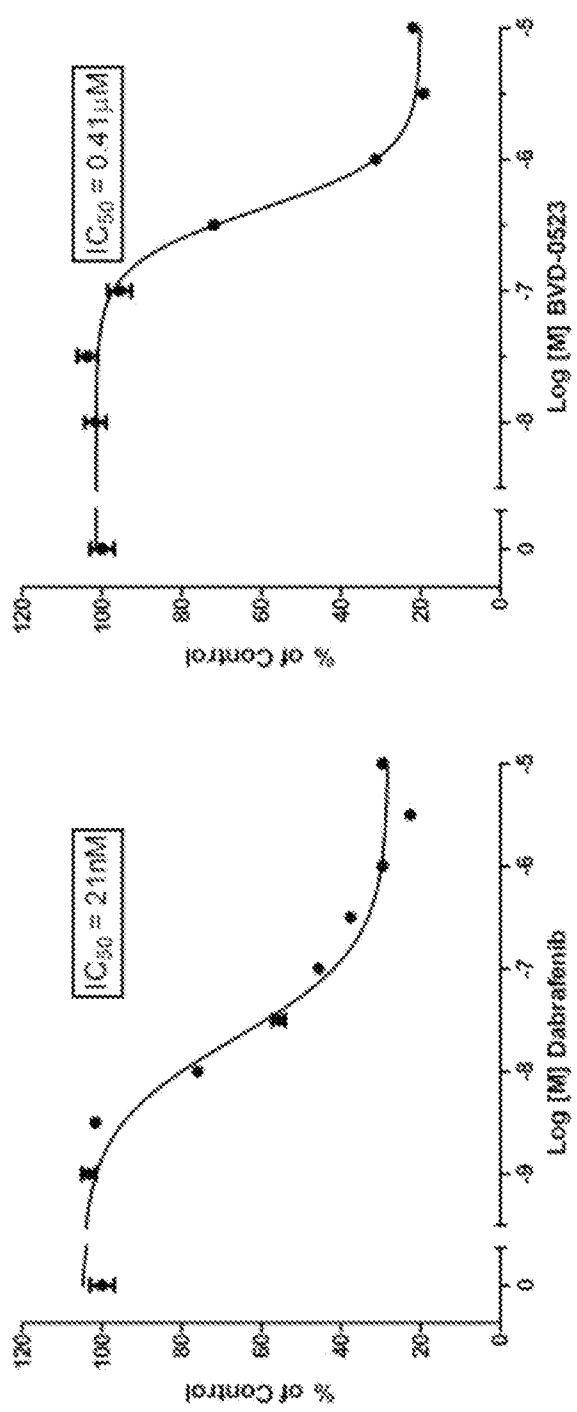

C
A375: Dabrafenib single agent
IC50 = 21nM
% of Control
Log [M] Dabrafenib
D
A375: BVD-0523 single agent (CellTiter-Glo)
IC50 = 0.41μM
% of Control
Log [M] BVD-0523

FIG. 13, Con't

E

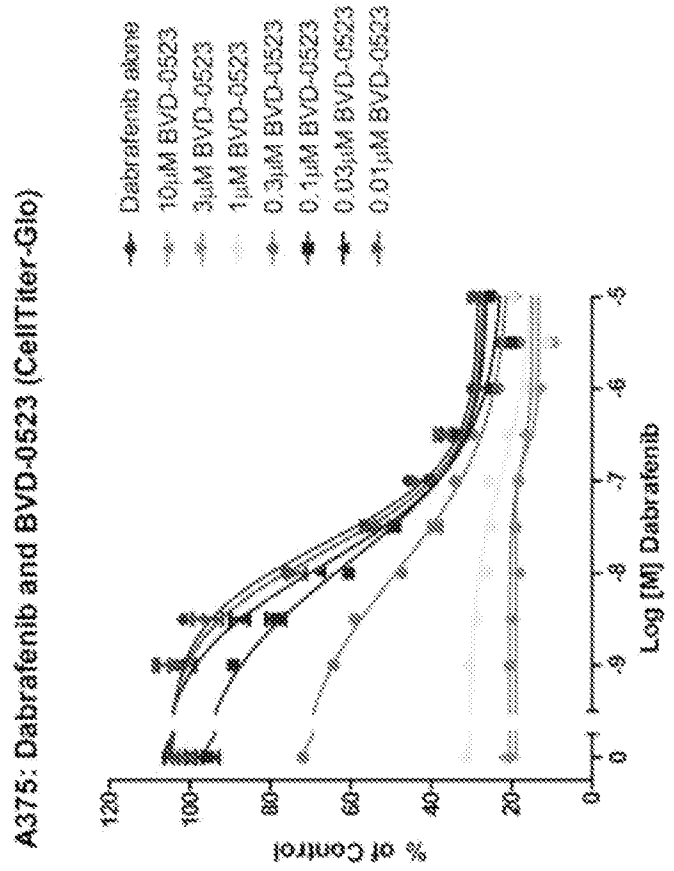

A375: Dabrafenib and BVD-0523 (CellTiter-Glo)
Dabrafenib alone
10μM BVD-0523
3μM BVD-0523
1μM BVD-0523
0.3μM BVD-0523
0.1μM BVD-0523
0.03μM BVD-0523
0.01μM BVD-0523
% of Control
120
100
80
60
40
20
0
-5
-6
-7
-8
-9
0
Log [M] Dabrafenib

FIG. 14

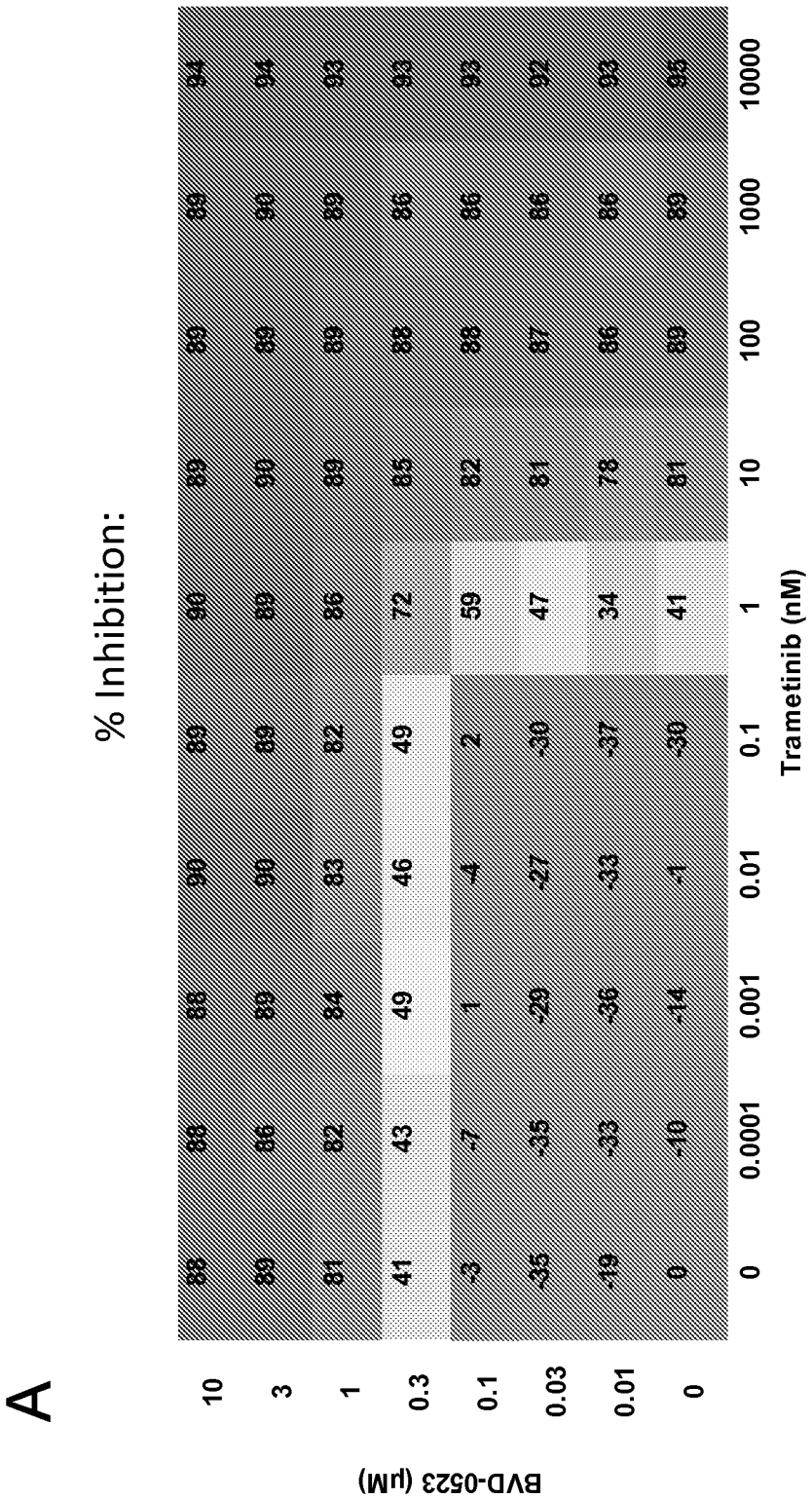
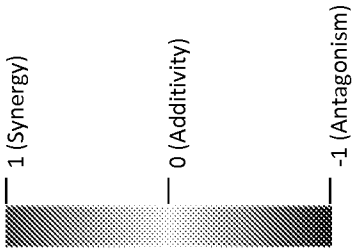

A
% Inhibition:
BVD-0523 (μM)
10
3
1
0.3
0.1
0.03
0.01
0
Trametinib (nM)
0
0.0001
0.001
0.01
0.1
1
10
100
1000
10000
88 88 88 90 89 90 89 89 89 94
89 86 89 90 89 89 90 89 90 94
81 82 84 83 82 86 89 89 89 93
41 43 49 46 49 72 85 88 86 93
-3 -7 1 -4 2 59 82 88 86 93
-35 -35 -29 -27 -30 47 81 87 86 92
-19 -33 -36 -33 -37 34 78 86 86 93
0 -10 -14 -1 -30 41 81 89 89 95

FIG. 14, Con't

B

Excess over Bliss:



BVD-0523 (μM)

	Trametinib (nM)									
	0	0.0001	0.001	0.01	0.1	1	10	100	1000	10000
10	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
3	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
1	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
0.3	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
0.1	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
0.03	0.00 +/-0.00	0.13 +/-0.19	0.25 +/-0.16	0.10 +/-0.16	0.46 +/-0.19	0.26 +/-0.06	0.06 +/-0.02	0.02 +/-0.02	0.02 +/-0.03	-0.01 +/-0.01
0.01	0.00 +/-0.00	-0.03 +/-0.12	0.00 +/-0.20	-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	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. 14, Con't

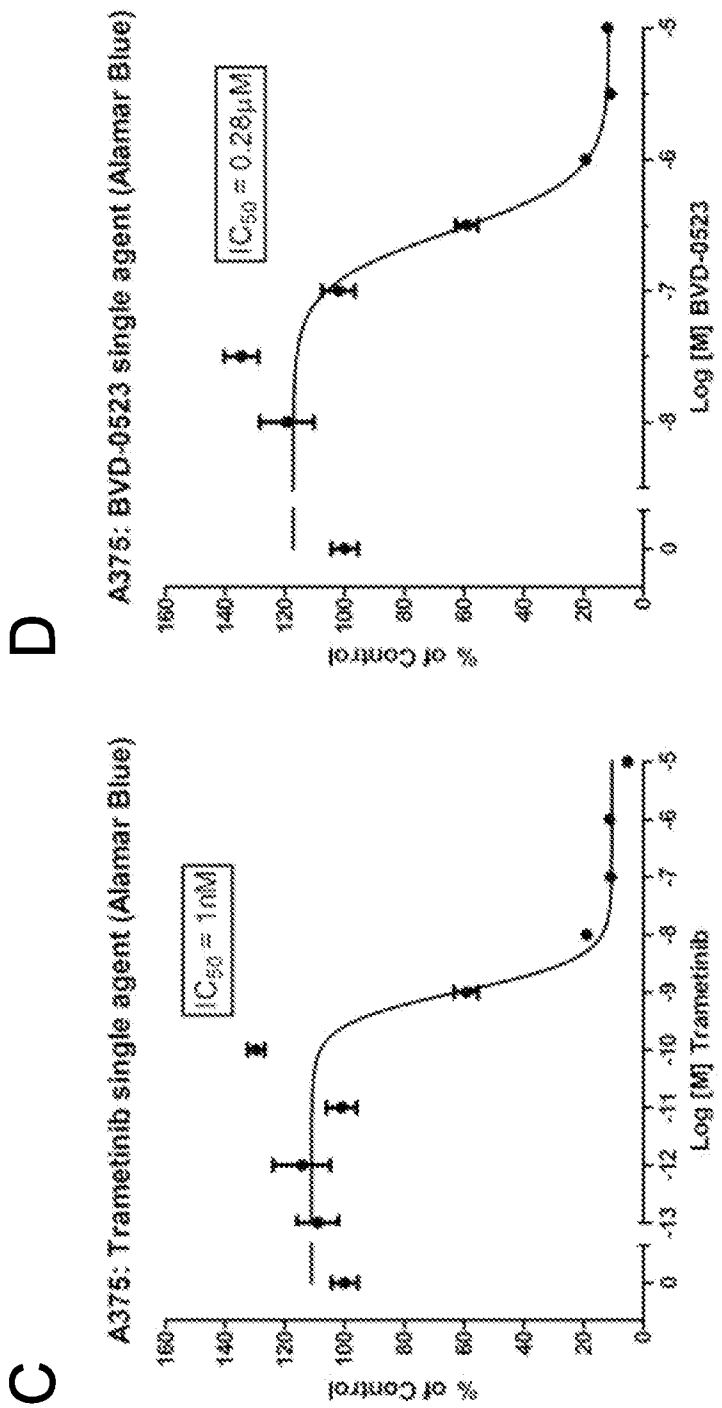

C
A375: Trametinib single agent (Alamar Blue)
IC50 = 1nM
% of Control
Log [M] Trametinib
D
A375: BVD-0523 single agent (Alamar Blue)
IC50 = 0.28μM
% of Control
Log [M] BVD-0523

FIG. 14, Con't

E

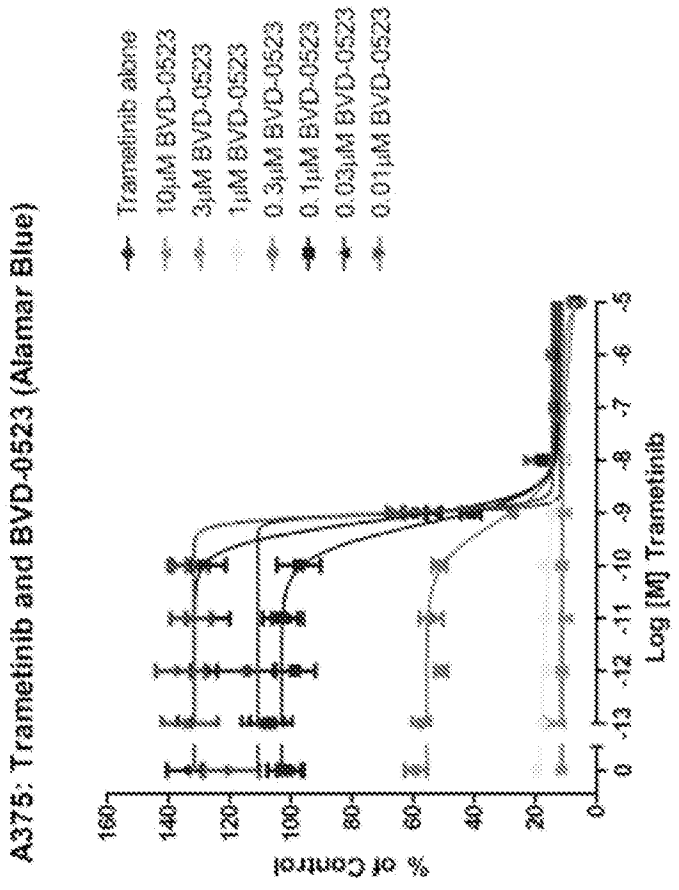

A375: Trametinib and BVD-0523 (Alamar Blue)
Trametinib alone
10μM BVD-0523
3μM BVD-0523
1μM BVD-0523
0.3μM BVD-0523
0.1μM BVD-0523
0.03μM BVD-0523
0.01μM BVD-0523
% of Control
160
140
120
100
80
60
40
20
0
0
-13
-12
-11
-10
-9
-8
-7
-6
-5
Log [M] Trametinib

FIG. 15

A

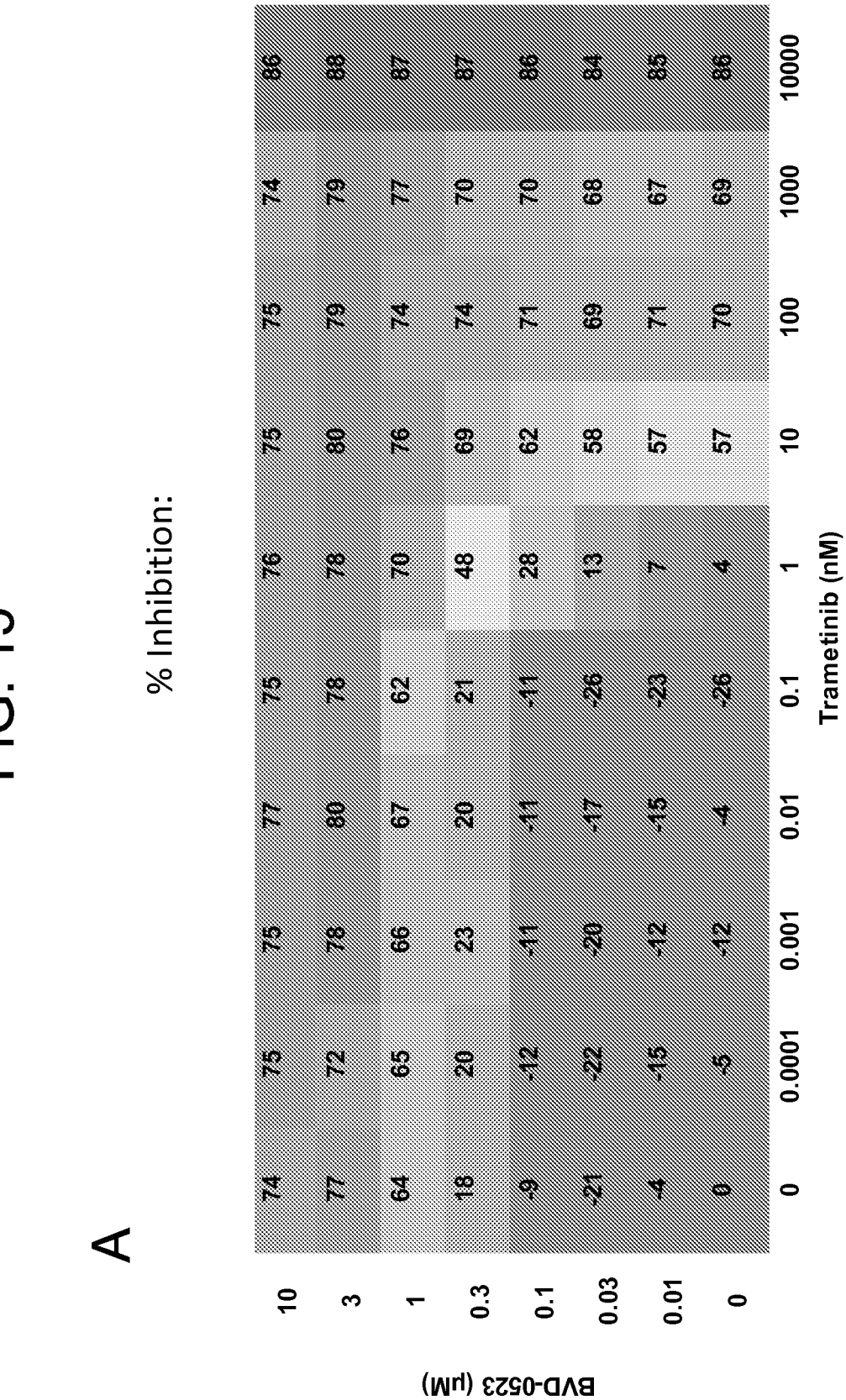

% Inhibition:
BVD-0523 (μM)
10
3
1
0.3
0.1
0.03
0.01
0
74 75 75 77 75 76 75 75 74 86
77 72 78 80 78 78 80 79 79 88
64 65 66 67 62 70 76 74 77 87
18 20 23 20 21 48 69 74 70 67
-9 -12 -11 -11 -11 28 62 71 70 86
-21 -22 -20 -17 -26 13 58 69 68 84
-4 -15 -12 -15 -23 7 57 71 67 85
0 -5 -12 -4 -26 4 57 70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

FIG. 15, Con't

B

Excess over Bliss:

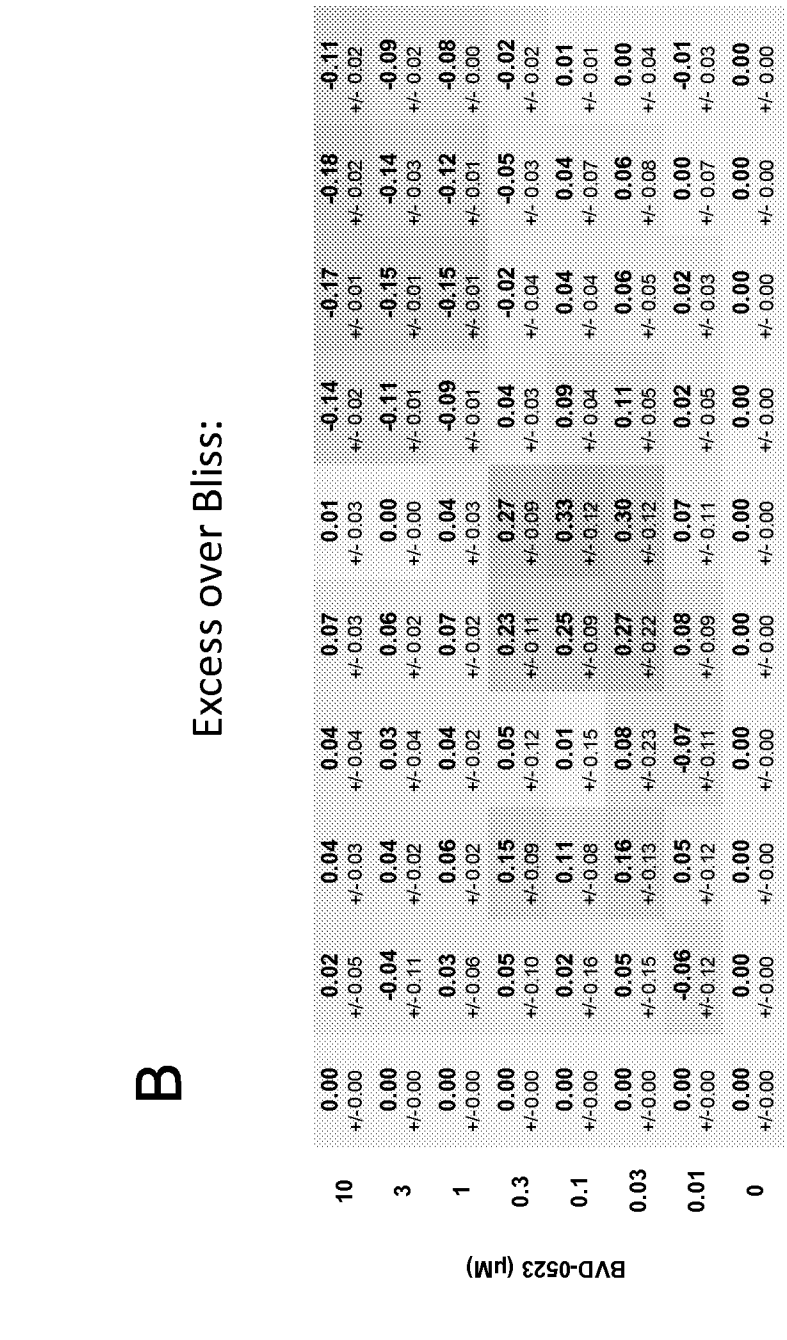


FIG. 15, Con't

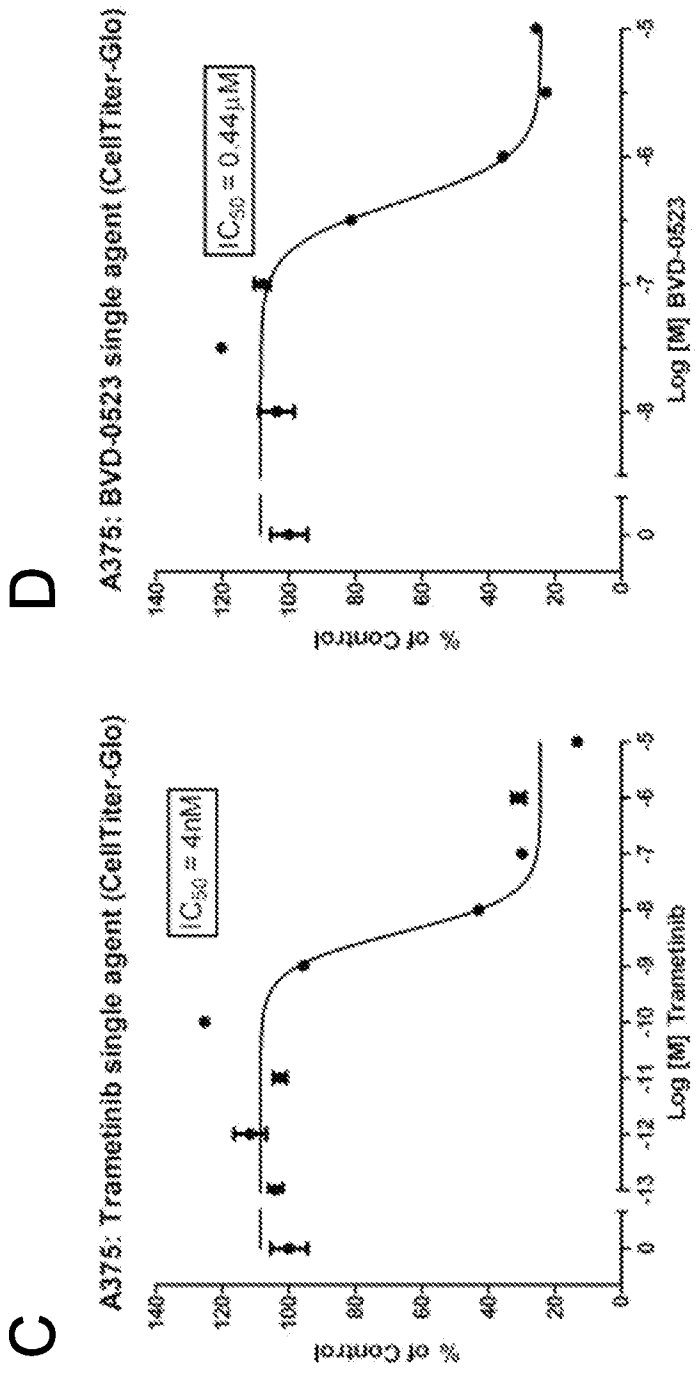

C
A375: Trametinib single agent (CellTiter-Glo)
IC50 = 4nM
% of Control
Log [M] Trametinib
D
A375: BVD-0523 single agent (CellTiter-Glo)
IC50 = 0.44μM
% of Control
Log [M] BVD-0523

FIG. 15, Con't

E

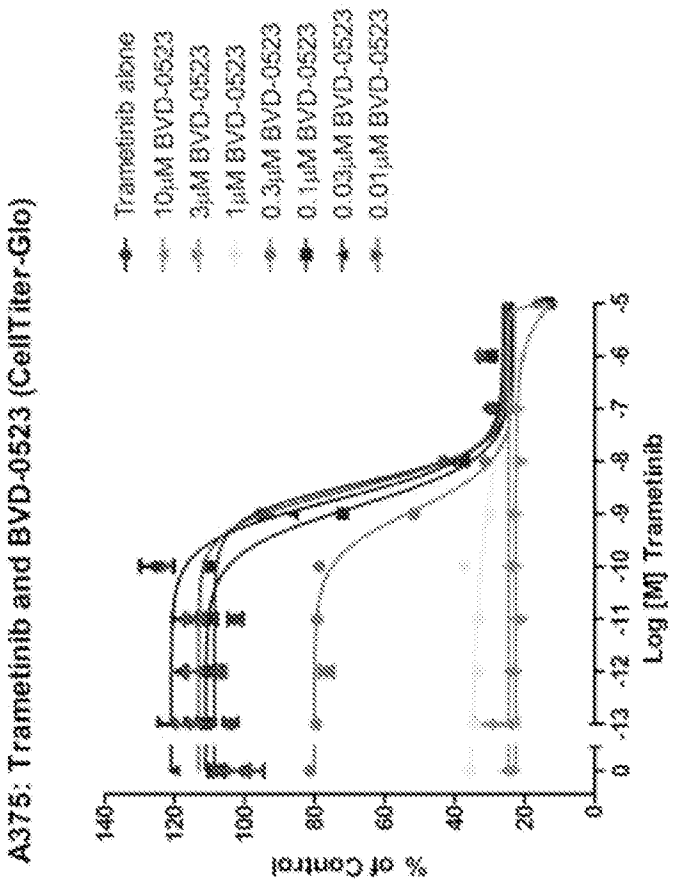

A375: Trametinib and BVD-0523 (CellTiter-Glo)
Trametinib alone
10μM BVD-0523
3μM BVD-0523
1μM BVD-0523
0.3μM BVD-0523
0.1μM BVD-0523
0.03μM BVD-0523
0.01μM BVD-0523
% of Control
140
120
100
80
60
40
20
0
0 -13 -12 -11 -10 -9 -8 -7 -6 -5
Log [M] Trametinib

FIG. 16

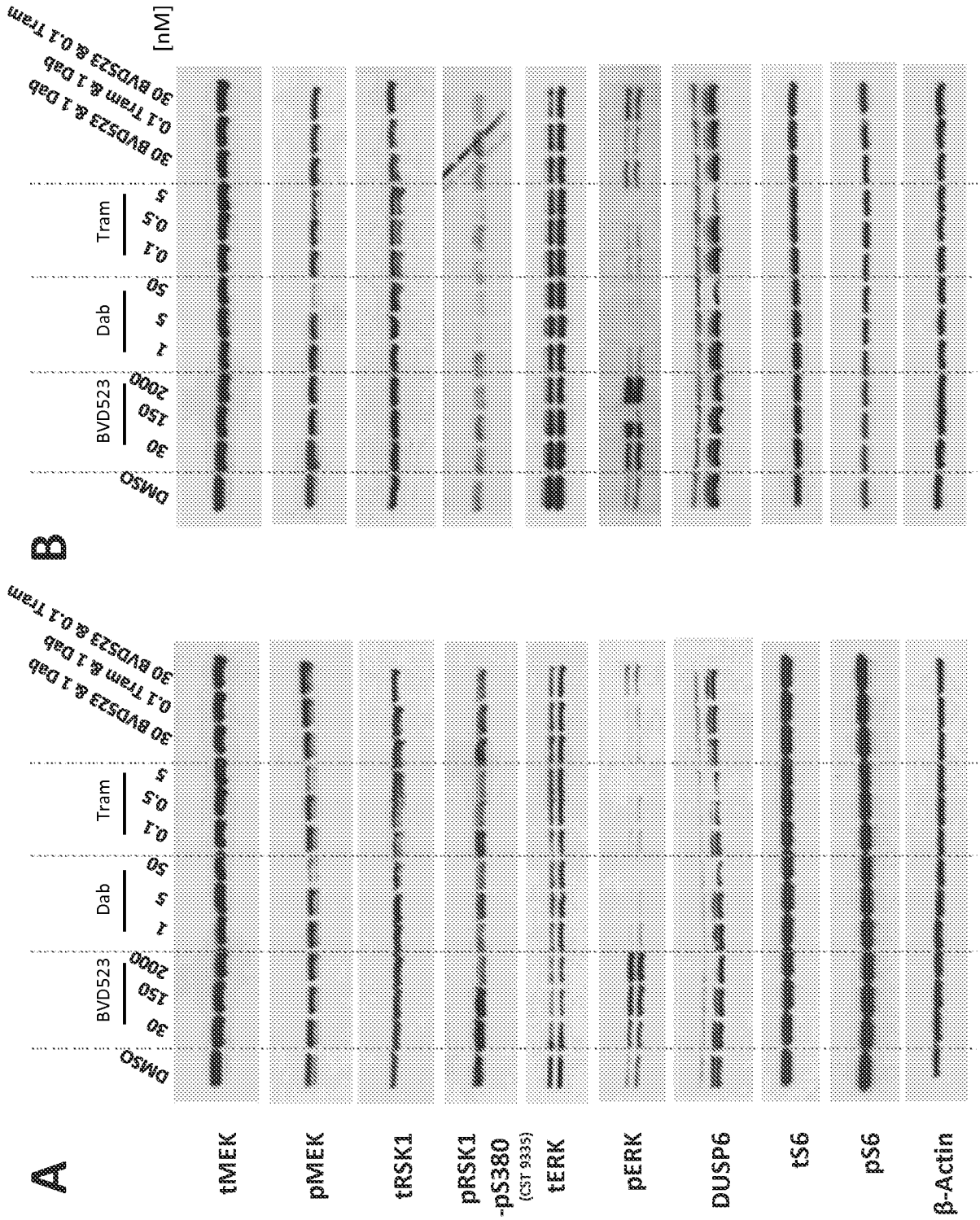

A
B
DMSO
BVD523
30
150
2000
Dab
1
5
50
Tram
0.1
0.5
5
30 BVD523 & 1 Dab
0.1 Tram & 1 Dab
30 BVD523 & 0.1 Tram
[nM]
tMEK
pMEK
tRSK1
pRSK1
-pS380
(CST 9335)
tERK
pERK
DUSP6
tS6
pS6
β-Actin

FIG. 16 Con't

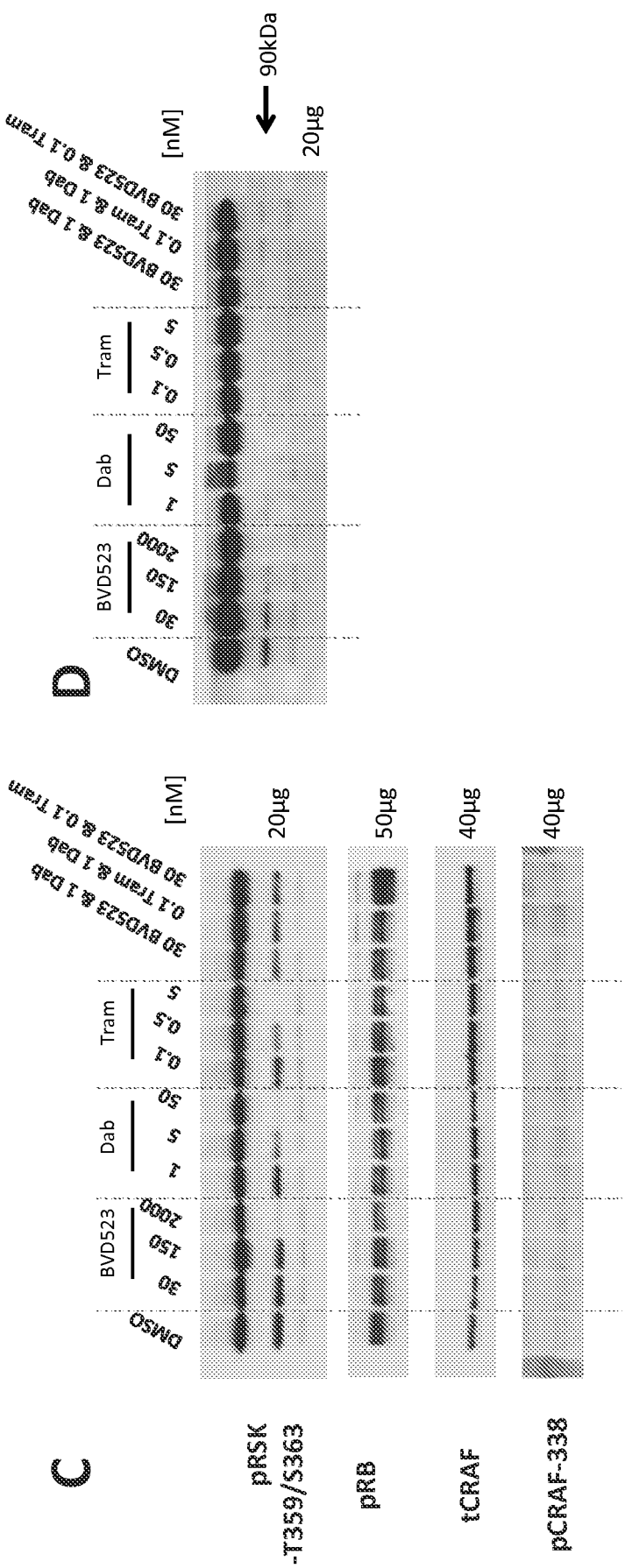

D
90kDa
20µg
[nM]
DMSO
BVD523
30
150
2000
Dab
1
5
50
Tram
0.1
0.5
5
30 BVD523 & 1 Dab
0.1 Tram & 1 Dab
30 BVD523 & 0.1 Tram
C
pRSK -T359/S363
pRB
tCRAF
pCRAF-338
20µg
50µg
40µg
40µg

FIG. 17

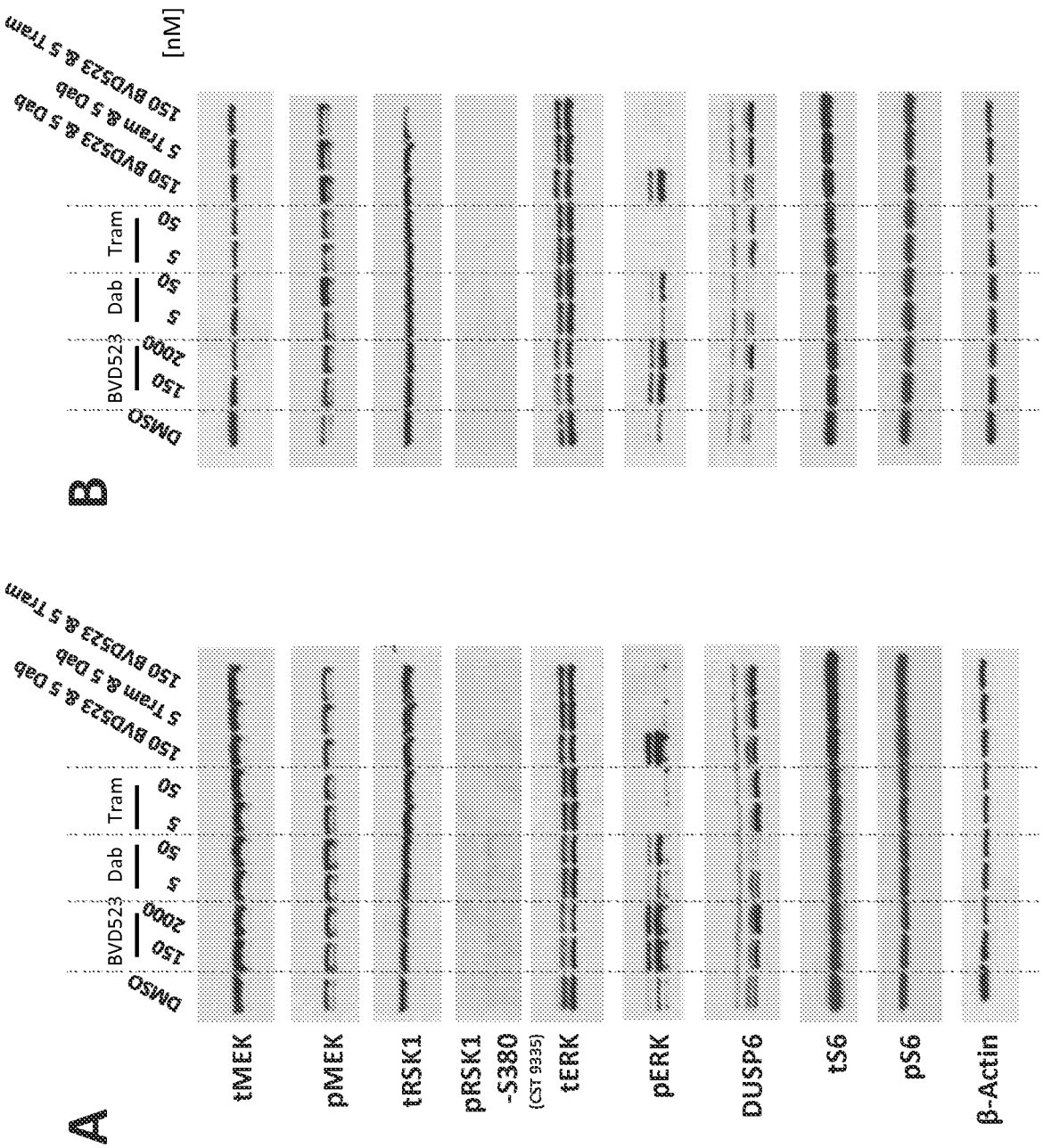

A
B
DMSO
BVD523
150
2000
Dab
5
50
Tram
5
50
150 BVD523 & 5 Dab
5 Tram & 5 Dab
150 BVD523 & 5 Tram
[nM]
tMEK
pMEK
tRSK1
pRSK1 -S380 (CST 9335)
tERK
pERK
DUSP6
tS6
pS6
β-Actin

FIG. 17 Con't

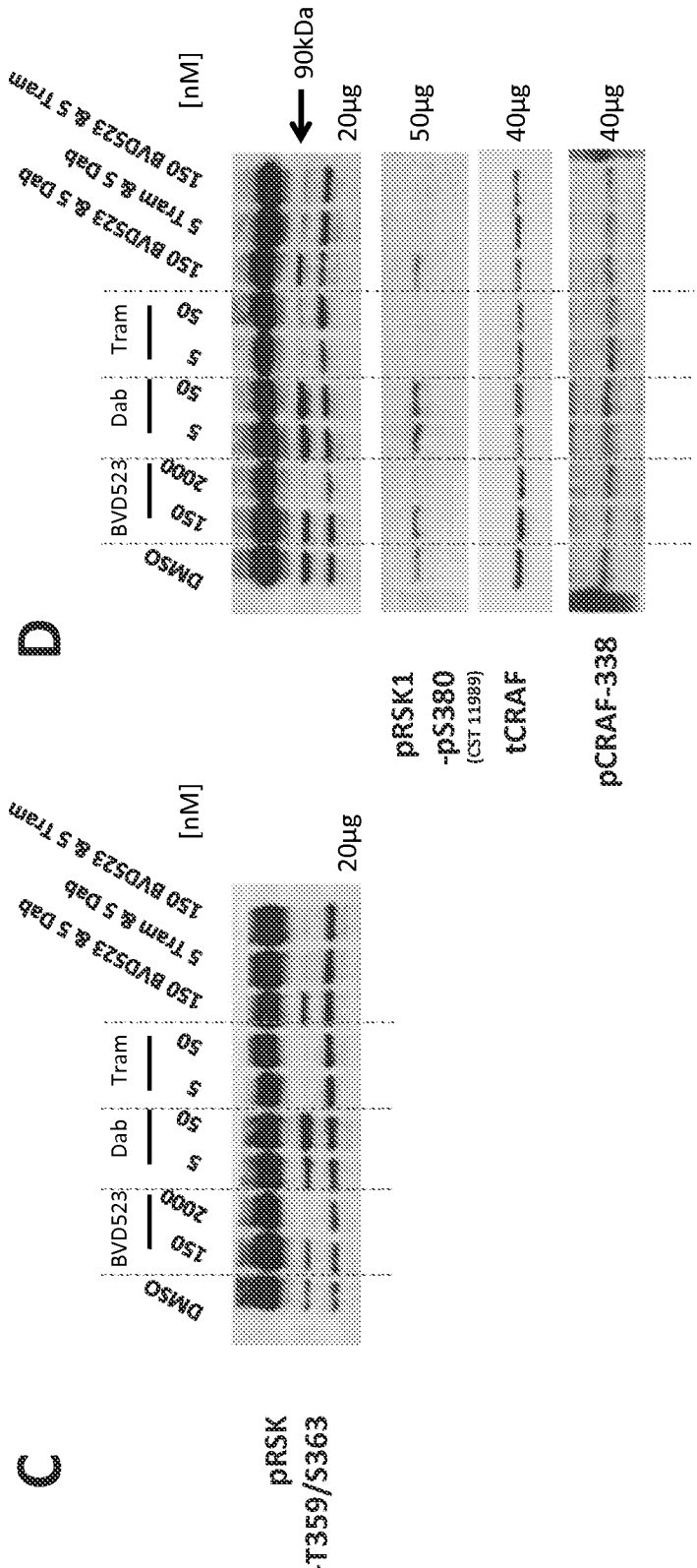

C
pRSK
-T359/S363
20µg
[nM]
DMSO
BVD523
150
2000
Dab
5
50
Tram
5
50
150 BVD523 & 5 Dab
5 Tram & 5 Dab
150 BVD523 & 5 Tram
D
90kDa
20µg
50µg
40µg
40µg
pRSK1
-pS380
(CST 11989)
tCRAF
pCRAF-338

FIG. 18

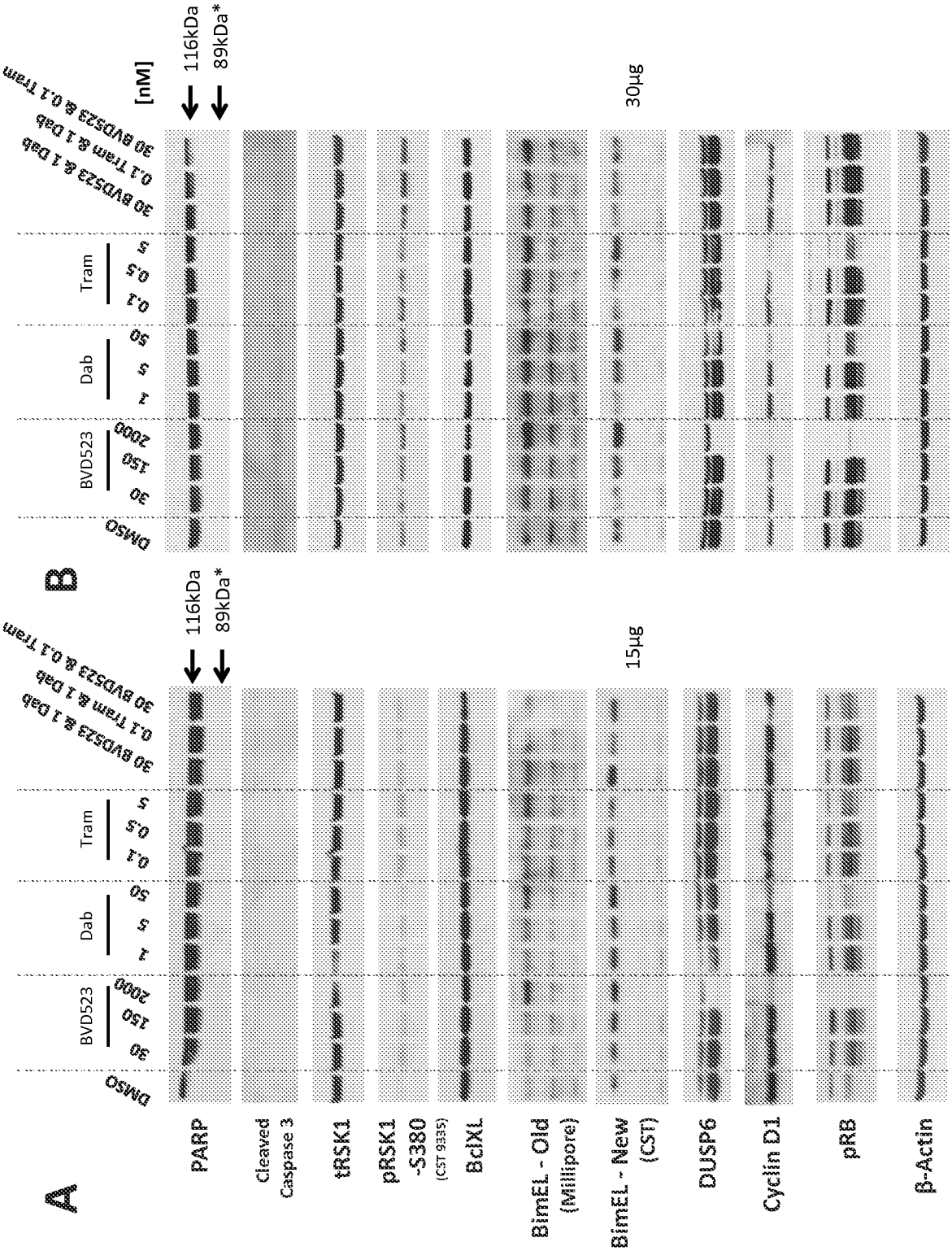

A
B
DMSO
BVD523
30
150
2000
Dab
1
5
50
Tram
0.1
0.5
5
30 BVD523 & 1 Dab
0.1 Tram & 1 Dab
30 BVD523 & 0.1 Tram
[nM]
116kDa
89kDa*
15µg
30µg
PARP
Cleaved Caspase 3
tRSK1
pRSK1 -S380 (CST 9335)
BclXL
BimEL - Old (Millipore)
BimEL - New (CST)
DUSP6
Cyclin D1
pRB
β-Actin

FIG. 18 Con't

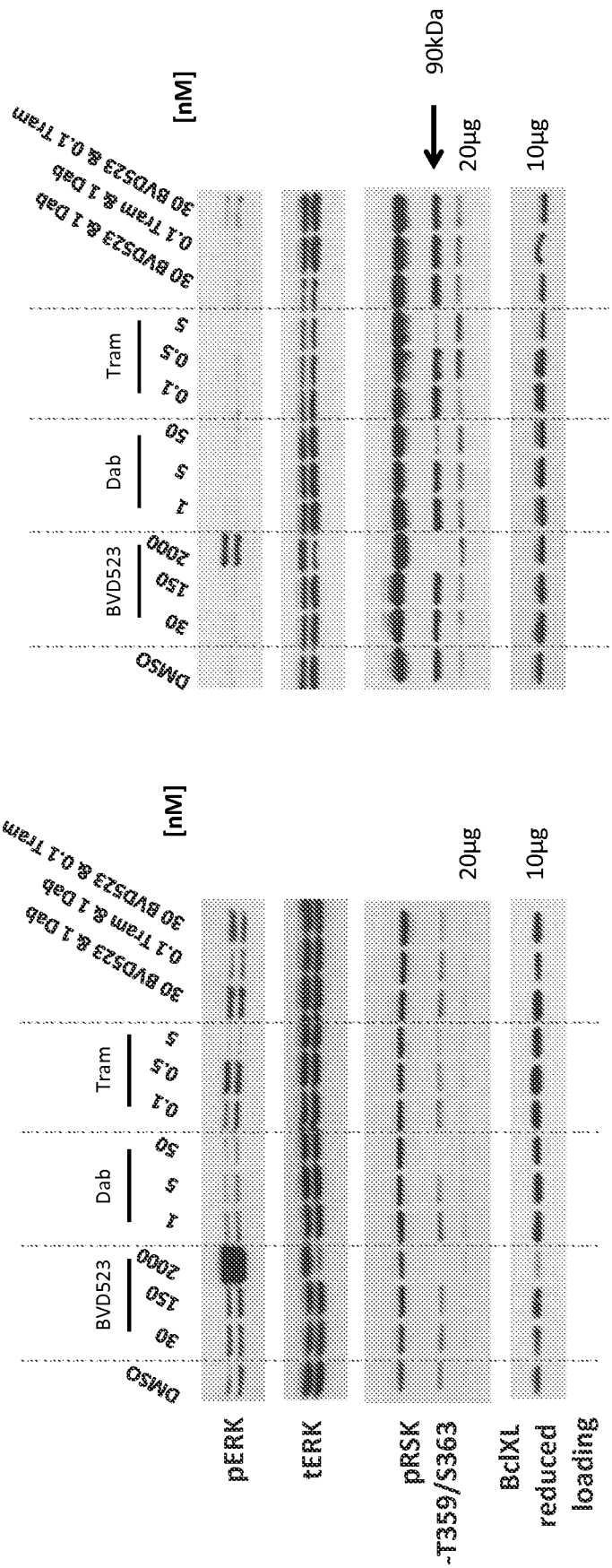

C
D
[nM]
DMSO
BVD523
30
150
2000
Dab
1
5
50
Tram
0.1
0.5
5
30 BVD523 & 1 Dab
0.1 Tram & 1 Dab
30 BVD523 & 0.1 Tram
90kDa
20µg
10µg
pERK
tERK
pRSK
-T359/S363
BclXL
reduced
loading

FIG. 19

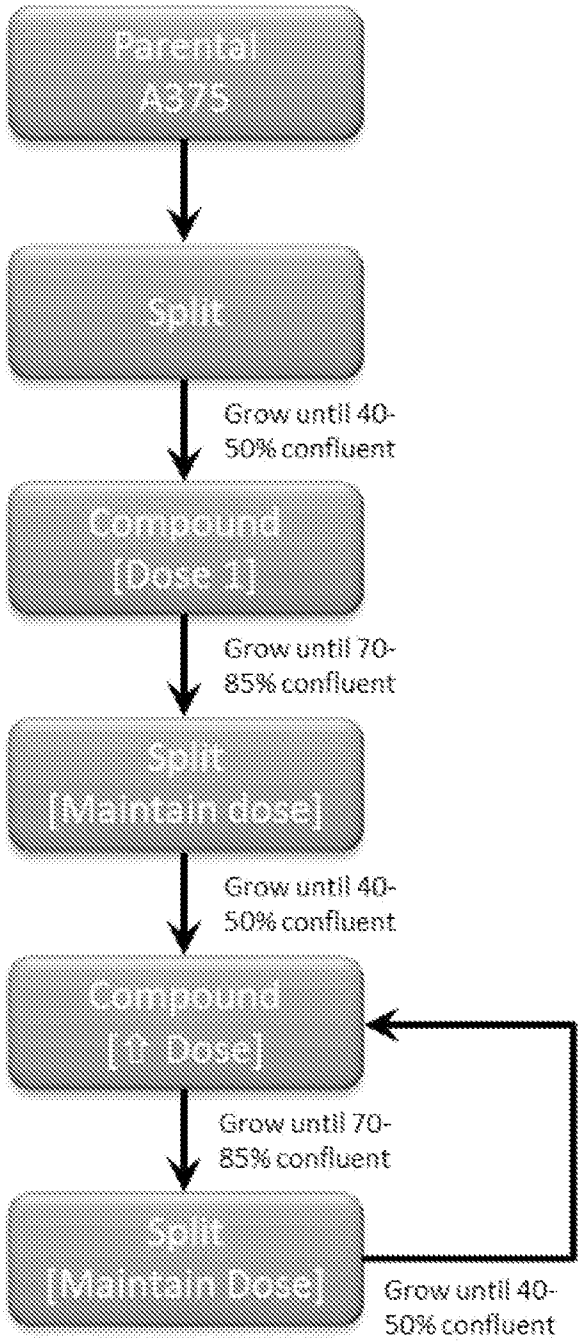

Parental A375
Split
Grow until 40-50% confluent
Compound [Dose 1]
Grow until 70-85% confluent
Split [Maintain dose]
Grow until 40-50% confluent
Compound [2 Dose]
Grow until 70-85% confluent
Split [Maintain Dose]
Grow until 40-50% confluent

FIG. 20

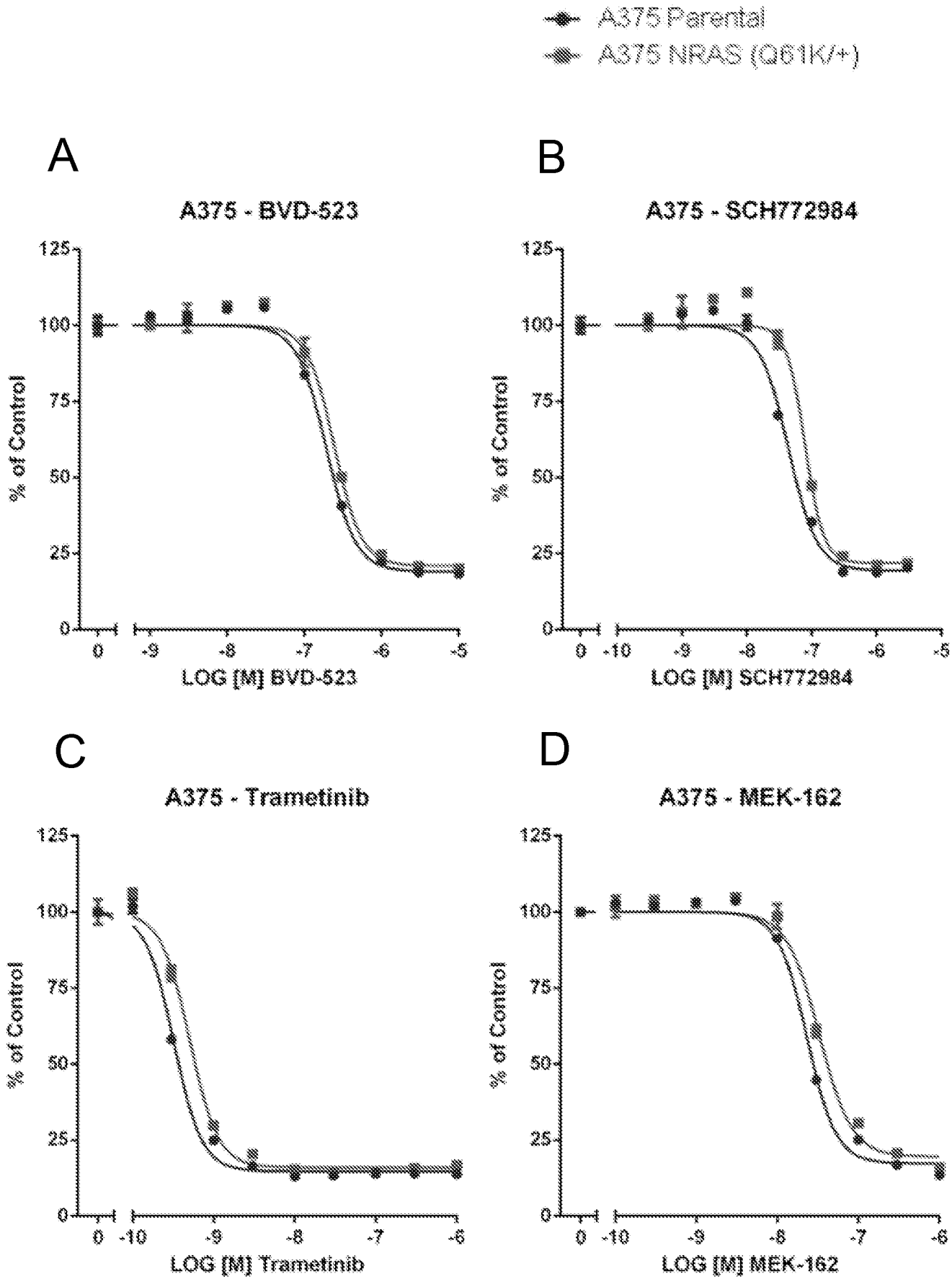

A375 Parental
A375 NRAS (Q61K/+)
A
A375 - BVD-523
% of Control
LOG [M] BVD-523
B
A375 - SCH772984
% of Control
LOG [M] SCH772984
C
A375 - Trametinib
% of Control
LOG [M] Trametinib
D
A375 - MEK-162
% of Control
LOG [M] MEK-162

FIG. 20, Con't

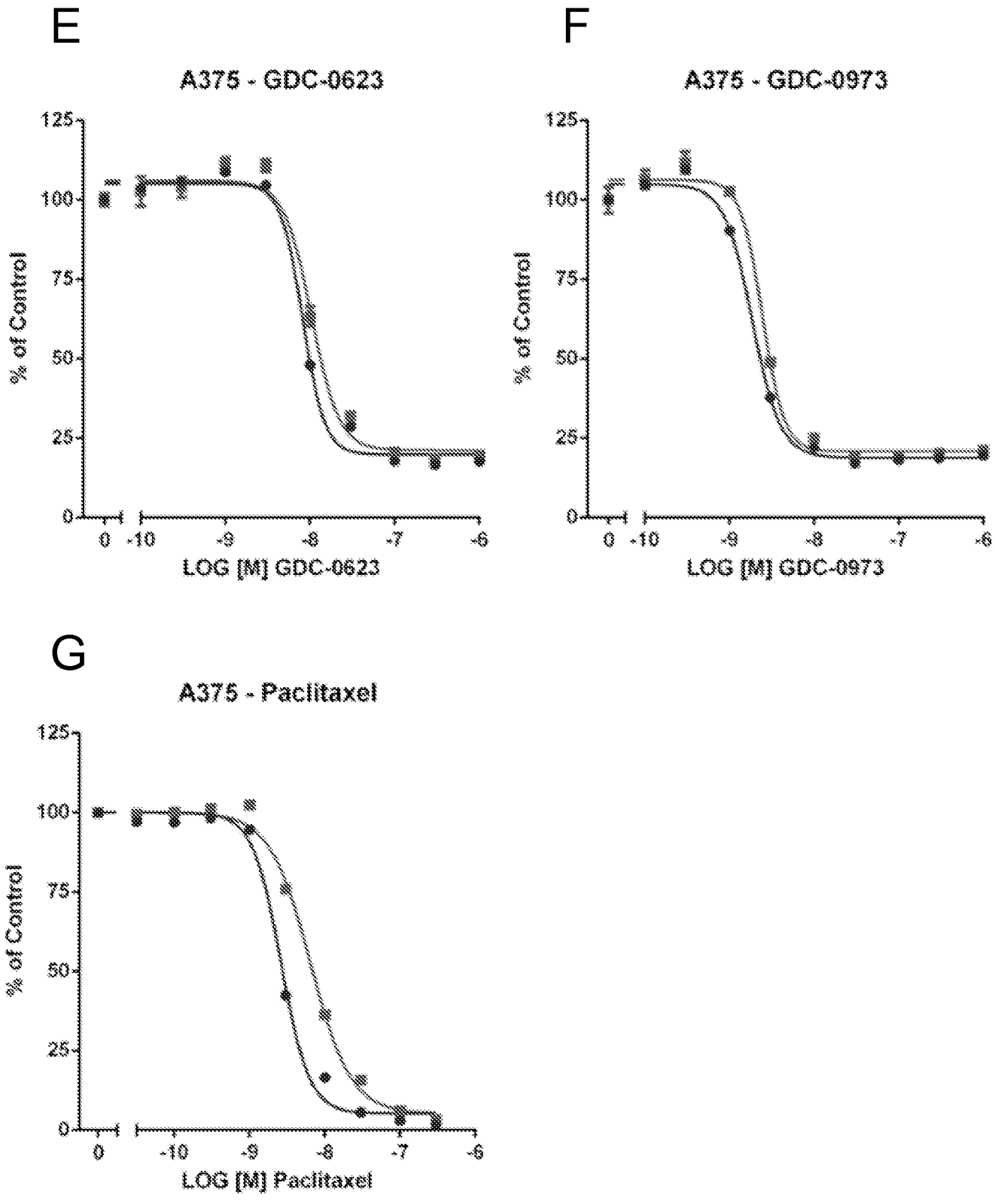

E
A375 - GDC-0623
% of Control
125
100
75
50
25
0
0
-10
-9
-8
-7
-6
LOG [M] GDC-0623
F
A375 - GDC-0973
% of Control
LOG [M] GDC-0973
G
A375 - Paclitaxel
% of Control
LOG [M] Paclitaxel

FIG. 21

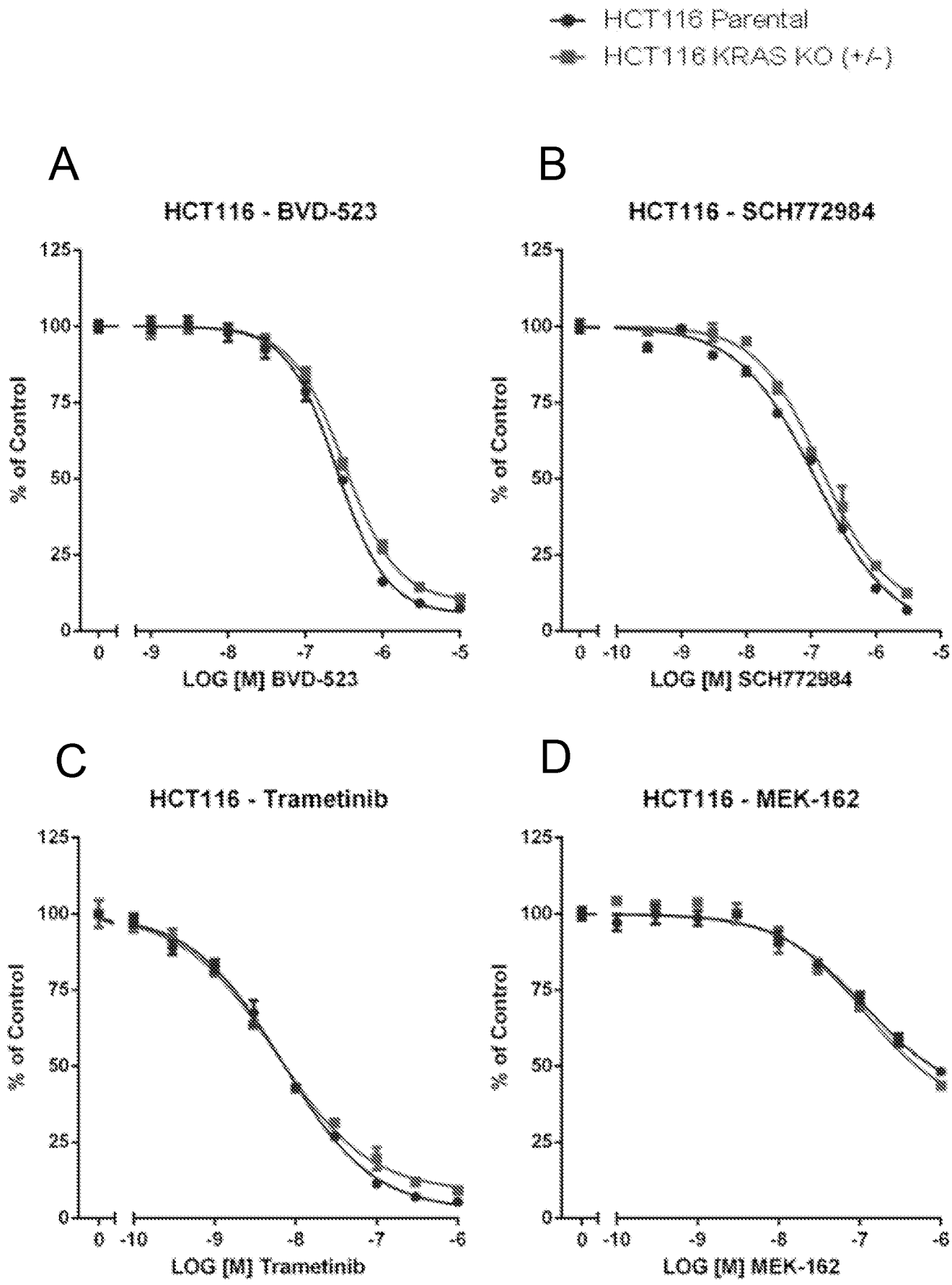

HCT116 Parental
HCT116 KRAS KO (+/-)
A
HCT116 - BVD-523
% of Control
LOG [M] BVD-523
B
HCT116 - SCH772984
% of Control
LOG [M] SCH772984
C
HCT116 - Trametinib
% of Control
LOG [M] Trametinib
D
HCT116 - MEK-162
% of Control
LOG [M] MEK-162

FIG. 21, Con't

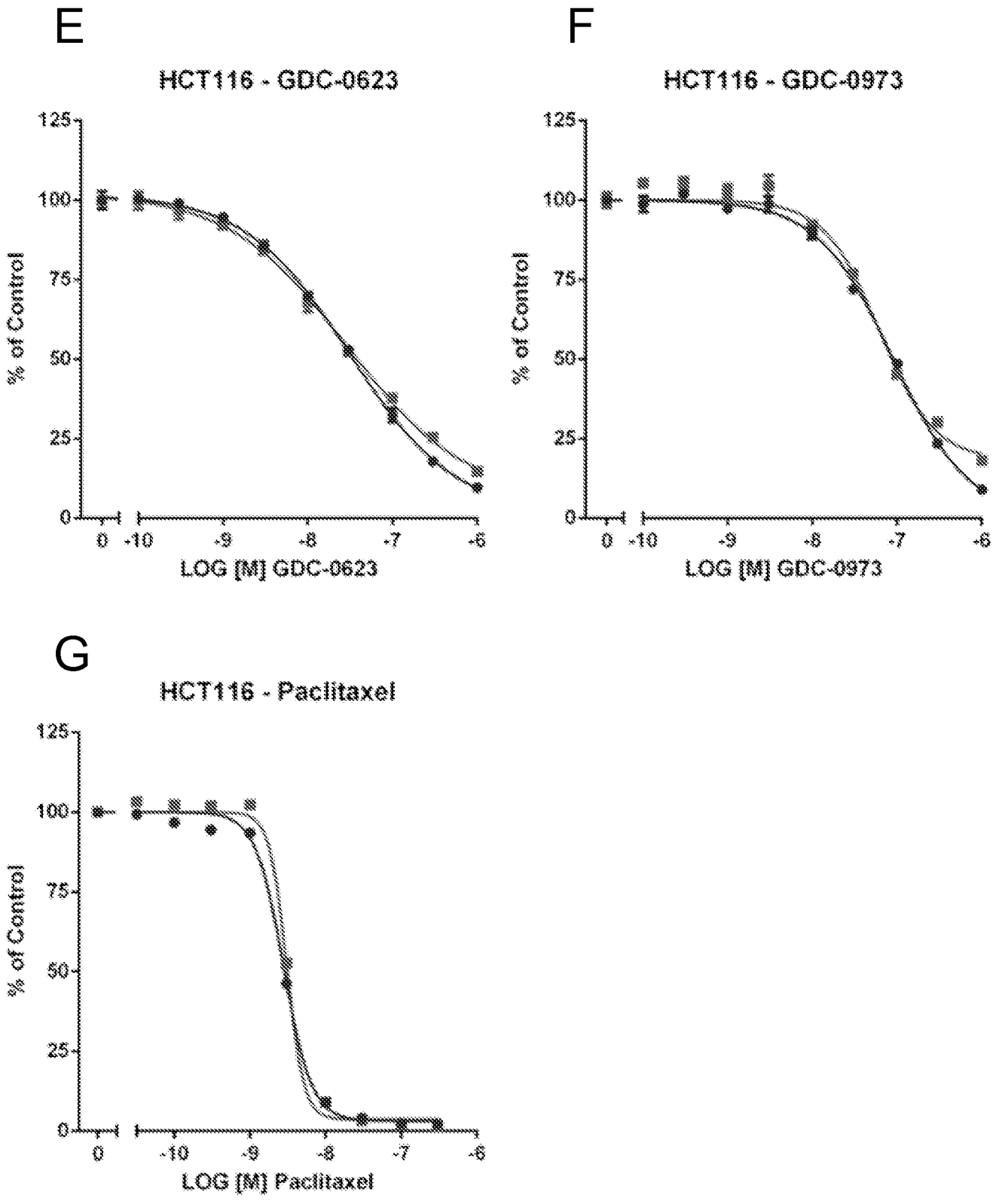

E
HCT116 - GDC-0623
% of Control
125
100
75
50
25
0
0
-10
-9
-8
-7
-6
LOG [M] GDC-0623
F
HCT116 - GDC-0973
% of Control
LOG [M] GDC-0973
G
HCT116 - Paclitaxel
% of Control
LOG [M] Paclitaxel

FIG. 22

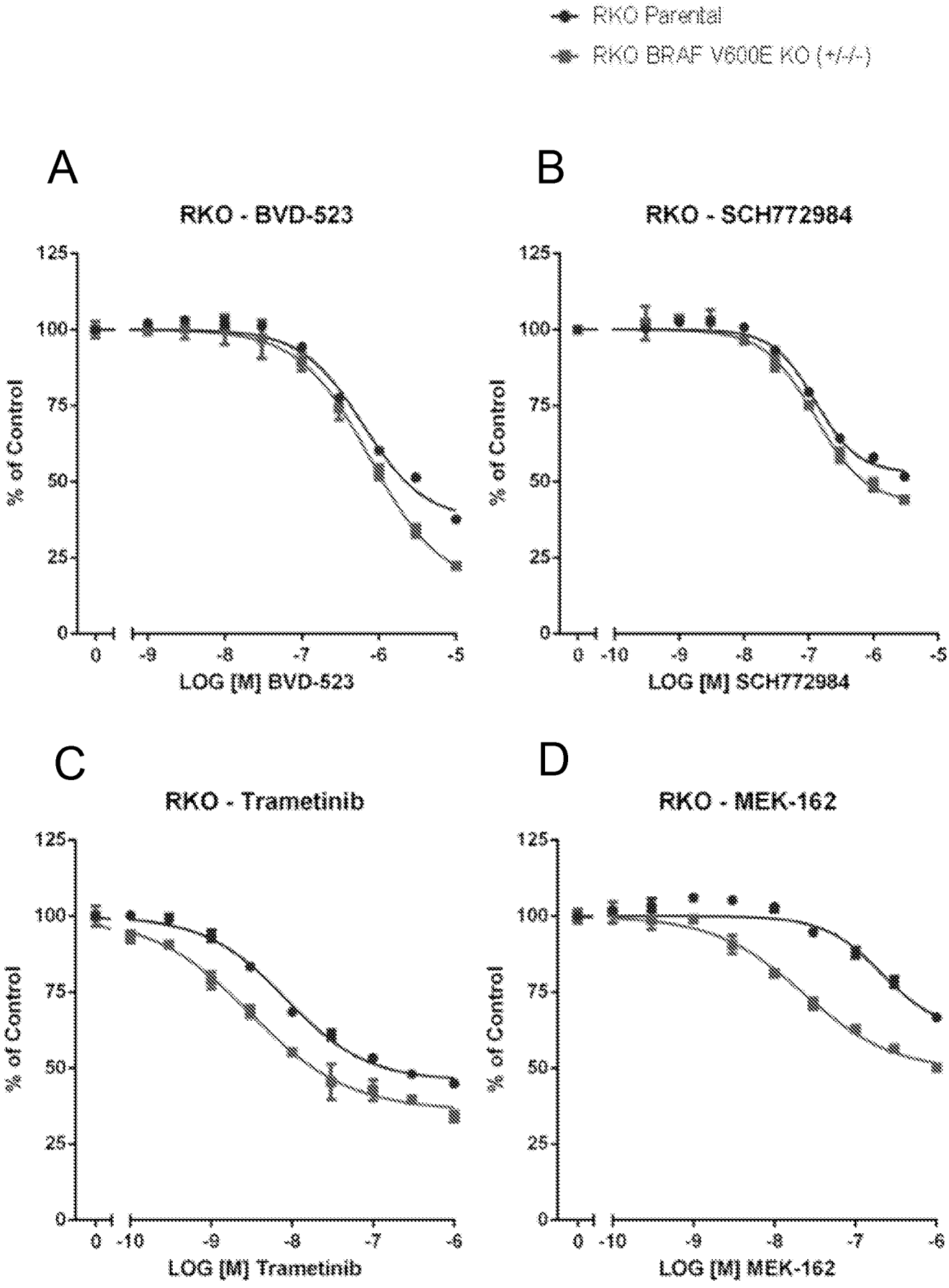

RKO Parental
RKO BRAF V600E KO (+/-/-)
A
RKO - BVD-523
% of Control
LOG [M] BVD-523
B
RKO - SCH772984
% of Control
LOG [M] SCH772984
C
RKO - Trametinib
% of Control
LOG [M] Trametinib
D
RKO - MEK-162
% of Control
LOG [M] MEK-162

FIG. 22, Con't

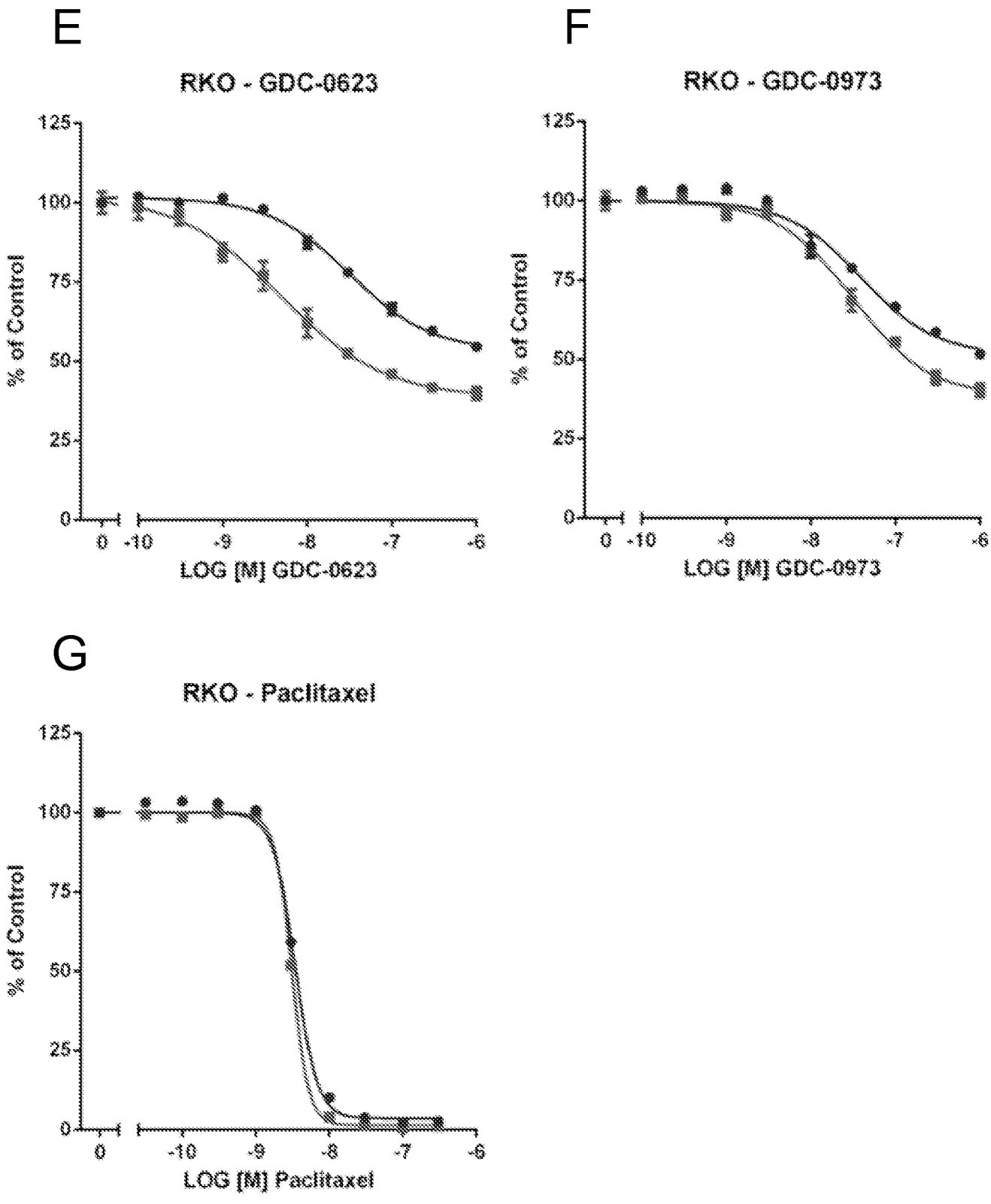

E
RKO - GDC-0623
% of Control
125
100
75
50
25
0
0
-10
-9
-8
-7
-6
LOG [M] GDC-0623
F
RKO - GDC-0973
% of Control
125
100
75
50
25
0
0
-10
-9
-8
-7
-6
LOG [M] GDC-0973
G
RKO - Paclitaxel
% of Control
125
100
75
50
25
0
0
-10
-9
-8
-7
-6
LOG [M] Paclitaxel

FIG. 23

A

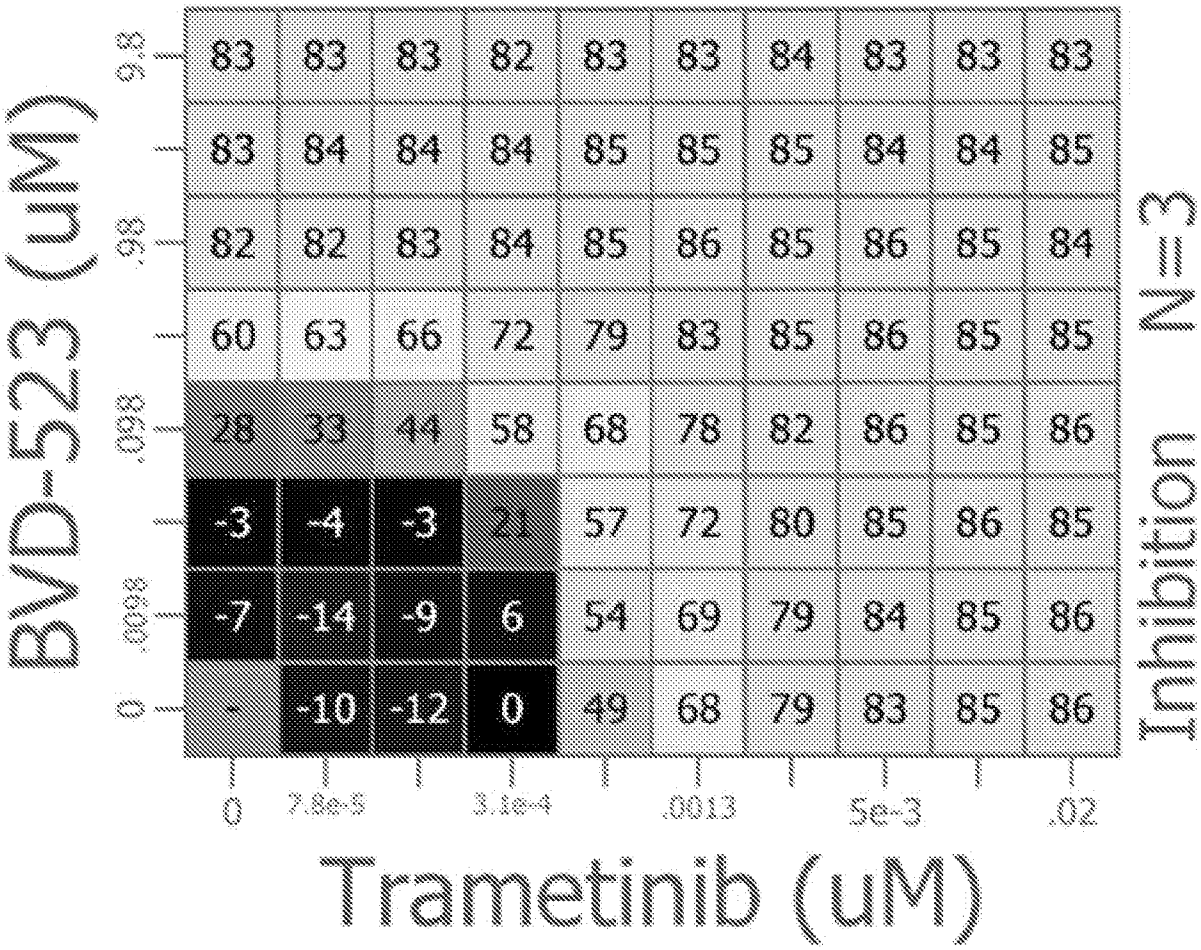

BVD-523 (uM)
9.8
.98
.098
.0098
0
83 83 83 82 83 83 84 83 83 83
83 84 84 84 85 85 85 84 84 85
82 82 83 84 85 86 85 86 85 84
60 63 66 72 79 83 85 86 85 85
28 33 44 58 68 78 82 86 85 86
-3 -4 -3 21 57 72 80 85 86 85
-7 -14 -9 6 54 69 79 84 85 86
- -10 -12 0 49 68 79 83 85 86
0
7.8e-5
3.1e-4
.0013
5e-3
.02
Trametinib (uM)
Inhibition N=3

FIG. 23, Con't

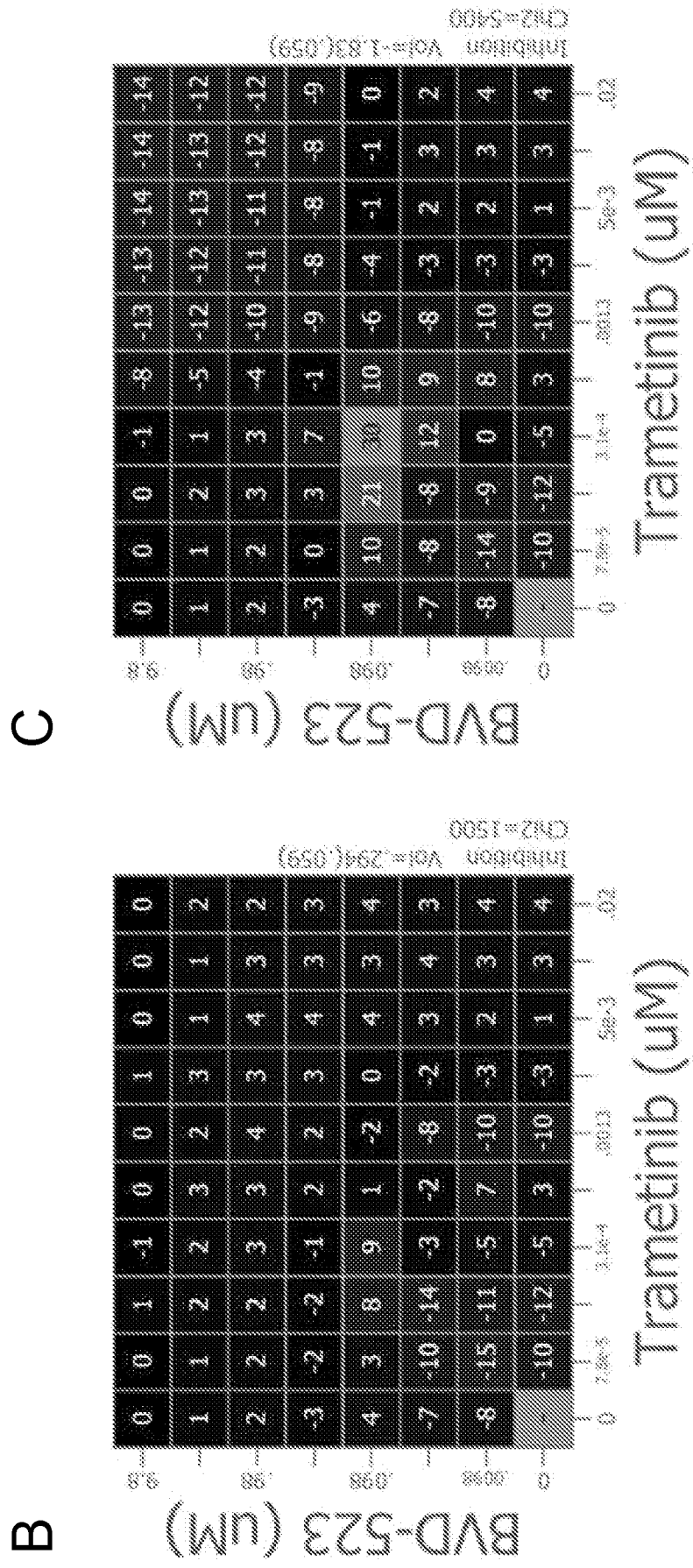


FIG. 23, Con't

D

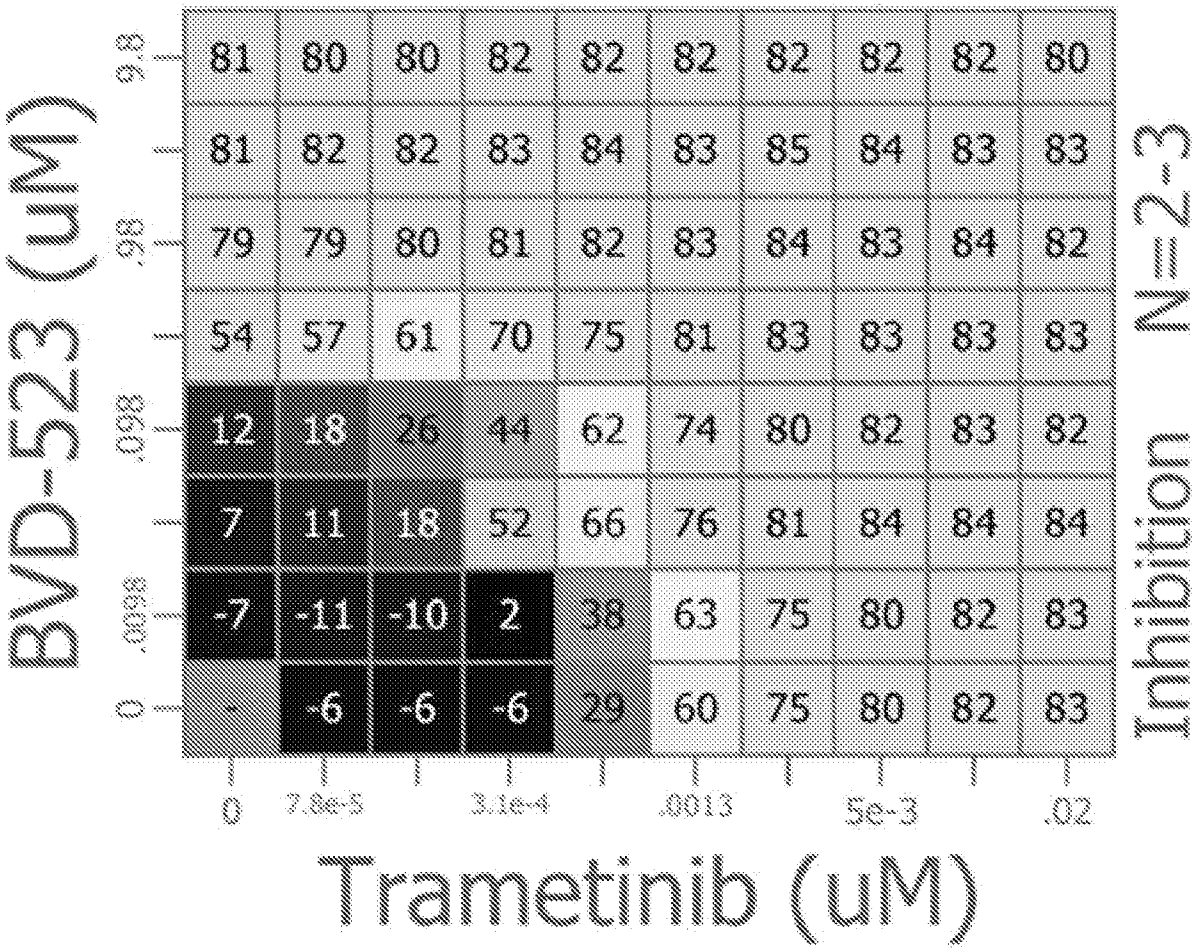
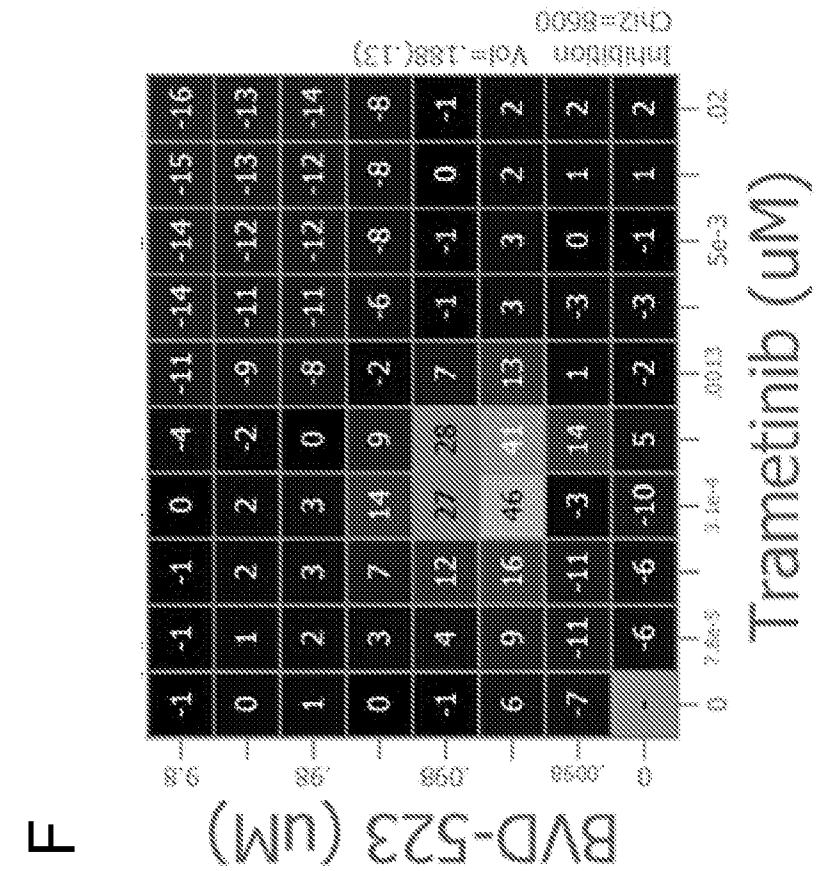

BVD-523 (uM)
9.8
.98
.098
.0098
0
81 80 80 82 82 82 82 82 82 80
81 82 82 83 84 83 85 84 83 83
79 79 80 81 82 83 84 83 84 82
54 57 61 70 75 81 83 83 83 83
12 18 26 44 62 74 80 82 83 82
7 11 18 52 66 76 81 84 84 84
-7 -11 -10 2 38 63 75 80 82 83
- -6 -6 -6 29 60 75 80 82 83
0
7.8e-5
3.1e-4
.0013
5e-3
.02
Trametinib (uM)
Inhibition N=2-3

FIG. 23, Con't


F
BVD-523 (uM)
Trametinib (uM)
Inhibition Vol=.188(.13)
CN2=8600

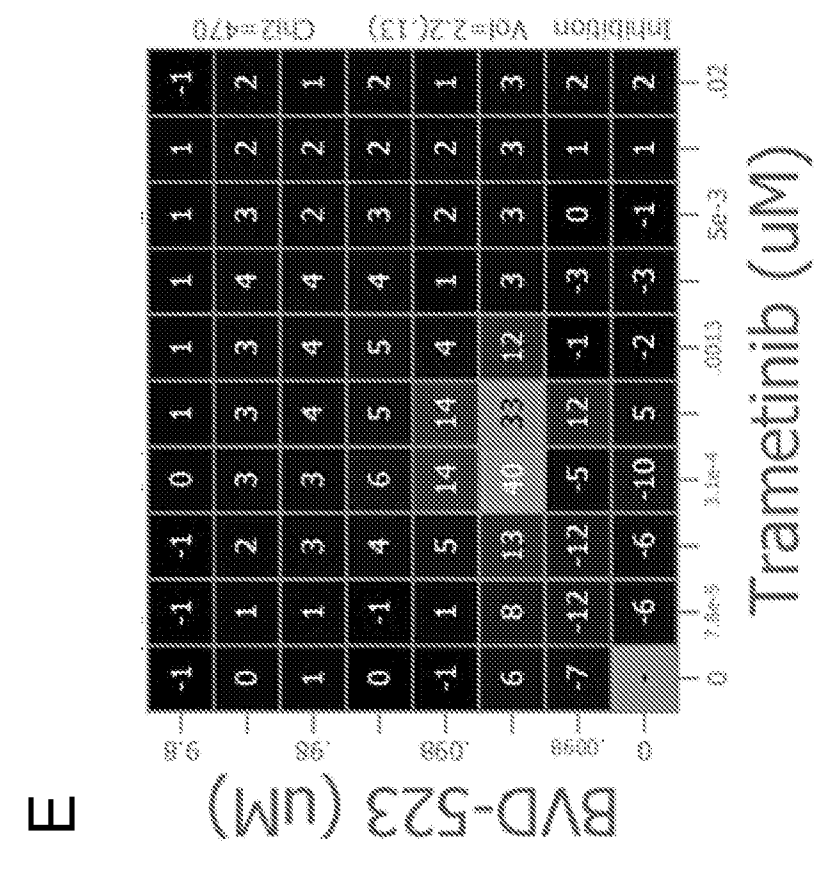
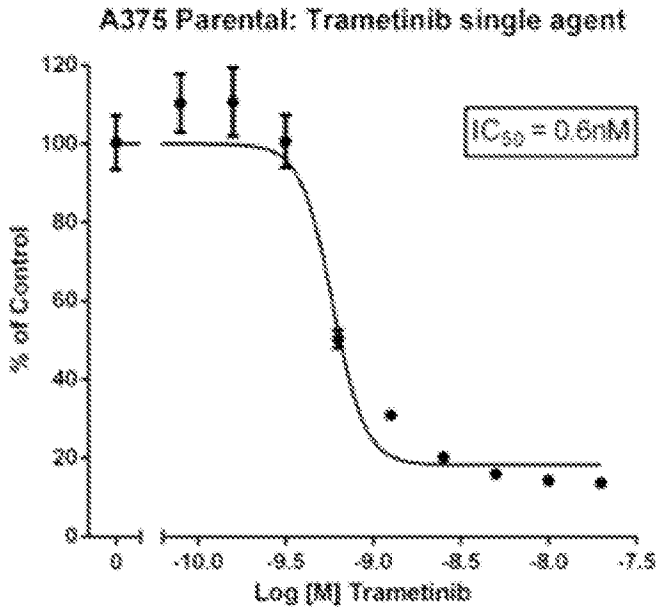
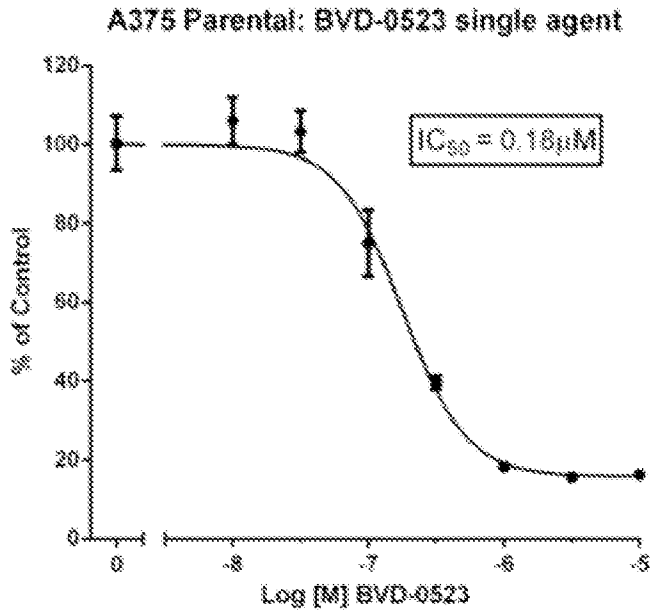

E
BVD-523 (uM)
Trametinib (uM)
Inhibition Vol=2.2(.13) CN2=470

FIG. 23, Con't

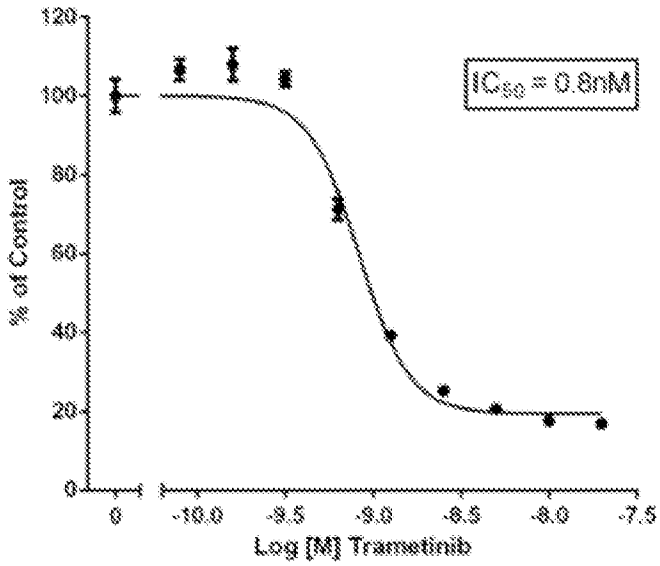
G



H



I



J

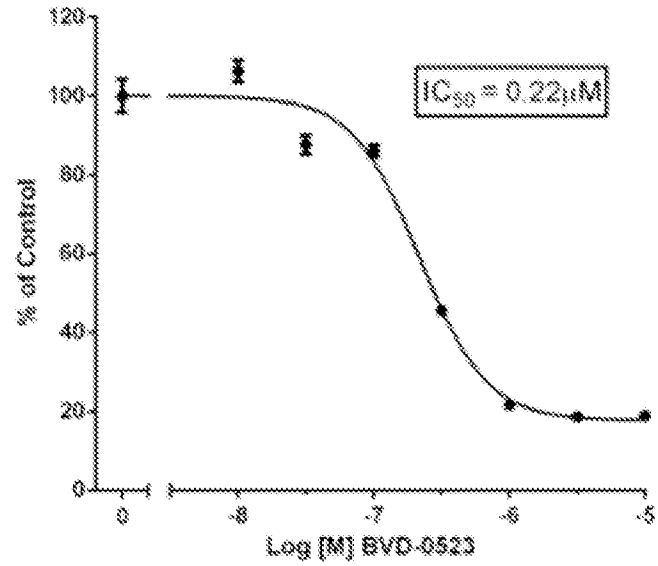


FIG. 24

A

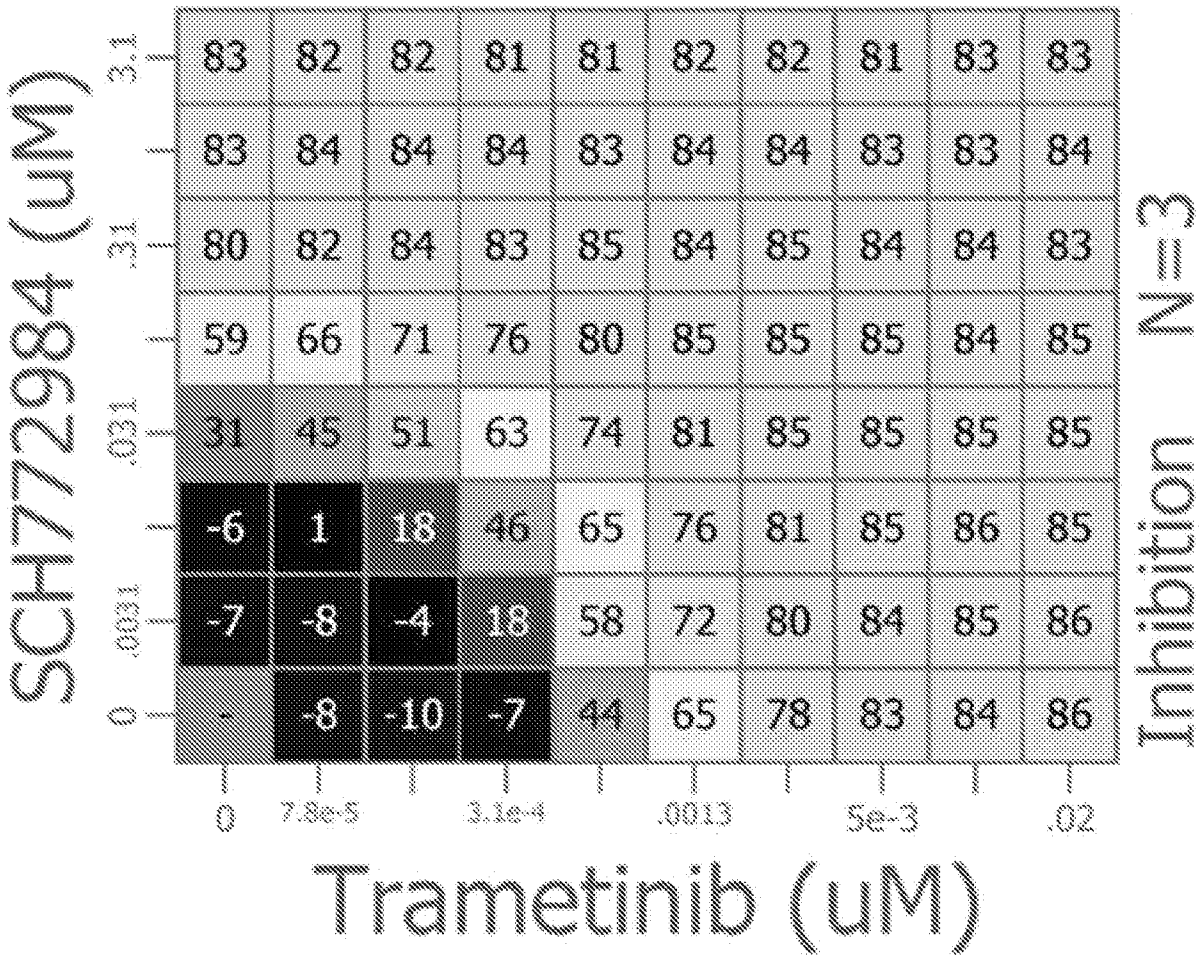

SCH772984 (uM)
3.1
.31
.031
.0031
0
83 82 82 81 81 82 82 81 83 83
83 84 84 84 83 84 84 83 83 84
80 82 84 83 85 84 85 84 84 83
59 66 71 76 80 85 85 85 84 85
31 45 51 63 74 81 85 85 85 85
-6 1 18 46 65 76 81 85 86 85
-7 -8 -4 18 58 72 80 84 85 86
- -8 -10 -7 44 65 78 83 84 86
0
7.8e-5
3.1e-4
.0013
5e-3
.02
Trametinib (uM)
Inhibition N=3

FIG. 24, Con't

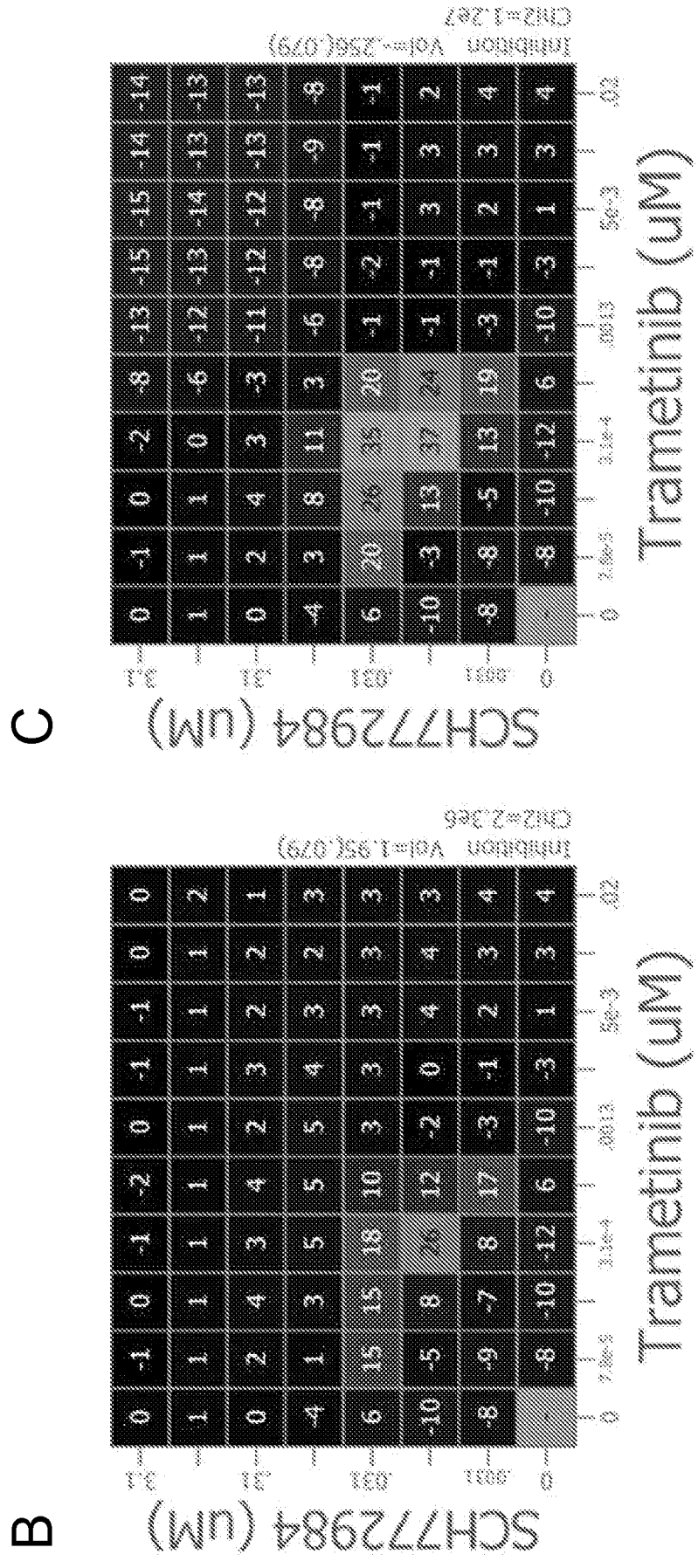

B
C
SCH772984 (uM)
Trametinib (uM)
Inhibition Vol=1.95E.079)
CHI2=2.3e6
Inhibition Vol=-.25E(.079)
CHI2=1.2e7

FIG. 24, Con't

D

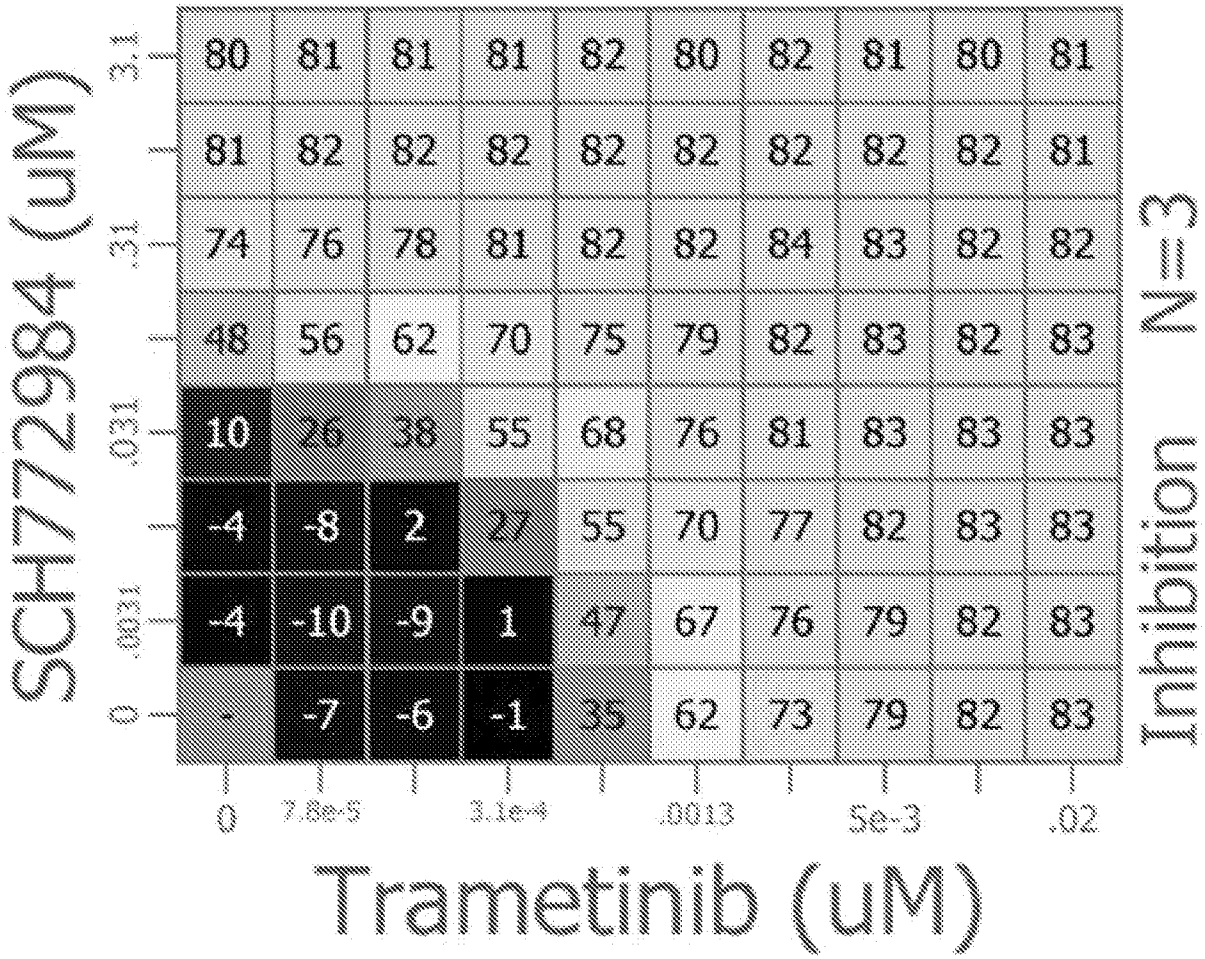

SCH772984 (uM)
3.1
.31
.031
.0031
0
80 81 81 81 82 80 82 81 80 81
81 82 82 82 82 82 82 82 82 81
74 76 78 81 82 82 84 83 82 82
48 56 62 70 75 79 82 83 82 83
10 26 38 55 68 76 81 83 83 83
-4 -8 2 27 55 70 77 82 83 83
-4 -10 -9 1 47 67 76 79 82 83
- -7 -6 -1 35 62 73 79 82 83
0
7.8e-5
3.1e-4
.0013
5e-3
.02
Trametinib (uM)
Inhibition N=3

FIG. 24, Con't

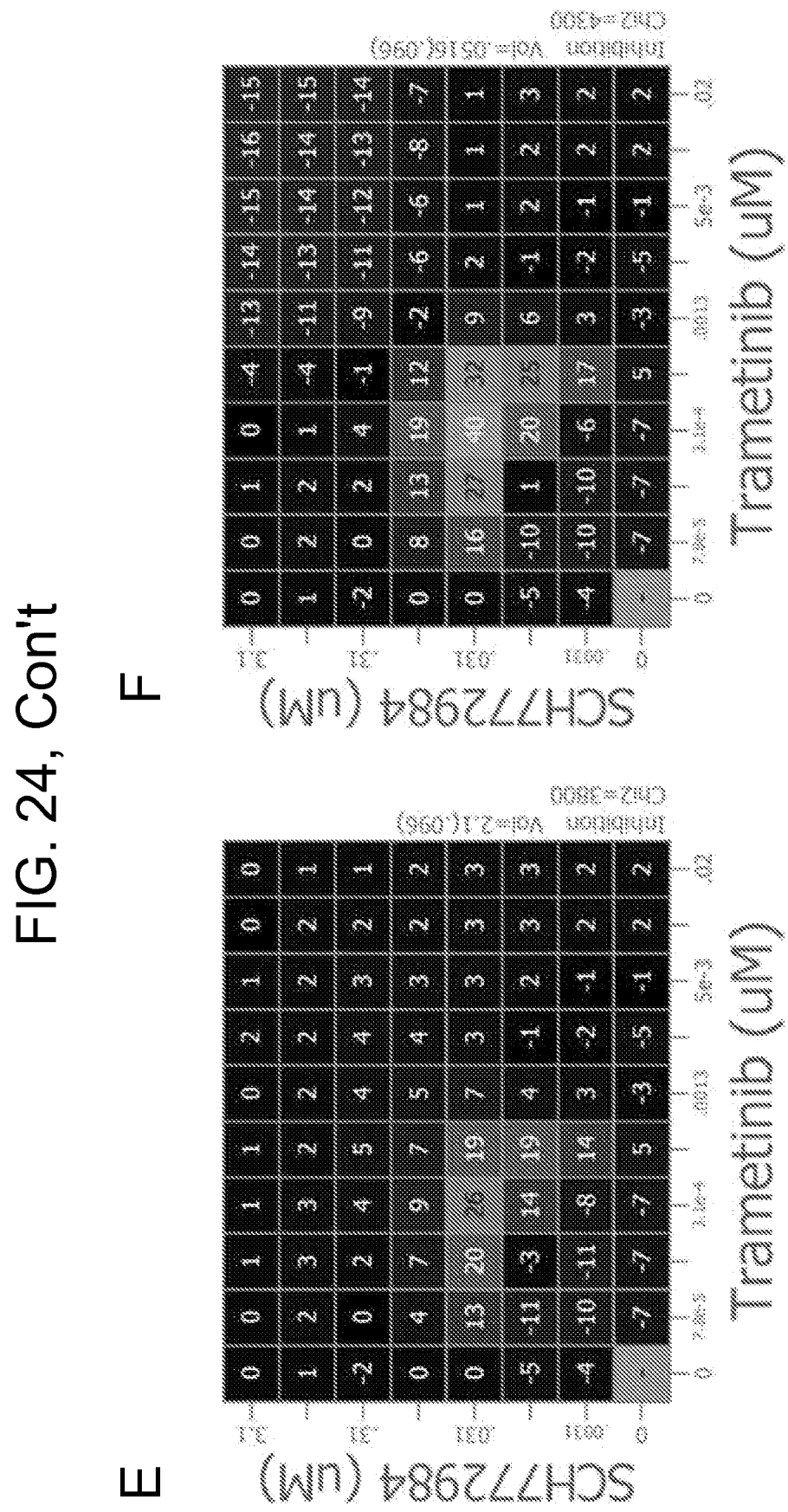
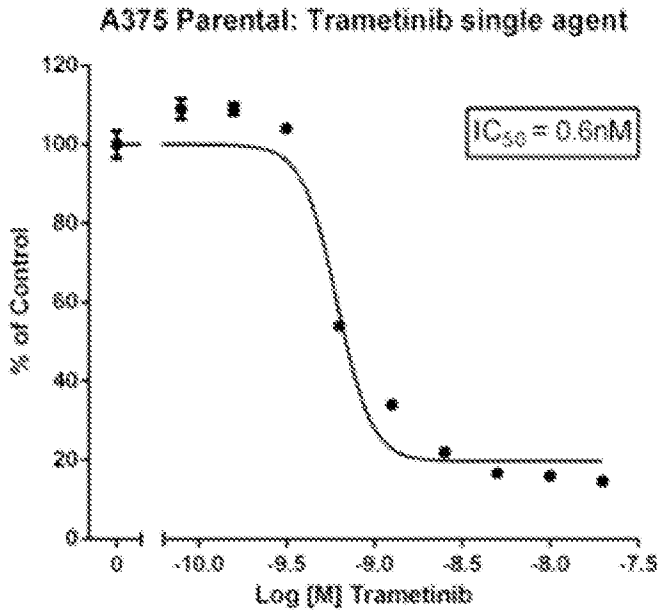
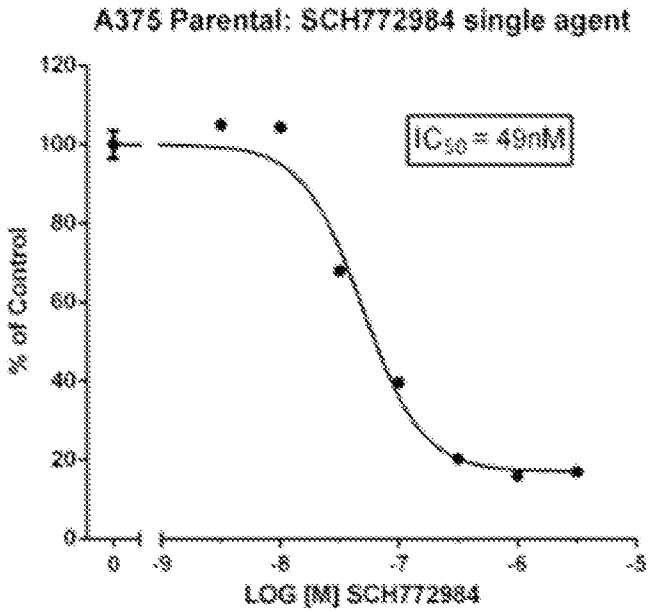


FIG. 24, Con't

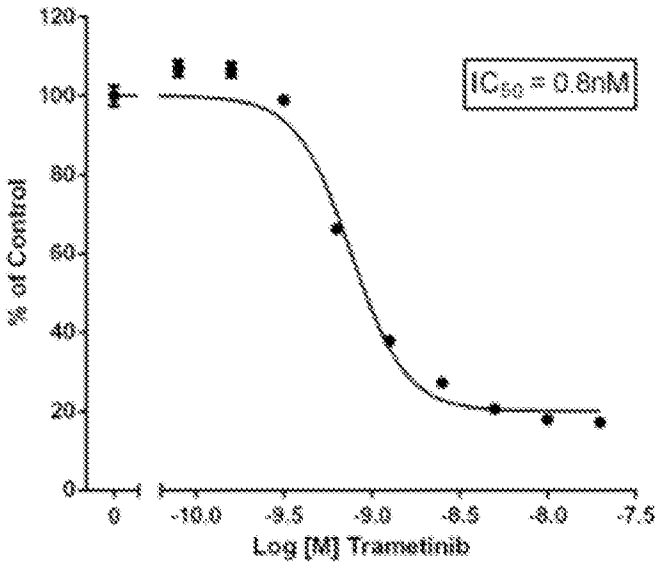
G



H



I



J

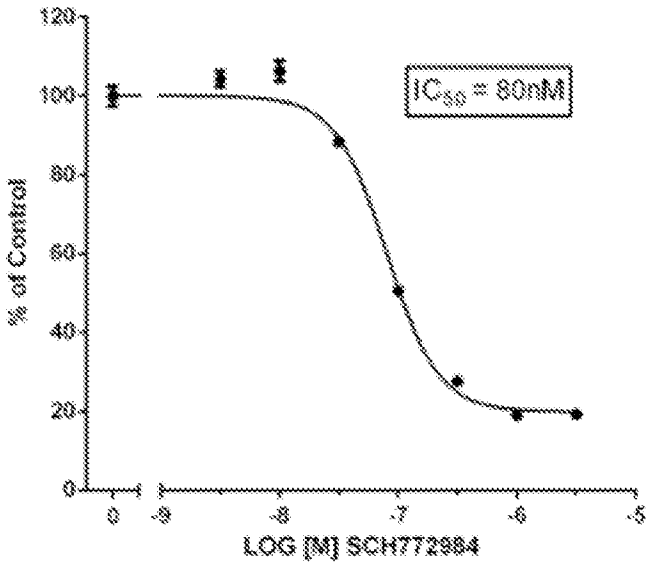


FIG. 25

A

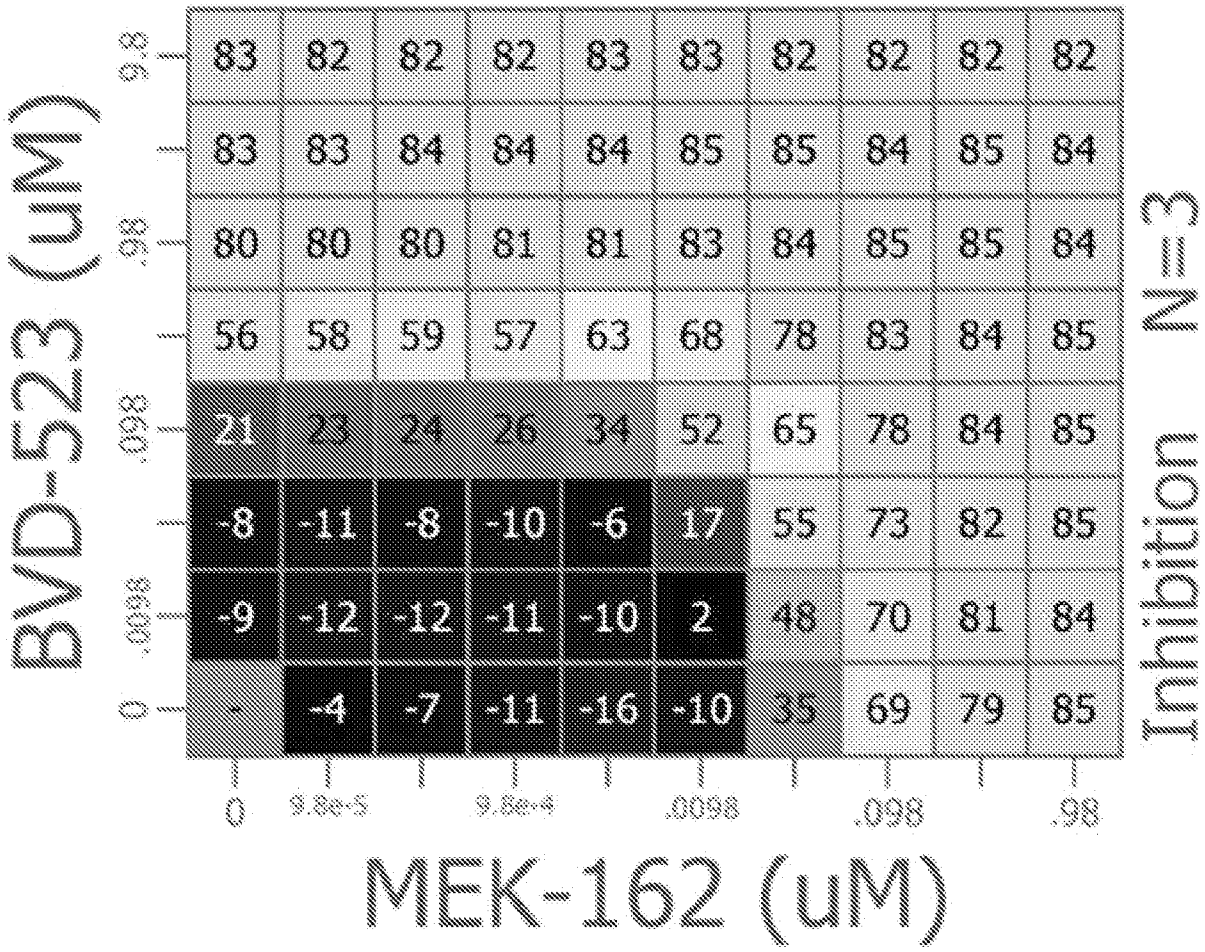

BVD-523 (uM)
9.8
.98
.098
.0098
0
83 82 82 82 83 83 82 82 82 82
83 83 84 84 84 85 85 84 85 84
80 80 80 81 81 83 84 85 85 84
56 58 59 57 63 68 78 83 84 85
21 23 24 26 34 52 65 78 84 85
-8 -11 -8 -10 -6 17 55 73 82 85
-9 -12 -12 -11 -10 2 48 70 81 84
- -4 -7 -11 -16 -10 35 69 79 85
0
9.8e-5
9.8e-4
.0098
.098
.98
MEK-162 (uM)
Inhibition N=3

FIG. 25, Con't

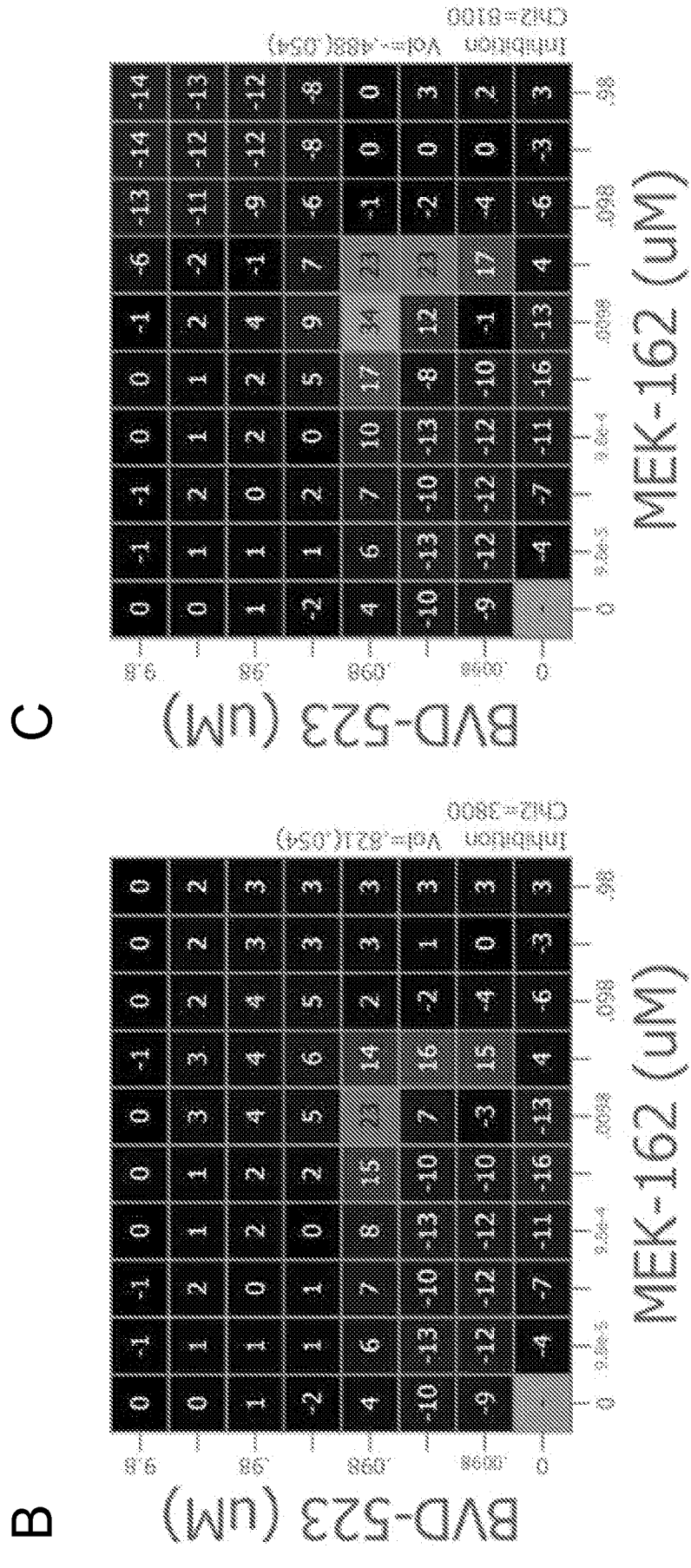

B
C
BVD-523 (uM)
MEK-162 (uM)
Inhibition Vol=-.821(.054)
CN2=3800
Inhibition Vol=-.482(.054)
CN2=8100

FIG. 25, Con't

D

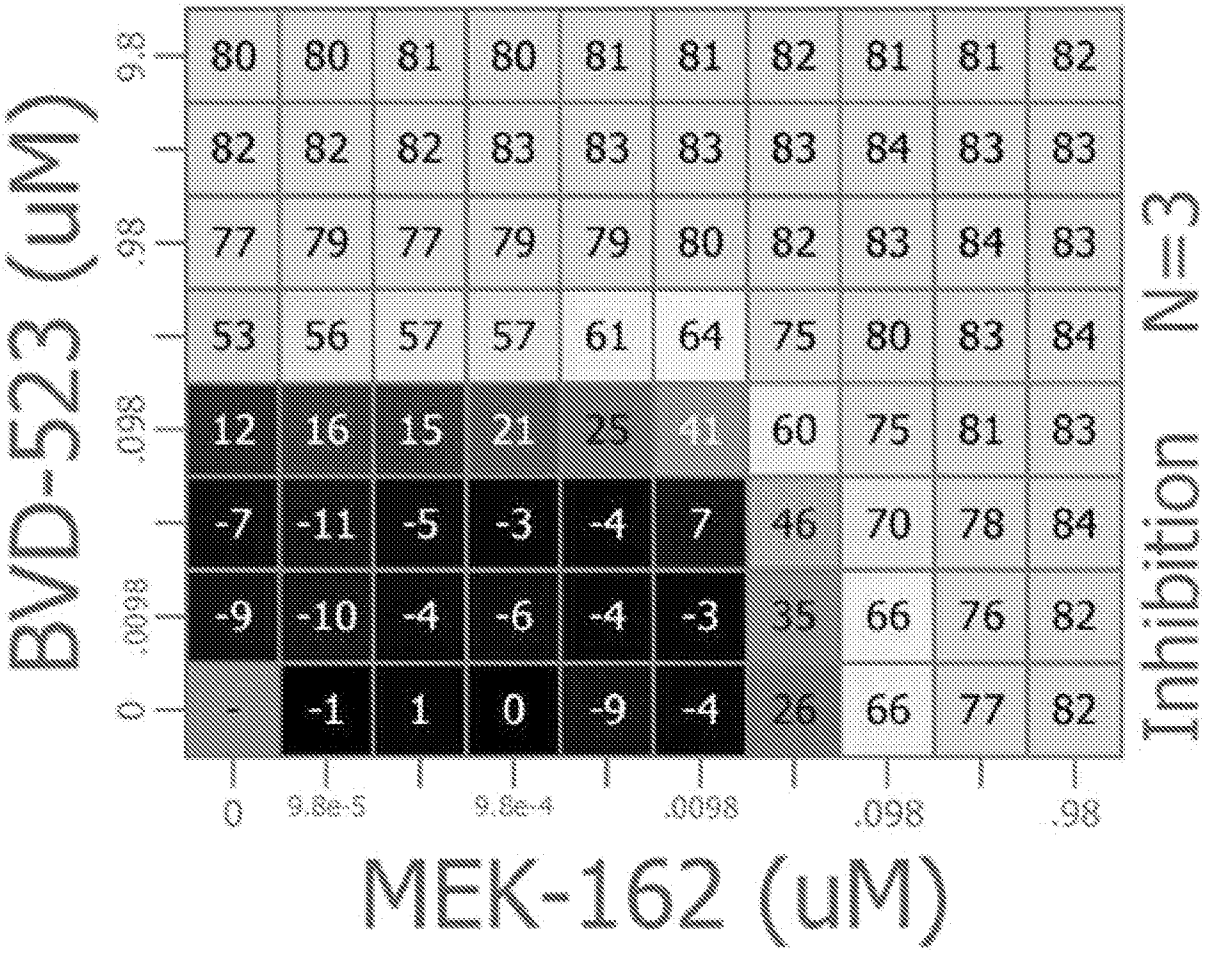

BVD-523 (uM)
9.8
.98
.098
.0098
0
80 80 81 80 81 81 82 81 81 82
82 82 82 83 83 83 83 84 83 83
77 79 77 79 79 80 82 83 84 83
53 56 57 57 61 64 75 80 83 84
12 16 15 21 25 41 60 75 81 83
-7 -11 -5 -3 -4 7 46 70 78 84
-9 -10 -4 -6 -4 -3 35 66 76 82
- -1 1 0 -9 -4 26 66 77 82
0
9.8e-5
9.8e-4
.0098
.098
.98
MEK-162 (uM)
Inhibition N=3

FIG. 25, Con't

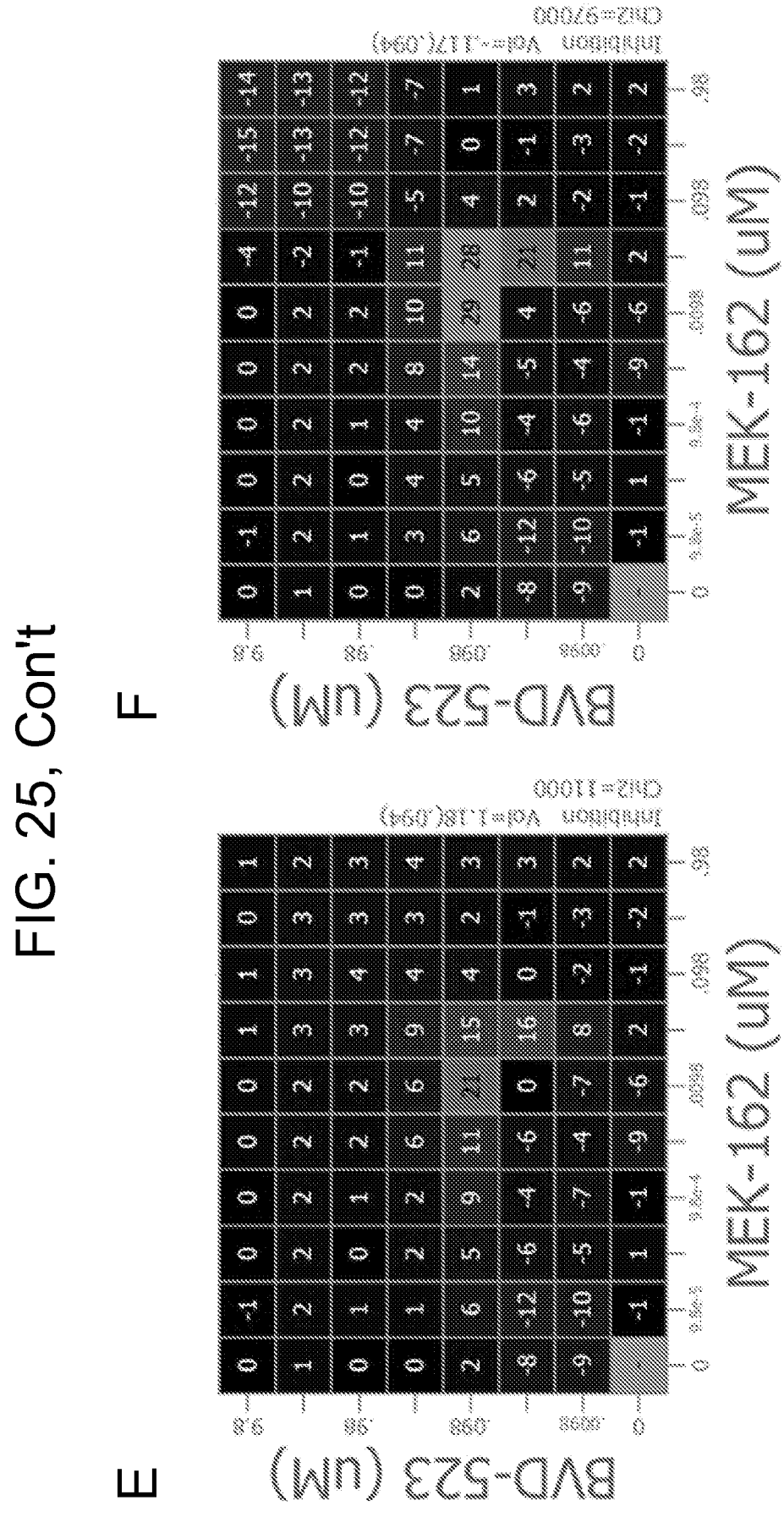
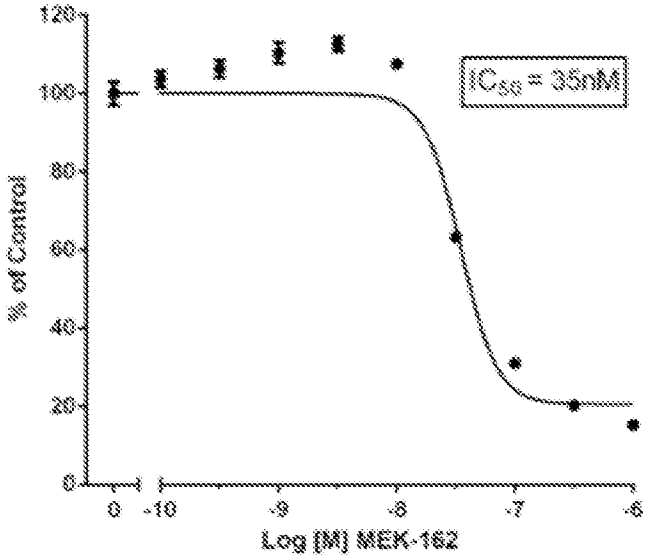
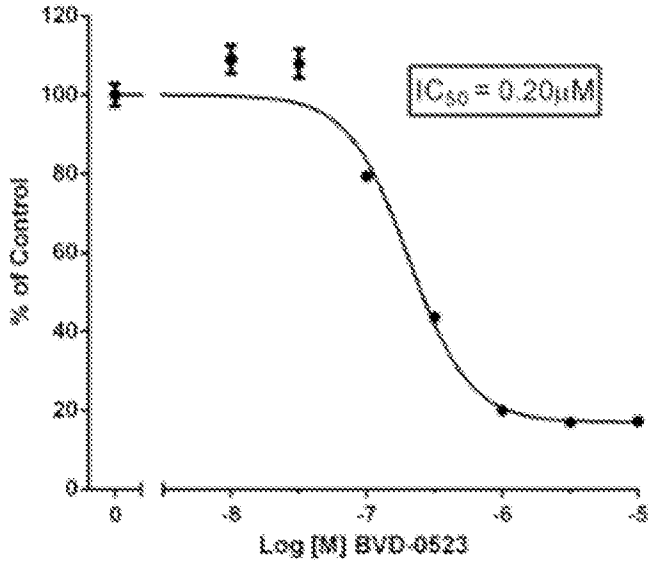

F
E
BVD-523 (uM)
MEK-162 (uM)
Inhibition
Vol=-.117(.094)
CH2=97000
Vol=1.18(.094)
CH2=11000

FIG. 25, Con't

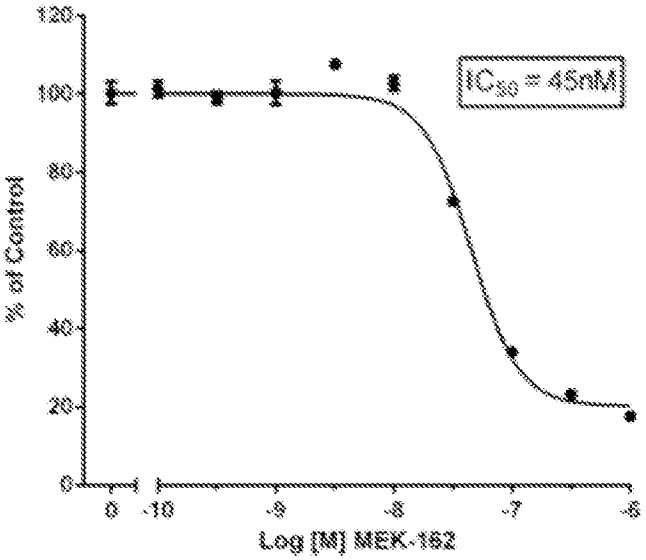
G



H



I



J

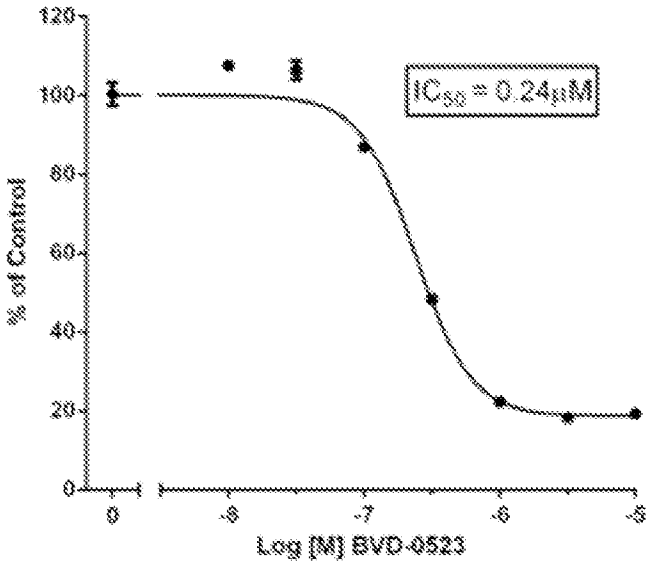


FIG. 26

A

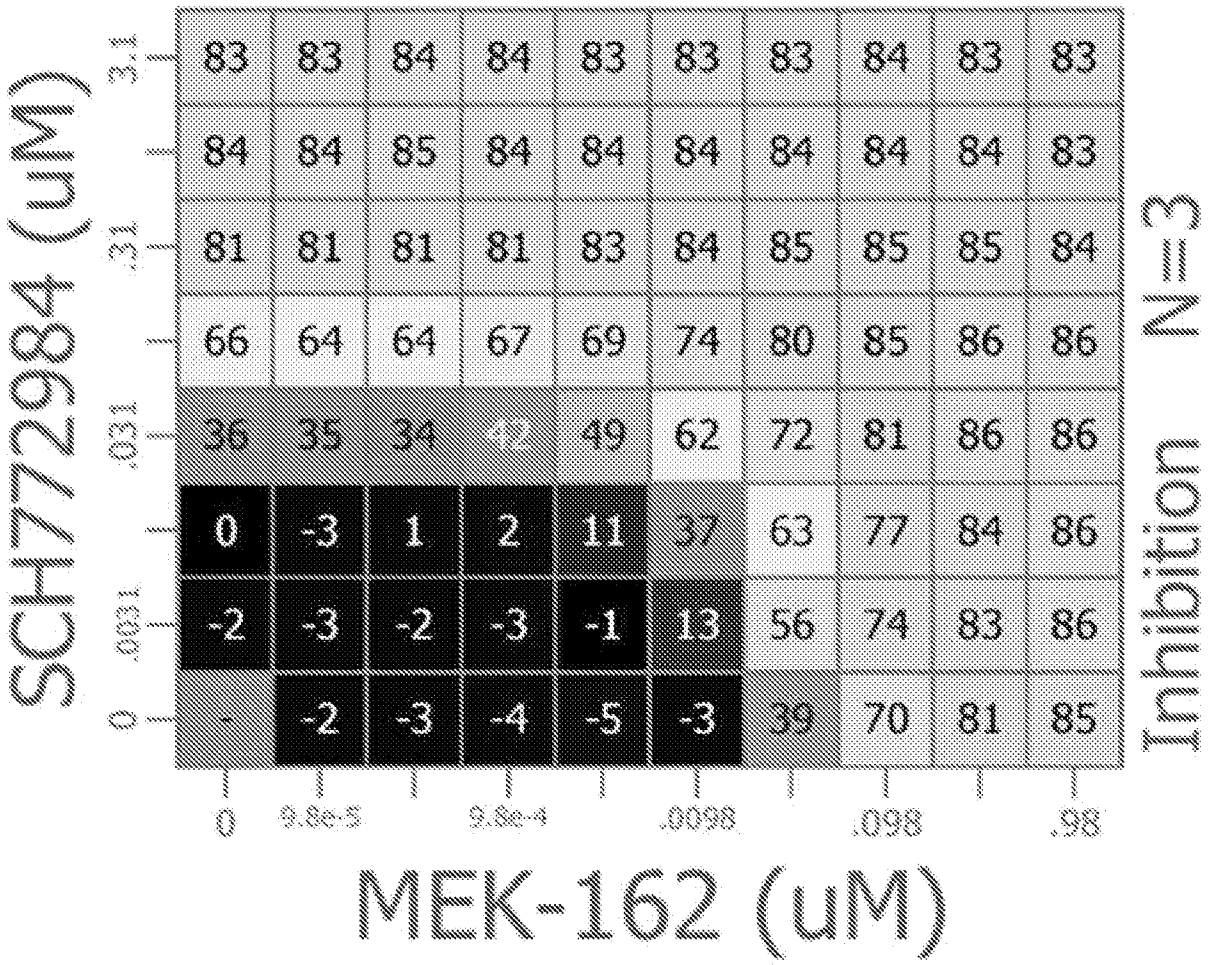

SCH772984 (uM)
3.1
.31
.031
.0031
0
83 83 84 84 83 83 83 84 83 83
84 84 85 84 84 84 84 84 84 83
81 81 81 81 83 84 85 85 85 84
66 64 64 67 69 74 80 85 86 86
36 35 34 42 49 62 72 81 86 86
0 -3 1 2 11 37 63 77 84 86
-2 -3 -2 -3 -1 18 56 74 83 86
- -2 -3 -4 -5 -3 39 70 81 85
0
9.8e-5
9.8e-4
.0098
.098
.98
MEK-162 (uM)
Inhibition N=3

FIG. 26, Con't

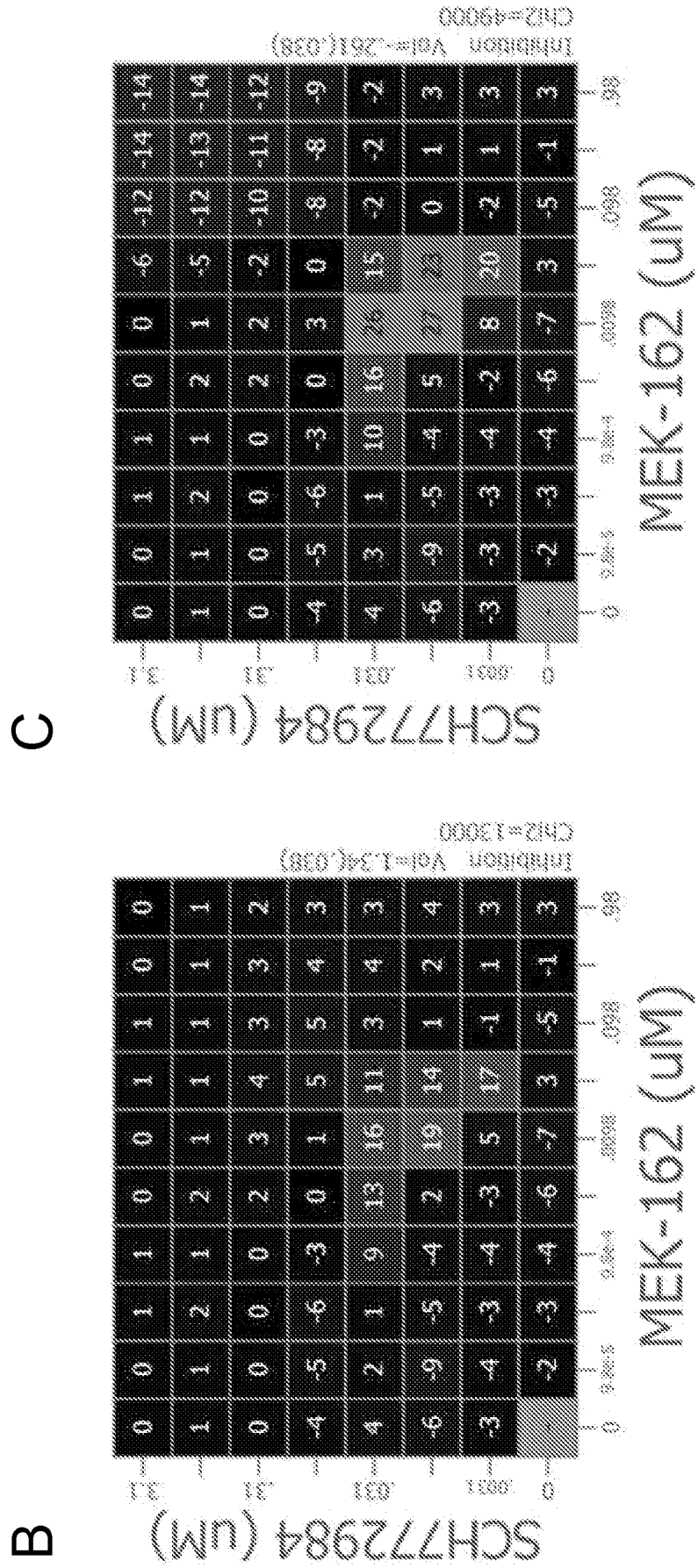

C
B
SCH772984 (uM)
MEK-162 (uM)
Inhibition Vol=-.261(.038)
Chi2=49000
Inhibition Vol=1.34(.038)
Chi2=13000

FIG. 26, Con't

D

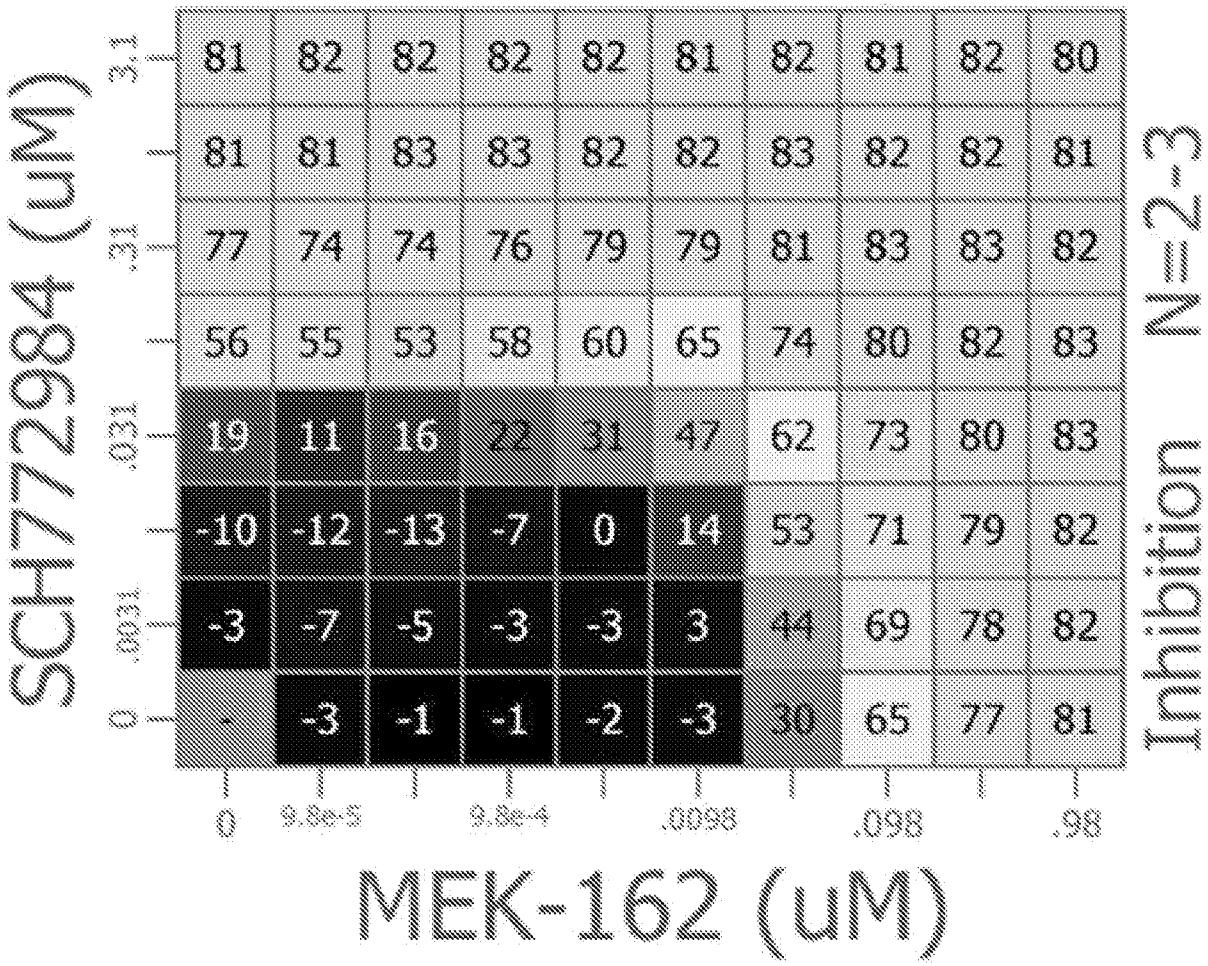
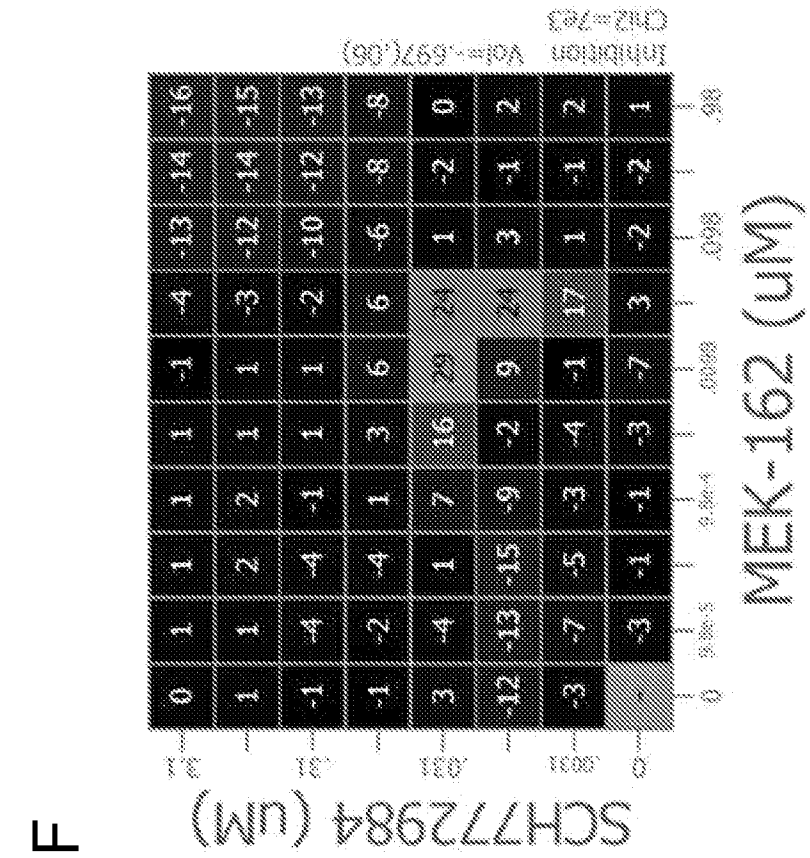

SCH772984 (uM)
3.1
.31
.031
.0031
0
81 82 82 82 82 81 82 81 82 80
81 81 83 83 82 82 83 82 82 81
77 74 74 76 79 79 81 83 83 82
56 55 53 58 60 65 74 80 82 83
19 11 16 22 31 47 62 73 80 83
-10 -12 -13 -7 0 14 53 71 79 82
-3 -7 -5 -3 -3 3 44 69 78 82
- -3 -1 -1 -2 -3 30 65 77 81
0
9.8e-5
9.8e-4
.0098
.098
.98
MEK-162 (uM)
Inhibition N=2-3

FIG. 26, Con't


F
SCH772984 (uM)
MEK-162 (uM)
Inhibition Vol=-.697(.06)
CN2=763

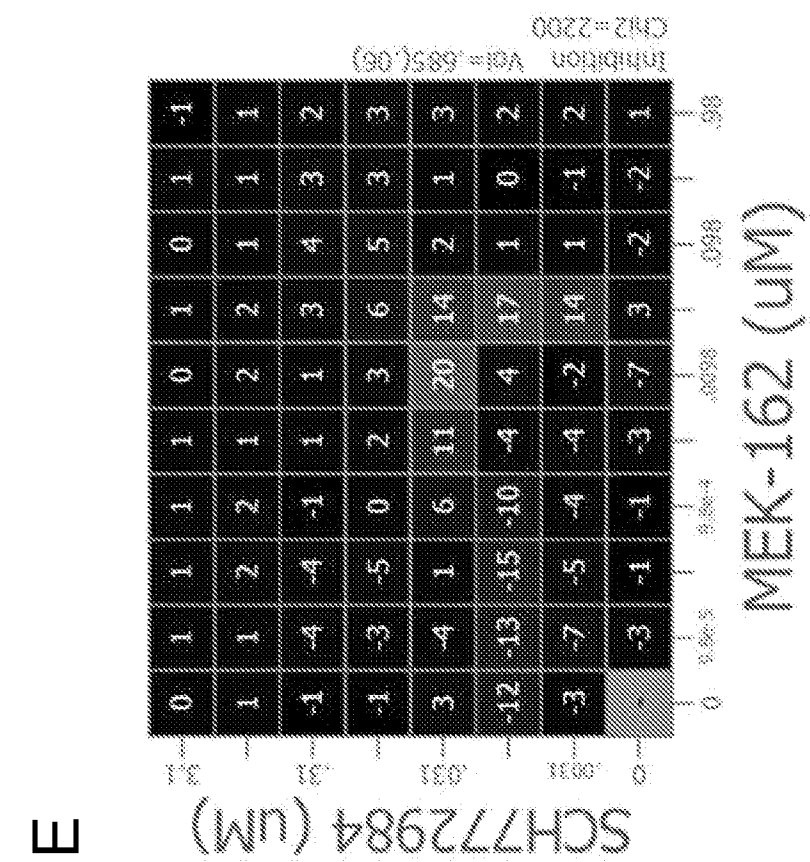
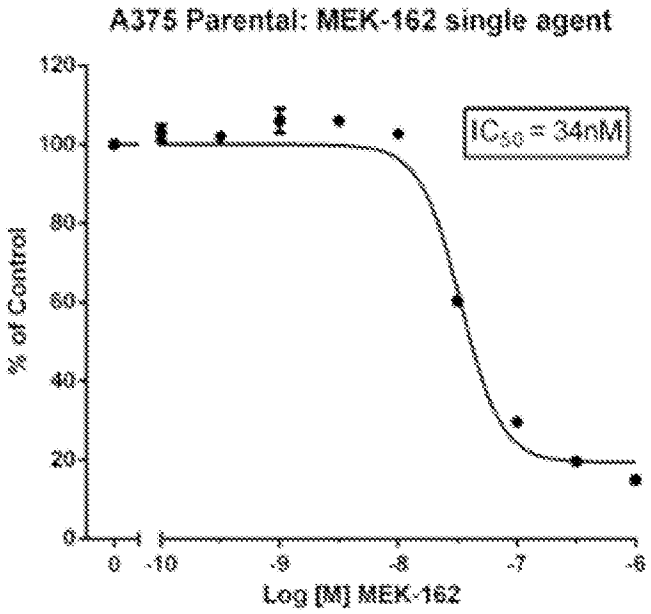
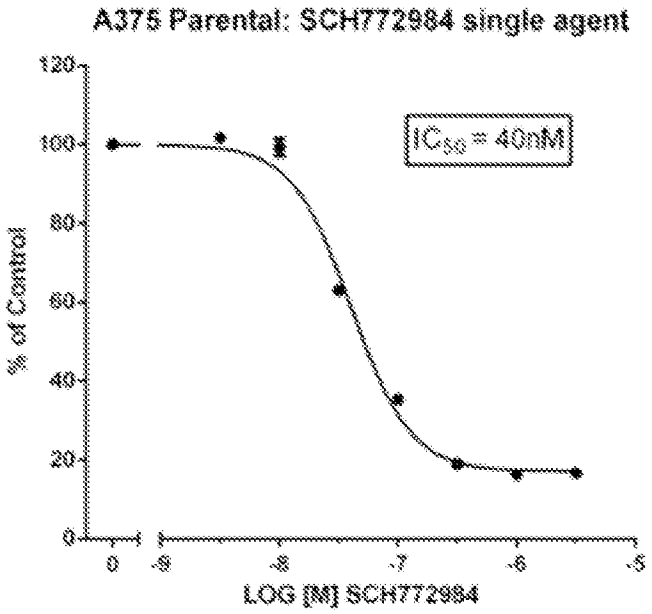

E
SCH772984 (uM)
MEK-162 (uM)
Inhibition Vol=-.685(.06)
CN2=2200

FIG. 26, Con't

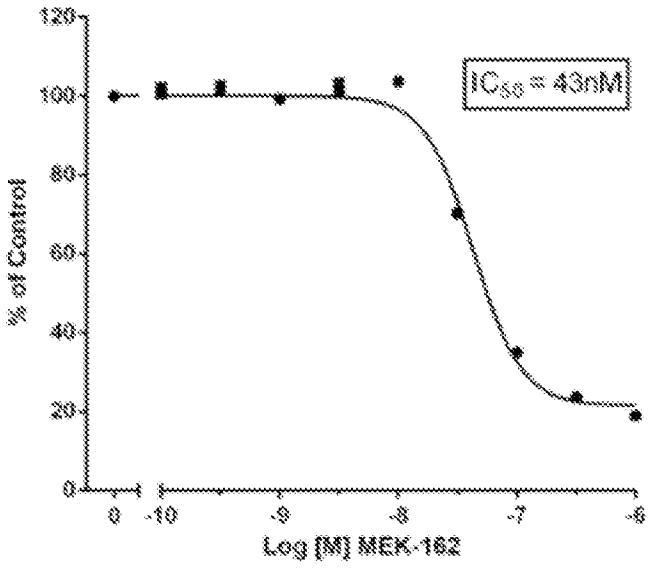
G



H



I



J

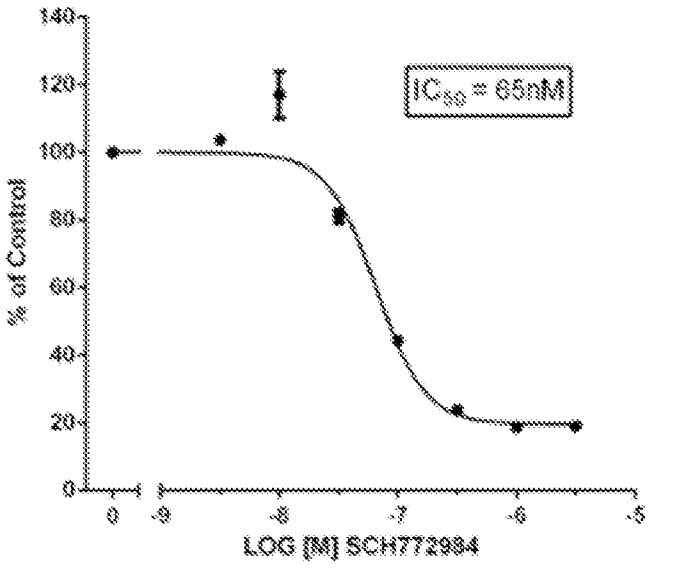


FIG. 27

A

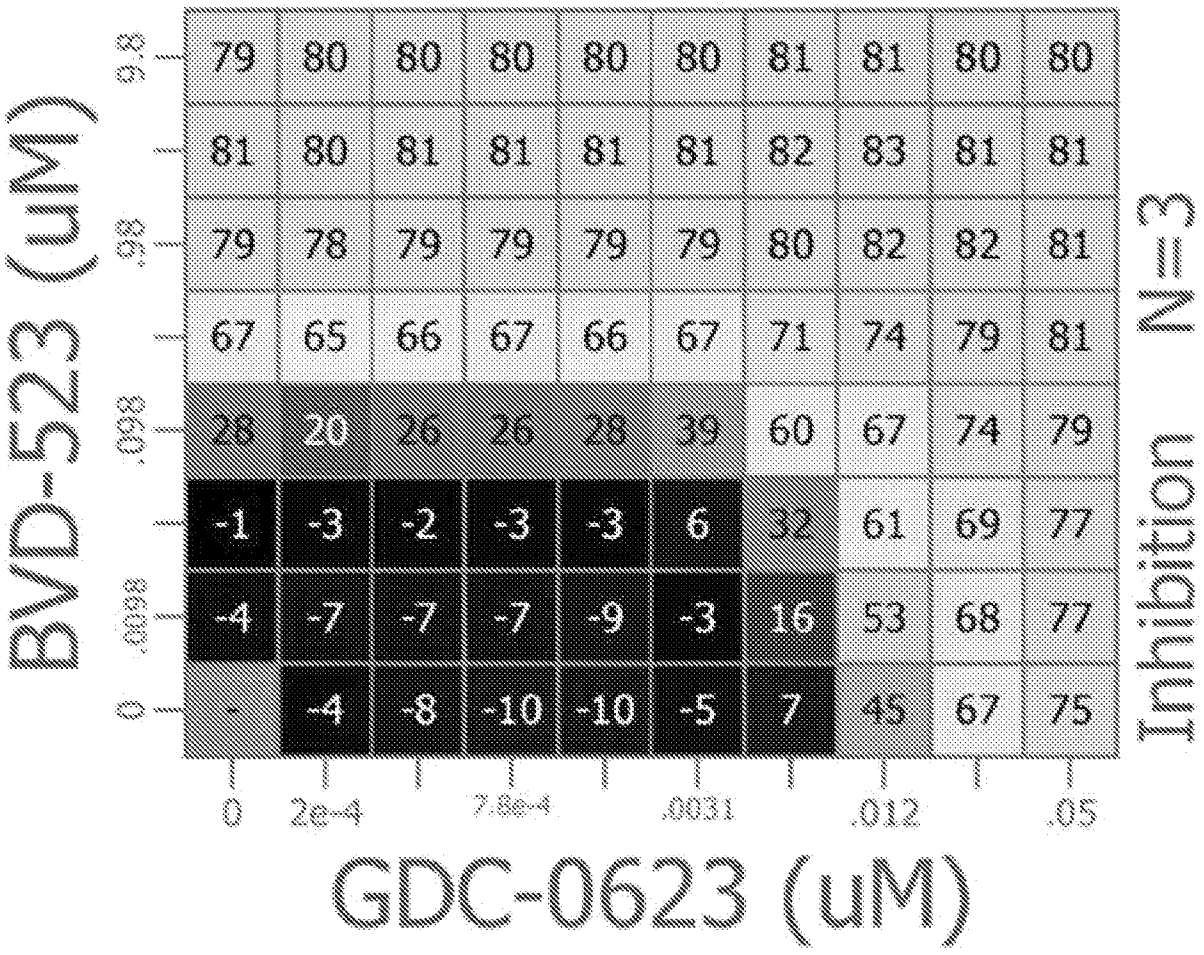

BVD-523 (uM)
9.8
.98
.098
.0098
0
79 80 80 80 80 80 81 81 80 80
81 80 81 81 81 81 82 83 81 81
79 78 79 79 79 79 80 82 82 81
67 65 66 67 66 67 71 74 79 81
28 20 26 26 28 39 60 67 74 79
-1 -3 -2 -3 -3 6 32 61 69 77
-4 -7 -7 -7 -9 -3 16 53 68 77
- -4 -8 -10 -10 -5 7 45 67 75
0
2e-4
7.8e-4
.0031
.012
.05
GDC-0623 (uM)
Inhibition N=3

FIG. 27, Con't

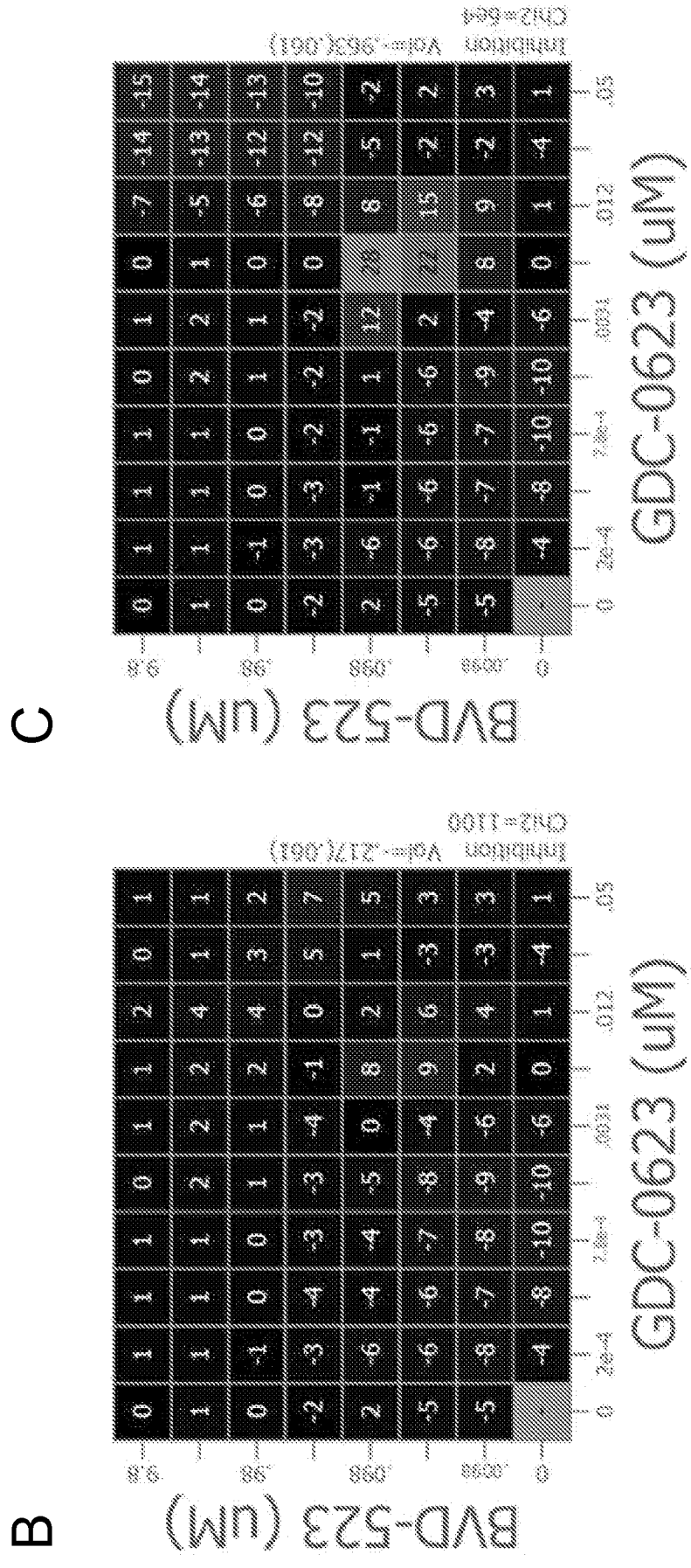

B
C
BVD-523 (uM)
GDC-0623 (uM)
Inhibition
Vol=.2137(.061)
CN2=1100
Vol=.9E3(.061)
CN2=664

FIG. 27, Con't

D

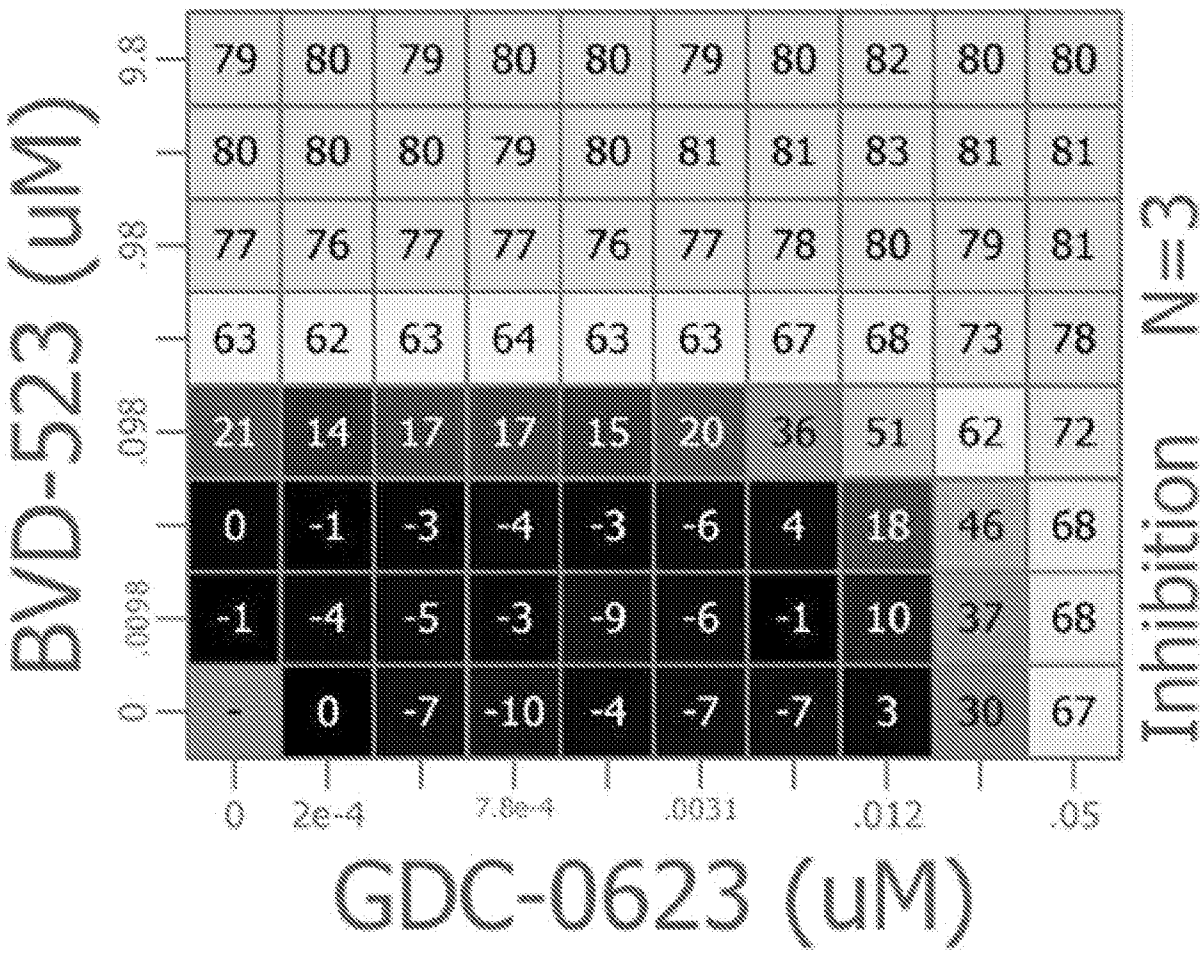
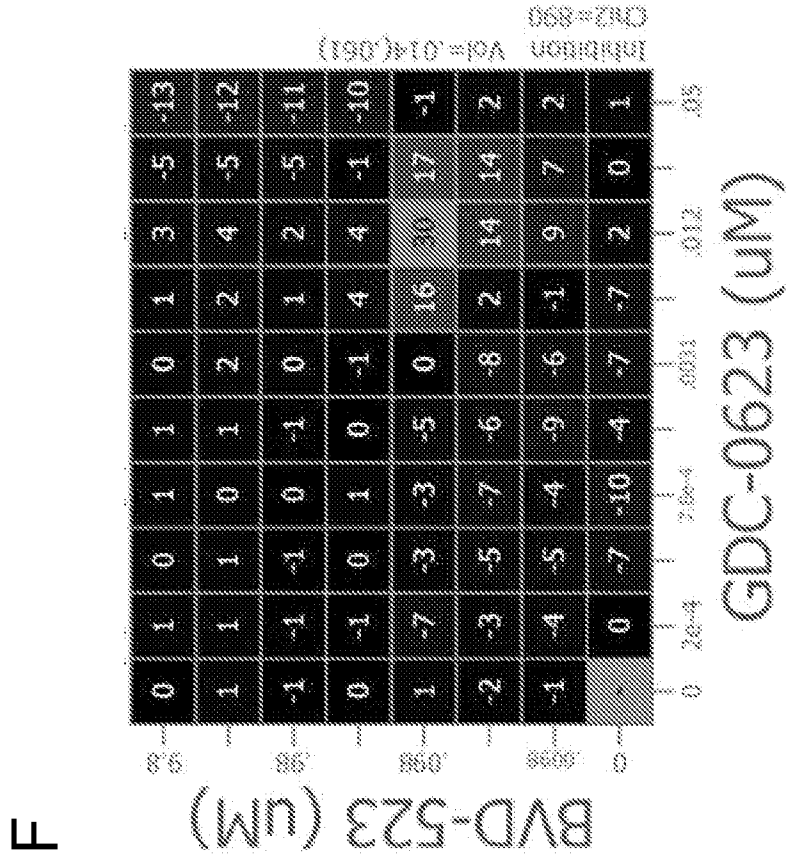

BVD-523 (uM)
9.8
.98
.098
.0098
0
79 80 79 80 80 79 80 82 80 80
80 80 80 79 80 81 81 83 81 81
77 76 77 77 76 77 78 80 79 81
63 62 63 64 63 63 67 68 73 78
21 14 17 17 15 20 36 51 62 72
0 -1 -3 -4 -3 -6 4 18 46 68
-1 -4 -5 -3 -9 -6 -1 10 37 68
- 0 -7 -10 -4 -7 -7 3 30 67
0
2e-4
7.8e-4
.0031
.012
.05
GDC-0623 (uM)
Inhibition N=3

FIG. 27, Con't


F
BVD-523 (uM)
GDC-0623 (uM)
Inhibition Vol=-.014(.061)
CN2=890

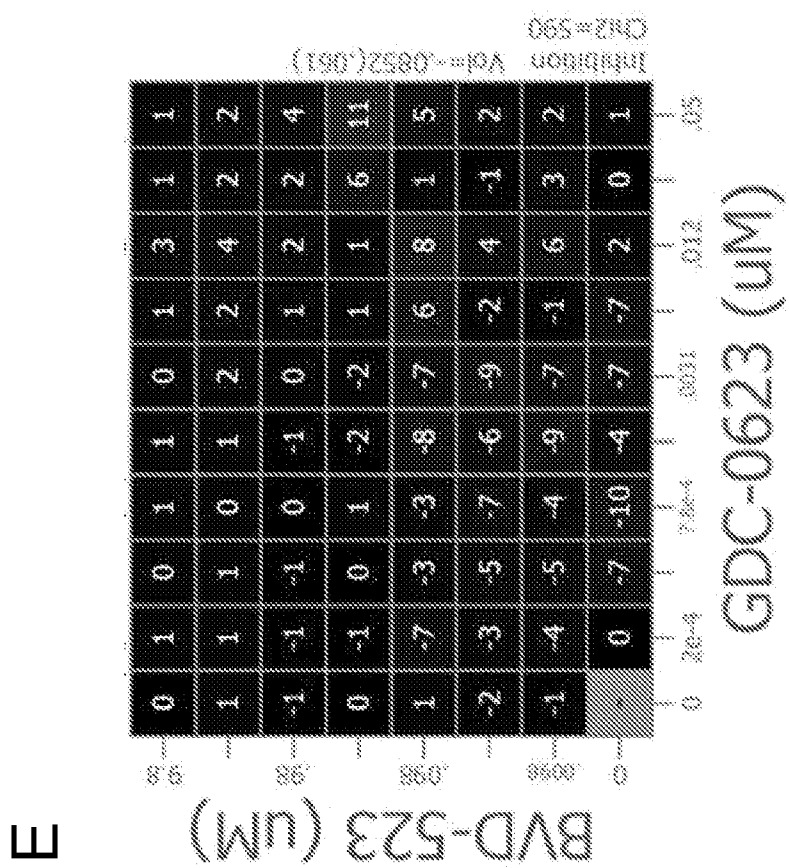
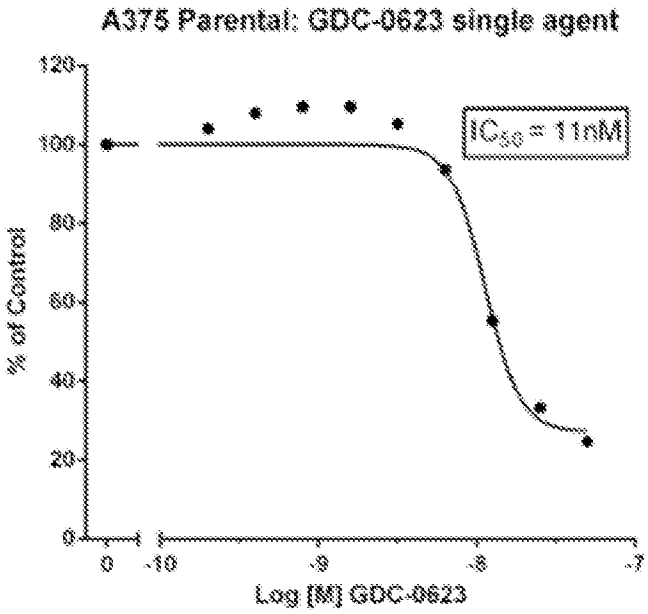
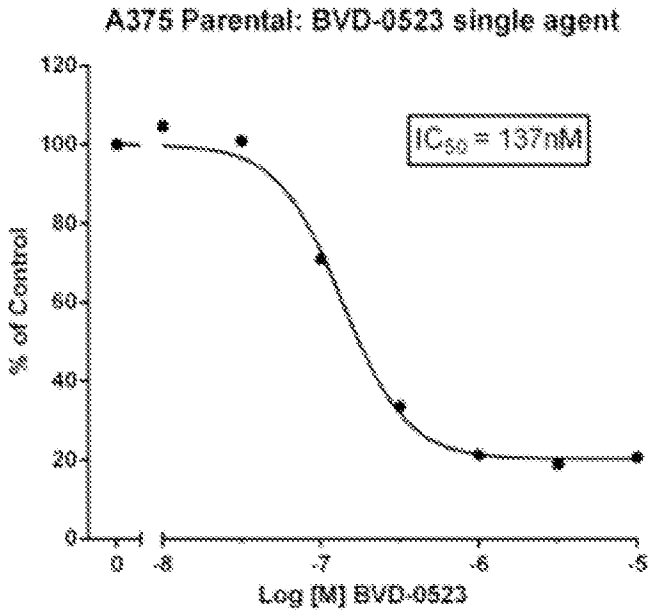

E
BVD-523 (uM)
GDC-0623 (uM)
Inhibition Vol=-.0852(.061)
CN2=590

FIG. 27, Con't

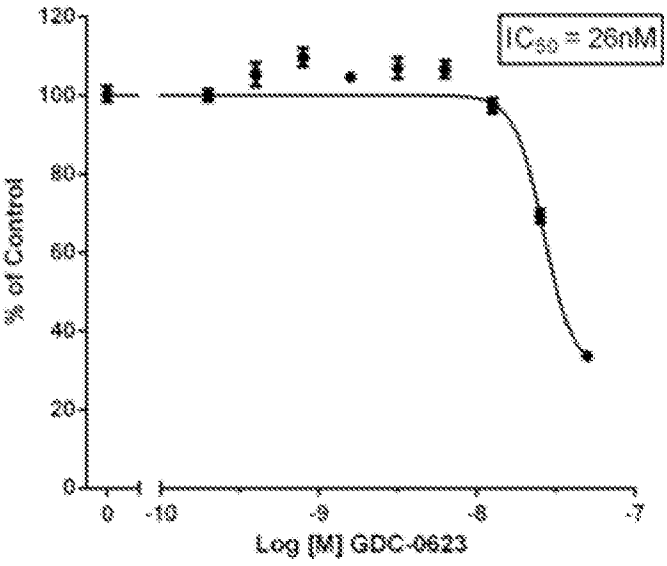
G



H



I



J

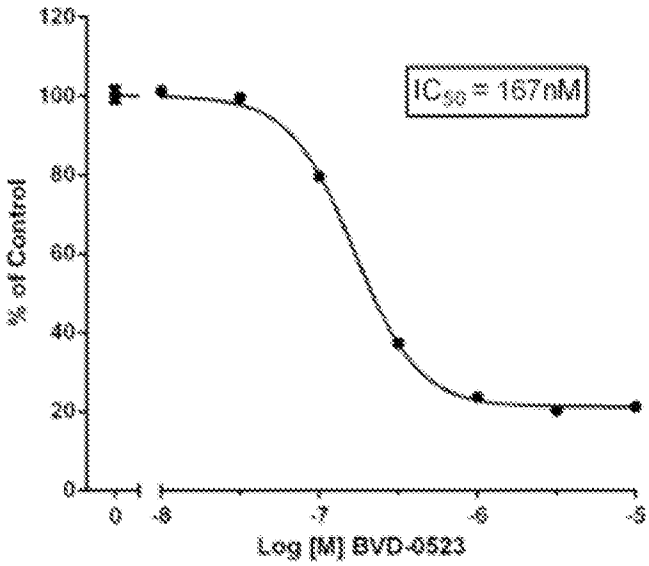


FIG. 28

A

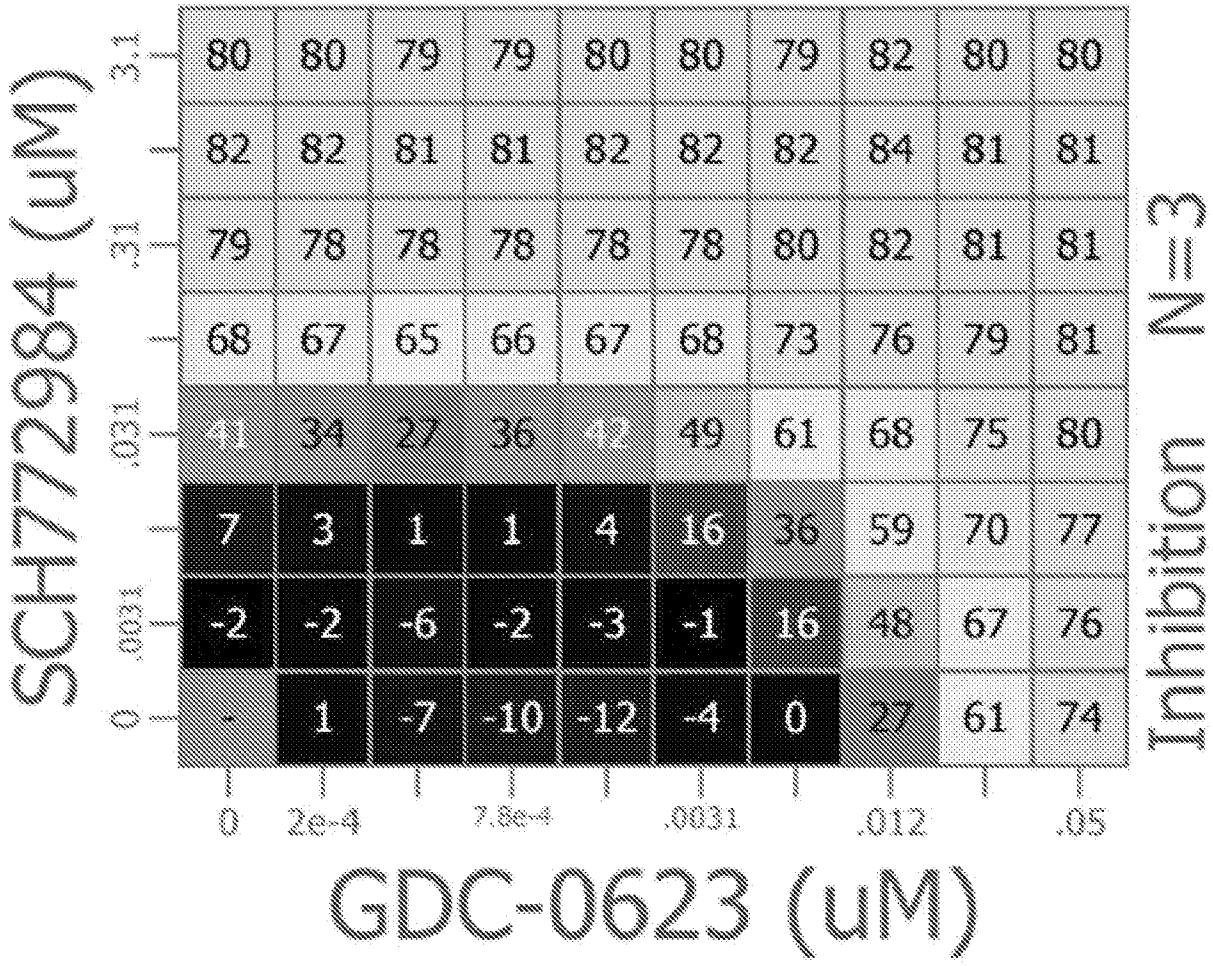

SCH772984 (uM)
3.1
.31
.031
.0031
0
80 80 79 79 80 80 79 82 80 80
82 82 81 81 82 82 82 84 81 81
79 78 78 78 78 78 80 82 81 81
68 67 65 66 67 68 73 76 79 81
41 34 27 36 42 49 61 68 75 80
7 3 1 1 4 16 36 59 70 77
-2 -2 -6 -2 -3 -1 16 48 67 76
- 1 -7 -10 -12 -4 0 27 61 74
0 2e-4 7.8e-4 .0031 .012 .05
GDC-0623 (uM)
Inhibition N=3

FIG. 28, Con't

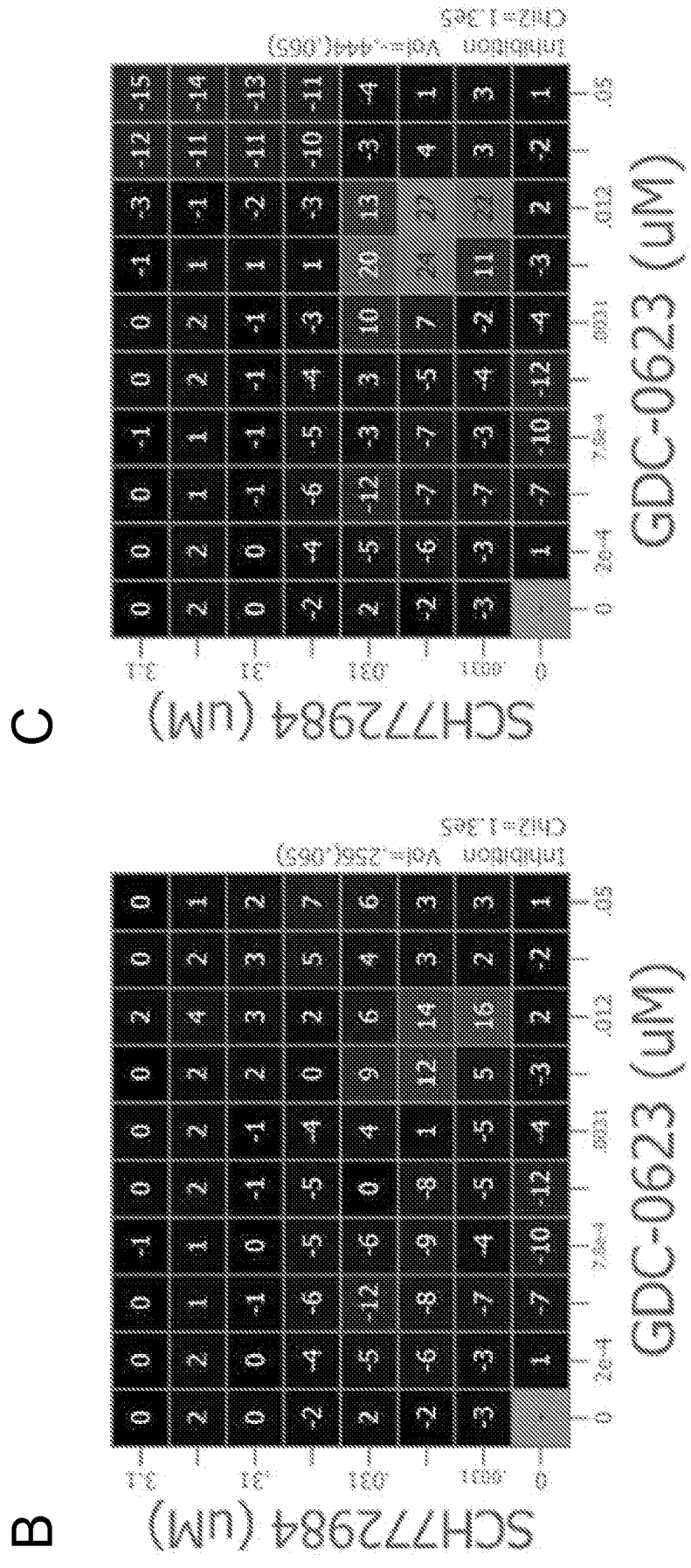

B
C
SCH772984 (uM)
GDC-0623 (uM)
Inhibition Vol=.255(.065)
CN2=1.3e5
Inhibition Vol=.444(.065)
CN2=1.3e5

FIG. 28, Con't

D

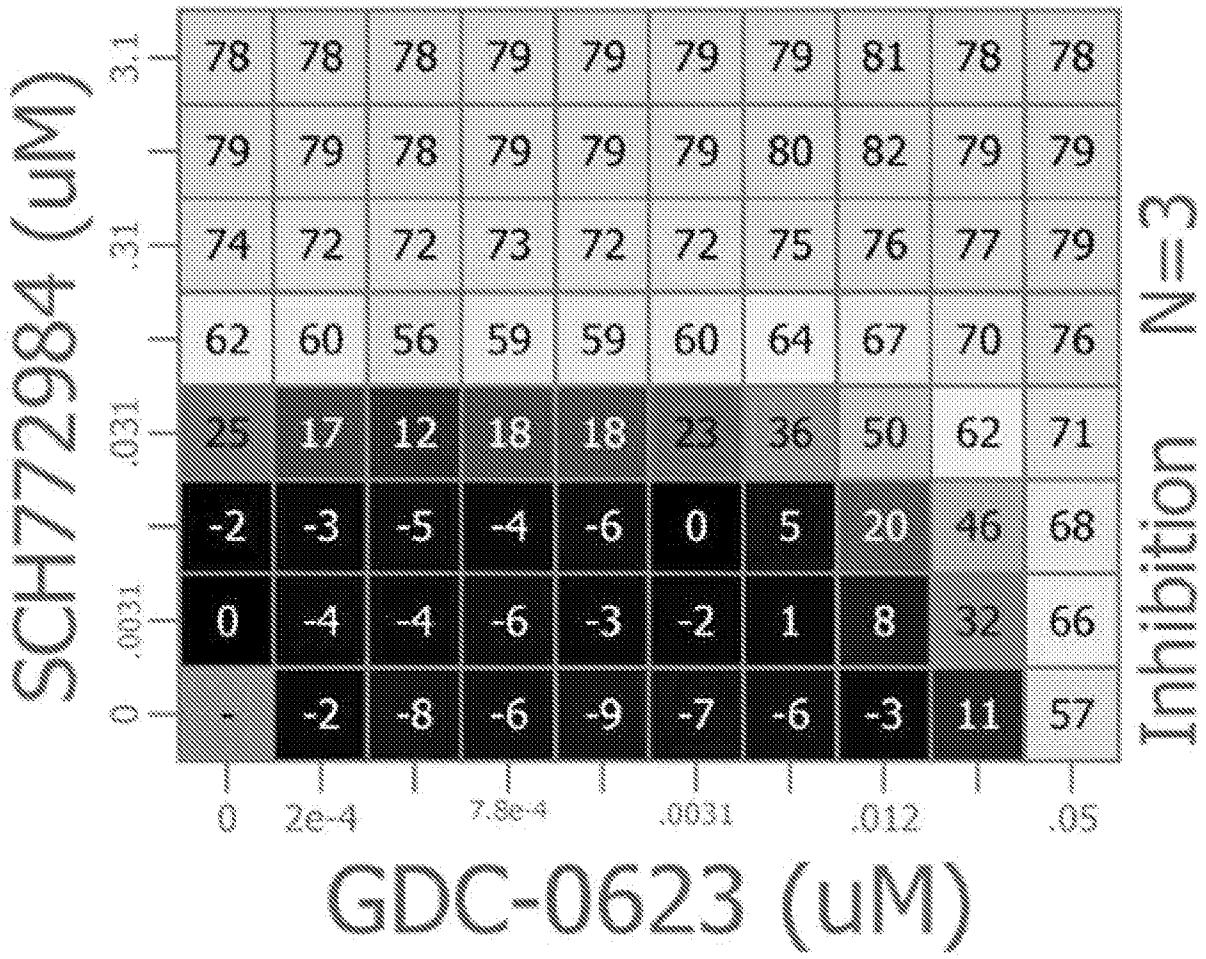

SCH772984 (uM)
3.1
.31
.031
.0031
0
78 78 78 79 79 79 79 81 78 78
79 79 78 79 79 79 80 82 79 79
74 72 72 73 72 72 75 76 77 79
62 60 56 59 59 60 64 67 70 76
25 17 12 18 18 23 36 50 62 71
-2 -3 -5 -4 -6 0 5 20 46 68
0 -4 -4 -6 -3 -2 1 8 32 66
- -2 -8 -6 -9 -7 -6 -3 11 57
Inhibition N=3
0
2e-4
7.8e-4
.0031
.012
.05
GDC-0623 (uM)

FIG. 28, Con't

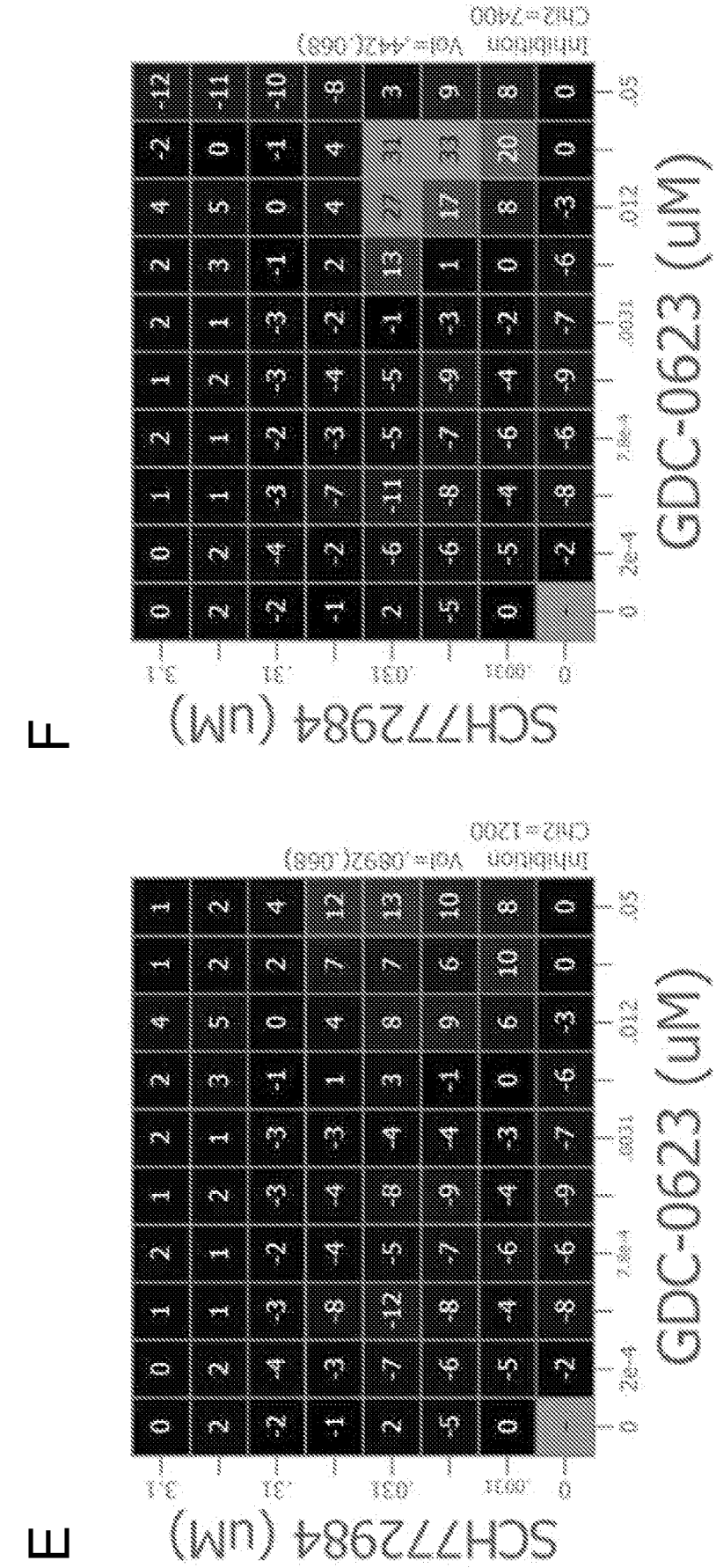
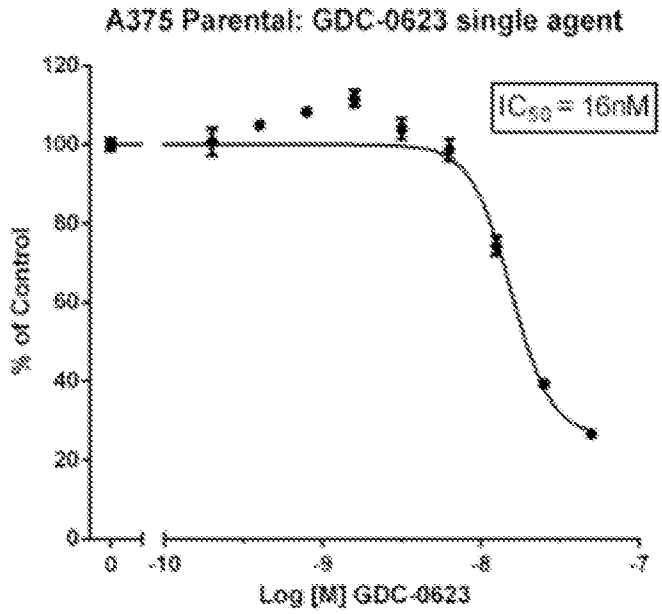
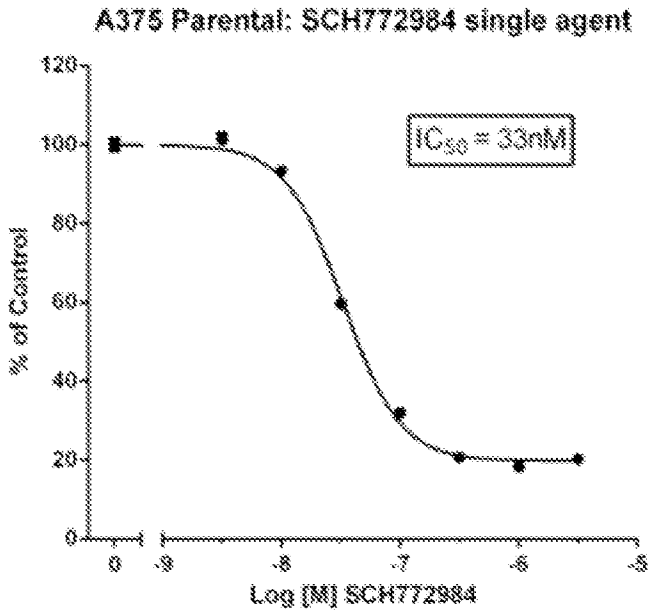

F
SCH772984 (uM)
GDC-0623 (uM)
Inhibition Vol=.4426(.068)
CH2=7400
E
SCH772984 (uM)
GDC-0623 (uM)
Inhibition Vol=.0892(.068)
CH2=1200

FIG. 28, Con't

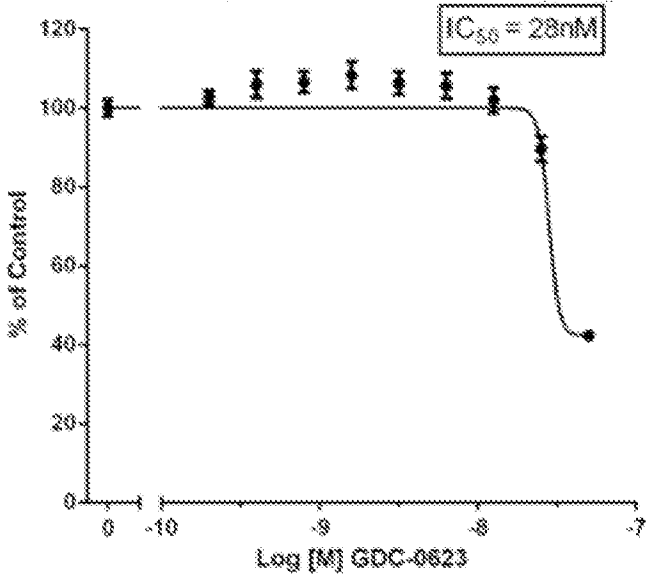
G



H



I



J

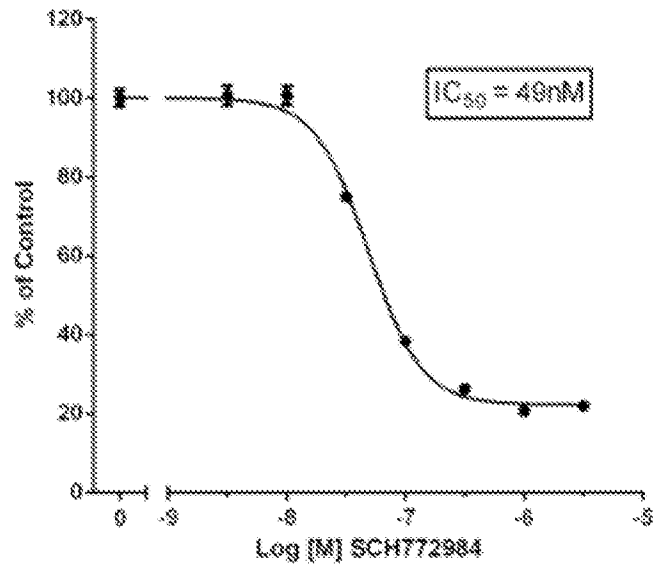


FIG. 29

A

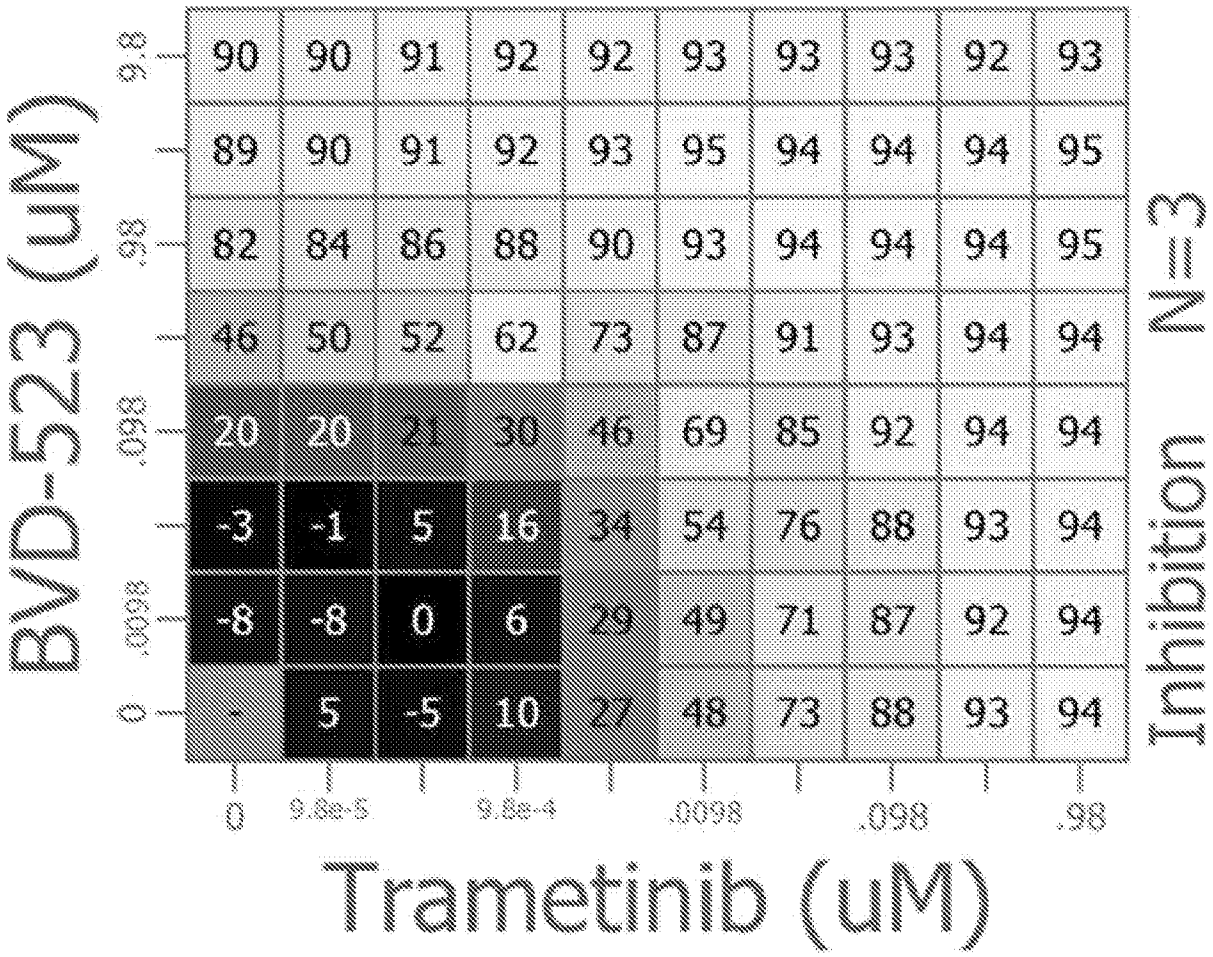

BVD-523 (uM)
9.8
.98
.098
.0098
0
90 90 91 92 92 93 93 93 92 93
89 90 91 92 93 95 94 94 94 95
82 84 86 88 90 93 94 94 94 95
46 50 52 62 73 87 91 93 94 94
20 20 21 30 46 69 85 92 94 94
-3 -1 5 16 34 54 76 88 93 94
-8 -8 0 6 29 49 71 87 92 94
- 5 -5 10 27 48 73 88 93 94
Inhibition N=3
0
9.8e-5
9.8e-4
.0098
.098
.98
Trametinib (uM)

FIG. 29, Con't

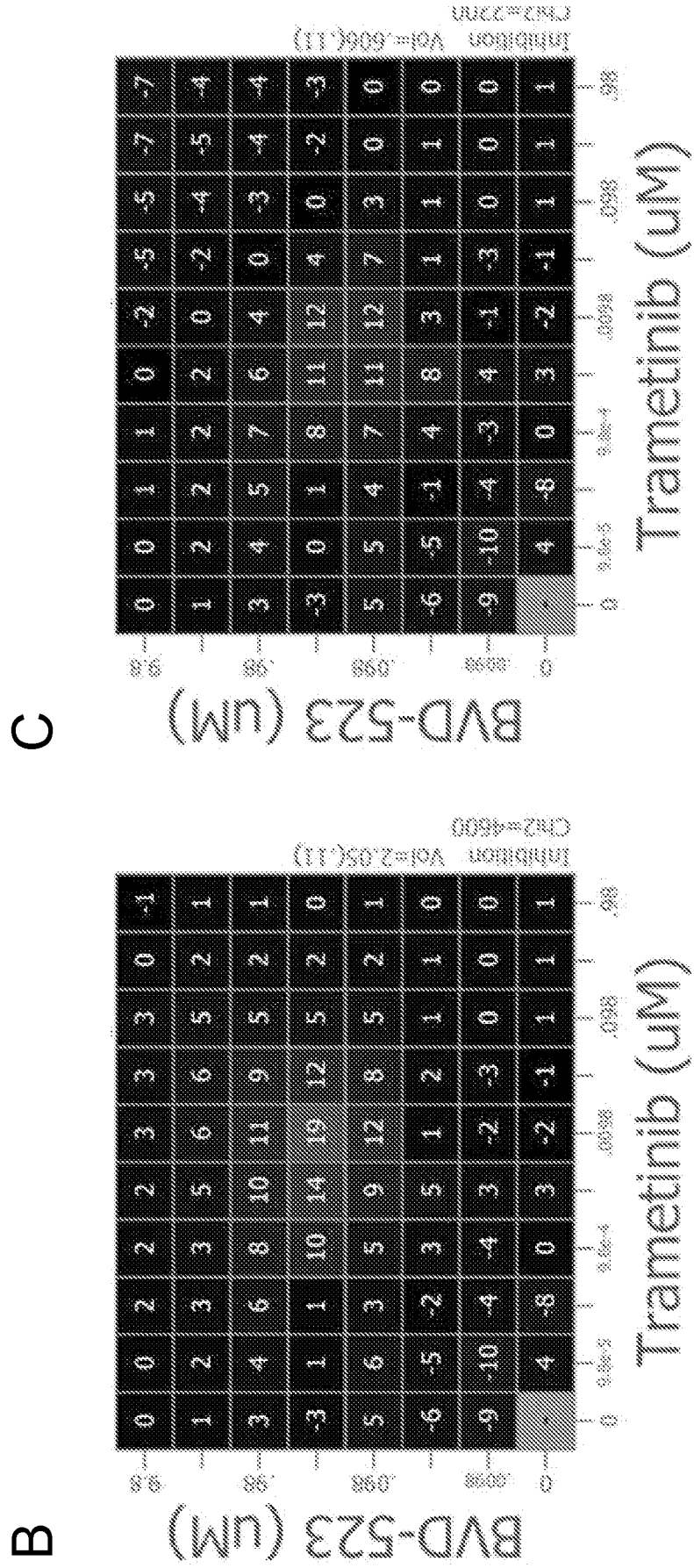

B
C
BVD-523 (uM)
Trametinib (uM)
Inhibition Vol=2.05(.11)
CM2=4600
Inhibition Vol=.606(.11)
CM2=2200

FIG. 29, Con't

D

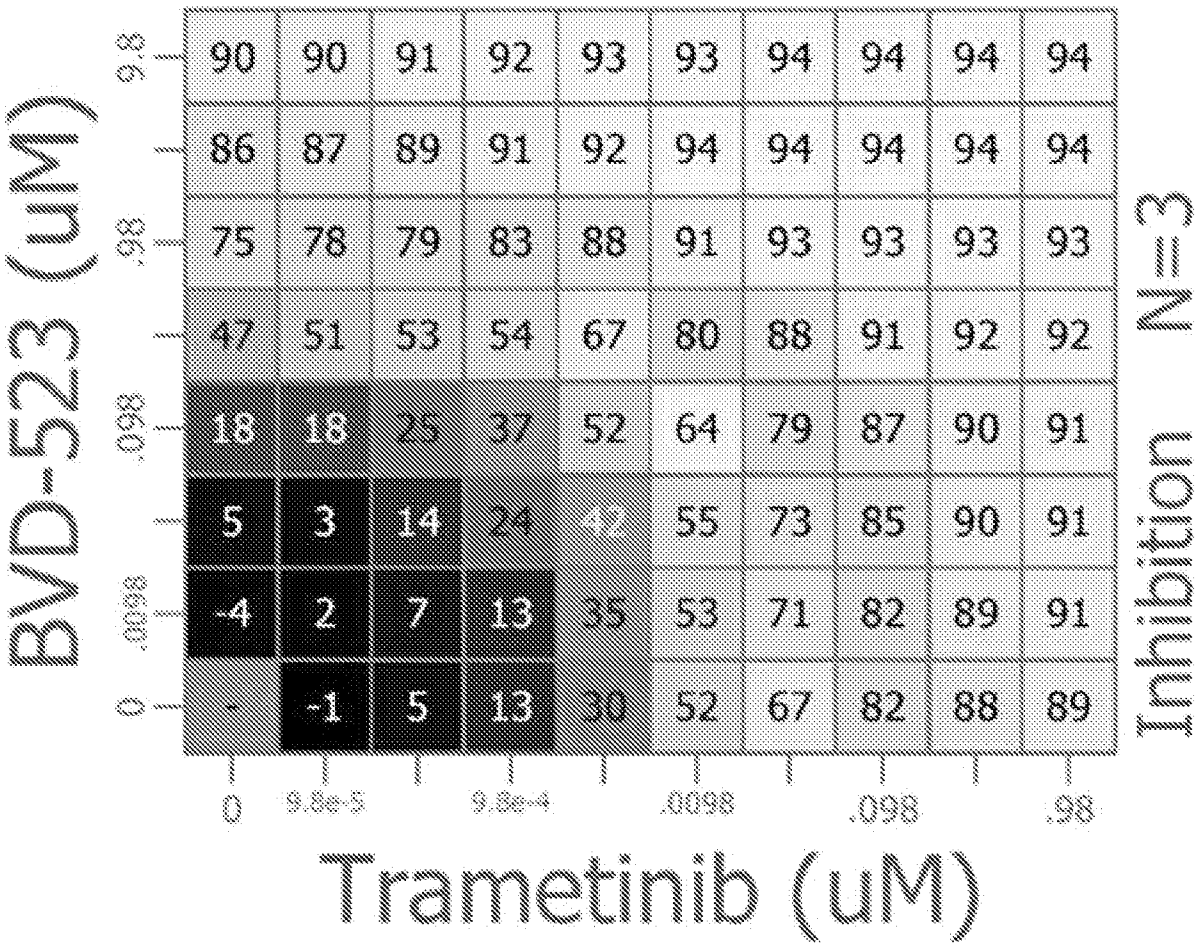
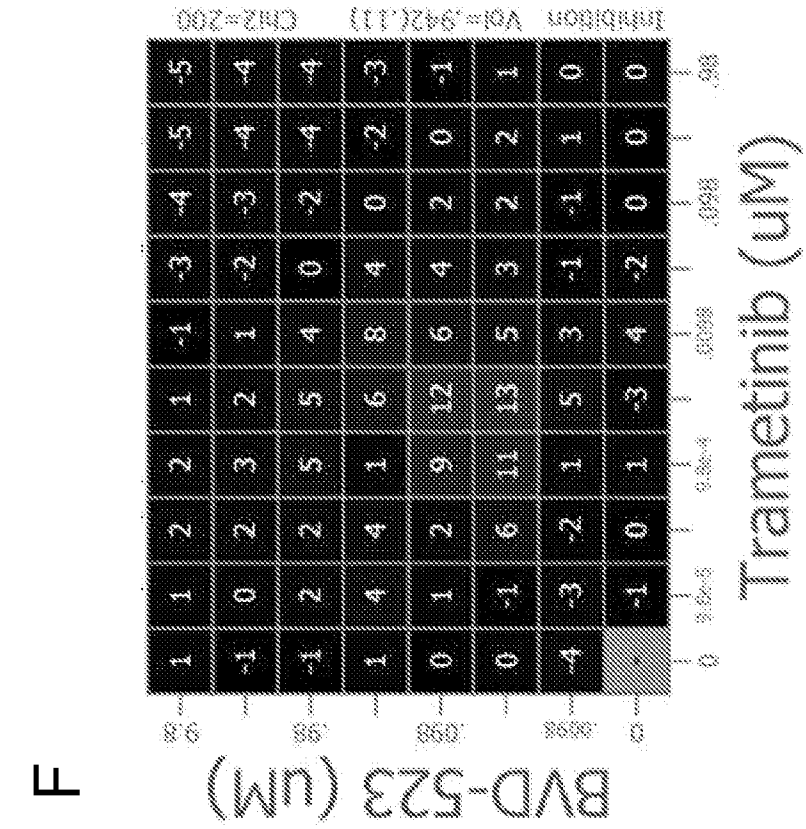

BVD-523 (uM)
9.8
.98
.098
.0098
0
90 90 91 92 93 93 94 94 94 94
86 87 89 91 92 94 94 94 94 94
75 78 79 83 88 91 93 93 93 93
47 51 53 54 67 80 88 91 92 92
18 18 25 37 52 64 79 87 90 91
5 3 14 24 42 55 73 85 90 91
-4 2 7 13 35 53 71 82 89 91
- -1 5 13 30 52 67 82 88 89
0
9.8e-5
9.8e-4
.0098
.098
.98
Trametinib (uM)
Inhibition N=3

FIG. 29, Con't


F
BVD-523 (uM)
Trametinib (uM)
Inhibition Vol=.942(.11) CH2=200

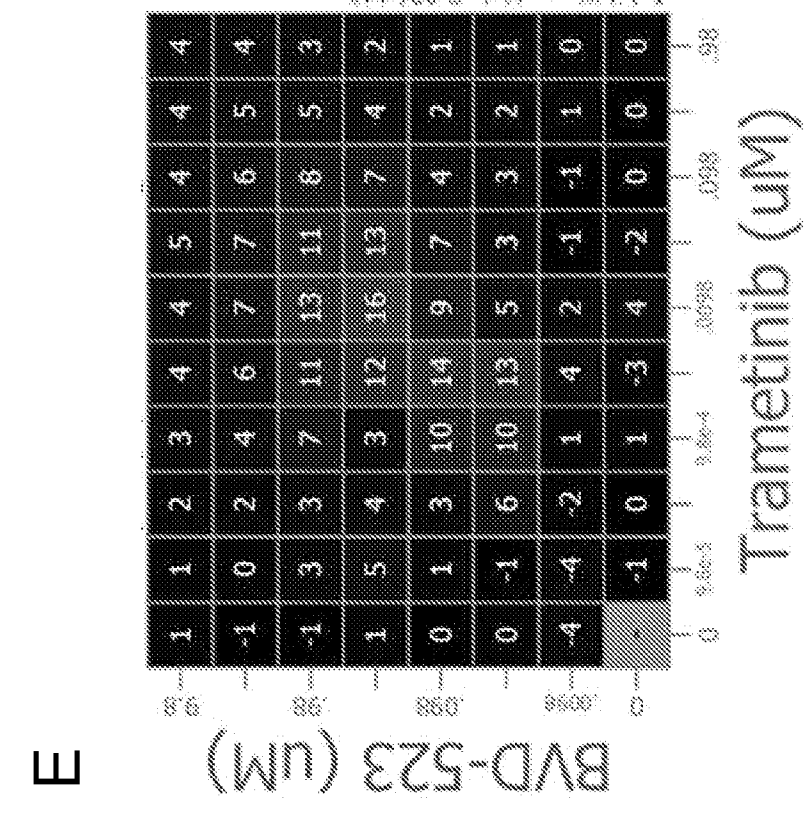
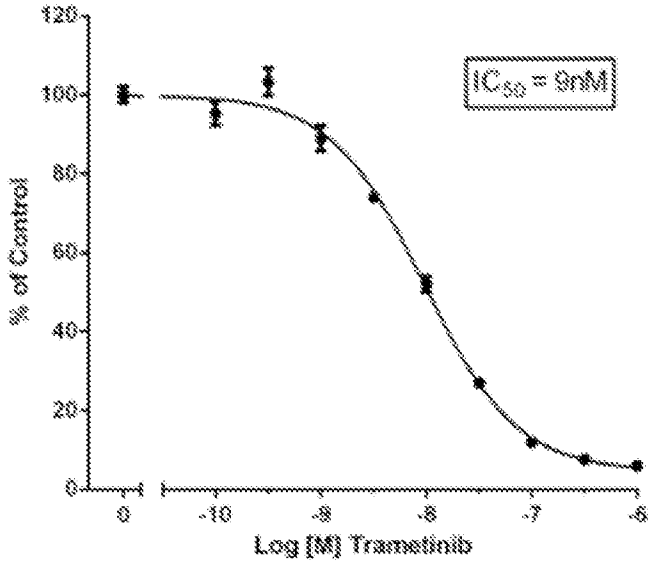
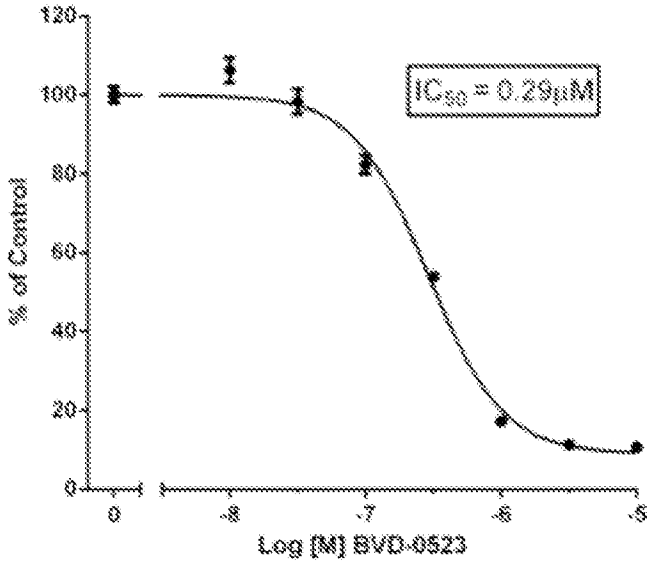

E
BVD-523 (uM)
Trametinib (uM)
Inhibition Vol=3.02(.11)
CH2=5400

FIG. 29, Con't

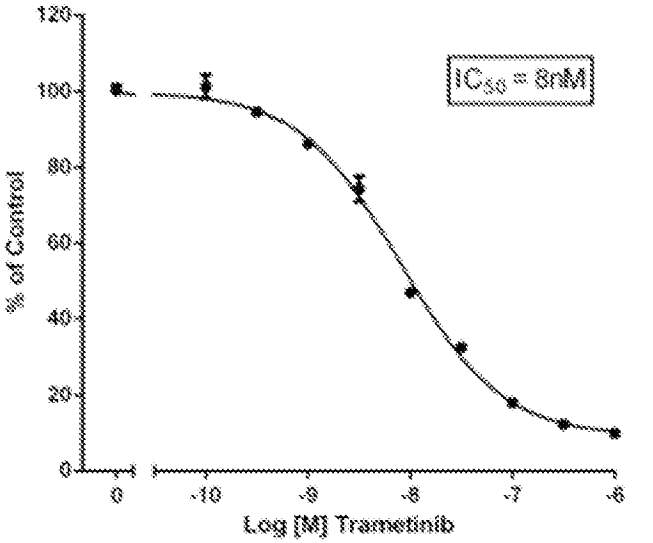
G



H



I



J

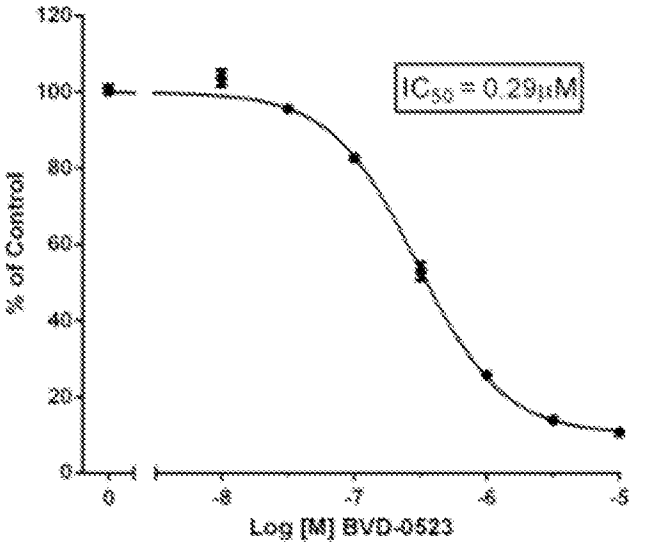


FIG. 30

A

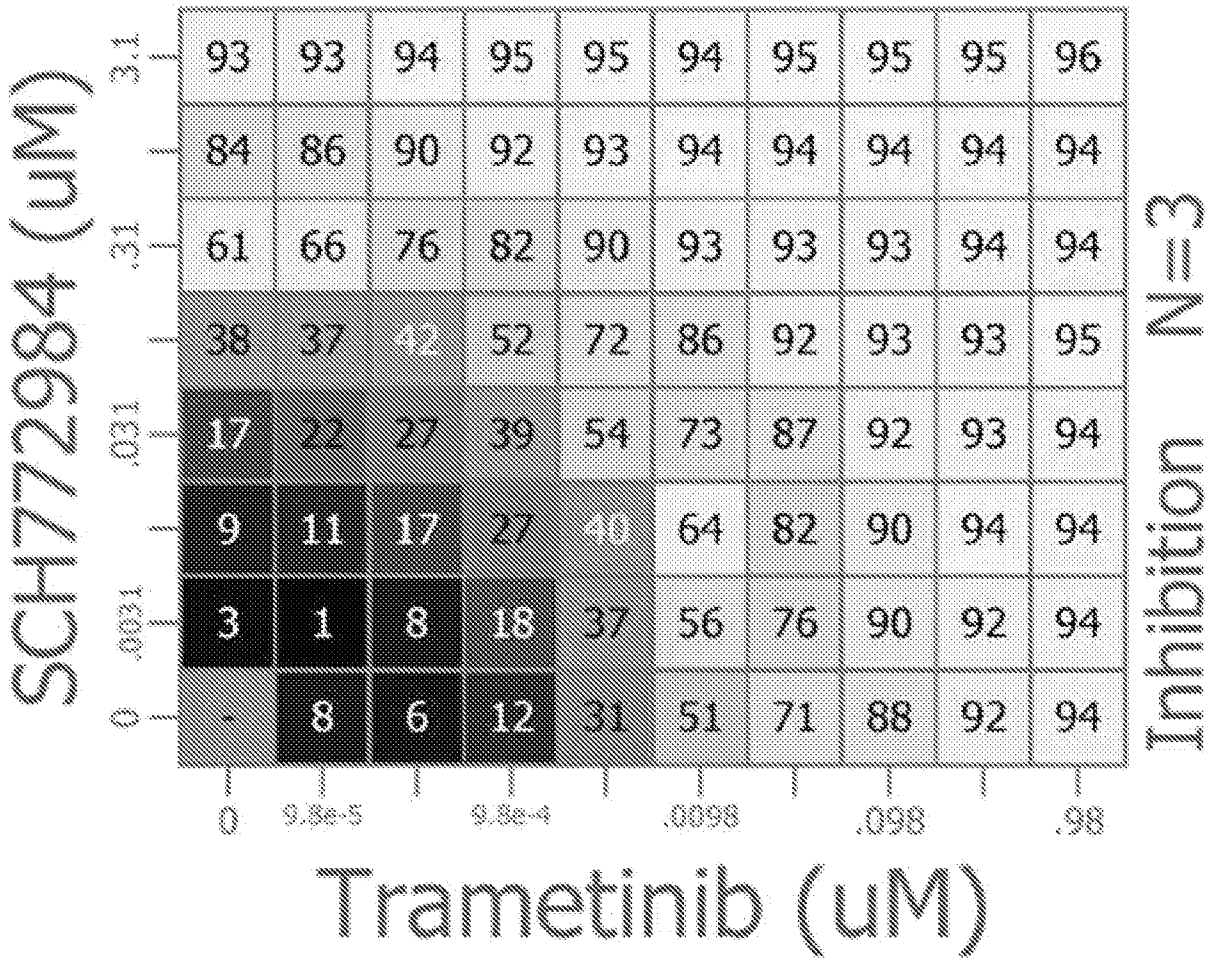

SCH772984 (uM)
3.1
.31
.031
.0031
0
93 93 94 95 95 94 95 95 95 96
84 86 90 92 93 94 94 94 94 94
61 66 76 82 90 93 93 93 94 94
38 37 42 52 72 86 92 93 93 95
17 22 27 39 54 73 87 92 93 94
9 11 17 27 40 64 82 90 94 94
3 1 8 18 37 56 76 90 92 94
- 8 6 12 31 51 71 88 92 94
0
9.8e-5
9.8e-4
.0098
.098
.98
Trametinib (uM)
Inhibition N=3

FIG. 30, Con't

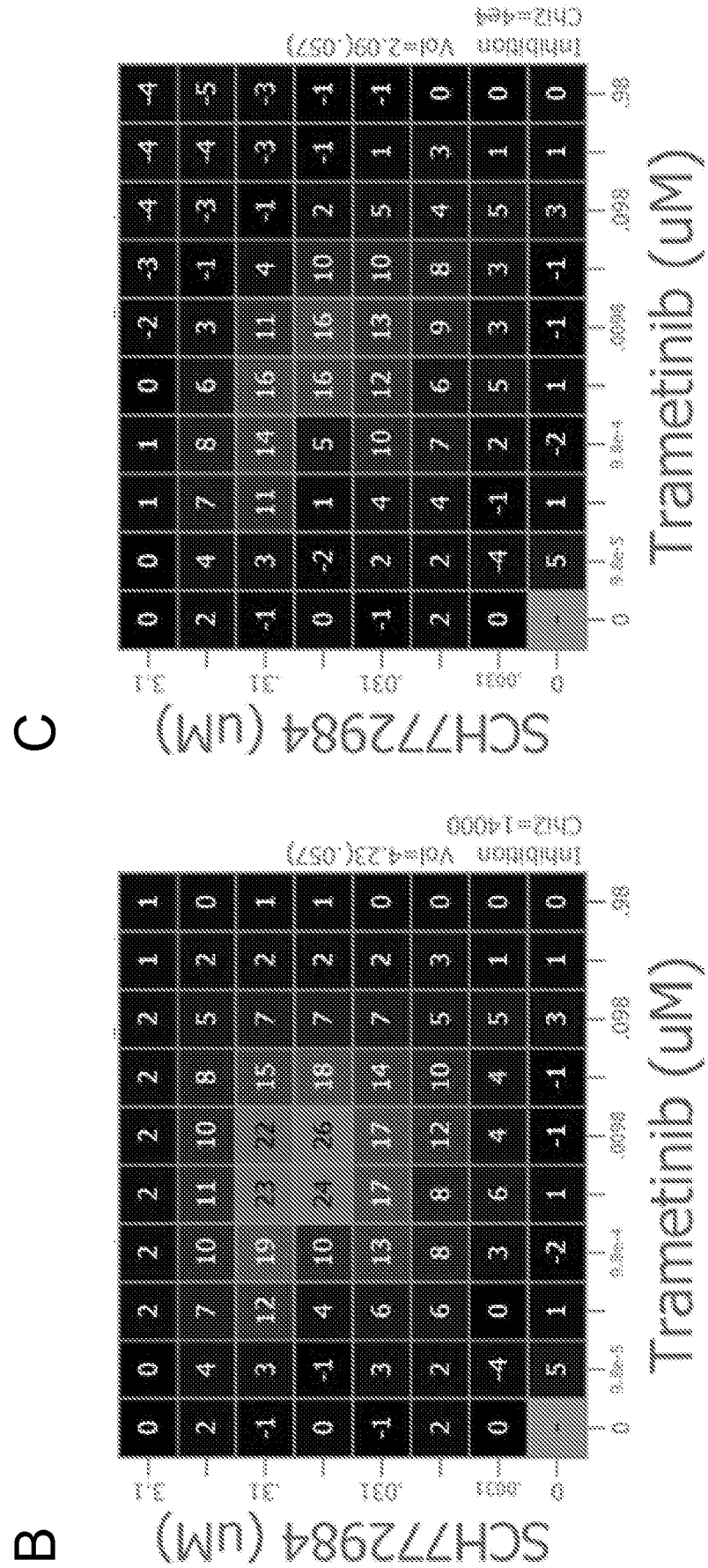

B
C
SCH772984 (uM)
Trametinib (uM)
Inhibition Vol=4.23(.057) CH2=14000
Inhibition Vol=2.09(.057) CH2=4e4
0
.0023
.031
.31
3.1
.0098
.098
.98
0 2 0 2 4 -1 0 -1 3 0 2 7 11 5 10 16 16 10 13 10 5 2 -1 -1 -3 -5 -4
0 2 0 2 4 -1 0 -1 3 0 2 7 12 4 6 13 17 17 12 8 6 3 -2 1 -1 -2

FIG. 30, Con't

D

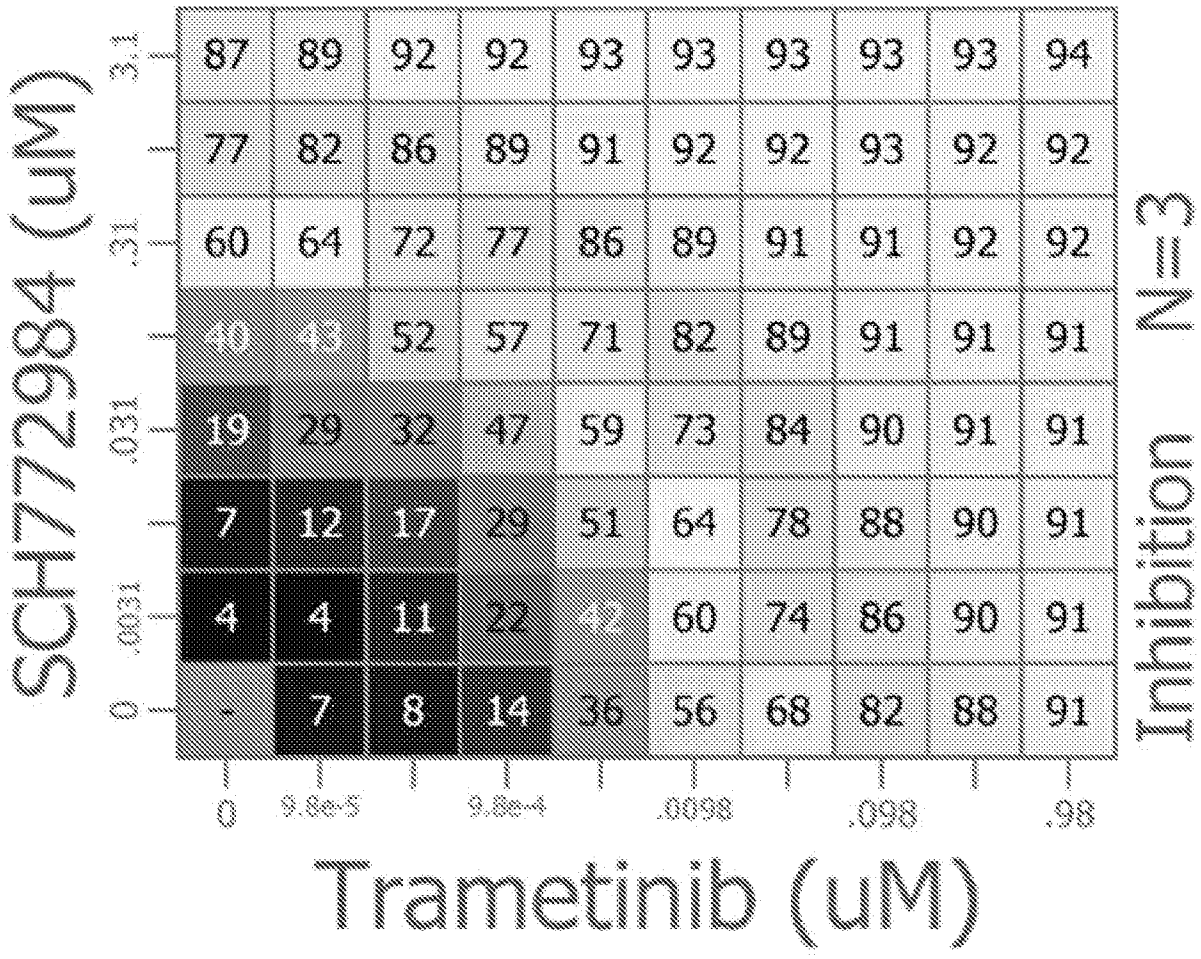

SCH772984 (uM)
3.1
.31
.031
.0031
0
87 89 92 92 93 93 93 93 93 94
77 82 86 89 91 92 92 93 92 92
60 64 72 77 86 89 91 91 92 92
40 45 52 57 71 82 89 91 91 91
19 29 32 47 59 73 84 90 91 91
7 12 17 29 51 64 78 88 90 91
4 4 11 22 42 60 74 86 90 91
- 7 8 14 36 56 68 82 88 91
0
9.8e-5
9.8e-4
.0098
.098
.98
Trametinib (uM)
Inhibition N=3

FIG. 30, Con't

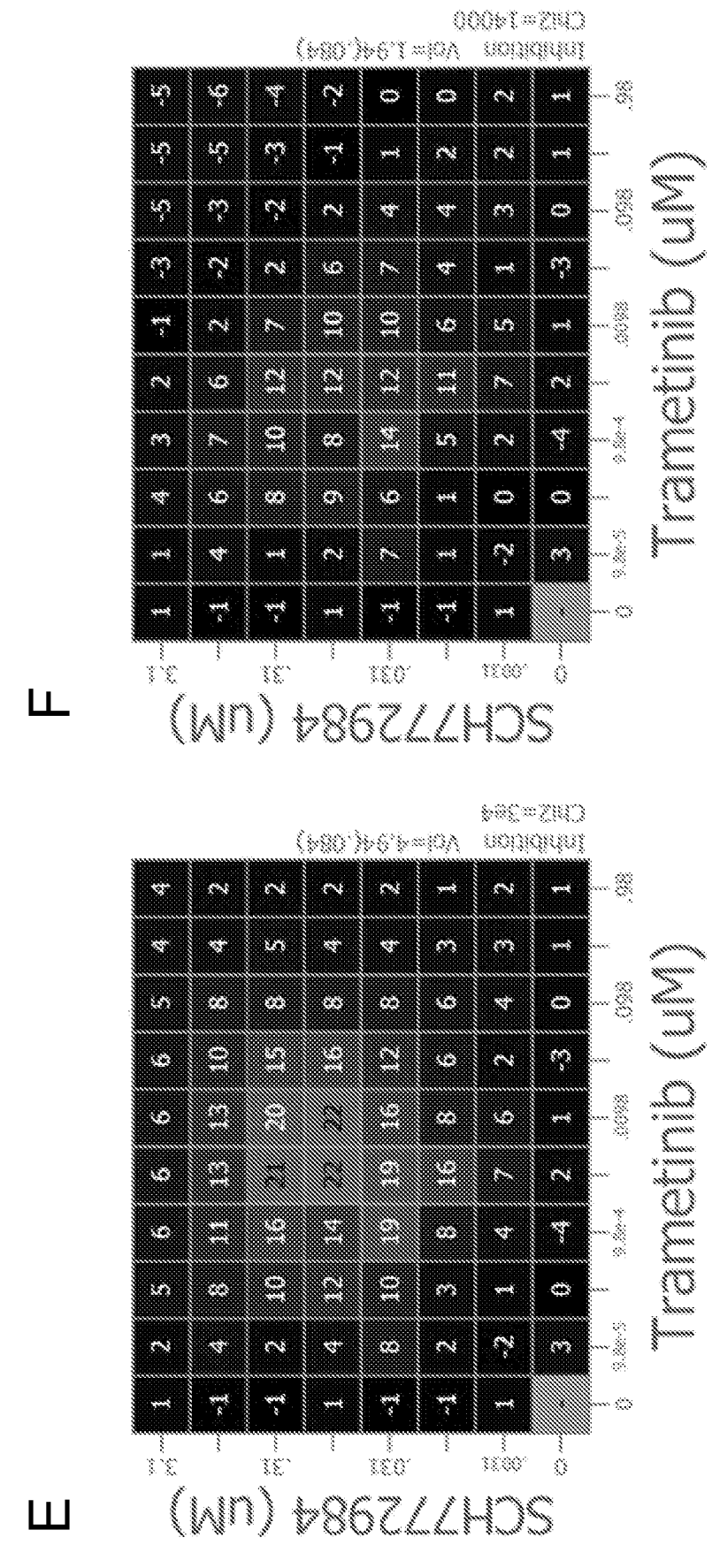
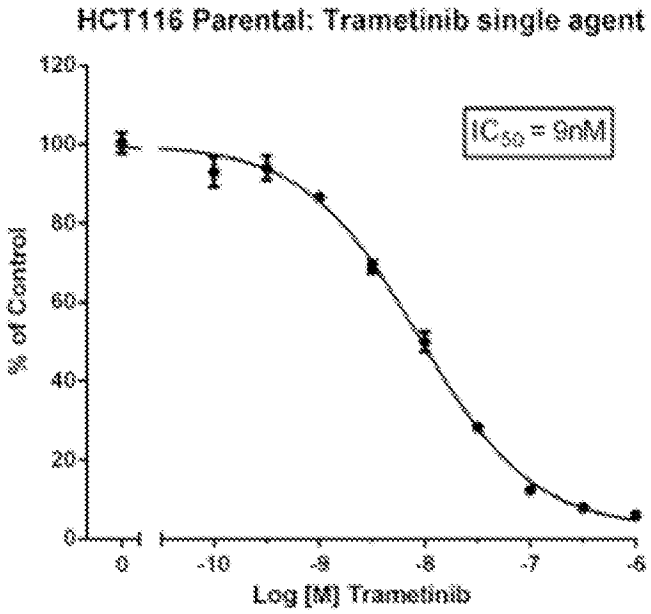
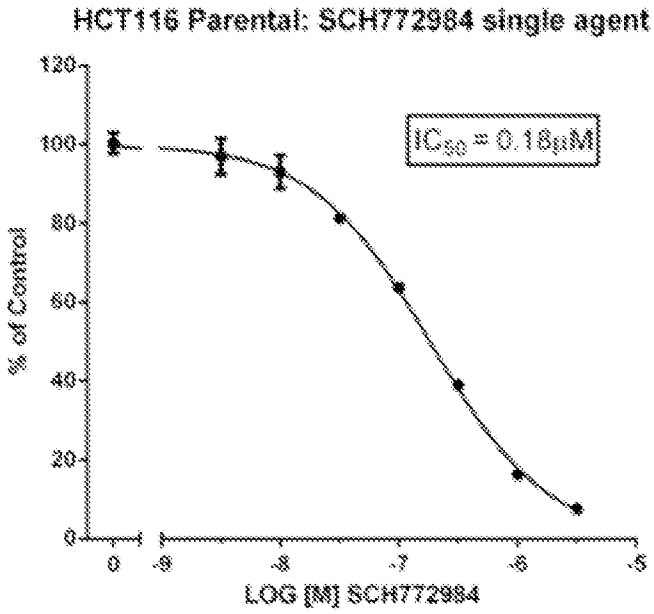

E
F
SCH772984 (uM)
Trametinib (uM)
Inhibition Vol=4.94(.084)
CM2=364
Inhibition Vol=1.94(.084)
CM2=1400

FIG. 30, Con't

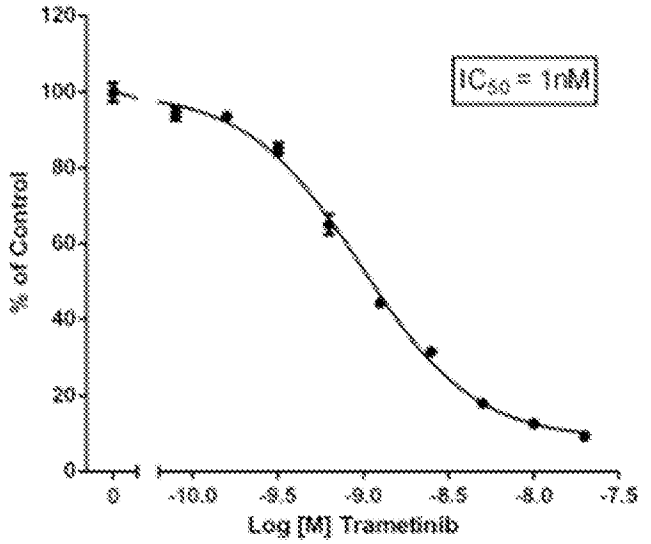
G



H



I



J

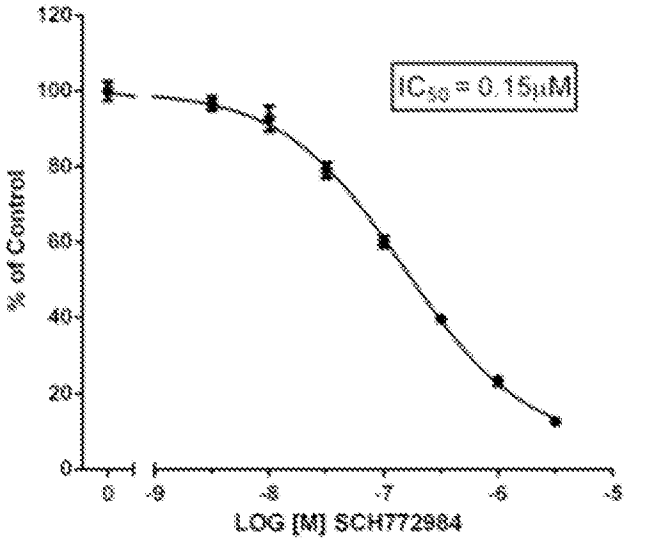


FIG. 31

A

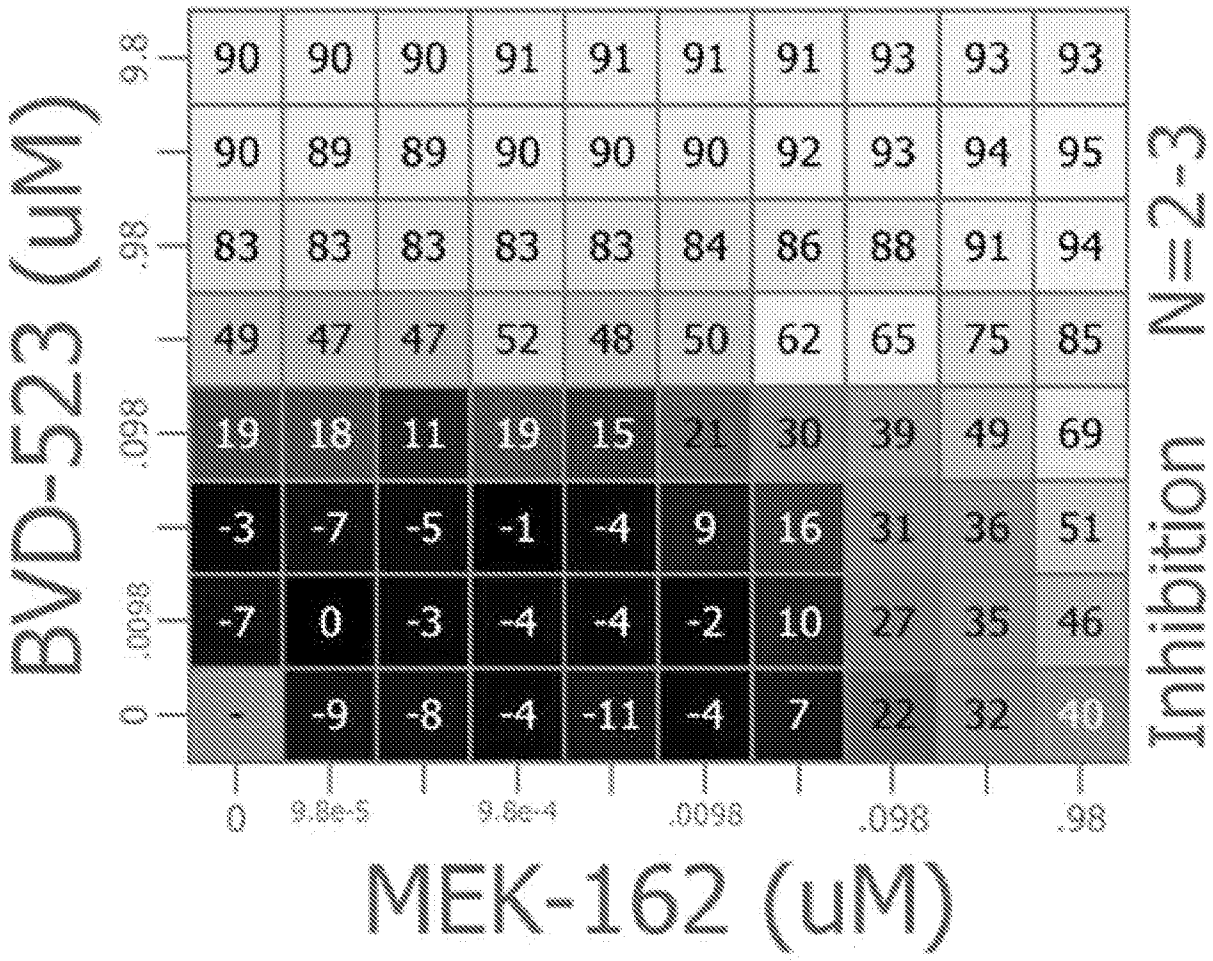

BVD-523 (uM)
9.8
.98
.098
.0098
0
90 90 90 91 91 91 91 93 93 93
90 89 89 90 90 90 92 93 94 95
83 83 83 83 83 84 86 88 91 94
49 47 47 52 48 50 62 65 75 85
19 18 11 19 15 21 30 39 49 69
-3 -7 -5 -1 -4 9 16 31 36 51
-7 0 -3 -4 -4 -2 10 27 35 46
- -9 -8 -4 -11 -4 7 22 32 40
0
9.8e-5
9.8e-4
.0098
.098
.98
MEK-162 (uM)
Inhibition N=2-3

FIG. 31, Con't

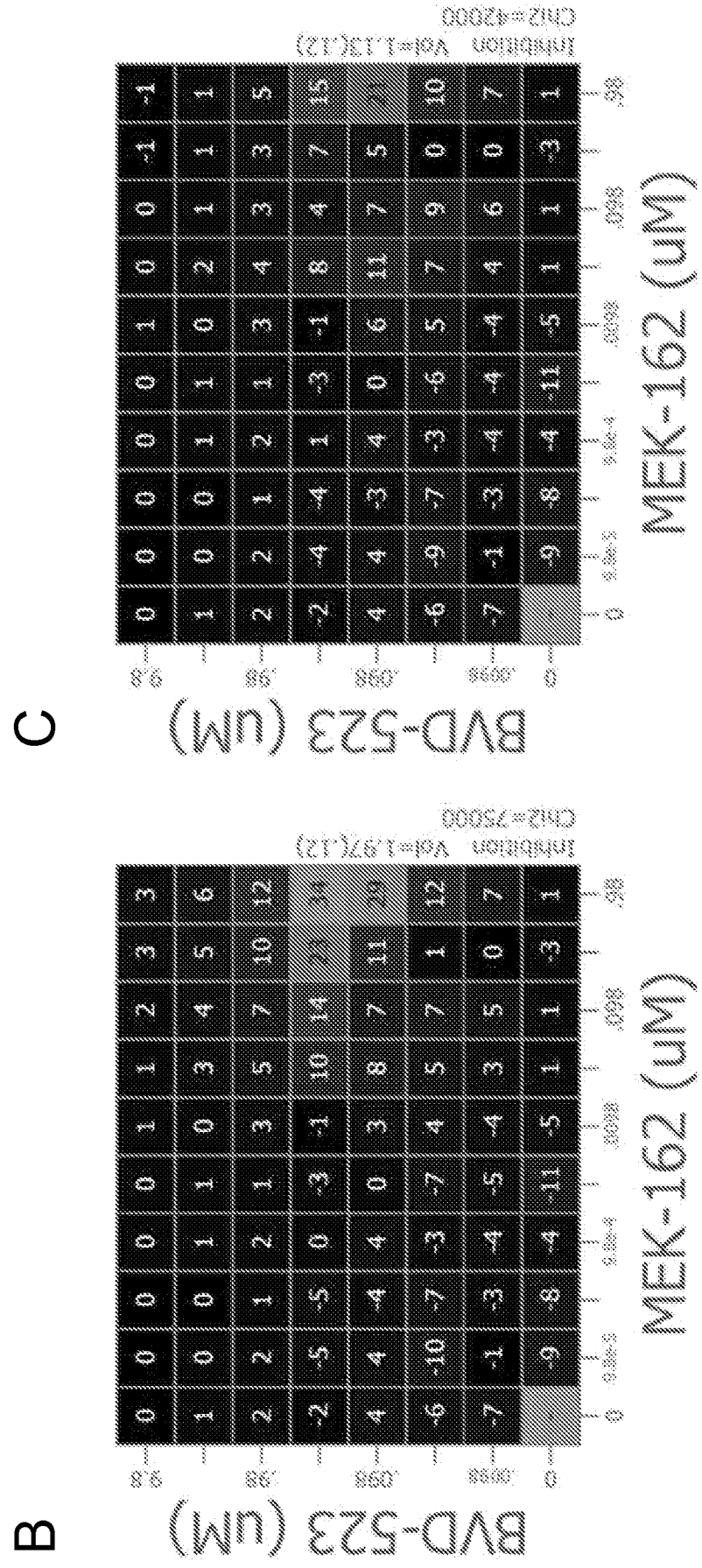

B
C
BVD-523 (uM)
MEK-162 (uM)
Inhibition Vol=1.13(.12)
Chl2=42000
Inhibition Vol=1.97(.12)
Chl2=75000

FIG. 31, Con't

D

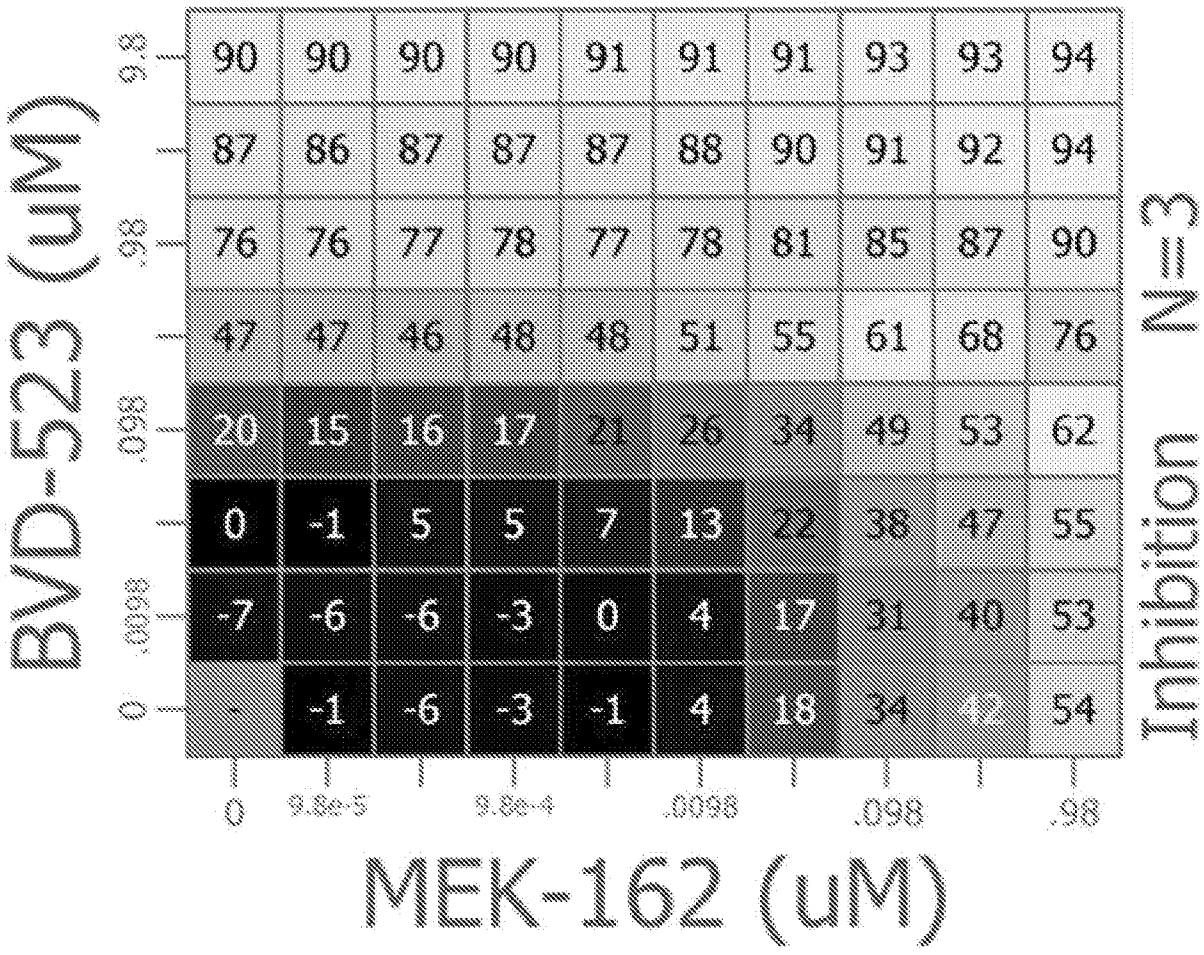

BVD-523 (uM)
.98
.098
.0098
0
90 90 90 90 91 91 91 93 93 94
87 86 87 87 87 88 90 91 92 94
76 76 77 78 77 78 81 85 87 90
47 47 46 48 48 51 55 61 68 76
20 15 16 17 21 26 34 49 53 62
0 -1 5 5 7 13 22 38 47 55
-7 -6 -6 -3 0 4 17 31 40 53
-1 -6 -3 -1 4 18 34 54
0
9.8e-5
9.8e-4
.0098
.098
.98
MEK-162 (uM)
Inhibition N=3

FIG. 31, Con't

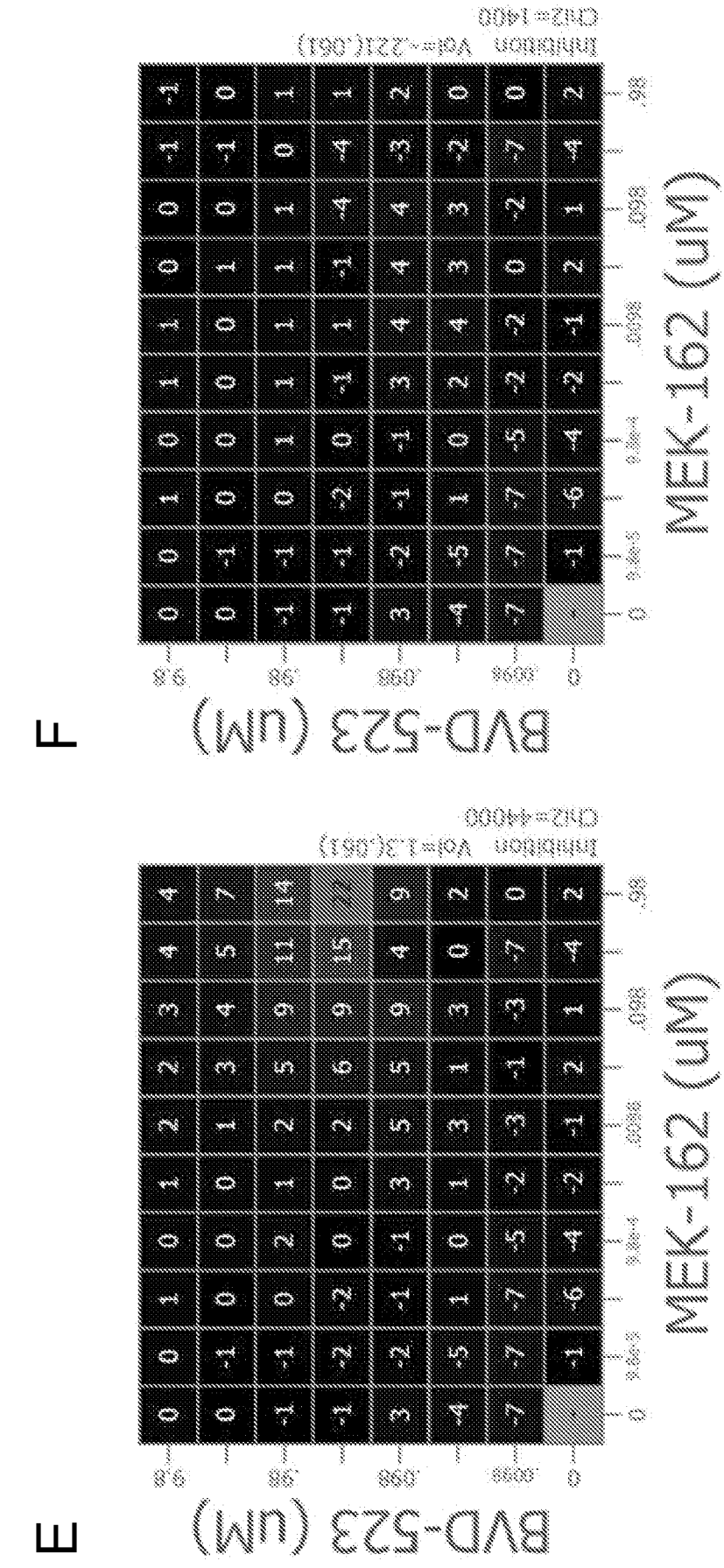
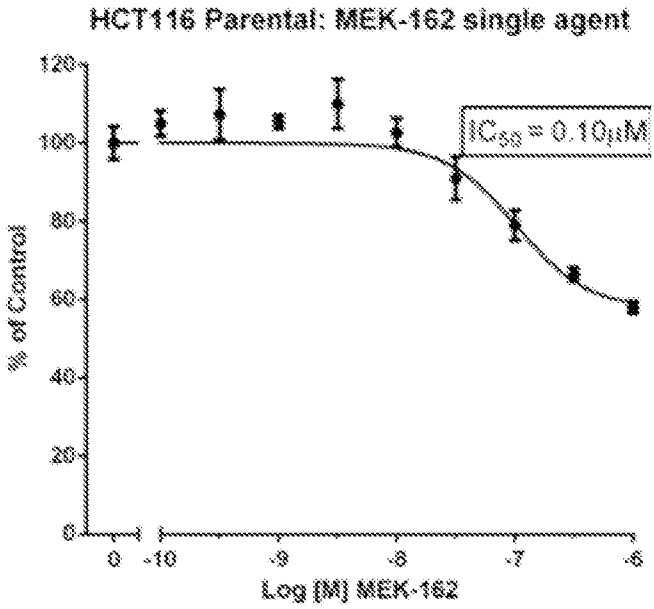
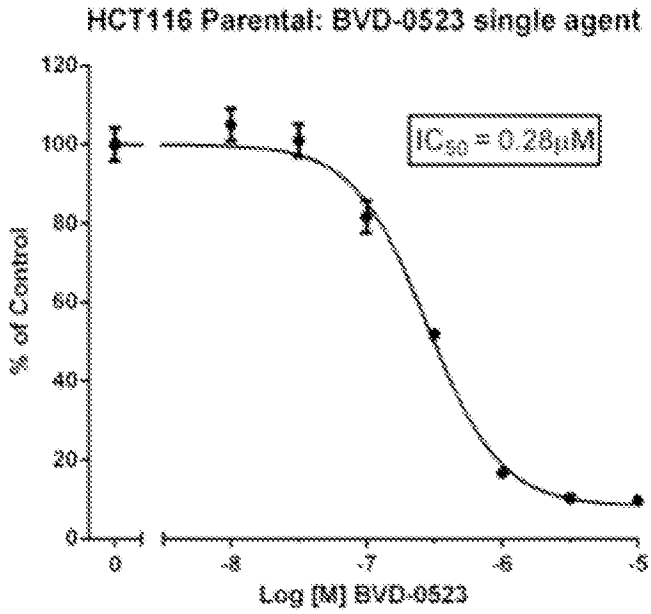

F
BVD-523 (uM)
MEK-162 (uM)
Inhibition Vol=-.221(.061)
CM2=1400
E
BVD-523 (uM)
MEK-162 (uM)
Inhibition Vol=1.3(.061)
CM2=44000

FIG. 31, Con't

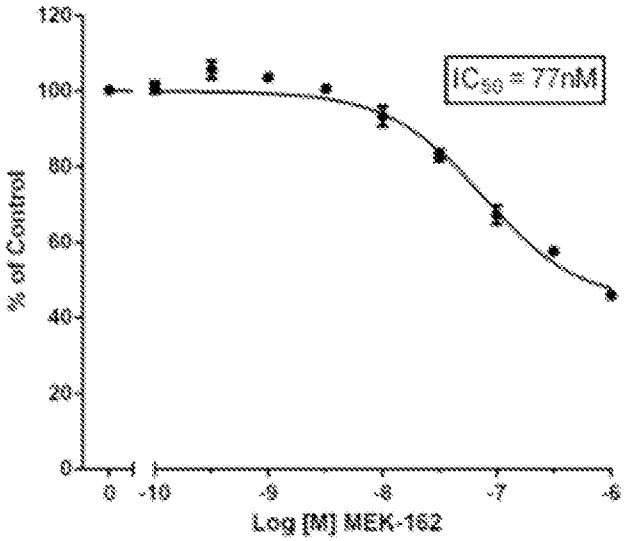
G



H



I



J

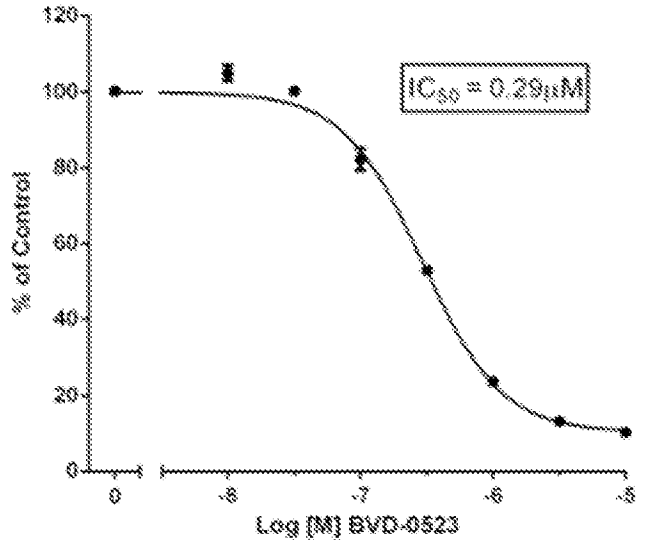


FIG. 32

A

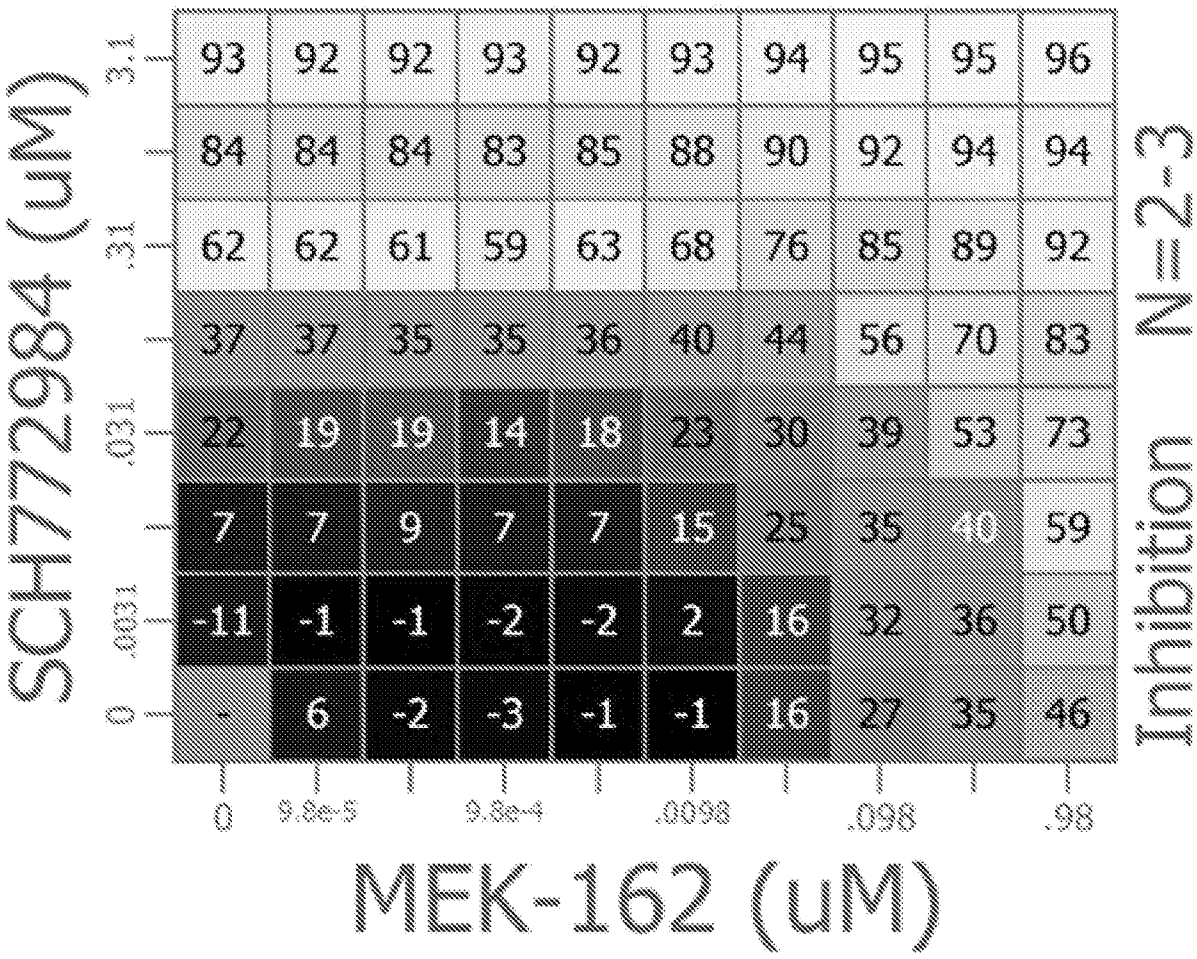

SCH772984 (uM)
3.1
.31
.031
.0031
0
93 92 92 93 92 93 94 95 95 96
84 84 84 83 85 88 90 92 94 94
62 62 61 59 63 68 76 85 89 92
37 37 35 35 36 40 44 56 70 83
22 19 19 14 18 23 30 39 53 73
7 7 9 7 7 15 25 35 40 59
-11 -1 -1 -2 -2 2 16 32 36 50
- 6 -2 -3 -1 -1 16 27 35 46
0
9.8e-5
9.8e-4
.0098
.098
.98
MEK-162 (uM)
Inhibition N=2-3

FIG. 32, Con't

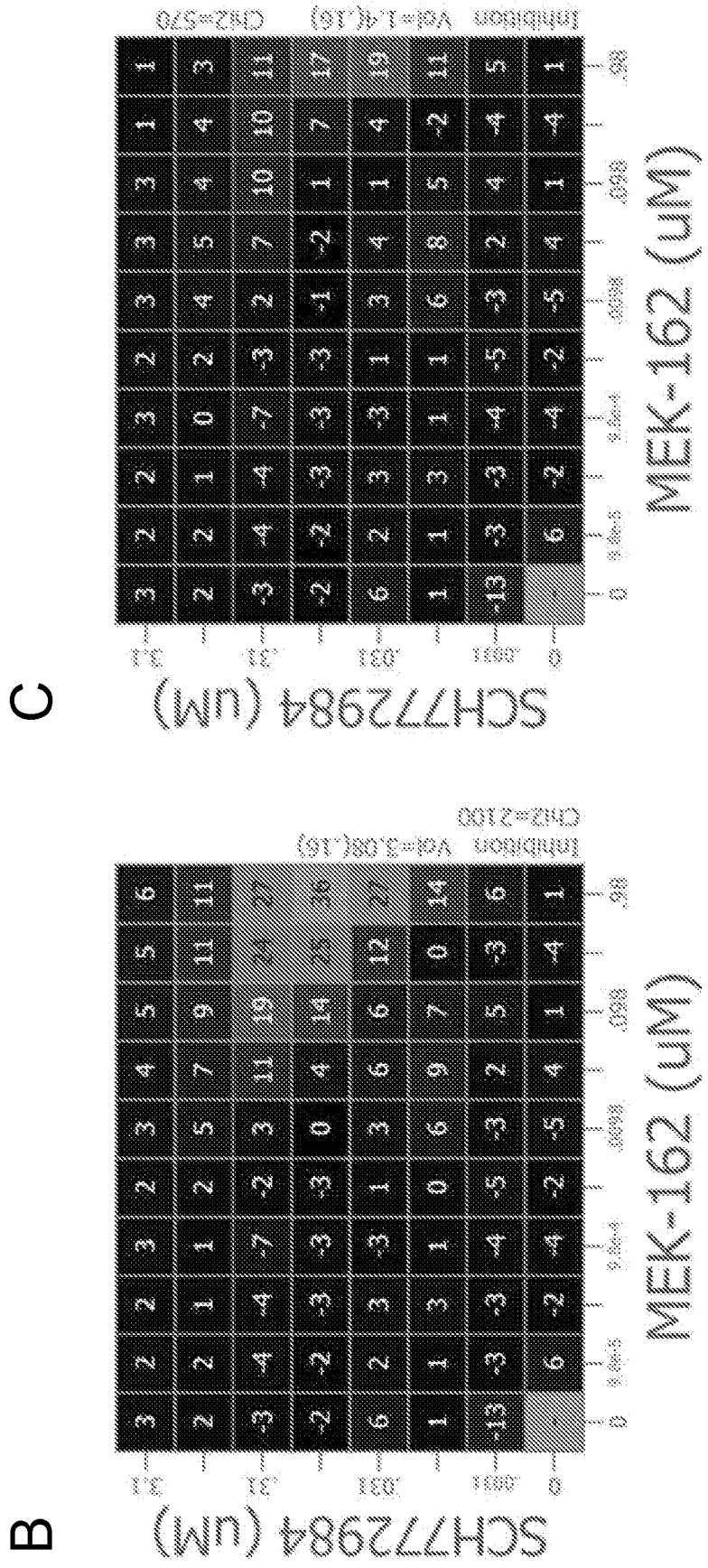

C
SCH772984 (uM)
MEK-162 (uM)
Inhibition Vol=1.4(.16) Chi2=570
B
SCH772984 (uM)
MEK-162 (uM)
Inhibition Vol=3.08(.16) Chi2=2100

FIG. 32, Con't

D

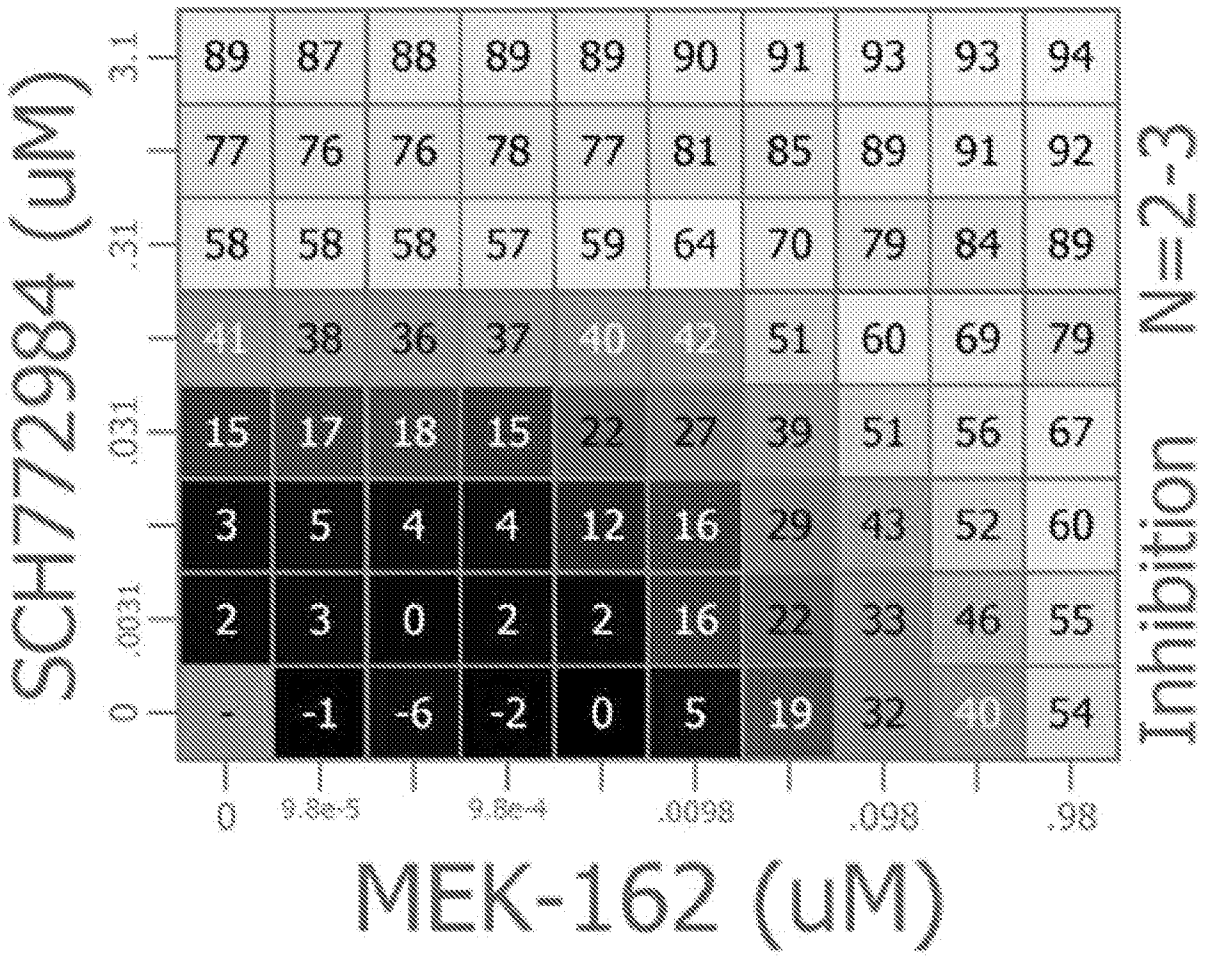
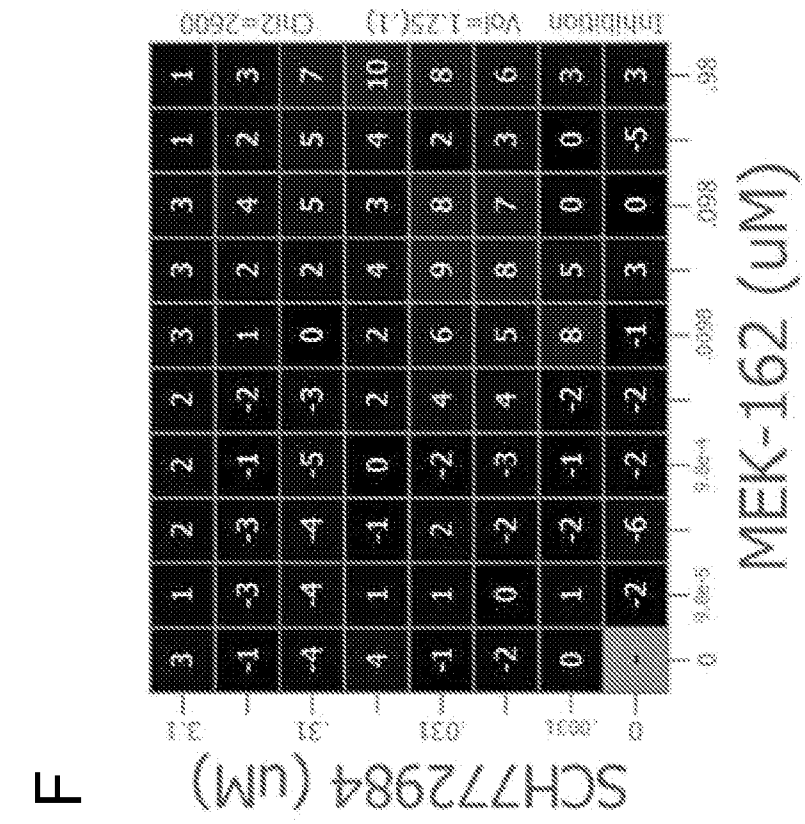

SCH772984 (uM)
3.1
.31
.031
.0031
0
89 87 88 89 89 90 91 93 93 94
77 76 76 78 77 81 85 89 91 92
58 58 58 57 59 64 70 79 84 89
41 38 36 37 40 42 51 60 69 79
15 17 18 15 22 27 39 51 56 67
3 5 4 4 12 16 29 43 52 60
2 3 0 2 2 16 22 33 46 55
- -1 -6 -2 0 5 19 32 40 54
0
9.8e-5
9.8e-4
.0098
.098
.98
MEK-162 (uM)
Inhibition N=2-3

FIG. 32, Con't


F
SCH772984 (uM)
MEK-162 (uM)
Inhibition
Vol=1.25(.1)
CN2=2600

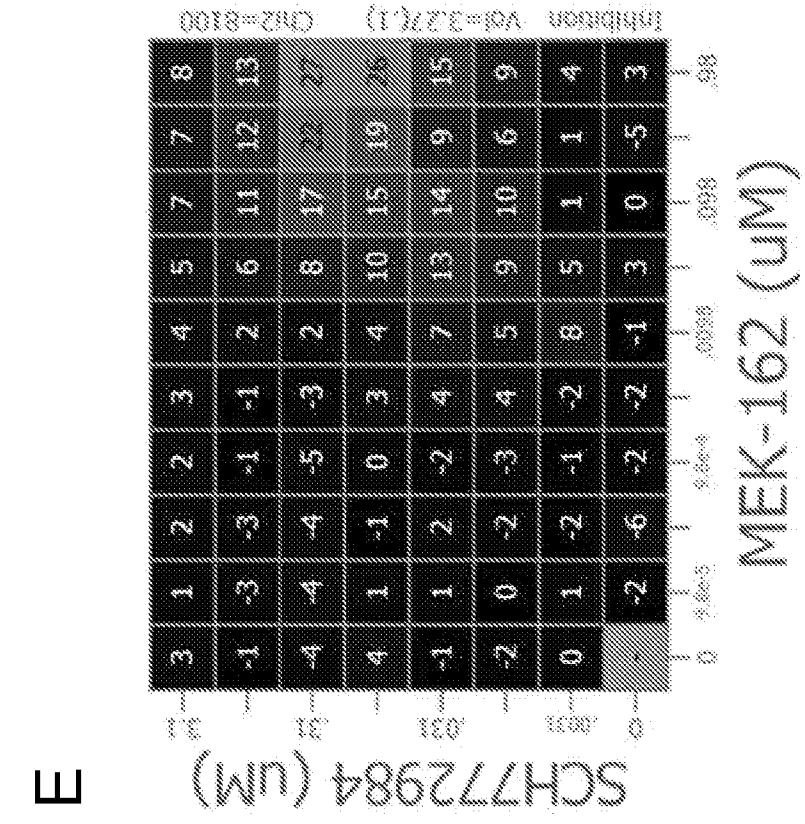
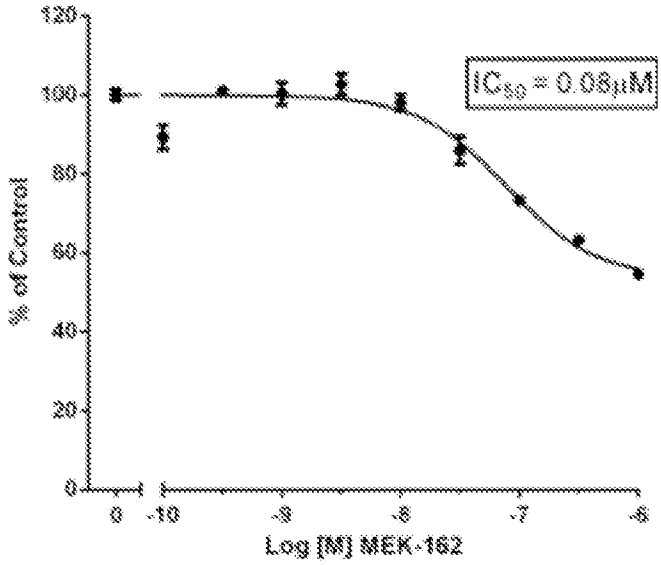
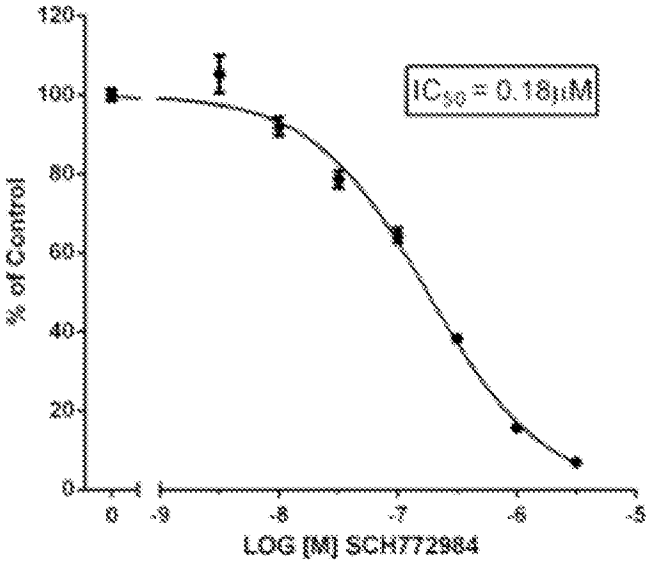

E
SCH772984 (uM)
MEK-162 (uM)
Inhibition
Vol=3.27(.1)
CN2=8100

FIG. 32, Con't

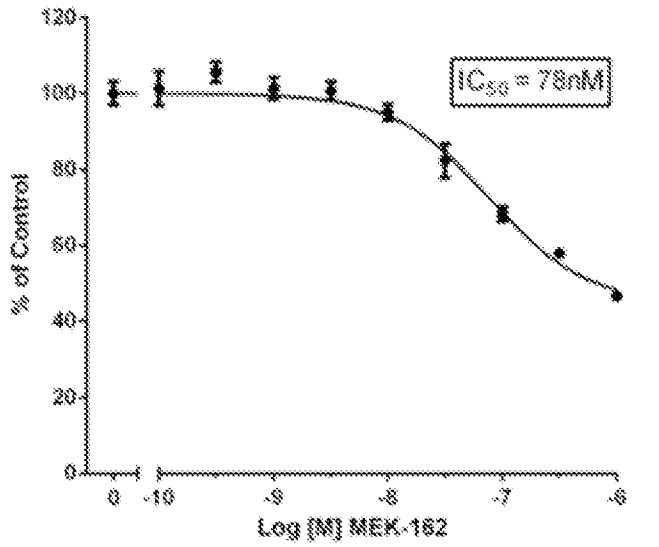
G



H



I



J

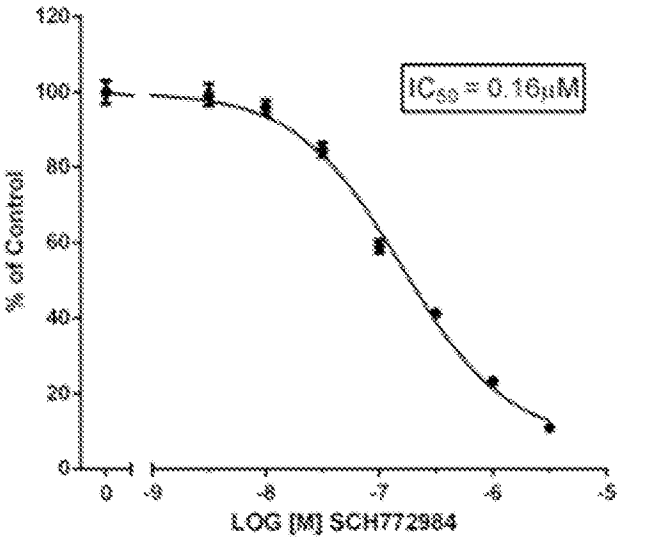


FIG. 33

A

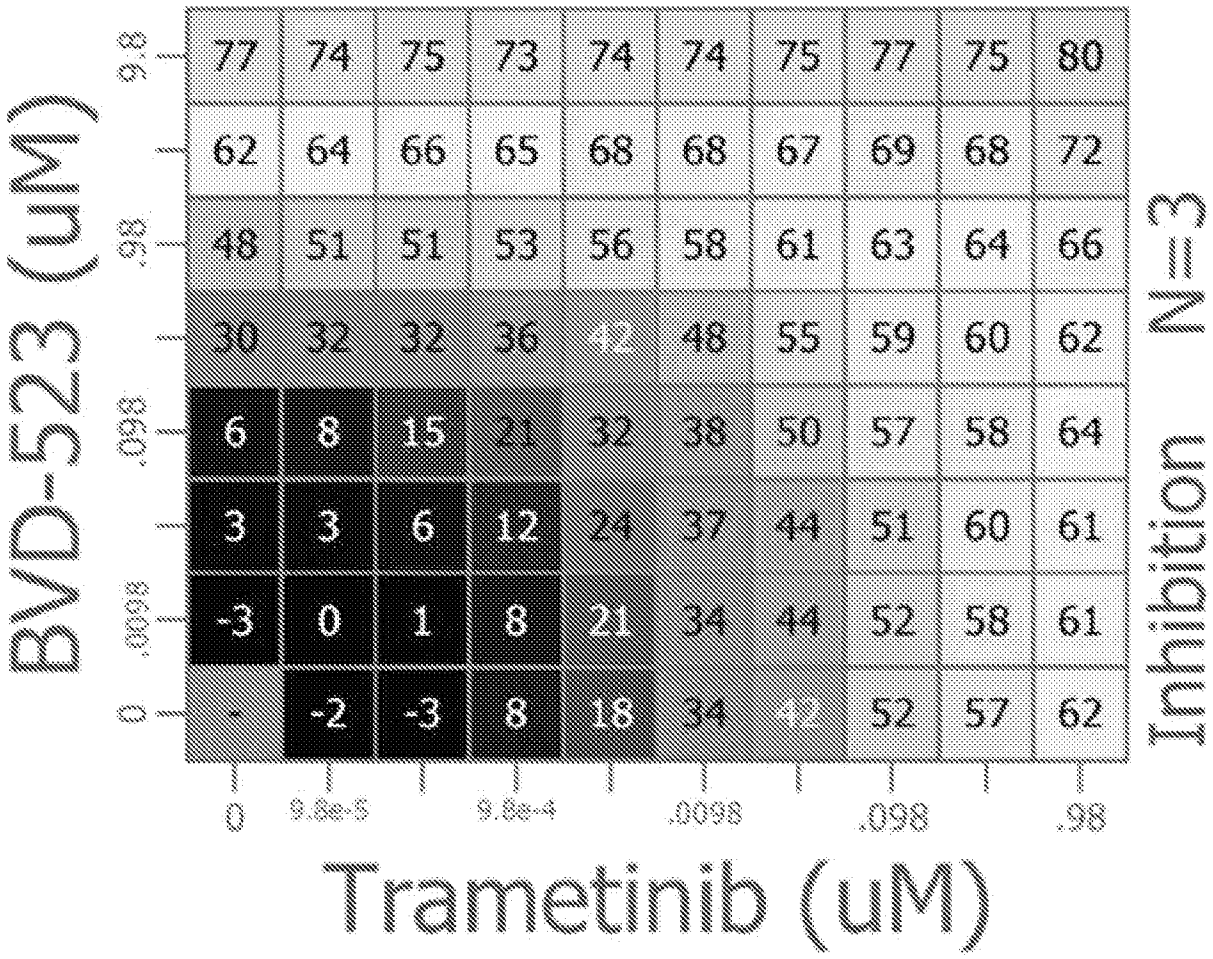

BVD-523 (uM)
9.8
.98
.098
.0098
0
77 74 75 73 74 74 75 77 75 80
62 64 66 65 68 68 67 69 68 72
48 51 51 53 56 58 61 63 64 66
30 32 32 36 42 48 55 59 60 62
6 8 15 21 32 38 50 57 58 64
3 3 6 12 24 37 44 51 60 61
-3 0 1 8 21 34 44 52 58 61
- -2 -3 8 18 34 42 52 57 62
0
9.8e-5
9.8e-4
.0098
.098
.98
Trametinib (uM)
Inhibition N = 3

FIG. 33, Con't

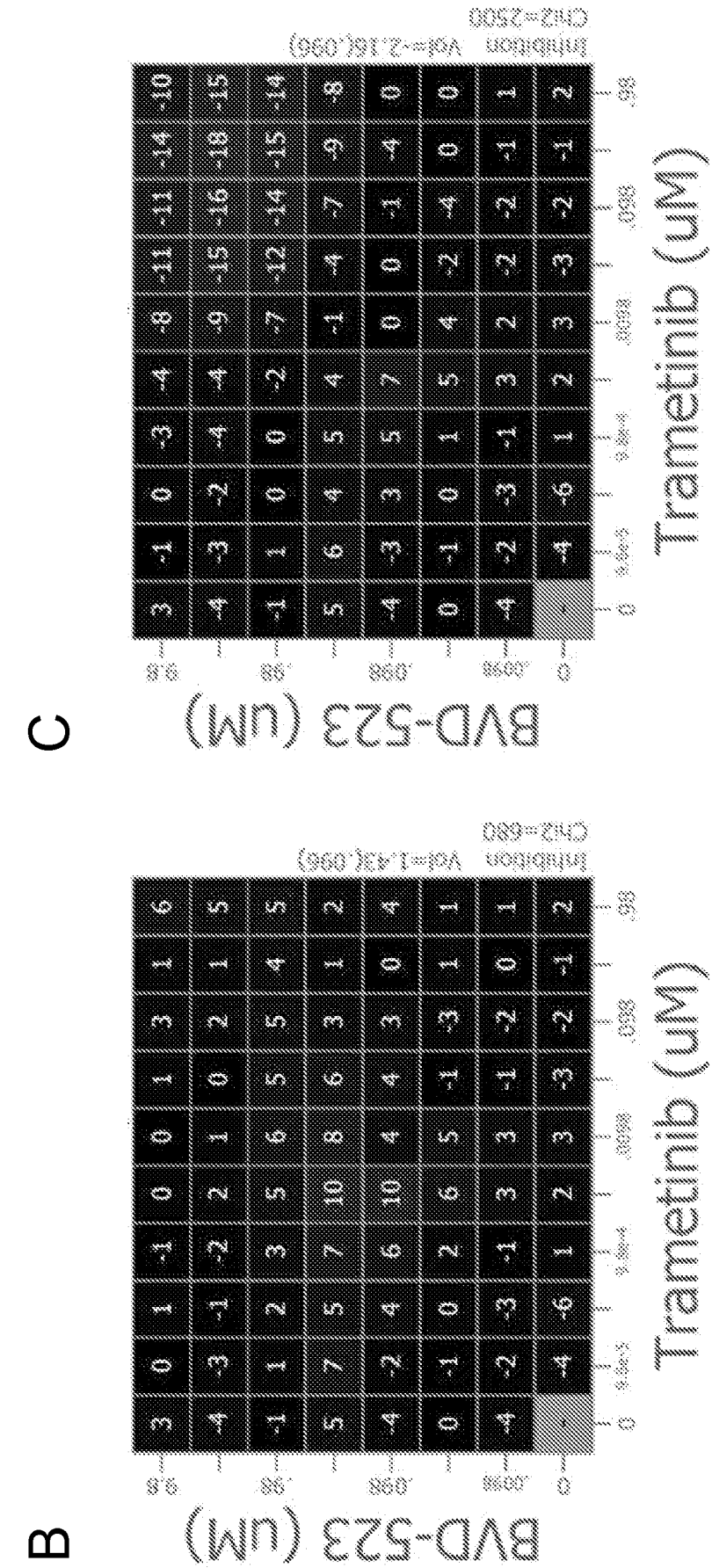

B
C
BVD-523 (uM)
Trametinib (uM)
Inhibition Vol=-1.43(.096)
CH2=680
Inhibition Vol=-2.16(.096)
CH2=2500

FIG. 33, Con't

D

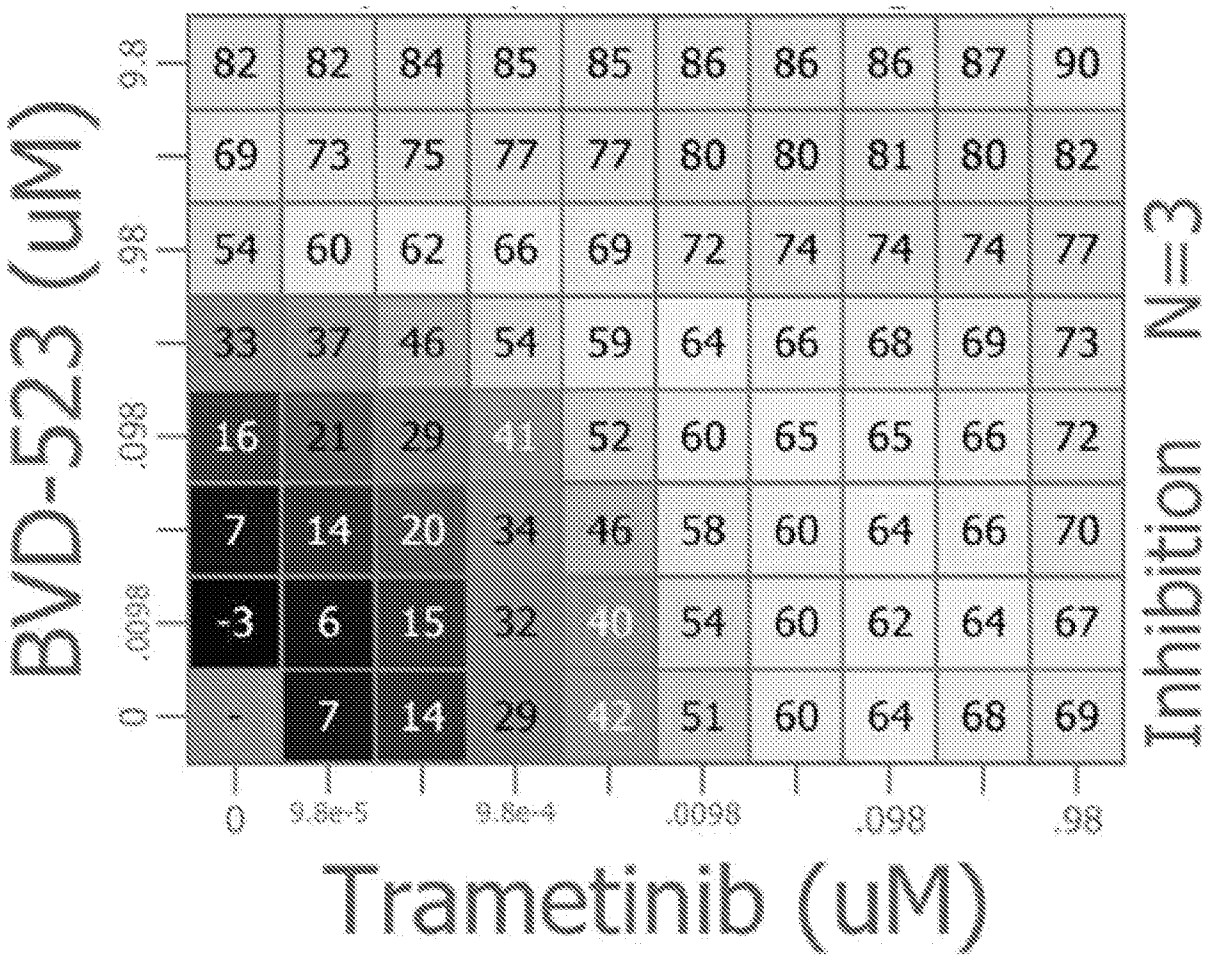
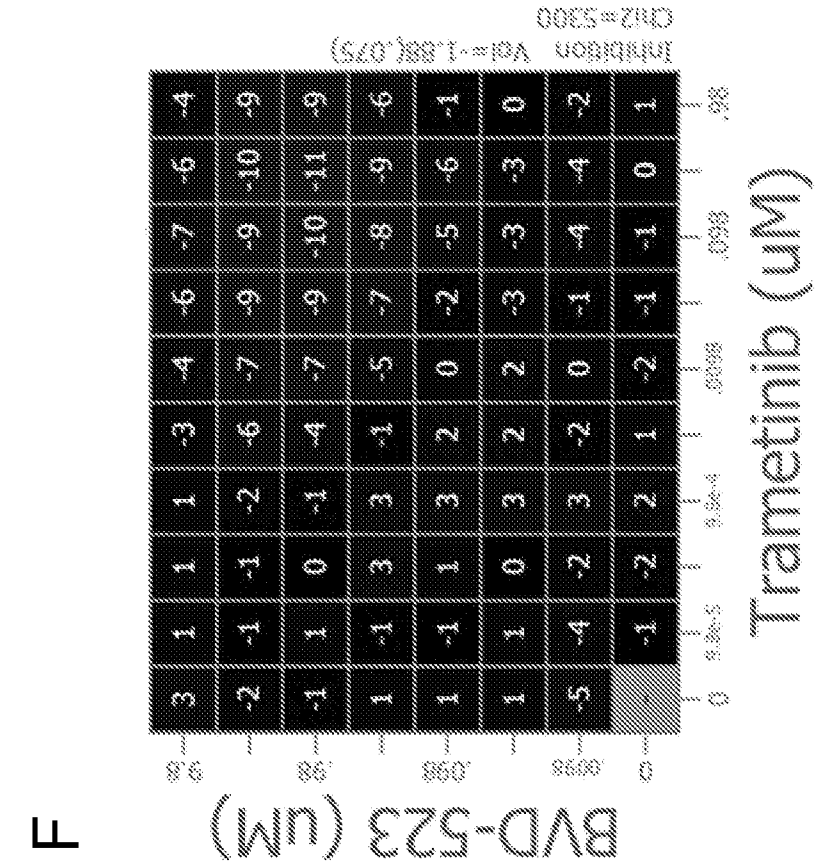

BVD-523 (uM)
9.8
.98
.098
.0098
0
82 82 84 85 85 86 86 86 87 90
69 73 75 77 77 80 80 81 80 82
54 60 62 66 69 72 74 74 74 77
33 37 46 54 59 64 66 68 69 73
16 21 29 41 52 60 65 65 66 72
7 14 20 34 46 58 60 64 66 70
-3 6 15 32 40 54 60 62 64 67
- 7 14 29 42 51 60 64 68 69
0
9.8e-5
9.8e-4
.0098
.098
.98
Trametinib (uM)
Inhibition N=3

FIG. 33, Con't


F
BVD-523 (uM)
Trametinib (uM)
Inhibition Vol=-1.88(.075)
Chl2=5300

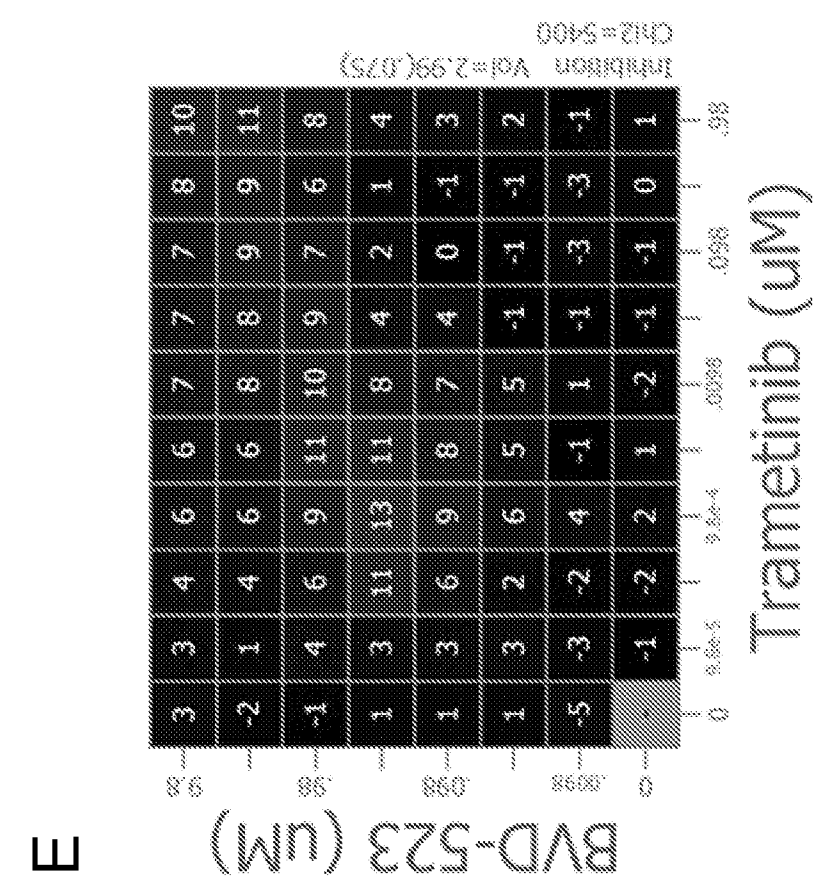
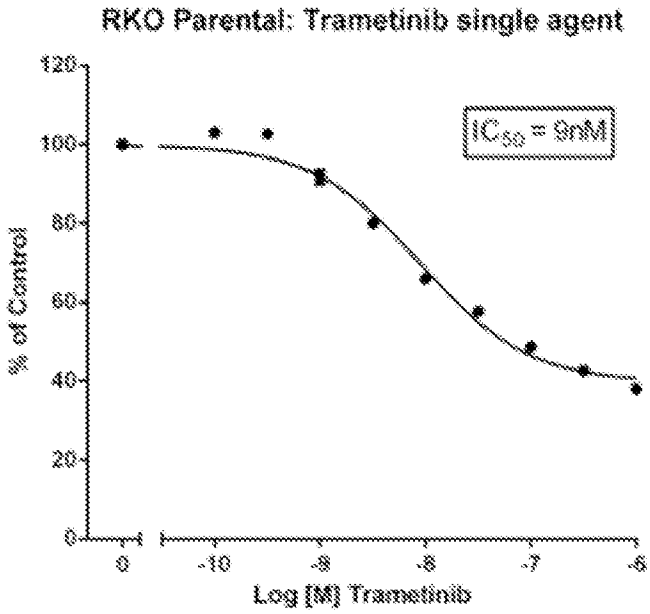
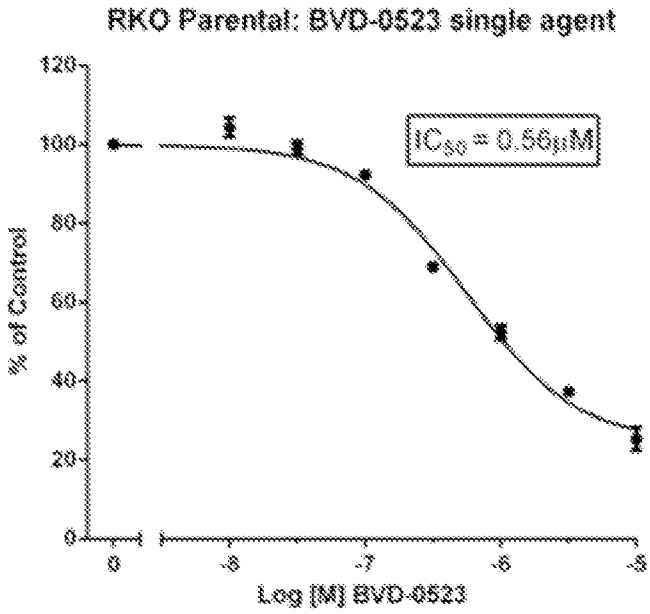

E
BVD-523 (uM)
Trametinib (uM)
Inhibition Vol=2.99(.075)
Chl2=5400

FIG. 33, Con't

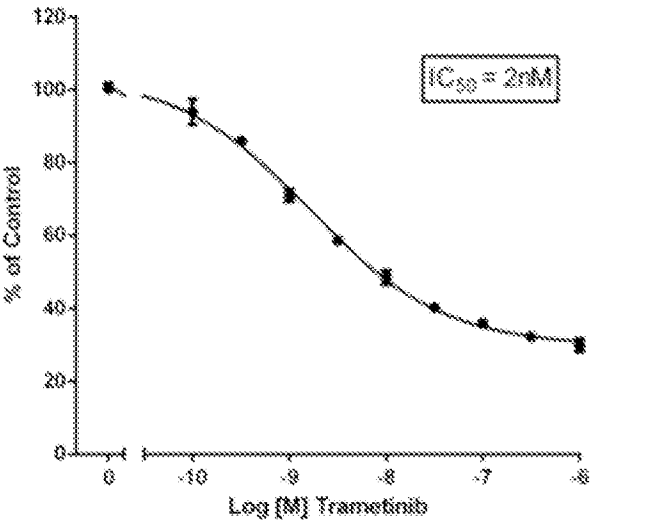
G



H



I



J

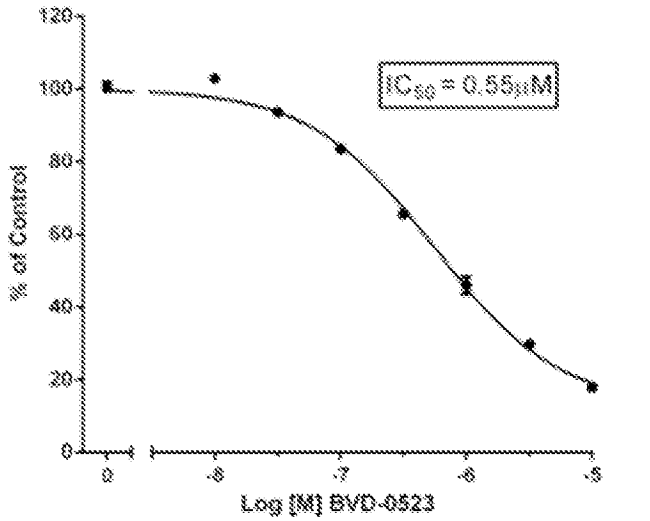


FIG. 34

A

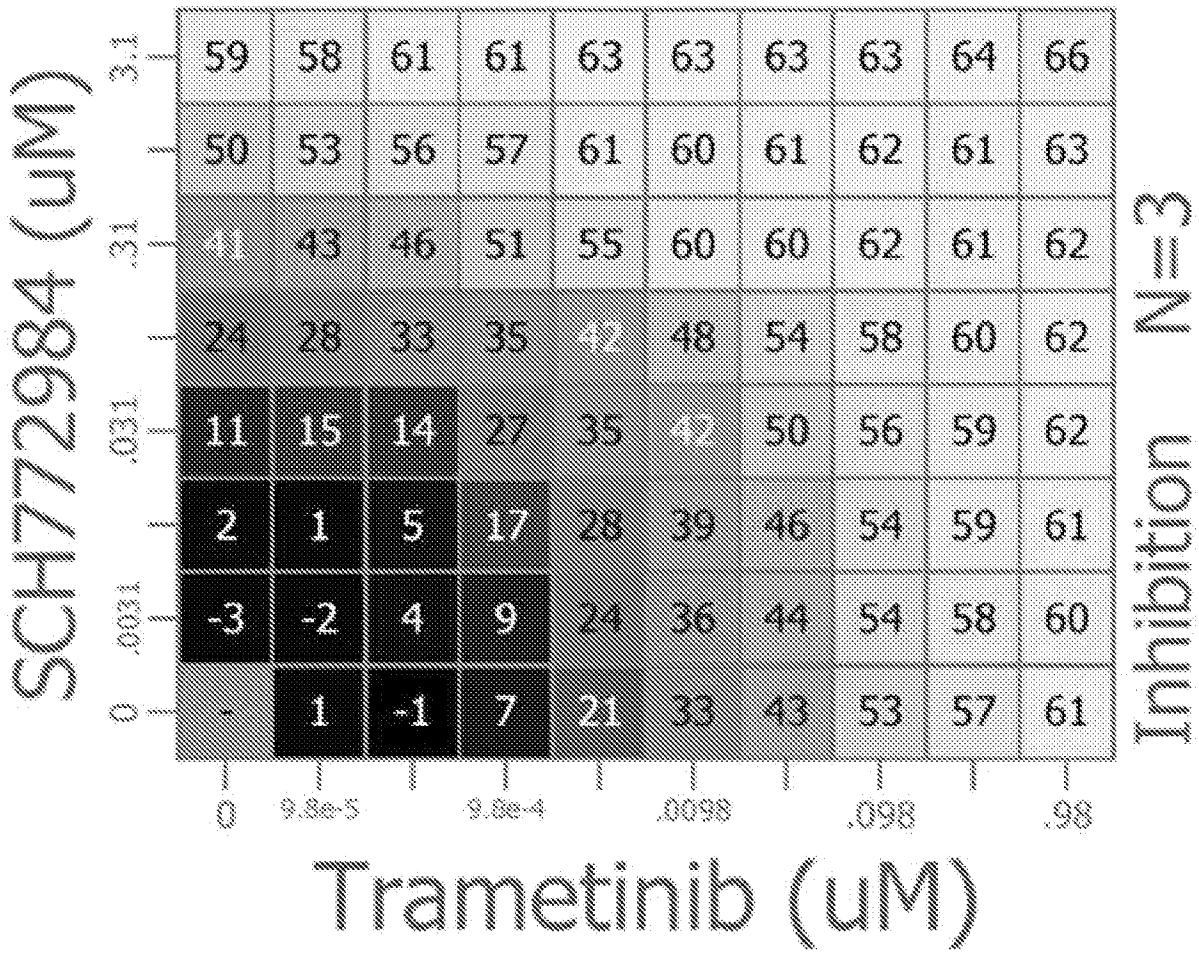

SCH772984 (uM)
3.1
.31
.031
.0031
0
59 58 61 61 63 63 63 63 64 66
50 53 56 57 61 60 61 62 61 63
41 43 46 51 55 60 60 62 61 62
24 28 33 35 42 48 54 58 60 62
11 15 14 27 35 42 50 56 59 62
2 1 5 17 28 39 46 54 59 61
-3 -2 4 9 24 36 44 54 58 60
- 1 -1 7 21 33 43 53 57 61
0
9.8e-5
9.8e-4
.0098
.098
.98
Trametinib (uM)
N=3
Inhibition

FIG. 34, Con't

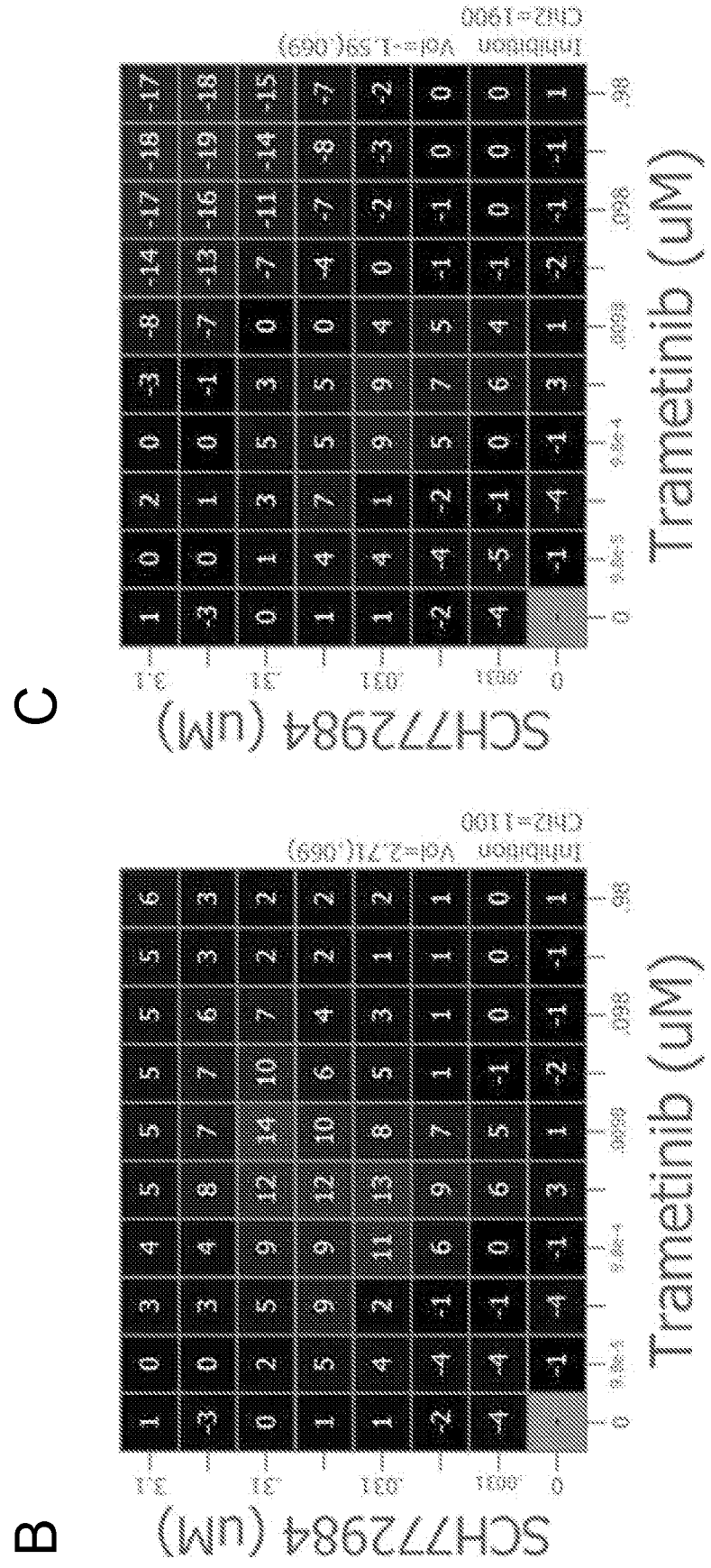

C
SCH772984 (uM)
Trametinib (uM)
Inhibition Vd=-1.59(.069)
CN2=1900
B
SCH772984 (uM)
Trametinib (uM)
Inhibition Vd=-2.71(.069)
CN2=1100

FIG. 34, Con't

D

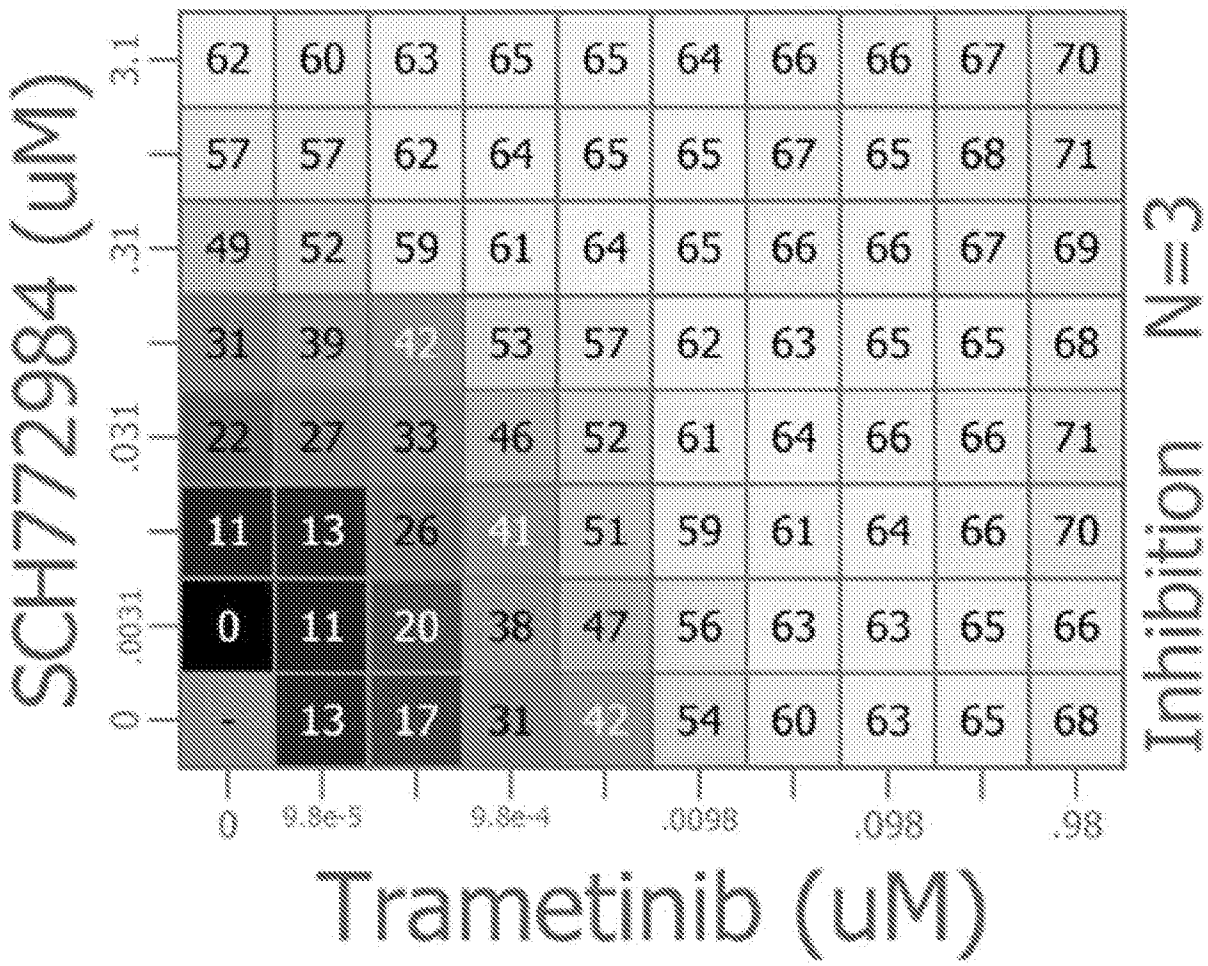

SCH772984 (uM)
3.1
.31
.031
.0031
0
62 60 63 65 65 64 66 66 67 70
57 57 62 64 65 65 67 65 68 71
49 52 59 61 64 65 66 66 67 69
31 39 48 53 57 62 63 65 65 68
22 27 33 46 52 61 64 66 66 71
11 13 26 41 51 59 61 64 66 70
0 11 20 38 47 56 63 63 65 66
- 13 17 31 42 54 60 63 65 68
0
9.8e-5
9.8e-4
.0098
.098
.98
Trametinib (uM)
Inhibition N=3

FIG. 34, Con't

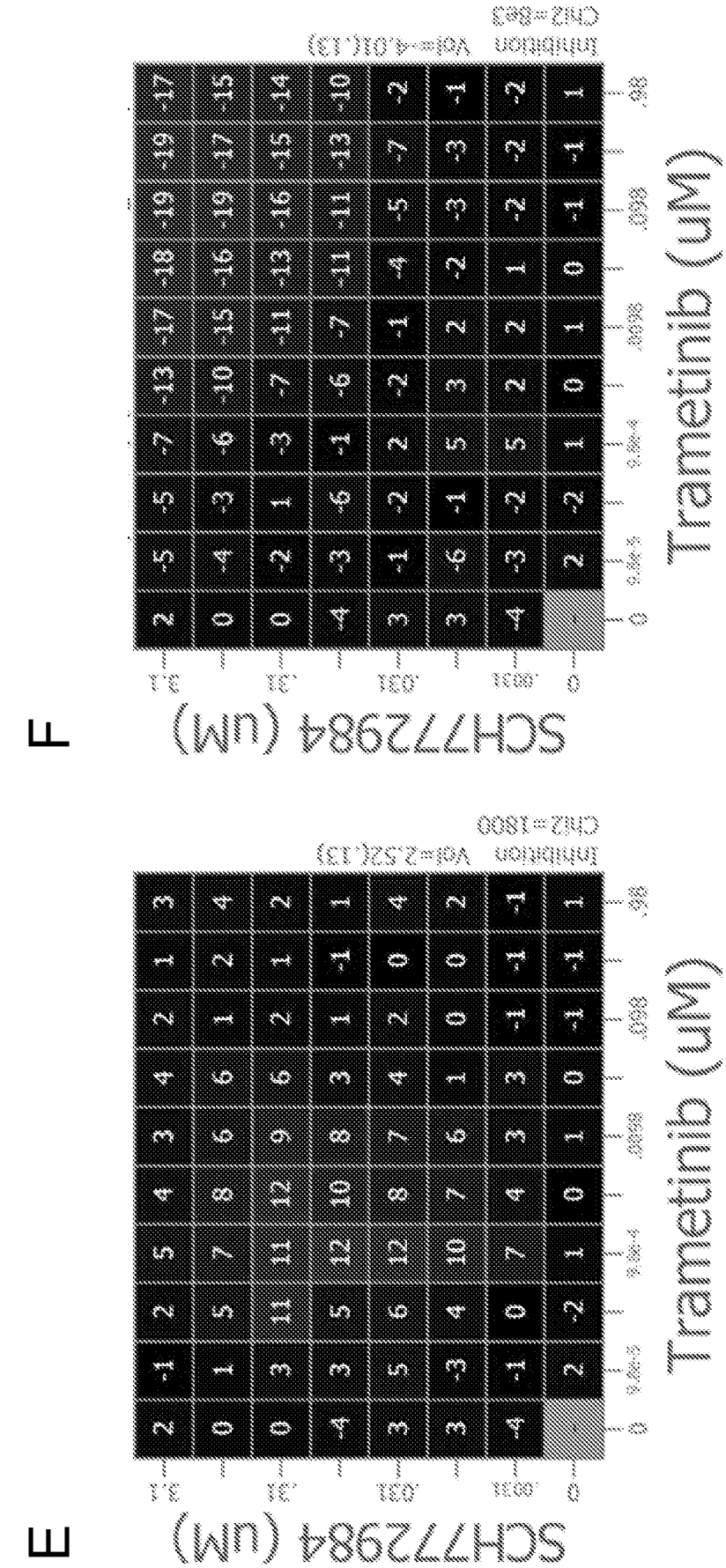
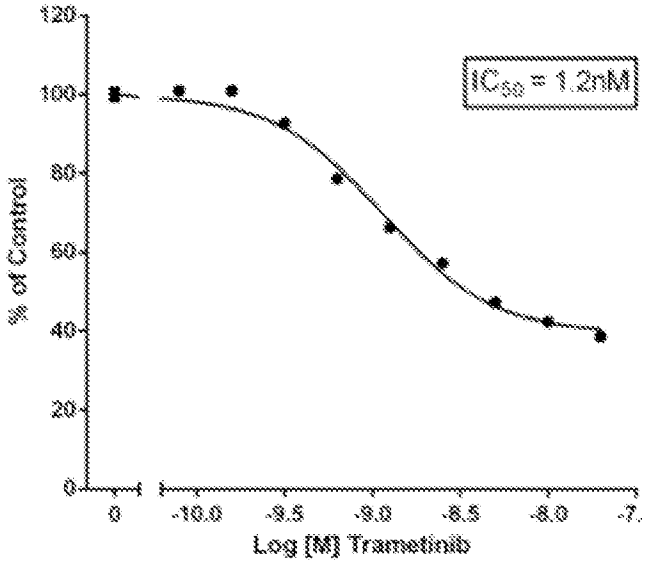
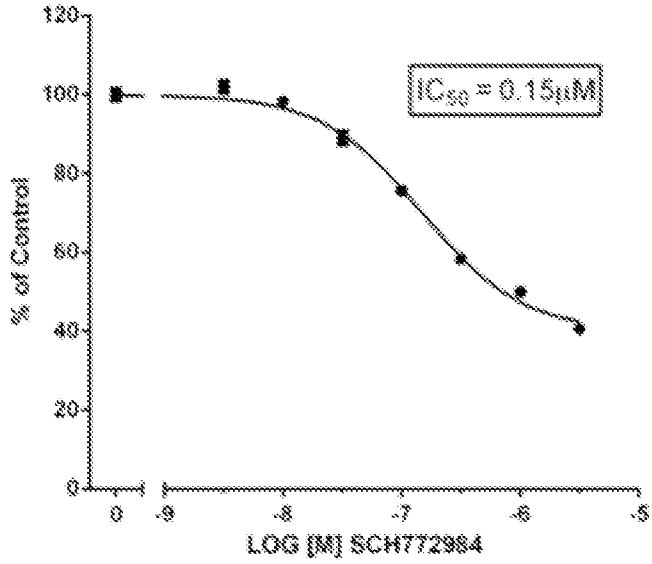

F
SCH772984 (uM)
Trametinib (uM)
Inhibition Vol=-4.01(.13)
Ch2=863
E
SCH772984 (uM)
Trametinib (uM)
Inhibition Vol=2.52(.13)
Ch2=1800

FIG. 34, Con't

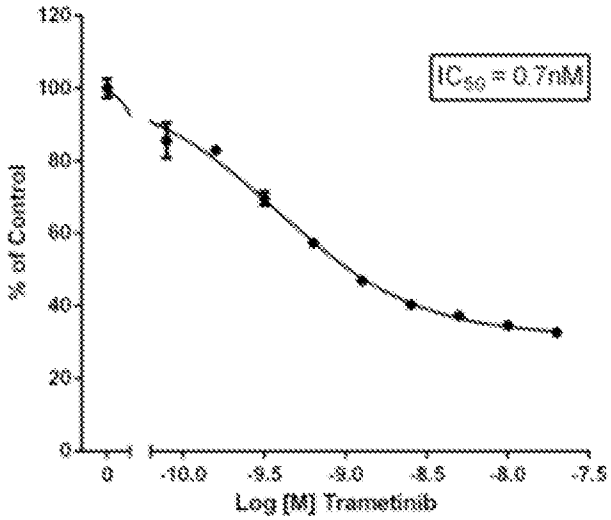
G



H



I



J

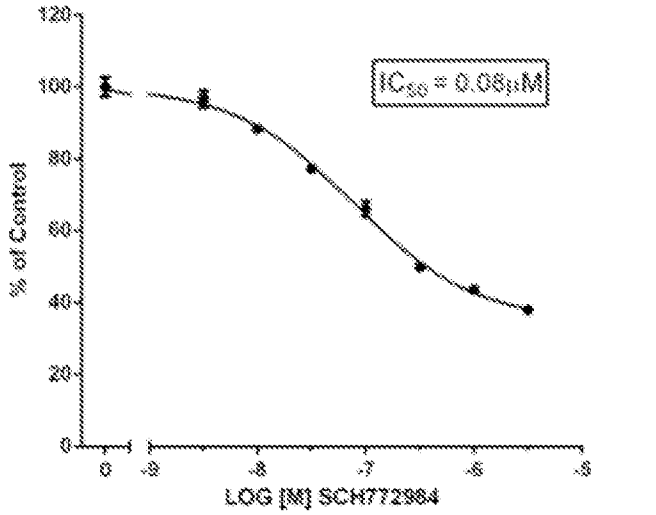


FIG. 35

A

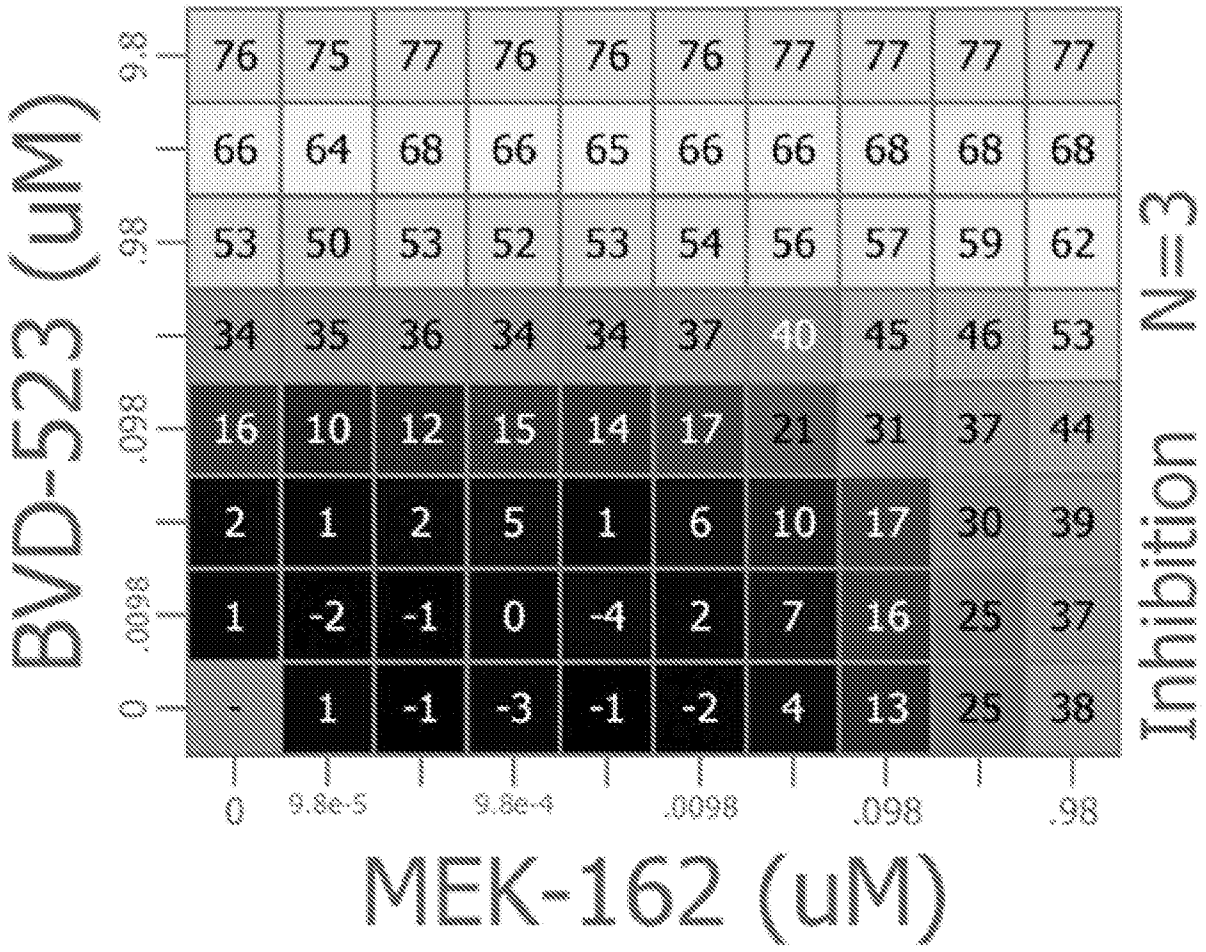

BVD-523 (uM)
.98
.098
.0098
0
76 75 77 76 76 76 77 77 77 77
66 64 68 66 65 66 66 68 68 68
53 50 53 52 53 54 56 57 59 62
34 35 36 34 34 37 40 45 46 53
16 10 12 15 14 17 21 31 37 44
2 1 2 5 1 6 10 17 30 39
1 -2 -1 0 -4 2 7 16 25 37
- 1 -1 -3 -1 -2 4 13 25 38
Inhibition N=3
0
9.8e-5
9.8e-4
.0098
.098
.98
MEK-162 (uM)

FIG. 35, Con't

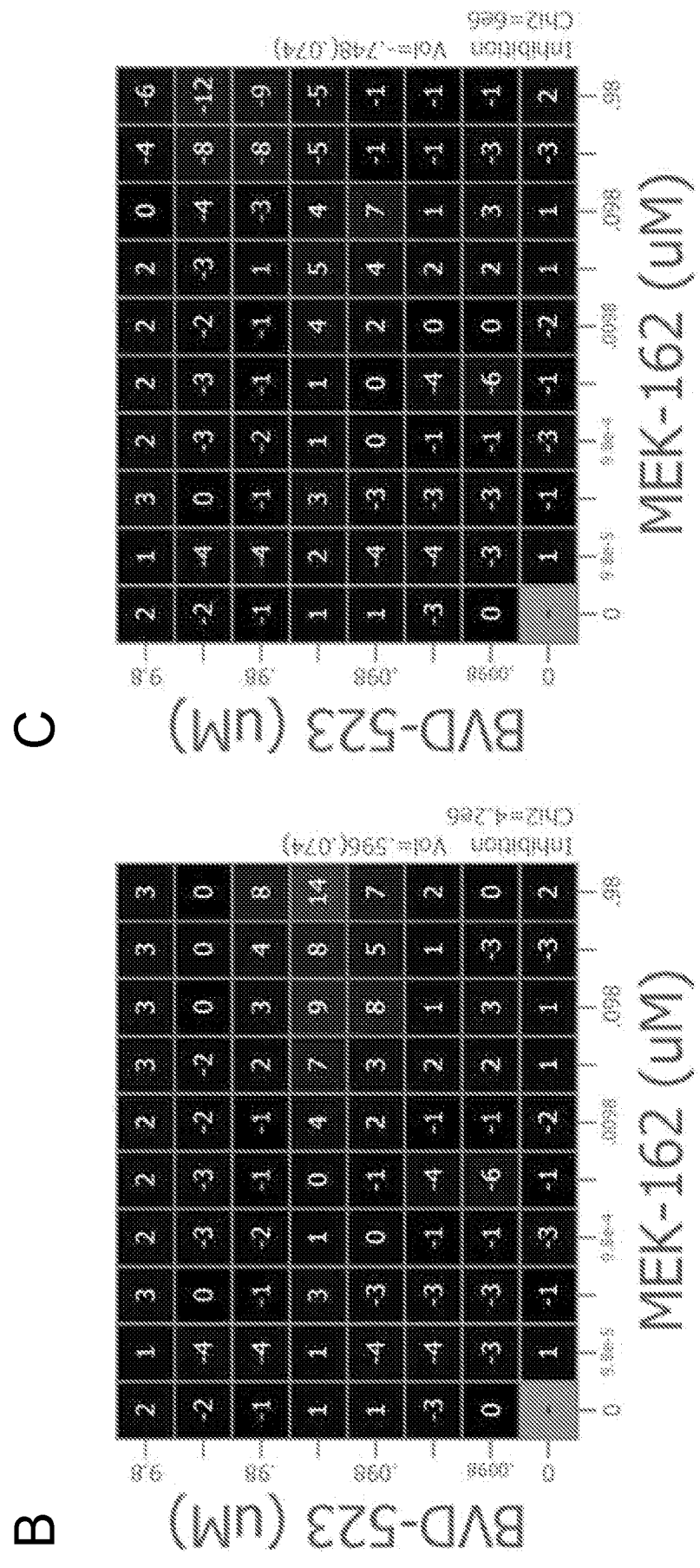

C
B
BVD-523 (uM)
MEK-162 (uM)
Inhibition Vol=-.748(.074)
Chi2=6.65
Inhibition Vol=-.598(.074)
Chi2=4.266

FIG. 35, Con't

D

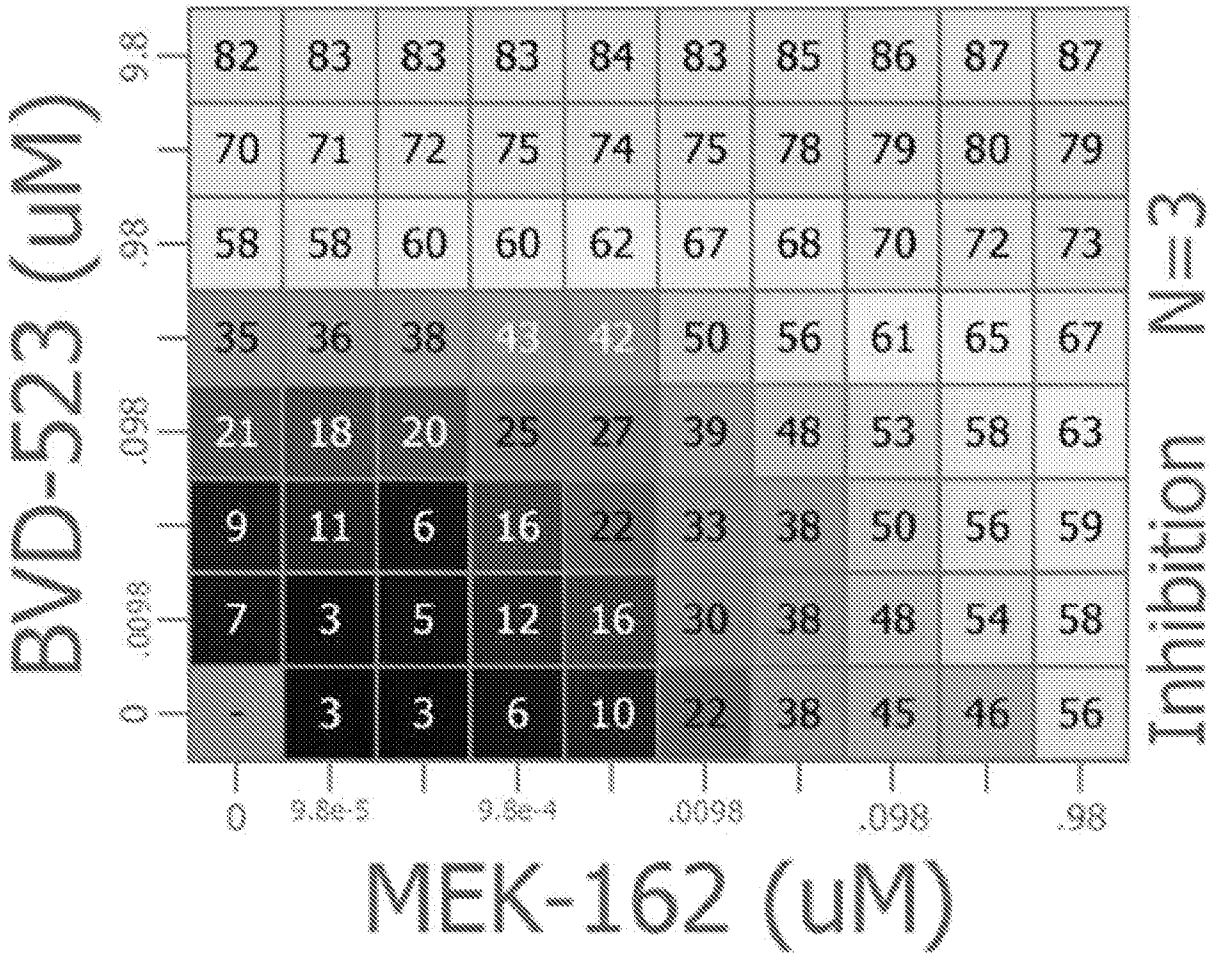
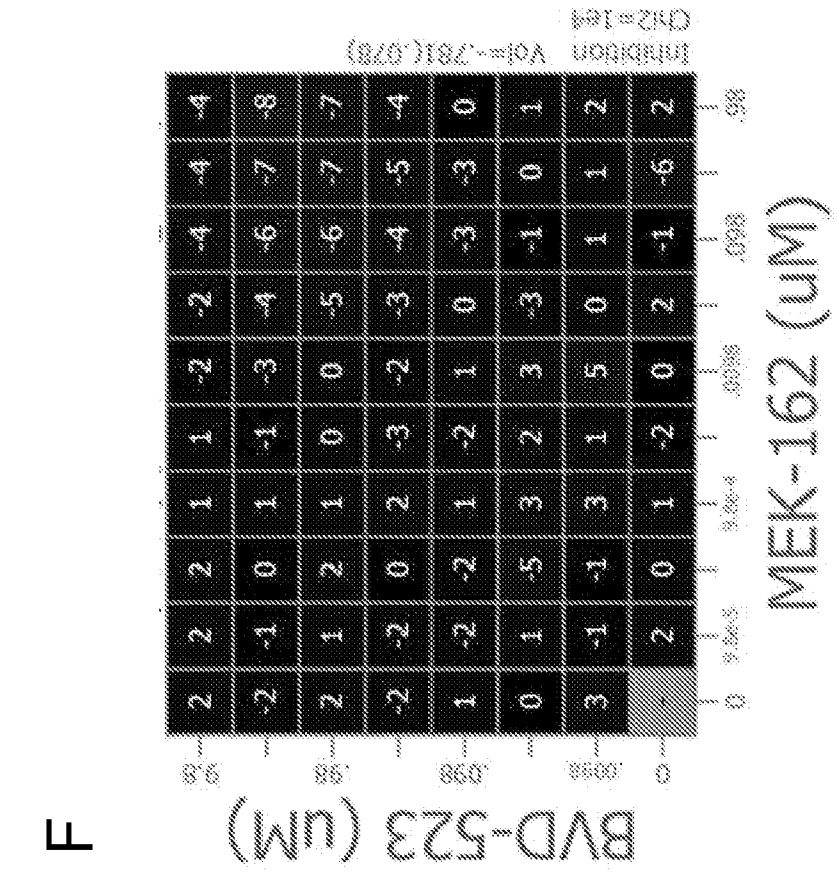

BVD-523 (uM)
9.8
.98
.098
.0098
0
82 83 83 83 84 83 85 86 87 87
70 71 72 75 74 75 78 79 80 79
58 58 60 60 62 67 68 70 72 73
35 36 38 43 42 50 56 61 65 67
21 18 20 25 27 39 48 53 58 63
9 11 6 16 22 33 38 50 56 59
7 3 5 12 16 30 38 48 54 58
- 3 3 6 10 22 38 45 46 56
0
9.8e-5
9.8e-4
.0098
.098
.98
MEK-162 (uM)
Inhibition N = 3

FIG. 35, Con't


F
BVD-523 (uM)
MEK-162 (uM)
InhibCon Val=-.781(.078)
Cn2=1e4

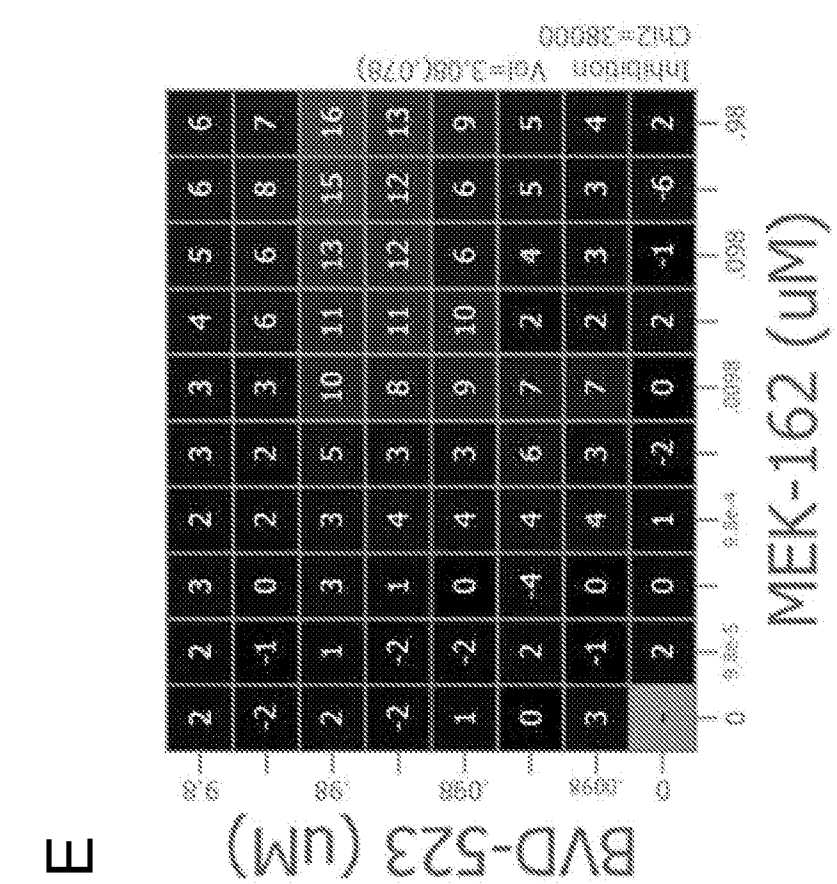
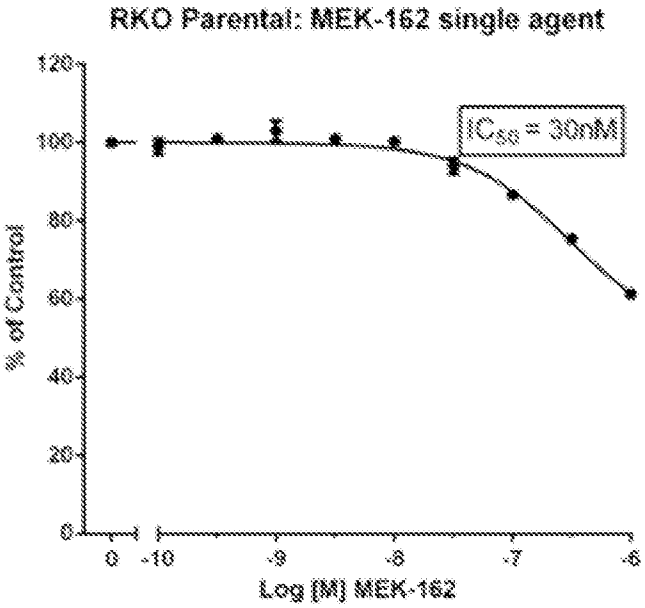
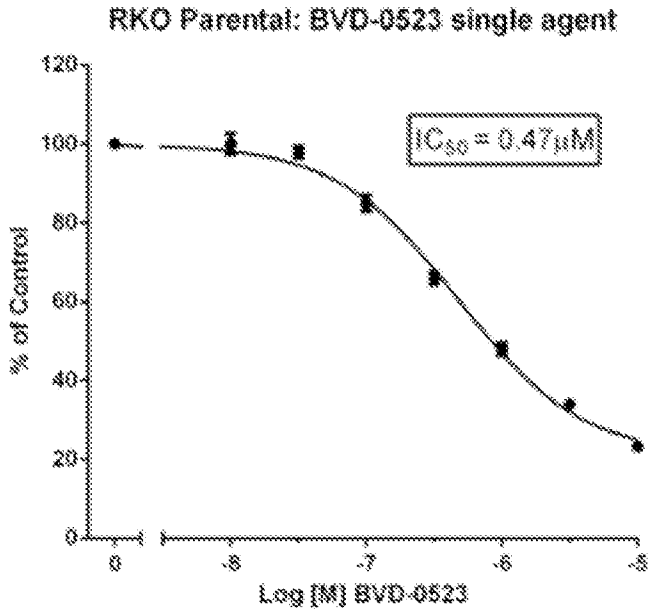

E
BVD-523 (uM)
MEK-162 (uM)
InhibCon Val=3.08(.078)
Cn2=38000

FIG. 35, Con't

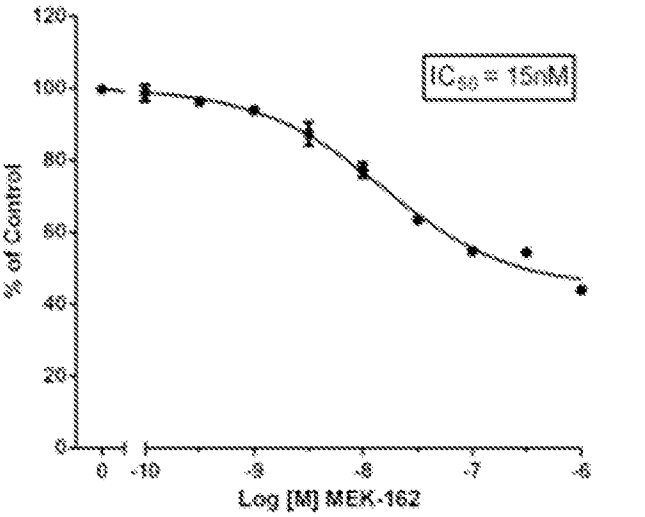
G



H



I



J

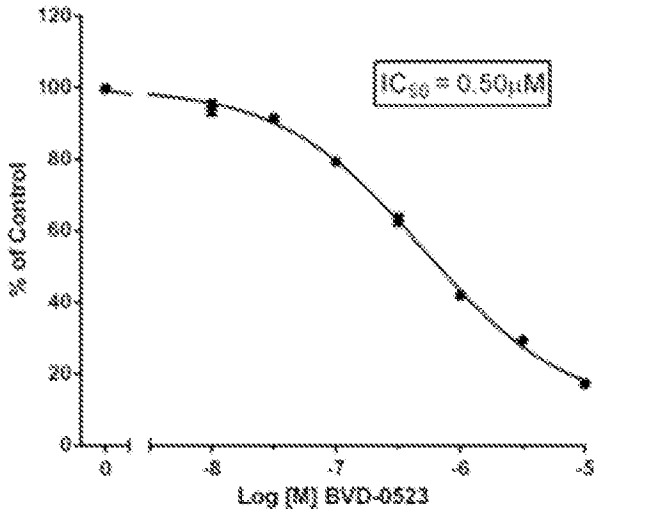


FIG. 36

A

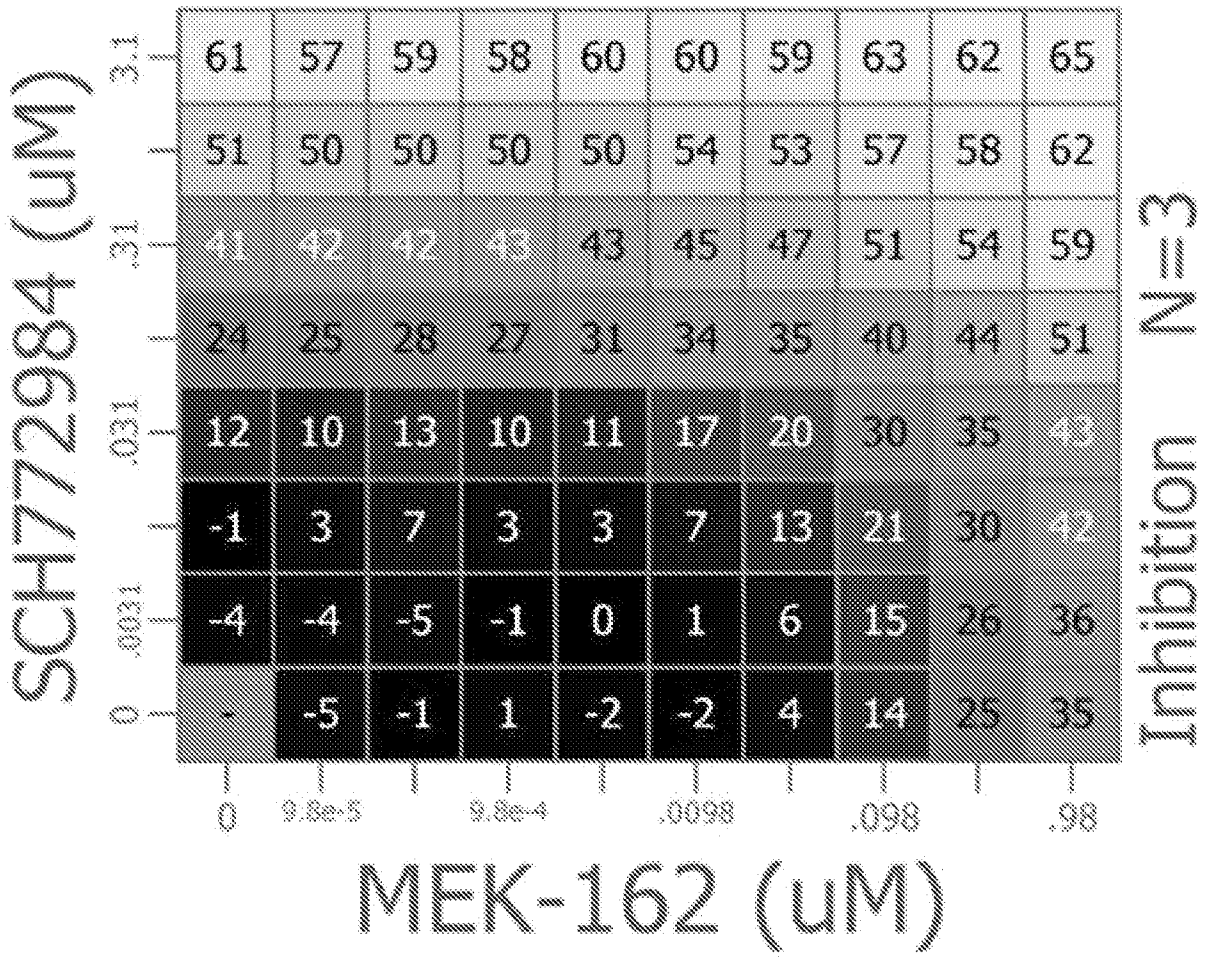

SCH772984 (uM)
3.1
.31
.031
.0031
0
61 57 59 58 60 60 59 63 62 65
51 50 50 50 50 54 53 57 58 62
41 42 42 43 43 45 47 51 54 59
24 25 28 27 31 34 35 40 44 51
12 10 13 10 11 17 20 30 35 43
-1 3 7 3 3 7 13 21 30 42
-4 -4 -5 -1 0 1 6 15 26 36
- -5 -1 1 -2 -2 4 14 25 35
0
9.8e-5
9.8e-4
.0098
.098
.98
MEK-162 (uM)
Inhibition N=3

FIG. 36, Con't

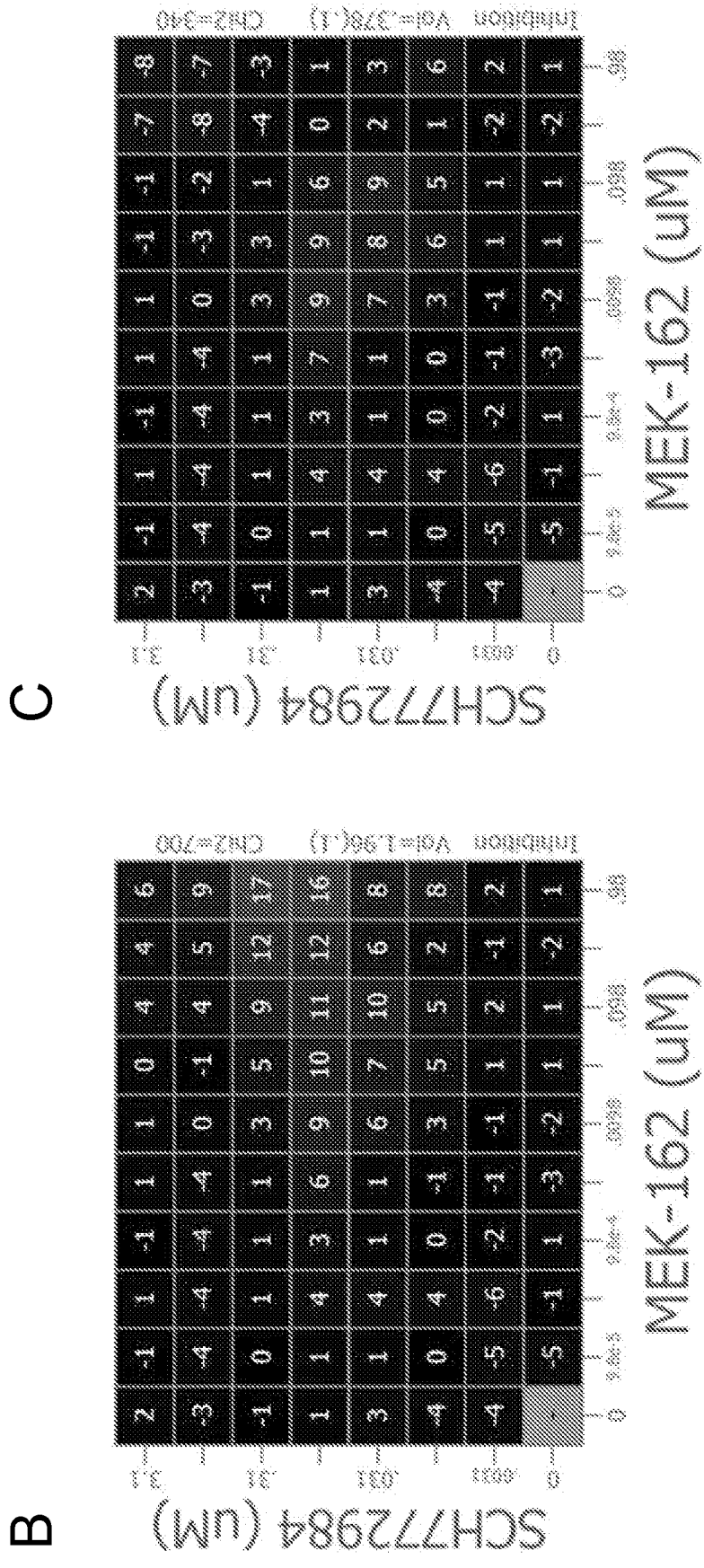

B
SCH772984 (uM)
MEK-162 (uM)
Inhibition Val=1.96(.1) CH2=700
C
SCH772984 (uM)
MEK-162 (uM)
Inhibition Val=.378(.1) CH2=340

FIG. 36, Con't

D

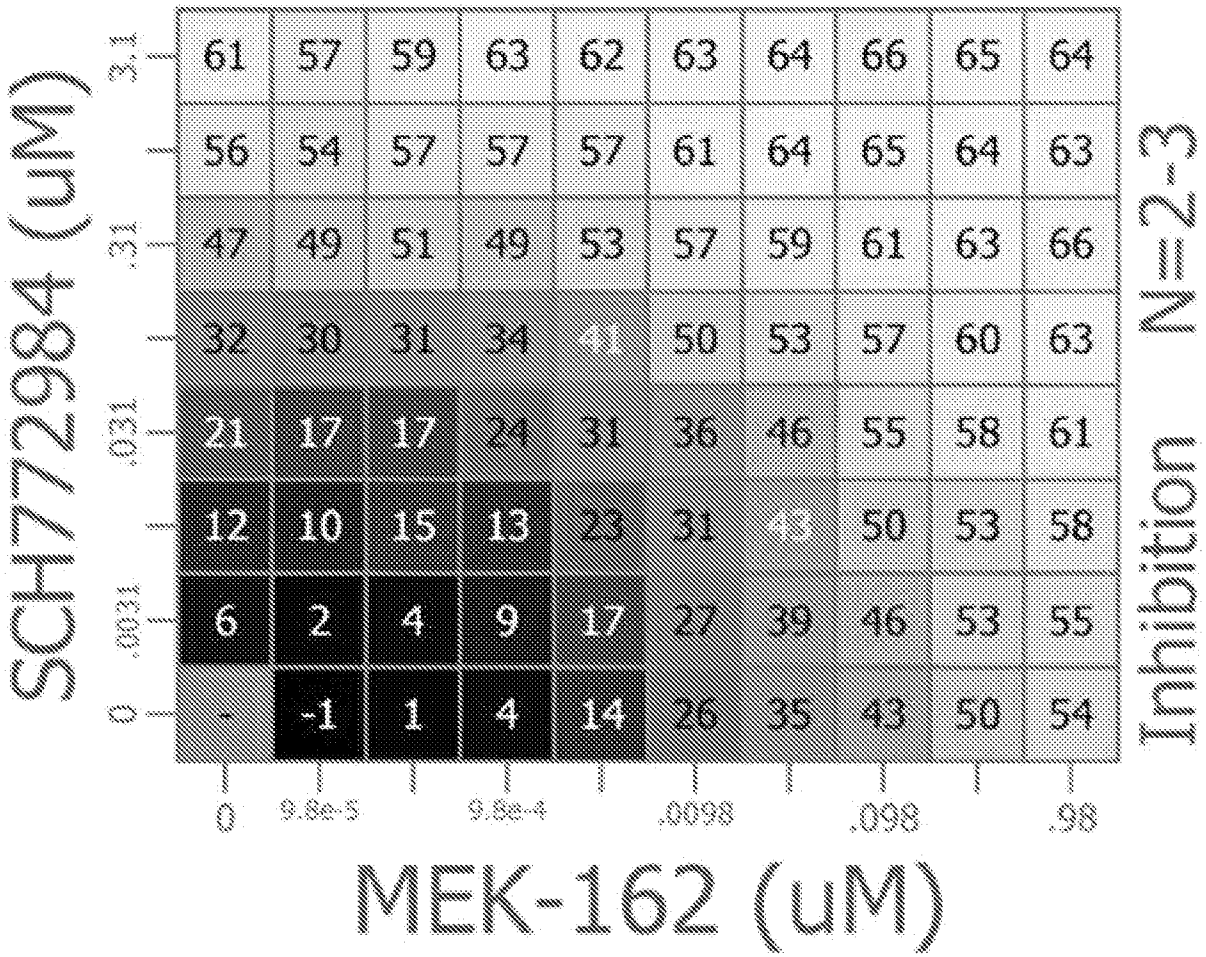
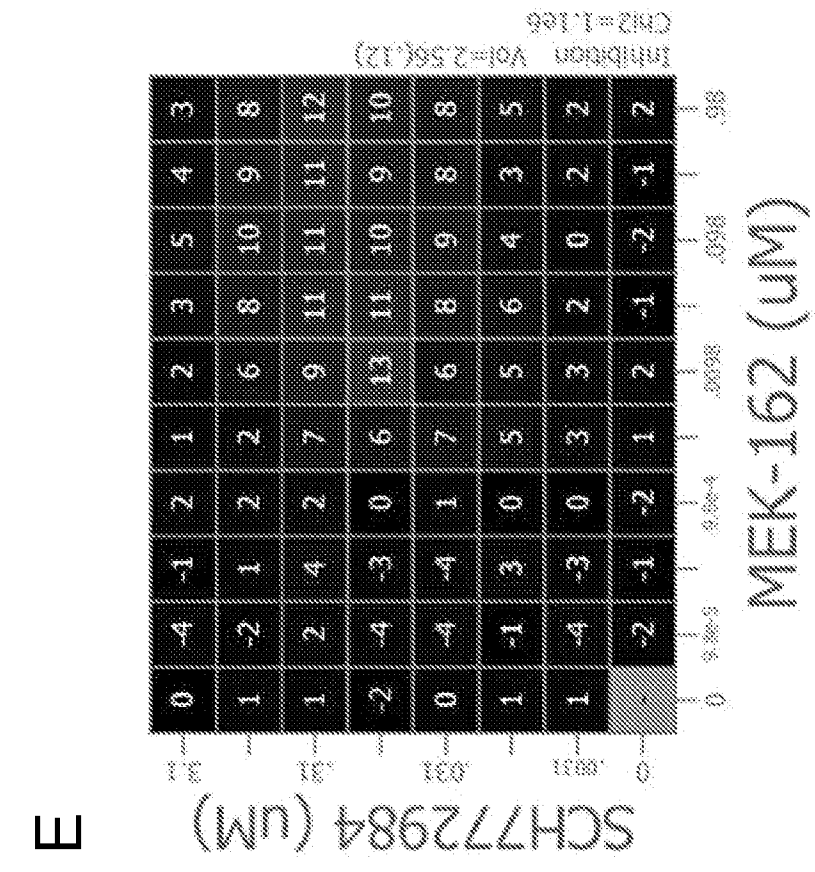

SCH772984 (uM)
3.1
.31
.031
.0031
0
61 57 59 63 62 63 64 66 65 64
56 54 57 57 57 61 64 65 64 63
47 49 51 49 53 57 59 61 63 66
32 30 31 34 41 50 53 57 60 63
21 17 17 24 31 36 46 55 58 61
12 10 15 13 23 31 43 50 53 58
6 2 4 9 17 27 39 46 53 55
- -1 1 4 14 26 35 43 50 54
0
9.8e-5
9.8e-4
.0098
.098
.98
MEK-162 (uM)
Inhibition N=2-3

FIG. 36, Con't


E
SCH772984 (uM)
MEK-162 (uM)
Inhibition Vol=-2.56(.12)
CM2=1.166

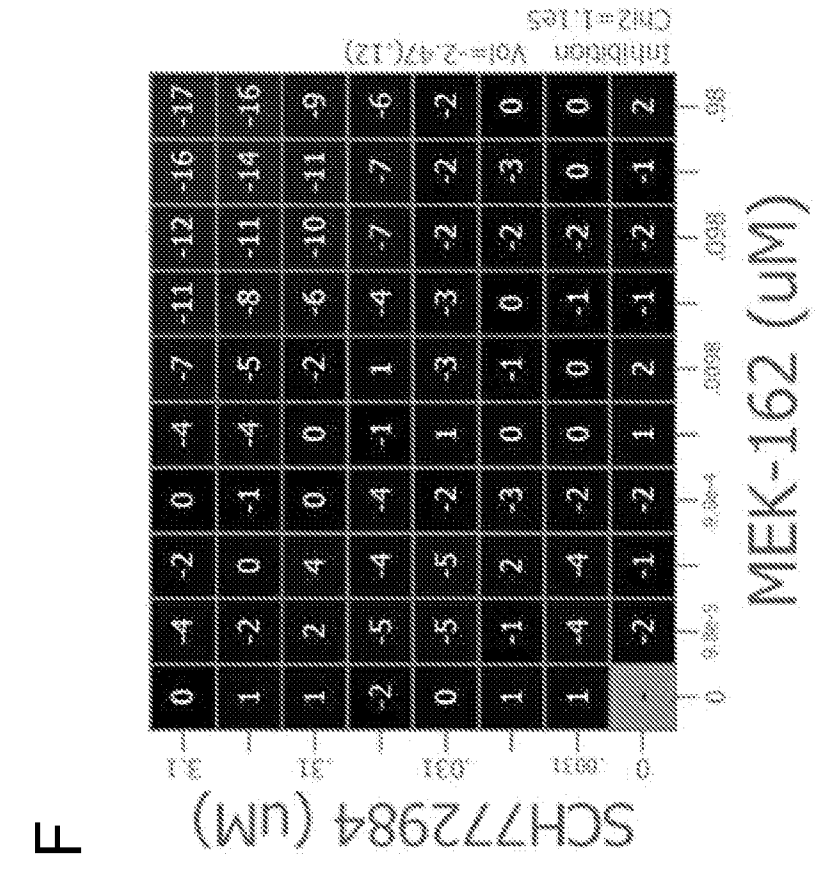
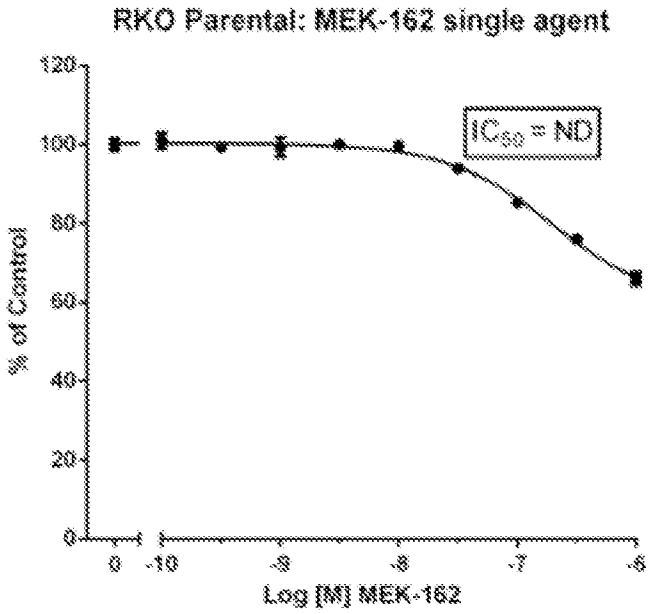
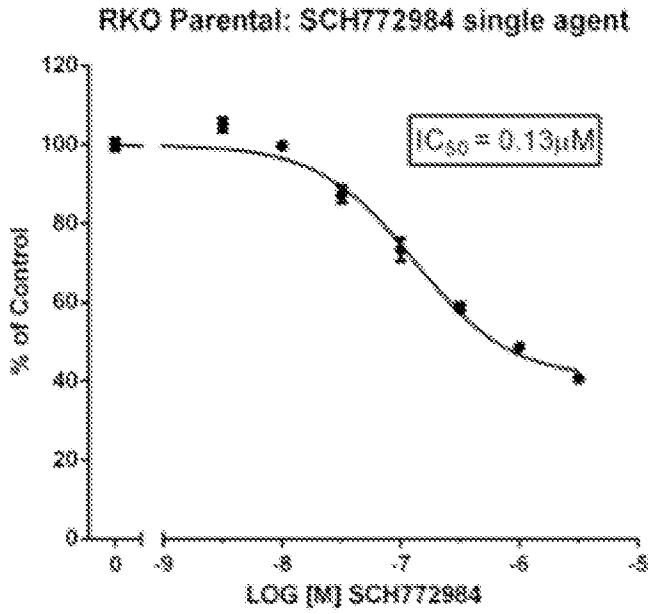

F
SCH772984 (uM)
MEK-162 (uM)
Inhibition Vol=-2.47(.12)
CM2=1.165

FIG. 36, Con't

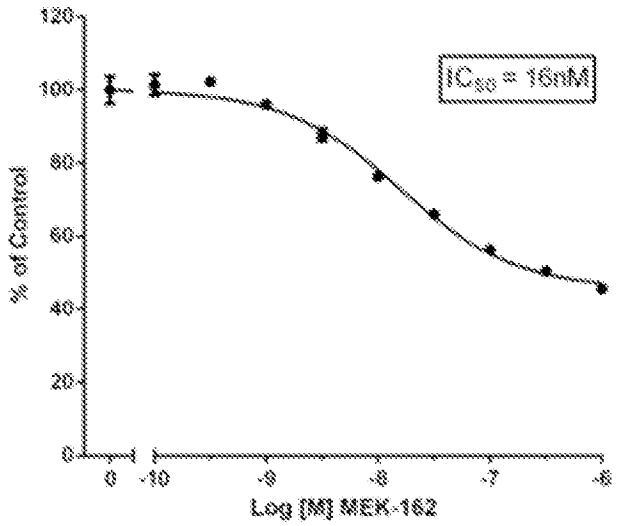
G



H



I



J

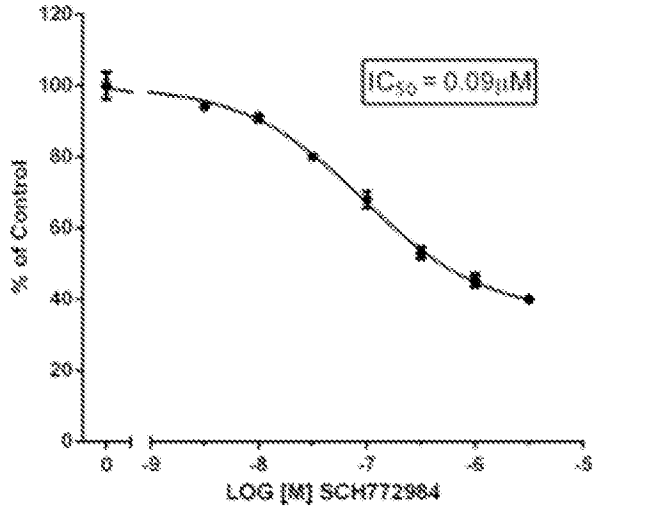


FIG. 37

A

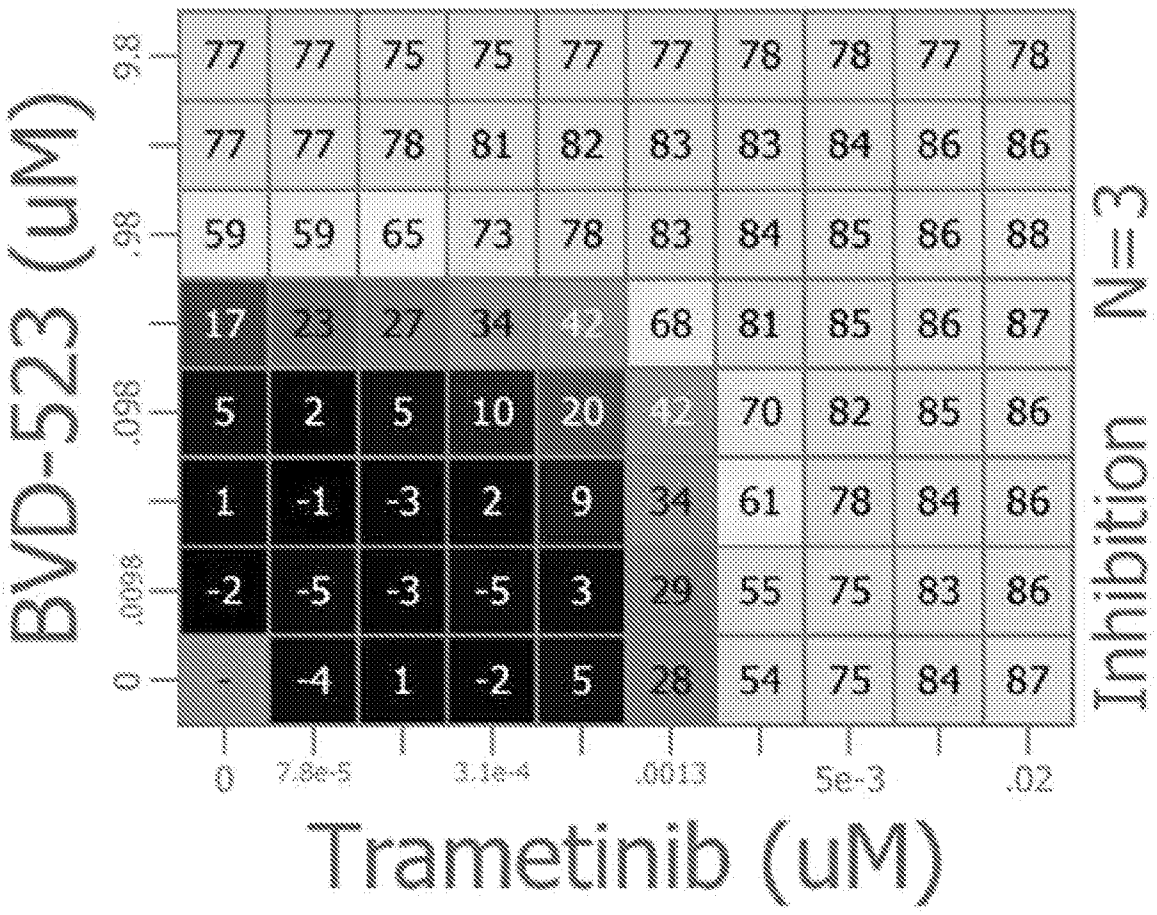

BVD-523 (uM)
9.8
.98
.098
.0098
0
77 77 75 75 77 77 78 78 77 78
77 77 78 81 82 83 83 84 86 86
59 59 65 73 78 83 84 85 86 88
17 23 27 34 42 68 81 85 86 87
5 2 5 10 20 42 70 82 85 86
1 -1 -3 2 9 34 61 78 84 86
-2 -5 -3 -5 3 29 55 75 83 86
- -4 1 -2 5 28 54 75 84 87
0 7.8e-5 3.1e-4 .0013 5e-3 .02
Trametinib (uM)
Inhibition N=3

FIG. 37, Con't

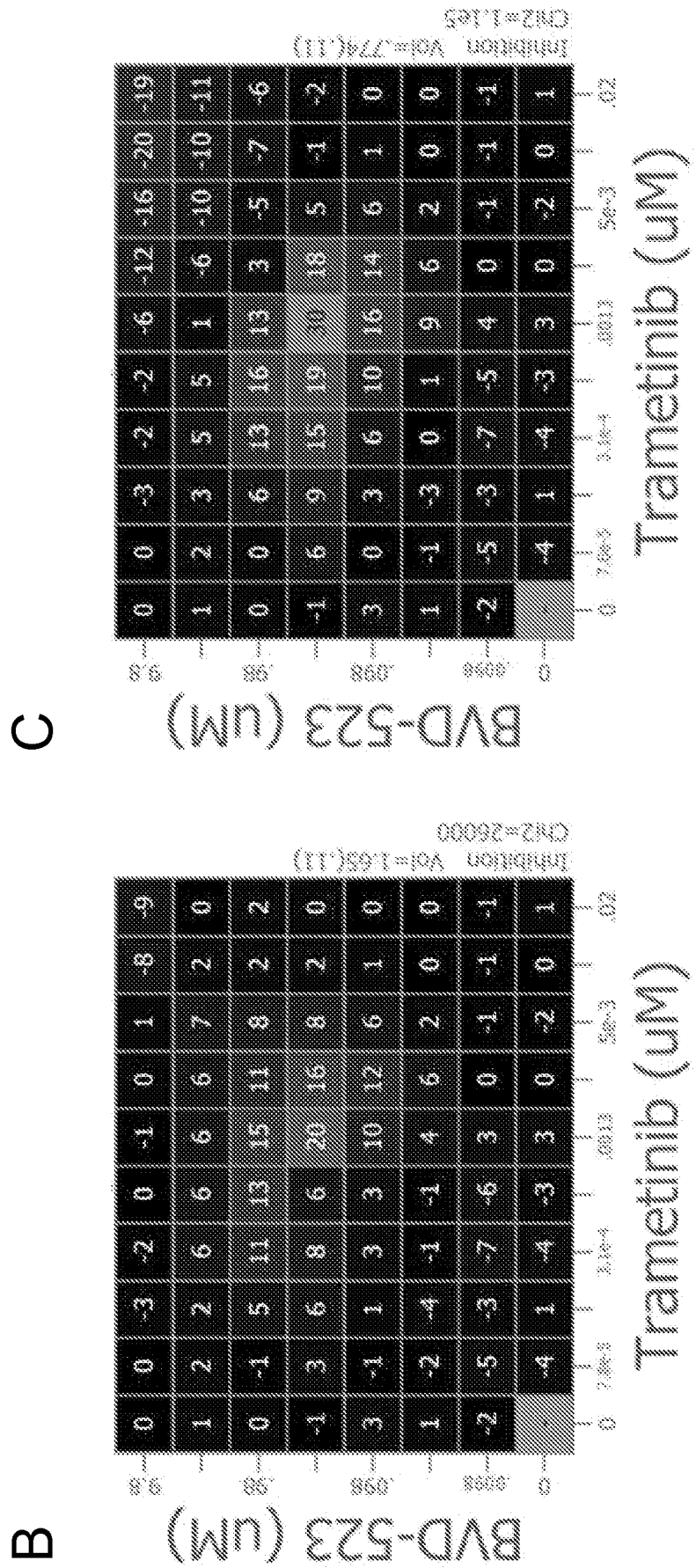

B
C
BVD-523 (uM)
Trametinib (uM)
Inhibition Vol=.774(.11)
CN2=1.165
Inhibition Vol=1.65(.11)
CN2=26000

FIG. 37, Con't

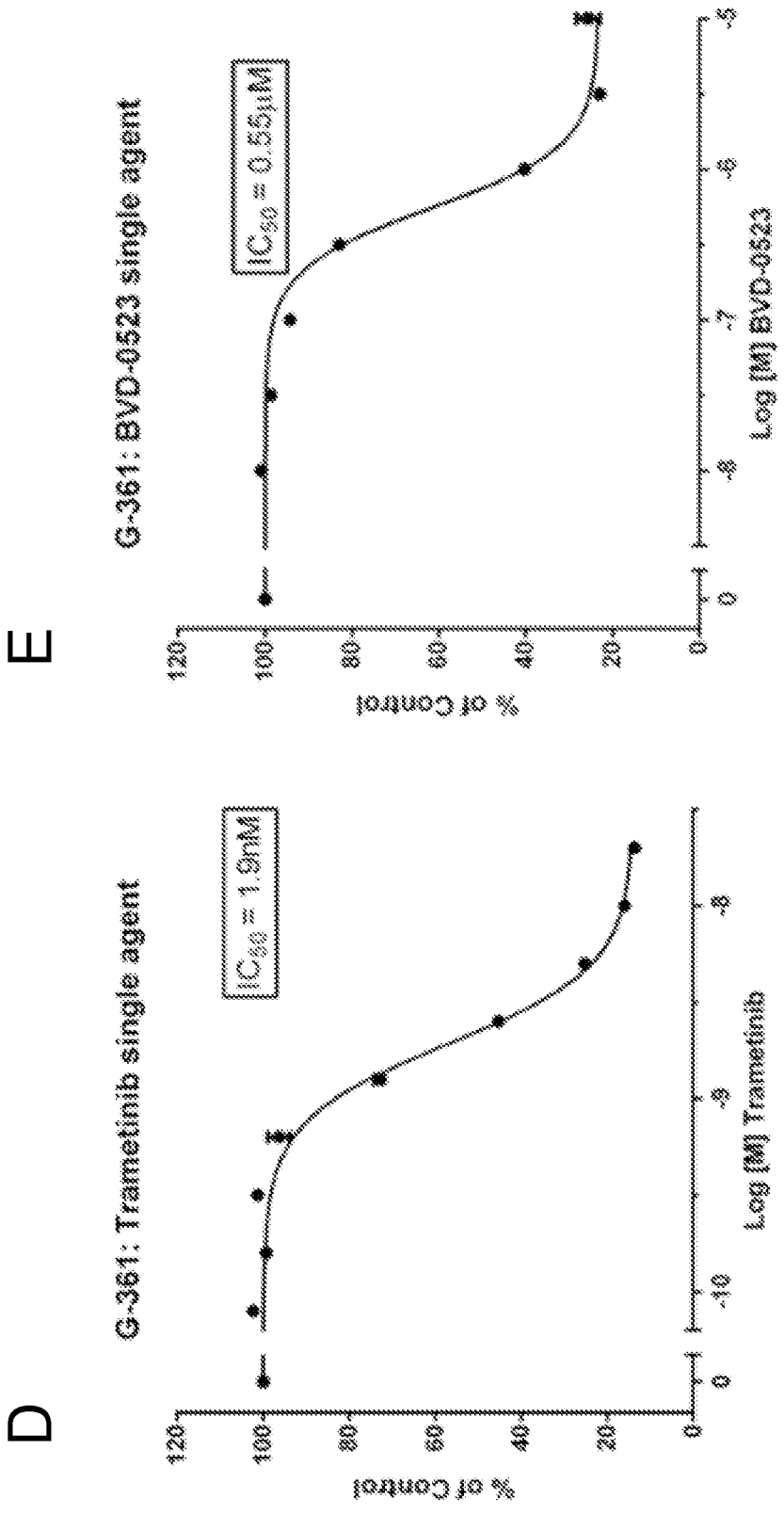

D
G-361: Trametinib single agent
IC50 = 1.9nM
% of Control
Log [M] Trametinib
E
G-361: BVD-0523 single agent
IC50 = 0.55μM
% of Control
Log [M] BVD-0523

FIG. 38

A

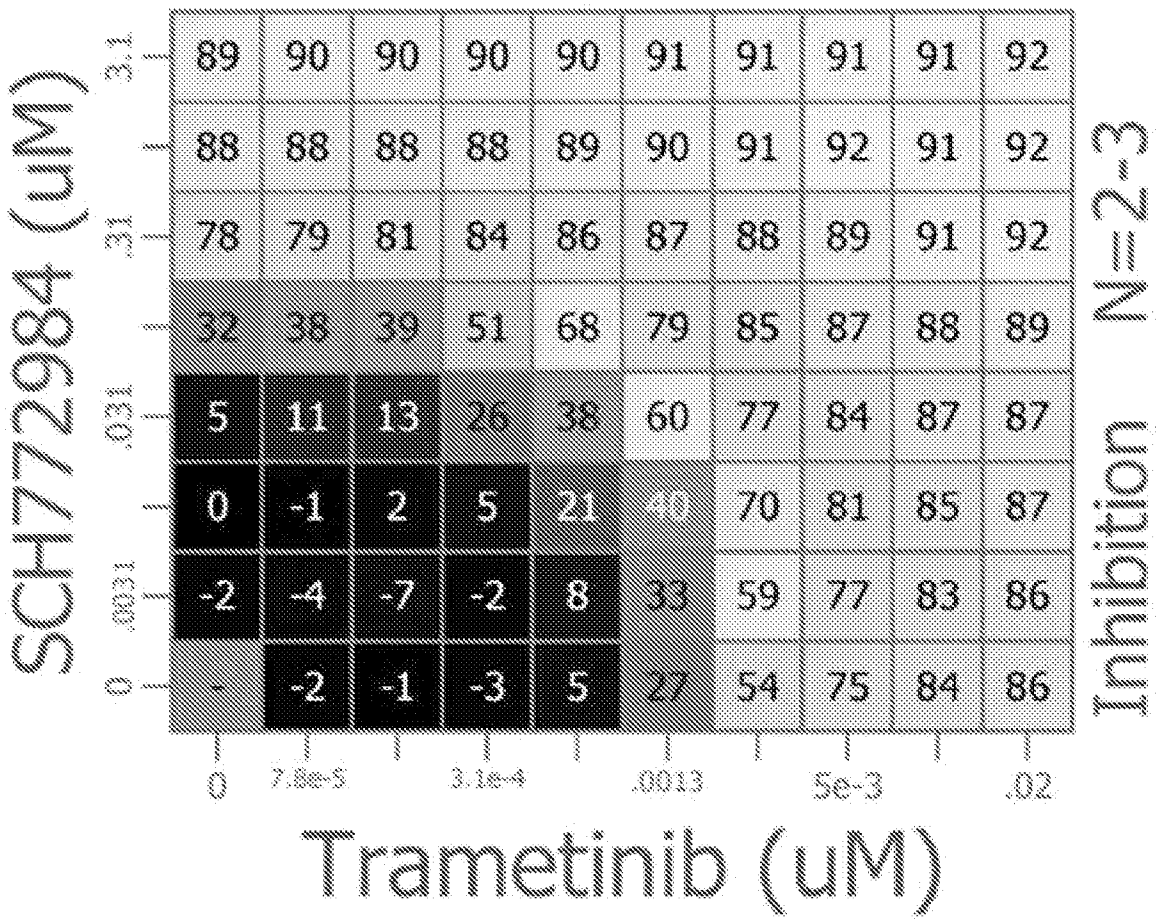

SCH772984 (uM)
3.1
31
.031
.0031
0
89 90 90 90 90 91 91 91 91 92
88 88 88 88 89 90 91 92 91 92
78 79 81 84 86 87 88 89 91 92
32 38 39 51 68 79 85 87 88 89
5 11 13 26 38 60 77 84 87 87
0 -1 2 5 21 40 70 81 85 87
-2 -4 -7 -2 8 33 59 77 83 86
- -2 -1 -3 5 27 54 75 84 86
0
7.8e-5
3.1e-4
.0013
5e-3
.02
Trametinib (uM)
Inhibition N=2-3

FIG. 38, Con't

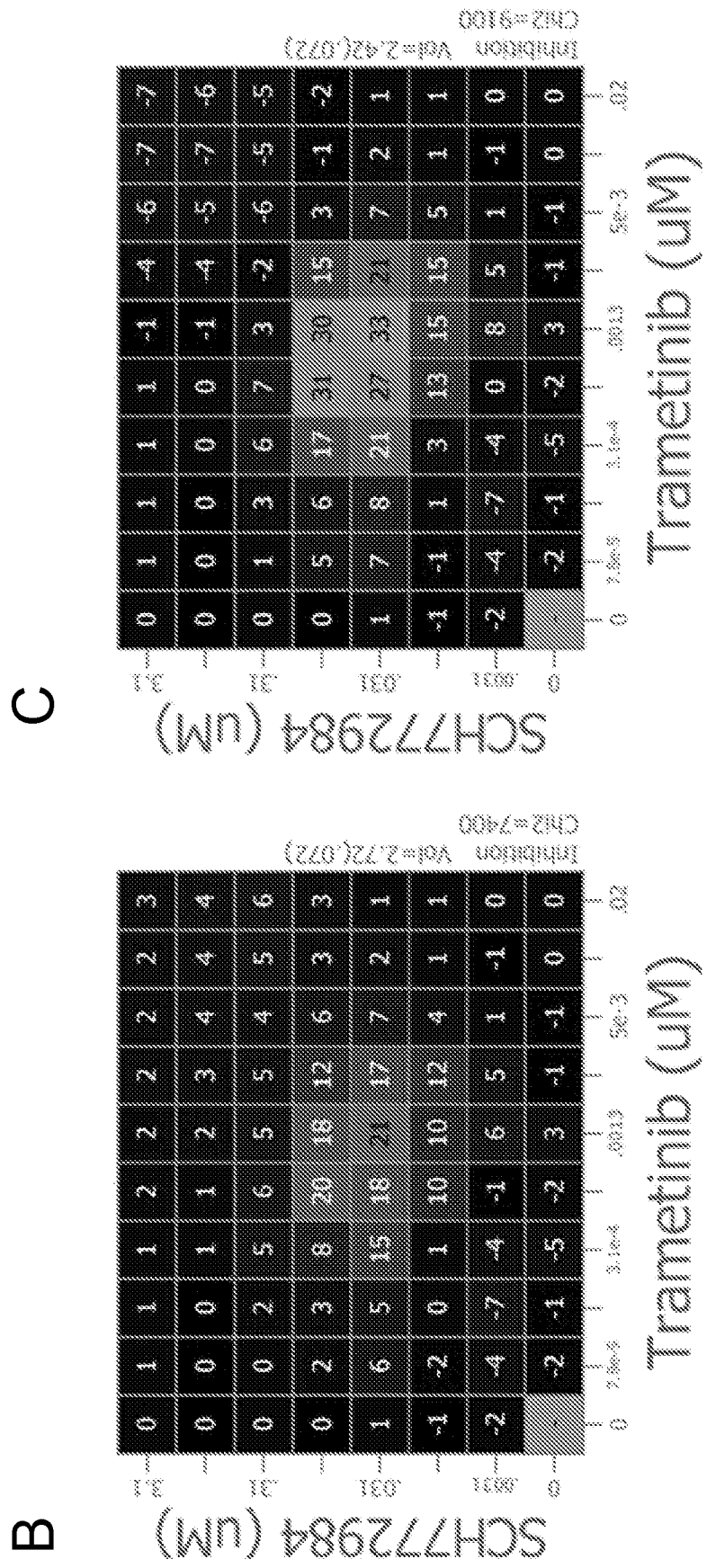

B
SCH772984 (uM)
Trametinib (uM)
Inhibition Vol=2.72(.072)
CN2=7400
C
SCH772984 (uM)
Trametinib (uM)
Inhibition Vol=2.42(.072)
CN2=9100

FIG. 38, Con't

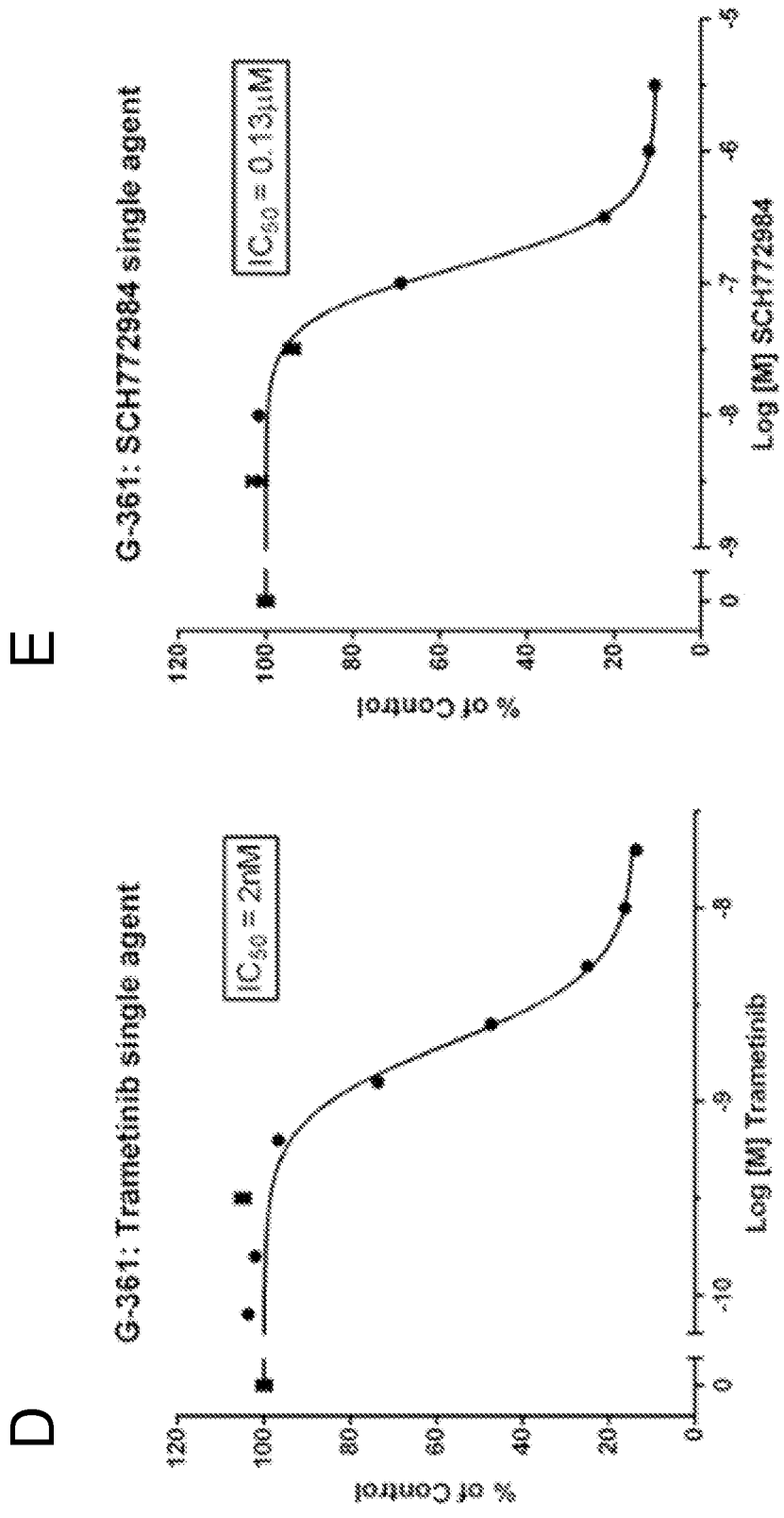

D
G-361: Trametinib single agent
IC50 = 2nM
% of Control
Log [M] Trametinib
E
G-361: SCH772984 single agent
IC50 = 0.13μM
% of Control
Log [M] SCH772984

FIG. 39

A

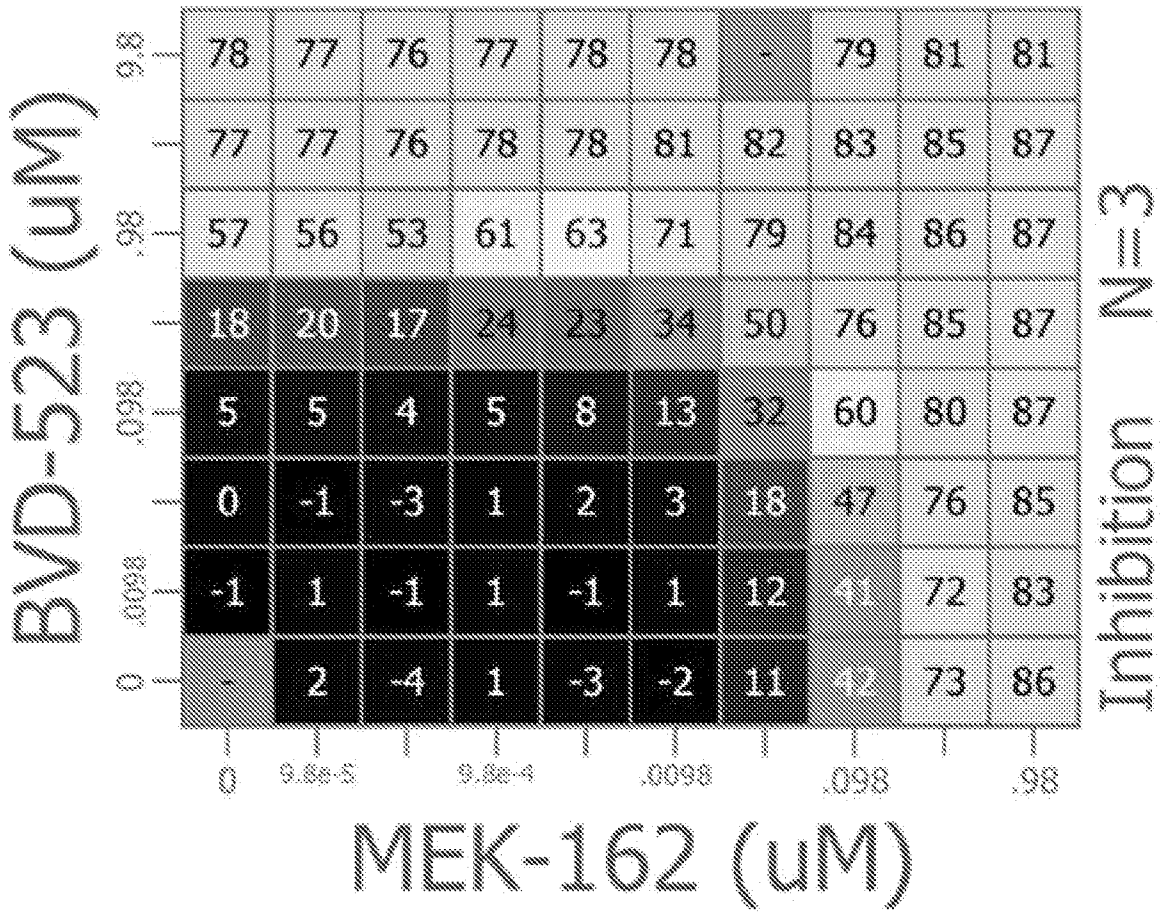

BVD-523 (uM)
9.8
.98
.098
.0098
0
78 77 76 77 78 78 - 79 81 81
77 77 76 78 78 81 82 83 85 87
57 56 53 61 63 71 79 84 86 87
18 20 17 24 23 34 50 76 85 87
5 5 4 5 8 13 32 60 80 87
0 -1 -3 1 2 3 18 47 76 85
-1 1 -1 1 -1 1 12 41 72 83
- 2 -4 1 -3 -2 11 42 73 86
0
9.8e-5
9.8e-4
.0098
.098
.98
MEK-162 (uM)
Inhibition N=3

FIG. 39, Con't

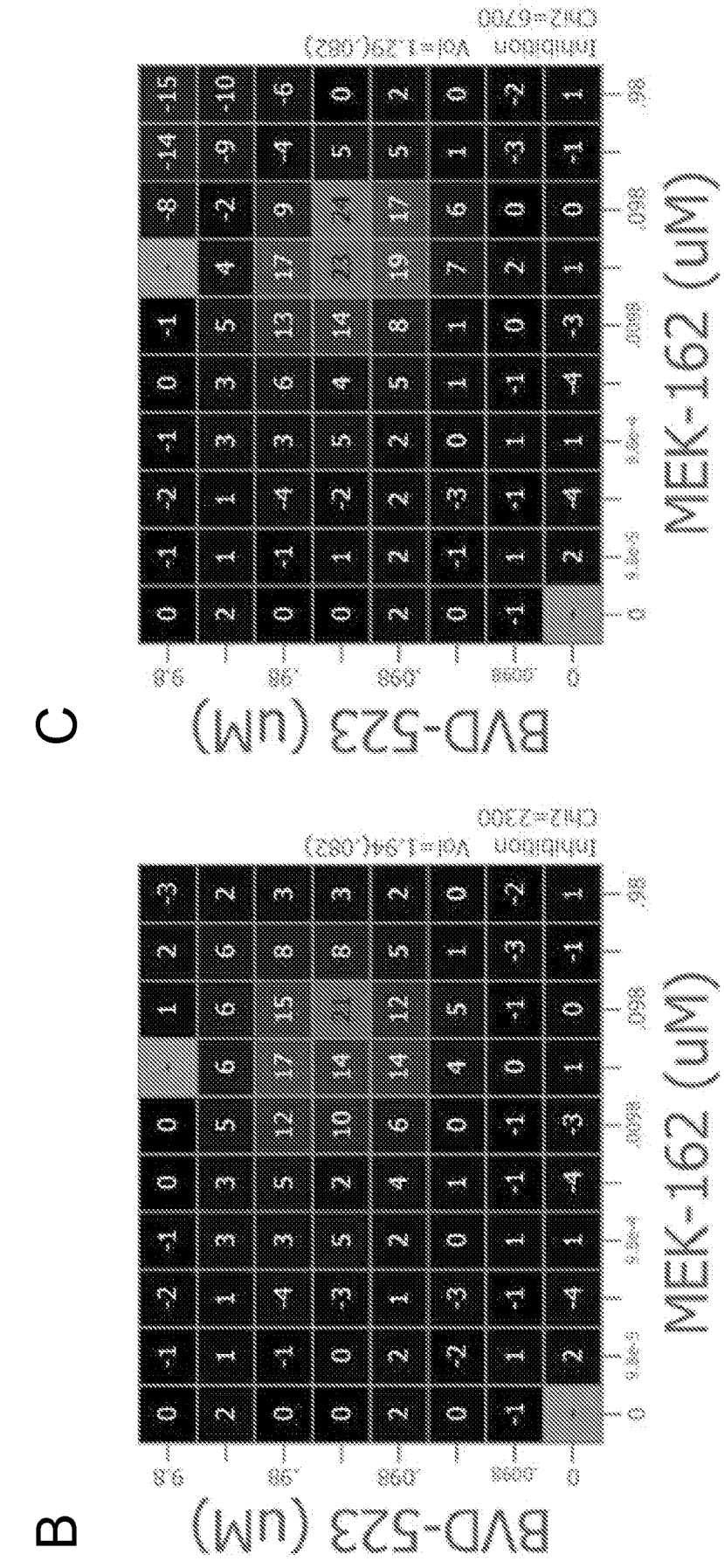

C
B
BVD-523 (uM)
MEK-162 (uM)
Inhibition Vol=1.294(.082) CM2=2300
Inhibition Vol=1.29(.082) CM2=6700

FIG. 39, Con't

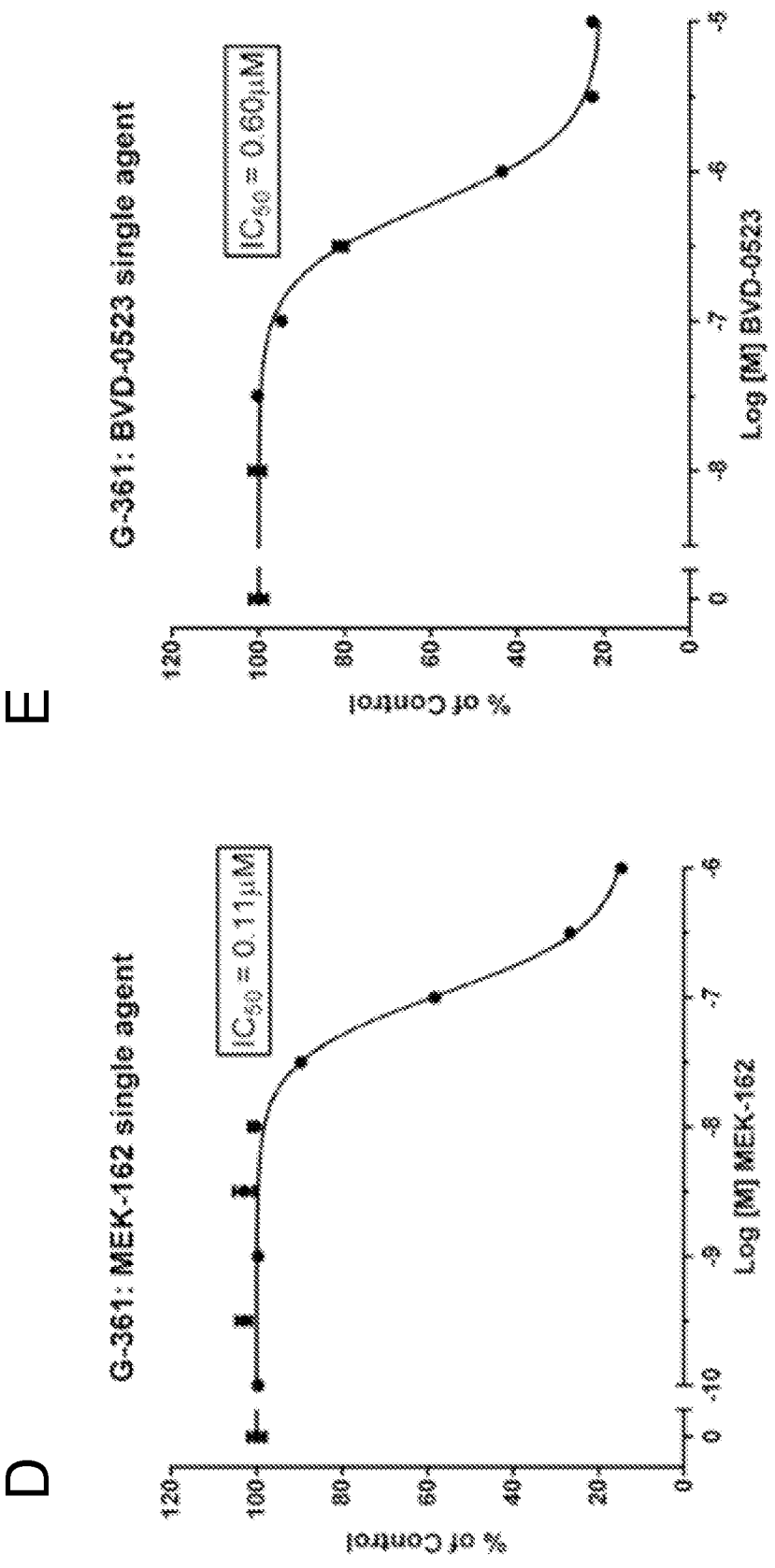

D
G-361: MEK-162 single agent
IC50 = 0.11μM
% of Control
Log [M] MEK-162
E
G-361: BVD-0523 single agent
IC50 = 0.60μM
% of Control
Log [M] BVD-0523

FIG. 40

A

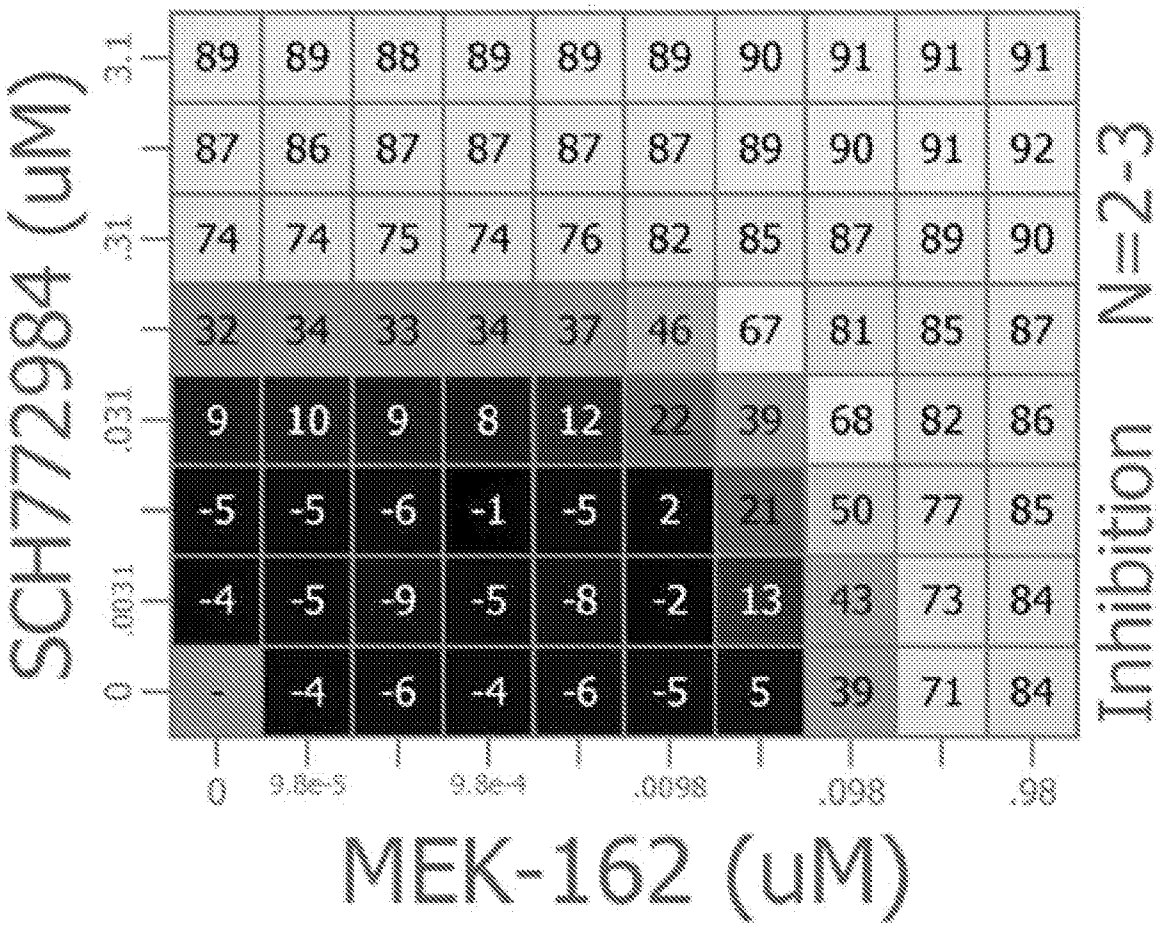

SCH772984 (uM)
3.1
.31
.031
.0031
0
89 89 88 89 89 89 90 91 91 91
87 86 87 87 87 87 89 90 91 92
74 74 75 74 76 82 85 87 89 90
32 34 33 34 37 46 67 81 85 87
9 10 9 8 12 22 39 68 82 86
-5 -5 -6 -1 -5 2 21 50 77 85
-4 -5 -9 -5 -8 -2 13 43 73 84
- -4 -6 -4 -6 -5 5 39 71 84
0
9.8e-5
9.8e-4
.0098
.098
.98
MEK-162 (uM)
Inhibition N=2-3

FIG. 40, Con't

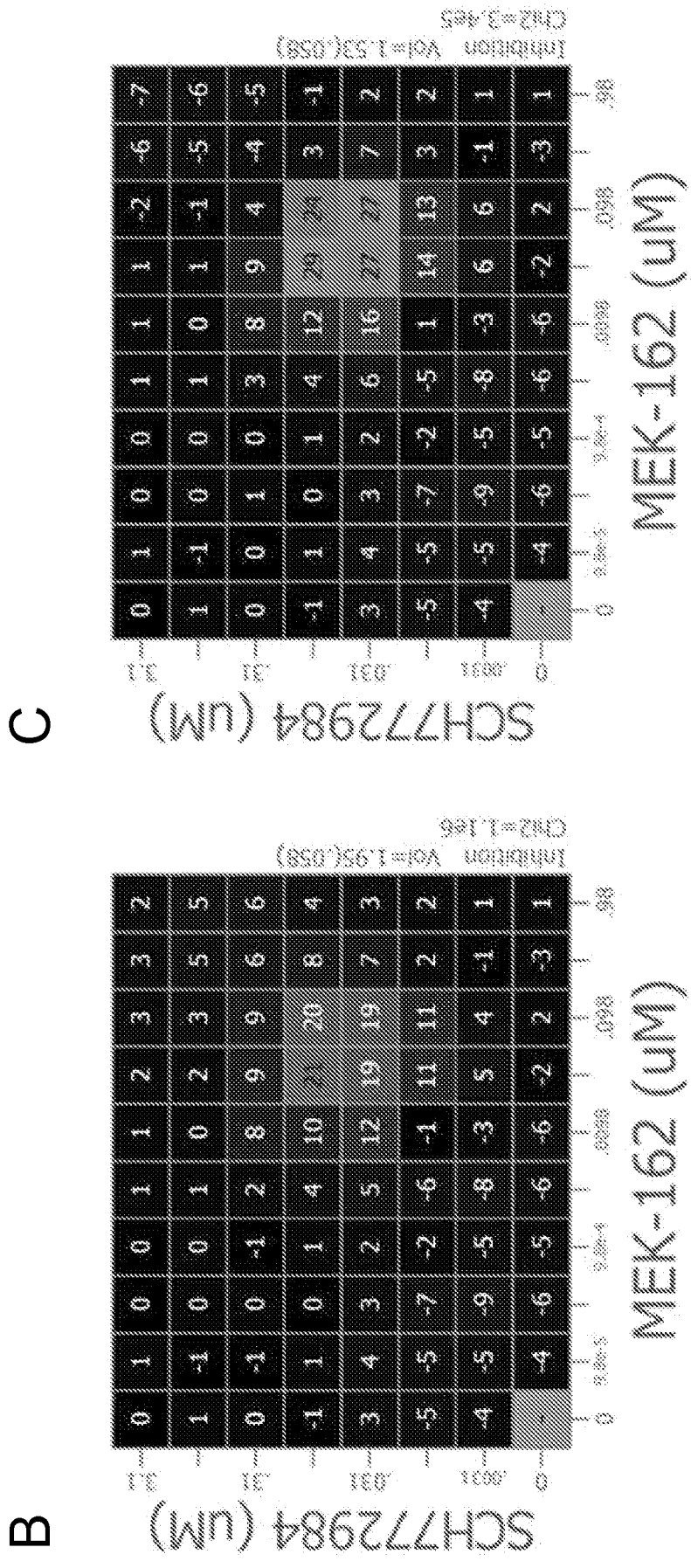

B
C
SCH772984 (uM)
MEK-162 (uM)
Inhibition Vol=1.53(.058)
Chi2=3.465
Inhibition Vol=1.95(.058)
Chi2=1.166

FIG. 40, Con't

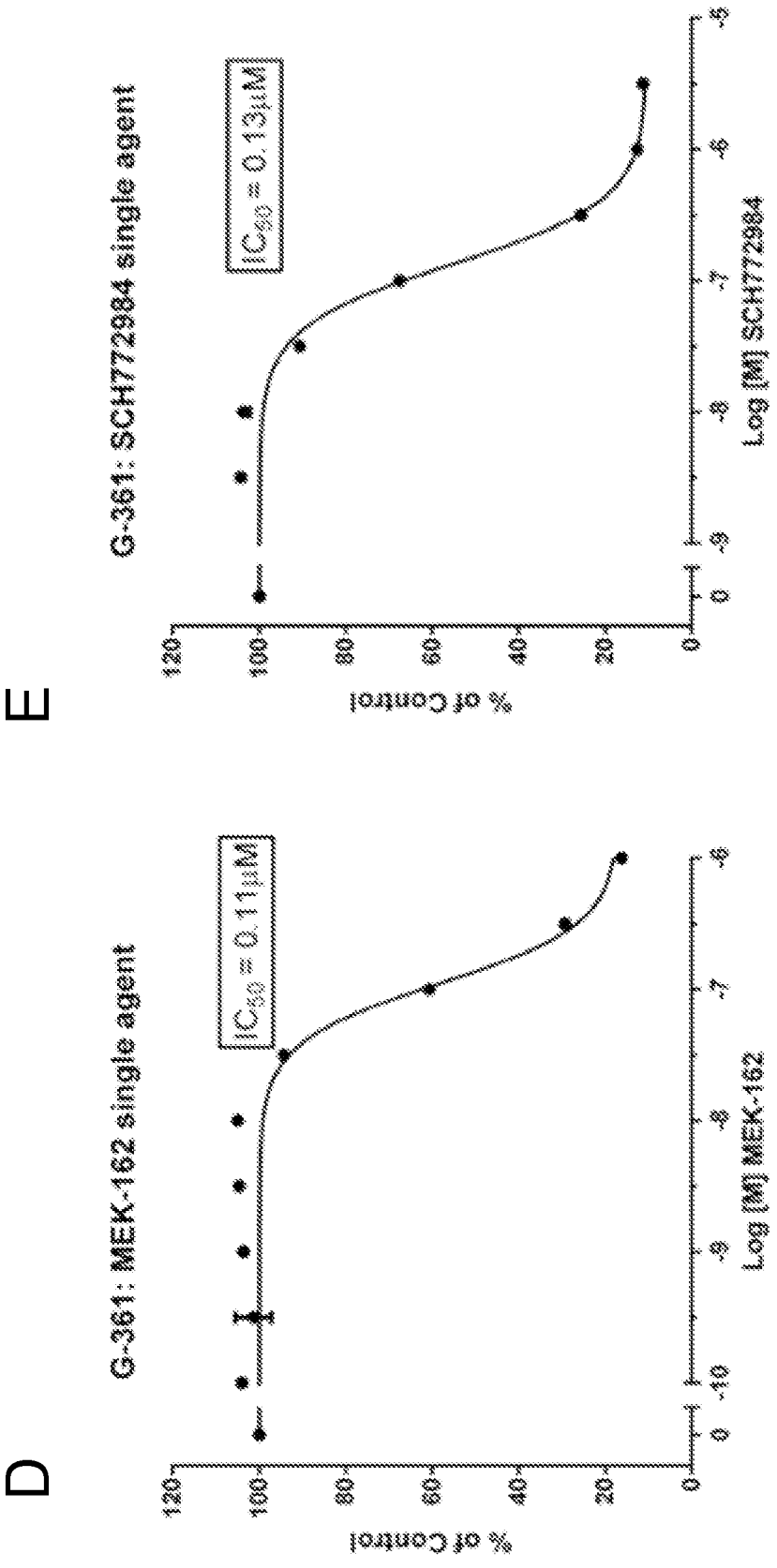

D
G-361: MEK-162 single agent
IC50 = 0.11μM
% of Control
Log [M] MEK-162
E
G-361: SCH772984 single agent
IC50 = 0.13μM
% of Control
Log [M] SCH772984

FIG. 41

A

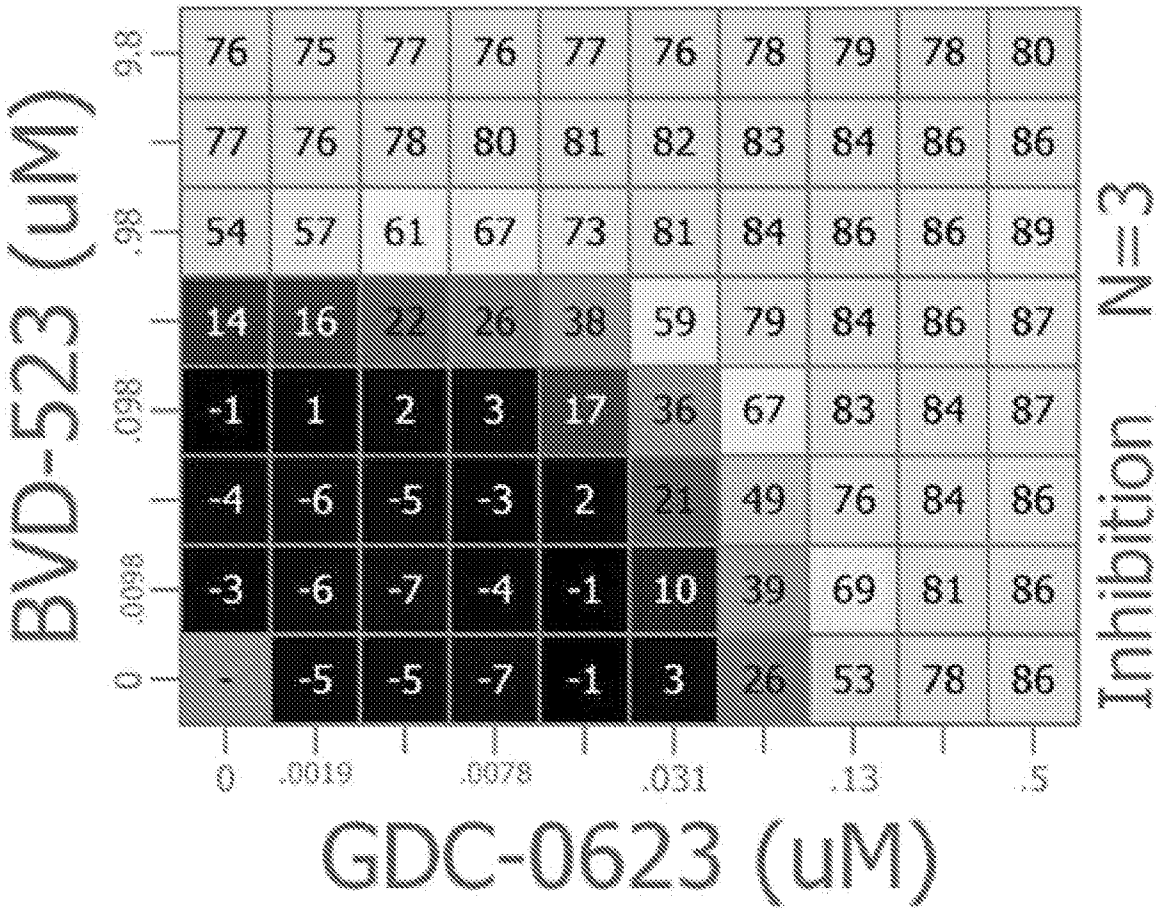

BVD-523 (uM)
9.8
.98
.098
.0098
0
76 75 77 76 77 76 78 79 78 80
77 76 78 80 81 82 83 84 86 86
54 57 61 67 73 81 84 86 86 89
14 16 22 26 38 59 79 84 86 87
-1 1 2 3 17 36 67 83 84 87
-4 -6 -5 -3 2 21 49 76 84 86
-3 -6 -7 -4 -1 10 39 69 81 86
- -5 -5 -7 -1 3 26 53 78 86
0 .0019 .0078 .031 .13 .5
GDC-0623 (uM)
Inhibition N=3

FIG. 41, Con't

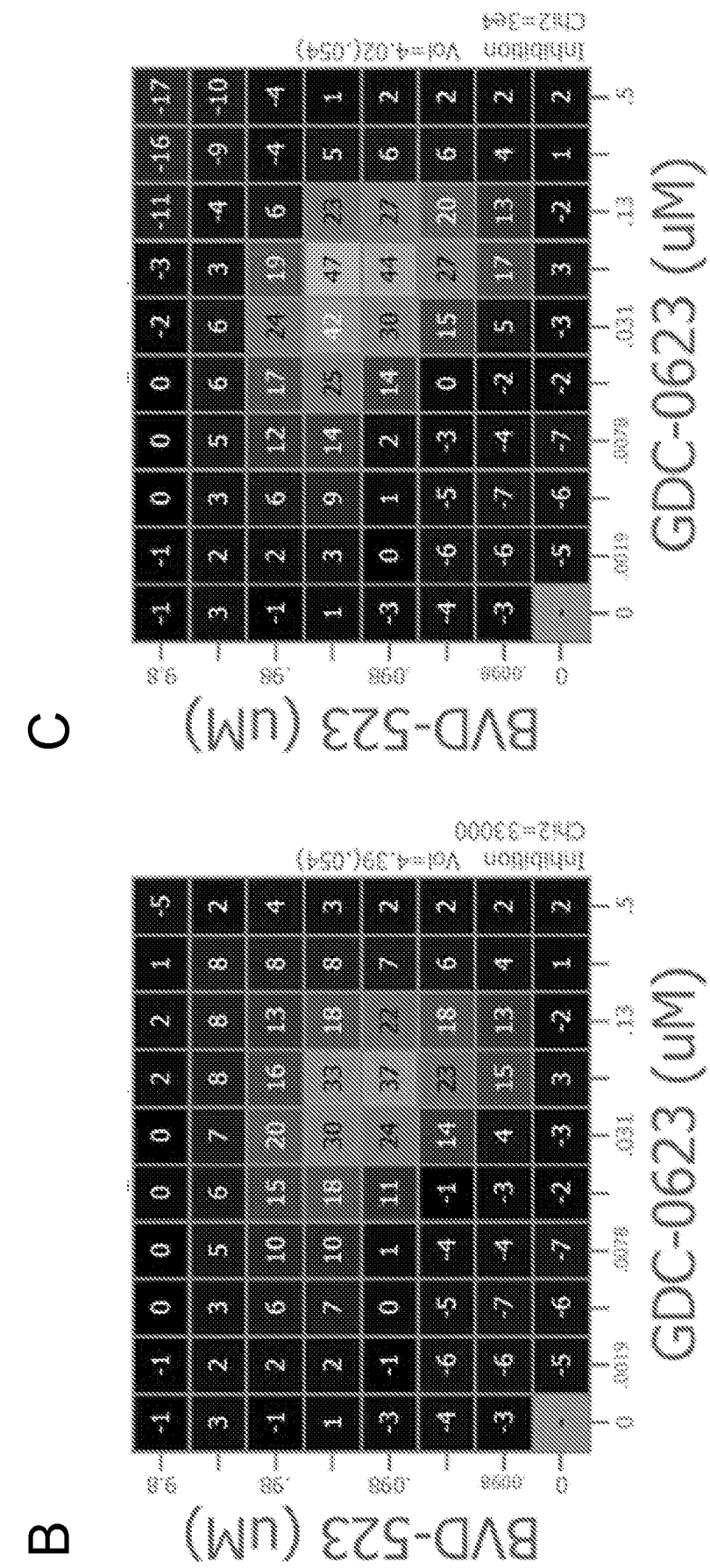

B
C
BVD-523 (uM)
GDC-0623 (uM)
Inhibition Vol=4.39(.054)
CN2=33000
Inhibition Vol=4.02(.054)
CN2=3e4

FIG. 41, Con't

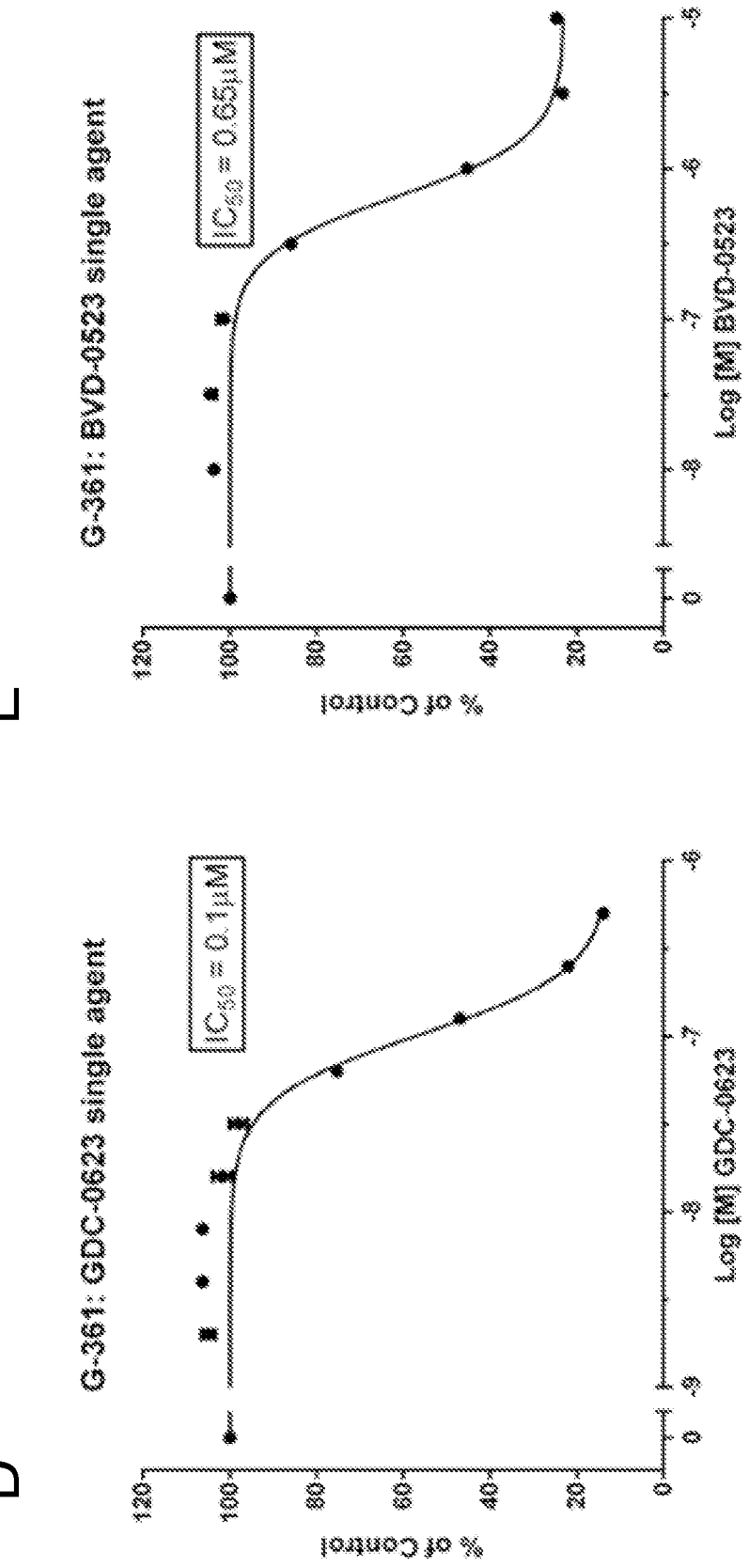

D
G-361: GDC-0623 single agent
IC50 = 0.1μM
% of Control
Log [M] GDC-0623
E
G-361: BVD-0523 single agent
IC50 = 0.65μM
% of Control
Log [M] BVD-0523

FIG. 42

A

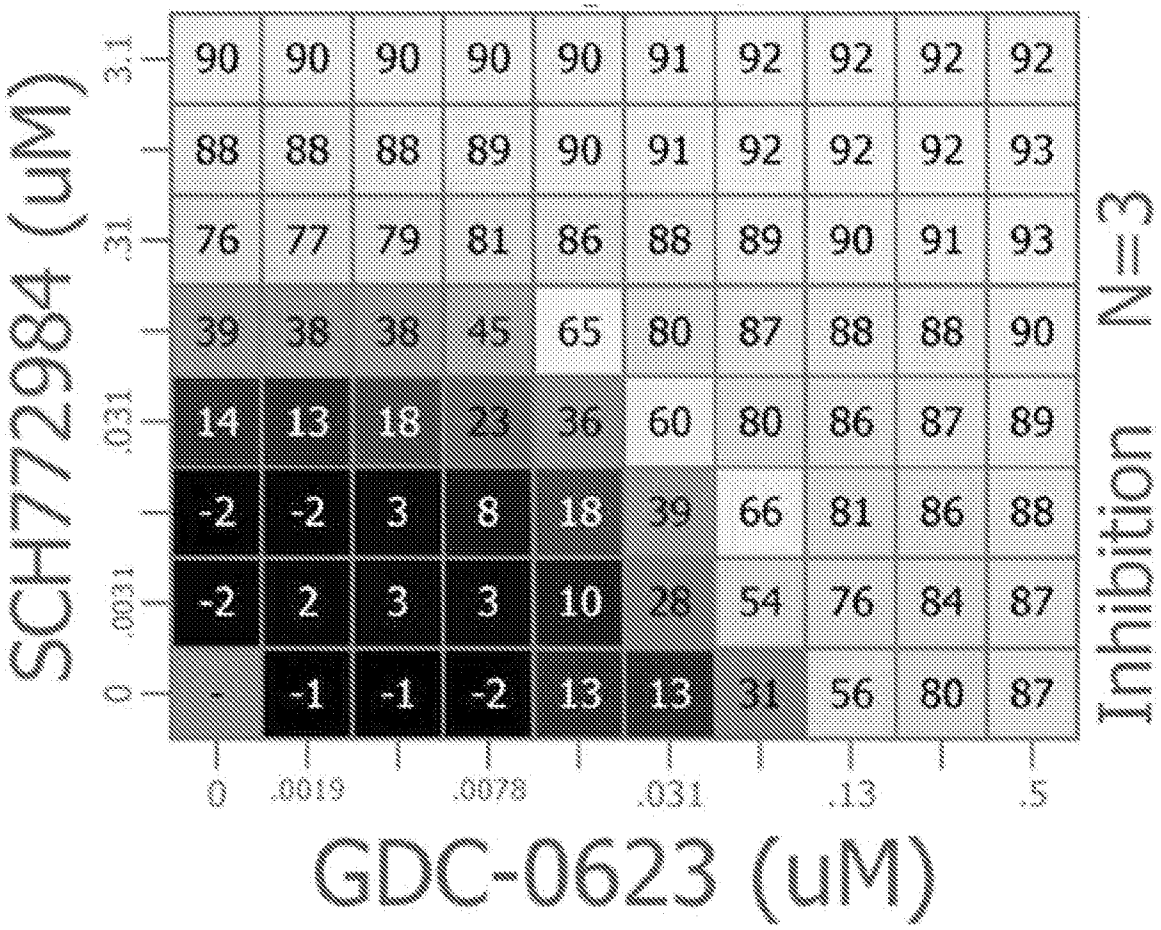

SCH772984 (uM)
3.1
.31
.031
.0031
0
90 90 90 90 90 91 92 92 92 92
88 88 88 89 90 91 92 92 92 93
76 77 79 81 86 88 89 90 91 93
39 38 38 45 65 80 87 88 88 90
14 13 18 23 36 60 80 86 87 89
-2 -2 3 8 18 39 66 81 86 88
-2 2 3 3 10 28 54 76 84 87
- -1 -1 -2 13 13 31 56 80 87
0 .0019 .0078 .031 .13 .5
GDC-0623 (uM)
Inhibition N=3

FIG. 42, Con't

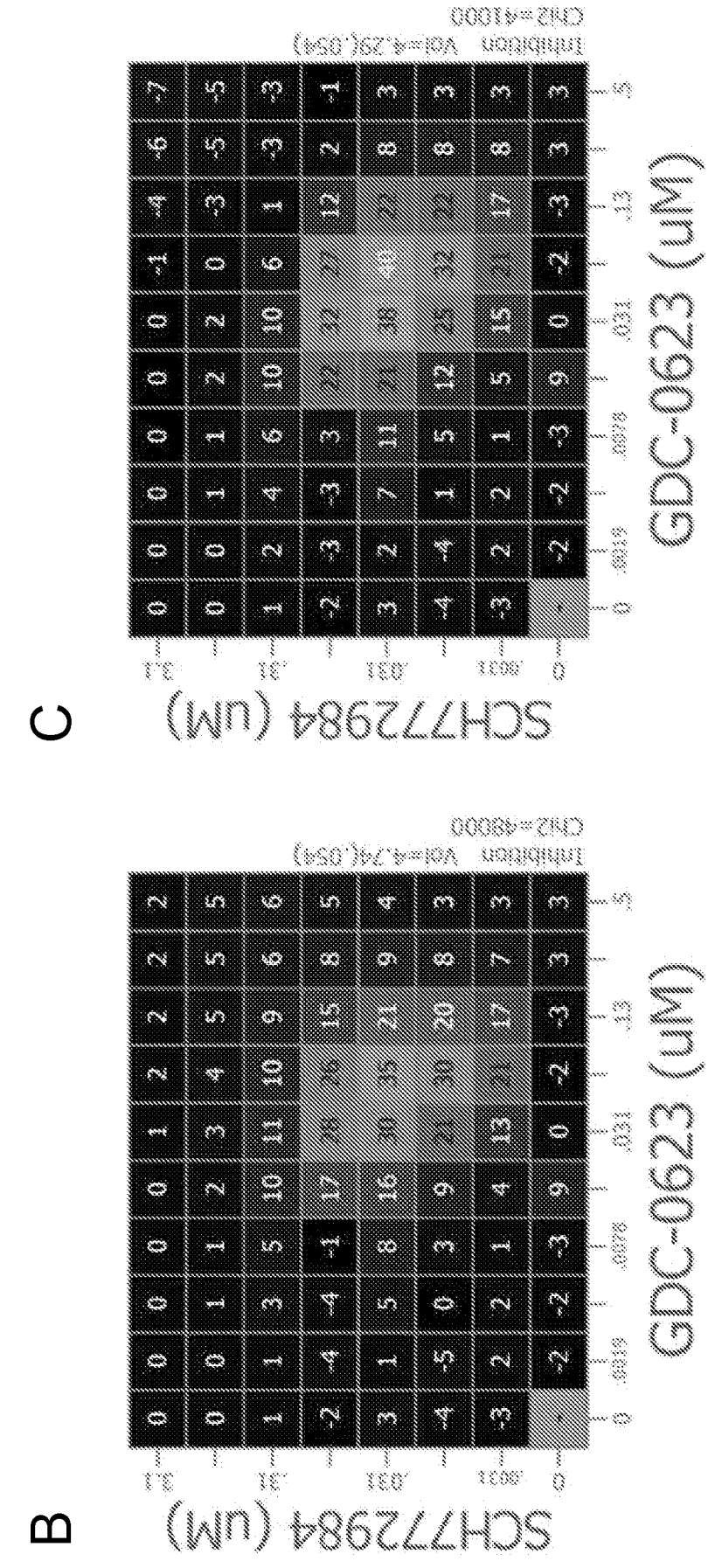

C
SCH772984 (uM)
GDC-0623 (uM)
Inhibition Vol=4.29(.054)
CN2=41000
B
SCH772984 (uM)
GDC-0623 (uM)
Inhibition Vol=4.74(.054)
CN2=48000

FIG. 42, Con't

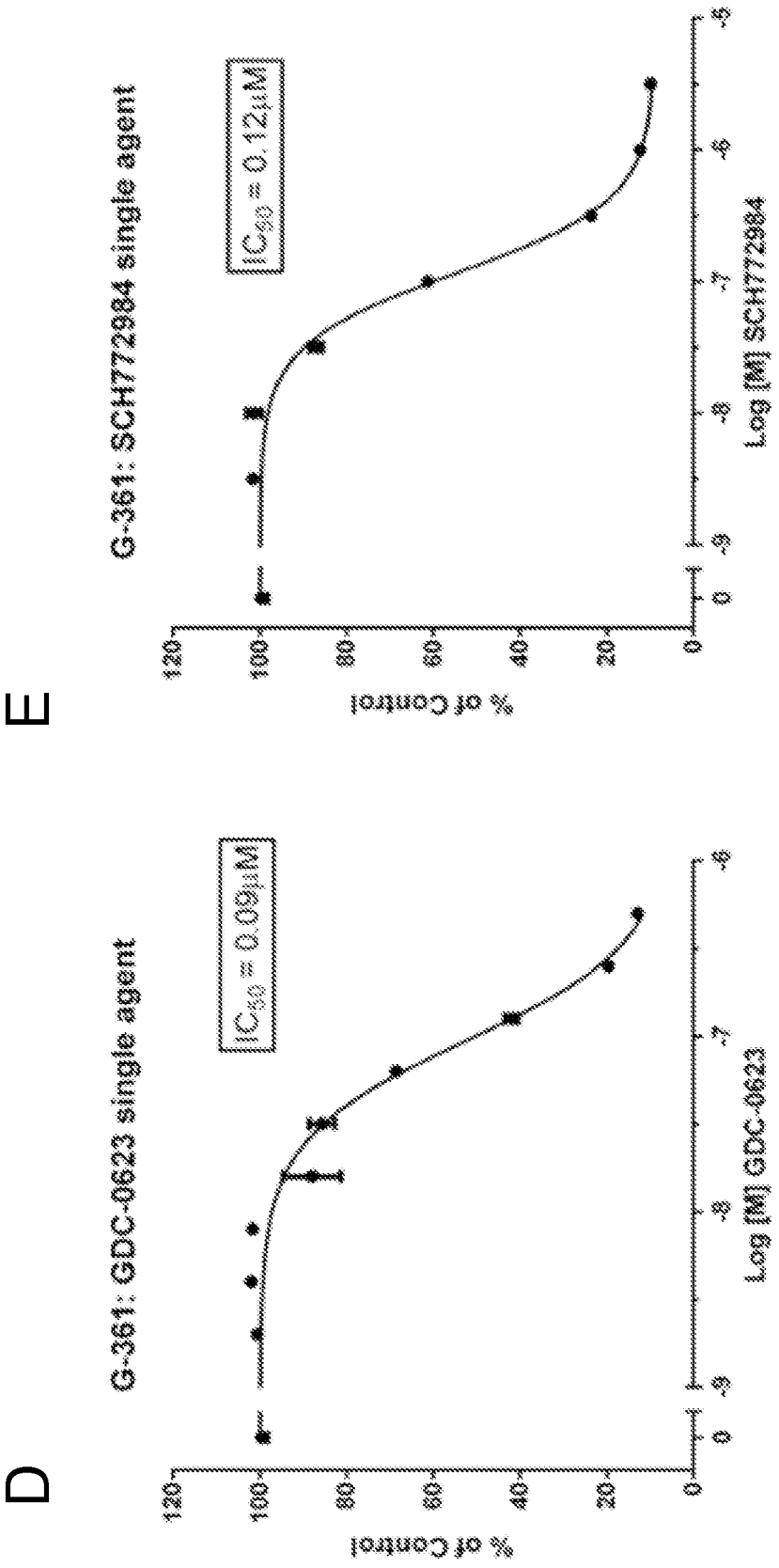

D
G-361: GDC-0623 single agent
IC50 = 0.09μM
% of Control
Log [M] GDC-0623
E
G-361: SCH772984 single agent
IC50 = 0.12μM
% of Control
Log [M] SCH772984

FIG. 43

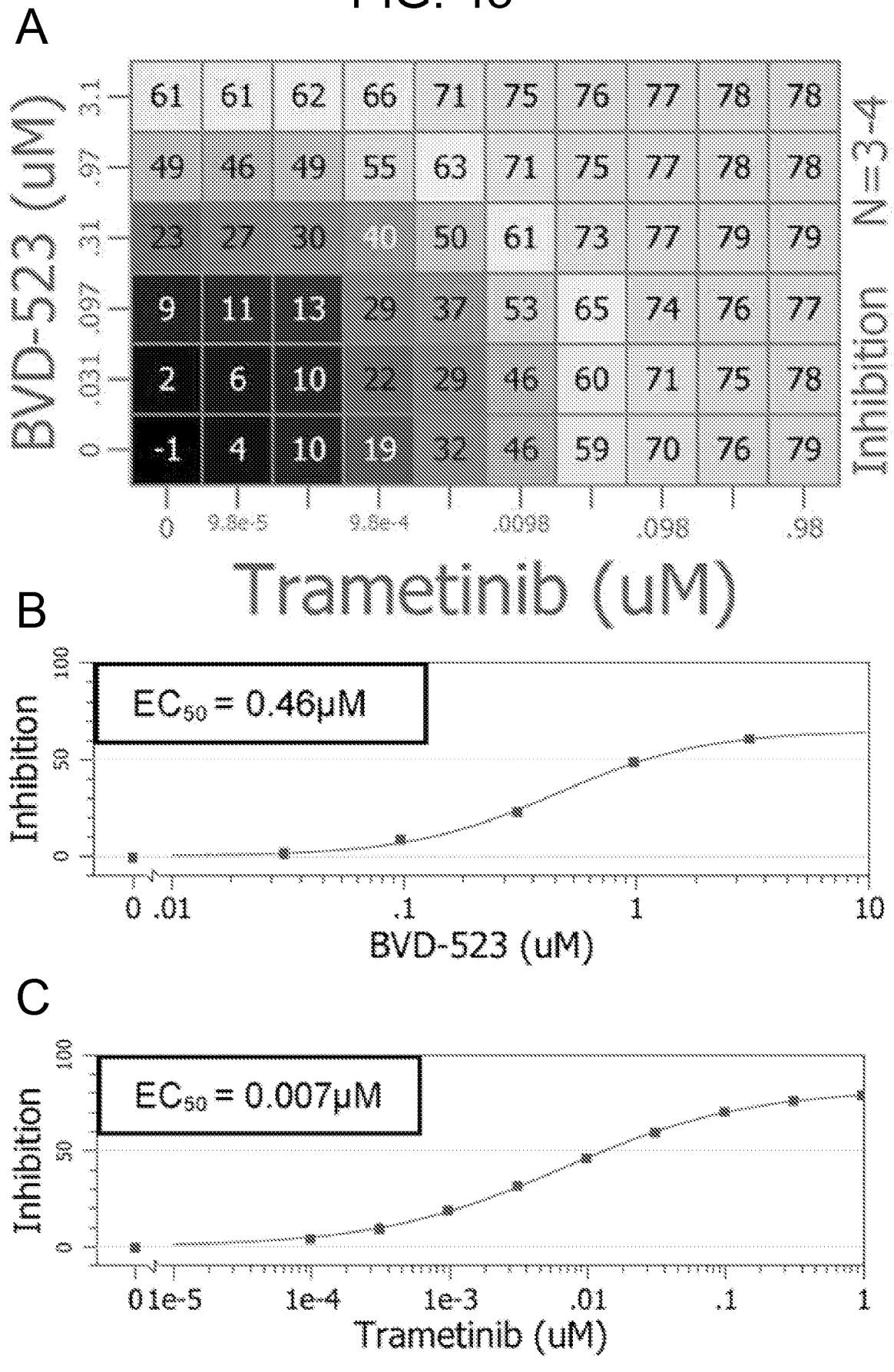

A
BVD-523 (uM)
3.1
.97
.31
.097
.031
0
61 61 62 66 71 75 76 77 78 78
49 46 49 55 63 71 75 77 78 78
23 27 30 40 50 61 73 77 79 79
9 11 13 29 37 53 65 74 76 77
2 6 10 22 29 46 60 71 75 78
-1 4 10 19 32 46 59 70 76 79
Inhibition N=3-4
0 9.8e-5 9.8e-4 .0098 .098 .98
Trametinib (uM)
B
Inhibition
100
50
0
EC50 = 0.46μM
0 .01 .1 1 10
BVD-523 (uM)
C
Inhibition
100
50
0
EC50 = 0.007μM
0 1e-5 1e-4 1e-3 .01 .1 1
Trametinib (uM)

FIG. 43, Con't

E
Inhibition
Vol=1.06(.05)
CH2=400
BVD-523 (uM)
0
.031
.097
.31
.97
3.1
Trametinib (uM)
0
.003
.008
.024
.08
.25
0 -1 -1 -1 0 0
-1 -1 -1 0 1 2
0 -1 -1 -1 0 1
2 0 -1 -1 -1 -1
-1 -1 3 2 2 -1
1 -5 -1 -1 -1 -5
0 -1 -2 -2 -4 -12
-1 -2 -3 -4 -8 -10
-2 -4 -4 -1 -1 -8
-4 -2 -3 -1 -1 -4
-8 -1 -1 -1 -1 -2
-11 -1 -1 -1 -1 -3
-13 -1 -1 -1 -1 -3
-14 -1 -1 -1 -1 -3
D
Inhibition
Vol=1.69(.05)
CH2=1300
BVD-523 (uM)
0
.031
.097
.31
.97
3.1
Trametinib (uM)
0
.003
.008
.024
.08
.25
0 -1 -1 -1 0 0
-1 -1 -1 0 1 2
0 -1 -1 -1 0 1
2 1 -2 -1 -1 -2
-1 1 3 2 2 0
1 -2 0 -2 -2 -2
0 1 -2 -2 -2 -1
1 -2 0 -2 -2 -2
0 1 -2 -2 -2 -2
2 1 -2 -2 -2 -2
-1 1 -2 -2 -2 -2
-2 1 -2 -2 -2 -2
-2 1 -2 -2 -2 -2
-2 1 -2 -2 -2 -2

FIG. 44

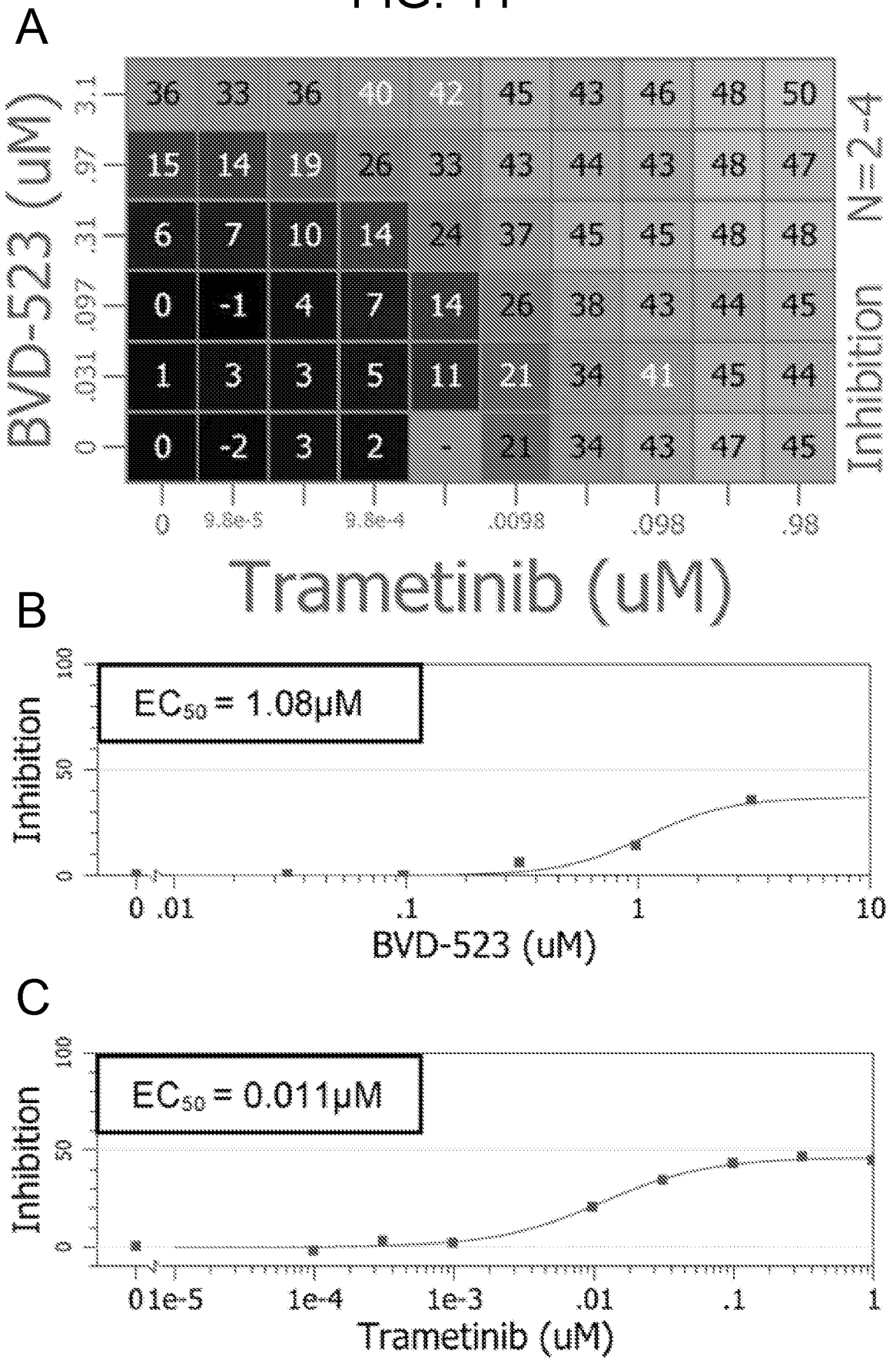

A
BVD-523 (uM)
3.1
.97
.31
.097
.031
0
36 33 36 40 42 45 43 46 48 50
15 14 19 26 33 43 44 43 48 47
6 7 10 14 24 37 45 45 48 48
0 -1 4 7 14 26 38 43 44 45
1 3 3 5 11 21 34 41 45 44
0 -2 3 2 - 21 34 43 47 45
N=2-4
Inhibition
0
9.8e-5
9.8e-4
.0098
.098
.98
Trametinib (uM)
B
Inhibition
100
50
0
EC50 = 1.08μM
0 .01
.1
1
10
BVD-523 (uM)
C
Inhibition
100
50
0
EC50 = 0.011μM
01e-5
1e-4
1e-3
.01
.1
1
Trametinib (uM)

FIG. 44, Con't

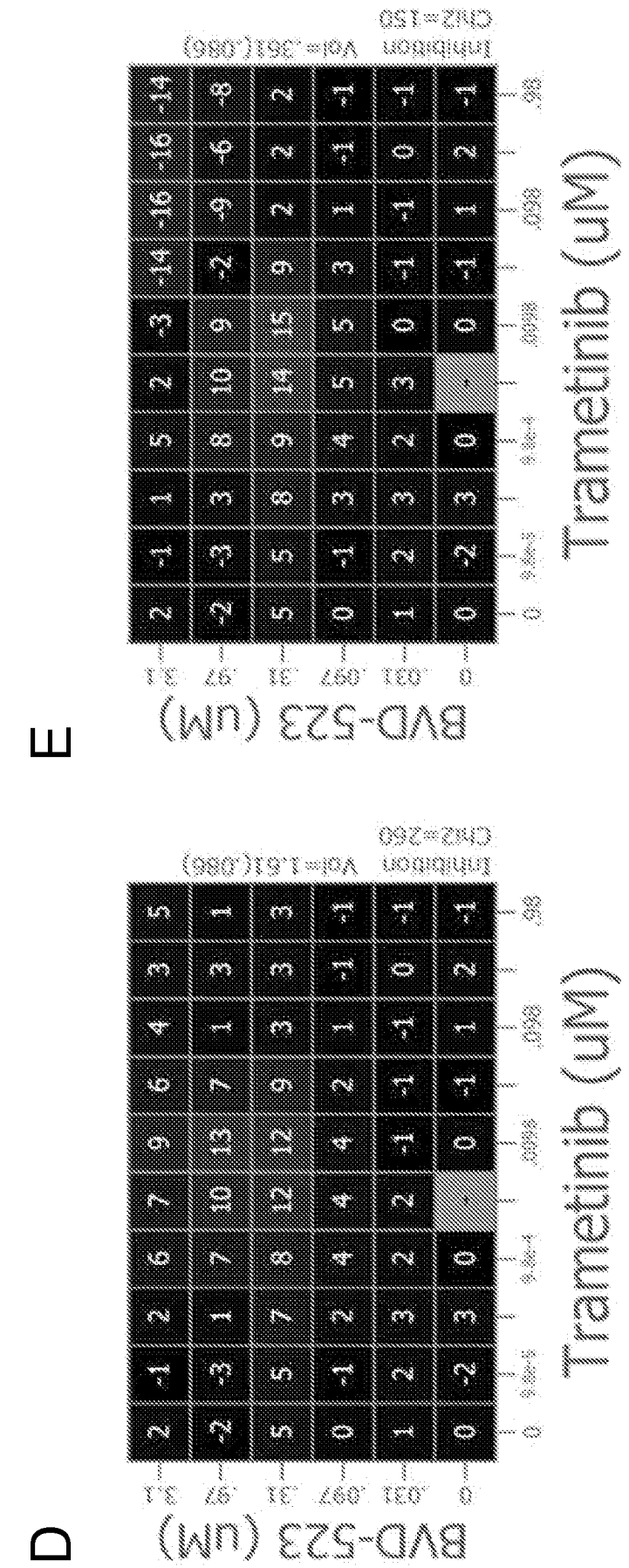

E
BVD-523 (uM)
0
.031
.097
.31
.97
3.1
Trametinib (uM)
0
.0412
.123
.37
1.1
3.3
10
30
Inhibition Vol=.361(.086)
CN2=150
D
BVD-523 (uM)
0
.031
.097
.31
.97
3.1
Trametinib (uM)
0
.0412
.123
.37
1.1
3.3
10
30
Inhibition Vol=1.61(.086)
CN2=260

FIG. 45

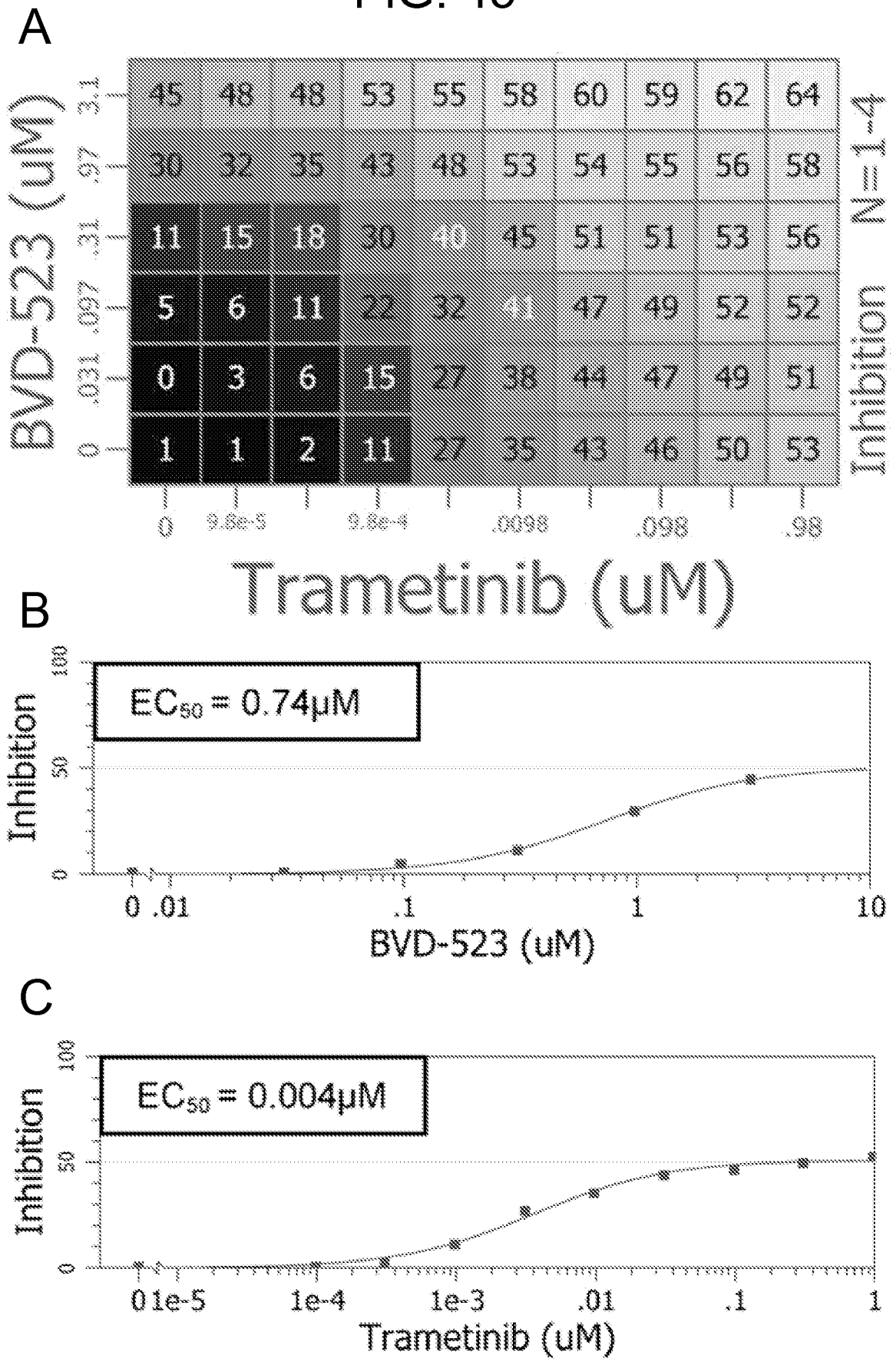
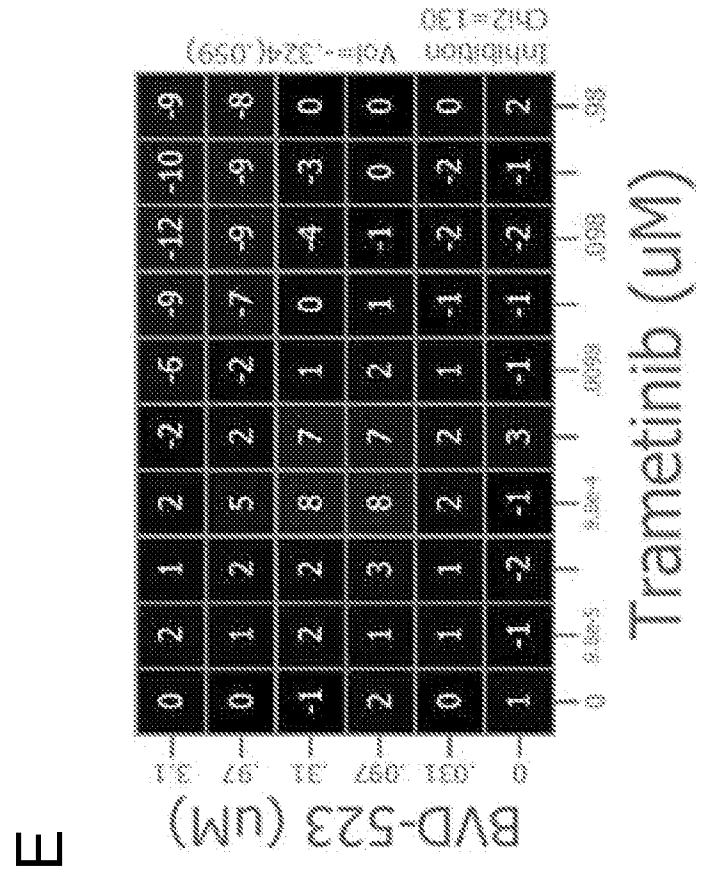

A
BVD-523 (uM)
3.1
.97
.31
.097
.031
0
45 48 48 53 55 58 60 59 62 64
30 32 35 43 48 53 54 55 56 58
11 15 18 30 40 45 51 51 53 56
5 6 11 22 32 41 47 49 52 52
0 3 6 15 27 38 44 47 49 51
1 1 2 11 27 35 43 46 50 53
Inhibition N=1-4
0
9.8e-5
9.8e-4
.0098
.098
.98
Trametinib (uM)
B
Inhibition
100
50
0
EC50 = 0.74μM
0 .01
.1
1
10
BVD-523 (uM)
C
Inhibition
100
50
0
EC50 = 0.004μM
01e-5
1e-4
1e-3
.01
.1
1
Trametinib (uM)

FIG. 45, Con't


E
BVD-523 (uM)
Trametinib (uM)
Inhibition
Vol=-.324(.059)
CN2=130

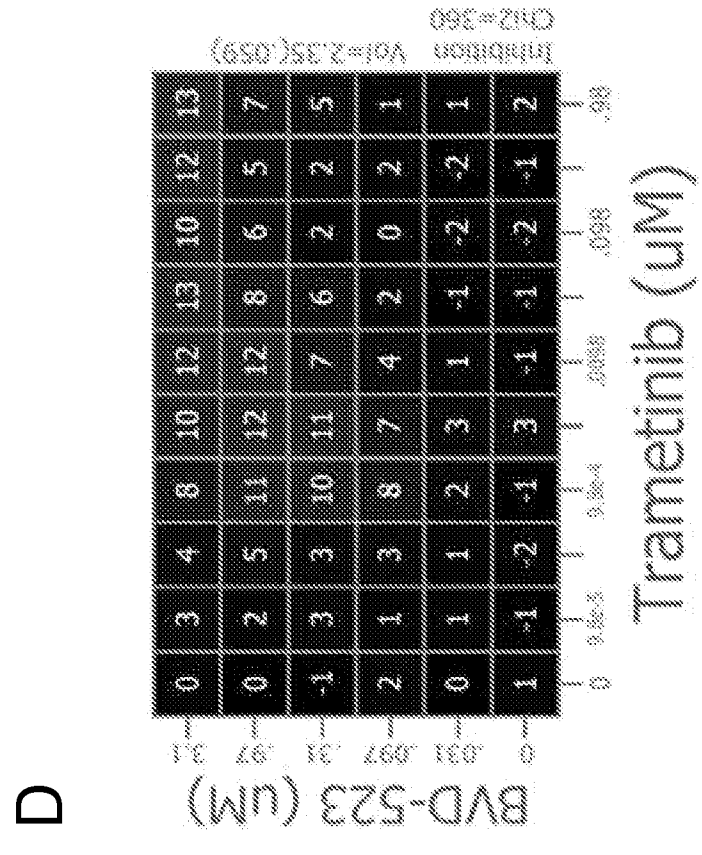

D
BVD-523 (uM)
Trametinib (uM)
Inhibition
Vol=2.35(.059)
CN2=360

FIG. 46

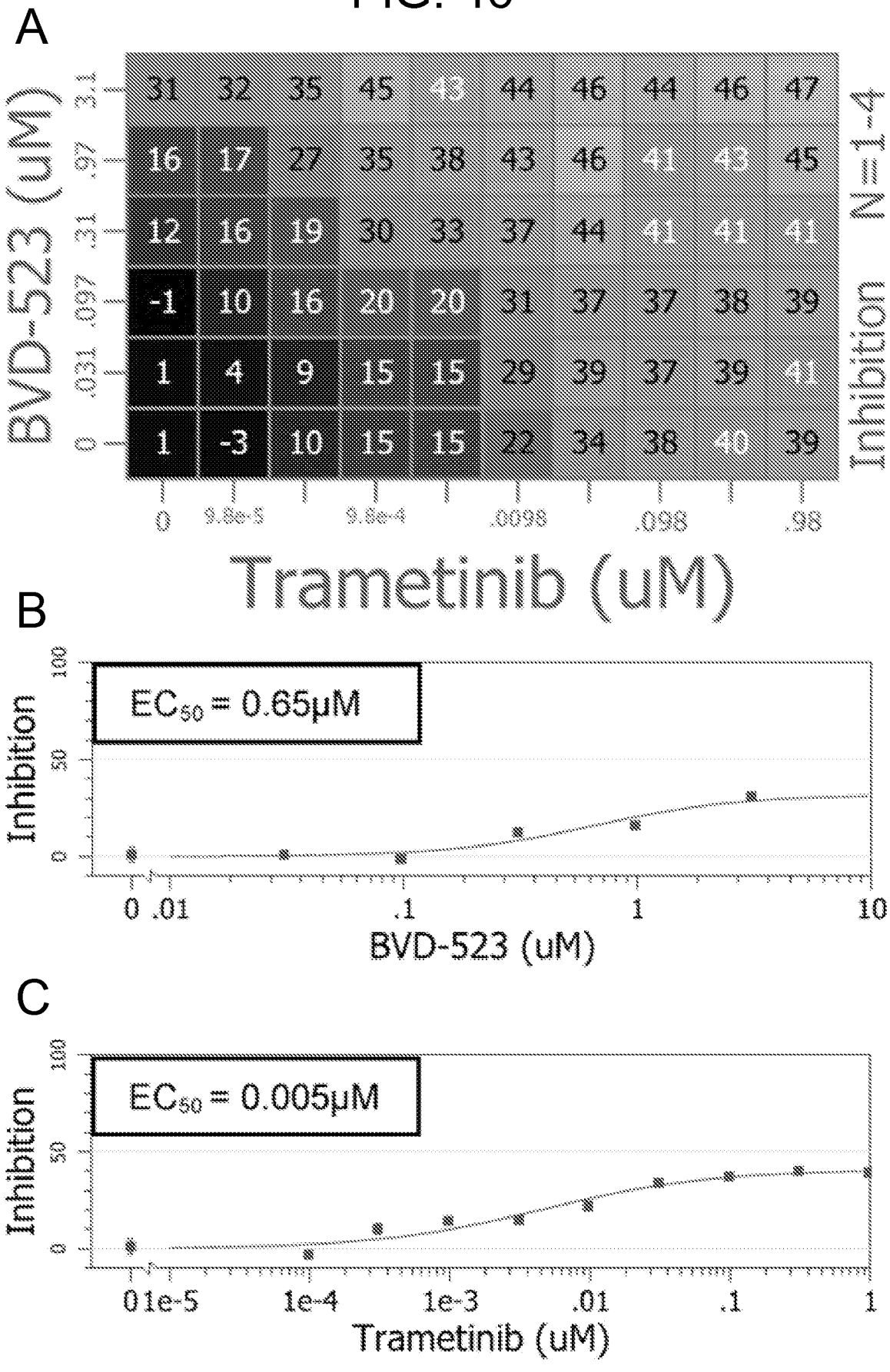
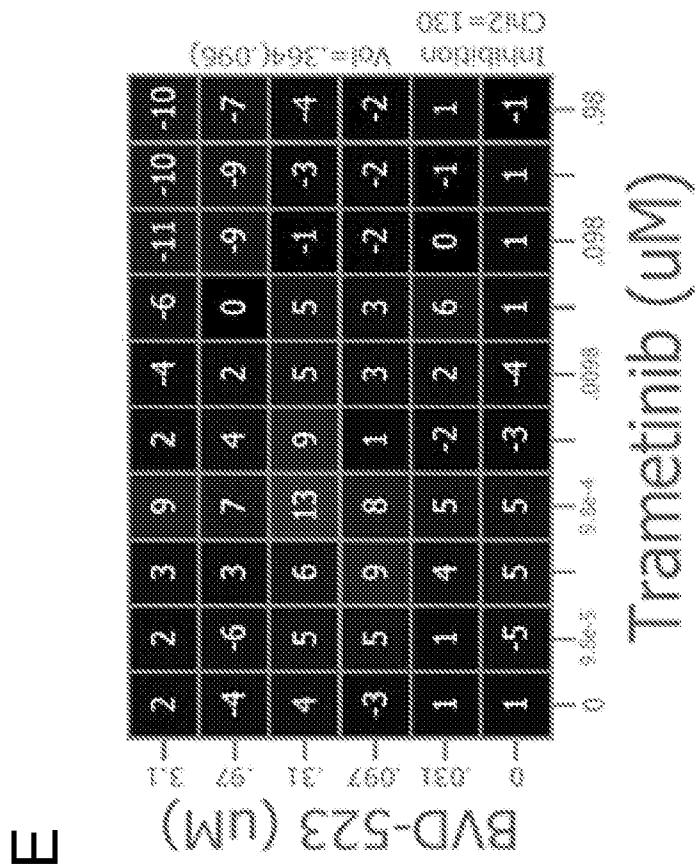

A
BVD-523 (uM)
3.1
.97
.31
.097
.031
0
31 32 35 45 43 44 46 44 46 47
16 17 27 35 38 43 46 41 43 45
12 16 19 30 33 37 44 41 41 41
-1 10 16 20 20 31 37 37 38 39
1 4 9 15 15 29 39 37 39 41
1 -3 10 15 15 22 34 38 40 39
Inhibition N=1-4
0
9.8e-5
9.8e-4
.0098
.098
.98
Trametinib (uM)
B
Inhibition
100
50
0
EC50 = 0.65μM
0 .01
.1
1
10
BVD-523 (uM)
C
Inhibition
100
50
0
EC50 = 0.005μM
01e-5
1e-4
1e-3
.01
.1
1
Trametinib (uM)

FIG. 46, Con't


E
Inhibition
Vol=.364(.996)
CN2=130
BVD-523 (uM)
Trametinib (uM)
0
.031
.097
.31
.97
3.1
0
.003
.01
.03
.1
.3
1
3
10

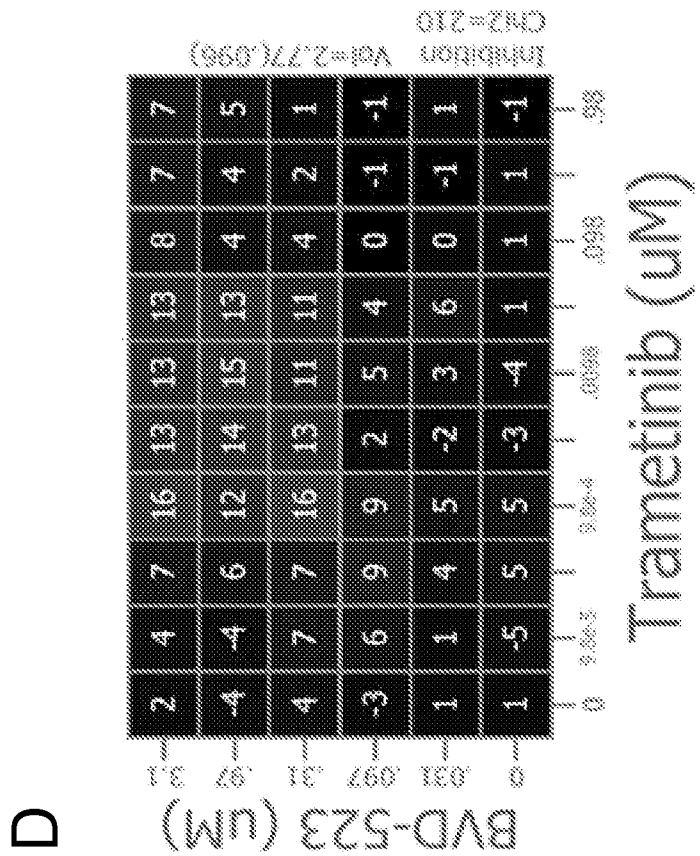

D
Inhibition
Vol=2.77(.996)
CN2=210
BVD-523 (uM)
Trametinib (uM)
0
.031
.097
.31
.97
3.1
0
.003
.01
.03
.1
.3
1
3
10

FIG. 47

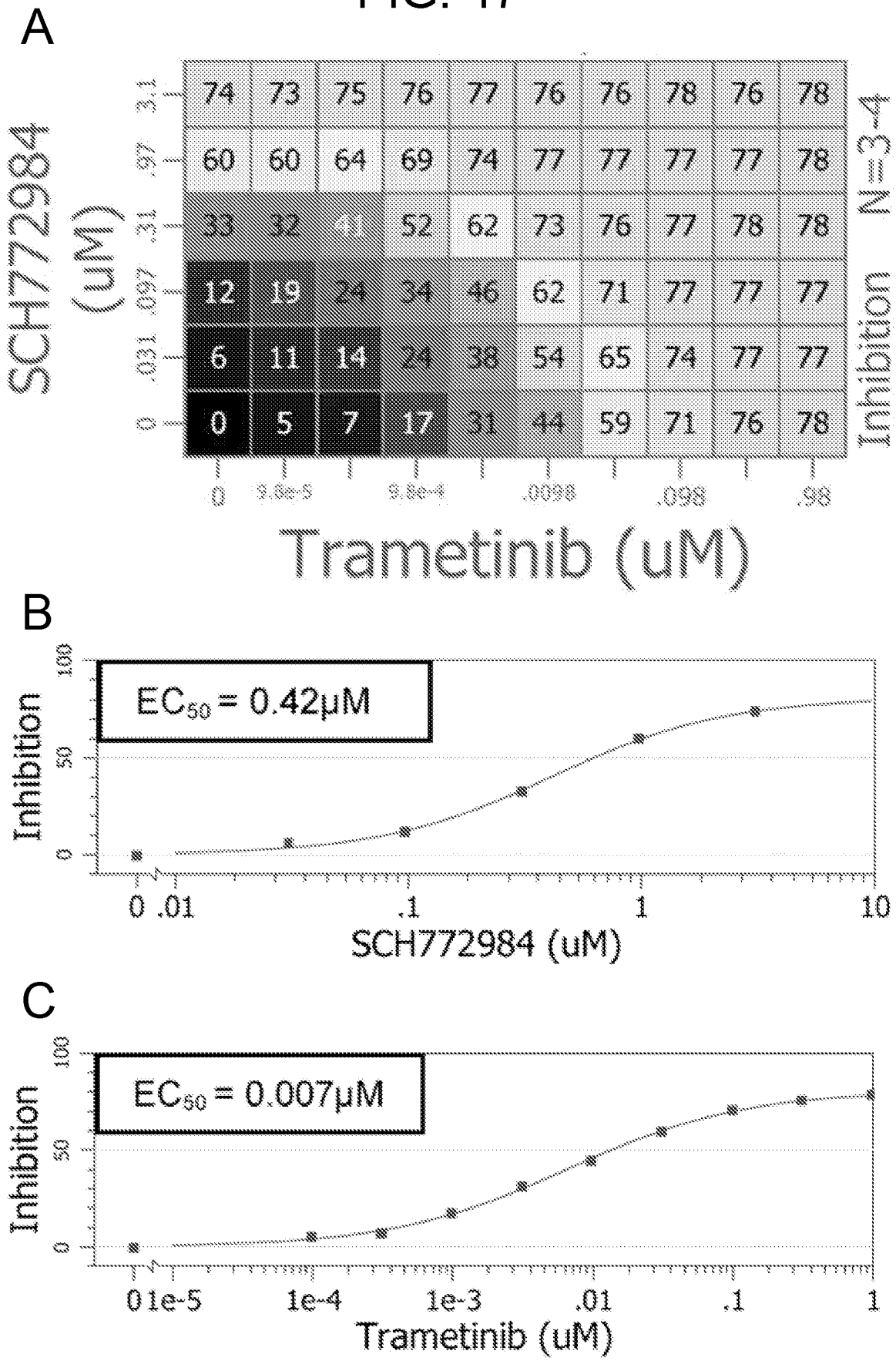
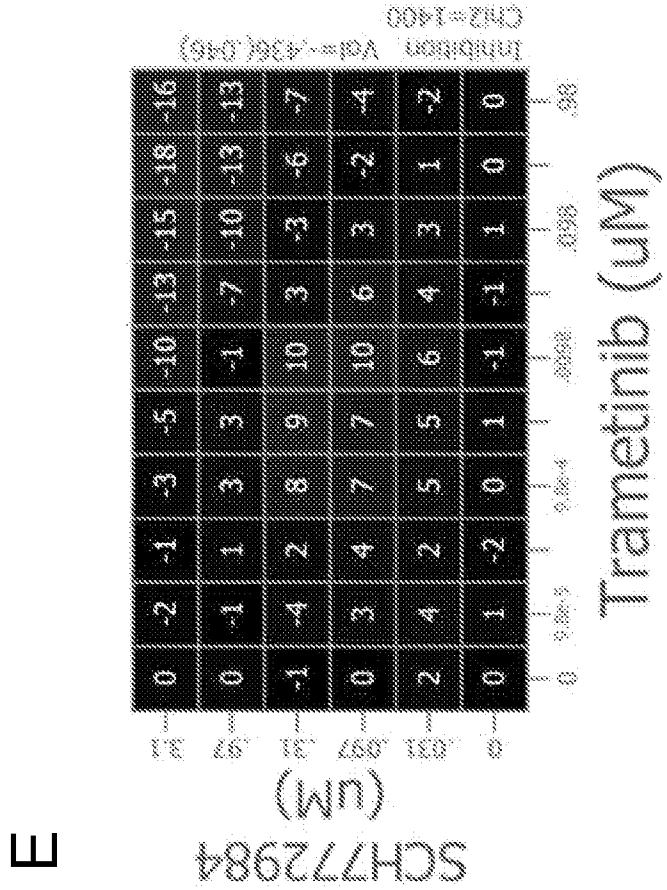

A
SCH772984 (uM)
3.1
.97
.31
.097
.031
0
74 73 75 76 77 76 76 78 76 78
60 60 64 69 74 77 77 77 77 78
33 32 41 52 62 73 76 77 78 78
12 19 24 34 46 62 71 77 77 77
6 11 14 24 38 54 65 74 77 77
0 5 7 17 31 44 59 71 76 78
Inhibition N=3-4
0
9.8e-5
9.8e-4
.0098
.098
.98
Trametinib (uM)
B
Inhibition
100
50
0
EC50 = 0.42μM
0 .01
.1
1
10
SCH772984 (uM)
C
Inhibition
100
50
0
EC50 = 0.007μM
01e-5
1e-4
1e-3
.01
.1
1
Trametinib (uM)

FIG. 47, Con't


E
SCH772984 (uM)
Trametinib (uM)
Inhibition Vol=-.436(.046)
CN2=1400

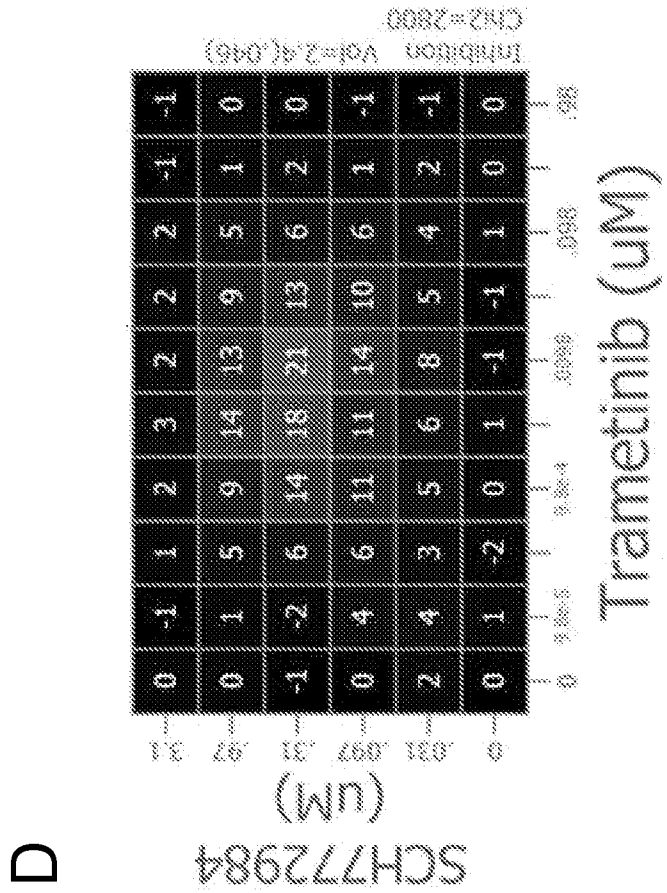

D
SCH772984 (uM)
Trametinib (uM)
Inhibition Vol=2.4(.046)
CN2=2800

FIG. 48

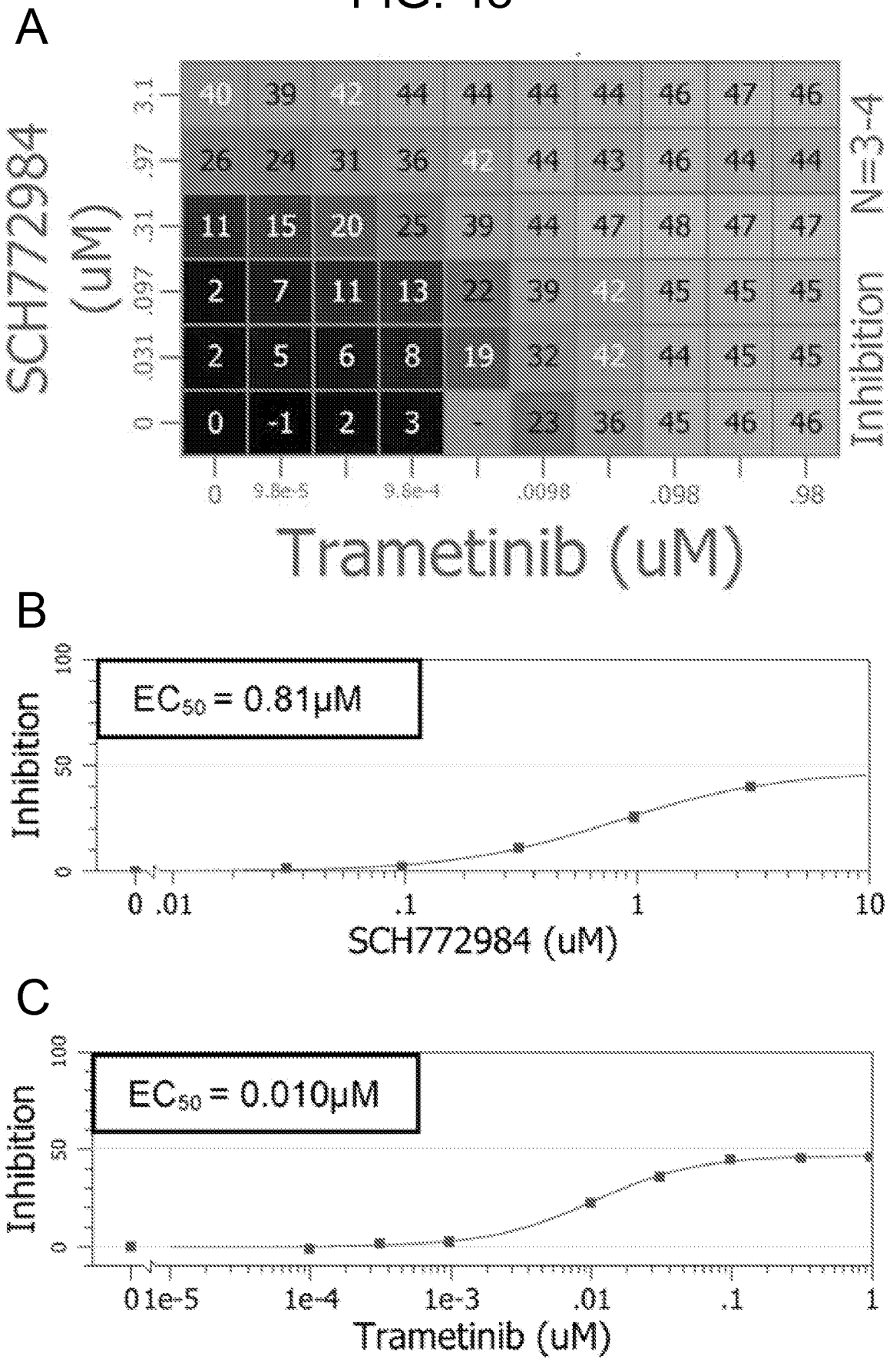

A
SCH772984 (uM)
3.1
.97
.31
.097
.031
0
40 39 42 44 44 44 44 46 47 46
26 24 31 36 42 44 43 46 44 44
11 15 20 25 39 44 47 48 47 47
2 7 11 13 22 39 42 45 45 45
2 5 6 8 19 32 42 44 45 45
0 -1 2 3 - 23 36 45 46 46
0
9.8e-5
9.8e-4
.0098
.098
.98
Trametinib (uM)
Inhibition N=3-4
B
Inhibition
100
50
0
EC50 = 0.81µM
0 .01 .1 1 10
SCH772984 (uM)
C
Inhibition
100
50
0
EC50 = 0.010µM
01e-5 1e-4 1e-3 .01 .1 1
Trametinib (uM)

FIG. 48, Con't

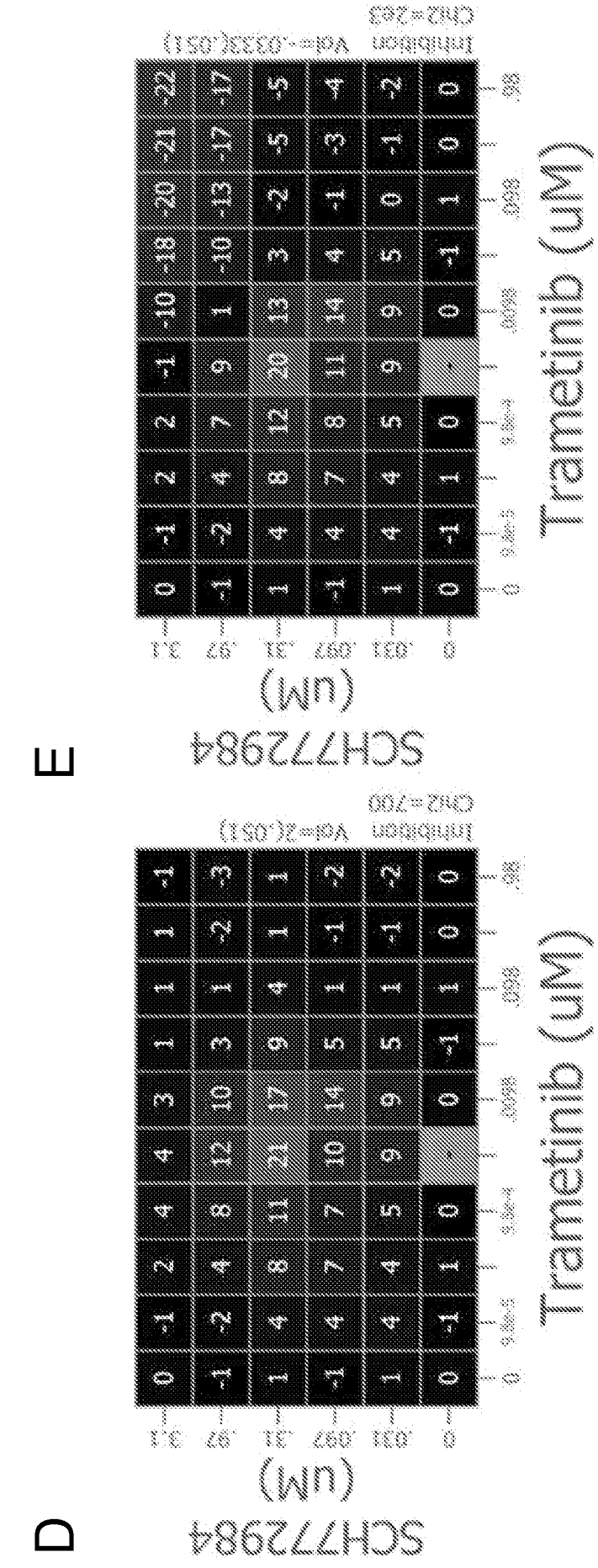
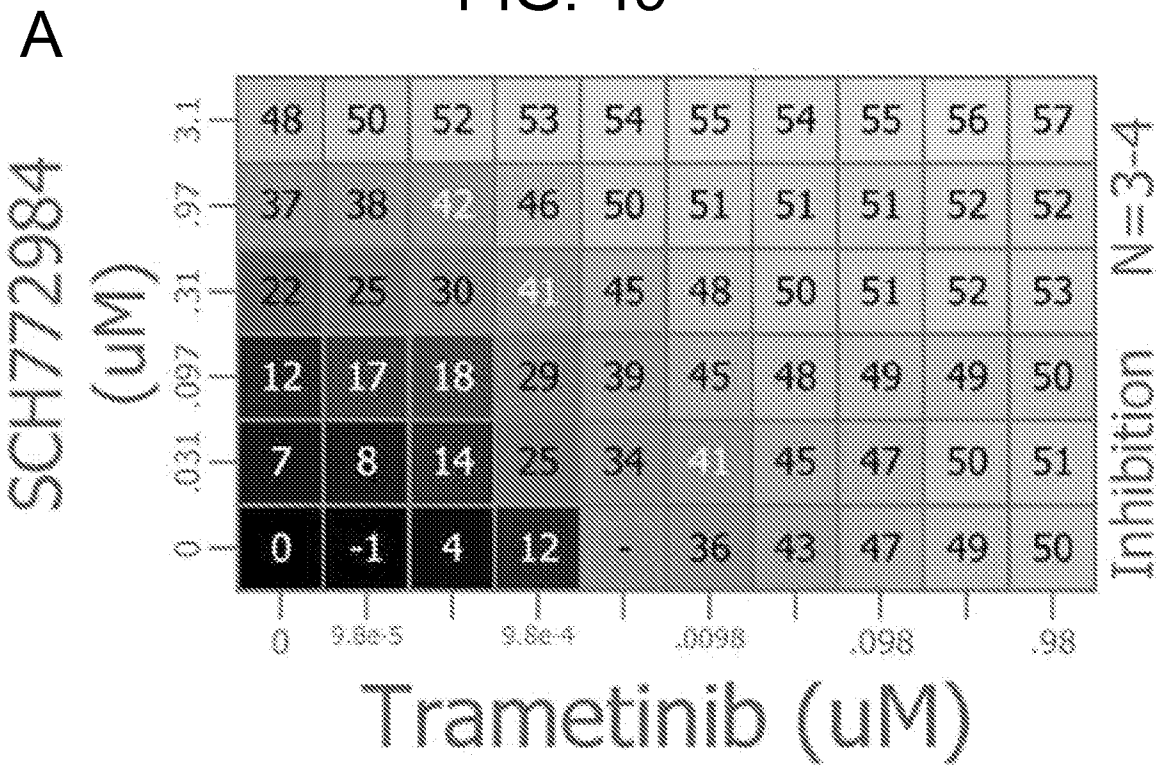
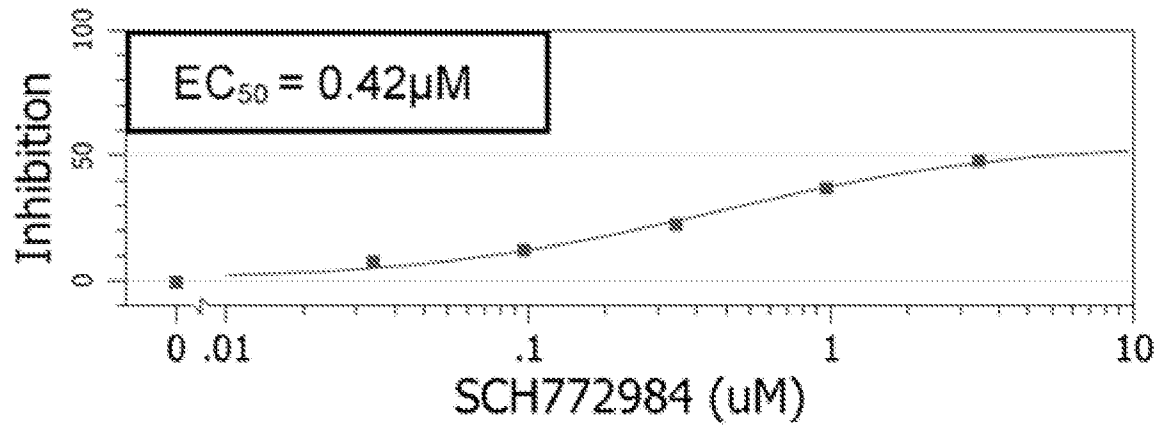

E
SCH772984
(uM)
Trametinib (uM)
Inhibition
Vol=-.0333(.051)
Chi2=263
D
SCH772984
(uM)
Trametinib (uM)
Inhibition
Vol=3(.051)
Chi2=709

FIG. 49


A
SCH772984 (uM)
3.1
.97
.31
.097
.031
0
48 50 52 53 54 55 54 55 56 57
37 38 42 46 50 51 51 51 52 52
22 25 30 41 45 48 50 51 52 53
12 17 18 29 39 45 48 49 49 50
7 8 14 25 34 41 45 47 50 51
0 -1 4 12 - 36 43 47 49 50
N=3-4
Inhibition
0
9.8e-5
9.8e-4
.0098
.098
.98
Trametinib (uM)


B
Inhibition
100
50
0
EC50 = 0.42μM
0 .01
.1
1
10
SCH772984 (uM)

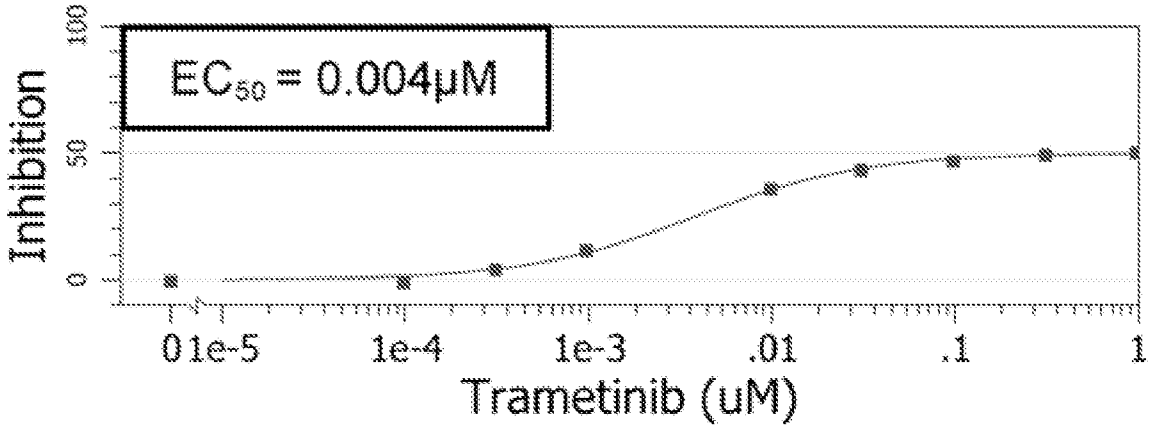

C
Inhibition
100
50
0
EC50 = 0.004μM
01e-5
1e-4
1e-3
.01
.1
1
Trametinib (uM)

FIG. 49, Con't

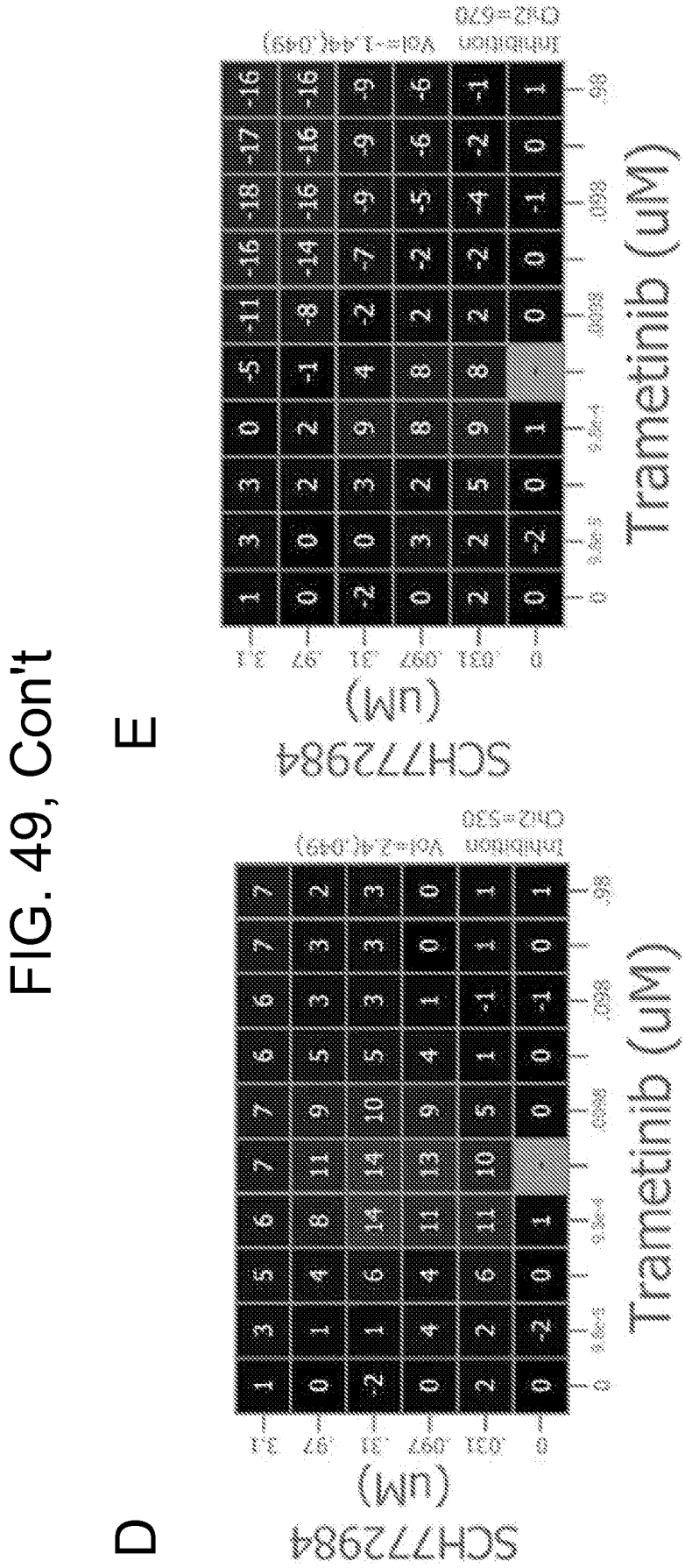
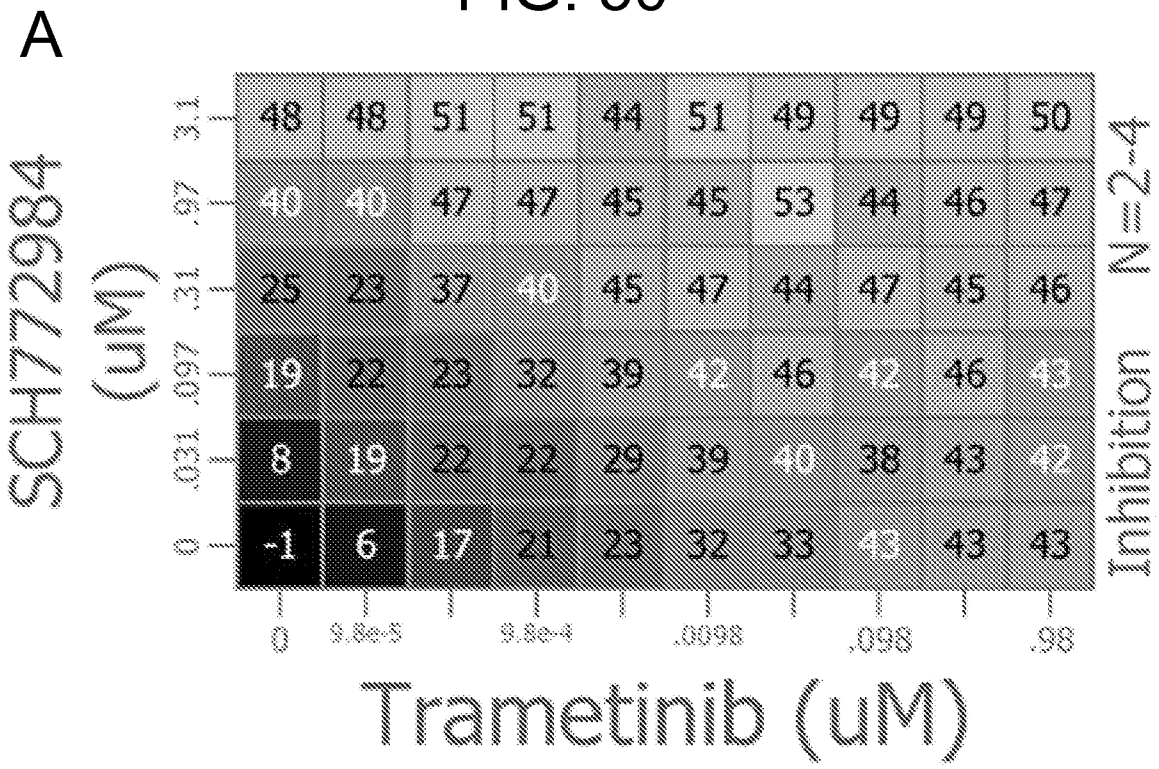
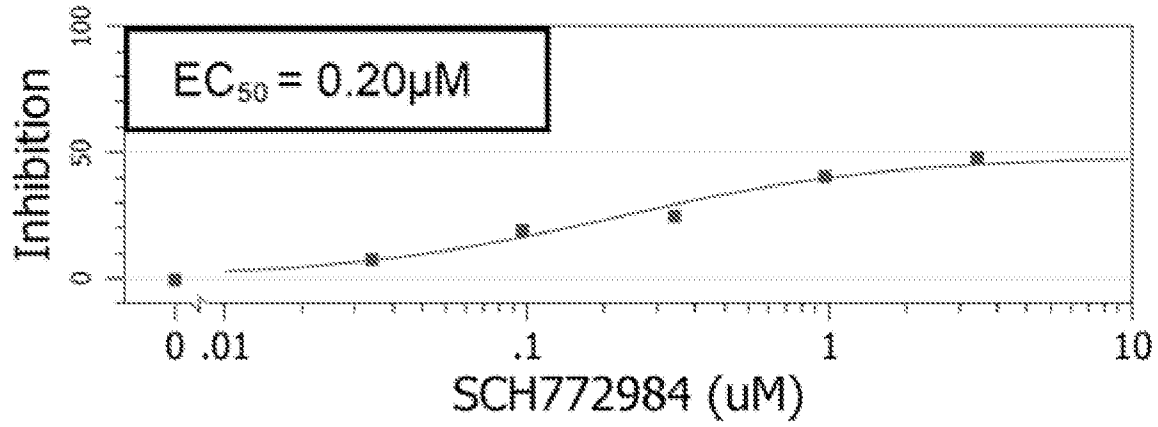

E
SCH772984 (uM)
Trametinib (uM)
Inhibition
D
SCH772984 (uM)
Trametinib (uM)
Inhibition

FIG. 50


A
SCH772984 (uM)
3.1
.97
.31
.097
.031
0
48 48 51 51 44 51 49 49 49 50
40 40 47 47 45 45 53 44 46 47
25 23 37 40 45 47 44 47 45 46
19 22 23 32 39 42 46 42 46 43
8 19 22 22 29 39 40 38 43 42
-1 6 17 21 23 32 33 43 43 43
0 9.8e-5 9.8e-4 .0098 .098 .98
Trametinib (uM)
Inhibition N=2-4


B
Inhibition
100
50
0
EC50 = 0.20μM
0 .01 .1 1 10
SCH772984 (uM)

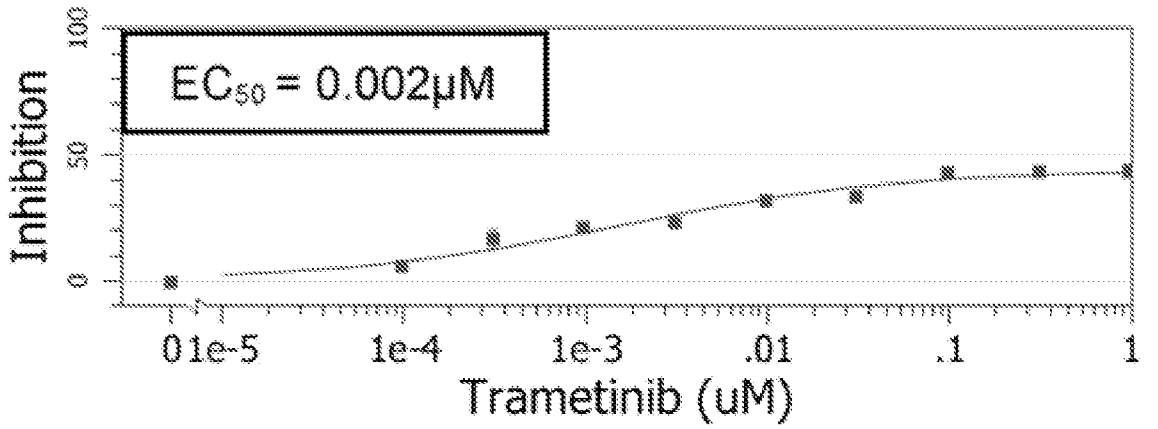
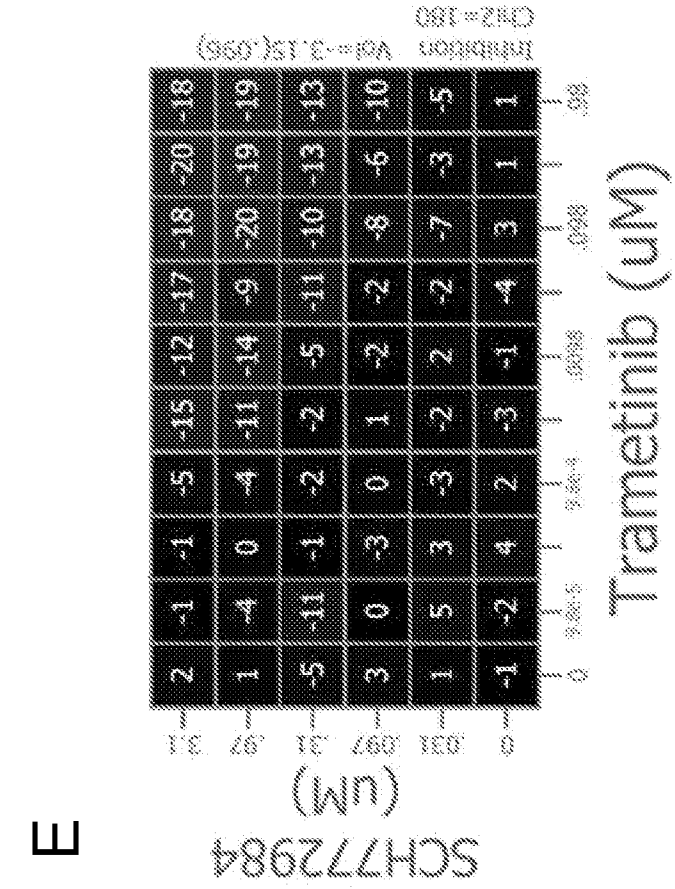

C
Inhibition
100
50
0
EC50 = 0.002μM
01e-5 1e-4 1e-3 .01 .1 1
Trametinib (uM)

FIG. 50, Con't


E
SCH772984
(uM)
Trametinib (uM)
Inhibition Vol=-3.15(.056)
CM2=180

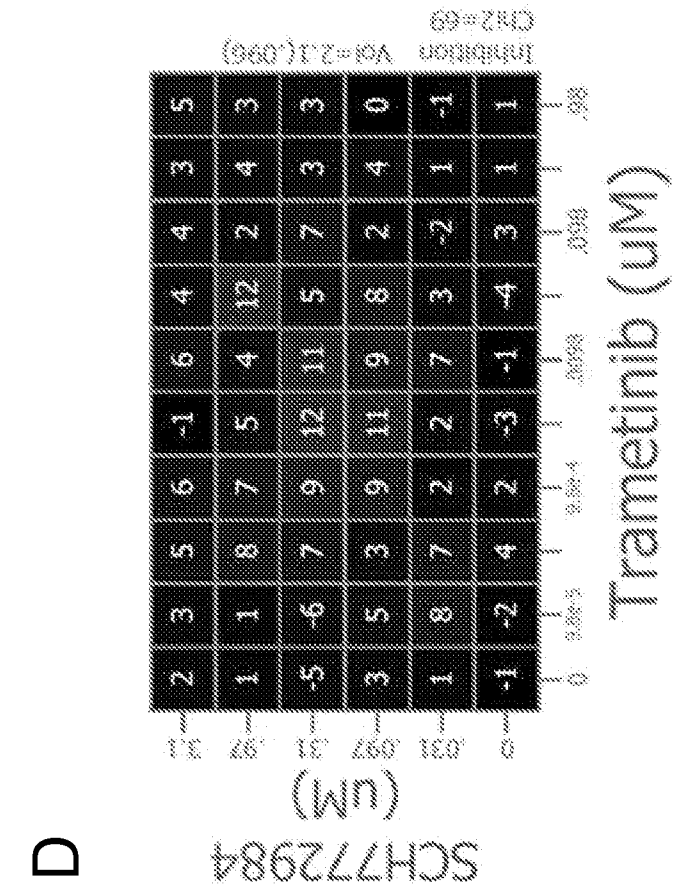

D
SCH772984
(uM)
Trametinib (uM)
Inhibition Vol=2.1(.096)
CM2=69

FIG. 51

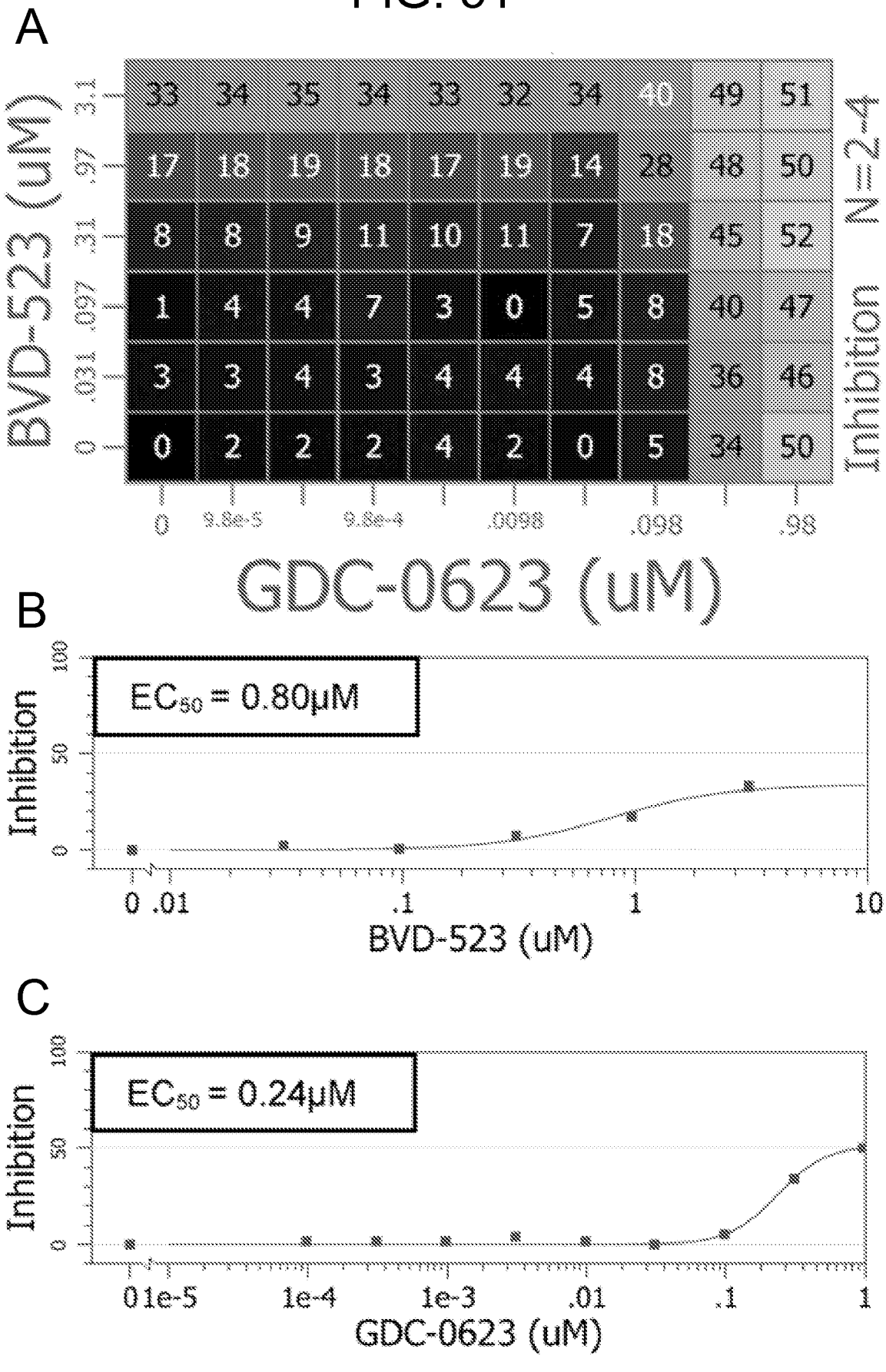

A
BVD-523 (uM)
3.1
.97
.31
.097
.031
0
33 34 35 34 33 32 34 40 49 51
17 18 19 18 17 19 14 28 48 50
8 8 9 11 10 11 7 18 45 52
1 4 4 7 3 0 5 8 40 47
3 3 4 3 4 4 4 8 36 46
0 2 2 2 4 2 0 5 34 50
Inhibition N=2-4
0
9.8e-5
9.8e-4
.0098
.098
.98
GDC-0623 (uM)
B
Inhibition
100
50
0
EC50 = 0.80μM
0 .01
.1
1
10
BVD-523 (uM)
C
Inhibition
100
50
0
EC50 = 0.24μM
01e-5
1e-4
1e-3
.01
.1
1
GDC-0623 (uM)

FIG. 51, Con't

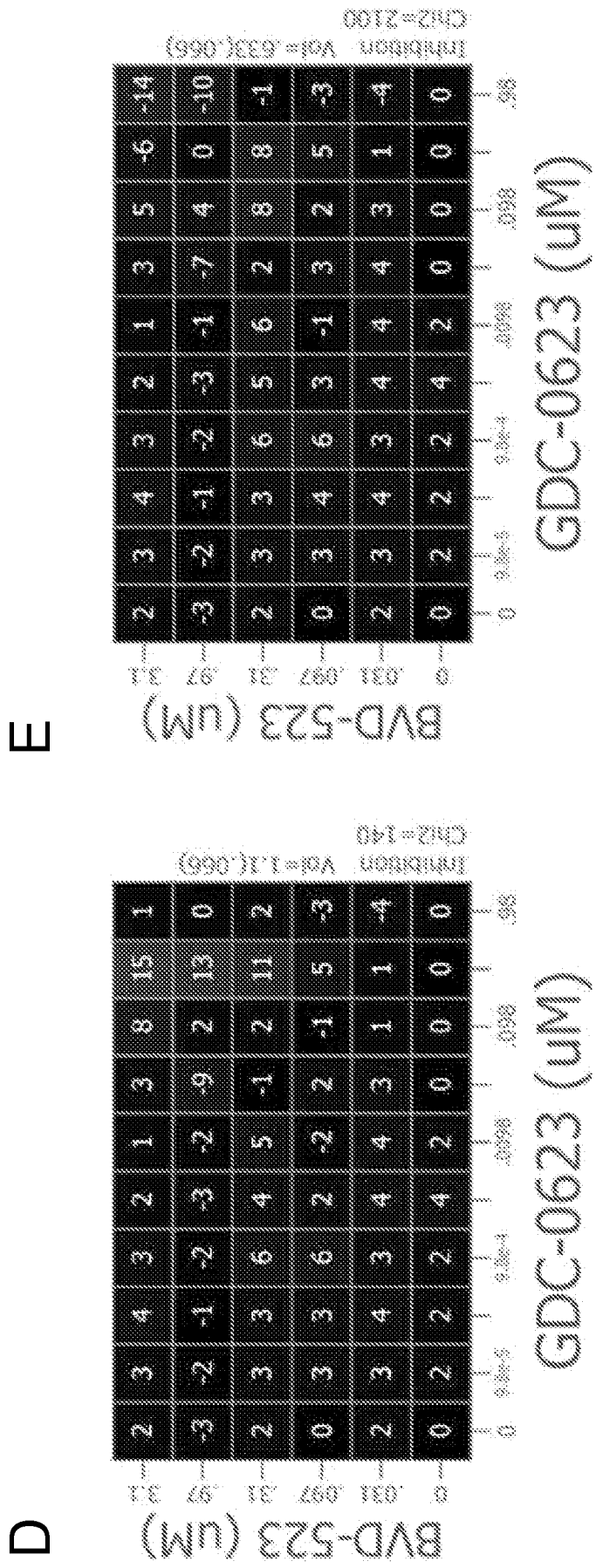

D
E
BVD-523 (uM)
GDC-0623 (uM)
Inhibition
Vol=1.1(.066)
Ch2=140
Vol=.633(.066)
Ch2=2100
0
.031
.097
.31
.97
3.1
0
20
40
60
80
100

FIG. 52

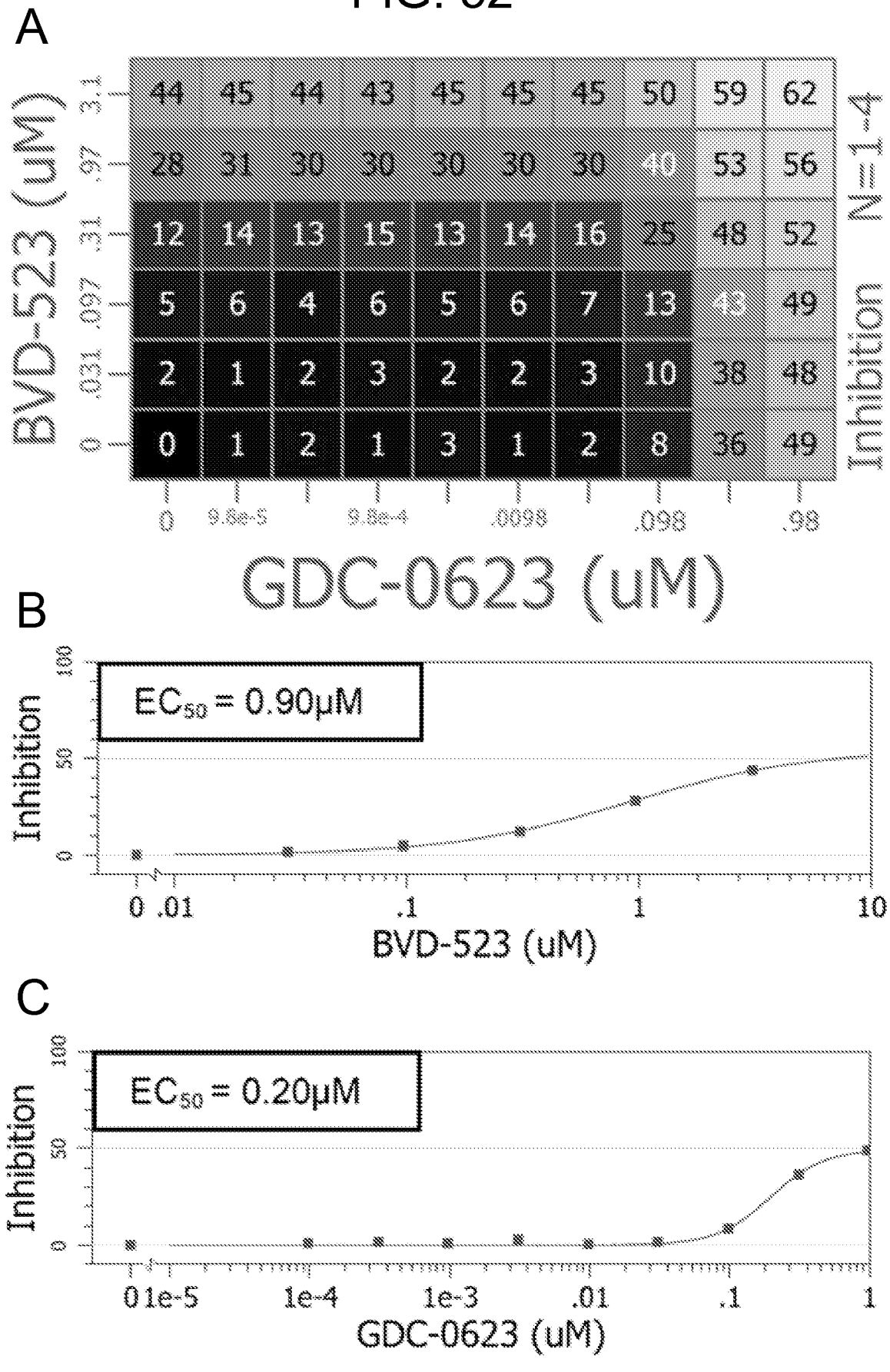

A
BVD-523 (uM)
3.1
.97
.31
.097
.031
0
44 45 44 43 45 45 45 50 59 62
28 31 30 30 30 30 30 40 53 56
12 14 13 15 13 14 16 25 48 52
5 6 4 6 5 6 7 13 43 49
2 1 2 3 2 2 3 10 38 48
0 1 2 1 3 1 2 8 36 49
N=1-4
Inhibition
0
9.8e-5
9.8e-4
.0098
.098
.98
GDC-0623 (uM)
B
Inhibition
100
50
0
EC50 = 0.90μM
0 .01
.1
1
10
BVD-523 (uM)
C
Inhibition
100
50
0
EC50 = 0.20μM
01e-5
1e-4
1e-3
.01
.1
1
GDC-0623 (uM)

FIG. 52, Con't

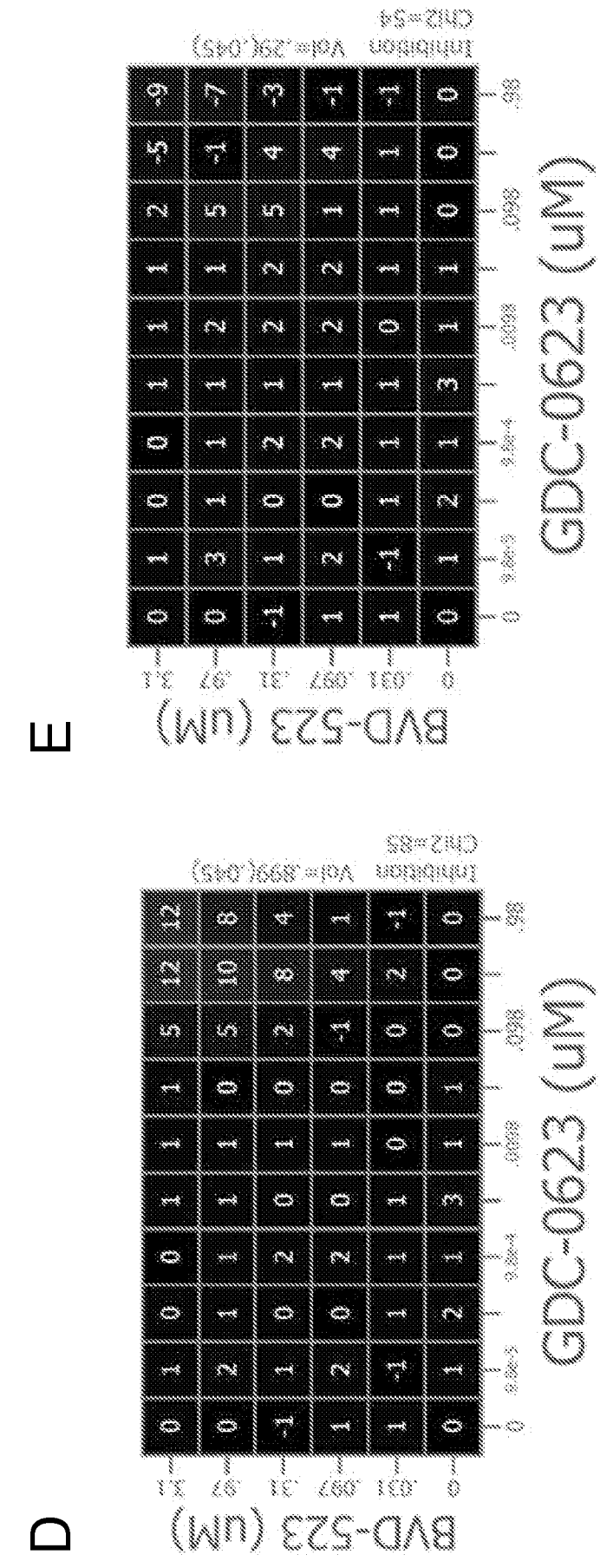

E
BVD-523 (uM)
GDC-0623 (uM)
Inhibition Vd=.29(.045)
CM2=54
D
BVD-523 (uM)
GDC-0623 (uM)
Inhibition Vd=.899(.045)
CM2=85

FIG. 53

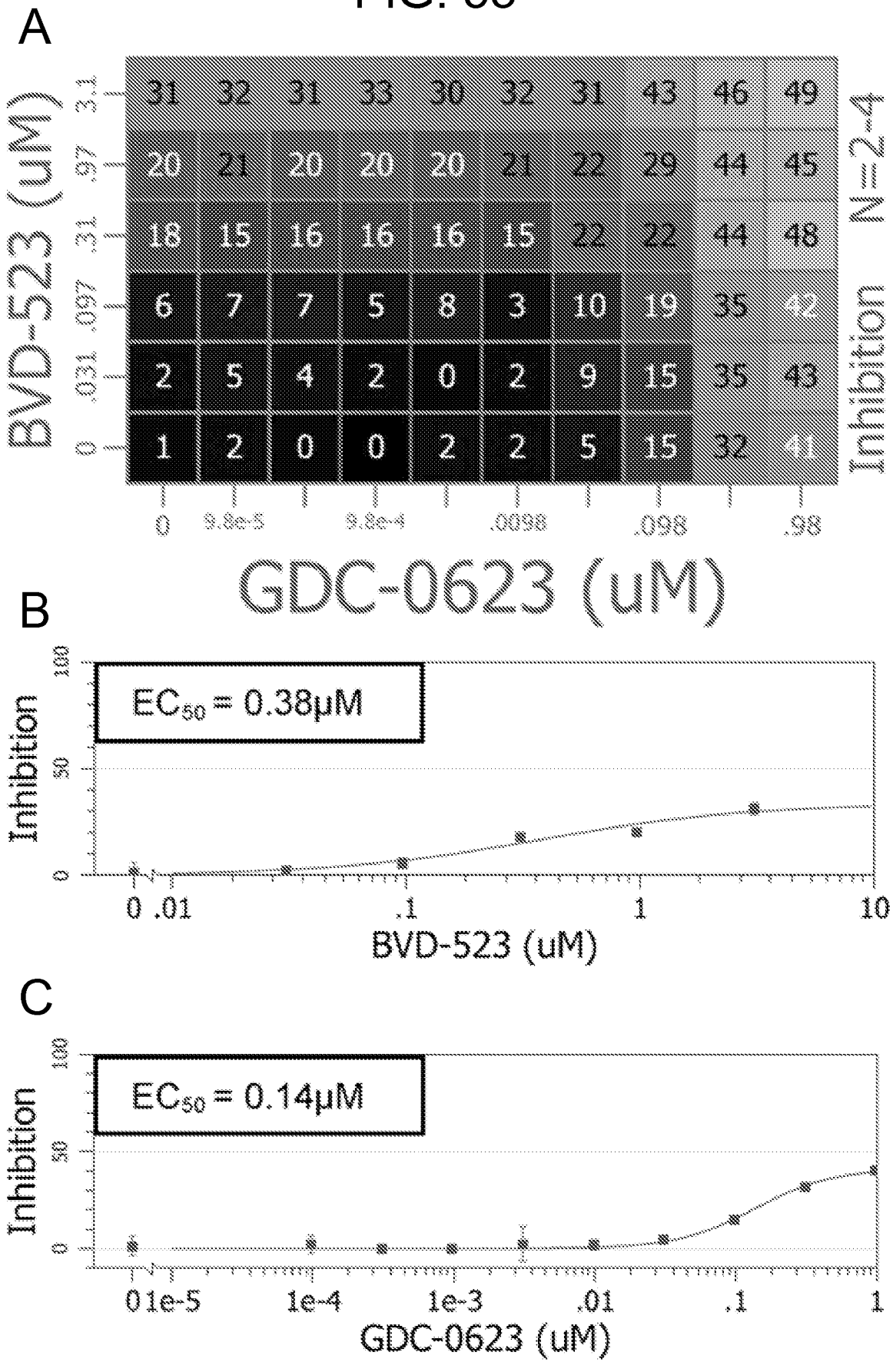

A
BVD-523 (uM)
3.1
.97
.31
.097
.031
0
31 32 31 33 30 32 31 43 46 49
20 21 20 20 20 21 22 29 44 45
18 15 16 16 16 15 22 22 44 48
6 7 7 5 8 3 10 19 35 42
2 5 4 2 0 2 9 15 35 43
1 2 0 0 2 2 5 15 32 41
Inhibition N=2-4
0 9.8e-5 9.8e-4 .0098 .098 .98
GDC-0623 (uM)
B
Inhibition
100
50
0
EC50 = 0.38μM
0 .01 .1 1 10
BVD-523 (uM)
C
Inhibition
100
50
0
EC50 = 0.14μM
01e-5 1e-4 1e-3 .01 .1 1
GDC-0623 (uM)

FIG. 53, Con't

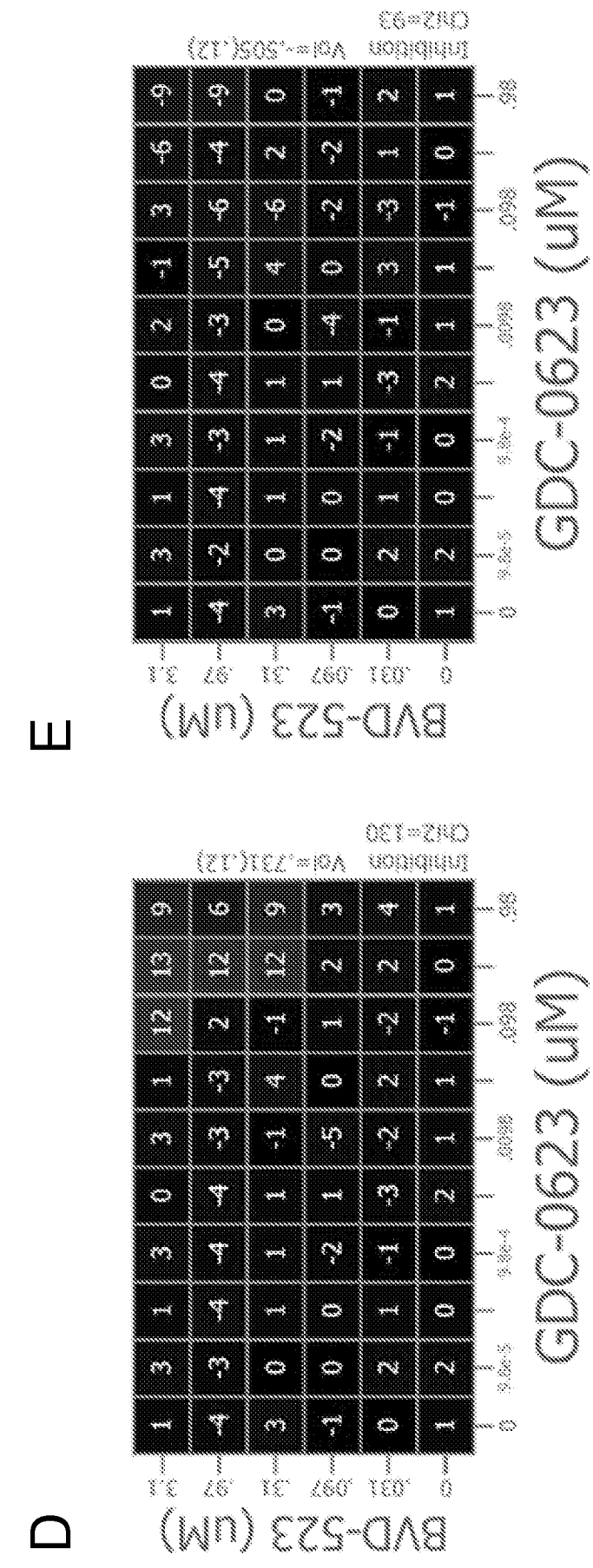
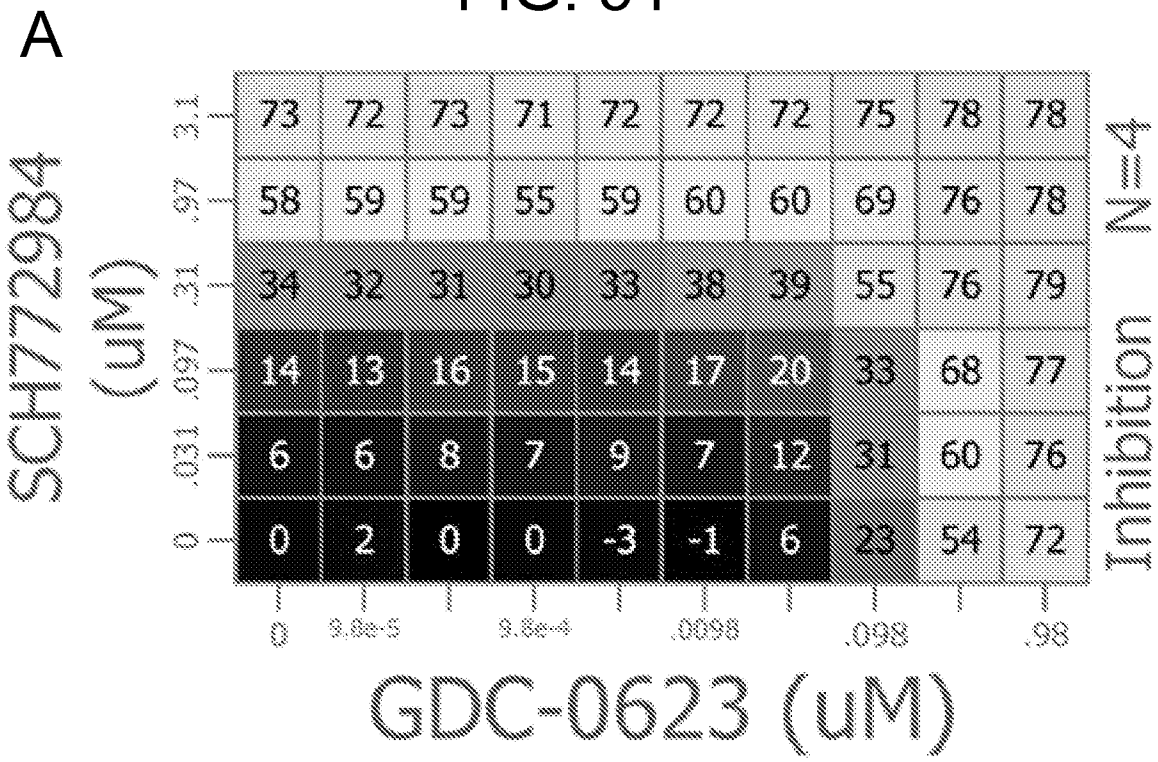
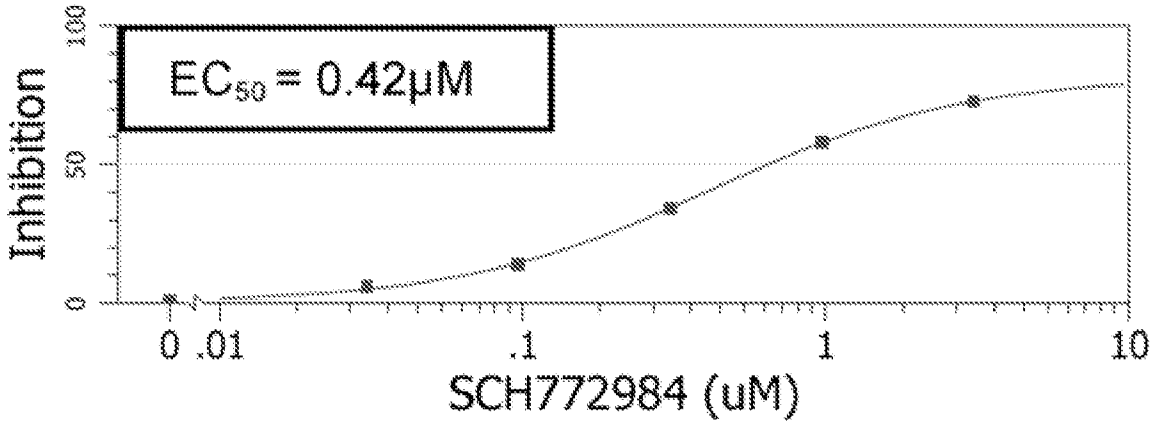

E
BVD-523 (uM)
GDC-0623 (uM)
Inhibition Val=-.505(.12) CN2=93
D
BVD-523 (uM)
GDC-0623 (uM)
Inhibition Val=.731(.12) CN2=130

FIG. 54


A
SCH772984 (uM)
3.1
.97
.31
.097
.031
0
73 72 73 71 72 72 72 75 78 78
58 59 59 55 59 60 60 69 76 78
34 32 31 30 33 38 39 55 76 79
14 13 16 15 14 17 20 33 68 77
6 6 8 7 9 7 12 31 60 76
0 2 0 0 -3 -1 6 23 54 72
N=4
Inhibition
0
9.8e-5
9.8e-4
.0098
.098
.98
GDC-0623 (uM)


B
Inhibition
100
50
0
EC50 = 0.42μM
0 .01
.1
1
10
SCH772984 (uM)

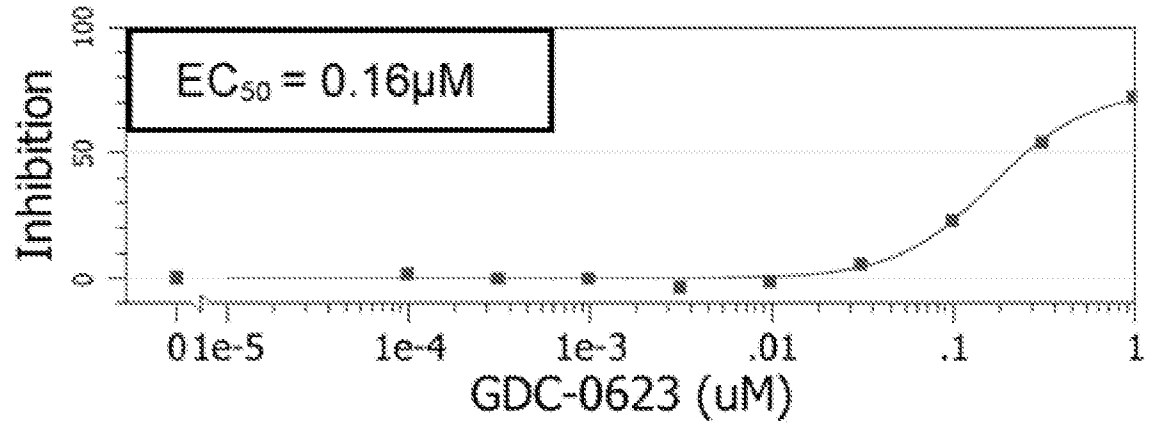

C
Inhibition
100
50
0
EC50 = 0.16μM
01e-5
1e-4
1e-3
.01
.1
1
GDC-0623 (uM)

FIG. 54, Con't

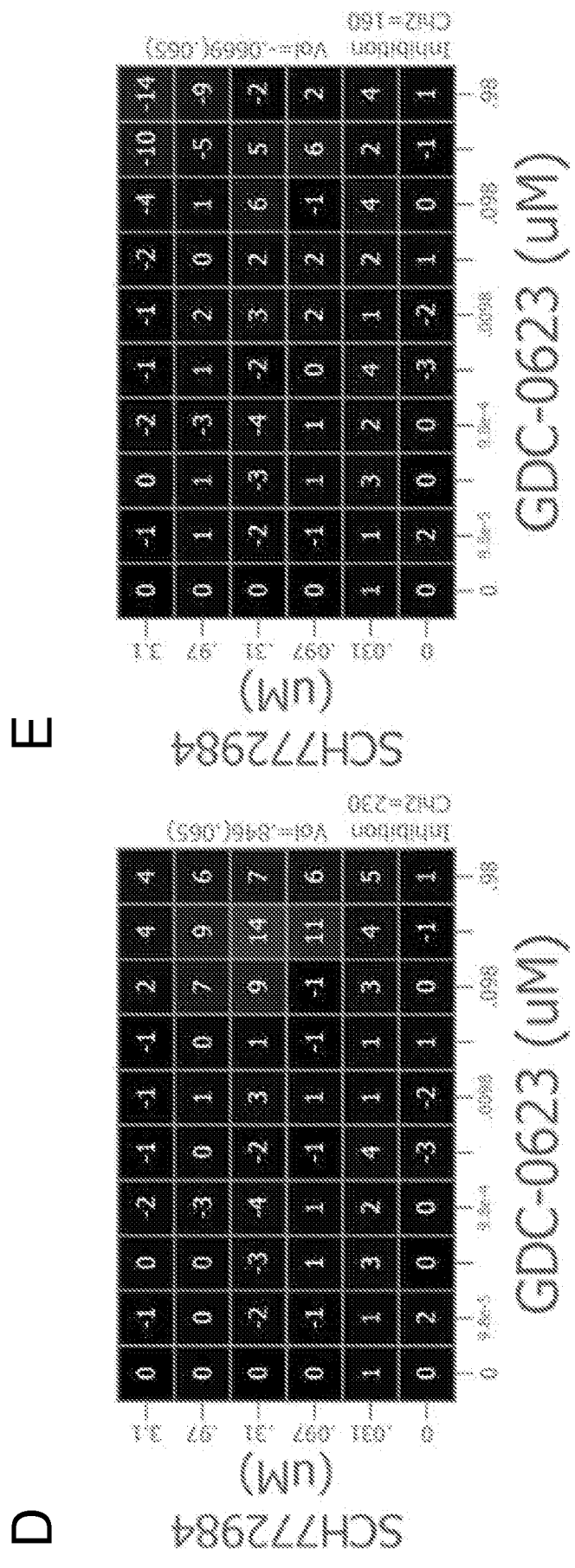
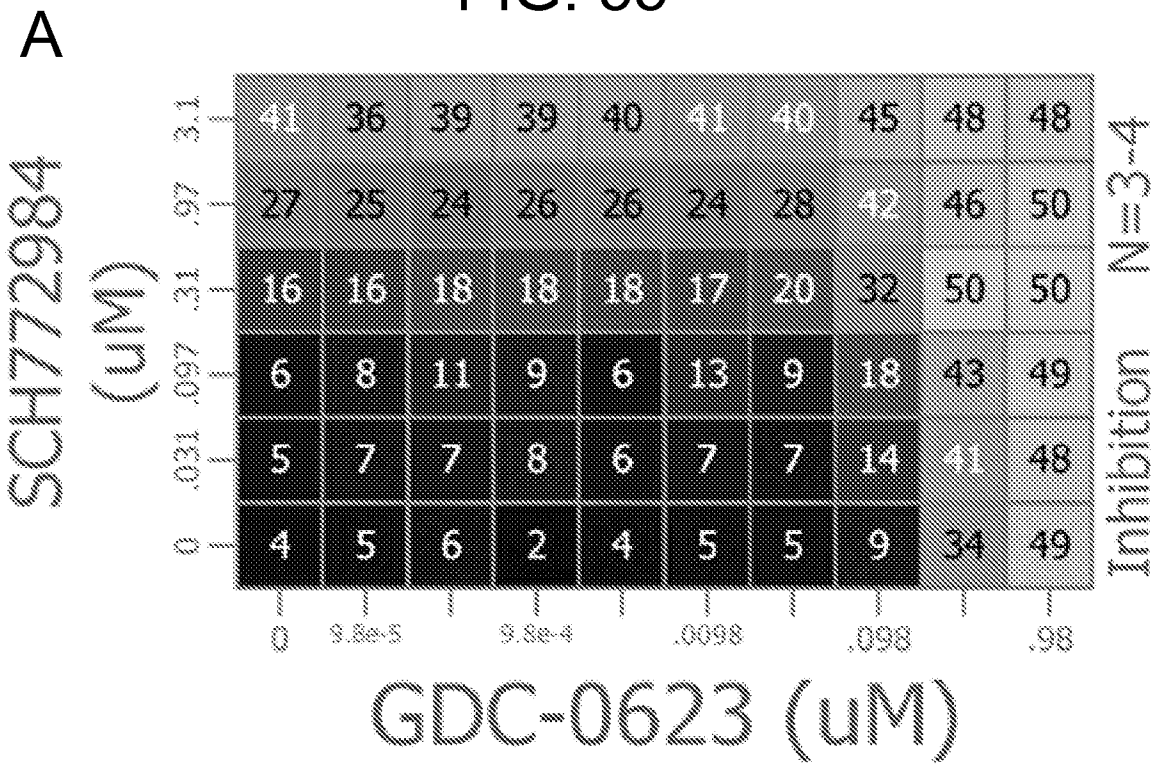
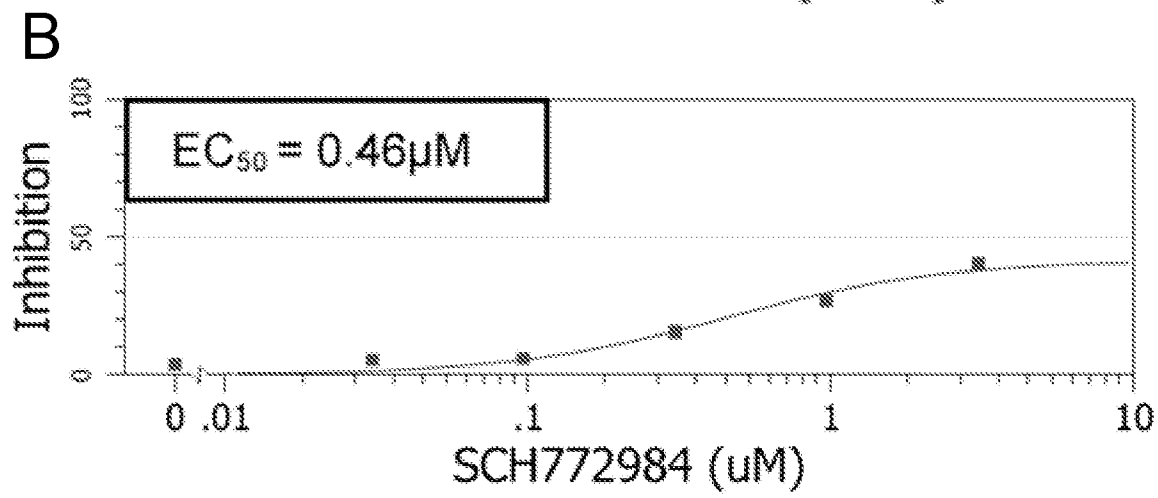

E
SCH772984 (uM)
GDC-0623 (uM)
Inhibition Vol=.0689(.065) CH2=160
D
SCH772984 (uM)
GDC-0623 (uM)
Inhibition Vol=.0456(.065) CH2=230

FIG. 55


A
SCH772984 (uM)
3.1
.97
.31
.097
.031
0
41 36 39 39 40 41 40 45 48 48
27 25 24 26 26 24 28 42 46 50
16 16 18 18 18 17 20 32 50 50
6 8 11 9 6 13 9 18 43 49
5 7 7 8 6 7 7 14 41 48
4 5 6 2 4 5 5 9 34 49
Inhibition N=3-4
0
9.8e-5
9.8e-4
.0098
.098
.98
GDC-0623 (uM)


B
Inhibition
100
50
0
EC50 = 0.46μM
0 .01
.1
1
10
SCH772984 (uM)

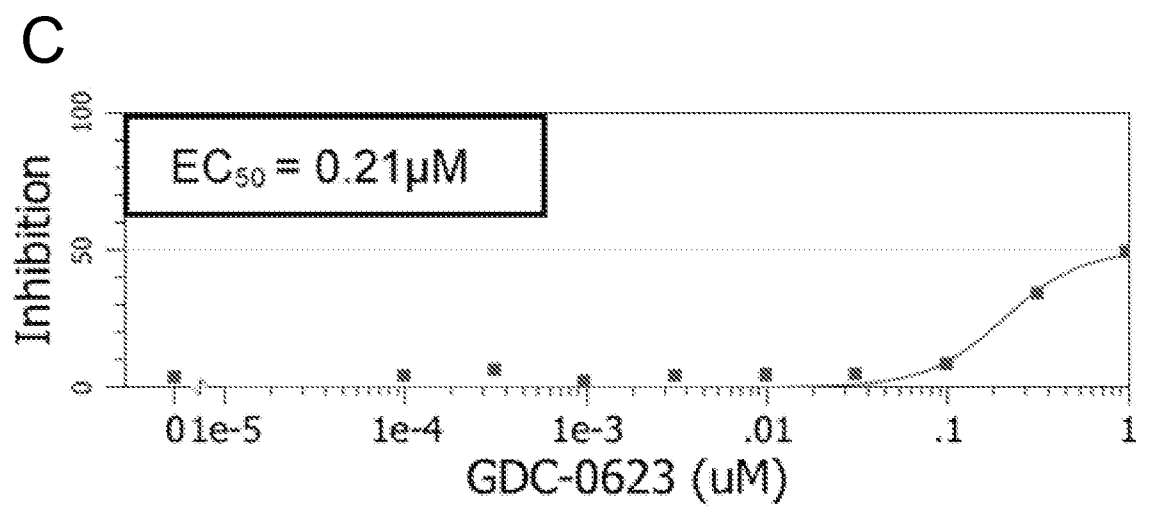
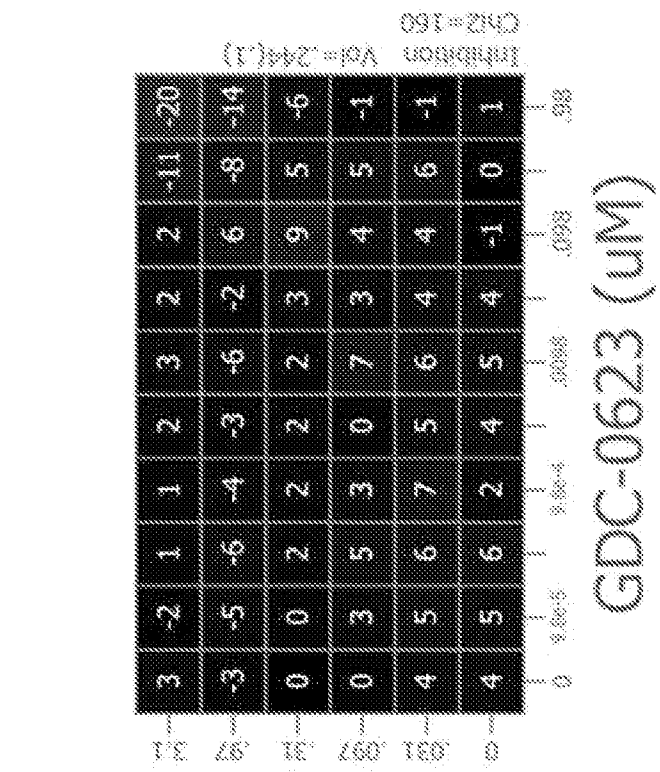

C
Inhibition
100
50
0
EC50 = 0.21μM
0 1e-5
1e-4
1e-3
.01
.1
1
GDC-0623 (uM)

FIG. 55, Con't


E
SCH772984
(uM)
GDC-0623 (uM)
Inhibition Vd=.244(.1)
CN2=160

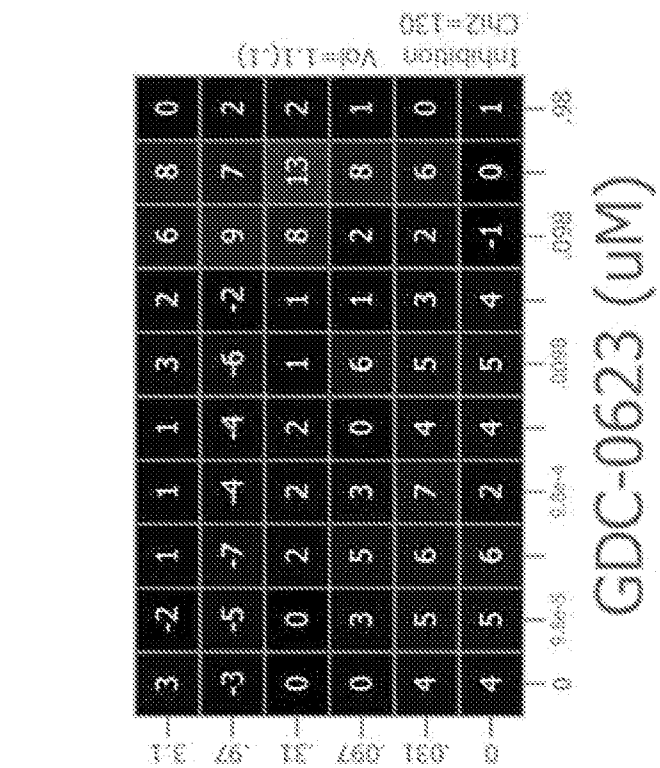
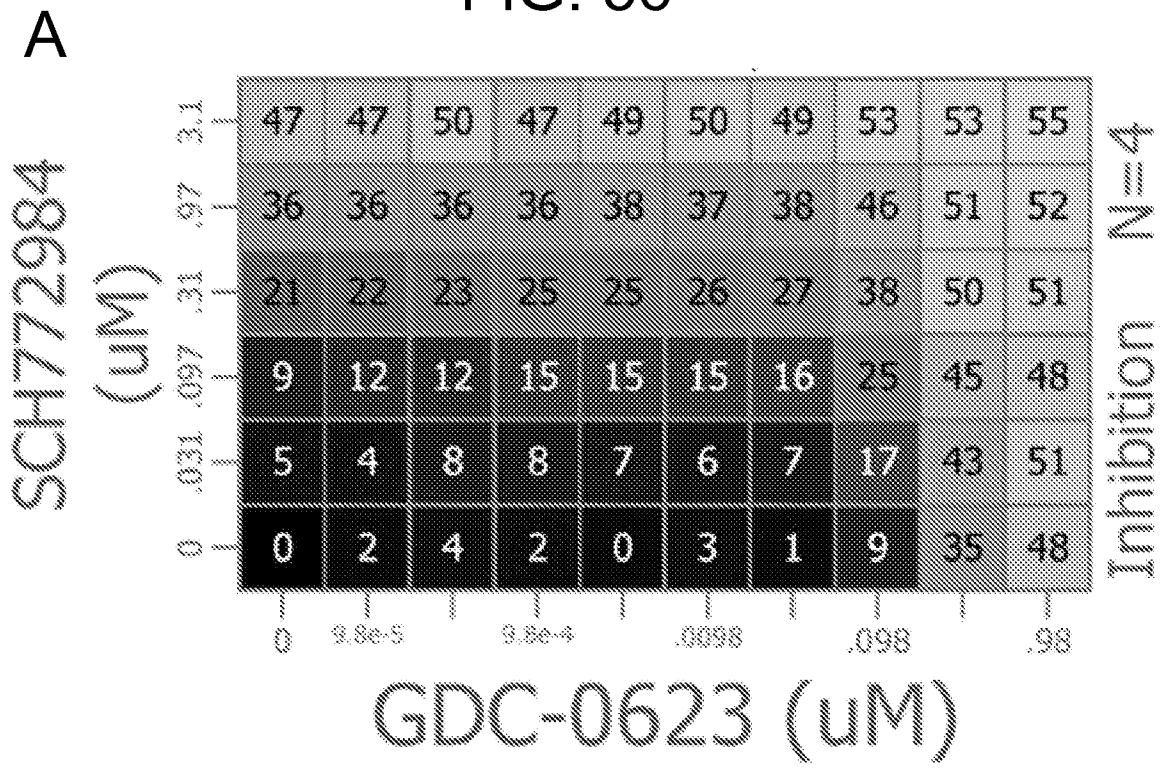
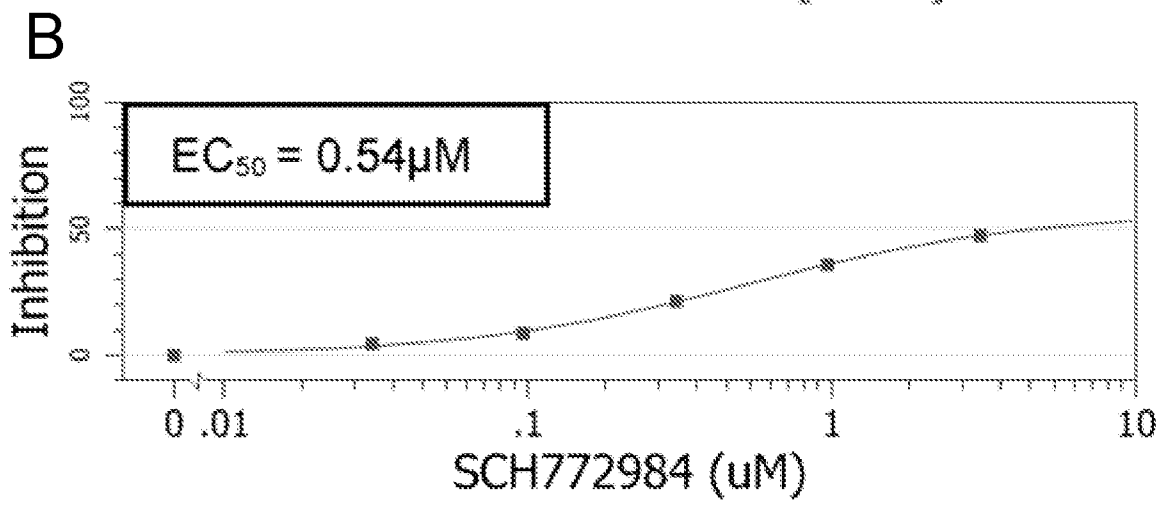

D
SCH772984
(uM)
GDC-0623 (uM)
Inhibition Vd=.1.1(.1)
CN2=130

FIG. 56


A
SCH772984 (uM)
3.1
.97
.31
.097
.031
0
47 47 50 47 49 50 49 53 53 55
36 36 36 36 38 37 38 46 51 52
21 22 23 25 25 26 27 38 50 51
9 12 12 15 15 15 16 25 45 48
5 4 8 8 7 6 7 17 43 51
0 2 4 2 0 3 1 9 35 48
Inhibition N=4
0
9.8e-5
9.8e-4
.0098
.098
.98
GDC-0623 (uM)


B
Inhibition
100
50
0
EC50 = 0.54μM
0 .01 .1 1 10
SCH772984 (uM)

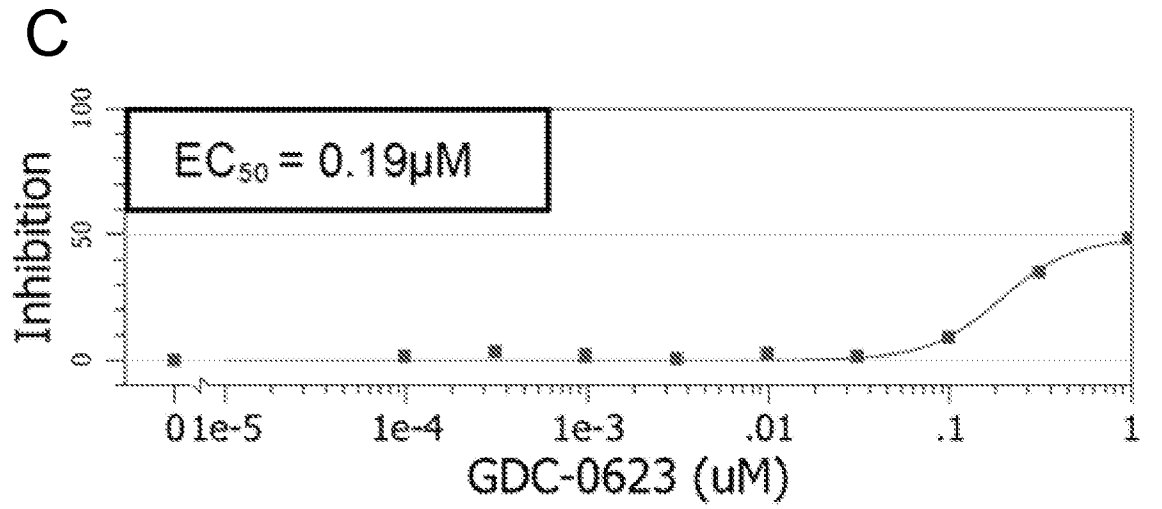

C
Inhibition
100
50
0
EC50 = 0.19μM
0 1e-5 1e-4 1e-3 .01 .1 1
GDC-0623 (uM)

FIG. 56, Con't

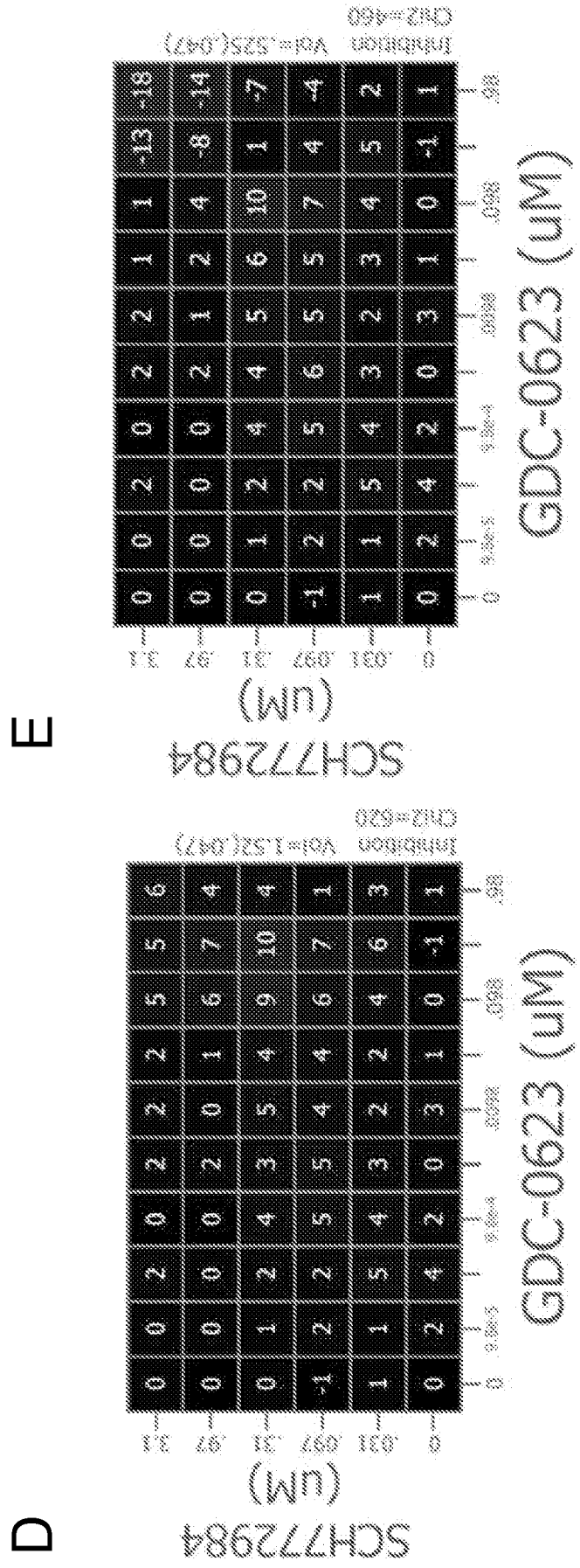
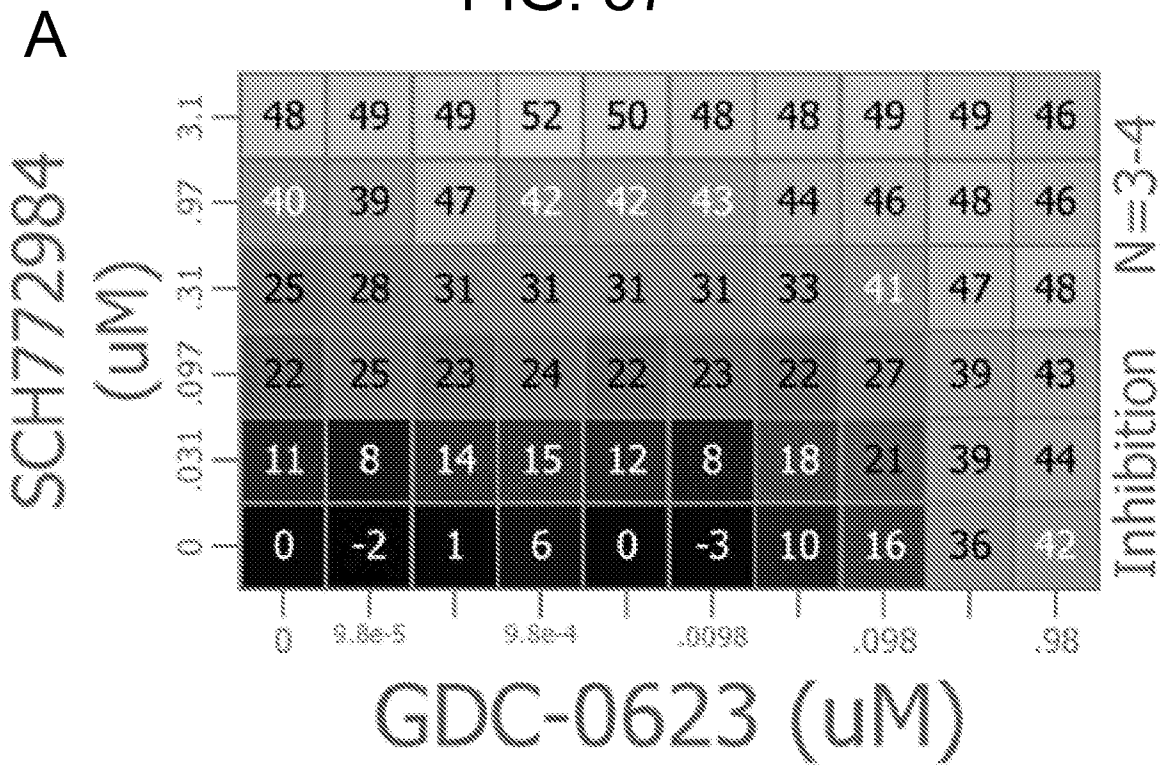
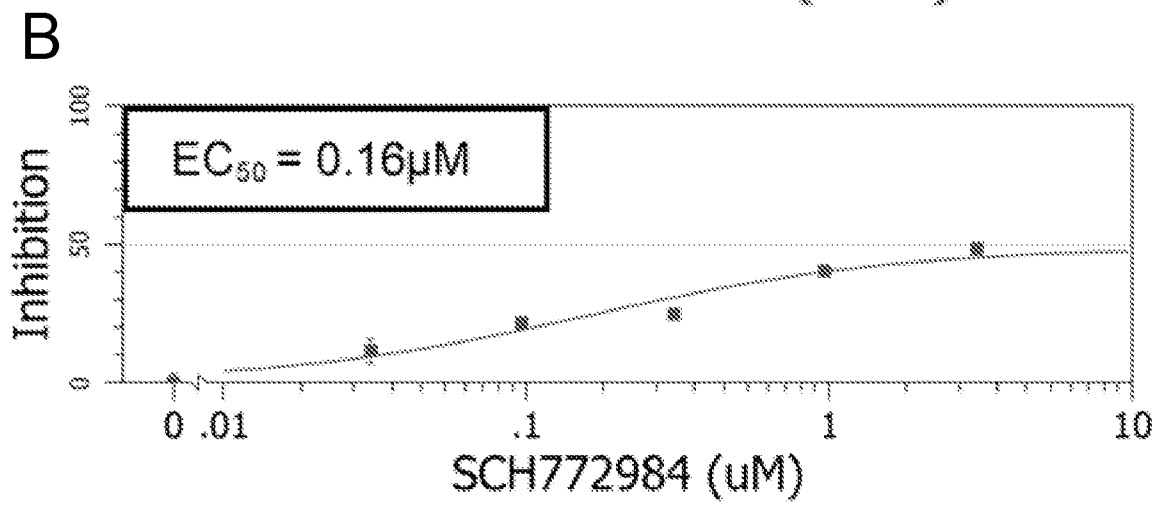

D
SCH772984
(uM)
GDC-0623 (uM)
Inhibition
Vol=1.52(.047)
CH2=620
E
SCH772984
(uM)
GDC-0623 (uM)
Inhibition
Vol=.525(.047)
CH2=460

FIG. 57


A
SCH772984 (uM)
3.1
.97
.31
.097
.031
0
48 49 49 52 50 48 48 49 49 46
40 39 47 42 42 43 44 46 48 46
25 28 31 31 31 31 33 41 47 48
22 25 23 24 22 23 22 27 39 43
11 8 14 15 12 8 18 21 39 44
0 -2 1 6 0 -3 10 16 36 42
Inhibition N=3-4
0
9.8e-5
9.8e-4
.0098
.098
.98
GDC-0623 (uM)


B
Inhibition
100
50
0
EC50 = 0.16μM
0 .01
.1
1
10
SCH772984 (uM)

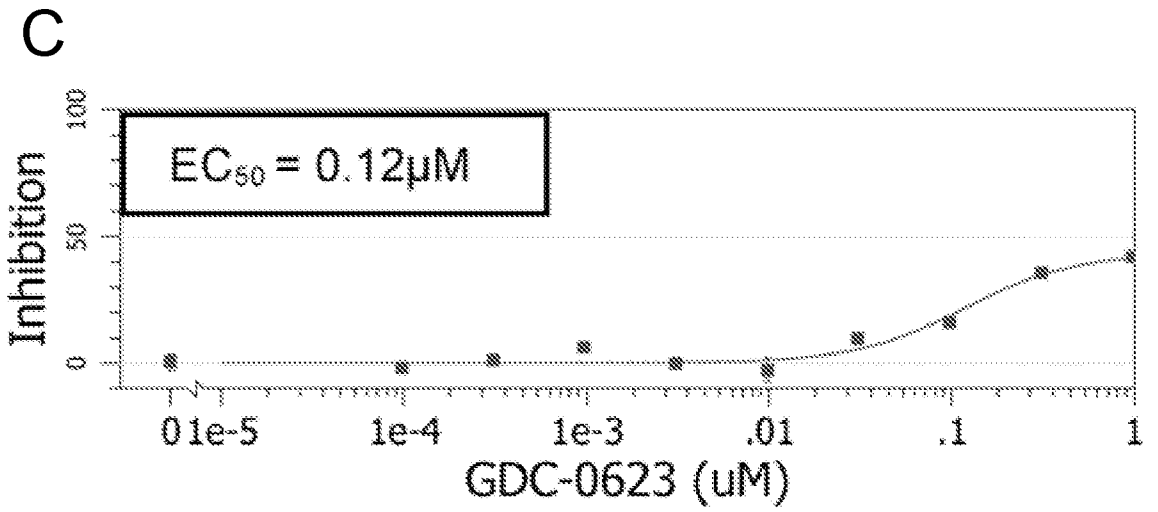

C
Inhibition
100
50
0
EC50 = 0.12μM
01e-5
1e-4
1e-3
.01
.1
1
GDC-0623 (uM)

FIG. 57, Con't

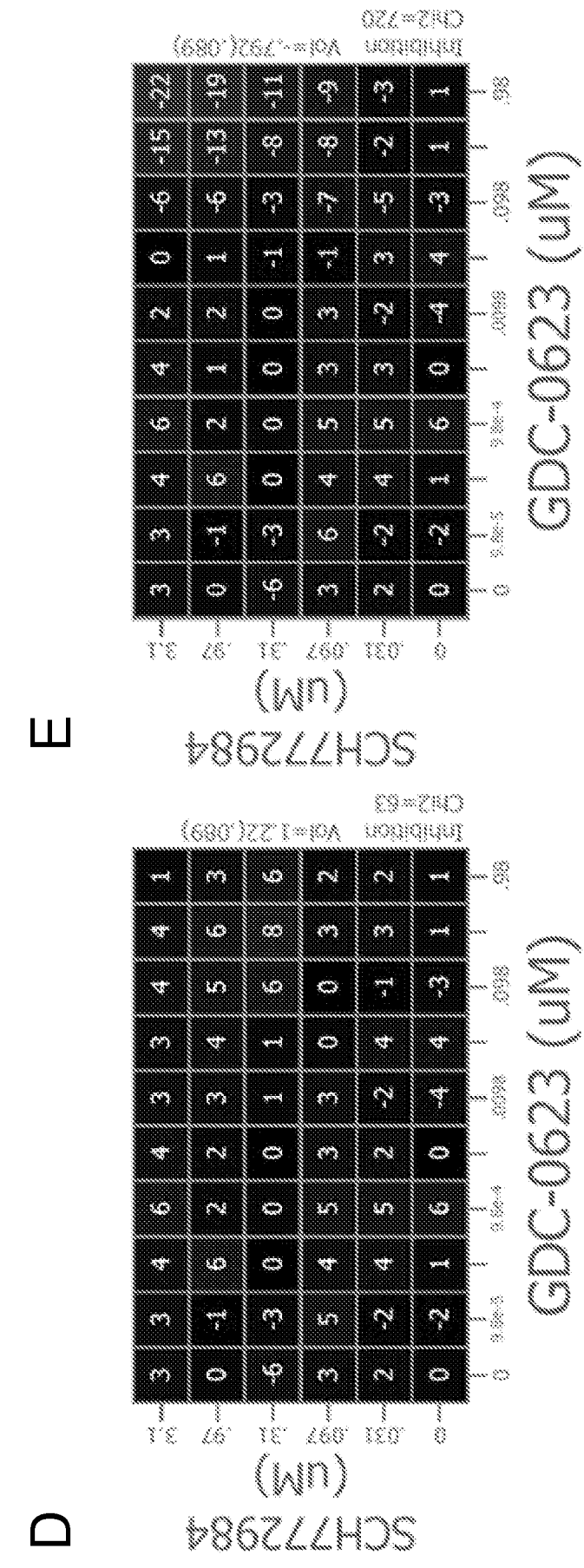
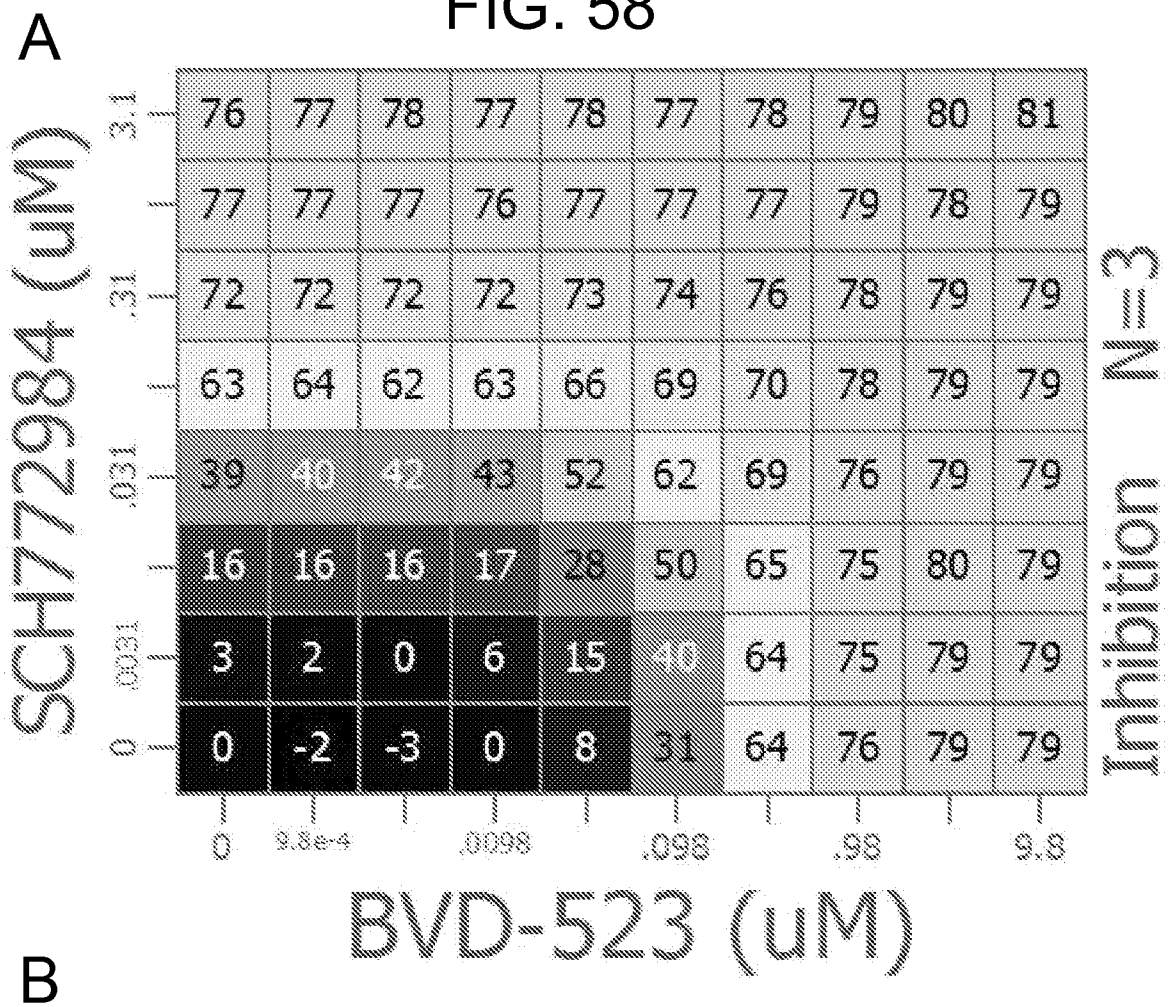
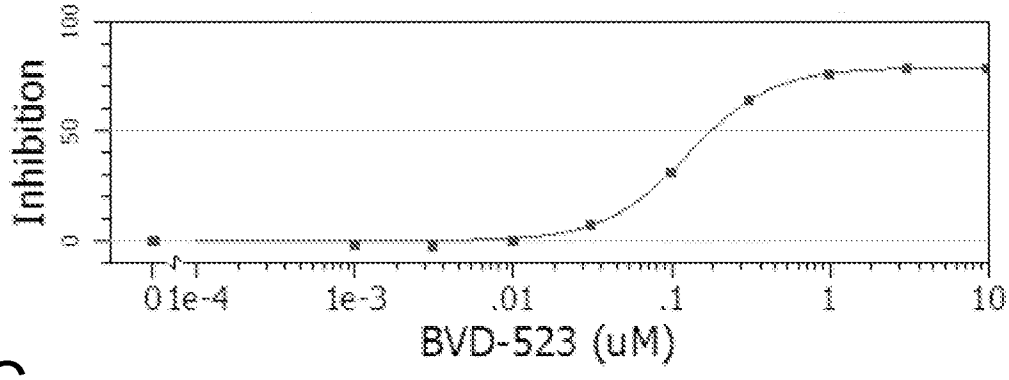

E
SCH772984 (uM)
GDC-0623 (uM)
Inhibition
D
SCH772984 (uM)
GDC-0623 (uM)
Inhibition

FIG. 58


A
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.31
.031
.0031
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77 77 77 76 77 77 77 79 78 79
72 72 72 72 73 74 76 78 79 79
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16 16 16 17 28 50 65 75 80 79
3 2 0 6 15 40 64 75 79 79
0 -2 -3 0 8 31 64 76 79 79
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Inhibition N=3


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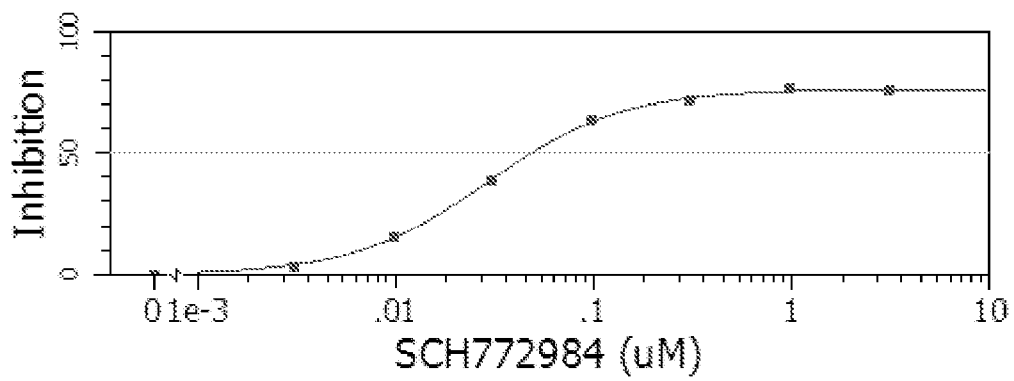
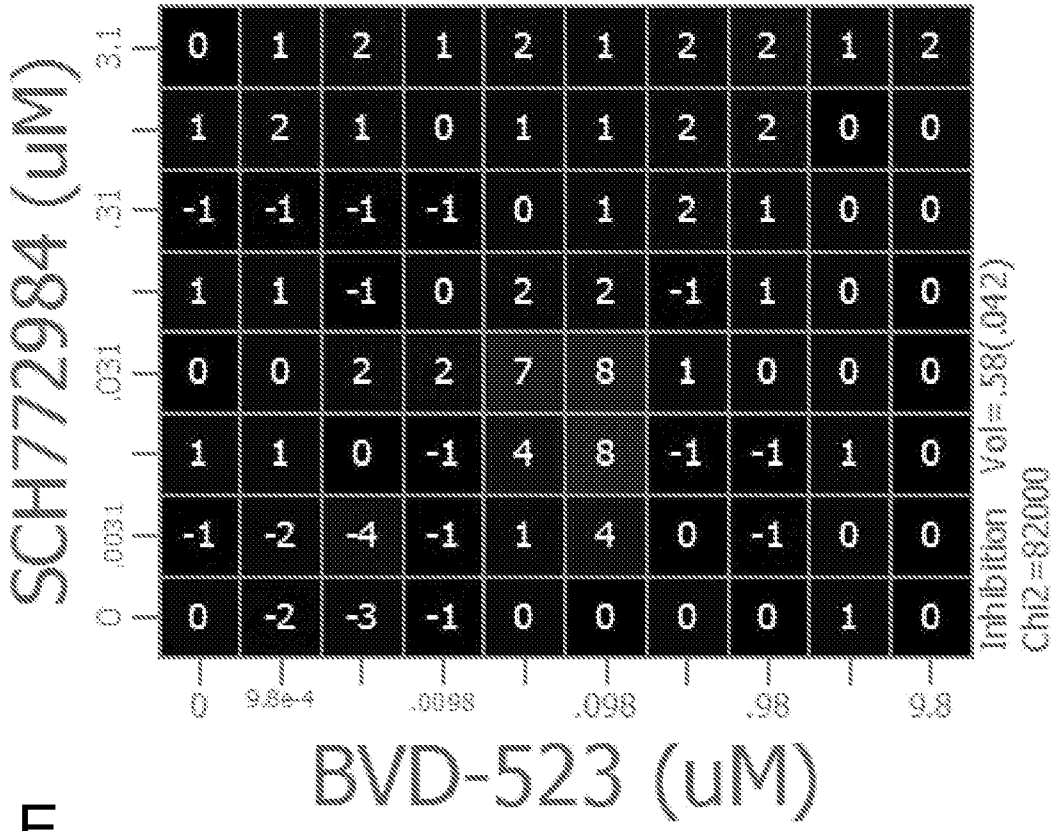
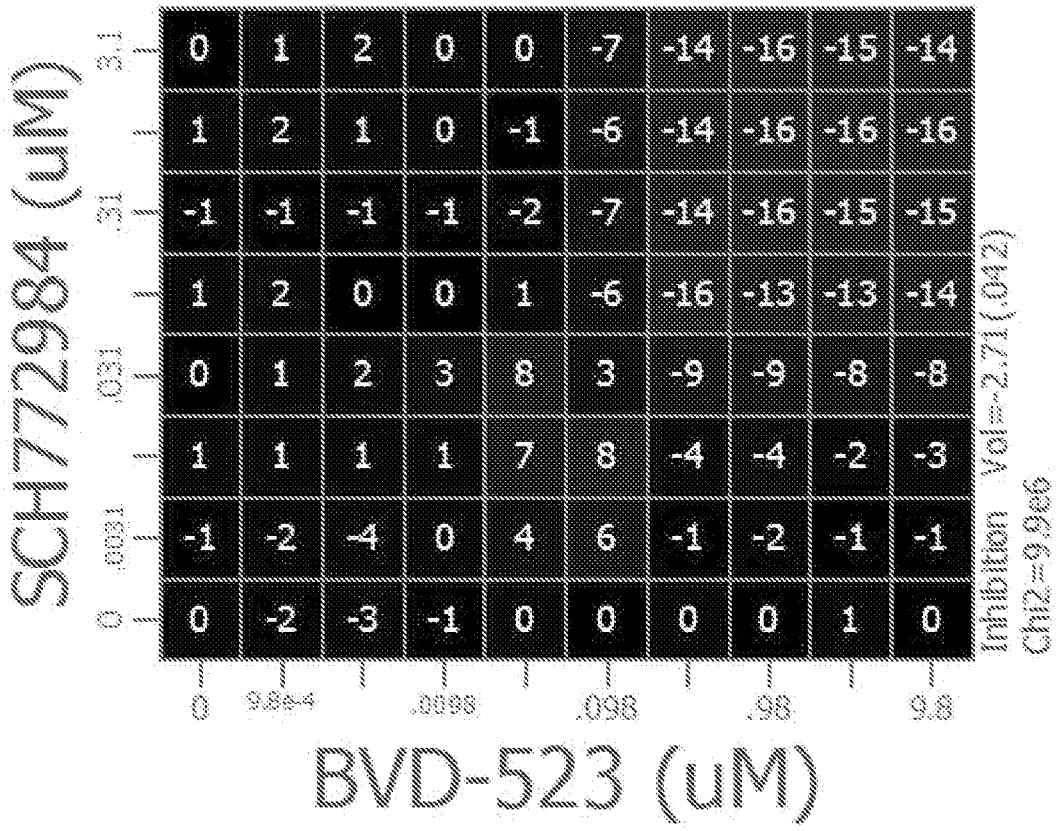

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SCH772984 (uM)

FIG. 58, Con't

D



E



SEQUENCE LISTING

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<120> CANCER TREATMENTS USING COMBINATIONS OF TYPE 2 MEK AND ERK INHIBITORS

<130> C065272/0375603

<140> US 61/919,625
<141> 2013-12-20

<160> 128

<170> PatentIn version 3.5

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<213> Homo sapiens

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tcgcgcctgt gaacggtggg gcaggagacc ctgtaggagg accccgggcc gcaggcccct 180

gaggagcgat gacggaatat aagctggtgg tggtgggcgc cggcggtgtg ggcaagagtg 240

cgctgaccat ccagctgatc cagaaccatt ttgtggacga atacgacccc actatagagg 300

attcctaccg gaagcaggtg gtcattgatg gggagacgtg cctgttggac atcctggata 360

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<213> Homo sapiens

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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 Thr Lys Ser Phe Glu Asp Ile His Gln 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 Ala Ala Arg Thr Val Glu Ser Arg
        115                 120                 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Tyr 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 His Lys Leu Arg Lys Leu Asn Pro Pro Asp Glu
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Ser Gly Pro Gly Cys Met Ser Cys Lys Cys Val Leu Ser
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tcgcgcctgt gaacggtggg gcaggagacc ctgtaggagg accccgggcc gcaggcccct      180

gaggagcgat gacggaatat aagctggtgg tggtgggcgc cggcggtgtg ggcaagagtg      240

cgctgaccat ccagctgatc cagaaccatt ttgtggacga atacgacccc actatagagg      300

attcctaccg gaagcaggtg gtcattgatg gggagacgtg cctgttggac atcctggata      360

ccgccggcca ggaggagtac agcgccatgc gggaccagta catgcgcacc ggggagggct      420

tcctgtgtgt gtttgccatc aacaacacca agtcttttga ggacatccac cagtacaggg      480

agcagatcaa acgggtgaag gactcggatg acgtgcccat ggtgctggtg gggaacaagt      540
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ccagctccgg gaccctctgg gacccccggg gacccatgtg acccagcggc ccctcgcgct 720

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tcaggacatg gaggtgccgg atgcaggaag gaggtgcaga cggaaggagg aggaaggaag 1020

gacggaagca aggaaggaag gaagggctgc tggagcccag tcaccccggg accgtgggcc 1080

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<211> 170
<212> PRT
<213> Homo sapiens

<400> 4

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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 Thr Lys Ser Phe Glu Asp Ile His Gln 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 Ala Ala Arg Thr Val Glu Ser Arg
115 120 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Tyr Ile Glu Thr
130 135 140

Ser Ala Lys Thr Arg Gln Gly Ser Arg Ser Gly Ser Ser Ser Ser Ser
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Gly Thr Leu Trp Asp Pro Pro Gly Pro Met
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<210> 5
<211> 1169
<212> DNA
<213> Homo sapiens

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tcgcgcctgt gaacggtggg gcaggagacc ctgtaggagg accccgggcc gcaggcccct 180

gaggagcgat gacggaatat aagctggtgg tggtgggcgc cggcggtgtg ggcaagagtg 240

cgctgaccat ccagctgatc cagaaccatt ttgtggacga atacgacccc actatagagg 300

attcctaccg gaagcaggtg gtcattgatg gggagacgtg cctgttggac atcctggata 360

ccgccggcca ggaggagtac agcgccatgc gggaccagta catgcgcacc ggggagggct 420

tcctgtgtgt gtttgccatc aacaacacca agtcttttga ggacatccac cagtacaggg 480

agcagatcaa acgggtgaag gactcggatg acgtgcccat ggtgctggtg gggaacaagt 540

gtgacctggc tgcacgcact gtggaatctc ggcaggctca ggacctcgcc cgaagctacg 600

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cgttggtgcg tgagatccgg cagcacaagc tgcggaagct gaaccctcct gatgagagtg 720

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<211> 189
<212> PRT
<213> Homo sapiens

<400> 6

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Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr

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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 Thr Lys Ser Phe Glu Asp Ile His Gln 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 Ala Ala Arg Thr Val Glu Ser Arg
115 120 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Tyr 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 His Lys Leu Arg Lys Leu Asn Pro Pro Asp Glu
165 170 175

Ser Gly Pro Gly Cys Met Ser Cys Lys Cys Val Leu Ser
180 185

<210> 7
<211> 1246
<212> DNA
<213> Rattus norvegicus

<400> 7
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aagcggtggg gcaggagctc ctggtttggc agcccctgta gaagcgatga cagaatacaa 180

gcttgtggtg gtgggcgctg gaggcgtggg aaagagtgcc ctgaccatcc agctgatcca 240

gaaccatttt gtggacgagt atgatcccac tatagaggac tcctaccgga aacaggtagt 300

cattgatggg gagacgtgtt tactggacat cttagacaca gcaggtcaag aagagtatag 360

tgccatgcgg gaccagtaca tgcgcacagg ggagggcttc ctctgtgtat ttgccatcaa 420

caacaccaag tcctttgaag acatccatca gtacagggag cagatcaagc gggtgaaaga 480

ttcagatgat gtgccaatgg tgctggtggg caacaagtgt gacctggccg ctcgcactgt 540

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gcataaactg cggaaactga acccgcctga tgagagtggc cctggctgca tgagctgcaa 720

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ctgtcggaag gaaggaaaga ggagggaagg aaggaaacga tgctggagcc agtccagtcc 840

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aactatccct gttgccactg gcacccaagt cctccgcccc tctcagctcc cttgggcgcc 960

tatgagggca catgttgaat cacagtaaat tatttgatgg tcttgacttg tctctggctg 1020

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cacaagaata gtcaggtgat atgaaaaaaa aaaaaaaaaa aaaaaa 1246

<210> 8
<211> 189
<212> PRT
<213> Rattus norvegicus

<400> 8

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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 Thr Lys Ser Phe Glu Asp Ile His Gln 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 Ala Ala Arg Thr Val Glu Ser Arg
115 120 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Tyr Ile Glu Thr
130 135 140

Ser Ala Lys Thr Arg Gln Gly Val Glu Asp Ala Phe Tyr Thr Leu Val

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Arg Glu Ile Arg Gln His Lys Leu Arg Lys Leu Asn Pro Pro Asp Glu
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Ser Gly Pro Gly Cys Met Ser Cys Lys Cys Val Leu Ser
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<212> DNA
<213> Rattus norvegicus

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<211> 189

<212> PRT
<213> Rattus norvegicus

<400> 10

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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 Thr Lys Ser Phe Glu Asp Ile His Gln 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 Ala Ala Arg Thr Val Glu Ser Arg
        115                 120                 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Tyr 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 His Lys Leu Arg Lys Leu Asn Pro Pro Asp Glu
                165                 170                 175

Ser Gly Pro Gly Cys Met Ser Cys Lys Cys Val Leu Ser
            180                 185
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<213> Mus musculus

<400> 11

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attgaagtgt tccgtccttg ctatcagcac tgggcactgt acttgggtga tggctacgtg      120

atcaacattg cacctataga tggcattcgc tcatcattta caagtgctaa gtccgtgttc      180

agcacaaagg ccttggtgaa aatgcagctt ttgaaggatg ttgtgggaaa tgacacatac      240

agaataaata acaagtacga cacaacatac cctcctcttc ctgtggagga ggtgatacaa      300
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cggtcagagt tccctattgg gcaggaagta gcctatgact tgctggtcaa caactgtgag 360

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ggcaccatcg gattggtggc agctggtatt gatatcttca cattcctcgg cttgtttccc 480

aaaagacaaa gaacgaaata ttag 504

<210> 12
<211> 167
<212> PRT
<213> Mus musculus

<400> 12

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Pro Gly Asp Leu Ile Glu Val Phe Arg Pro Cys Tyr Gln His Trp Ala
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Leu Tyr Leu Gly Asp Gly Tyr Val Ile Asn Ile Ala Pro Ile Asp Gly
35 40 45

Ile Arg Ser Ser Phe Thr Ser Ala Lys Ser Val Phe Ser Thr Lys Ala
50 55 60

Leu Val Lys Met Gln Leu Leu Lys Asp Val Val Gly Asn Asp Thr Tyr
65 70 75 80

Arg Ile Asn Asn Lys Tyr Asp Thr Thr Tyr Pro Pro Leu Pro Val Glu
85 90 95

Glu Val Ile Gln Arg Ser Glu Phe Pro Ile Gly Gln Glu Val Ala Tyr
100 105 110

Asp Leu Leu Val Asn Asn Cys Glu His Phe Val Thr Leu Leu Arg Tyr
115 120 125

Gly Glu Gly Val Ser Glu Gln Ala Asn Arg Ala Ile Gly Thr Ile Gly
130 135 140

Leu Val Ala Ala Gly Ile Asp Ile Phe Thr Phe Leu Gly Leu Phe Pro
145 150 155 160

Lys Arg Gln Arg Thr Lys Tyr
165

<210> 13
<211> 1455
<212> DNA
<213> Cavia porcellus

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tgtggccggg cgctcagcga ggcgccgccc gggctcgggg acgcgggccc gcggccatgt 120

cgctcggtgc gggacgccgc gcgtctctgt ccagctccgc ttccctgtcg cccgcgctcc 180

ccggccgccc gcgctccccc gctgtcccct gcgccctgga cccctagccg ctgctccgtg 240

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tgtggatgct ttgcaagctg tcatgaactg tcccaaacac cactggcctc ccagccctaa 1380

ctcccctccc agtttttcca gcctctgaca ggtgcaggtt gatttgcagt aaattatttg 1440

atggtcttga ctcca 1455

<210> 14
<211> 189
<212> PRT
<213> Cavia porcellus

<400> 14

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly Lys
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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

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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 Thr Lys Ser Phe Glu Asp Ile His Gln 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 Ala Thr Arg Thr Val Glu Ser Arg
        115                 120                 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Tyr 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 His Lys Leu Arg Lys Leu Asn Pro Pro Asp Glu
                165                 170                 175

Ser Gly Pro Gly Cys Met Ser Cys Lys Cys Val Leu Ser
            180                 185
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<210> 15
<211> 1694
<212> DNA
<213> Cavia porcellus

<400> 15

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tgtggccggg cgctcagcga ggcgccgccc gggctcgggg acgcgggccc gcggccatgt      120

cgctcggtgc gggacgccgc gcgtctctgt ccagctccgc ttccctgtcg cccgcgctcc      180

ccggccgccc gcgctccccc gctgtcccct gcgccctgga cccctagccg ctgctccgtg      240

gaccgcttgg gacgtgtcgg ccggggccgc gtctccccgc cgcccttccc ccgcgccgcg      300

tgcagccggc gcctgtggac gcacacgggc ctgcgccgct gtaggcgcgg ctgtcgggac      360

gctgcctgcc tcgacacgcc cgccggcggg caaggacctg ttcgggcggc cccgccagca      420

ggtgcctatg acctaggctt tttgcctacc cagcaacttc taatttgggt gcctggttgg      480

gagcggctca gctgtcaccc tgcctcggcg ccggcccctg cttccttaca ggccacgagg      540

tgcagcgggg tgcggtgaga ccctcagccc gctggaggtg ccacaggtgc cgccatcctg      600

gctggcgccc ttccagccac tccgctgggt ggcgcttggc tgagctggtc ctcctcacag      660

gtggggcaag agcccccgag tgccctgagc gtcagtccct ggaggagcca tgacggagta      720

caagcttgtg gtggtgggtg caggaggtgt ggggaagagc gccctgacta tccagctgat      780
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ccagaaccat tttgtggacg aatatgaccc caccatagag gattcatacc ggaagcaggt 840

ggtcattgat ggggagacct gtctgctgga tatcttggac acagctggcc aagaggagta 900

tagtgccatg cgggaccaat acatgcgcac tggggagggc ttcctttgtg tgttcgccat 960

caacaatacc aaatctttcg aggacatcca tcagtacagg gagcagatca agcgggtgaa 1020

ggactcagat gatgtgccca tggtgctggt gggaaacaaa tgtgacctgg ctacacgcac 1080

cgtggagtct cggcaggccc aagaccttgc ccgcagttac ggcattccct acattgagac 1140

atcagccaag acccgccagg gagtagaaga cgccttctat acactagttc gagagatccg 1200

gcagcacaaa ctgcggaagc tgaatccacc agatgagagt gggccagggt gcatgagctg 1260

caaatgtgtg ctatcctgat ccaggtgagc agggcccagc tggctccccg agccacagcc 1320

ctagccggcc agccagctaa gctgcacatc tactctgatg ttcctgggct tcctgaacct 1380

gctggtcccc ttgtctacga tcagtggcgt ccttcatgct ccatcctggc ccaggctcag 1440

gacacagagg taccagatgt ggggaagagg tacagaagga aggaaggaag gaaggaagga 1500

agtgccactg gagtccagcc agcccaggga tggtggatag aggcgactgc agaccctcct 1560

gtggatgctt tgcaagctgt catgaactgt cccaaacacc actggcctcc cagccctaac 1620

tcccctccca gtttttccag cctctgacag gtgcaggttg atttgcagta aattatttga 1680

tggtcttgac tcca 1694

<210> 16
<211> 189
<212> PRT
<213> Cavia porcellus

<400> 16

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 Thr Lys Ser Phe Glu Asp Ile His Gln 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 Ala Thr Arg Thr Val Glu Ser Arg
115 120 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Tyr 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 His Lys Leu Arg Lys Leu Asn Pro Pro Asp Glu
165 170 175

Ser Gly Pro Gly Cys Met Ser Cys Lys Cys Val Leu Ser
180 185

<210> 17
<211> 1180
<212> DNA
<213> Cavia porcellus

<400> 17
actgggccta cagtccccac cgcccgcgcc gcgagcccgc agcccgagcc gcacccgctg 60

cggacggagc ccatgcgcgg gcccagccag cgcccgcccg cgcccccgcc ccgccccggc 120

cccgggggca gttgcaccag cgagtggtgg ggcaagagcc cccgagtgcc ctgagcgtca 180

gtccctggag gagccatgac ggagtacaag cttgtggtgg tgggtgcagg aggtgtgggg 240

aagagcgccc tgactatcca gctgatccag aaccattttg tggacgaata tgaccccacc 300

atagaggatt cataccggaa gcaggtggtc attgatgggg agacctgtct gctggatatc 360

ttggacacag ctggccaaga ggagtatagt gccatgcggg accaatacat gcgcactggg 420

gagggcttcc tttgtgtgtt cgccatcaac aataccaaat ctttcgagga catccatcag 480

tacagggagc agatcaagcg ggtgaaggac tcagatgatg tgcccatggt gctggtggga 540

aacaaatgtg acctggctac acgcaccgtg gagtctcggc aggcccaaga ccttgcccgc 600

agttacggca ttccctacat tgagacatca gccaagaccc gccagggagt agaagacgcc 660

ttctatacac tagttcgaga gatccggcag cacaaactgc ggaagctgaa tccaccagat 720

gagagtgggc cagggtgcat gagctgcaaa tgtgtgctat cctgatccag gtgagcaggg 780

cccagctggc tccccgagcc acagccctag ccggccagcc agctaagctg cacatctact 840

ctgatgttcc tgggcttcct gaacctgctg gtccccttgt ctacgatcag tggcgtcctt 900

catgctccat cctggcccag gctcaggaca cagaggtacc agatgtgggg aagaggtaca 960

gaaggaagga aggaaggaag gaaggaagtg ccactggagt ccagccagcc cagggatggt 1020

ggatagaggc gactgcagac cctcctgtgg atgctttgca agctgtcatg aactgtccca 1080

aacaccactg gcctcccagc cctaactccc ctcccagttt ttccagcctc tgacaggtgc 1140

aggttgattt gcagtaaatt atttgatggt cttgactcca 1180

<210> 18
<211> 189
<212> PRT
<213> Cavia porcellus

<400> 18

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 Thr Lys Ser Phe Glu Asp Ile His Gln 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 Ala Thr Arg Thr Val Glu Ser Arg
115 120 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Tyr 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 His Lys Leu Arg Lys Leu Asn Pro Pro Asp Glu
165 170 175

Ser Gly Pro Gly Cys Met Ser Cys Lys Cys Val Leu Ser
180 185

<210> 19
<211> 1270
<212> DNA
<213> Cavia porcellus

<400> 19
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tgtggccggg cgctcagcga ggcgccgccc gggctcgggg acgcgggccc gcggccatgt 120

cgctcggtgc gggacgccgc gcgtctctgt ccagctccgc ttccctgtcg cccgcgctcc 180

ccggccgccc gcgctccccc gctgtcccct gcgccctgga cccctagccg ctgctccgtg 240

gaccgcttgg gacgtgtcgg ccggggccgc gtctccccgc cgcccttccc ccgcgccgcg 300

tgcagccggc gcctgtggac gcacacgggc ctgcgccgct gtaggcgcgg ctgtcgggac 360

gctgcctgcc tcgacacgcc cgccggcggg caaggacctg ttcgggcggc cccgccagca 420

ggtgcctatg acctaggctt tttgcctacc cagcaacttc taatttgggt gcctggttgg 480

gagcggctca gctgtcaccc tgcctcggcg ccggcccctg cttccttaca ggccacgagg 540

tgcagcgggg tgcggtgaga ccctcagccc gctggaggtg ccacaggtgc cgccatcctg 600

gctggcgccc ttccagccac tccgctgggt ggcgcttggc tgagctggtc ctcctcacag 660

gtggggcaag agcccccgag tgccctgagc gtcagtccct ggaggagcca tgacggagta 720

caagcttgtg gtggtgggtg caggaggtgt ggggaagagc gccctgacta tccagctgat 780

ccagaaccat tttgtggacg aatatgaccc caccatagag gattcatacc ggaagcaggt 840

ggtcattgat ggggagacct gtctgctgga tatcttggac acagctggcc aagaggagta 900

tagtgccatg cgggaccaat acatgcgcac tggggagggc ttcctttgtg tgttcgccat 960

caacaatacc aaatctttcg aggacatcca tcagtacagg gagcagatca agcgggtgaa 1020

ggactcagat gatgtgccca tggtgctggt gggaaacaaa tgtgacctgg ctacacgcac 1080

cgtggagtct cggcaggccc aagaccttgc ccgcagttac ggcattccct acattgagac 1140

atcagccaag acccgccagg gcagccgctc tggctctggc ttcagctccg ggacccactg 1200

ggaacccctg ggatccatgt gacccatcgg cccccatgct ggagtagaag acgccttcta 1260

tacactagtt 1270

<210> 20
<211> 170
<212> PRT
<213> Cavia porcellus

<400> 20

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 Thr Lys Ser Phe Glu Asp Ile His Gln 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 Ala Thr Arg Thr Val Glu Ser Arg
115 120 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Tyr Ile Glu Thr
130 135 140

Ser Ala Lys Thr Arg Gln Gly Ser Arg Ser Gly Ser Gly Phe Ser Ser
145 150 155 160

Gly Thr His Trp Glu Pro Leu Gly Ser Met
165 170

<210> 21
<211> 696
<212> DNA
<213> Canis lupus

<400> 21
ggctgagagc agcttcctca gcaggtggga caggagacct cgttggcgtc ctgtgctgcg 60

tcccgtgagg agccatgacg gagtataagc tggtggtggt gggcgctgga ggcgtgggca 120

agagcgccct gaccatccag ctcatccaga accacttcgt ggatgagtac gaccccacca 180

tcgaggactc ctatcggaag caagtggtca tcgacgggga gacgtgcctg ctggacatcc 240

tggacacagc gggccaggag gagtacagcg ccatgcggga ccagtacatg cgcacggggg 300

agggctttct ctgtgtattt gccatcaaca acaccaagtc ctttgaggac atccaccagt 360

acagggagca gatcaagcga gtgaaggact ctgacgacgt gcccatggtg ctggtgggga 420

acaagtgtga cctggctgct cgcaccgtgg agtcccggca ggcgcaggac ctcgcccgca 480

gctacggcat cccctacatc gagacgtcag ccaagacgcg ccagggcagc cggtctggct 540

ctggctccag ctccgggacc ctctgggacc ctccgggacc cccgtgaccc agcggccct 600

agcgctggcg tggaggatgc cttctacacg ctggtgcgag agattcgaca gcacaaggtg 660

cgcaagctga gcccgcccga cgagggaggc ccaggc 696

<210> 22
<211> 170
<212> PRT
<213> Canis lupus

<400> 22

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 Thr Lys Ser Phe Glu Asp Ile His Gln 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 Ala Ala Arg Thr Val Glu Ser Arg
115 120 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Tyr Ile Glu Thr
130 135 140

Ser Ala Lys Thr Arg Gln Gly Ser Arg Ser Gly Ser Gly Ser Ser Ser
145 150 155 160

Gly Thr Leu Trp Asp Pro Pro Gly Pro Pro
165 170

<210> 23
<211> 956
<212> DNA
<213> Canis lupus

<400> 23
gctgagagca gcttcctcag caggtgggac aggagacctc gttggcgtcc tgtgctgcgt 60

cccgtgagga gccatgacgg agtataagct ggtggtggtg ggcgctggag gcgtgggcaa 120

gagcgccctg accatccagc tcatccagaa ccacttcgtg gatgagtacg accccaccat 180

cgaggactcc tatcggaagc aagtggtcat cgacggggag acgtgcctgc tggacatcct 240

ggacacagcg ggccaggagg agtacagcgc catgcgggac cagtacatgc gcacggggga 300

gggctttctc tgtgtatttg ccatcaacaa caccaagtcc tttgaggaca tccaccagta 360

cagggagcag atcaagcgag tgaaggactc tgacgacgtg cccatggtgc tggtggggaa 420

caagtgtgac ctggctgctc gcaccgtgga gtcccggcag gcgcaggacc tcgcccgcag 480

ctacggcatc ccctacatcg agacgtcagc caagacgcgc cagggcgtgg aggatgcctt 540

ctacacgctg gtgcgagaga ttcgacagca caaggtgcgc aagctgagcc cgcccgacga 600

gggaggccca ggctgcatga gctgcaagtg cctgctgtcc tgacgtcccc tccagggcca 660

cgttggcagc cccgctggtc ctctgtgccc caggcgcaca ggctcggggc gaggaggtgc 720

cggaagctgg gaggaggcgc ggaaggagga aggaggaggg cgaggaagga aggaagcgcc 780

cccggggccc ggccagccca ggccccctgg acaggggggag cacggacctc ccagggcgct 840

ttgcacagac tgtcgtgaac tgaggccacg ggcccccccg gctgtcactc tcccccagtc 900

ccgtccttgc ccgcggggca aaggctgagt cgcagtaaat tatttgatgg tcttga 956

<210> 24
<211> 189
<212> PRT
<213> Canis lupus

<400> 24

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 Thr Lys Ser Phe Glu Asp Ile His Gln 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 Ala Ala Arg Thr Val Glu Ser Arg
115 120 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Tyr 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 His Lys Val Arg Lys Leu Ser Pro Pro Asp Glu
165 170 175

Gly Gly Pro Gly Cys Met Ser Cys Lys Cys Leu Leu Ser
180 185

<210> 25
<211> 593
<212> DNA
<213> Felis catus

<400> 25
gccgcgatcc cctgaggaac gatgacggaa tataagctcg tggtggtggg cgctggaggt 60

gtggggaaga gtgccctgac catccagctc atccagaacc acttcgtgga tgagtatgac 120

cccaccatcg aggactccta tcggaagcaa gtggttattg atggcgagac gtgcctactg 180

gacattttgg acacggcggg ccaggaggag tatagcgcca tgcgggacca gtacatgcgc 240

actggagaag gcttcctctg tgtgtttgcc atcaacaata ccaagtcctt tgaggacatc 300

caccagtaca gggagcaaat caagcgagtg aaggactccg atgacgtgcc catggtgttg 360

gtggggaaca agtgcgacct ggccgcgcgc accgtggagt cccggcaggc gcaggacctc 420

gcccgcagct acggcatccc gtacatcgag acgtcggcca agactcgcca gggtgtggag 480

gacgctttct acacgctggt ccgagagatc cggcaacaca aggtgcggaa gctgagcccg 540

cccgacgagg gtggccccgg ctgcatgagc tgcaagtgcc tgctctcctg acg 593

<210> 26
<211> 189
<212> PRT
<213> Felis catus

<400> 26

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 Thr Lys Ser Phe Glu Asp Ile His Gln 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 Ala Ala Arg Thr Val Glu Ser Arg
115 120 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Tyr 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 His Lys Val Arg Lys Leu Ser Pro Pro Asp Glu

165 170 175

Gly Gly Pro Gly Cys Met Ser Cys Lys Cys Leu Leu Ser
180 185

<210> 27
<211> 675
<212> DNA
<213> Felis catus

<400> 27
gccgcgatcc cctgaggaac gatgacggaa tataagctcg tggtggtggg cgctggaggt 60

gtggggaaga gtgccctgac catccagctc atccagaacc acttcgtgga tgagtatgac 120

cccaccatcg aggactccta tcggaagcaa gtggttattg atggcgagac gtgcctactg 180

gacattttgg acacggcggg ccaggaggag tatagcgcca tgcgggacca gtacatgcgc 240

actggagaag gcttcctctg tgtgtttgcc atcaacaata ccaagtcctt tgaggacatc 300

caccagtaca gggagcaaat caagcgagtg aaggactccg atgacgtgcc catggtgttg 360

gtggggaaca agtgcgacct ggccgcgcgc accgtggagt cccggcaggc gcaggacctc 420

gcccgcagct acggcatccc gtacatcgag acgtcggcca agactcgcca gggcagccgc 480

tctggctctg gctccagctc cgggaccctc tgggaccctc cgggaccccc gtgacccagc 540

ggcccctagc gctggtgtgg aggacgcttt ctacacgctg gtccgagaga tccggcaaca 600

caaggtgcgg aagctgagcc cgcccgacga gggtggcccc ggctgcatga gctgcaagtg 660

cctgctctcc tgacg 675

<210> 28
<211> 170
<212> PRT
<213> Felis catus

<400> 28

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 Thr Lys Ser Phe Glu Asp Ile His Gln 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 Ala Ala Arg Thr Val Glu Ser Arg
        115                 120                 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Tyr Ile Glu Thr
    130                 135                 140

Ser Ala Lys Thr Arg Gln Gly Ser Arg Ser Gly Ser Gly Ser Ser Ser
145                 150                 155                 160

Gly Thr Leu Trp Asp Pro Pro Gly Pro Pro
                165                 170
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<210> 29
<211> 978
<212> DNA
<213> Bos taurus

<400> 29

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ccgccgcgga cgggacccat gcgtcgggcg agccctgcgc cccggccccg gcccctgccg       60

ccgccccccgc tccggccccg gcccgggggg cagtcgagcc agtgagcggt gggaccggcg      120

accactgcag cgcctcgtgc tgcggtctct tgaggagcaa tgacggagta taagctcgtg      180

gtggtgggcg ccggtggcgt ggggaagagc gccctgacta tccagctcat tcagaatcac      240

ttcgtggacg agtacgaccc caccatcgag gactcctacc ggaagcaagt ggtcatcgat      300

ggggagacgt gcctgctgga catcctggac acagcgggcc aggaggaata cagcgccatg      360

cgagaccagt acatgcgcac cggggagggc tttctctgcg tgtttgctat caaccacgtc      420

aagtccttcg aggacatcca ccagtaccgg gagcagatca agcgggtgaa ggactcggat      480

gacgtgccca tggtgttggt tgggaacaag tgcgacctgg ccgcgcgcac cgtggagtct      540

cggcaggccc aggacctcgc ccgcagctac ggcatcccgt acatcgagac ctccgccaag      600

acccgccagg gcgtggagga tgctttctac accctggtgc gcgagatccg gcagcacaag      660

gtgcgcaagc tgagcccgcc ggacgagggc ggccccggct gcctgagctg caggtgcctg      720

ctctcctgac ggcagcgtgg gcgcggagcg ctgggtgcca tgcaggaggc ggcgcagcag      780

gggtggaggg aggtgccgcc agagcccagc cccccaggcc agtgggcagt gcccgcgggc      840

ctcccgggac gcttcgcaca gactctggtg aactgatgct gctggccccc agcctcgctc      900

tcctccagcc ctgtcctggc ccagcgggcg caggccgagt cgcagtaaat tatttcatgg      960

tcttgaaaaa aaaaaaaa                                                    978
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<210> 30
<211> 189
<212> PRT
<213> Bos taurus

<400> 30

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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 His Val Lys Ser Phe Glu Asp Ile His Gln 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 Ala Ala Arg Thr Val Glu Ser Arg
        115                 120                 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Tyr 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 His Lys Val Arg Lys Leu Ser Pro Pro Asp Glu
                165                 170                 175

Gly Gly Pro Gly Cys Leu Ser Cys Arg Cys Leu Leu Ser
            180                 185
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<210> 31
<211> 1060
<212> DNA
<213> Bos taurus

<400> 31

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cgagaccagt acatgcgcac cggggagggc tttctctgcg tgtttgctat caaccacgtc      420
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<211> 170
<212> PRT
<213> Bos taurus

<400> 32

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Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr
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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 His Val Lys Ser Phe Glu Asp Ile His Gln 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 Ala Ala Arg Thr Val Glu Ser Arg
115 120 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Tyr Ile Glu Thr
130 135 140

Ser Ala Lys Thr Arg Gln Gly Ser Arg Ser Gly Ser Gly Ser Ser Ser

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Gly Thr Leu Trp Asp Pro Pro Gly Pro Pro
165 170

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<212> DNA
<213> Bos taurus

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<210> 34
<211> 189

<212> PRT
<213> Bos taurus

<400> 34

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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 His Val Lys Ser Phe Glu Asp Ile His Gln 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 Ala Ala Arg Thr Val Glu Ser Arg
115 120 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Tyr 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 His Lys Val Arg Lys Leu Ser Pro Pro Asp Glu
165 170 175

Gly Gly Pro Gly Cys Leu Ser Cys Arg Cys Leu Leu Ser
180 185

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<211> 962
<212> DNA
<213> Gallus gallus

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tgttgatgag tacgacccca caatagagga ttcctacaga aagcaagtcg tcatcgatgg 240

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<211> 189
<212> PRT
<213> Gallus gallus

<400> 36

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Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly
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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 Thr Lys Ser Phe Glu Asp Ile His Gln Tyr
85 90 95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Asp Asp Val Pro Met Val
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Leu Val Gly Asn Lys Cys Asp Leu Pro Ala Arg Thr Val Glu Thr Arg
115 120 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Tyr 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

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Ser Gly Pro Gly Cys Met Asn Cys Lys Cys Val Ile Ser
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<212> DNA
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aataaaaata gttacagtga caaaaaaaaa aaaaaa 5436

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<211> 189

<212> PRT
<213> Homo sapiens

<400> 38

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Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly
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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
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Val Phe Ala Ile Asn Asn Thr Lys Ser Phe Glu Asp Ile His His Tyr
85 90 95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Glu Asp Val Pro Met Val
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Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr Lys
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Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Phe Ile Glu Thr
130 135 140

Ser Ala Lys Thr Arg Gln Arg Val Glu Asp Ala Phe Tyr Thr Leu Val
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<211> 188
<212> PRT
<213> Homo sapiens

<400> 40

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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 Thr Lys Ser Phe Glu Asp Ile His His Tyr
85 90 95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Glu Asp Val Pro Met Val
100 105 110

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Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr Lys
        115                 120                 125


Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Phe Ile Glu Thr
    130                 135                 140


Ser Ala Lys Thr Arg Gln Gly Val Asp Asp Ala Phe Tyr Thr Leu Val
145                 150                 155                 160


Arg Glu Ile Arg Lys His Lys Glu Lys Met Ser Lys Asp Gly Lys Lys
                165                 170                 175


Lys Lys Lys Lys Ser Lys Thr Lys Cys Val Ile Met
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<212> DNA
<213> Rattus norvegicus

<400> 41

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caagaggagt acagtgcaat gagggaccag tacatgagaa ctggggaggg ctttctttgt      240

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<212> PRT
<213> Rattus norvegicus

<400> 42

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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 Thr Lys Ser Phe Glu Asp Ile His His Tyr
85 90 95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Glu Asp Val Pro Met Val
100 105 110

Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr Lys
115 120 125

Gln Ala Gln Glu Leu Ala Arg Ser Tyr Gly Ile Pro Phe Ile Glu Thr
130 135 140

Ser Ala Lys Thr Arg Gln Gly Val Asp Asp Ala Phe Tyr Thr Leu Val
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Arg Glu Ile Arg Lys His Lys Glu Lys Met Ser Lys Asp Gly Lys Lys
165 170 175

Lys Lys Lys Lys Ser Arg Thr Arg Cys Ile Val Met
180 185

<210> 43
<211> 4670
<212> DNA
<213> Mus musculus

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agggctttct ttgtgtattt gccataaata atactaaatc atttgaagat attcaccatt 480

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<211> 188

<212> PRT
<213> Mus musculus

<400> 44

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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 Thr Lys Ser Phe Glu Asp Ile His His Tyr
85 90 95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Glu Asp Val Pro Met Val
100 105 110

Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr Lys
115 120 125

Gln Ala Gln Glu Leu Ala Arg Ser Tyr Gly Ile Pro Phe Ile Glu Thr
130 135 140

Ser Ala Lys Thr Arg Gln Gly Val Asp Asp Ala Phe Tyr Thr Leu Val
145 150 155 160

Arg Glu Ile Arg Lys His Lys Glu Lys Met Ser Lys Asp Gly Lys Lys
165 170 175

Lys Lys Lys Lys Ser Arg Thr Arg Cys Thr Val Met
180 185

<210> 45
<211> 2068
<212> DNA
<213> Oryctolagus cuniculus

<400> 45
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<210> 46
<211> 238
<212> PRT
<213> Oryctolagus cuniculus

<400> 46

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            20                  25                  30

Gln Arg Gly Glu Glu Glu Ala Gln Thr Cys Cys Gly Cys Arg Phe Pro
        35                  40                  45

Leu Leu Leu Ala Leu Leu Gln Leu Ala Leu Gly Val Ala Val Thr Val
    50                  55                  60

Val Gly Phe Leu Met Ala Ser Val Ser Ser Ser Leu Leu Val Arg Ala
65                  70                  75                  80

Thr Pro Tyr Trp Ala Gly Ile Ile Val Cys Val Val Ala Tyr Leu Gly
                85                  90                  95

Leu Phe Met Leu Cys Val Ser Tyr Gln Val Asp Glu Arg Thr Cys Ile
            100                 105                 110

Gln Phe Ser Met Lys Leu Leu Tyr Phe Val Leu Ser Ala Leu Gly Leu
        115                 120                 125

Val Val Cys Val Leu Ala Val Ala Phe Ala Ala His His Tyr Ser Leu
    130                 135                 140

Leu Thr His Leu Thr Cys Glu Asn Ala Pro Asp Ser Cys Gln Cys Lys
145                 150                 155                 160

Leu Pro Ser Ser Glu Pro Leu Ser Arg Thr Phe Val Tyr Arg Asp Val
                165                 170                 175

Thr Asp Cys Thr Ser Ile Thr Gly Thr Phe Gln Val Phe Leu Leu Val
            180                 185                 190

Gln Met Val Leu Asn Leu Val Cys Gly Leu Val Cys Leu Val Ala Cys
        195                 200                 205

Phe Val Met Trp Lys His Arg Tyr Gln Val Phe Tyr Val Gly Val Arg
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Met Cys Pro Leu Ser Ala Ser Glu Gly Gln Gln Gln Lys Val
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<212> DNA
<213> Cavia porcellus

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aatgtgattt gccttctaga acagtagaca caaaacaagc tcaggactta gcaagaagtt 540

atggaattcc ttttattgaa acatcagcaa agacaagaca gagagtggag gatgcttttt 600

atacattggt gagagagatt cgacaataca gattgaaaaa aatcagcaaa gaagaaaaga 660

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cgttagttcg agaaattcga aaacataaag aaaagatgag caaagatggt aaaaagaaga 780

aaaagaagtc gaagacaaag tgtataatta tgtaaataca atttgtactt ttttcttaag 840

gcatacttaa gtaaaagtgg taatttttgt acattacact aaattattag cttttgtttt 900

agcattactt aattcttttc ctatttcatg caaactgtta gcttttatct taaatgctca 960

ttttaaaatg acagtggaaa ccttttattt cctcttaagt gccagtattc cctgcatttt 1020

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<212> PRT
<213> Cavia porcellus

<400> 48

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Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr
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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 Thr Lys Ser Phe Glu Asp Ile His His Tyr
85 90 95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Glu Asp Val Pro Met Val

100 105 110

Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr Lys
115 120 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Phe Ile Glu Thr
130 135 140

Ser Ala Lys Thr Arg Gln Arg Val Glu Asp Ala Phe Tyr Thr Leu Val
145 150 155 160

Arg Glu Ile Arg Gln Tyr Arg Leu Lys Lys Ile Ser Lys Glu Glu Lys
165 170 175

Thr Pro Gly Cys Val Lys Ile Lys Lys Cys Ile Ile Met Gly Val Asp
180 185 190

Asp Ala Phe Tyr Thr Leu Val Arg Glu Ile Arg Lys His Lys Glu Lys
195 200 205

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210 215 220

Ile Ile Met
225

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atcactttgt ggatgaatat gatcctacaa tagaggattc ctacaggaaa caagtagtaa 180

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caatgaggga ccagtacatg aggactgggg agggctttct ttgtgtattt gccataaata 300

atactaaatc ttttgaagat attcaccatt atagagaaca aattaaaaga gttaaagact 360

ctgaagatgt acctatggtc ctagtaggaa ataaatgtga tttgccttct agaacagtag 420

acacaaaaca agctcaggac ttagcaagaa gttatggaat tccttttatt gaaacatcag 480

caaagacaag acagggtgtt gatgatgcct tctatacgtt agttcgagaa attcgaaaac 540

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taattatgta aatacaattt gtacttttt cttaaggcat acttaagtaa aagtggtaat 660

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<212> PRT
<213> Cavia porcellus

<400> 50

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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 Thr Lys Ser Phe Glu Asp Ile His His Tyr
85 90 95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Glu Asp Val Pro Met Val
100 105 110

Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr Lys
115 120 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Phe Ile Glu Thr
130 135 140

Ser Ala Lys Thr Arg Gln Gly Val Asp Asp Ala Phe Tyr Thr Leu Val
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Arg Glu Ile Arg Lys His Lys Glu Lys Met Ser Lys Asp Gly Lys Lys
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Lys Lys Lys Lys Ser Lys Thr Lys Cys Ile Ile Met
180 185

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aattccttt attgaaacat cagcaaagac aagacagaga gtggaggatg ctttttatac 480

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tggctgtgtg aaaattaaaa aatgcattgt aatgggtgtt gacgatgcct tctatacatt 600

agttcgagaa attcgaaaac ataaagaaaa gatgagcaaa gatggtaaaa agaagaaaaa 660

gaagtcaaag acaaagtgta taattatgta aatacaattt gtacttttt cttaaggcat 720

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caatgcctgt gaaaaagaaa ctgaatacct gagatttctg tcttggggtt tttggtgcat 960

gcagttgatt acttcctatt tttcttacca attgtgaact ttggtgtgaa acaaattaat 1020

gaagctttcg aatcatccct attctgtgtt ttacctagtc acatacatgg attaattact 1080

aattataact tcagttgata tttcatgatt ggttttactg aaacattgag ggaacatgaa 1140

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atggtgacta tga 4993

<210> 52
<211> 4993
<212> PRT
<213> Canis lupus

<400> 52

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35 40 45

Ala Gly Gly Cys Ala Ala Gly Ala Gly Thr Gly Cys Cys Thr Thr Gly
50 55 60

Ala Cys Gly Ala Thr Ala Cys Ala Gly Cys Thr Ala Ala Thr Thr Cys
65 70 75 80

Ala Gly Ala Ala Thr Cys Ala Cys Thr Thr Thr Gly Thr Gly Gly Ala
85 90 95

Thr Gly Ala Ala Thr Ala Thr Gly Ala Thr Cys Cys Thr Ala Cys Ala
100 105 110

Ala Thr Ala Gly Ala Gly Gly Ala Thr Thr Cys Cys Thr Ala Cys Ala
115 120 125

Gly Gly Ala Ala Ala Cys Ala Ala Gly Thr Ala Gly Thr Ala Ala Thr

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Cys Thr Cys Thr Thr Gly Gly Ala Thr Ala Thr Thr Cys Thr Cys Gly
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Ala Cys Ala Cys Ala Gly Cys Ala Gly Gly Thr Cys Ala Ala Gly Ala
            180                 185                 190

Gly Gly Ala Gly Thr Ala Cys Ala Gly Thr Gly Cys Ala Ala Thr Gly
        195                 200                 205

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Gly Gly Ala Cys Thr Gly Gly Gly Gly Ala Gly Gly Gly Cys Thr Thr
225                 230                 235                 240

Thr Cys Thr Thr Thr Gly Thr Gly Thr Ala Thr Thr Thr Gly Cys Cys
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            260                 265                 270

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Cys Cys Ala Thr Thr Ala Thr Ala Gly Ala Gly Ala Ala Cys Ala Ala
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305                 310                 315                 320

Ala Cys Thr Cys Thr Gly Ala Ala Gly Ala Thr Gly Thr Ala Cys Cys
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Thr Ala Thr Gly Gly Thr Cys Cys Thr Ala Gly Thr Ala Gly Gly Ala
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Ala Ala Thr Ala Ala Ala Thr Gly Thr Gly Ala Thr Thr Thr Gly Cys
        355                 360                 365

Cys Thr Thr Cys Thr Ala Gly Ala Ala Cys Ala Gly Thr Ala Gly Ala
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Cys Ala Cys Ala Ala Ala Ala Cys Ala Gly Gly Cys Thr Cys Ala Gly
385                 390                 395                 400

Gly Ala Cys Thr Thr Ala Gly Cys Ala Ala Gly Ala Ala Gly Thr Thr
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420 425 430

Thr Gly Ala Ala Ala Cys Ala Thr Cys Ala Gly Cys Ala Ala Ala Gly
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450 455 460

Ala Gly Gly Ala Thr Gly Cys Thr Thr Thr Thr Thr Ala Thr Ala Cys
465 470 475 480

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Cys Gly Ala Cys Ala Ala Thr Ala Cys Ala Gly Ala Thr Thr Gly Ala
500 505 510

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Thr Gly Thr Gly Thr Gly Ala Ala Ala Ala Thr Thr Ala Ala Ala Ala
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565 570 575

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580 585 590

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595 600 605

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610 615 620

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645 650 655

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675 680 685

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690 695 700

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705 710 715 720

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725 730 735

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Cys Ala Cys Thr Ala Ala Ala Thr Thr Ala Thr Thr Ala Gly Cys Ala
755 760 765

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770 775 780

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785 790 795 800

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805 810 815

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Gly Ala Ala Ala Cys Thr Thr Thr Thr Thr Cys Cys Thr Cys Thr Ala
850 855 860

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865 870 875 880

Gly Ala Gly Thr Thr Thr Thr Gly Gly Thr Thr Thr Thr Gly Ala Ala
885 890 895

Cys Thr Ala Gly Cys Ala Ala Thr Gly Cys Cys Thr Gly Thr Gly Ala
900 905 910

Ala Ala Ala Ala Gly Ala Ala Ala Cys Thr Gly Ala Ala Thr Ala Cys
915 920 925

Cys Thr Gly Ala Gly Ala Thr Thr Thr Cys Thr Gly Thr Cys Thr Thr
930 935 940

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945 950 955 960

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980 985 990

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995 1000 1005

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1070 1075 1080

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1085 1090 1095

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1100 1105 1110

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1325 1330 1335

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1760 1765 1770

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1835 1840 1845

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1850 1855 1860

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1865 1870 1875

Cys Thr Thr Thr Thr Thr Ala Ala Ala Ala Ala Cys Ala Thr Thr
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1895 1900 1905

Thr Thr Thr Gly Gly Gly Gly Gly Cys Ala Gly Gly Gly Gly Gly
1910 1915 1920

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1925 1930 1935

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1940 1945 1950

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1955 1960 1965

Ala Ala Ala Ala Thr Cys Thr Cys Thr Ala Gly Thr Gly Thr Thr

1970 1975 1980

Gly Gly Cys Thr Ala Gly Thr Thr Cys Thr Cys Ala Ala Cys Ala
1985 1990 1995

Thr Thr Gly Gly Cys Thr Ala Ala Ala Gly Thr Ala Ala Cys Ala
2000 2005 2010

Thr Thr Thr Cys Ala Thr Ala Ala Ala Cys Ala Cys Thr Thr Thr
2015 2020 2025

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Thr Ala Thr Thr Thr Ala Ala Gly Ala Ala Thr Ala Thr Cys Thr
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2060 2065 2070

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2075 2080 2085

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Ala Gly Thr Thr Thr Thr Gly Gly Gly Cys Ala Ala Ala Thr Cys
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Cys Thr Thr Cys Ala Thr Gly Thr Thr Ala Ala Gly Thr Cys Ala
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Thr Cys Thr Cys Ala Ala Ala Gly Gly Cys Thr Ala Thr Ala Thr
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Cys Thr Ala Gly Cys Ala Thr Cys Ala Ala Cys Thr Ala Thr Gly
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Thr Gly Ala Thr Thr Thr Ala Cys Ala Thr Thr Cys Ala Gly Thr
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Thr Thr Ala Cys Ala Thr Ala Ala Gly Gly Ala Thr Ala Thr Ala
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Cys Cys Thr Ala Thr Thr Thr Gly Thr Cys Ala Ala Thr Cys Thr
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Cys Ala Gly Cys Ala Cys Ala Ala Thr Cys Thr Gly Thr Ala Ala
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Cys Thr Thr Thr Thr Thr Ala Cys Cys Thr Ala Thr Gly Thr Thr
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Cys Thr Cys Thr Thr Cys Ala Gly Cys Gly Cys Cys Ala Gly Thr
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Cys Thr Thr Ala Gly Gly Cys Ala Ala Ala Gly Thr Thr Gly Thr
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Gly Cys Ala Ala Gly Ala Gly Gly Thr Gly Ala Gly Gly Thr Thr
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Gly Ala Thr Cys Thr Cys Cys Gly Gly Thr Ala Gly Cys Ala Gly
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Gly Thr Ala Cys Thr Cys Cys Thr Cys Thr Cys Cys Cys Ala Thr
2435 2440 2445

Gly Thr Thr Ala Gly Thr Gly Thr Cys Ala Thr Cys Thr Thr Gly
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Cys Cys Thr Gly Cys Cys Thr Ala Cys Cys Thr Thr Cys Thr Ala
2465 2470 2475

Cys Ala Thr Gly Cys Cys Cys Cys Ala Thr Gly Ala Cys Thr Thr

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Cys Cys  Cys Gly Ala Ala Cys  Cys Thr Cys Ala Ala  Gly Ala Thr
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Gly Thr  Ala Gly Thr Gly Cys  Thr Gly Cys Thr Thr  Thr Gly Gly
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Ala Thr  Ala Thr Cys Thr Cys  Cys Ala Thr Gly Ala  Gly Gly Thr
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Ala Ala  Thr Ala Ala Gly Thr  Cys Ala Cys Ala Thr  Thr Ala Gly
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Thr Cys  Ala Gly Gly Cys Thr  Cys Ala Ala Cys Ala  Thr Ala Ala
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Thr Cys  Thr Gly Ala Cys Ala  Gly Ala Thr Ala Cys  Thr Gly Thr
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Ala Gly  Thr Gly Gly Gly Ala  Thr Thr Thr Gly Ala  Thr Cys Thr
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Ala Ala  Thr Ala Gly Cys Thr  Ala Ala Thr Thr Thr  Thr Cys Ala
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Gly Gly  Thr Gly Gly Thr Ala  Ala Cys Thr Gly Thr  Ala Thr Cys
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Thr Thr  Ala Gly Thr Gly Ala  Cys Thr Ala Ala Gly  Thr Ala Gly
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Thr Cys  Ala Thr Ala Thr Cys  Thr Gly Thr Gly Ala  Thr Gly Thr
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Gly Thr  Ala Gly Ala Cys Ala  Gly Ala Cys Cys Cys  Thr Ala Thr
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Ala Ala  Ala Ala Cys Thr Ala  Gly Gly Ala Cys Thr  Ala Gly Cys
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Cys Cys  Thr Gly Gly Thr Ala  Ala Cys Gly Gly Thr  Gly Ala Thr
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Ala Cys  Ala Thr Thr Cys Cys  Ala Thr Thr Ala Thr  Thr Thr Thr
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Cys Thr  Thr Ala Cys Ala Ala  Thr Gly Ala Ala Ala  Ala Ala Thr
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Thr Thr  Ala Thr Thr Cys Ala  Ala Cys Ala Ala Ala  Thr Ala Cys
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Thr Thr  Gly Ala Gly Thr Gly  Cys Cys Thr Gly Cys  Thr Ala Gly
    2945                2950                2955

Ala Thr  Gly Cys Cys Ala Gly  Gly Thr Thr Cys Thr  Ala Cys Ala
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Cys Ala  Ala Gly Gly Cys Ala  Cys Cys Gly Gly Gly  Gly Ala Thr
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Thr Ala  Cys Thr Gly Thr Thr  Ala Thr Thr Thr Thr  Ala Gly Ala
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Gly Thr  Gly Gly Thr Cys Thr  Gly Thr Ala Gly Thr  Ala Thr Ala
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Thr Thr  Ala Gly Thr Gly Ala  Gly Gly Cys Ala Thr  Thr Thr Gly
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Gly Cys  Ala Cys Ala Thr Gly  Ala Cys Cys Cys Ala  Gly Ala Gly
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Ala Thr  Ala Ala Thr Ala Thr  Ala Ala Thr Gly Cys  Ala Thr Ala
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Thr Thr  Thr Thr Ala Gly Thr  Thr Thr Thr Gly Cys  Ala Cys Ala
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Gly Ala  Ala Gly Gly Gly Ala  Thr Ala Thr Gly Gly  Thr Cys Thr
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Cys Thr  Ala Ala Gly Gly Thr  Thr Thr Thr Thr Thr  Cys Cys Ala
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Gly Cys  Thr Cys Thr Ala Ala  Ala Ala Thr Ala Ala  Thr Thr Gly
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Thr Thr  Cys Gly Cys Thr Cys  Thr Gly Ala Thr Thr  Cys Cys Ala
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Ala Thr  Ala Ala Ala Cys Thr  Gly Thr Thr Thr Ala  Ala Thr Cys
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Ala Ala  Gly Cys Thr Ala Cys  Thr Thr Thr Ala Thr  Ala Thr Ala
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Ala Ala  Thr Cys Ala Cys Thr  Thr Thr Ala Cys Thr  Thr Cys Ala
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Thr Thr  Ala Thr Thr Thr Thr  Ala Ala Ala Gly Ala  Ala Gly Thr
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Ala Ala  Ala Cys Thr Thr Gly  Ala Cys Thr Ala Thr  Ala Thr Thr
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    3245                3250                3255

Gly Thr  Thr Thr Thr Thr Thr  Ala Thr Thr Thr Gly  Gly Gly Ala
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Thr Ala  Ala Thr Thr Ala Thr  Gly Thr Gly Ala Thr  Thr Cys Thr
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Gly Thr  Thr Gly Gly Gly Ala  Thr Ala Cys Thr Thr  Ala Thr Ala
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Thr Ala  Gly Thr Ala Cys Ala  Cys Ala Thr Thr Ala  Ala Ala Thr
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Thr Gly  Thr Ala Thr Gly Thr  Cys Ala Gly Ala Thr  Gly Ala Thr
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Ala Ala  Cys Ala Thr Thr Ala  Ala Ala Ala Thr Thr  Cys Cys Cys
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Cys Thr  Thr Gly Gly Thr Cys  Thr Cys Thr Gly Thr  Gly Thr Ala
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Ala Thr  Thr Thr Ala Ala Ala  Thr Ala Thr Thr Gly  Ala Gly Thr
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Thr Thr  Thr Ala Thr Cys Thr  Gly Gly Gly Thr Gly  Thr Gly Ala
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Ala Thr  Ala Ala Ala Cys Ala  Gly Ala Thr Gly Cys  Cys Thr Gly
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Ala Ala  Cys Thr Ala Ala Thr  Thr Cys Ala Cys Ala  Gly Ala Ala
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Ala Ala  Gly Gly Ala Ala Ala  Cys Thr Thr Cys Thr  Gly Thr Gly
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Thr Ala  Ala Ala Ala Ala Gly  Thr Cys Ala Gly Thr  Cys Cys Ala
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Ala Thr  Thr Thr Cys Thr Gly  Ala Ala Ala Thr Gly  Cys Thr Ala
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Thr Gly  Cys Thr Ala Ala Ala  Cys Thr Ala Cys Ala  Gly Gly Thr
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Thr Thr  Ala Thr Gly Gly Ala  Ala Cys Ala Thr Thr  Ala Gly Ala
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Thr Ala  Gly Gly Gly Thr Gly  Thr Thr Ala Ala Gly  Ala Cys Thr
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Thr Thr  Ala Thr Ala Thr Ala  Gly Thr Ala Cys Thr  Thr Cys Cys
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Thr Cys  Thr Thr Gly Thr Thr  Thr Cys Thr Ala Thr  Ala Cys Ala
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Ala Gly  Ala Gly Ala Ala Ala  Gly Ala Ala Ala Thr  Gly Gly Cys
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Cys Ala  Thr Ala Cys Thr Thr  Cys Ala Gly Gly Ala  Ala Thr Thr
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Gly Cys  Ala Gly Thr Gly Cys  Ala Thr Ala Ala Cys  Thr Gly Ala
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Gly Gly  Gly Ala Thr Thr Thr  Thr Thr Ala Gly Gly  Ala Cys Thr
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Cys Thr  Thr Gly Ala Ala Thr  Thr Thr Thr Thr Gly  Ala Thr Gly
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Thr Ala  Gly Cys Cys Gly Gly  Gly Cys Ala Ala Cys  Thr Thr Thr
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Thr Thr  Thr Thr Ala Gly Gly  Cys Ala Gly Thr Gly  Gly Thr Ala
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Ala Thr  Thr Ala Thr Cys Cys  Thr Thr Thr Ala Thr  Thr Ala Thr
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Gly Thr  Gly Ala Ala Thr Thr  Thr Thr Gly Ala Ala  Thr Gly Gly
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Gly Thr  Thr Thr Thr Thr Gly  Thr Ala Gly Ala Gly  Ala Thr Thr
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Thr Thr  Ala Ala Ala Ala Gly  Gly Gly Gly Ala Gly  Cys Gly Cys
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Thr Ala  Ala Thr Cys Cys Thr  Ala Gly Ala Ala Ala  Thr Ala Ala
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Ala Thr  Ala Thr Thr Ala Thr  Gly Thr Ala Ala Thr  Thr Ala Thr
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Gly Cys  Thr Ala Ala Ala Thr  Thr Ala Cys Ala Thr  Ala Gly Thr
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Cys Thr  Thr Ala Gly Ala Cys  Ala Thr Thr Ala Ala  Cys Ala Thr
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Gly Thr  Thr Thr Gly Thr Gly  Gly Ala Ala Gly Ala  Ala Thr Gly
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Thr Ala  Gly Cys Ala Gly Ala  Gly Gly Thr Ala Thr  Gly Thr Ala
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Gly Thr  Ala Thr Ala Ala Thr  Thr Thr Gly Ala Gly  Thr Gly Ala
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Ala Thr  Ala Thr Thr Cys Cys  Cys Ala Ala Thr Thr  Ala Gly Gly
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Ala Ala  Thr Thr Cys Thr Ala  Gly Gly Cys Thr Cys  Thr Ala Gly
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Thr Thr  Thr Ala Ala Cys Thr  Gly Ala Gly Thr Cys  Ala Cys Ala
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Cys Thr  Gly Cys Ala Thr Ala  Gly Gly Ala Ala Thr  Thr Thr Ala
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Gly Ala  Ala Cys Cys Thr Ala  Ala Cys Thr Thr Cys  Thr Ala Gly
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Gly Thr  Thr Ala Thr Cys Ala  Ala Ala Ala Thr Cys  Thr Thr Thr
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Gly Cys  Cys Ala Cys Cys Ala  Thr Thr Gly Cys Ala  Cys Ala Ala
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    4010                4015                4020

Thr Thr  Thr Thr Gly Thr Cys  Cys Thr Ala Ala Thr  Ala Thr Ala
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Thr Ala  Gly Ala Gly Ala Ala  Ala Cys Thr Thr Thr  Gly Thr Gly
    4040                4045                4050

Ala Gly  Gly Cys Ala Thr Gly  Thr Thr Cys Ala Gly  Thr Thr Gly
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Cys Gly  Gly Thr Thr Thr Gly  Cys Ala Cys Ala Ala  Gly Thr Thr
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Cys Ala  Thr Cys Thr Cys Ala  Thr Thr Thr Gly Thr  Ala Thr Thr
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Cys Cys  Ala Gly Thr Gly Ala  Thr Thr Thr Thr Thr  Thr Thr Thr
    4100                4105                4110

Cys Thr  Thr Cys Thr Ala Ala  Cys Cys Ala Thr Thr  Thr Thr Thr
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Thr Thr  Ala Ala Ala Cys Ala  Ala Cys Ala Thr Gly  Thr Ala Cys
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Ala Cys  Ala Thr Thr Gly Thr  Thr Thr Thr Thr Thr  Thr Thr Gly
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Gly Thr  Ala Gly Gly Cys Ala  Ala Thr Gly Ala Ala  Ala Ala Cys
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Thr Gly  Thr Cys Ala Thr Thr  Thr Cys Cys Ala Thr  Thr Gly Thr
    4175                4180                4185

Cys Ala  Ala Ala Cys Ala Gly  Thr Ala Ala Thr Thr  Cys Cys Thr
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Cys Gly  Ala Thr Ala Ala Cys  Thr Gly Thr Ala Thr  Thr Ala Ala
    4205                4210                4215

Thr Gly  Gly Thr Thr Thr Thr  Thr Ala Ala Ala Ala  Ala Ala Cys
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Cys Ala  Thr Cys Ala Gly Thr  Thr Ala Cys Thr Thr  Thr Ala Ala
    4235                4240                4245

Ala Ala  Cys Thr Gly Ala Ala  Thr Thr Thr Ala Thr  Ala Thr Thr
    4250                4255                4260

Thr Ala  Ala Thr Ala Ala Cys  Thr Thr Cys Thr Gly  Thr Ala Thr
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    4265                4270                4275

Thr Ala  Gly Thr Ala Thr Thr  Gly Gly Gly Thr Ala  Gly Cys Ala
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Thr Gly  Ala Ala Ala Thr Cys  Thr Cys Thr Ala Thr  Thr Gly Ala
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Gly Ala  Ala Ala Thr Thr Gly  Ala Ala Cys Ala Gly  Cys Ala Thr
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Ala Cys  Ala Ala Cys Thr Ala  Gly Thr Ala Gly Cys  Thr Gly Thr
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Ala Ala  Ala Thr Thr Cys Cys  Thr Thr Cys Ala Gly  Ala Ala Ala
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Gly Thr  Gly Ala Ala Ala Ala  Thr Thr Ala Thr Thr  Thr Cys Thr
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Thr Cys  Cys Thr Ala Ala Ala  Gly Ala Thr Ala Thr  Cys Thr Thr
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Gly Ala  Cys Ala Thr Cys Ala  Gly Thr Gly Cys Thr  Thr Gly Ala
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Ala Gly  Ala Ala Thr Ala Gly  Thr Cys Ala Thr Ala  Ala Cys Thr
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Gly Ala  Ala Ala Ala Ala Thr  Cys Ala Ala Ala Gly  Thr Thr Thr
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Thr Thr  Ala Cys Thr Thr Gly  Cys Ala Gly Ala Ala  Ala Thr Gly
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Thr Cys  Cys Ala Thr Thr Ala  Thr Ala Gly Gly Gly  Gly Gly Cys
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Cys Cys  Cys Cys Cys Thr Cys  Cys Thr Cys Ala Thr  Ala Gly Ala
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Gly Cys  Thr Gly Ala Ala Thr  Gly Gly Gly Thr Thr  Ala Thr Gly
    4550                4555                4560

Thr Ala  Ala Thr Gly Thr Thr  Thr Thr Ala Thr Cys  Cys Ala Ala
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Ala Ala  Gly Thr Thr Thr Cys  Cys Ala Ala Thr Thr  Cys Cys Ala
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Cys Thr  Gly Thr Cys Thr Thr  Gly Thr Gly Thr Thr  Thr Thr Cys
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Ala Thr  Gly Thr Thr Gly Ala  Ala Ala Ala Thr Ala  Cys Thr Thr
    4610                4615                4620

Thr Thr  Gly Cys Ala Thr Thr  Thr Thr Thr Cys Cys  Thr Thr Thr
    4625                4630                4635

Gly Ala  Gly Thr Gly Cys Cys  Ala Ala Thr Thr Thr  Cys Thr Thr
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Ala Cys  Thr Ala Gly Thr Ala  Cys Thr Ala Thr Thr  Thr Cys Thr
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Thr Ala  Ala Thr Gly Thr Ala  Ala Cys Ala Thr Gly  Thr Thr Thr
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Ala Cys  Cys Thr Gly Gly Ala  Ala Thr Gly Thr Ala  Thr Thr Thr
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Thr Ala  Ala Cys Thr Ala Thr  Thr Thr Thr Thr Gly  Thr Ala Thr
    4700                4705                4710

Ala Gly  Thr Gly Thr Ala Ala  Ala Cys Thr Gly Ala  Ala Ala Cys
    4715                4720                4725

Ala Thr  Gly Cys Ala Cys Ala  Thr Thr Thr Thr Gly  Thr Ala Cys
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Ala Thr  Thr Gly Thr Gly Cys  Thr Thr Thr Thr Thr  Thr Thr Thr
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Gly Thr  Gly Gly Gly Ala Cys  Ala Thr Ala Thr Gly  Cys Ala Gly
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Thr Gly  Thr Gly Ala Thr Cys  Cys Ala Gly Thr Thr  Gly Thr Thr
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aaaattgcta aattacatag tcttagacat taacatgttt gtggaagaat gtagcagagg 3780

tatgtagtat aatttgagtg aatattccca attaggaatt ctaggctcta gtttaactga 3840

gtcacactgc ataggaattt agaacctaac ttctaggtta tcaaaatctt tgccaccatt 3900

gcacaatttt gtcctaatat atagagaaac tttgtgaggc atgttcagtt gcggtttgca 3960

caagttcatc tcatttgtat tccagtgatt ttttttcttc taaccatttt tttaaacaac 4020

atgtacacat tgtttttttt ggtaggcaat gaaaactgtc atttccattg tcaaacagta 4080

attcctcgat aactgtatta atggttttta aaaaaccatc agttacttta aaactgaatt 4140

tatatttaat aacttctgta ttagtattgg gtagcatgaa atctctattg agaaattgaa 4200

cagcatacaa ctagtagctg taaattcctt cagaaagtga aaattatttc ttcctaaaga 4260

tatcttgaca tcagtgcttg aagaatagtc ataactagat taataattgt tttagttaaa 4320

cagttttaag tgcctgtttc agatgatgat aggcaattta gatgaattta ggaaaaatca 4380

aagtttttac ttgcagaaat gtccattata gggggccccc ctcctcatag agctgaatgg 4440

gttatgtaat gttttatcca aaagtttcca attccactgt cttgtgtttt catgttgaaa 4500

atacttttgc atttttcctt tgagtgccaa tttcttacta gtactatttc ttaatgtaac 4560

atgtttacct ggaatgtatt ttaactattt ttgtatagtg taaactgaaa catgcacatt 4620

ttgtacattg tgctttttt tgtgggacat atgcagtgtg atccagttgt tttccatcat 4680

ttggttgcgc tgacctagga atgttggtca tatcaaacat taaatttaaa aatgaccact 4740

cttttaatta aaattaactt ttaaatgttt ataggagtat gtgctgtgaa gtgatctgaa 4800

atttgtaata tttttgtcat gaactgtact gctcctaatt attgtaatgt aataaaaata 4860

gttatggtga ctatga 4876

<210> 54
<211> 188
<212> PRT
<213> Canis lupus

<400> 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 Thr Lys Ser Phe Glu Asp Ile His His Tyr
85 90 95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Glu Asp Val Pro Met Val
100 105 110

Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr Lys
115 120 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Phe Ile Glu Thr
130 135 140

Ser Ala Lys Thr Arg Gln Gly Val Asp Asp Ala Phe Tyr Thr Leu Val
145 150 155 160

Arg Glu Ile Arg Lys His Lys Glu Lys Met Ser Lys Asp Gly Lys Lys
165 170 175

Lys Lys Lys Lys Ser Lys Thr Lys Cys Ile Ile Met
180 185

<210> 55
<211> 1394
<212> DNA
<213> Felis catus

<400> 55
gctgaaaatg actgaatata aacttgtggt agttggagct ggtggcgtag gcaagagtgc 60

cttgacgata cagctaattc agaatcactt tgtggatgaa tatgatccta caatagagga 120

ttcctacagg aaacaagtag taattgatgg agaaacctgt ctcttggata ttctcgacac 180

agcaggtcaa gaggagtaca gtgcaatgag ggaccagtac atgaggactg gggagggctt 240

tctttgcgta tttgccataa ataatactaa atcatttgaa gatattcacc actatagaga 300

acaaataaaa agagttaaag actctgaaga tgtacctatg gtcctagtag gaaataaatg 360

tgatttgcct tctagaacag tagatacaaa acaggctcag gacttagcaa gaagttatgg 420

aattcctttt attgaaacat cagcaaagac aagacagggt gttgacgatg ccttctatac 480

attagttcga gaaattcgaa aacataaaga aaagatgagc aaagatggta aaaagaagaa 540

aaagaagtca aagacaaagt gtataattat gtaaatacaa tttgtacttt tttcttaagg 600

catacttaag taaaagtggt aatttttgta cattacacta aattattagc atttgtttta 660

gcattaccta attttctgct ccatccaaac tgttagcttt tatcttgaat gcttatttta 720

aatgacagtg gaaacttttt ttcctctaag tgccagtatt ccctgagttt tggtttttga 780

actagcaatg cctgtgaaaa agaaactgaa tacctgagat ttctgtcttg gggtttttgg 840

tgcatgcagt tgattacttc ctatttttct taccaattgt gaactttggt gtgaaacaaa 900

ttaatgaaac tttcgaatca tccctattct gtgtttcatg tagtcacata catggattaa 960

ttactaatta taacttcagt tgagatttca tgattcgttt tactgaaaca ttgagggaac 1020

atgaatttat gggcttcttg tagattcatc ttgtaggtat taatgtccta tagtttcagt 1080

cacccttaat gaatgtaaag ttacactgtt cataaaagtt tctccatctt ttcactgctg 1140

tttgtcatcg tcacgctccc ccaaaatatt atatttttc tataaaaagg gaaaaaagga 1200

aaaaaataca aggcaatgga aaatattaaa aggcatttac tttctgtatt agataaattc 1260

ctataatact ctgaatagct tttcctgtta aggcagaccc agtatgtgat gaggattata 1320

gcaaccattt tggggctata tttacatgct actaaatttt tgtaataatt gaaaaaattt 1380

taacatgtat aaaa 1394

<210> 56
<211> 188
<212> PRT
<213> Felis catus

<400> 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
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 Thr Lys Ser Phe Glu Asp Ile His His Tyr
85 90 95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Glu Asp Val Pro Met Val
100 105 110

Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr Lys
115 120 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Phe Ile Glu Thr
130 135 140

Ser Ala Lys Thr Arg Gln Gly Val Asp Asp Ala Phe Tyr Thr Leu Val
145 150 155 160

Arg Glu Ile Arg Lys His Lys Glu Lys Met Ser Lys Asp Gly Lys Lys
165 170 175

Lys Lys Lys Lys Ser Lys Thr Lys Cys Ile Ile Met
180 185

<210> 57
<211> 1512
<212> DNA
<213> Felis catus

<400> 57
tgctgaaaat gactgaatat aaacttgtgg tagttggagc tggtggcgta ggcaagagtg 60

ccttgacgat acagctaatt cagaatcact ttgtggatga atatgatcct acaatagagg 120

attcctacag gaaacaagta gtaattgatg gagaaacctg tctcttggat attctcgaca 180

cagcaggtca agaggagtac agtgcaatga gggaccagta catgaggact ggggagggct 240

ttctttgcgt atttgccata aataatacta aatcatttga agatattcac cactatagag 300

aacaaataaa aagagttaaa gactctgaag atgtacctat ggtcctagta ggaaataaat 360

gtgatttgcc ttctagaaca gtagatacaa aacaggctca ggacttagca agaagttatg 420

gaattccttt tattgaaaca tcagcaaaga caagacagag agtggaggat gctttttata 480

cattggtgag agagatccga cagtacagat tgaaaaaaat caacaaagaa gaaaagactc 540

ctggctgtgt gaaaattaaa aaatgcattg taatgggtgt tgacgatgcc ttctatacat 600

tagttcgaga aattcgaaaa cataaagaaa agatgagcaa agatggtaaa aagaagaaaa 660

agaagtcaaa gacaaagtgt ataattatgt aaatacaatt tgtacttttt tcttaaggca 720

tacttaagta aaagtggtaa tttttgtaca ttacactaaa ttattagcat ttgttttagc 780

attacctaat tttctgctcc atccaaactg ttagctttta tcttgaatgc ttattttaaa 840

tgacagtgga aacttttttt cctctaagtg ccagtattcc ctgagttttg gttttgaac 900

tagcaatgcc tgtgaaaaag aaactgaata cctgagattt ctgtcttggg gttttggtg 960

catgcagttg attacttcct atttttctta ccaattgtga actttggtgt gaaacaaatt 1020

aatgaaactt tcgaatcatc cctattctgt gtttcatgta gtcacataca tggattaatt 1080

actaattata acttcagttg agatttcatg attcgtttta ctgaaacatt gagggaacat 1140

gaatttatgg gcttcttgta gattcatctt gtaggtatta atgtcctata gtttcagtca 1200

cccttaatga atgtaaagtt acactgttca taaaagtttc tccatctttt cactgctgtt 1260

tgtcatcgtc acgctccccc aaaatattat atttttctta taaaaaggga aaaaaggaaa 1320

aaaatacaag gcaatggaaa atattaaaag gcatttactt tctgtattag ataaattcct 1380

ataatactct gaatagcttt tcctgttaag gcagacccag tatgtgatga ggattatagc 1440

aaccattttg gggctatatt tacatgctac taaatttttg taataattga aaaaatttta 1500

acatgtataa aa 1512

<210> 58
<211> 227
<212> PRT
<213> Felis catus

<400> 58

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly Lys
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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 Thr Lys Ser Phe Glu Asp Ile His His Tyr
85 90 95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Glu Asp Val Pro Met Val
100 105 110

Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr Lys
115 120 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Phe Ile Glu Thr
130 135 140

Ser Ala Lys Thr Arg Gln Arg Val Glu Asp Ala Phe Tyr Thr Leu Val
145 150 155 160

Arg Glu Ile Arg Gln Tyr Arg Leu Lys Lys Ile Asn Lys Glu Glu Lys
165 170 175

Thr Pro Gly Cys Val Lys Ile Lys Lys Cys Ile Val Met Gly Val Asp
180 185 190

Asp Ala Phe Tyr Thr Leu Val Arg Glu Ile Arg Lys His Lys Glu Lys
195 200 205

Met Ser Lys Asp Gly Lys Lys Lys Lys Lys Lys Ser Lys Thr Lys Cys
210 215 220

Ile Ile Met
225

<210> 59
<211> 2144
<212> DNA
<213> Bos taurus

<400> 59
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catttctgac tgggagcgag cgcggcgcag gcactgaagg cagcggcggg ggccagaggc 120

tcggcggctc ccaggtgagg gagagaggcc tgctgaaaat gactgaatat aaacttgtgg 180

tagttggagc tggtggcgta ggcaagagtg ccttgacgat acagctaatt cagaatcact 240

ttgtggatga atatgatcct acgatagagg attcctacag gaaacaagta gtaattgatg 300

gagaaacctg tctcttggat attctcgaca cagcaggtca agaggagtac agtgcaatga 360

gggaccagta catgaggact ggggagggct ttctttgtgt atttgccata aataatacta 420

aatcatttga agatattcac cattatagag aacaaataaa aagagttaaa gactctgaag 480

atgtacctat ggttctagta ggaaataaat gtgatttgcc ttctagaaca gtagacacaa 540

aacaggctca ggacttagca agaagttatg gaattccttt tattgaaaca tcagcaaaga 600

caagacaggg tgttgacgat gccttctata cattagttcg agaaattcga aaacataaag 660

aaaagatgag caaagatggt aaaaagaaga aaaagaagtc aaagacaaag tgtataatta 720

tgtaaataca atttgtactt ttttcttaag gcatacttaa gtaaaagtgg taatttttgt 780

atattacact aaattattag catttgtttt agcattatct aattttcttt ctgctccatc 840

catactgtta gcttttatct tgaatgctta ttttaaaatg acagtggaaa ctttttttcct 900

ctaagtgcca gtattccctg cgttttggtt tttgaactag caatgcctgt gaaaaagaaa 960

ctgaacaccc aagatttttg tcttggggtt tttggtgcat gcagttgatt acttcctatt 1020

tttcttatca attgtgaact ttagtgtgaa acaaattaat gaggctttca aatcatccct 1080

attgtattgt tttatctagt cacacacatg gattaattac taattataac ttcagttgag 1140

atttcatgat tggttttact gaaacatcga gggaacatga atttatgggc ttcctatagt 1200

ttcatcttgt aggtatcatt gtcctatagt ttcagttacc cttaatgaat gtcaggttac 1260

actgttcaca aaggttttct tctttccact gctatttgtc aaatggtcac gttccctaaa 1320

atactatatt ttttctataa aaaaaagaaa aaaatggaaa aaaatacaag gcaatggaaa 1380

atattaaaag gccacttact ttccacatta ggtaaattcc tataatgctc tgaatagctt 1440

tttatgttaa ggcagaccca gtaggtaatg aggattagaa caagcatttt gggactatat 1500

ttacatgctt taaatttttg taataacaaa aaaattttaa catgtataaa gaattctcat 1560

aggaattaaa tacagtctcc ctgtgtcaga ttgctctttc ttagcataaa tctttttctt 1620

gaacttcaat ctttaaaagt agttttaatt ctactgatag tgatgtaaaa gattatttgg 1680

gccagttagc ttggtaggtg ttacagagac cagggtggca tagccgggcc ttgtgtgaac 1740

ctttaagcta catggagagt ttcacagtgt ggactgcatc cctgtggtct tccattgttg 1800

ccatgccttg gttggtcaaa aacaaggact tgcagagaga ttgaatagct cagcaaggta 1860

cattctcatt atgtcgtagt cctactcagg aacatcactt ttttaaaata aaaaacccca 1920

aaaaacagaa cttaaaaaaa aaaacaacat tattttaaat gagattttcg gtggggtgga 1980

aagattttaa tttttttaa acgatgaaat gaaaaaatgt caaaatcttg agtattggct 2040

agttctcttt aacactggct aaagtaacat ttttgtaaac acttcagtac agtctggtcc 2100

attattaaga atatctaatg cttatacaat aaagtaatgc taac 2144

<210> 60
<211> 188
<212> PRT
<213> Bos taurus

<400> 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 Thr Lys Ser Phe Glu Asp Ile His His Tyr
85 90 95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Glu Asp Val Pro Met Val
100 105 110

Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr Lys
115 120 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Phe Ile Glu Thr
130 135 140

Ser Ala Lys Thr Arg Gln Gly Val Asp Asp Ala Phe Tyr Thr Leu Val
145 150 155 160

Arg Glu Ile Arg Lys His Lys Glu Lys Met Ser Lys Asp Gly Lys Lys
165 170 175

Lys Lys Lys Lys Ser Lys Thr Lys Cys Ile Ile Met
180 185

<210> 61
<211> 1010
<212> DNA
<213> Bos taurus

<400> 61
ggcggtggcg gcggcggcgg cggtggcggt ggcggttcgg ccagtactcc cggcccccgc 60

catttctgac tgggagcgag cgcggcgcag gcactgaagg cagcggcggg ggccagaggc 120

tcggcggctc ccaggtgagg gagagaggcc tgctgaaaat gactgaatat aaacttgtgg 180

tagttggagc tggtggcgta ggcaagagtg ccttgacgat acagctaatt cagaatcact 240

ttgtggatga atatgatcct acgatagagg attcctacag gaaacaagta gtaattgatg 300

gagaaacctg tctcttggat attctcgaca cagcaggtca agaggagtac agtgcaatga 360

gggaccagta catgaggact ggggagggct ttctttgtgt atttgccata aataatacta 420

aatcatttga agatattcac cattatagag aacaaataaa aagagttaaa gactctgaag 480

atgtacctat ggttctagta ggaaataaat gtgatttgcc ttctagaaca gtagacacaa 540

aacaggctca ggacttagca agaagttatg gaattccttt tattgaaaca tcagcaaaga 600

caagacagag agtggaggat gctttttata cattggtgag agagatccga caatacagat 660

tgaaaaaaat cagcaaagaa gaaaagactc ctggctgtgt gaaaattaaa aaatgcattg 720

taatgggtgt tgacgatgcc ttctatacat tagttcgaga aattcgaaaa cataaagaaa 780

agatgagcaa agatggtaaa aagaagaaaa agaagtcaaa gacaaagtgt ataattatgt 840

aaatacaatt tgtacttttt tcttaaggca tacttaagta aaagtggtaa tttttgtata 900

ttacactaaa ttattagcat ttgttttagc attatctaat tttctttctg ctccatccat 960

actgttagct tttatcttga atgcttattt taaaatgaca gtggaaactt 1010

<210> 62
<211> 227
<212> PRT
<213> Bos taurus

<400> 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 Thr Lys Ser Phe Glu Asp Ile His His Tyr
85 90 95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Glu Asp Val Pro Met Val
100 105 110

Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr Lys
115 120 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Phe Ile Glu Thr
130 135 140

Ser Ala Lys Thr Arg Gln Arg Val Glu Asp Ala Phe Tyr Thr Leu Val
145 150 155 160

Arg Glu Ile Arg Gln Tyr Arg Leu Lys Lys Ile Ser Lys Glu Glu Lys
165 170 175

Thr Pro Gly Cys Val Lys Ile Lys Lys Cys Ile Val Met Gly Val Asp

180 185 190

Asp Ala Phe Tyr Thr Leu Val Arg Glu Ile Arg Lys His Lys Glu Lys
195 200 205

Met Ser Lys Asp Gly Lys Lys Lys Lys Lys Ser Lys Thr Lys Cys
210 215 220

Ile Ile Met
225

<210> 63
<211> 797
<212> DNA
<213> Bos taurus

<400> 63
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atttctgact gggagcgagc gcggcgcagg cactgaaggc agcggcgggg gccagaggct 120

cggcggctcc caggtgaggg agagaggcct gctgaaaatg actgaatata aacttgtggt 180

agttggagct ggtggcgtag gcaagagtgc cttgacgata cagctaattc agaatcactt 240

tgtggatgaa tatgatccta cgatagagga ttcctacagg aaacaagtag taattgatgg 300

agaaacctgt ctcttggata ttctcgacac agcaggtcaa gaggagtaca gtgcaatgag 360

ggaccagtac atgaggactg gggagggctt tctttgtgta tttgccataa ataatactaa 420

atcatttgaa gatattcacc attatagaga acaaataaaa agagttaaag actctgaaga 480

tgtacctatg gttctagtag gaaataaatg tgatttgcct tctagaacag tagacacaaa 540

acaggctcag gacttagcaa gaagttatgg aattcctttt attgaaacat cagcaaagac 600

aagacagaga gtggaggatg ctttttatac attggtgaga gagatccgac aatacagatt 660

gaaaaaaatc agcaaagaag aaaagactcc tggctgtgtg aaaattaaaa aatgcattgt 720

aatgtaatct gggtgttgac gatgccttct atacattagt tcgagaaatt cgaaaacata 780

aagaaaagat gagcaaa 797

<210> 64
<211> 189
<212> PRT
<213> Bos taurus

<400> 64

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

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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 Thr Lys Ser Phe Glu Asp Ile His His Tyr
                85                  90                  95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Glu Asp Val Pro Met Val
            100                 105                 110

Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr Lys
        115                 120                 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Phe Ile Glu Thr
    130                 135                 140

Ser Ala Lys Thr Arg Gln Arg Val Glu Asp Ala Phe Tyr Thr Leu Val
145                 150                 155                 160

Arg Glu Ile Arg Gln Tyr Arg Leu Lys Lys Ile Ser Lys Glu Glu Lys
                165                 170                 175

Thr Pro Gly Cys Val Lys Ile Lys Lys Cys Ile Val Met
            180                 185
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<210> 65
<211> 1112
<212> DNA
<213> Gallus gallus

<400> 65

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aagagcgcct tgacaataca gctcattcag aaccactttg tggatgagta tgaccctacc      120

atagaggatt cctacagaaa gcaagtagta attgatgggg aaacctgtct cttggatatt      180

cttgatacag caggtcaaga agaatatagt gcaatgaggg accaatatat gagaacagga      240

gaaggctttc tgtgtgtttt tgctataaac aatacaaaat cttttgaaga tattcaccat      300

tatagggaac aaataaagag agttaaagac tctgaagatg tcccaatggt gctagtagga      360

aacaaatgtg atttgccttc cagaacagta gatacaaaac aagctcagga tttagcaaga      420

agttatggaa ttccttttat tgaaacatca gcaaagacaa gacagggtgt tgatgatgcc      480

ttctatacat tagttcgaga aatcagaaaa cacaaagaga agatgagcaa agatggtaaa      540

aagaagaaaa agaagacaaa gacaaagtgt ataattatgt aaatacaatg tatccttatt      600

cttaagacgt actgaagtaa tttttgtaca ttacactaaa ttattagcat ttgtttttag      660

cattacttta ctttctgctt catgatcctg ttagctttac ctgaatgctt gttttaaatg      720

acagtggaaa cttcattcct cttaaagtgc cagtattctt tgagtgttgg ttcttgaact      780
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agcaatgcct gtgaagaaaa ataaaaacaa atgaaaaaaa aaaaaacaca caaaaacctg 840

agaactgtct taggactctt tggtgcatgc acagttgcta acttcctatt tttcttactg 900

attgtgaact tctgttccgt gcgtaaacaa aacaatgaaa cgatctacac gttctaacat 960

ccccccttcat ttgtactctc ttatttttta catctggttg ggaaaacgga ccagttagtg 1020

acaaagactt tattttcaga cttccttcta atttcgactg actgcaatat agagagacca 1080

gaagccttta tagtcttcct gtagattttg ct 1112

<210> 66
<211> 188
<212> PRT
<213> Gallus gallus

<400> 66

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 Thr Lys Ser Phe Glu Asp Ile His His Tyr
85 90 95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Glu Asp Val Pro Met Val
100 105 110

Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr Lys
115 120 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Phe Ile Glu Thr
130 135 140

Ser Ala Lys Thr Arg Gln Gly Val Asp Asp Ala Phe Tyr Thr Leu Val
145 150 155 160

Arg Glu Ile Arg Lys His Lys Glu Lys Met Ser Lys Asp Gly Lys Lys
165 170 175

Lys Lys Lys Lys Thr Lys Thr Lys Cys Ile Ile Met
180 185

<210> 67
<211> 4454
<212> DNA
<213> Homo sapiens

<400> 67
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<210> 68
<211> 189
<212> PRT
<213> Homo sapiens

<400> 68

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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
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Arg Glu Ile Arg Gln Tyr Arg Met Lys Lys Leu Asn Ser Ser Asp Asp
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Gly Thr Gln Gly Cys Met Gly Leu Pro Cys Val Val Met
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<210> 69
<211> 1326
<212> DNA
<213> Rattus norvegicus

<400> 69
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<210> 70
<211> 189
<212> PRT
<213> Rattus norvegicus

<400> 70

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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 Glu Asp
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Gly Thr Gln Gly Cys Met Gly Leu Pro Cys Val Val Met
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<210> 71
<211> 4470
<212> DNA
<213> Mus musculus

<400> 71

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caaaagcctc ccgaggcggg gtctgcggag tttgaggttt ttgctggtgt gaaatgactg      180

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aagtggtgat tgatggtgag acctgcctgc tggacatact ggacacagct ggacaagagg      360

agtacagtgc catgagagac cagtacatga ggacaggcga agggttcctc tgtgtatttg      420
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<210> 72
<211> 189
<212> PRT
<213> Mus musculus

<400> 72

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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> 73
<211> 570
<212> DNA
<213> Cavia porcellus

<400> 73
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cgaaaacagg tggttataga tggtgaaact tgtctgttgg atattctgga tacagctgga 180

caagaggagt acagtgccat gagagaccaa tacatgagga caggcgaagg cttcctctgt 240

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<210> 74
<211> 189
<212> PRT
<213> Cavia porcellus

<400> 74

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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
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Gly Thr Gln Gly Cys Met Gly Leu Pro Cys Val Val Met

180 185

<210> 75
<211> 1220
<212> DNA
<213> Cavia porcellus

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<212> PRT
<213> Cavia porcellus

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50 55 60

Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys
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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
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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

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165 170 175

Gly Thr Gln Gly Cys Met Gly Leu Pro Cys Val Val Met
180 185

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<212> DNA
<213> Canis lupus

<400> 77
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<213> Canis lupus

<400> 78

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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
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Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Asp Asp Val Pro Met Val
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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
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165 170 175

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180 185

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<213> Felis catus

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<211> 189
<212> PRT
<213> Felis catus

<400> 80

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Glu Thr Cys Leu Leu Asp Ile Leu Asp Thr Ala Gly Gln Glu Glu Tyr
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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
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Leu Val Gly Asn Lys Cys Asp Leu Pro Thr Arg Thr Val Asp Thr Lys
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Gln Ala His Glu Leu Ala Lys Ser Tyr Gly Ile Pro Phe Ile Glu Thr
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Ser Ala Lys Thr Arg Gln Gly Val Glu Asp Ala Phe Tyr Thr Leu Val
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Gly Thr Gln Gly Cys Met Gly Leu Pro Cys Val Val Met
180 185

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<211> 4283
<212> DNA
<213> Bos taurus

<400> 81
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<212> PRT
<213> Bos taurus

<400> 82

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

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<211> 4825
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<213> Gallus gallus

<400> 83

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<400> 86

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Ile Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu
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Asp Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala
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Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln
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Gln Leu Leu Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser
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Ser Ala Ser Met Asp Thr Val Thr Ser Ser Ser Ser Ser Ser Ser Leu Ser

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Val Leu Pro Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val Ala
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Pro Asn Lys Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr Val
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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
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Val Leu Glu Asn Val Pro Leu Thr Thr His Asn Phe Val Arg Lys Thr
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Gly Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys Ser
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Ala Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu
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Gln Gln Leu Leu Glu Ser Leu Val Phe Gln Thr Pro Thr Asp Val Ser
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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
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Trp Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu
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Val Leu Glu Asn Val Pro Leu Thr Thr His Asn Phe Val Arg Lys Thr
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Gly Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys Ser
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Thr Glu Val Pro Leu Met Cys Val Asn Tyr Asp Gln Leu Asp Leu Leu
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Phe Val Ser Lys Phe Phe Glu His His Pro Val Pro Gln Glu Glu Ala
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Phe Ser Ala Glu Thr Thr Leu Pro Ser Gly Cys Ser Ser Ala Pro Pro
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Ser Asp Ser Ile Gly Pro Gln Ile Leu Thr Ser Pro Ser Pro Ser Lys
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Ser Ile Pro Ile Pro Gln Pro Phe Arg Pro Ala Asp Glu Asp His Arg
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Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Glu Lys Phe Pro Glu Val
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Glu Leu Gln Asp Gln Arg Asp Leu Ile Arg Asp Gln Gly Phe Arg Gly
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Asp Gly Ala Pro Leu Asn Gln Leu Met Arg Cys Leu Arg Lys Tyr Gln
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Arg Asp Ser Ser Asp Asp Trp Glu Ile Pro Asp Gly Gln Ile Thr Val
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Trp His Gly Asp Val Ala Val Lys Met Leu Asn Val Thr Ala Pro Thr
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Thr Arg His Val Asn Ile Leu Leu Phe Met Gly Tyr Ser Thr Lys Pro
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Gln Leu Ala Ile Val Thr Gln Trp Cys Glu Gly Ser Ser Leu Tyr His
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His Leu His Ile Ile Glu Thr Lys Phe Glu Met Ile Lys Leu Ile Asp
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Leu Thr Val Lys Ile Gly Asp Phe Gly Leu Ala Thr Val Lys Ser Arg
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Trp Ser Gly Ser His Gln Phe Glu Gln Leu Ser Gly Ser Ile Leu Trp
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Met Ala Pro Glu Val Ile Arg Met Gln Asp Lys Asn Pro Tyr Ser Phe
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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
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Ser Leu Asn Arg Ala Gly Phe Gln Thr Glu Asp Phe Ser Leu Tyr Ala
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Leu Leu Asp Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu
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Glu Cys Cys Ala Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile
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Gly Trp Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val
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Gln Gly Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys
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Ser Thr Glu Val Pro Leu Met Cys Val Asn Tyr Asp Gln Leu Asp Leu
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Leu Phe Val Ser Lys Phe Phe Glu His His Pro Val Pro Gln Glu Glu
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Lys Ser Ile Pro Ile Pro Gln Pro Phe Arg Pro Ala Asp Glu Asp His
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His Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Glu Lys Phe Pro Glu
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Val Glu Leu Gln Asp Gln Arg Asp Leu Ile Arg Asp Gln Gly Phe Arg
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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
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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> 91
<211> 2232
<212> DNA
<213> Oryctolagus cuniculus

<400> 91

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gaatacacca gcaagctaga tgccctccaa caaagagaac agcagttatt ggaatcccta      180

gtttttcaaa atcccacaga tgtgtcacgg agcaacccca agtcaccaca aaaacctatt      240

gttagagtct tcctgcccaa caaacagagg acagtggtac ctgcaagatg tggagttacg      300

gttcgagaca gtctaaagaa agcgctgatg atgagaggtc tgatcccaga atgctgtgct      360

gtttacagaa ttcaggatgg agagaagaag ccaattggct gggacactga tatttcctgg      420

ctcactggag aagagctgca tgtggaagtg ttagagaatg tcccactcac cacacataac      480

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ccactgatgt gtgttaatta tgaccaactt gatttgctgt ttgtctccaa gttctttgaa      660

caccacccag taccacagga ggaggcctcc ttagcagaga ctgccctcac atctgggtca      720

tcgccttccg cacctccctc agactctatt gggcaccaaa ttctcaccag tccgtcccct      780
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gtcaatattg atgaaaaatt cccagaagtg gaattacagg atcaaaggga cttgattaga 960

gaccaagggt ttcgtggtga tggagcccct ttgaaccagc tgatgcgctg tcttcggaaa 1020

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gccttcaagt ag 2232

<210> 92
<211> 743
<212> PRT
<213> Oryctolagus cuniculus

<400> 92

Met Gly Asn Val Trp Asn Ile Lys Gln Met Ile Lys Leu Thr Gln Glu
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His Ile Glu Ala Leu Leu Asp Lys Phe Gly Gly Glu His Asn Pro Pro
20 25 30

Ser Ile Tyr Leu Glu Ala Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala

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        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
    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
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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

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
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<211> 2186
<212> DNA
<213> Cavia porcellus

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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

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ccaggagagg aagatcatcg aaatcaattt gggcagcgag accggtcctc atctgctccc 960

aatgtgcata taaacacaat agaacctgtc aatattgatg atttgattag agaccaaggg 1020

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gcatcagaac cctccttgaa tcgggctggt ttccaaacag aggattttag tctctatgct 2100

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<210> 94
<211> 719
<212> PRT
<213> Cavia porcellus

<400> 94

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Phe Asn Gly Asp Met Glu Leu Glu Ala Gly Ala Gly Ala Ala Ala Ser

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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
        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
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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

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

<210> 95
<211> 3229
<212> DNA
<213> Canis lupus

<400> 95
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ctaatcccag agtgctgtgc tgtttacaga attcaggatg gagagaagaa accgattggc 180

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ttttaaagaa agatcattat ccttttctct acctaaatat ggggagtctt agcataatga 3060

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tttatctaga atatgcaacc taaaataaaa atggtggtgt ctccattca 3229

<210> 96
<211> 617
<212> PRT
<213> Canis lupus

<400> 96

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Ser Lys Val Pro Ala Arg Cys Gly Val Thr Val Arg Asp Ser Leu Lys
20 25 30

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

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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
        435                 440                 445
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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
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Gly Tyr Gly Glu Phe Ala Ala Phe Lys
    610                 615
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<211> 1889
<212> DNA
<213> Canis lupus

<400> 97

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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
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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

ttcgtagtga tggaggatca accacaggtt tgtctgccac ccccccctgcc tcattgcctg 1080

gctcactcac taatgtaaaa gcattacaga aatctccagg acctcagcgg gaaagaaaat 1140

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atcagtttga acagttgtct ggatccattt tgtggatggc accagaagtg atccgaatgc 1740

aagacaaaaa cccatatagc ttccagtcag atgtatacgc atttgggatt gttctatatg 1800

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gatcacggtg tcatgagatc aagccccac 1889

<210> 98
<211> 615
<212> PRT
<213> Canis lupus

<400> 98

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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 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
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

Asn Arg Asp Gln Leu Arg Ser
610 615

<210> 99
<211> 3521
<212> DNA
<213> Felis catus

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<221> misc_feature
<222> (630)..(649)
<223> n is a, c, g, or t

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gaaccactga tgctaatgtt gaaggtgacc tttgcaggct ctccactact cataccaaag 180

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caacacagca tagtgtctat ggcagtatct ggatttggcc gggggaagtg cccaagagga 360

gacagtcagg ctgtgtccta cggccaagga cctgcactta tttttgcatg cagtggttta 420

gcacagggaa gagaacgaag taggaaatcg gagccatgga aacggcagag cggaggaaac 480

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gctcctagga ttacgtcacg caccccgcga aaactgaaat gtactgtgtg tggtctttta 600

attgaactat cttccttatg tgcacttaan nnnnnnnnnn nnnnnnnnng cggcggcggc 660

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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

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aaacctatcg ttagagtctt cctgcctaat aaacagagga cagtggtacc tgcaagatgt 1140

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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

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ttatacacct tagcaataga ctgaatttct ttttataaat t 3521

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<211> 974
<212> PRT
<213> Felis catus

<220>
<221> misc_feature
<222> (210)..(217)
<223> Xaa can be any naturally occurring amino acid

<400> 100

Met Pro Asn Leu Ser Leu Cys His His Gly Gln Phe Ala His Val Pro
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Thr Val Ser Ala Leu Gly Tyr Phe Val Ile Cys Leu Gly His Cys Pro
20 25 30

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
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

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        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

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
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<211> 3853
<212> DNA
<213> Bos taurus

<400> 101

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ctccccccgc cctcagcctc ccttcccccc ccccgcccag cagcggtcgc tcgggcccgg      180

ctctcggtta taagatggcg gcgctgagtg gcggcggcgg cggcggcggc ggtggcgcgg      240
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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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Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly Trp Asp Thr Asp
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Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly Ser Gly Ser Phe Gly
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Thr Val Tyr Lys Gly Lys Trp His Gly Asp Val Ala Val Lys Met Leu
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Val Gly Lys Thr Leu Leu Ser Lys Arg Gln Asn Ser Glu Val Ile Arg
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Gly Phe Gln Thr Glu Asp Phe Ser Leu Tyr Ala Cys Ala Ser Pro Lys
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Ile Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu
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Asp Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala
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Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln
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Gln Leu Leu Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser
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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
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Arg Ser Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu
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Pro Asn Lys Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr Val
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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
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Trp Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu
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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 Glu Pro Pro
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Ile Leu Thr Ser Pro Ser Pro Ser Lys Ser Ile Pro Ile Pro Gln Pro
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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
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Asn Ile Asp Asp Leu Ile Arg Asp Gln Gly Phe Arg Ser Asp Gly Gly
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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
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Gly Arg Arg Asp Ser Ser Asp Asp Trp Glu Ile Pro Asp Gly Gln Ile
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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
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Pro Thr Pro Gln Gln Leu Gln Ala Phe Lys Asn Glu Val Gly Val Leu
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Arg Lys Thr Arg His Val Asn Ile Leu Leu Phe Met Gly Tyr Ser Thr
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Lys Pro Gln Leu Ala Ile Val Thr Gln Trp Cys Glu Gly Ser Ser Leu
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Tyr His His Leu His Ile Ile Glu Thr Lys Phe Glu Met Ile Lys Leu
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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
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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
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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
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Arg Ser Asn Cys Pro Lys Ala Met Lys Arg Leu Met Ala Glu Cys Leu
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Lys Lys Lys Arg Asp Glu Arg Pro Leu Phe Pro Gln Val Gly Lys Thr
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Leu Leu Ser Lys Arg Gln Asn Ser Glu Val Ile Arg Glu Lys Asp Lys
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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
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Glu Asp Phe Ser Leu Tyr Ala Cys Ala Ser Pro Lys Thr Pro Ile Gln
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Val Glu Val Gly Ile
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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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Gln Leu Leu Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser
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Ser Ala Ser Thr Asp Thr Val Thr Ser 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
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Arg Ser Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu
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Pro Asn Lys Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr Val
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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
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Trp Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu
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Val Leu Glu Asn Val Pro Leu Thr Thr His Asn Phe Val Arg Lys Thr
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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
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
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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
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Asp Arg Asn Arg Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp Asp
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Trp Glu Ile Pro Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly Ser
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Gly Ser Phe Gly Thr Val Tyr Lys Gly Lys Trp His Gly Asp Val Ala
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Val Lys Met Leu Asn Val Thr Ala Pro Thr Pro Gln Gln Leu Gln Ala
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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
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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
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Asn Ile Asn Asn Arg Asp Gln Ile Ile Phe Met Val Gly Arg Gly Tyr

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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 Met Ala Ala Leu Ser Gly Gly Gly
740 1 5

Gly Gly Gly Gly Gly Gly Ala Glu Gln Gly Gln Ala Leu Phe Asn Gly
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Asp Met Glu Pro Glu Ala Gly Ala Ala Ala Ser Ser Ala Ala Asp Pro
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Ala Ile Pro Glu Glu Val Trp Asn Ile Lys Gln Met Ile Lys Leu Thr
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Gln Glu His Ile Glu Ala Leu Leu Asp Lys Phe Gly Gly Glu His Asn
60 65 70

Pro Pro Ser Ile Tyr Leu Glu Ala Tyr Glu Glu Tyr Thr Ser Lys Leu
75 80 85

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

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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
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Thr His Asn Phe Val Arg Lys Thr Phe Phe Thr Leu Ala Phe Cys Asp
235 240 245

Phe Cys Arg Lys Leu Leu Phe Gln Gly Phe Arg Cys Gln Thr Cys Gly
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Tyr Lys Phe His Gln Arg Cys Ser Thr Glu Val Pro Leu Met Cys Val
265 270 275 280

Asn Tyr Asp Gln Leu Asp Leu Leu Phe Val Ser Lys Phe Phe Glu His
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His Pro Ile Pro Gln Glu Glu Ala Ser Leu Ala Glu Thr Thr Leu Pro
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Cys Gly Ser Ser Pro Ser Ala Pro Pro Ser Asp Ser Ile Gly Pro Pro
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Ile Leu Thr Ser Pro Ser Pro Ser Lys Ser Ile Pro Ile Pro Gln Pro
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Arg Ser Ser Ser Ala Pro Asn Val His Ile Asn Thr Ile Glu Pro Val
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Asn Ile Asp Asp Leu Ile Arg Asp Gln Gly Phe Arg Ser Asp Gly Gly
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Ser Thr Thr Gly Leu Ser Ala Thr Pro Pro Ala Ser Leu Pro Gly Ser
395 400 405

Leu Ser Asn Val Lys Ala Leu Gln Lys Ser Pro Gly Pro Gln Arg Glu
410 415 420

Arg Lys Ser Ser Ser Ser Ser Glu Asp Arg Asn Arg Met Lys Thr Leu
425 430 435 440

Gly Arg Arg Asp Ser Ser Asp Asp Trp Glu Ile Pro Asp Gly Gln Ile
445 450 455

Thr Val Gly Gln Arg Ile Gly Ser Gly Ser Phe Gly Thr Val Tyr Lys

460 465 470

Gly Lys Trp His Gly Asp Val Ala Val Lys Met Leu Asn Val Thr Ala
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Pro Thr Pro Gln Gln Leu Gln Ala Phe Lys Asn Glu Val Gly Val Leu
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Arg Lys Thr Arg His Val Asn Ile Leu Leu Phe Met Gly Tyr Ser Thr
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Lys Pro Gln Leu Ala Ile Val Thr Gln Trp Cys Glu Gly Ser Ser Leu
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Leu Trp Met Ala Pro Glu Val Ile Arg Met Gln Asp Lys Asn Pro Tyr
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Met Thr Gly Gln Leu Pro Tyr Ser Asn Ile Asn Asn Arg Asp Gln Ile
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Ile Phe Met Val Gly Arg Gly Tyr Leu Ser Pro Asp Leu Ser Lys Val
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Arg Ser Asn Cys Pro Lys Ala Met Lys Arg Leu Met Ala Glu Cys Leu
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Lys Lys Lys Arg Asp Glu Arg Pro Leu Phe Pro Gln Val Gly Lys Thr
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Ile Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu
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Asp Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala
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Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln
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Gln Leu Leu Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser
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Ser Ala Ser Thr Asp Thr Val Thr Ser Ser Ser Ser Ser Ser Leu Ser
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Val Leu Pro Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val Ser
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Arg Ser Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu

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Phe Phe Thr Leu Ala Phe Cys Asp Phe Cys Arg Lys Leu Leu Phe Gln
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Pro Ser Asp Ser Ile Gly Pro Pro Ile Leu Thr Ser Pro Ser Pro Ser
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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 Asp Leu Ile Arg Asp
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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
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Lys Ser Pro Gly Pro Gln Arg Glu Arg Lys Ser Ser Ser Ser Ser Glu
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420 425 430

Asp Arg Asn Arg Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp Asp
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Trp Glu Ile Pro Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly Ser
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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
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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

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Trp Leu Gln Val Tyr Met
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<400> 118

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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
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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
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Asp Arg Asn Arg Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp Asp
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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
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Leu Leu Phe Met Gly Tyr Ser Thr Lys Pro Gln Leu Ala Ile Val Thr
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Gln Trp Cys Glu Gly Ser Ser Leu Tyr His His Leu His Ile Ile Glu
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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
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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
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Ile Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu
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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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Gln Leu Leu Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser
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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
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Arg Ser Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu
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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
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Cys Cys Ala Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly
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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
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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
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Thr Glu Val Pro Leu Met Cys Val Asn Tyr Asp Gln Leu Asp Leu Leu
275 280 285

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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
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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
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Pro Pro Ala Ser Leu Pro Gly Ser Leu Ser Asn Val Lys Ala Leu Gln
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Lys Ser Pro Gly Pro Gln Arg Glu Arg Lys Ser Ser Ser Ser Ser Glu
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Asp Arg Asn Arg Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp Asp

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Trp Glu Ile Pro Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly Ser
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Gly Ser Phe Gly Thr Val Tyr Lys Gly Lys Trp His Gly Asp Val Ala
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Val Lys Met Leu Asn Val Thr Ala Pro Thr Pro Gln Gln Leu Gln Ala
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Phe Lys Asn Glu Val Gly Val Leu Arg Lys Thr Arg His Val Asn Ile
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Leu Leu Phe Met Gly Tyr Ser Thr Lys Pro Gln Leu Ala Ile Val Thr
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Thr Lys Phe Glu Met Ile Lys Leu Ile Asp Ile Ala Arg Gln Thr Ala
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Gln Gly Met Asp Tyr Leu His Ala Lys Ser Ile Ile His Arg Asp Leu
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Lys Ser Asn Asn Ile Phe Leu His Glu Asp Leu Thr Val Lys Ile Gly
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Asp Phe Gly Leu Ala Thr Val Lys Ser Arg Trp Ser Gly Ser His Gln
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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
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Ile Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu
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Asp Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala
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Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln
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Gln Leu Leu Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser
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Ser Ala Ser Thr Asp Thr Val Thr Ser Ser Ser Ser Ser Ser Leu Ser
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Val Leu Pro Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val Ser
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Arg Ser Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu

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Cys Cys Ala Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly
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Val Leu Glu Asn Val Pro Leu Thr Thr His Asn Phe Val Arg Lys Thr
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Gly Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys Ser
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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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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
        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
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Pro Pro Ala Ser Leu Pro Gly Ser Leu Ser Asn Val Lys Ala Leu Gln
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Lys Ser Pro Gly Pro Gln Arg Glu Arg Lys Ser Ser Ser Ser Ser Glu
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Asp Arg Asn Arg Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp Asp
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Trp Glu Ile Pro Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly Ser
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Gly Ser Phe Gly Thr Val Tyr Lys Gly Lys Trp His Gly Asp Val Ala
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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
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Thr Lys Phe Glu Met Ile Lys Leu Ile Asp Ile Ala Arg Gln Thr Ala
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Gln Gly Met Asp Tyr Leu His Ala Lys Ser Ile Ile His Arg Asp Leu
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Asp Phe Gly Leu Ala Thr Val Lys Ser Arg Trp Ser Gly Ser His Gln
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35 40 45

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Phe Cys Arg Lys Leu Leu Phe Gln Gly Phe Arg Cys Gln Thr Cys Gly
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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
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Leu Ser Asn Val Lys Ala Leu Gln Lys Ser Pro Gly Pro Gln Arg Glu
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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
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Gly Lys Trp His Gly Asp Val Ala Val Lys Met Leu Asn Val Thr Ala
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Pro Thr Pro Gln Gln Leu Gln Ala Phe Lys Asn Glu Val Gly Val Leu
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Lys Pro Gln Leu Ala Ile Val Thr Gln Trp Cys Glu Gly Ser Ser Leu
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Tyr His His Leu His Ile Ile Glu Thr Lys Phe Glu Met Ile Lys Leu
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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
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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
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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
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Glu Asp Phe Ser Leu Tyr Ala Cys Ala Ser Pro Lys Thr Pro Ile Gln
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Lys Phe Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala Tyr
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Leu Leu Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser Ser
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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
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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
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Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Asp Leu Ile Arg Asp Gln
    370                 375                 380
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Gly Phe Arg Ser Asp Gly Gly Ser Thr Thr Gly Leu Ser Ala Thr Pro
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Pro Ala Ser Leu Pro Gly Ser Leu Thr Asn Val Lys Ala Leu Gln Lys
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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
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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
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Ile Asn Asn Arg Asp Gln Ile Ile Phe Met Val Gly Arg Gly Tyr Leu
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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
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Gln Thr Glu Asp Phe Ser Leu Tyr Ala Cys Ala Ser Pro Lys Thr Pro
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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
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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
        275                 280                 285
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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
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Leu Arg Lys Thr Arg His Val Asn Ile Leu Leu Phe Met Gly Tyr Ser
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Thr Lys Pro Gln Leu Ala Ile Val Thr Gln Trp Cys Glu Gly Ser Ser
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Leu Tyr His His Leu His Ile Ile Glu Thr Lys Phe Glu Met Ile Lys
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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

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
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Ser Glu Pro Ser Leu Asn Arg Ala Gly Phe Gln Thr Glu Asp Phe Ser
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Leu Tyr Ala Cys Ala Ser Pro Lys Thr Pro Ile Gln Ala Gly Gly Tyr
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Gly Gly Phe Pro Val His
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