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(56) Related Art
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KAREN E. SHEPPARD ET AL, EUROPEAN JOURNAL OF CANCER, AMSTERDAM, NL, (2013-12-01), vol. 49, no. 18, doi:10.1016/j.ejca.2013.08.007, ISSN 0959-8049, pages 3936 - 3944
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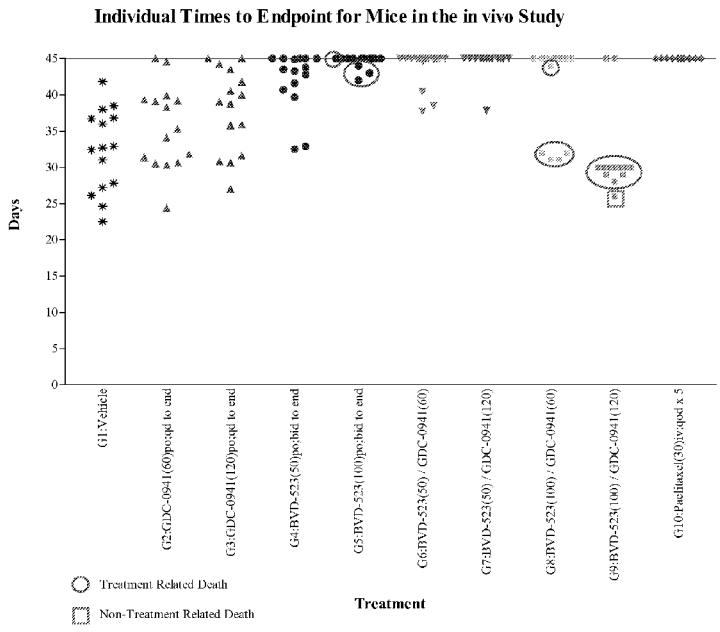
[Continued on next page]

(54) Title: CANCER TREATMENTS USING COMBINATIONS OF PI3K/AKT PATHWAY AND ERK INHIBITORS

FIG. 1



(57) Abstract: The present invention provides, inter alia, methods, kits, and compositions for treating or ameliorating the effects of a cancer in a subject in need thereof. This 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 an inhibitor of the PI3K/Akt pathway or a pharmaceutically acceptable salt thereof. Also provided are methods of treating or ameliorating the effects of a subject with cancer in which the subject has a somatic KRAS and a somatic PIK3CA mutation or in which the cancer is refractory to a therapy selected from RAF inhibitor therapy, MEK inhibitor therapy, and RAF and MEK inhibitor therapy.

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CANCER TREATMENTS USING COMBINATIONS OF PI3K/AKT PATHWAY AND ERK INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit of U.S. Patent Application Serial No. 61/919,638, 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, kits and pharmaceutical compositions 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 an inhibitor of the PI3K/Akt pathway 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 "0375601.txt", file size of 447 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] Mutations affecting the MAPK and PI3K/Akt signaling pathways are observed at high frequencies in a variety of cancers. Drug inhibitors that target components of the MAPK signaling pathway show clinical efficacy in a many cancers, particularly those bearing mutations in the BRAF protein kinase. Both RAF and MEK kinase inhibitors are approved for single-agent use in advanced metastatic BRAF mutant melanoma, and the combination of dabrafenib and trametinib is currently undergoing Food and Drug Administration (FDA) review for this indication.

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

[0006] In particular, a number of treated cancers bearing mutations affecting the MAPK signaling pathway develop additional, nascent lesions that affect the PI3K pathway. For example, PIK3CA-activating mutations are a frequent source of acquired resistance in these cancers. In this case,

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mechanistically distinct inhibitors targeting only the MAPK pathway are not sufficient for effective therapy.

[0007] In view of the foregoing limitations, novel targeted agents and therapies are needed to treat such cancers. The present invention is directed to meeting these and other needs.

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 an inhibitor of the PI3K/Akt pathway or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer.

[0008B] In a particular embodiment, 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 an inhibitor of the PI3K/Akt pathway or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer, wherein the inhibitor of the PI3K/Akt

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pathway is selected from the group consisting of pictilisib (GDC-0941), BYL719, BKM120, PF-04691502, 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. The method comprises administering to the subject an effective amount of (i) BVD-523 or a pharmaceutically acceptable salt thereof and (ii) pictilisib (GDC-0941) or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer.

[0009A] In another particular embodiment, 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 pictilisib (GDC-0941) 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] 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-

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cancer agent, which is a PI3K/Akt inhibitor or a pharmaceutically acceptable salt thereof, packaged together with instructions for their use.

[0010A] In another 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 PI3K/Akt inhibitor or a pharmaceutically acceptable salt thereof, packaged together with instructions for their use, wherein the inhibitor of the PI3K/Akt pathway is selected from the group consisting of pictilisib (GDC-0941), BYL719, BKM120, PF-04691502, 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] Another embodiment of the present invention is a method for treating or ameliorating the effects of a subject with cancer. The method comprises:

(a) identifying a subject with cancer that has a somatic KRAS mutation and a somatic PIK3CA mutation; and

(b) administering to the subject with somatic KRAS and PIK3CA mutations 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 an inhibitor of the PI3K/Akt pathway or a

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pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer.

[0011A] In another particular aspect, the present invention provides a method for treating or ameliorating the effects of a subject with cancer comprising: (a) identifying a subject with cancer that has a somatic KRAS mutation and a somatic PIK3CA mutation; and (b) administering to the subject with somatic KRAS and PIK3CA mutations 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 an inhibitor of the PI3K/Akt pathway or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer, wherein the inhibitor of the PI3K/Akt pathway is selected from the group consisting of pictilisib (GDC-0941), BYL719, BKM120, PF-04691502, 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] An additional embodiment of the present invention is a method for treating or ameliorating the effects of a subject with cancer. The method comprises:

(a) identifying a subject with cancer that is refractory to a therapy selected from the group consisting of RAF inhibitor therapy, MEK inhibitor therapy, and RAF and MEK inhibitor therapy; and

(b) administering to the subject identified in step (a) an effective amount of (i) a first anti-cancer agent, which is BVD-523 or a

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pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is an inhibitor of the PI3K/Akt pathway or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer.

[0012A] In a further particular aspect the present invention provides a method for treating or ameliorating the effects of a subject with cancer comprising: (a) identifying a subject with cancer that is refractory to a therapy selected from the group consisting of RAF inhibitor therapy, MEK inhibitor therapy, and RAF and MEK inhibitor therapy; and (b) administering to the subject identified in step (a) 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 an inhibitor of the PI3K/Akt pathway or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer, wherein the inhibitor of the PI3K/Akt pathway is selected from the group consisting of pictilisib (GDC-0941), BYL719, BKM120, PF-04691502, 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] 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 an inhibitor of the PI3K/Akt pathway or a pharmaceutically acceptable salt thereof, wherein

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

[0013A] In yet another 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, 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 an inhibitor of the PI3K/Akt pathway or a pharmaceutically acceptable salt thereof, wherein the inhibitor of the PI3K/Akt pathway is selected from the group consisting of pictilisib (GDC-0941), BYL719, BKM120, PF-04691502, 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.

[0014] 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 an inhibitor of the PI3K/Akt pathway or a pharmaceutically acceptable salt thereof.

[0014A] In a particular embodiment, 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

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pharmaceutically acceptable salt thereof and (ii) a second anti-cancer agent, which is a an inhibitor of the PI3K/Akt pathway or a pharmaceutically acceptable salt thereof, wherein the inhibitor of the PI3K/Akt pathway is selected from the group consisting of pictilisib (GDC-0941), BYL719, BKM120, PF-04691502, 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] 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.

[0016] FIG. 1 is a plot showing individual times to endpoint for mice treated with various doses of a PI3K inhibitor (GDC-0941), an ERK inhibitor

[FOLLOWED BY PAGE 6]

(BVD-523), or a combination of the two in the *in vivo* study. The number in the parenthesis indicate the dose in mg/kg.

[0017] FIG. 2A is a line graph showing mean tumor growth in mice treated with various doses of GDC-0941, BVD-523, or a combination of the two in the *in vivo* study. FIG. 2B is a Kaplan-Meier plot for the *in vivo* study. The number in the parenthesis indicate the dose in mg/kg.

[0018] FIG. 3 is a line graph showing percent mean body weight (BW) changes from day 1 in the *in vivo* study.

[0019] FIG. 4 shows that both direct ERK substrate phosphorylation and known effector pathways are modulated following acute and prolonged treatment with BVD-523 *in vitro*. Western blots were performed using a variety of antibodies to detect changes in whole-cell lysates of cancer lines exposed to BVD-523. In the A375 BRAF mutant cell line (a human melanoma cell line) and in the HCT116 KRAS mutant cell line (a human colorectal carcinoma cell line), phosphorylation of ERK-dependent residues (T359/S363) in RSK 1 and 2 proteins was reduced after 4 hours of treatment with BVD-523 at micromolar concentrations. Following 24 hours of treatment, direct substrate inhibition was maintained in BRAF mutant cell lines, and the MAPK feedback phosphatase DUSP6 was greatly reduced, suggesting durable and nearly complete MAPK pathway inhibition. Lastly, consistent with cytostatic effects of BVD-523 across multiple cell line backgrounds, the MAPK effector and G1/S-cell-cycle determinant gene cyclin-D1 was greatly reduced after 24 hours of treatment. In the A375 cell line, while the apoptosis effector and ERK substrate Bim-EL was increased following prolonged treatment, increased apoptosis was not observed, consistent with a lack of PARP

cleavage, as well as other observations (not shown) that additional factors influence the capacity for BVD-523 to induce cell death.

[0020] FIG. 5 shows a schematic of the mitogen-activated protein kinase (MAPK) pathway.

[0021] FIG. 6 shows the results of single agent proliferation assays in HCT116 isogenic cells in McCoy's 5A containing either 10% FBS or 1% charcoal-stripped FBS (CS-FBS). Proliferation results are shown for treatment with BYL719 (FIG. 6A), BKM120 (FIG. 6B), INK128 (FIG. 6C), PF-004691502 (FIG. 6D), BVD-523 (FIG. 6E), SCH772984 (FIG. 6F), Paclitaxel (FIG. 6G), and GDC-0941 (FIG. 6H).

[0022] FIG. 7 shows the results of the combination of BVD-523 and BYL719 in parental HCT116 and HCT116 PIK3CA (+/-) cells. FIG. 7A shows a dose matrix showing inhibition (%) for the combination in parental HCT116 cells. FIG. 7B shows Loewe excess for the combination in 7A and FIG. 7C shows Bliss excess for the combination in 7A. FIG. 7D shows a dose matrix showing inhibition (%) for the combination in HCT116 PIK3CA (+/-) cells. FIG. 7E shows Loewe excess for the combination in 7D and FIG. 7F shows Bliss excess for the combination in 7D. FIG. 7G – FIG. 7H show the results of single agent proliferation assays for the combination in 7A. FIG. 7I – FIG. 7J show the results of single agent proliferation assays for the combination in 7D.

[0023] FIG. 8 shows the results of the combination of SCH772984 and BYL719 in parental HCT116 and HCT116 PIK3CA (+/-) cells. FIG. 8A shows a dose matrix showing inhibition (%) for the combination in parental HCT116 cells. FIG. 8B shows Loewe excess for the combination in 8A and FIG. 8C shows Bliss excess for the combination in 8A. FIG. 8D shows a dose matrix

showing inhibition (%) for the combination in HCT116 PIK3CA (+/-) cells. FIG. 8E shows Loewe excess for the combination in 8D and FIG. 8F shows Bliss excess for the combination in 8D. FIG. 8G – FIG. 8H show the results of single agent proliferation assays for the combination in 8A. FIG. 8I – FIG. 8J show the results of single agent proliferation assays for the combination in 8D.

[0024] FIG. 9 shows the results of the combination of BVD-523 and BKM120 in parental HCT116 and HCT116 PIK3CA (+/-) cells. FIG. 9A shows a dose matrix showing inhibition (%) for the combination in parental HCT116 cells. FIG. 9B shows Loewe excess for the combination in 9A and FIG. 9C shows Bliss excess for the combination in 9A. FIG. 9D shows a dose matrix showing inhibition (%) for the combination in HCT116 PIK3CA (+/-) cells. FIG. 9E shows Loewe excess for the combination in 9D and FIG. 9F shows Bliss excess for the combination in 9D. FIG. 9G – FIG. 9H show the results of single agent proliferation assays for the combination in 9A. FIG. 9I – FIG. 9J show the results of single agent proliferation assays for the combination in 9D.

[0025] FIG. 10 shows the results of the combination of SCH772984 and BKM120 in parental HCT116 and HCT116 PIK3CA (+/-) cells. FIG. 10A shows a dose matrix showing inhibition (%) for the combination in parental HCT116 cells. FIG. 10B shows Loewe excess for the combination in 10A and FIG. 10C shows Bliss excess for the combination in 10A. FIG. 10D shows a dose matrix showing inhibition (%) for the combination in HCT116 PIK3CA (+/-) cells. FIG. 10E shows Loewe excess for the combination in 10D and FIG. 10F shows Bliss excess for the combination in 10D. FIG. 10G – FIG. 10H show the results of single agent proliferation assays for the combination

in 10A. FIG. 10I – FIG. 10J show the results of single agent proliferation assays for the combination in 10D.

[0026] FIG. 11 shows the results of the combination of BVD-523 and INK128 in parental HCT116 and HCT116 PIK3CA (+/-) cells. FIG. 11A shows a dose matrix showing inhibition (%) for the combination in parental HCT116 cells. FIG. 11B shows Loewe excess for the combination in 11A and FIG. 11C shows Bliss excess for the combination in 11A. FIG. 11D shows a dose matrix showing inhibition (%) for the combination in HCT116 PIK3CA (+/-) cells. FIG. 11E shows Loewe excess for the combination in 11D and FIG. 11F shows Bliss excess for the combination in 11D. FIG. 11G – FIG. 11H show the results of single agent proliferation assays for the combination in 11A. FIG. 11I – FIG. 11J show the results of single agent proliferation assays for the combination in 11D.

[0027] FIG. 12 shows the results of the combination of SCH772984 and INK128 in parental HCT116 and HCT116 PIK3CA (+/-) cells. FIG. 12A shows a dose matrix showing inhibition (%) for the combination in parental HCT116 cells. FIG. 12B shows Loewe excess for the combination in 12A and FIG. 12C shows Bliss excess for the combination in 12A. FIG. 12D shows a dose matrix showing inhibition (%) for the combination in HCT116 PIK3CA (+/-) cells. FIG. 12E shows Loewe excess for the combination in 12D and FIG. 12F shows Bliss excess for the combination in 12D. FIG. 12G – FIG. 12H show the results of single agent proliferation assays for the combination in 12A. FIG. 12I – FIG. 12J show the results of single agent proliferation assays for the combination in 12D.

[0028] FIG. 13 shows the results of the combination of BVD-523 and PF-004691502 in parental HCT116 and HCT116 PIK3CA (+/-) cells. FIG. 13A shows a dose matrix showing inhibition (%) for the combination in parental HCT116 cells. FIG. 13B shows Loewe excess for the combination in 13A and FIG. 13C shows Bliss excess for the combination in 13A. FIG. 13D shows a dose matrix showing inhibition (%) for the combination in HCT116 PIK3CA (+/-) cells. FIG. 13E shows Loewe excess for the combination in 13D and FIG. 13F shows Bliss excess for the combination in 13D. FIG. 13G – FIG. 13H show the results of single agent proliferation assays for the combination in 13A. FIG. 13I – FIG. 13J show the results of single agent proliferation assays for the combination in 13D.

[0029] FIG. 14 shows the results of the combination of SCH772984 and PF-004691502 in parental HCT116 and HCT116 PIK3CA (+/-) cells. FIG. 14A shows a dose matrix showing inhibition (%) for the combination in parental HCT116 cells. FIG. 14B shows Loewe excess for the combination in 14A and FIG. 14C shows Bliss excess for the combination in 14A. FIG. 14D shows a dose matrix showing inhibition (%) for the combination in HCT116 PIK3CA (+/-) cells. FIG. 14E shows Loewe excess for the combination in 14D and FIG. 14F shows Bliss excess for the combination in 14D. FIG. 14G – FIG. 14H show the results of single agent proliferation assays for the combination in 14A. FIG. 14I – FIG. 14J show the results of single agent proliferation assays for the combination in 14D.

[0030] FIG. 15 shows a comparison of single agent proliferation responses in parental HCT116 and HCT116 PIK3CA (+/-). Proliferation results are shown for treatment with BYL719 (FIG. 15A), BKM120 (FIG. 15B),

INK128 (FIG. 15C), PF-004691502 (FIG. 15D), BVD-523 (FIG. 15E), and SCH772984 (FIG. 15F).

[0031] FIG. 16 shows results of focused concentration combination assays in the HCT116 PIK3CA (+/-) isogenic cell line pair. FIG. 16A shows viability and Bliss scores for combinations with BVD-523 in parental HCT116 cells. FIG. 16B shows viability and Bliss scores for combinations with BVD-523 in HCT116 PIK3CA (+/-) cells. FIG. 16C shows viability and Bliss scores for combinations with SCH772984 in parental HCT116 cells. FIG. 16D shows viability and Bliss scores for combinations with SCH772984 in HCT116 PIK3CA (+/-) cells.

[0032] FIG. 17 shows the results of the combination of BVD-523 and BYL719 in parental DLD-1 and DLD-1 PIK3CA (+/-) cells. FIG. 17A shows a dose matrix showing inhibition (%) for the combination in parental DLD-1 cells. FIG. 17B shows Loewe excess for the combination in 17A and FIG. 17C shows Bliss excess for the combination in 17A. FIG. 17D shows a dose matrix showing inhibition (%) for the combination in DLD-1 PIK3CA (+/-) cells. FIG. 17E shows Loewe excess for the combination in 17D and FIG. 17F shows Bliss excess for the combination in 17D. FIG. 17G – FIG. 17H show the results of single agent proliferation assays for the combination in 17A. FIG. 17I – FIG. 17J show the results of single agent proliferation assays for the combination in 17D.

[0033] FIG. 18 shows the results of the combination of SCH772984 and BYL719 in parental DLD-1 and DLD-1 PIK3CA (+/-) cells. FIG. 18A shows a dose matrix showing inhibition (%) for the combination in parental DLD-1 cells. FIG. 18B shows Loewe excess for the combination in 18A and FIG.

18C shows Bliss excess for the combination in 18A. FIG. 18D shows a dose matrix showing inhibition (%) for the combination in DLD-1 PIK3CA (+/-) cells. FIG. 18E shows Loewe excess for the combination in 18D and FIG. 18F shows Bliss excess for the combination in 18D. FIG. 18G – FIG. 18H show the results of single agent proliferation assays for the combination in 18A. FIG. 18I – FIG. 18J show the results of single agent proliferation assays for the combination in 18D.

[0034] FIG. 19 shows the results of the combination of BVD-523 and BKM120 in parental DLD-1 and DLD-1 PIK3CA (+/-) cells. FIG. 19A shows a dose matrix showing inhibition (%) for the combination in parental DLD-1 cells. FIG. 19B shows Loewe excess for the combination in 19A and FIG. 19C shows Bliss excess for the combination in 19A. FIG. 19D shows a dose matrix showing inhibition (%) for the combination in DLD-1 PIK3CA (+/-) cells. FIG. 19E shows Loewe excess for the combination in 19D and FIG. 19F shows Bliss excess for the combination in 19D. FIG. 19G – FIG. 19H show the results of single agent proliferation assays for the combination in 19A. FIG. 19I – FIG. 19J show the results of single agent proliferation assays for the combination in 19D.

[0035] FIG. 20 shows the results of the combination of SCH772984 and BKM120 in parental DLD-1 and DLD-1 PIK3CA (+/-) cells. FIG. 20A shows a dose matrix showing inhibition (%) for the combination in parental DLD-1 cells. FIG. 20B shows Loewe excess for the combination in 20A and FIG. 20C shows Bliss excess for the combination in 20A. FIG. 20D shows a dose matrix showing inhibition (%) for the combination in DLD-1 PIK3CA (+/-) cells. FIG. 20E shows Loewe excess for the combination in 20D and FIG. 20F

shows Bliss excess for the combination in 20D. FIG. 20G – FIG. 20H show the results of single agent proliferation assays for the combination in 20A. FIG. 20I – FIG. 20J show the results of single agent proliferation assays for the combination in 20D.

[0036] FIG. 21 shows the results of the combination of BVD-523 and INK128 in parental DLD-1 and DLD-1 PIK3CA (+/-) cells. FIG. 21A shows a dose matrix showing inhibition (%) for the combination in parental DLD-1 cells. FIG. 21B shows Loewe excess for the combination in 21A and FIG. 21C shows Bliss excess for the combination in 21A. FIG. 21D shows a dose matrix showing inhibition (%) for the combination in DLD-1 PIK3CA (+/-) cells. FIG. 21E shows Loewe excess for the combination in 21D and FIG. 21F shows Bliss excess for the combination in 21D. FIG. 21G – FIG. 21H show the results of single agent proliferation assays for the combination in 21A. FIG. 21I – FIG. 21J show the results of single agent proliferation assays for the combination in 21D.

[0037] FIG. 22 shows the results of the combination of SCH772984 and INK128 in parental DLD-1 and DLD-1 PIK3CA (+/-) cells. FIG. 22A shows a dose matrix showing inhibition (%) for the combination in parental DLD-1 cells. FIG. 22B shows Loewe excess for the combination in 22A and FIG. 22C shows Bliss excess for the combination in 22A. FIG. 22D shows a dose matrix showing inhibition (%) for the combination in DLD-1 PIK3CA (+/-) cells. FIG. 22E shows Loewe excess for the combination in 22D and FIG. 22F shows Bliss excess for the combination in 22D. FIG. 22G – FIG. 22H show the results of single agent proliferation assays for the combination in 22A.

FIG. 22I – FIG. 22J show the results of single agent proliferation assays for the combination in 22D.

[0038] FIG. 23 shows the results of the combination of BVD-523 and PF-004691502 in parental DLD-1 and DLD-1 PIK3CA (+/-) cells. FIG. 23A shows a dose matrix showing inhibition (%) for the combination in parental DLD-1 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 DLD-1 PIK3CA (+/-) 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.

[0039] FIG. 24 shows the results of the combination of SCH772984 and PF-004691502 in parental DLD-1 and DLD-1 PIK3CA (+/-) cells. FIG. 24A shows a dose matrix showing inhibition (%) for the combination in parental DLD-1 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 DLD-1 PIK3CA (+/-) 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.

[0040] FIG. 25 shows a comparison of single agent proliferation responses in parental DLD-1 and DLD-1 PIK3CA (+/-). Proliferation results are shown for treatment with BYL719 (FIG.25A), BKM120 (FIG. 25B), INK128 (FIG. 25C), PF-004691502 (FIG. 25D), BVD-523 (FIG. 25E), and SCH772984 (FIG. 25F).

[0041] FIG. 26A shows Lowe Volumes for the combinations tested. FIG. 26B shows Bliss Volumes for the combinations tested. FIG. 26C shows Synergy Scores for the combinations tested.

[0042] FIG. 27 shows the results of the combination of BVD-523 and SCH772984. FIG. 27A shows a dose matrix showing inhibition (%) for the combination in A375 cells. FIG. 27B – FIG. 27C show the results of single agent proliferation assays for the combination in 27A. FIG. 27D shows Loewe excess for the combination in 27A and FIG. 27E shows Bliss excess for the combination in 27A.

DETAILED DESCRIPTION OF THE INVENTION

[0043] 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 an inhibitor of the PI3K/Akt pathway or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer.

[0044] 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.

[0045] 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.

[0046] As used herein, a “subject” is a mammal, preferably, a human. In addition to humans, which is a preferred mammal in the present invention, other 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.

[0047] 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,

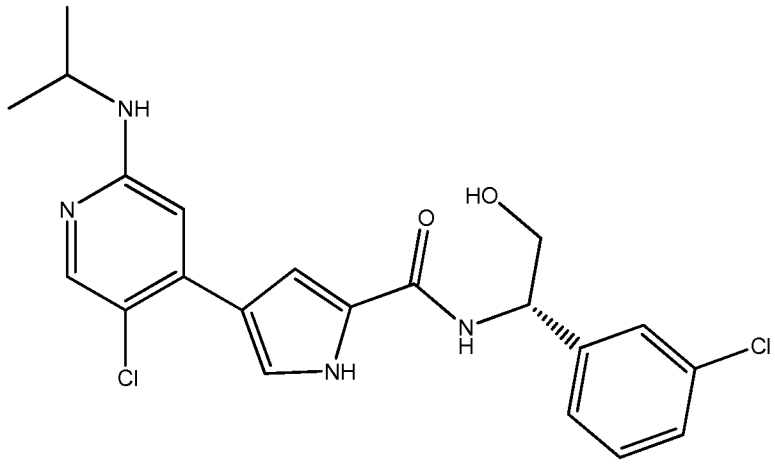
cervical cancer, colon cancer, endometrial cancer, esophageal cancer, extrahepatic bile duct cancer, Ewing family of cancers, extracranial germ cell cancer, eye cancer, gallbladder cancer, gastric cancer, germ cell tumor, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma, kidney cancer, large intestine cancer, laryngeal cancer, leukemia, lip and oral cavity cancer, liver cancer, lung 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.

[0048] Examples of hematologic tumors/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.

[0049] Preferably, the cancer is selected from the group consisting of a cancer of the large intestine, breast cancer, liver cancer, colon cancer, pancreatic cancer, endometrial cancers, stomach cancer, lung cancer, and leukemia. More preferably, the cancer is colon cancer.

[0050] 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. 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. 4).

[0051] As used herein, an "inhibitor" of the PI3K/Akt pathway is any substance that decreases the expression or the activity of phosphatidylinositol-3 kinases (PI3Ks) or downstream proteins, such as Akt. PI3Ks, when activated, phosphorylate the inositol ring 3'-OH group in inositol phospholipids to generate the second messenger phosphatidylinositol-3,4,5-trisphosphate (PI-3,4,5-P(3)). Akt interacts with these phospholipids, causing it to translocate to the inner membrane, where it is phosphorylated and activated. Activated Akt modulates the function of numerous substrates involved in the regulation of cell survival, cell cycle progression and cellular growth.

[0052] Non-limiting examples of inhibitors 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., Hydrabad, India), PI3 kinase delta inhibitors-2, Incozen (Incozen Therapeutics), PI3 kinase inhibitor, Roche-4 (Roche Holdings Inc.), PI3 kinase inhibitors, Roche (Roche Holdings Inc.), PI3 kinase inhibitors, Roche-5 (Roche Holdings Inc.), PI3-alpha/delta inhibitors, Pathway Therapeutics (Pathway Therapeutics Ltd., South San Francisco, 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 (GDC-0941) (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. Preferably, the inhibitor of the PI3K/Akt pathway is pictilisib (GDC-0941) or a pharmaceutically acceptable salt thereof.

[0053] In one aspect of this embodiment, the subject with cancer has a somatic KRAS mutation or is refractory to MAPK pathway inhibitor treatment. In another aspect of this embodiment, the subject with cancer has a somatic KRAS mutation and a somatic PIK3CA mutation.

[0054] 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 a substitution, deletion, insertion, or a fusion. Methods for identifying mutations in nucleic acids, such as the above-listed RAS genes, are known in the art. Non-limiting examples include PCR, sequencing, hybrid capture, in-solution capture, molecular inversion probes, fluorescent in situ hybridization (FISH) assays, and combinations thereof.

[0055] 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.

[0056] 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.

[0057] 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).

[0058] 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.

[0059] The following Tables 1 and 2 show the SEQ ID Nos. of representative nucleic acid and amino acid sequences of wild type K-RAS and PIK3CA from various animal sources, respectively, in the sequence listing. These sequences may be used in methods for identifying subjects with a mutant K-RAS and/or PIK3CA genotype (such as in the methods set forth below).

Table 1: K-RAS sequences

SEQ ID No.	polypeptide or nucleic acid sequence	Organism	Other Information
1	nucleic acid	human	isoform a
2	polypeptide	human	isoform a
3	nucleic acid	human	isoform b
4	polypeptide	human	isoform b
5	nucleic acid	rat (Rattus	

SEQ ID No.	polypeptide or nucleic acid sequence	Organism	Other Information
		norvegicus)	
6	polypeptide	rat (Rattus norvegicus)	
7	nucleic acid	mouse, Mus musculus	
8	polypeptide	mouse, Mus musculus	
9	nucleic acid	rabbit, Oryctolagus cuniculus	
10	polypeptide	rabbit, Oryctolagus cuniculus	
11	nucleic acid	guinea pig, Cavia porcellus	variant 1
12	polypeptide	guinea pig, Cavia porcellus	variant 1
13	nucleic acid	guinea pig, Cavia porcellus	variant 2
14	polypeptide	guinea pig, Cavia porcellus	variant 2
15	nucleic acid	dog, Canis lupus familiaris	variant 1
16	polypeptide	dog, Canis lupus familiaris	variant 1
17	nucleic acid	dog, Canis lupus familiaris	variant 2
18	polypeptide	dog, Canis lupus familiaris	variant 2
19	nucleic acid	cat, Felis catus	variant 1
20	polypeptide	cat, Felis catus	variant 1
21	nucleic acid	cat, Felis catus	variant 2
22	polypeptide	cat, Felis catus	variant 2
23	nucleic acid	cow, Bos taurus	
24	polypeptide	cow, Bos taurus	
25	nucleic acid	cow, Bos taurus	variant X2
26	polypeptide	cow, Bos taurus	variant X2
27	nucleic acid	cow, Bos taurus	variant X3
28	polypeptide	cow, Bos taurus	variant X3
29	nucleic acid	chicken, Gallus gallus	
30	polypeptide	chicken, Gallus gallus	

Table 2: PIK3CA sequences

SEQ ID No.	polypeptide or nucleic acid sequence	Organism
31	nucleic acid	human
32	polypeptide	human
33	nucleic acid	rat (Rattus norvegicus)
34	polypeptide	rat (Rattus norvegicus)
35	nucleic acid	mouse, Mus musculus
36	polypeptide	mouse, Mus musculus
37	nucleic acid	rabbit, Oryctolagus cuniculus
38	nucleic acid	guinea pig, Cavia porcellus
39	polypeptide	guinea pig, Cavia porcellus
40	nucleic acid	dog, Canis lupus familiaris
41	polypeptide	dog, Canis lupus familiaris
42	nucleic acid	cat, Felis catus
43	polypeptide	cat, Felis catus
44	nucleic acid	cow, Bos taurus
45	polypeptide	cow, Bos taurus
46	nucleic acid	chicken, Gallus gallus
47	polypeptide	chicken, Gallus gallus

[0060] As used herein, being “refractory” to a MAPK pathway inhibitor treatment means that the MAPK pathway inhibitor has reduced efficacy in treating cancer.

[0061] As used herein, “mitogen-activated protein kinase (MAPK) pathway inhibitor” means any substance that reduces the activity, expression or phosphorylation of proteins in the MAPK pathway that result in a reduction of cell growth or an increase in cell death.

[0062] An overview of the mammalian MAPK cascades is shown in FIG. 5. The details of the MAPK pathways are reviewed in *e.g.*, Akinleye *et al.*, 2013. Briefly, with respect to the ERK1/2 module in FIG. 5 (light purple box), the MAPK 1/2 signaling cascade is activated by ligand binding to receptor tyrosine kinases (RTK). The activated receptors recruit and phosphorylate adaptor proteins Grb2 and SOS, which then interact with

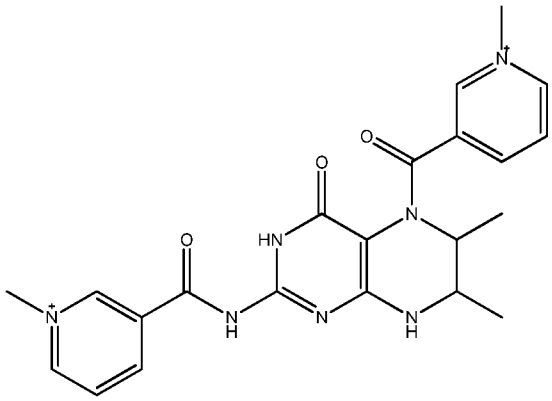
membrane-bound GTPase Ras and cause its activation. In its activated GTP-bound form, Ras recruits and activates Raf kinases (A-Raf, B-Raf, and C-Raf/RaF-1). The activated Raf kinases activate MAPK 1/2 (MKK1/2), which in turn catalyzes the phosphorylation of threonine and tyrosine residues in the activation sequence Thr-Glu-Tyr of ERK1/2. With respect to the JNK/p38 module (yellow box in FIG. 5), upstream kinases, MAP3Ks, such as MEKK1/4, ASK1/2, and MLK1/2/3, activate MAP2K3/6 (MKK3/6), MAP2K4 (MKK4), and MAP2K7 (MKK7). These MAP2K's then activate JNK protein kinases, including JNK1, JNK2, and JNK3, as well as p38 α/β/γ/δ. To execute their functions, JNKs activate several transcription factors, including c-Jun, ATF-2, NF-ATc1, HSF-1 and STAT3. With respect to the ERK5 module (blue box in FIG. 5), the kinases upstream of MAP2K5 (MKK5) are MEKK2 and MEKK3. The best characterized downstream target of MEK5 is ERK5, also known as big MAP kinase 1 (BMK1) because it is twice the size of other MAPKs.

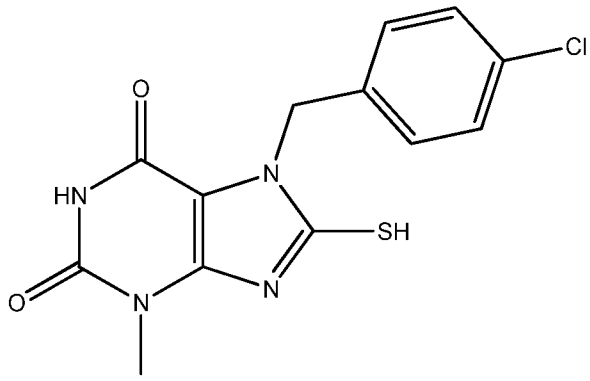
[0063] Non-limiting examples of MAPK pathway inhibitors according to the present invention include RAS inhibitors, RAF inhibitors, MEK inhibitors, ERK1/2 inhibitors, pharmaceutically acceptable salts thereof, and combinations thereof.

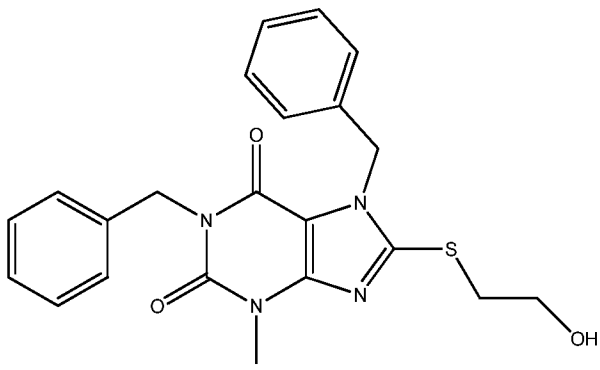
[0064] As used herein, a "RAS inhibitor" means those substances that (i) directly interact with RAS, *e.g.*, by binding to RAS and (ii) decrease the expression or the activity of RAS. Non-limiting examples of RAS inhibitors according to the present invention include, but are not limited to, farnesyl transferase inhibitors (such as, *e.g.*, tipifarnib and lonafarnib), farnesyl group-containing small molecules (such as, *e.g.*, salirasib and TLN-4601), DCAI, as

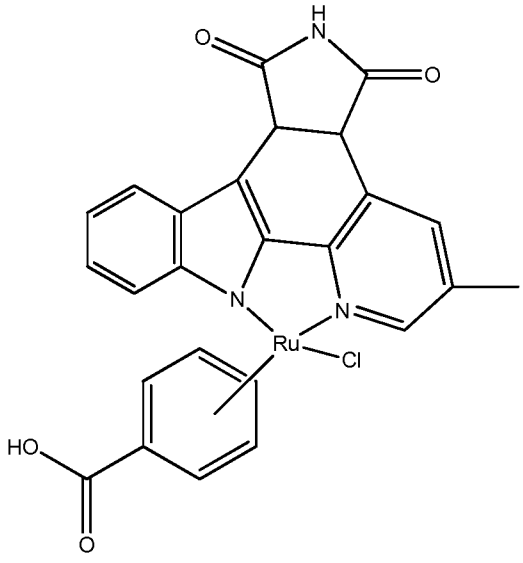
described by Maurer (Maurer, *et al.*, 2012), Kobe0065 and Kobe2602, as described by Shima (Shima, *et al.*, 2013), and HBS 3 (Patgiri, *et al.*, 2011), and AIK-4 (Allinky).

[0065] As used herein, a "RAF inhibitor" means those substances that (i) directly interacts with RAF, *e.g.*, by binding to RAF and (ii) decrease the expression or the activity of RAF, such as, *e.g.*, A-RAF, B-RAF, and C-RAF (Raf-1). Non-limiting exemplary RAF inhibitors include:

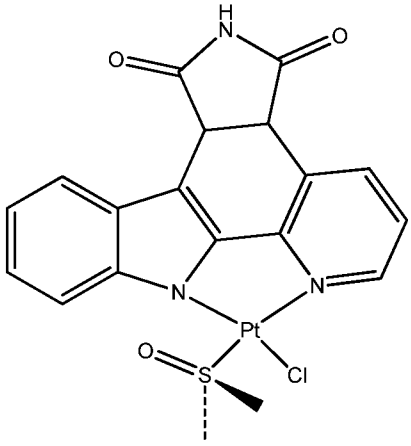
Compound 7  (Li *et al.*, 2010),

Compound 9  (*Id.*),

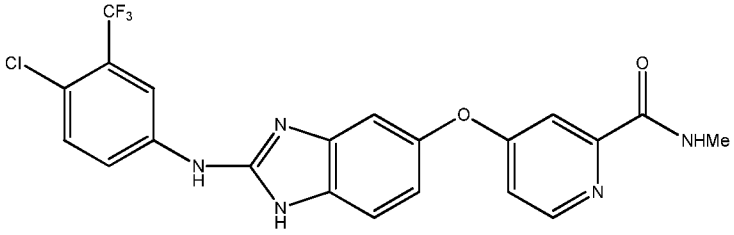
Compound 10  (*Id.*),



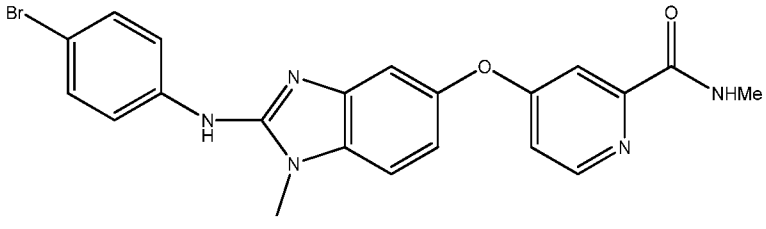
Compound 13 (*Id.*),



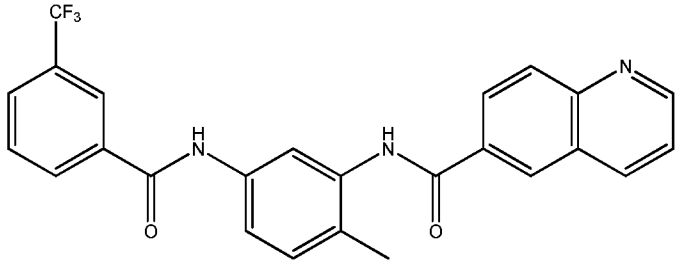
Compound 14 (*Id.*),

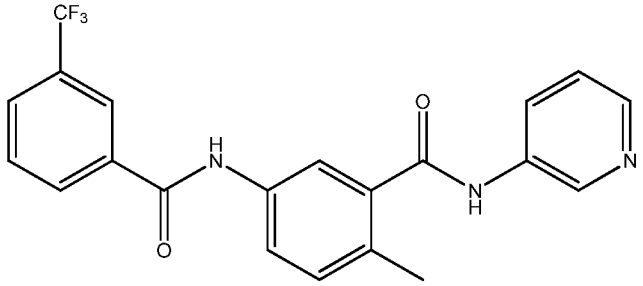


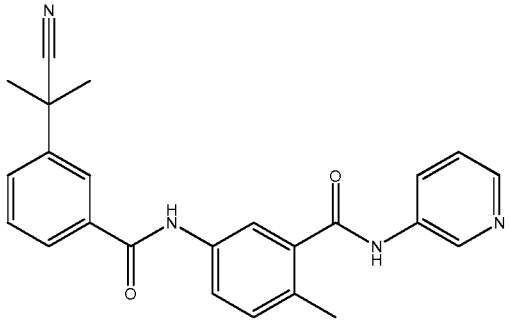
Compound 15 (*Id.*),

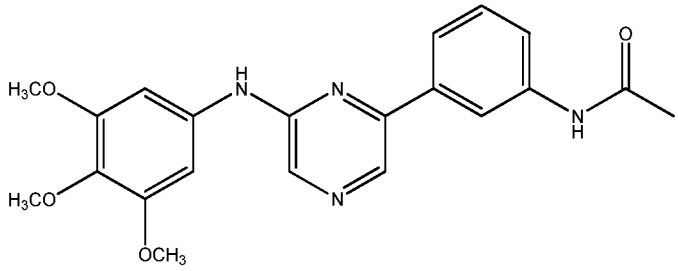


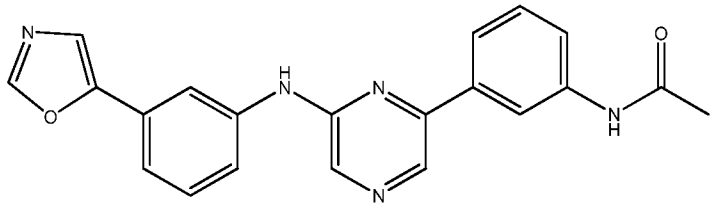
Compound 16 (*Id.*),

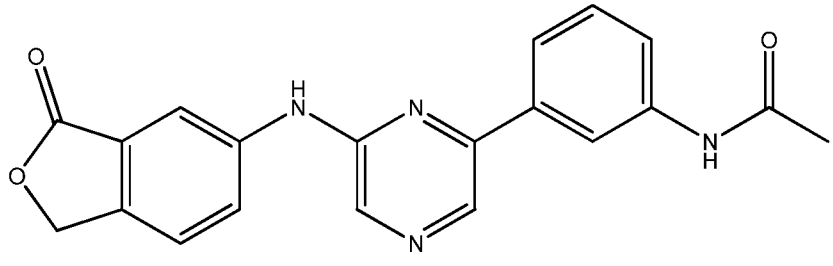
Compound 18  (*Id.*),

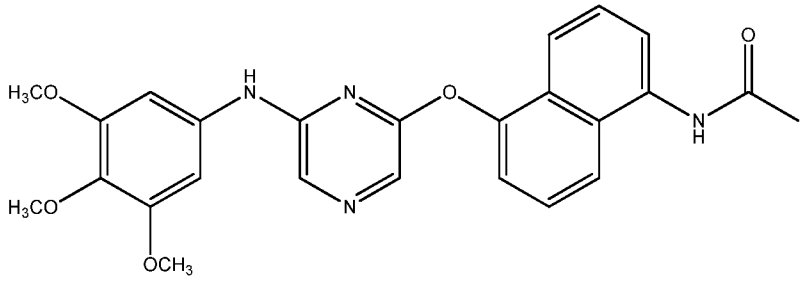
Compound 19  (*Id.*),

Compound 20  (*Id.*),

Compound 21  (*Id.*),

Compound 22  (*Id.*),

Compound 23  (*Id.*),



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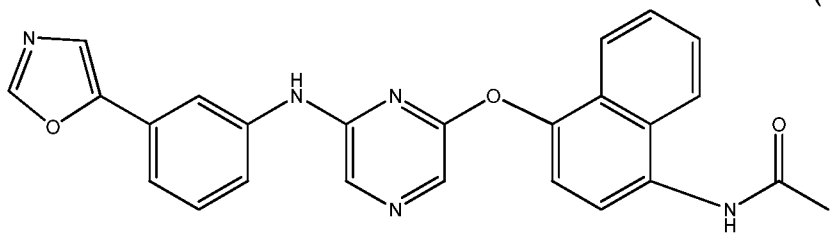
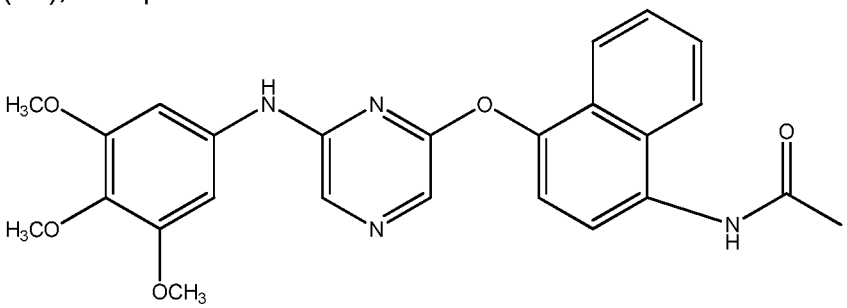
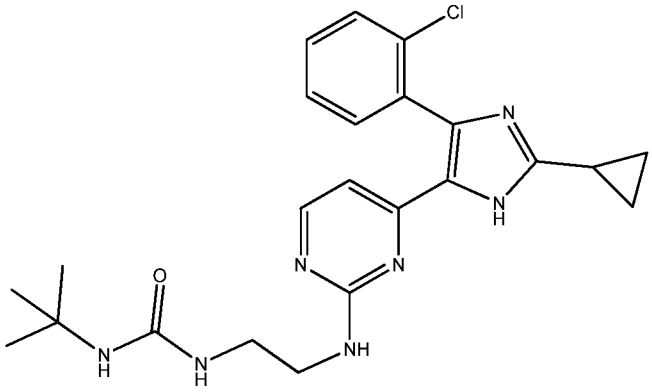


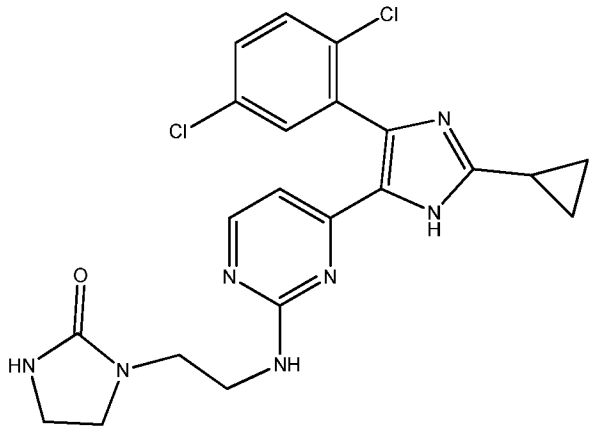
Compound 25 (*Id.*), Compound 26



(*Id.*), Compound 27



(*Id.*),



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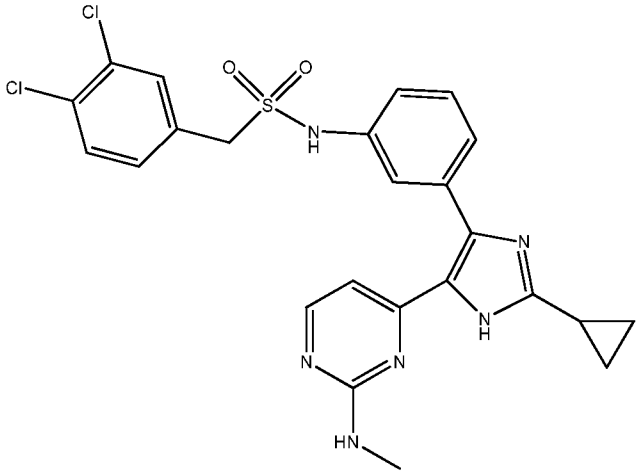

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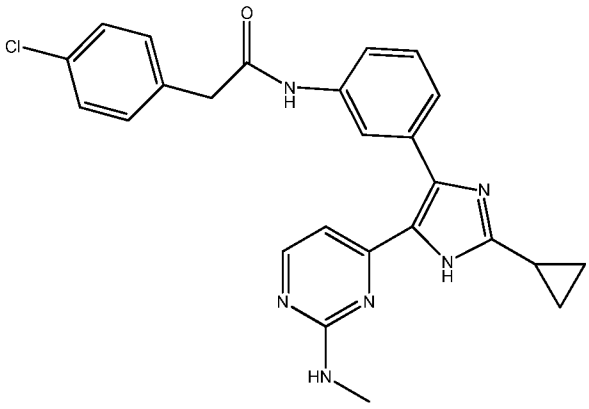

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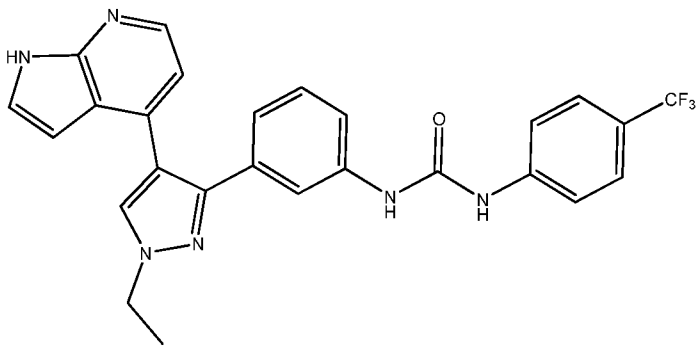

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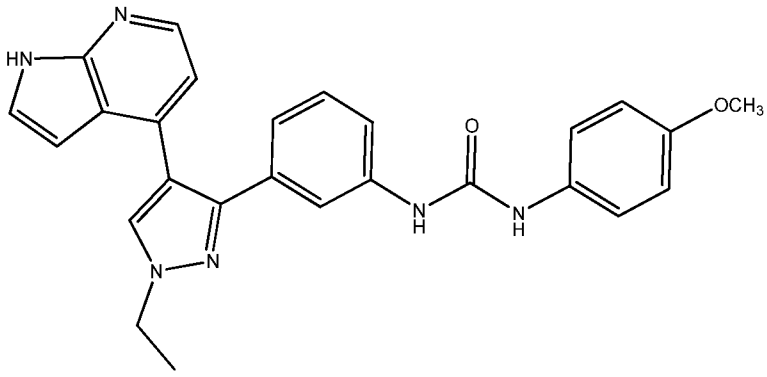

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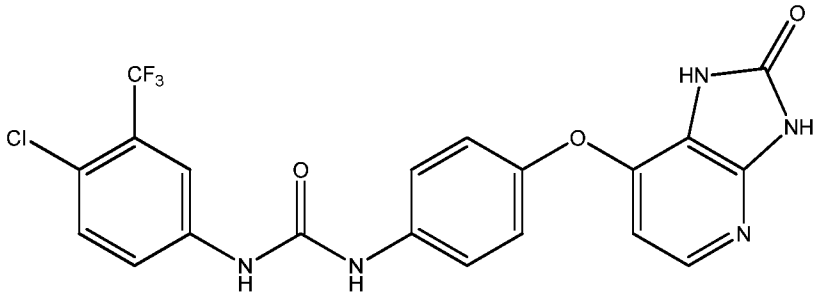
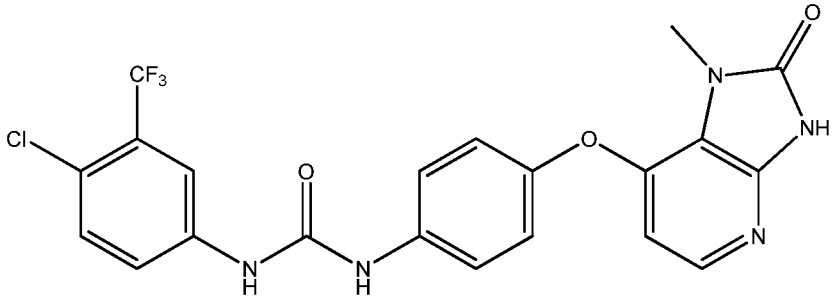
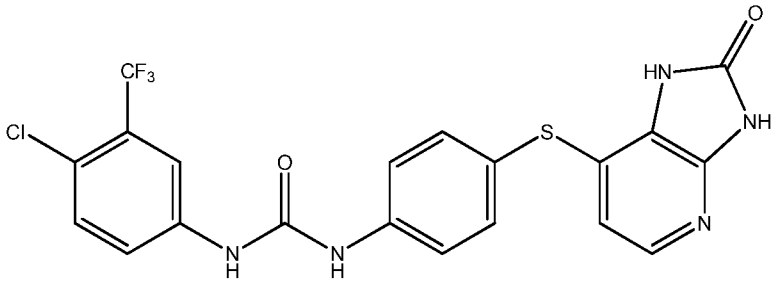
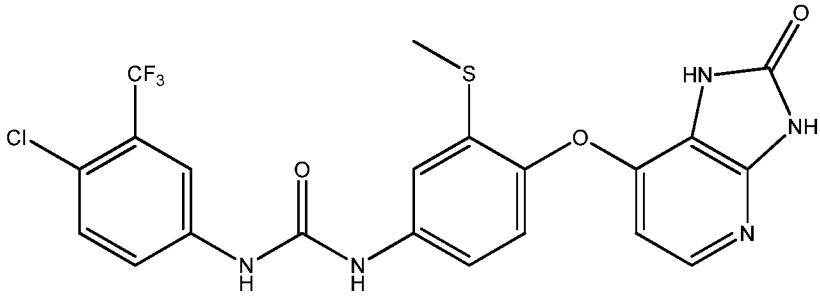
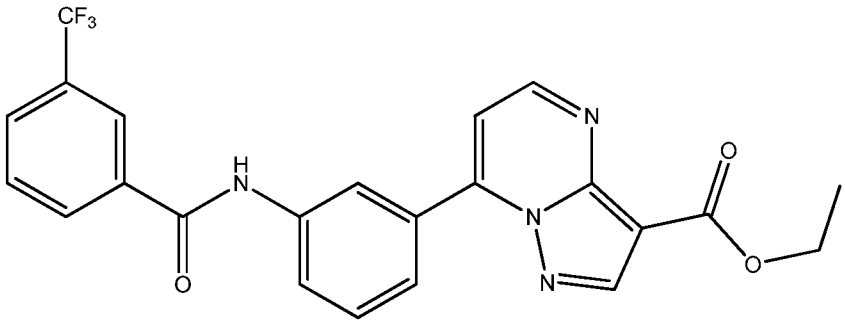
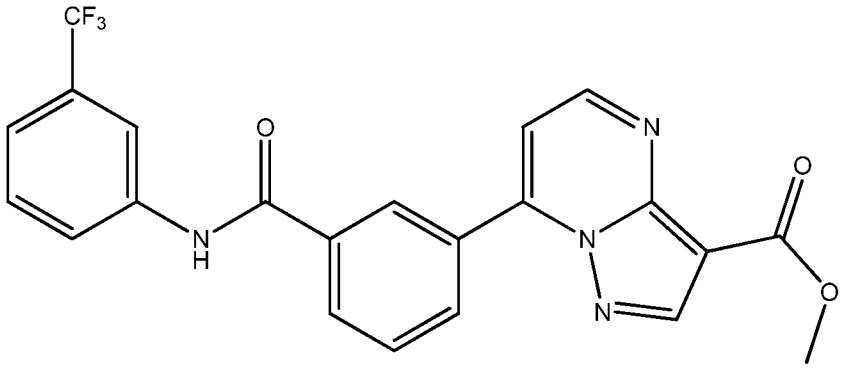
Compound 34  (*Id.*),

Compound 35  (*Id.*),

Compound 36  (*Id.*),

Compound 37  (*Id.*),

Compound 38  (*Id.*),



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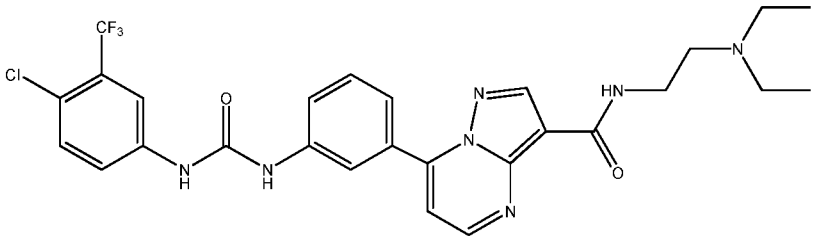

Compound 40 (*Id.*),

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

336372 (AstraZeneca), pharmaceutically acceptable salts thereof, and combinations thereof.

[0066] As used herein, a "MEK inhibitor" means those substances that (i) directly interact with MEK, *e.g.*, by binding to MEK and (ii) decrease the expression or the activity of MEK. Therefore, inhibitors that act upstream of MEK, such as RAS inhibitors and RAF inhibitors, are not MEK inhibitors according to the present invention. Non-limiting examples of MEK inhibitors according to the present invention include anthrax toxin, antroquinonol (Golden Biotechnology), ARRY-142886 (6-(4-bromo-2-chloro-phenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxy-ethoxy)-amide) (Array BioPharma), ARRY-438162 (Array BioPharma), AS-1940477 (Astellas), AS-703988 (Merck KGaA), bentamapimod (Merck KGaA), BI-847325 (Boehringer Ingelheim), E-6201 (Eisai), GDC-0623 (Hoffmann-La Roche), GDC-0973 (cobimetinib) (Hoffmann-La Roche), L783277 (Merck), lethal factor portion of anthrax toxin, MEK162 (Array BioPharma), PD 098059 (2-(2'-amino-3'-methoxyphenyl)-oxanaphthalen-4-one) (Pfizer), PD 184352 (CI-1040) (Pfizer), PD-0325901 (Pfizer), pimasertib (Santhera Pharmaceuticals), RDEA119 (Ardea Biosciences/Bayer), refametinib (AstraZeneca), RG422 (Chugai Pharmaceutical Co.), RO092210 (Roche), RO4987655 (Hoffmann-La Roche), RO5126766 (Hoffmann-La Roche), selumetinib (AZD6244) (AstraZeneca), SL327 (Sigma), TAK-733 (Takeda), trametinib (Japan Tobacco), U0126 (1,4-diamino-2,3-dicyano-1,4-bis(2-aminophenylthio)butadiene) (Sigma), WX-554 (Wilex), YopJ polypeptide (Mittal *et al.*, 2010), pharmaceutically acceptable salts thereof, and combinations thereof.

[0067] As used herein, an "ERK1/2 inhibitor" means those substances that (i) directly interact with ERK1 and/or ERK2, *e.g.*, by binding to ERK1/2 and (ii) decrease the expression or the activity of ERK1 and/or ERK2 protein kinases. Therefore, inhibitors that act upstream of ERK1/2, such as MEK inhibitors and RAF inhibitors, are not ERK1/2 inhibitors according to the present invention. Non-limiting examples of ERK1/2 inhibitors according to the present invention include AEZS-131 (Aeterna Zentaris), AEZS-136 (Aeterna Zentaris), BVD-523 (BioMed Valley Discoveries, Inc.), SCH-722984 (Merck & Co.), SCH-772984 (Merck & Co.), SCH-900353 (MK-8353) (Merck & Co.), pharmaceutically acceptable salts thereof, and combinations thereof.

[0068] In an additional aspect of this embodiment, the method further comprises administering 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.

[0069] 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), 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.

[0070] Examples of therapeutic antibodies that may be used in the present invention include rituximab (Rituxan), Cetuximab (Erbitux), bevacizumab (Avastin), and Ibritumomab (Zevalin).

[0071] 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.

[0072] Cytotoxic agents according to the present invention also include inhibitors of the mTOR pathway. Non-limiting examples of such inhibitors include zotarolimus (AbbVie), umirolimus (Biosensors), temsirolimus (Pfizer), sirolimus (Pfizer), sirolimus NanoCrystal (Elan Pharmaceutical Technologies), sirolimus TransDerm (TransDerm), sirolimus-PNP (Samyang), everolimus (Novartis), biolimus A9 (Biosensors), ridaforolimus (Ariad), rapamycin, TCD-10023 (Terumo), DE-109 (MacuSight), MS-R001 (MacuSight), MS-R002 (MacuSight), MS-R003 (MacuSight), Perceiva (MacuSight), XL-765 (Exelixis), quinacrine (Cleveland BioLabs), PKI-587 (Pfizer), PF-04691502 (Pfizer), GDC-0980 (Genentech and Piramed), dactolisib (Novartis), CC-223 (Celgene), PWT-33597 (Pathway Therapeutics), P-7170 (Piramal Life Sciences), LY-3023414 (Eli Lilly), INK-128 (Takeda), GDC-0084 (Genentech), DS-7423 (Daiichi Sankyo), DS-3078 (Daiichi Sankyo), CC-115 (Celgene), CBLC-137 (Cleveland BioLabs), AZD-2014 (AstraZeneca), X-480 (Xcovery), X-414 (Xcovery), EC-0371 (Endocyte), VS-5584 (Verastem), PQR-401 (Piqur), PQR-316 (Piqur), PQR-311 (Piqur), PQR-309 (Piqur), PF-06465603 (Pfizer), NV-128 (Novogen), nPT-MTOR (Biotica Technology), BC-210 (Biotica Technology), WAY-600 (Biotica Technology), WYE-354 (Biotica Technology), WYE-687 (Biotica Technology), LOR-220

(Lorus Therapeutics), HMPL-518 (Hutchison China MediTech), GNE-317 (Genentech), EC-0565 (Endocyte), CC-214 (Celgene), ABTL-0812 (Ability Pharmaceuticals), and pharmaceutically acceptable salts thereof, and combinations thereof.

[0073] 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.

[0074] 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.

[0075] 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).

[0076] In the present invention, "photoactive therapeutic agent" means compounds and compositions that become active upon exposure to light. Certain examples of photoactive therapeutic agents are described in U.S. Patent Application Serial No. 2011/0152230 A1, "Photoactive Metal Nitrosyls For Blood Pressure Regulation And Cancer Therapy."

[0077] In the present invention, "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.

[0078] 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.

[0079] 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.

[0080] 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.

[0081] 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.

[0082] 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)

BVD-523 or a pharmaceutically acceptable salt thereof and (ii) pictilisib (GDC-0941) or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer.

[0083] 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.

[0084] 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.

[0085] In an additional aspect of this embodiment, the pictilisib (GDC-0941) or a pharmaceutically acceptable salt thereof is administered in the form of a pharmaceutical composition further comprising a pharmaceutically acceptable carrier or diluent.

[0086] In another aspect of this embodiment, the method further comprises administering at least one additional therapeutic agent, preferably an inhibitor of the mTOR pathway, as disclosed herein.

[0087] 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.

[0088] 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 PI3K/Akt inhibitor or a pharmaceutically acceptable salt thereof, packaged together with instructions for their use.

[0089] The kits may include suitable storage containers, *e.g.*, ampules, vials, tubes, etc., for each anti-cancer agent of the present invention (which may *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 anti-cancer agents or pharmaceutical compositions containing same and other optional reagents.

[0090] Suitable and preferred PI3K/Akt 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.

[0091] In an additional aspect of this embodiment, the kit further comprises at least one additional therapeutic agent, preferably an inhibitor of the mTOR pathway, as disclosed herein.

[0092] 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.

[0093] An additional embodiment of the present invention is a method for treating or ameliorating the effects of a subject with cancer comprising:

(a) identifying a subject with cancer that has a somatic KRAS mutation and a somatic PIK3CA mutation; and

(b) administering to the subject with somatic KRAS and PIK3CA mutations 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 an inhibitor of the PI3K/Akt pathway or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer.

[0094] Suitable and preferred PI3K/Akt inhibitors and subjects are as set forth above. 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.

[0095] In one aspect of this embodiment, identifying a subject with cancer that has somatic KRAS and PIK3CA mutations comprises:

(a) obtaining a biological sample from the subject; and

(b) screening the sample to determine whether the subject has a somatic KRAS and PIK3CA mutations.

[0096] 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.

[0097] In this embodiment, the screening comprises detection of at least one of the KRAS and PIK3CA mutations using a method as disclosed herein. Preferably the screening method is selectee from PCR, sequencing, hybrid capture, in-solution capture, MIP, and combinations thereof. Other preferred methods include FISH, Sanger sequencing, deep sequencing, and combinations thereof.

[0098] In another aspect of this embodiment, the method further comprises administering at least one additional therapeutic agent, preferably an inhibitor of the mTOR pathway, as disclosed herein.

[0099] 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.

[0100] An additional embodiment of the present invention is a method for treating or ameliorating the effects of a subject with cancer. The method comprises:

(a) identifying a subject with cancer that is refractory to a therapy selected from the group consisting of RAF inhibitor therapy, MEK inhibitor therapy, and RAF and MEK inhibitor therapy; and

(b) administering to the subject identified in step (a) 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 an inhibitor of the PI3K/Akt pathway or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer.

[0101] RAF inhibitors and MEK inhibitors are as disclosed herein. Suitable and preferred PI3K/Akt inhibitors and subjects are also as set forth above. 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.

[0102] In one aspect of this embodiment, identifying a subject with cancer that is refractory to a therapy selected from the group consisting of RAF inhibitor therapy, MEK inhibitor therapy, and RAF and MEK inhibitor therapy comprises:

(a) obtaining a biological sample from the subject; and

(b) screening the sample to determine whether the subject has a somatic BRAF mutation.

[0103] In this embodiment, the screening comprises detection of a somatic BRAF mutation using a method as disclosed herein. Preferably, the screening method is selected from PCR, sequencing, hybrid capture, in-solution capture, MIP, and combinations thereof. Other preferred screening methods include FISH, Sanger sequencing, deep sequencing, and combinations thereof. The following Table 3 shows the SEQ ID Nos. of representative nucleic acid and amino acid sequences of wild type BRAF from various animal sources the sequence listing. These sequences may be used in methods for identifying subjects with a mutant BRAF genotype (such as in the methods disclosed herein).

Table 3: B-RAF sequences

SEQ	polypeptide or	Organism	Other Information

ID No.	nucleic acid sequence		
48	nucleic acid	human	
49	polypeptide	human	
50	nucleic acid	rat (Rattus norvegicus)	
51	polypeptide	rat (Rattus norvegicus)	
52	nucleic acid	mouse, Mus musculus	
53	polypeptide	mouse, Mus musculus	
54	nucleic acid	rabbit, Oryctolagus cuniculus	
55	polypeptide	rabbit, Oryctolagus cuniculus	
56	nucleic acid	guinea pig, Cavia porcellus	
57	polypeptide	guinea pig, Cavia porcellus	
58	nucleic acid	dog, Canis lupus familiaris	variant x1
59	polypeptide	dog, Canis lupus familiaris	variant x1
60	nucleic acid	dog, Canis lupus familiaris	variant x2
61	polypeptide	dog, Canis lupus familiaris	variant x2
62	nucleic acid	cat, Felis catus	
63	polypeptide	cat, Felis catus	
64	nucleic acid	cow, Bos taurus	variant X1
65	polypeptide	cow, Bos taurus	variant X1
66	nucleic acid	cow, Bos taurus	variant X2
67	polypeptide	cow, Bos taurus	variant X2
68	nucleic acid	cow, Bos taurus	variant X3
69	polypeptide	cow, Bos taurus	variant X3
70	nucleic acid	cow, Bos taurus	variant X4
71	polypeptide	cow, Bos taurus	variant X4
72	nucleic acid	cow, Bos taurus	variant X5
73	polypeptide	cow, Bos taurus	variant X5
74	nucleic acid	cow, Bos taurus	variant X6
75	polypeptide	cow, Bos taurus	variant X6
76	nucleic acid	cow, Bos taurus	variant X7
77	polypeptide	cow, Bos taurus	variant X7
78	nucleic acid	cow, Bos taurus	variant X8
79	polypeptide	cow, Bos taurus	variant X8
80	nucleic acid	cow, Bos taurus	variant X9
81	polypeptide	cow, Bos taurus	variant X9
82	nucleic acid	cow, Bos taurus	variant X10
83	polypeptide	cow, Bos taurus	variant X10
84	nucleic acid	cow, Bos taurus	variant X11
85	polypeptide	cow, Bos taurus	variant X11
86	nucleic acid	cow, Bos taurus	variant 2
87	polypeptide	cow, Bos taurus	variant 2
88	nucleic acid	horse, Equus caballus	
89	polypeptide	horse, Equus caballus	
90	nucleic acid	chicken, Gallus gallus	

91	polypeptide	chicken, Gallus gallus

[0104] In another aspect of this embodiment, the method further comprises administering at least one additional therapeutic agent, preferably an inhibitor of the mTOR pathway, as disclosed herein.

[0105] 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.

[0106] 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 an inhibitor of the PI3K/Akt pathway 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.

[0107] Suitable and preferred PI3K/Akt inhibitors and subjects are also as set forth above. 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.

[0108] In one aspect of this embodiment, the pharmaceutical composition further comprises at least one additional therapeutic agent, preferably an inhibitor of the mTOR pathway, as disclosed herein.

[0109] 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.

[0110] 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.

[0111] 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 an inhibitor of the PI3K/Akt pathway or a pharmaceutically acceptable salt thereof. In this embodiment, "contacting" means bringing BVD-523, an inhibitor of the PI3K/Akt pathway, 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, an inhibitor of

the PI3K/Akt pathway, and optionally other therapeutic agents to a culture media in which the cancer cells are located.

[0112] Suitable and preferred PI3K/Akt inhibitors are also as set forth above. 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.

[0113] 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.

[0114] 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.

[0115] 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 mTOR pathway, as disclosed herein.

[0116] In a further aspect of this embodiment, contacting the cancer cell with the first and second anti-cancer agents provides a synergistic effect compared to contacting with either anti-cancer agent alone.

[0117] In the present invention, an "effective amount" or a “therapeutically effective amount” of an anti-cancer agent of the invention including pharmaceutical compositions containing same that are disclosed herein is an amount of such agent 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 an agent or composition according to the invention will be that amount of the agent or composition, which is the lowest dose effective to produce the desired effect. The effective dose of an agent 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.

[0118] A suitable, non-limiting example of a dosage of BVD-523, a PI3K/Akt pathway inhibitor, or another 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 BVD-523, a PI3K/Akt pathway inhibitor, or another anti-cancer agent disclosed herein may be administered as two, three, four, five, six or more sub-doses, administered separately at appropriate intervals throughout the day.

[0119] BVD-523, PI3K/Akt pathway inhibitors, other anti-cancer agents, or pharmaceutical compositions containing same of the present invention may be administered in any desired and effective manner: for oral ingestion, or as an ointment or drop for local administration to the eyes, or for parenteral or other administration in any appropriate manner such as intraperitoneal, subcutaneous, topical, intradermal, inhalation, intrapulmonary, rectal, vaginal, sublingual, intramuscular, intravenous, intraarterial, intrathecal, or intralymphatic. Further, BVD-523, PI3K/Akt pathway inhibitors, other anti-cancer agents, or pharmaceutical compositions containing same of the present invention may be administered in conjunction with other treatments. BVD-523, PI3K/Akt pathway inhibitors, other anti-cancer agents, or the pharmaceutical compositions containing the same of the present invention may be encapsulated or otherwise protected against gastric or other secretions, if desired.

[0120] 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.).

[0121] 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 diluents or carriers 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.

[0122] 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.

[0123] 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.

[0124] 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.

[0125] 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.

[0126] 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.

[0127] 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.

[0128] 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.

[0129] 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.

[0130] 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.

[0131] 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.

[0132] 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.

[0133] 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 for the in vivo study

Mice

[0134] Female athymic nude mice (Crl:NU(Ncr)-*Foxn1*^{nu}, Charles River) were eight weeks old with a body weight (BW) range of 14.6 to 25.7 grams on Day 1 of the study. The animals were fed *ad libitum* water (reverse osmosis, 1 ppm Cl), and NIH 31 Modified and Irradiated Lab Diet® consisting of 18.0% crude protein, 5.0% crude fat, and 5.0% crude fiber. The mice were housed on irradiated Enrich-o'cobs™ Laboratory Animal Bedding in static microisolators on a 12-hour light cycle at 20-22°C (68-72°F) and 40-60% humidity.

Tumor Cell Culture

[0135] HCT116 human colon carcinoma cells were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum, 2 mM glutamine, 100 units/mL penicillin G sodium, 100 µg/mL streptomycin sulfate, and 25 µg/mL gentamicin. The tumor cells were grown in tissue culture flasks in a humidified incubator at 37°C, in an atmosphere of 5% CO_2 and 95% air.

In Vivo Implantation and Tumor Growth

[0136] The HCT116 cells used for implantation were harvested during exponential growth and resuspended in 50% Matrigel (BD Biosciences): 50% phosphate buffered saline at a concentration of 2.5 x 10^7 cells/mL. On the day of tumor implant, each test mouse was injected subcutaneously in the right flank with 5 x 10^6 cells (0.2 mL cell suspension), and tumor growth was monitored as the average size approached the target range of 100 to 150

mm^3. Tumors were measured in two dimensions using calipers, and volume was calculated using the formula:

$$\text{Tumor Volume } (mm^3) = (w^2 \times l) / 2$$

where w = width and l = length, in mm, of the tumor. Tumor weight may be estimated with the assumption that 1 mg is equivalent to 1 mm^3 of tumor volume.

[0137] Ten days after tumor implantation, designated as Day 1 of the study, the animals were sorted into nine groups (Groups 1-9) each consisting of fifteen mice and one group (Group 10) consisting of ten mice. Individual tumor volumes ranged from 88 to 172 mm^3 and group mean tumor volumes were 130 or 131 mm^3.

Therapeutic Agents

[0138] BVD-523 and GDC-0941 were supplied as dry powders and were stored at room temperature.

[0139] BVD-523 doses were prepared by suspending the required amount of BVD-523 powder in 1% carboxymethyl cellulose (CMC) in deionized water ("Vehicle"). A 10 mg/mL BVD-523 stock was prepared, and was used to dose the 100 mg/kg BVD-523 group. Aliquots of the stock were diluted with the vehicle to a concentration of 5.0 mg/mL, which provided a 50 mg/kg BVD-523 dosage in a dosing volume of 10 mL/kg. The BVD-523 doses were stored at 4°C for up to one week. The 1% CMC vehicle was used to dose the control group.

[0140] GDC-0941 doses were formulated in 0.5% methylcellulose: 0.2% Tween 80 in deionized water. A 12 mg/mL GDC-0941 stock was

prepared, and was used to dose the 120 mg/kg GDC-0941 group. Aliquots of the stock were diluted with the vehicle to a concentration of 6.0 mg/mL to provide the 60 mg/kg GDC-0941 dosage in a dosing volume of 10 mL/kg. The GDC-0941 doses were stored at 4°C for up to one week.

[0141] Paclitaxel (Lot CP2N10007) was purchased as a dry powder from Phyton Biotech, LLC (Fort Worth, TX). A paclitaxel stock solution (30 mg/mL) in 50% ethanol: 50% Cremophor EL was prepared and stored at room temperature protected from light during the dosing period. On each day of dosing, an aliquot of the paclitaxel stock was diluted with 5% dextrose in water (D5W) to yield a 3.0 mg/mL paclitaxel dosing solution in a vehicle consisting of 5% ethanol: 5% Cremophor EL: 90% D5W.

Treatment

[0142] On Day 1 of the study, mice were sorted into nine groups (Group 1-9) each consisting of fifteen mice and one group (Group 10) consisting of ten mice, and dosing was initiated according to the treatment plan summarized in Table 4 below. All doses were given by oral gavage (p.o.) except paclitaxel, which was given i.v. For each agent, the dosing volume of 10 mL/kg (0.2 mL per 20 grams of BW) was scaled to the BW of the individual animal. The GDC-0941 doses were to be given once daily (qd) until study end (qd to end), whereas the vehicle and BVD-523 doses were to be given twice daily (bid) until study end (bid to end). For bid dosing, dosing was initiated in the afternoon of Day 1, so that one dose was given on the first day ("first day 1 dose"). Due to toxicity, dosing in the 100 mg/kg BVD-523 combination groups was modified during the study, as described below.

Controls

[0143] Group 1 received 1% CMC vehicle p.o. bid to end, and served as the control group for calculation of %TGD. Group 10 received paclitaxel i.v. at 30 mg/kg once every other day (qod) for five doses (qod x 5), and served as the positive control for the model.

Monotherapy Treatments

[0144] Groups 2 and 3 received 60 and 120 mg/kg GDC-0941, respectively, p.o. qd to end. Groups 4 and 5 received 50 and 100 mg/kg BVD-523, respectively, p.o. bid to end.

Combination Treatments

[0145] Groups 6 and 7 received the combinations of 50 mg/kg BVD-523 with 60 or 120 mg/kg GDC-0941, respectively. Groups 8 and 9 were scheduled to receive the combinations of 100 mg/kg BVD-523 with 60 or 120 mg/kg GDC-0941, respectively. However, due to emerging toxicity, dosing in Group 9 was ended on Day 29 and a dosing holiday was given on Days 31 and 32 in Group 8. The final dosing schedules are shown in Table 5.

Endpoint and Tumor Growth Delay (TGD) Analysis

[0146] Tumors were measured using calipers twice per week, and each animal was euthanized when its tumor reached the pre-determined tumor volume endpoint of 2000 mm^3 or on the final day, whichever came first. Animals that exited the study for tumor volume endpoint were documented as euthanized for tumor progression (TP), with the date of euthanasia. The time to endpoint (TTE) for analysis was calculated for each mouse by the following equation:

$$TTE = [\log_{10}(\text{endpoint volume}) - b] / m$$

where TTE is expressed in days, endpoint volume is expressed in mm^3, b is the intercept, and m is the slope of the line obtained by linear regression of a log-transformed tumor growth data set. The data set consists of the first observation that exceeded the endpoint volume used in analysis and the three consecutive observations that immediately preceded the attainment of this endpoint volume. The calculated TTE is usually less than the TP date, the day on which the animal was euthanized for tumor size. Animals with tumors that did not reach the endpoint volume were assigned a TTE value equal to the last day of the study. Any animal classified as having died from NTR (non-treatment-related) causes due to accident (NTRa) or due to unknown etiology (NTRu) were excluded from TTE calculations (and all further analyses). Animals classified as TR (treatment-related) deaths or NTRm (non-treatment-related death due to metastasis) were assigned a TTE value equal to the day of death.

[0147] Treatment outcome was evaluated from TGD, defined as the increase in the median TTE in a treatment group compared to the control group:

$$TGD = T - C,$$

expressed in days, or as a percentage of the median TTE of the control group:

$$\%TGD = [(T-C) / C] \times 100$$

where:

T = median TTE for a treatment group, and

C = median TTE for the designated control group.

Criteria for Regression Responses

[0148] Treatment efficacy may be determined from the incidence and magnitude of regression responses observed during the study. Treatment may cause partial regression (PR) or complete regression (CR) of the tumor in an animal. In a PR response, the tumor volume was 50% or less of its Day 1 volume for three consecutive measurements during the course of the study, and equal to or greater than 13.5 mm^3 for one or more of these three measurements. In a CR response, the tumor volume was less than 13.5 mm^3 for three consecutive measurements during the course of the study. An animal with a CR response at the termination of the study was additionally classified as a tumor-free survivor (TFS). Animals were monitored for regression responses.

Toxicity

[0149] Animals were weighed daily on Days 1-5, then twice per week until completion of the study. The mice were observed frequently for overt signs of any adverse, TR side effects, and clinical signs were recorded when observed. Individual BW loss was monitored as per protocol, and any animal whose weight exceeded the limits for acceptable BW loss was euthanized. Group mean BW loss also was monitored as per protocol. Dosing was to be suspended in any group that exceeded the limits for acceptable mean BW loss. If mean BW recovered, then dosing was to be resumed in that group, but at a lower dosage or less frequent dosing schedule. Acceptable toxicity for the maximum tolerated dose (MTD) was defined as a group mean BW loss of less than 20% during the study and not more than 10% TR deaths. A death was classified as TR if attributable to treatment side effects as

evidenced by clinical signs and/or necropsy, or may also be classified as TR if due to unknown causes during the dosing period or within 14 days of the last dose. A death was classified as NTR if there was no evidence that death was related to treatment side effects. NTR deaths may be further characterized based on cause of death. A death was classified as NTRa if it resulted from an accident or human error. A death was classified as NTRm if necropsy indicated that it may have resulted from tumor dissemination by invasion and/or metastasis. A death was classified as NTRu if the cause of death was unknown and there was no available evidence of death related to treatment side effects, metastasis, accident or human error, although death due to treatment side effects cannot be excluded.

Sampling

[0150] When available, five mice per group were euthanized by terminal cardiac puncture under carbon dioxide anesthesia at 3, 6, and 12 hours post-final dose, and the full blood volumes were collected. For each sample, the serum was separated and stored frozen at -80°C until shipment. In addition, the tumors of these mice were harvested and divided into two parts. One part was snap-frozen and stored at -80°C. The other part was fixed for 16 to 24 hours in 10% neutral buffered formalin, and then transferred to 70% ethanol.

Statistical and Graphical Analyses

[0151] Prism (GraphPad) for Windows 3.03 was used for graphical presentations and statistical analyses.

[0152] The logrank test, which evaluates overall survival experience, was used to analyze the significance of the differences between the TTE values of two groups. Logrank analysis includes the data for all animals in a group except those assessed as NTR deaths. Two-tailed statistical analyses were conducted at significance level $P = 0.05$. The statistical tests were not adjusted for multiple comparisons. Prism summarizes test results as not significant (ns) at $P > 0.05$, significant (symbolized by "*") at $0.01 < P < 0.05$, very significant ("**") at $0.001 < P \leq 0.01$, and extremely significant ("***") at $P \leq 0.001$. Because tests of statistical significance do not provide an estimate of the magnitude of the difference between groups, all levels of significance were described as either significant or not significant within the text of this example. Groups with regimens above the MTD were not evaluated statistically.

[0153] A scatter plot was constructed to show TTE values for individual mice, by group. Group mean tumor volumes were plotted as a function of time. When an animal exited the study due to tumor size, the final tumor volume recorded for the animal was included with the data used to calculate the mean volume at subsequent time points. Error bars (when present) indicate one standard error of the mean (SEM). Tumor growth plots excluded the data for NTR deaths, and were truncated after 50% of the assessable animals in a group had exited the study or after the second TR death in a group, whichever came first. Kaplan-Meir plots show the percentage of animals in each group remaining in the study versus time. The Kaplan-Meier plot and logrank test share the same TTE data sets. Percent mean BW changes from Day 1 were calculated for each group for each day of BW

measurement, and were plotted as a function of time. BW plots excluded the data for NTR deaths, and were truncated after 50% of the assessable animals in a group had exited the study.

Example 2

Results of the *in vivo* study

[0154] Groups in the *in vivo* study were treated in accordance with the modified protocol as set forth in Table 4. The experiment was terminated on Day 45. Table 5 presents a summary of the treatment responses for each group.

Table 4 - Protocol Design for the HCT116-e399 Study.

Group	n	Treatment Regimen 1				Treatment Regimen 2			
		Agent	mg/kg	Route	Schedule	Agent	mg/kg	Route	Schedule
1	15	Vehicle	-	po	bid to end first day 1 dose	-	-	-	-
2	15	GDC-0941	60	po	qd to end	-	-	-	-
3	15	GDC-0941	120	po	qd to end	-	-	-	-
4	15	BVD-523	50	po	bid to end first day 1 dose	-	-	-	-
5	15	BVD-523	100	po	bid to end first day 1 dose	-	-	-	-
6	15	BVD-523	50	po	bid to end first day 1 dose	GDC-0941	60	po	qd to end
7	15	BVD-523	50	po	bid to end first day 1	GDC-	120	po	qd to end

					dose	0941			
8	15	BVD-523	100	po	bid to end first day 1 dose[a]	GDC-0941	60	po	qd to end[a]
9	15	BVD-523	100	po	bid to end first day 1 dose[b]	GDC-0941	120	po	qd to end[b]
10	10	Paclitaxel	30	iv	qod x 5	-	-	-	-

Vehicle = 1% CMC in deionized water

Note: All bid doses were started on the afternoon of the first day of dosing, so a single dose was given on the first and last days ("bid first 1 day dose").

[a]Group 8 dosing holiday on Days 31-32. Final BVD-523 schedule = bid x 30 first day 1 dose/2/bid to end first day 1 dose, and GDC-0941 schedule = 31/1/qd to end.

[b]Group 9 dosing ended on Day 29. Final BVD-523 schedule = bid x28 first day 1 dose, and GDC-0941 schedule = qd x 29

Table 5 - Response Summary in the HCT116-e399 Study

Group	n	Treatment Regimen				Median TTE	T-C	%TGD	Statistical Significance				MTV (n)	Regressions			Mean BW Nadir	Deaths	
		Agent	mg/kg	Route	Schedule				vs G1	vs G2	vs G3	vs G4	D45	PR	CR	TFS		TR	NTR
1	15	Vehicle	-	po	bid to end	32.7	-	-	-	-	-	-	-	0	0	0	-	0	0
2	15	GDC-0941	60	po	qd to end	35.3	2.6	8	ns	-	-	-	1568 (1)	0	0	0	-	0	0
3	15	GDC-0941	120	po	qd to end	39.0	6.3	19	**	-	-	-	1857 (2)	0	0	0	-	0	0
4	15	BVD-523	50	po	bid to end	43.5	10.8	33	***	-	-	-	1666 (5)	0	0	0	-	0	0
5	15	BVD-523	100	po	bid to end	45.0	12.3	38	ne	-	-	-	405(11)	0	0	0	-	4	0
6	15	BVD-523 GDC-0941	50 60	po po	bid to end qd to end	45.0	12.3	38	***	***	-	ns	1226 (10)	0	0	0	-	0	0
7	15	BVD-523 GDC-0941	50 120	po po	bid to end qd to end	45.0	12.3	38	***	-	***	***	1268 (14)	0	0	0	-	0	0
8	15	BVD-523 GDC-0941	100 60	po po	bid x 30/2/ bid to end 31/1/ qd to end	45.0	12.3	38	ne	-	-	-	363(10)	0	0	0	-6.7 % Day 45	5	0
9	14	BVD-523 GDC-0941	100 120	po po	bid x 28 qd x 29	30.0	-	-	ne	-	-	-	1492 (2)	0	0	0	-	1 2	1
10	10	Paclitaxel	30	iv	qod x 5	45.0	12.3	38	***	-	-	-	688(10)	8	0	0	-8.7 % Day 11	0	0

Study Endpoint = 2000 mm^3; Study Duration = 45 Days. n = number of animals in a group not dead from accidental or unknown causes (NTR deaths excluded from TGD calculations). Vehicle = 1% CMC in deionized water. Note: All bid doses were started on the afternoon of the first day of dosing, so a single dose was given on the first and last days. Group 8 received a dosing holiday on Days 31-32 due to toxicity. Group 9 dosing was ended on Day 29 due to toxicity. TTE = time to endpoint, T-C = difference between median TTE (days) of treated versus control group, %TGD = [(T-C)/C] x 100. The maximum T-C in this study is 12.3 days (38%), compared to Group 1. Statistical Significance (Logrank test): ne = not evaluated (above MTD), ns = not significant, * = $P \leq 0.05$, ** = $P \leq 0.01$, *** = $P \leq 0.001$, compared to group indicated. MTV (n) = median tumor volume (mm^3) for the number of animals on the day of TGD analysis (excludes animals attaining tumor volume endpoint). PR = partial regressions; CR = total number complete regressions; TFS = tumor free survivors, i.e. CRs at end of study. Mean BW Nadir = lowest group mean body weight, as % change from Day 1; "-" indicates no decrease in mean body weight was observed. TR = treatment-related death; NTR = non-treatment-related death

[0155] FIG. 1 is a scatter plot showing the individual TTEs for each group. FIG. 2 presents plots of mean tumor growth (2A) and Kaplan-Meier survival (2B) for each group in the study. FIG. 3 presents plots of percent mean BW changes from Day 1 for each group. Table 6 below shows the clinical observations and study events recorded during the study.

Table 6 – HCT116-e399 Clinical Observations & Study Events

Group	Animals	Date	Day	Clinical Observations & Study Events
2	6, 8	6/3/2013	36	Tumor ulcerated/cannibalized. (LR)
3	5	5/28/2013	30	Found on cage top; dehydrated, but active. (JCH)
3	10, 11, 3, 4, 9	6/3/2013	36	Tumore ulcerated/cannibalized. (LR)
4	13	4/30/2013	2	Day 2 body weight carried over from Day 1
4	11, 3, 5	6/3/2013	36	Tumor ulcerated. (LR)
4	7, 8	6/10/2013	43	Tumor ulcerated. (LR)
5	6	6/3/2013	36	Tumor ulcerated. (LR)
5	5	6/9/2013	42	Found dead; beyond necropsy; TR by definition. (AR)
5	6	6/10/2013	43	Found dead; beyond necropsy; TR. (LP)
5	14	6/10/2013	43	Tumor ulcerated (LR)
5	3, 4	6/10/2013	43	Cool to the touch; slightly dehydrated. (KAS)
5	3	6/11/2013	44	Found dead; necropsy: impacted stomach, no evidence of gavage error; TR by definition (ER)
5	4	6/12/2013	45	Found dead; TR by definition (LR)
6	7	6/3/2013	36	Tumor ulcerated. (LR)
7	13, 6	6/3/2013	36	Tumor ulcerated. (LR)
8	14, 15	5/29/2013	31	Found dead; beyond necropsy; TR by definition. (LR)

Group	Animals	Date	Day	Clinical Observations & Study Events
8	All	5/29/2013	31	Stop dosing per PM. (AHR) EDC dosing stopped (AHR)
8	10, 3	5/30/2013	32	Found dead; beyond necropsy; TR by definition. (LR)
8	All	5/31/2013	33	Resume dosing per PM. (LR) EDC dosing resumed (LR).
8	9	6/3/2013	36	Cool to the touch. (LR)
8	7	6/11/2013	44	Cold to the touch; lethargic. (CS) Found dead; necropsy: impacted large stomach, autolyzed intestines, no evidence of gavage error; TR by definition. (ER)
9	10	5/24/2013	26	Found dead; beyond necropsy; unable to check for gavage error; NTRu (non-treatment-related (death) of unknown causes or etiology). (LR)
9	12	5/26/2013	28	Found dead; beyond necropsy; unable to check for gavage error; TR by definition. (AJW)
9	4	5/27/2013	29	Found dead; negative for gavage error; all other organs appear normal; TR. (KST)

[0156] The clinical observations included occasional notes of tumor ulceration, known to occur in the absence of treatment. The ulcerated tumors were deemed not to impact overall interpretation of activity, and therefore, all mice with ulcerated tumors were included in the data set for analysis. The detailed results of statistical analyses are located in Tables 7 and 8.

Table 7 - Statistical Analysis

Groups Compared	Vehicle(-) (po)bid to end	Vehicle(-) (po)bid to end	Vehicle(-) (po)bid to end	Vehicle(-) (po)bid to end	Vehicle(-) (po)bid to end	Vehicle(-) (po)bid to end	Vehicle(-) (po)bid to end
	Group 1 vs 2	Group 1 vs 3	Group 1 vs 4	Group 1 vs 5	Group 1 vs 6	Group 1 vs 7	Group 1 vs 8
	MR228(60) (po)qd to end	MR228(120) (po)qd to end	MR216(50) (po)bid to end	MR216(100) (po)bid to end	MR216(50) (po)bid to end / MR228(60) (po)qd to end	MR216(50) (po)bid to end / MR228(120) (po)qd to end	MR216(100) (po)bid x 30 /2/bid to end / MR228(60) (po)31/1/qd to end
Logrank test							
Chi square	2.635	7.162	21.86	Not Evaluated (Above MTD)	28.49	31.3	Not Evaluated (Above MTD)
Df	1	1	1		1	1	
P value	0.1045	0.0074	P<0.0001		P<0.0001	P<0.0001	
P value summary	ns	**	***		***	***	
Are survival curves diff.?	No	Yes	Yes		Yes	Yes	
Median survival							
Column A	32.7	32.7	32.7		32.7	32.7	
Column B	35.3	39	43.5		Undefined	Undefined	
Ratio	0.9263	0.8385	0.7517				
95% CI of ratio	0.4436 to 1.409	0.3626 to 1.314	0.3025 to 1.201				
Hazard Ratio							
Ratio	1.775	2.507	4.813		8.443	32.65	
95% CI of ratio	0.8748 to 4.154	1.364 to 7.456	4.060 to 30.70		6.347 to 54.19	7.700 to 69.58	

Table 8 - Statistical Analysis

Groups Compared	Vehicle(-) (po)bid to end	Vehicle(-) (po)bid to end	MR228(60) (po)qd to end	MR228(120) (po)qd to end	MR216(50) (po)bid to end	MR216(50) (po)bid to end
	Group 1 vs 9	Group 1 vs 10	Group 2 vs 6	Group 3 vs 7	Group 4 vs 6	Group 4 vs 7
	MR216(100) (po)bid x28 / MR228(120) (po)qd x29	Paclitaxel(30) (iv)qod x 5	MR216(50) (po)bid to end / MR228(60) (po)qd to end	MR216(50) (po)bid to end / MR228(120) (po)qd to end	MR216(50) (po)bid to end / MR228(60) (po)qd to end	MR216(50) (po)bid to end / MR228(120) (po)qd to end
Logrank Test						
Chi square	Not Evaluated (Above MTD)	24.03	17.43	19.75	3.17	10.91
Df		1	1	1	1	1
P value		P<0.0001	P<0.0001	P<0.0001	0.075	0.001
P value summary		***	***	***	ns	***
Are survival curves diff.?		Yes	Yes	Yes	No	Yes
Median survival						
Column A		32.7	35.3	39	43.5	43.5
Column B		Undefined	Undefined	Undefined	Undefined	Undefined
Ratio						
95% CI of ratio						
Hazard Ratio						
Ratio		Undefined	6.205	22.41	2.546	13.73
95% CI of ratio			3.136 to 23.70	4.075 to 37.39	0.9103 to 7.088	2.287 to 25.55

Efficacy

Growth of HCT116 Human Colorectal Carcinomas in Control Mice (Group 1)

[0157] Group 1 mice received 1% CMC vehicle p.o. bid to end and served as the control group for analysis of efficacy. All control tumors attained the 2000 mm^3 endpoint with a median TTE of 32.7 days, establishing a maximum possible TGD of 12.3 days (38%) for the 45-day study (Table 5).

The scatter plot shows a relatively broad but uniform distribution of Group 1 TTEs (FIG. 1). Mean tumor growth for controls was progressive (FIG. 2A).

Response to GDC-0941 as Monotherapy (Groups 2 and 3)

[0158] Groups 2 and 3 received GDC-0941 as monotherapy at 60 and 120 mg/kg, respectively, p.o. qd to end. The median TTEs for Groups 2 and 3 were 35.3 and 39.0 days, respectively, corresponding to TGDs of 2.6 days (8%) and 6.3 days (19%), with a significant survival difference only for the 120 mg/kg GDC-0941 group compared to controls (Group 1 vs. 2, $P > 0.05$; Group 1 vs. 3, $P < 0.01$). No regressions were recorded (Table 5). Group 2 had one 45-day survivor, whereas Group 3 had two 45-day survivors, and all other tumors in these groups attained the 2000 mm^3 endpoint volume (Table 5). The mean tumor growth plots for Groups 2 and 3 indicated negligible dose-related delays consistent with the TGDs (FIG. 2A).

Response to BVD-523 as Monotherapy (Groups 4 and 5)

[0159] Groups 4 and 5 received BVD-523 as monotherapy at 50 and 100 mg/kg, respectively, p.o. bid to end. The median TTEs for Groups 4 and 5 were 43.5 and 45.0 days, respectively, which corresponded to TGD of 10.8 days (33%) for the 50 mg/kg BVD-523 group and the maximum TGD (12.3 days, 38%) for the 100 mg/kg BVD-523 group (Table 5). However, Group 5 had four TR deaths during the final days of the study (Days 42–45), and therefore this regimen was above the MTD and was not evaluated statistically (FIG. 1 and Table 5). Logrank analysis detected a significant survival benefit for the 50 mg/kg BVD-523 treatment (Group 1 vs. 4, $P < 0.001$). No regressions were recorded in either group (Table 5). Group 4 had five 45-day survivors, and all other tumors in this group attained the 2000 mm^3 endpoint

volume, whereas the eleven Group 5 mice that did not die due to treatment were 45-day survivors (Table 5). The mean tumor growth plots for the 50 and 100 mg/kg BVD-523 groups illustrated dose-related delays (FIG. 2A).

Response to Treatment with BVD-523 Combined with GDC-0941 (Groups 6–9)

[0160] Groups 6 and 7 received 50 mg/kg BVD-523 with 60 or 120 mg/kg GDC-0941, respectively, on the planned schedules (Table 5). The median TTEs for Groups 6 and 7 were each 45.0 days, corresponding to the maximum TGD (12.3 days, 38%), with a significant overall survival benefit compared to controls (Group 1 vs. 6 or 7, $P < 0.001$). No regression responses were recorded in either group (Table 5). Group 6 had five tumors that attained the 2000 mm^3 endpoint and ten 45-day survivors, whereas fourteen Group 7 mice were 45-day survivors (Table 5). Both combinations produced superior survival to the corresponding GDC-0941 treatment (Group 2 vs. 6 or 3 vs. 7, $P < 0.001$). The Group 7 combination was also superior to the corresponding BVD-523 regimen (Group 4 vs. 6, $P > 0.05$; Group 4 vs. 7, $P < 0.001$). Mean tumor growth for Group 6 was similar to that for the 50 mg/kg BVD-523 monotherapy (Group 4), while mean tumor growth for Group 7 showed greater delay compared to both Groups 3 and 4 (FIG. 2A).

[0161] Groups 8 and 9 received 100 mg/kg BVD-523 with 60 or 120 mg/kg GDC-0941, respectively, on schedules modified due to toxicity (Table 5). As indicated in Table 5, Group 8 received a 2-day dosing holiday on Days 31–32, while Group 9 dosing was terminated on Day 29 (Table 5). The median TTE for Group 8 was 45.0 days, corresponding to the maximum TGD (12.3 days, 38%). However, 5/15 TR deaths were recorded (four on Days 31–

32 and one on Day 44), and this regimen was above the MTD and was not evaluated statistically (FIG. 1 and Table 5). The other ten Group 8 mice were 45-day survivors. Group 9 had one NTRu death on Day 26 and twelve TR deaths from Days 28-30, and this regimen was also above the MTD and was not evaluated statistically (FIG. 1 and Table 5). The two remaining Group 9 mice were 45-day survivors. The mean tumor growth plots for Groups 8 and 9 were comparable to the plot for Group 5, the 100 mg/kg BVD-523 monotherapy (FIG. 2A).

Response to Paclitaxel Treatment (Group 10)

[0162] The paclitaxel treatment resulted in a median TTE of 45.0 days, which corresponded to the maximum TGD (12.3 days, 38%), and a significant overall survival benefit compared to controls (Group 1 vs. 10, $P < 0.001$). Group 10 had 8/10 PR responses, which were the only regressions recorded in the study (Table 5). The mean tumor growth plot for this group indicated noteworthy activity (FIG. 2A).

Side Effects

[0163] Table 5 provides a summary of maximum mean BW losses, TR and NTR deaths. FIG. 3 presents plots of percent mean BW changes from Day 1 for each group.

[0164] The 60 and 120 mg/kg GDC-0941 groups (Groups 2 and 3) and the 50 mg/kg BVD-523 group (Group 4) had no TR or NTR deaths, no mean BW losses, and no noteworthy adverse clinical signs. Likewise, the two-drug combinations of these regimens (Groups 6 and 7) had no TR or NTR deaths, no mean BW losses, and no noteworthy adverse clinical signs.

[0165] The 100 mg/kg BVD-523 group (Group 5) had no mean BW loss, but four Group 5 mice were found dead near study end on Days 42, 43, 44 and 45, respectively. Group 5 had no reported adverse clinical signs until Day 43, when two mice were noted to be dehydrated and cool to the touch (Table 6). The combinations of 100 mg/kg BVD-523 with 60 or 120 mg/kg GDC-0941 (Groups 8 and 9) resulted in five and twelve TR deaths, respectively (Table 5). Group 8 had two TR deaths on Day 31, and a dosing holiday was initiated. Two additional TR deaths were recorded on Day 32. Dosing was resumed on Day 33, with no adverse effects noted until Day 44, when one additional TR death was recorded (Table 6). Group 8 had a mean BW nadir of -6.7% on Day 45 (Table 5). Group 9 had one death due to unknown etiology (NTRu) on Day 26, followed by one TR death on Day 28 and two TR deaths on Day 29, when dosing was ended. Nine additional Group 9 animals were found dead on Day 30, and these deaths were also assessed as TR. Thus, the 100 mg/kg BVD-523 mono- and combination therapies were above the MTD.

[0166] The present study also evaluated combinations of BVD-523 with GDC-0941 for efficacy in the HCT116 human colorectal carcinoma xenograft model. BVD-523 was administered p.o. at 50 or 100 mg/kg on a bid schedule and GDC-0941 was given p.o. at 60 or 120 mg/kg on a daily schedule, alone and in combination.

[0167] BVD-523 at 100 mg/kg p.o. bid to end, either alone or combined with GDC-0941, was above the MTD. The 100 mg/kg BVD-523 monotherapy was acceptably tolerated until Day 42, when the first of four TR deaths occurred. The 100 mg/kg BVD-523 / 60 mg/kg GDC-0941 combination had

the first death on Day 31, and a total of five TR deaths; whereas the 100 mg/kg BVD-523 / 120 mg/kg GDC-0941 combination had the first death on Day 26, and a total of twelve TR deaths. Thus, the addition of GDC-0941 shortened the onset of toxicity and increased the extent of toxicity in a dose-related manner. All other regimens in the study were well tolerated, and could be evaluated for efficacy.

[0168] The median TTE for controls was 32.7 days, establishing a maximum possible TGD of 12.3 days (38%) for the 45-day study. The paclitaxel positive control treatment resulted in the maximum TGD and eight PRs, consistent with expected activity in this tumor model (DRS-NC internal data).

[0169] The 50 mg/kg BVD-523 monotherapy resulted in marginal TGD of 10.8 days (33%), but a significant survival difference versus controls ($P < 0.001$). The 60 and 120 mg/kg GDC-0941 monotherapies produced small dose-related TGDs of 2.6 days (8%) and 6.3 days (19%), and significance versus controls for the higher GDC-0941 dosage ($P < 0.01$). However, GDC-0941 showed negligible delay on the tumor growth plot (FIG. 2A).

[0170] The 50 mg/kg BVD-523 / 60 or 120 mg/kg GDC-0941 combinations each produced the maximum TGD, although they were distinct in the numbers of 45-day survivors (10/15 vs. 14/15). Both regimens were statistically superior to the corresponding GDC-0941 monotherapy, and the 50 mg/kg BVD-523 / 120 mg/kg GDC-0941 combination was also statistically superior to the 50 mg/kg BVD-523 monotherapy.

[0171] In summary, BVD-523 at 50 mg/kg p.o. bid to end was active. GDC-0941 was inactive at 60 mg/kg p.o. qd to end, and negligibly active at

120 mg/kg. BVD-523 at 100 mg/kg p.o. bid to end, alone or combined, was above the maximum tolerated dose (MTD). The combination of 50 mg/kg BVD-523 / 120 mg/kg GDC-0941 was statistically superior to either monotherapy alone.

Example 3

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

[0172] 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 9 (for the 4-hour treatment) and Table 10 (for the 24-hour treatment) below.

Table 9 – 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-	90	Millipore	04-419	1:40000	o/n 4˚C 5%	anti-rabbit

Antigen	Size (kDa)	Supplier	Cat No	Dilution	Incubation / Block Conditions	Secondary
T359/S363					BSA	
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 10 – Antibody details

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

Antigen	Size (kDa)	Supplier	Cat No	Dilution	Incubation / Block Conditions	Secondary
pRB (Ser780)	105	Cell Signaling	9307	1:2000	o/n 4˚C 5% BSA	anti-rabbit
CCND1	34	Abcam	ab6152	1:500	o/n 4˚C 5% milk	anti-mouse
Bim-EL	23	Millipore	AB17003	1:1000	o/n 4˚C 5% BSA	anti-rabbit
Bim-EL	23	Cell Signaling	2933	1:1000	o/n 4˚C 5% BSA	anti-rabbit
BCL-xL	30	Cell Signaling	2762	1:2000	o/n 4˚C 5% BSA	anti-rabbit
PARP	116/89	Cell Signaling	9542	1:1000	o/n 4˚C 5% milk	anti-rabbit
Cleaved Caspase 3	17,19	Cell Signaling	9664X	1:1000	o/n 4˚C 5% milk	anti-rabbit
DUSP6	48	Cell Signaling	3058S	1:1000	o/n 4°C 5% BSA	anti-rabbit
pRSK1/2 pS380	90	Cell Signaling	9335	1:1000	o/n 4°C 5% BSA	anti-rabbit
pRSK1/2 pS380	90	Cell Signaling	11989	1:2000	o/n 4°C 5% BSA	anti-rabbit
pRSK-T359/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

[0173] FIG. 4 shows 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.

[0174] 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.

[0175] 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.

[0176] 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.

[0177] In sum, FIG. 4 shows that BVD-523 inhibits the MAPK signaling pathway and may be more favorable compared to RAF or MEK inhibition in this setting.

[0178] 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 4

Cell culture studies of PI3K-MTOR and ERK inhibitors

Single Agent Proliferation Assay

[0179] Cells were seeded in 96-well plates at the densities and media conditions indicated in Table 11 in McCoy's 5A containing either 10% FBS or 1% charcoal-stripped FBS (CS-FBS), and allowed to adhere overnight prior to addition of compound or vehicle control. Compounds were prepared from DMSO stocks to give the desired final concentrations. The final DMSO concentration was constant at 0.1%. Test compounds were incubated with the cells for 72h at 37°C, 5% CO_2 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

[0180] Cells were seeded into triplicate 96-well plates at the densities indicated in Table 11 in McCoy's 5A media containing 2.5% FBS and allowed to adhere overnight prior to addition of test compound or vehicle control. Combinations were tested using either a 10x8 or for the follow-up HCT116 study a 3x1 dose matrix.

[0181] Test compounds were incubated with the cells for 72h at 37°C, 5% CO_2 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.

[0182] For the 10x8 combination assays the 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).

[0183] The 3x1 combination assay follow-up experiment was analysed using the Bliss additivity model in Microsoft Excel as follows: first, predicted fractional inhibition values for combined inhibition were calculated using the equation $C_{bliss} = A + B - (A \times B)$ 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 were then subtracted from the experimentally observed fractional inhibition values to give an 'excess over Bliss' value which were plotted as heat maps ± SD. Excess of Bliss values greater than 0 indicate synergy, whereas values less than 0 indicate antagonism.

Table 11 - Cell Line Seeding Density and Growth Media

Cell Line	Seeding Density in 10% FBS (cells/well)	Seeding Density in 1% CS-FBS (cells/well)	Seeding Density in 2.5% FBS (cells/well)
HCT116 Parental	1000	3000	2000
HCT116 PIK3CA (+/-)	3000	4500	7500
DLD-1 Parental	-	-	2000
DLD-1 PIK3CA (+/-)	-	-	3000

[0184] The aim of this study was to assess the effects on cell viability of combining ERK inhibitors with a panel of PI3K-MTOR inhibitors (Table 12) in HCT116 and DLD1 cell line pairs that are isogenic for the presence or absence of PIK3CA activating mutations. (Table 13).

Table 12 – Description of PI3K-MTOR Inhibitors Studied

Inhibitor	Selectivity
BYL719	PI3K α-selective inhibitor
BKM120	Pan-PI3K (α/β/δ/γ) inhibitor
INK128	mTOR inhibitor
PF-04691502	PI3K/mTOR dual inhibitor

Table 13 – Description of Cell Lines Studied

Cell Line	Description
HCT116 Parental	Heterozygous parental cells containing one mutant PIK3CA allele (H1047R) and one wild type allele
HCT116 PIK3CA (+/-)	Knock out of mutant KRAS allele in heterozygous parental cells Knock-out of PIK3CA mutant allele (H1047R) in heterozygous parental cells
DLD-1 Parental	Heterozygous parental cells containing one mutant PIK3CA allele (E545K) and one wild type allele
DLD-1 PIK3CA (+/-)	Knock-out of PIK3CA mutant allele (E545K) in heterozygous parental cells

[0185] Initial single agent assays were performed in the HCT116 isogenic cells in order to select appropriate concentration ranges to use in the combination assays (FIG. 6, Table 14). As high levels of serum can potentially mask interactions between targeted agents and specific mutant genotypes, due to an excess of growth factors, these assays were performed under both standard (10% FBS) and reduced serum conditions (1% charcoal-stripped FBS).

Table 14 – Single agent IC50 values (μM) for each compound in the HCT116 PIK3CA (+/-) isogenic cell line pair

Compound	HCT116 Parental		HCT116 PIK3CA (+/-)	
	10% FBS	1% CS-FBS	10% FBS	1% CS-FBS
BYL719	n.d.	n.d.	n.d.	n.d.
BKM120	0.62	0.53	0.52	1.03
INK128	0.05	0.03	0.07	0.02
PF-04691502	0.29	0.07	0.42	1.54
BVD-523	0.17	0.02	0.12	0.01
SCH772984	0.14	0.03	0.08	0.01
Paclitaxel	0.002	0.003	0.002	0.003
GDC-0941	1.53	0.06	n.d.	n.d.

[0186] Although, there were apparent differences in the calculated IC_{50} values between the two serum conditions, a reliable interpretation of these differences was confounded by the poor levels of cell growth and compromised cell health (microscopic observations) under the reduced serum conditions. As an intermediate to these conditions, all the combination assays were therefore performed in medium containing 2.5% serum.

[0187] 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.

[0188] BVD-523 showed strong synergistic interactions with BYL719, BKM120 and PF04691502, and modestly synergistic with BKM120, in the parental HCT116 cell line, which carries the PIK3CA mutation. Potential

synergies were also observed in the HCT116 isogenic cell line lacking the PIK3CA mutation, however, the strength and/or windows of synergy tended to be smaller relative to the parental line.

[0189] A similar pattern of results was seen with a second benchmark ERK inhibitor SCH772984 in this HCT116 isogenic pair supporting the notion that these synergies are specifically related to inhibition of ERK and not due to an off-target effect. (FIG. 7 – FIG. 15)

[0190] These results were confirmed in the HCT116 isogenics in a repeat experiment using a narrower range of inhibitor concentrations. (FIG. 16) BVD-523 and SCH772984 also showed a similar pattern of potentially synergistic interactions in the DLD-1 isogenic cells. (FIG. 17 – FIG. 25) However, in contrast to the HCT116 cells, synergies were weaker and there was little difference in the magnitude of synergy between the cell line lacking the PIK3CA mutation relative to the parental line. (FIG. 26)

[0191] In summary, these results suggest synergistic interactions between BVD-523 and PI3K-MTOR pathway inhibitors in cancer cell lines that are either wild type or mutated for PIK3CA.

[0192] Single agent dose-response curves in 2.5% serum were derived from the combination assay plates. IC_{50} values are a mean derived from n=4 separate combinations. A comparison of the single agent dose responses derived from the combination assay data in the HCT116 isogenics showed that the cell line lacking the PIK3CA mutation was more sensitive to BVD-523 relative to the parental line that contained the mutation. A similar result was seen with SCH772984. This may indicate that PIK3CA mutation status is a

potential biomarker for predicting response to single agent BVD-523 treatment. (Table 15)

Table 15 – Differential sensitivity to ERK inhibition in HCT116 isogenics

	IC_{50} (μM)	
	HCT116 Parental	HCT116 PIK3CA (+/-)
BVD-523	0.13	0.04
SCH772984	0.21	0.03

Example 5

Combination Interactions Between ERK inhibitors

[0193] RAF mutant melanoma cell line A375 cells were cultured in DMEM with 10% FBS and seeded into triplicate 96-well plates at an initial density of 2000 cells per well. Combination interactions between ERK inhibitors BVD-523 and SCH772984 were analized after 72 hours as described above in Example 4. Viability was determined using CellTiter-Glo® reagent (Promega, Madison, WI) according to manufacturer's instructions and luminescence was detected using the BMG FLUOstar plate reader (BMG Labtech, Ortenberg, Germany).

[0194] 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. 27).

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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[0195] All documents cited in this application are hereby incorporated by reference as if recited in full herein.

[0196] 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 an inhibitor of the PI3K/Akt pathway or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer,

wherein the inhibitor of the PI3K/Akt pathway is selected from the group consisting of pictilisib (GDC-0941), BYL719, BKM120, PF-04691502, 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 inhibitor of the PI3K/Akt pathway is pictilisib (GDC-0941) or a pharmaceutically acceptable salt thereof.

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6. The method according to claim 1, wherein the subject with cancer has a somatic KRAS mutation or is refractory to MAPK pathway inhibitor treatment.

7. The method according to claim 6, wherein the subject with cancer has a somatic KRAS mutation and a somatic PIK3CA mutation.

8. The method according to claim 6, wherein the cancer is selected from the group consisting of a cancer of the large intestine, breast cancer, liver cancer, colon cancer, pancreatic cancer, endometrial cancers, stomach cancer, lung cancer, and leukemia.

9. The method according to claim 6, wherein the cancer is colon cancer.

10. The method according to claim 1 further comprising administering 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.

11. The method according to claim 10, wherein the additional therapeutic agent is an inhibitor of the mTOR pathway.

12. The method according to claim 11, wherein the inhibitor of the mTOR pathway is selected from the group consisting of zotarolimus (AbbVie), umirolimus (Biosensors), temsirolimus (Pfizer), sirolimus (Pfizer), sirolimus NanoCrystal (Elan Pharmaceutical Technologies), sirolimus TransDerm (TransDerm), sirolimus-PNP (Samyang), everolimus (Novartis), biolimus A9

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(Biosensors), ridaforolimus (Ariad), rapamycin, TCD-10023 (Terumo), DE-109 (MacuSight), MS-R001 (MacuSight), MS-R002 (MacuSight), MS-R003 (MacuSight), Perceiva (MacuSight), XL-765 (Exelixis), quinacrine (Cleveland BioLabs), PKI-587 (Pfizer), PF-04691502 (Pfizer), GDC-0980 (Genentech and Piramed), dactolisib (Novartis), CC-223 (Celgene), PWT-33597 (Pathway Therapeutics), P-7170 (Piramal Life Sciences), LY-3023414 (Eli Lilly), INK-128 (Takeda), GDC-0084 (Genentech), DS-7423 (Daiichi Sankyo), DS-3078 (Daiichi Sankyo), CC-115 (Celgene), CBLC-137 (Cleveland BioLabs), AZD-2014 (AstraZeneca), X-480 (Xcovery), X-414 (Xcovery), EC-0371 (Endocyte), VS-5584 (Verastem), PQR-401 (Piqur), PQR-316 (Piqur), PQR-311 (Piqur), PQR-309 (Piqur), PF-06465603 (Pfizer), NV-128 (Novogen), nPT-MTOR (Biotica Technology), BC-210 (Biotica Technology), WAY-600 (Biotica Technology), WYE-354 (Biotica Technology), WYE-687 (Biotica Technology), LOR-220 (Lorus Therapeutics), HMPL-518 (Hutchison China MediTech), GNE-317 (Genentech), EC-0565 (Endocyte), CC-214 (Celgene), ABTL-0812 (Ability Pharmaceuticals), and pharmaceutically acceptable salts thereof, and combinations thereof.

13. 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 pictilisib (GDC-0941) or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer,

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

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

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

16. The method according to claim 14, wherein the mammal is a human.

17. The method according to claim 13, 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.

18. The method according to claim 13, wherein the pictilisib (GDC-0941) or a pharmaceutically acceptable salt thereof is administered in the form of a pharmaceutical composition further comprising a pharmaceutically acceptable carrier or diluent.

19. The method according to claim 13, wherein the subject with cancer has a KRAS mutation or is refractory to MAPK pathway inhibitor treatment.

20. The method according to claim 19, wherein the subject with cancer has a somatic KRAS mutation and a somatic PIK3CA mutation.

21. The method according to claim 19, wherein the cancer is selected from the group consisting of a cancer of the large intestine, breast cancer, liver

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cancer, colon cancer, pancreatic cancer, endometrial cancers, stomach cancer, lung cancer, and leukemia.

22. The method according to claim 21, wherein the cancer is colon cancer

23. The method according to claim 13 further comprising administering 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.

24. The method according to claim 23, wherein the additional therapeutic agent is an inhibitor of the mTOR pathway.

25. The method according to claim 24, wherein the inhibitor of the mTOR pathway is selected from the group consisting of zotarolimus (AbbVie), umirolimus (Biosensors), temsirolimus (Pfizer), sirolimus (Pfizer), sirolimus NanoCrystal (Elan Pharmaceutical Technologies), sirolimus TransDerm (TransDerm), sirolimus-PNP (Samyang), everolimus (Novartis), biolimus A9 (Biosensors), ridaforolimus (Ariad), rapamycin, TCD-10023 (Terumo), DE-109 (MacuSight), MS-R001 (MacuSight), MS-R002 (MacuSight), MS-R003 (MacuSight), Perceiva (MacuSight), XL-765 (Exelixis), quinacrine (Cleveland BioLabs), PKI-587 (Pfizer), PF-04691502 (Pfizer), GDC-0980 (Genentech and Piramed), dactolisib (Novartis), CC-223 (Celgene), PWT-33597 (Pathway Therapeutics), P-7170 (Piramal Life Sciences), LY-3023414 (Eli Lilly), INK-128 (Takeda), GDC-0084 (Genentech), DS-7423 (Daiichi Sankyo), DS-3078 (Daiichi Sankyo), CC-115 (Celgene), CBLC-137 (Cleveland BioLabs), AZD-

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26. 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 PI3K/Akt inhibitor or a pharmaceutically acceptable salt thereof, packaged together with instructions for their use,

wherein the inhibitor of the PI3K/Akt pathway is selected from the group consisting of pictilisib (GDC-0941), BYL719, BKM120, PF-04691502, 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.

27. The kit according to claim 26, wherein the subject is a mammal.

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28. The kit according to claim 27, wherein the mammal is selected from the group consisting of humans, primates, farm animals, and domestic animals.

29. The kit according to claim 27, wherein the mammal is a human.

30. The kit according to claim 26, wherein the inhibitor of the PI3K/Akt pathway is pictilisib (GDC-0941) or a pharmaceutically acceptable salt thereof.

31. The kit according to claim 26, wherein the subject with cancer has a somatic KRAS mutation or is refractory to MAPK pathway inhibitor treatment.

32. The kit according to claim 31, wherein the subject with cancer has a somatic KRAS mutation and a somatic PIK3CA mutation.

33. The kit according to claim 31, wherein the cancer is selected from the group consisting of a cancer of the large intestine, breast cancer, liver cancer, colon cancer, pancreatic cancer, endometrial cancers, stomach cancer, lung cancer, and leukemia.

34. The kit according to claim 31, wherein the cancer is colon cancer

35. The kit according to claim 26 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.

36. The kit according to claim 35, wherein the additional therapeutic agent is an inhibitor of the mTOR pathway.

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37. The kit according to claim 36, wherein the inhibitor of the mTOR pathway is selected from the group consisting of zotarolimus (AbbVie), umirolimus (Biosensors), temsirolimus (Pfizer), sirolimus (Pfizer), sirolimus NanoCrystal (Elan Pharmaceutical Technologies), sirolimus TransDerm (TransDerm), sirolimus-PNP (Samyang), everolimus (Novartis), biolimus A9 (Biosensors), ridaforolimus (Ariad), rapamycin, TCD-10023 (Terumo), DE-109 (MacuSight), MS-R001 (MacuSight), MS-R002 (MacuSight), MS-R003 (MacuSight), Perceiva (MacuSight), XL-765 (Exelixis), quinacrine (Cleveland BioLabs), PKI-587 (Pfizer), PF-04691502 (Pfizer), GDC-0980 (Genentech and Piramed), dactolisib (Novartis), CC-223 (Celgene), PWT-33597 (Pathway Therapeutics), P-7170 (Piramal Life Sciences), LY-3023414 (Eli Lilly), INK-128 (Takeda), GDC-0084 (Genentech), DS-7423 (Daiichi Sankyo), DS-3078 (Daiichi Sankyo), CC-115 (Celgene), CBLC-137 (Cleveland BioLabs), AZD-2014 (AstraZeneca), X-480 (Xcovery), X-414 (Xcovery), EC-0371 (Endocyte), VS-5584 (Verastem), PQR-401 (Piqur), PQR-316 (Piqur), PQR-311 (Piqur), PQR-309 (Piqur), PF-06465603 (Pfizer), NV-128 (Novogen), nPT-MTOR (Biotica Technology), BC-210 (Biotica Technology), WAY-600 (Biotica Technology), WYE-354 (Biotica Technology), WYE-687 (Biotica Technology), LOR-220 (Lorus Therapeutics), HMPL-518 (Hutchison China MediTech), GNE-317 (Genentech), EC-0565 (Endocyte), CC-214 (Celgene), ABTL-0812 (Ability Pharmaceuticals), and pharmaceutically acceptable salts thereof, and combinations thereof.

38. A method for treating or ameliorating the effects of a subject with cancer comprising:

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(a) identifying a subject with cancer that has a somatic KRAS mutation and a somatic PIK3CA mutation; and

(b) administering to the subject with somatic KRAS and PIK3CA mutations 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 an inhibitor of the PI3K/Akt pathway or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer,

wherein the inhibitor of the PI3K/Akt pathway is selected from the group consisting of pictilisib (GDC-0941), BYL719, BKM120, PF-04691502, 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.

39. The method according to claim 38, wherein identifying a subject with cancer that has somatic KRAS and PIK3CA mutations comprises:

(c) obtaining a biological sample from the subject; and

(d) screening the sample to determine whether the subject has a somatic KRAS and PIK3CA mutations.

40. The method according to claim 39, wherein the screening comprises detection of at least one of the KRAS and PIK3CA mutations using a method

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selected from the group consisting of PCR, sequencing, hybrid capture, in-solution capture, molecular inversion probes, and combinations thereof.

41. The method according to claim 39, wherein the screening comprises detection of at least one of the KRAS and PIK3CA mutations using a method selected from the group consisting of a fluorescent in situ hybridization (FISH) assay, Sanger sequencing, deep sequencing, and combinations thereof.

42. The method according to claim 38, wherein the subject is a mammal.

43. The method according to claim 42, wherein the mammal is selected from the group consisting of humans, primates, farm animals, and domestic animals.

44. The method according to claim 42, wherein the mammal is a human.

45. The method according to claim 38, wherein the inhibitor of the PI3K/Akt pathway is pictilisib (GDC-0941) or a pharmaceutically acceptable salt thereof.

46. The method according to claim 38, wherein the cancer is selected from the group consisting of liver cancer, colon cancer, stomach cancer, lung cancer, and leukemia.

47. The method according to claim 46, wherein the cancer is colon cancer.

48. The method according to claim 38 further comprising administering 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

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radiosensitizing agent, a hormone, an anti-angiogenesis agent, and combinations thereof.

49. The method according to claim 48, wherein the additional therapeutic agent is an inhibitor of the mTOR pathway.

50. The method according to claim 49, wherein the inhibitor of the mTOR pathway is selected from the group consisting of zotarolimus (AbbVie), umirolimus (Biosensors), temsirolimus (Pfizer), sirolimus (Pfizer), sirolimus NanoCrystal (Elan Pharmaceutical Technologies), sirolimus TransDerm (TransDerm), sirolimus-PNP (Samyang), everolimus (Novartis), biolimus A9 (Biosensors), ridaforolimus (Ariad), rapamycin, TCD-10023 (Terumo), DE-109 (MacuSight), MS-R001 (MacuSight), MS-R002 (MacuSight), MS-R003 (MacuSight), Perceiva (MacuSight), XL-765 (Exelixis), quinacrine (Cleveland BioLabs), PKI-587 (Pfizer), PF-04691502 (Pfizer), GDC-0980 (Genentech and Piramed), dactolisib (Novartis), CC-223 (Celgene), PWT-33597 (Pathway Therapeutics), P-7170 (Piramal Life Sciences), LY-3023414 (Eli Lilly), INK-128 (Takeda), GDC-0084 (Genentech), DS-7423 (Daiichi Sankyo), DS-3078 (Daiichi Sankyo), CC-115 (Celgene), CBLC-137 (Cleveland BioLabs), AZD-2014 (AstraZeneca), X-480 (Xcovery), X-414 (Xcovery), EC-0371 (Endocyte), VS-5584 (Verastem), PQR-401 (Piqur), PQR-316 (Piqur), PQR-311 (Piqur), PQR-309 (Piqur), PF-06465603 (Pfizer), NV-128 (Novogen), nPT-MTOR (Biotica Technology), BC-210 (Biotica Technology), WAY-600 (Biotica Technology), WYE-354 (Biotica Technology), WYE-687 (Biotica Technology), LOR-220 (Lorus Therapeutics), HMPL-518 (Hutchison China MediTech), GNE-317 (Genentech), EC-0565 (Endocyte), CC-214 (Celgene), ABTL-0812

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(Ability Pharmaceuticals), and pharmaceutically acceptable salts thereof, and combinations thereof.

51. A method for treating or ameliorating the effects of a subject with cancer comprising:

(a) identifying a subject with cancer that is refractory to a therapy selected from the group consisting of RAF inhibitor therapy, MEK inhibitor therapy, and RAF and MEK inhibitor therapy; and

(b) administering to the subject identified in step (a) 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 an inhibitor of the PI3K/Akt pathway or a pharmaceutically acceptable salt thereof, to treat or ameliorate the effects of the cancer,

wherein the inhibitor of the PI3K/Akt pathway is selected from the group consisting of pictilisib (GDC-0941), BYL719, BKM120, PF-04691502, 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.

52. The method according to claim 51, wherein identifying a subject with cancer that is refractory to a therapy selected from the group consisting of RAF inhibitor therapy, MEK inhibitor therapy, and RAF and MEK inhibitor therapy comprises:

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(a) obtaining a biological sample from the subject; and

(b) screening the sample to determine whether the subject has a somatic BRAF mutation.

53. The method according to claim 52, wherein the screening comprises detection of a BRAF mutation using a method selected from the group consisting of PCR, sequencing, hybrid capture, in-solution capture, molecular inversion probes, and combinations thereof.

54. The method according to claim 52, wherein the screening comprises detection of a BRAF mutation using a method selected from the group consisting of a fluorescent in situ hybridization (FISH) assay, Sanger sequencing, deep sequencing, and combinations thereof.

55. The method according to claim 51, wherein the subject is a mammal.

56. The method according to claim 55, wherein the mammal is selected from the group consisting of humans, primates, farm animals, and domestic animals.

57. The method according to claim 55, wherein the mammal is a human.

58. The method according to claim 51, wherein the inhibitor of the PI3K/Akt pathway is pictilisib (GDC-0941) or a pharmaceutically acceptable salt thereof.

59. The method according to claim 51, wherein the cancer is selected from the group consisting of a cancer of the large intestine, breast cancer, pancreatic cancer, skin cancer, and endometrial cancers.

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60. The method according to claim 51 further comprising administering 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.

61. The method according to claim 60, wherein the additional therapeutic agent is an inhibitor of the mTOR pathway.

62. The method according to claim 61, wherein the inhibitor of the mTOR pathway is selected from the group consisting of zotarolimus (AbbVie), umirolimus (Biosensors), temsirolimus (Pfizer), sirolimus (Pfizer), sirolimus NanoCrystal (Elan Pharmaceutical Technologies), sirolimus TransDerm (TransDerm), sirolimus-PNP (Samyang), everolimus (Novartis), biolimus A9 (Biosensors), ridaforolimus (Ariad), rapamycin, TCD-10023 (Terumo), DE-109 (MacuSight), MS-R001 (MacuSight), MS-R002 (MacuSight), MS-R003 (MacuSight), Perceiva (MacuSight), XL-765 (Exelixis), quinacrine (Cleveland BioLabs), PKI-587 (Pfizer), PF-04691502 (Pfizer), GDC-0980 (Genentech and Piramed), dactolisib (Novartis), CC-223 (Celgene), PWT-33597 (Pathway Therapeutics), P-7170 (Piramal Life Sciences), LY-3023414 (Eli Lilly), INK-128 (Takeda), GDC-0084 (Genentech), DS-7423 (Daiichi Sankyo), DS-3078 (Daiichi Sankyo), CC-115 (Celgene), CBLC-137 (Cleveland BioLabs), AZD-2014 (AstraZeneca), X-480 (Xcovery), X-414 (Xcovery), EC-0371 (Endocyte), VS-5584 (Verastem), PQR-401 (Piqur), PQR-316 (Piqur), PQR-311 (Piqur), PQR-309 (Piqur), PF-06465603 (Pfizer), NV-128 (Novogen), nPT-MTOR

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(Biotica Technology), BC-210 (Biotica Technology), WAY-600 (Biotica Technology), WYE-354 (Biotica Technology), WYE-687 (Biotica Technology), LOR-220 (Lorus Therapeutics), HMPL-518 (Hutchison China MediTech), GNE-317 (Genentech), EC-0565 (Endocyte), CC-214 (Celgene), ABTL-0812 (Ability Pharmaceuticals), and pharmaceutically acceptable salts thereof, and combinations thereof.

63. 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 an inhibitor of the PI3K/Akt pathway or a pharmaceutically acceptable salt thereof, wherein the inhibitor of the PI3K/Akt pathway is selected from the group consisting of pictilisib (GDC-0941), BYL719, BKM120, PF-04691502, 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.

64. The pharmaceutical composition according to claim 63, wherein the subject is a mammal.

65. The pharmaceutical composition according to claim 64, wherein the mammal is selected from the group consisting of humans, primates, farm animals, and domestic animals.

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66. The pharmaceutical composition according to claim 64, wherein the mammal is a human.

67. The pharmaceutical composition according to claim 63, wherein the inhibitor of the PI3K/Akt pathway is pictilisib (GDC-0941) or a pharmaceutically acceptable salt thereof.

68. The pharmaceutical composition according to claim 63, wherein the subject with cancer has a somatic KRAS mutation or is refractory to MAPK pathway inhibitor treatment.

69. The pharmaceutical composition according to claim 63, wherein the subject with cancer has a somatic KRAS mutation and a somatic PIK3CA mutation.

70. The pharmaceutical composition according to claim 63, wherein the cancer is selected from the group consisting of a cancer of the large intestine, breast cancer, liver cancer, colon cancer, pancreatic cancer, endometrial cancers, stomach cancer, lung cancer, and leukemia.

71. The pharmaceutical composition according to claim 63, wherein the cancer is colon cancer.

72. The pharmaceutical composition according to claim 63 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.

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73. The pharmaceutical composition according to claim 72, wherein the additional therapeutic agent is an inhibitor of the mTOR pathway.

74. The pharmaceutical composition according to claim 73, wherein the inhibitor of the mTOR pathway is selected from the group consisting of zotarolimus (AbbVie), umirolimus (Biosensors), temsirolimus (Pfizer), sirolimus (Pfizer), sirolimus NanoCrystal (Elan Pharmaceutical Technologies), sirolimus TransDerm (TransDerm), sirolimus-PNP (Samyang), everolimus (Novartis), biolimus A9 (Biosensors), ridaforolimus (Ariad), rapamycin, TCD-10023 (Terumo), DE-109 (MacuSight), MS-R001 (MacuSight), MS-R002 (MacuSight), MS-R003 (MacuSight), Perceiva (MacuSight), XL-765 (Exelixis), quinacrine (Cleveland BioLabs), PKI-587 (Pfizer), PF-04691502 (Pfizer), GDC-0980 (Genentech and Piramed), dactolisib (Novartis), CC-223 (Celgene), PWT-33597 (Pathway Therapeutics), P-7170 (Piramal Life Sciences), LY-3023414 (Eli Lilly), INK-128 (Takeda), GDC-0084 (Genentech), DS-7423 (Daiichi Sankyo), DS-3078 (Daiichi Sankyo), CC-115 (Celgene), CBLC-137 (Cleveland BioLabs), AZD-2014 (AstraZeneca), X-480 (Xcovery), X-414 (Xcovery), EC-0371 (Endocyte), VS-5584 (Verastem), PQR-401 (Piqur), PQR-316 (Piqur), PQR-311 (Piqur), PQR-309 (Piqur), PF-06465603 (Pfizer), NV-128 (Novogen), nPT-MTOR (Biotica Technology), BC-210 (Biotica Technology), WAY-600 (Biotica Technology), WYE-354 (Biotica Technology), WYE-687 (Biotica Technology), LOR-220 (Lorus Therapeutics), HMPL-518 (Hutchison China MediTech), GNE-317 (Genentech), EC-0565 (Endocyte), CC-214 (Celgene), ABTL-0812 (Ability Pharmaceuticals), and pharmaceutically acceptable salts thereof, and combinations thereof.

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75. The pharmaceutical composition according to claim 63, which is in a unit dosage form comprising both anti-cancer agents.

76. The pharmaceutical composition according to claim 63 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.

77. The pharmaceutical composition according to claim 63, wherein the first and second anti-cancer agents are co-administered to the subject.

78. The pharmaceutical composition according to claim 63, wherein the first and second anti-cancer agents are administered to the subject serially.

79. The pharmaceutical composition according to claim 78, wherein the first anti-cancer agent is administered to the subject before the second anti-cancer agent.

80. The pharmaceutical composition according to claim 78, wherein the second anti-cancer agent is administered to the subject before the first anti-cancer agent.

81. 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 an inhibitor of the PI3K/Akt pathway or a pharmaceutically acceptable salt thereof

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wherein the inhibitor of the PI3K/Akt pathway is selected from the group consisting of pictilisib (GDC-0941), BYL719, BKM120, PF-04691502, 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.

82. The method according to claim 81, wherein the cancer cell is mammalian cancer cell.

83. The method according to claim 82, wherein the mammalian cancer cell is obtained from a mammal selected from the group consisting of humans, primates, farm animals, and domestic animals.

84. The method according to claim 82, wherein the mammalian cancer cell is a human cancer cell.

85. The method according to claim 81, wherein the inhibitor of the PI3K/Akt pathway is pictilisib (GDC-0941) or a pharmaceutically acceptable salt thereof.

86. The method according to claim 81, wherein the subject with cancer has a somatic KRAS mutation or is refractory to MAPK pathway inhibitor treatment.

87. The method according to claim 86, wherein the subject with cancer has a somatic KRAS mutation and a somatic PIK3CA mutation.

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88. The method according to claim 86, wherein the cancer is selected from the group consisting of a cancer of the large intestine, breast cancer, liver cancer, colon cancer, pancreatic cancer, endometrial cancers, stomach cancer, lung cancer, and leukemia.

89. The method according to claim 86, wherein the cancer is colon cancer.

90. The method according to claim 81 further comprising contacting the cancer cell with 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.

91. The method according to claim 90, wherein the additional therapeutic agent is an inhibitor of the mTOR pathway.

92. The method according to claim 91, wherein the inhibitor of the mTOR pathway is selected from the group consisting of zotarolimus (AbbVie), umirolimus (Biosensors), temsirolimus (Pfizer), sirolimus (Pfizer), sirolimus NanoCrystal (Elan Pharmaceutical Technologies), sirolimus TransDerm (TransDerm), sirolimus-PNP (Samyang), everolimus (Novartis), biolimus A9 (Biosensors), ridaforolimus (Ariad), rapamycin, TCD-10023 (Terumo), DE-109 (MacuSight), MS-R001 (MacuSight), MS-R002 (MacuSight), MS-R003 (MacuSight), Perceiva (MacuSight), XL-765 (Exelixis), quinacrine (Cleveland BioLabs), PKI-587 (Pfizer), PF-04691502 (Pfizer), GDC-0980 (Genentech and Piramed), dactolisib (Novartis), CC-223 (Celgene), PWT-33597 (Pathway Therapeutics), P-7170 (Piramal Life Sciences), LY-3023414 (Eli Lilly), INK-

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128 (Takeda), GDC-0084 (Genentech), DS-7423 (Daiichi Sankyo), DS-3078 (Daiichi Sankyo), CC-115 (Celgene), CBLC-137 (Cleveland BioLabs), AZD-2014 (AstraZeneca), X-480 (Xcovery), X-414 (Xcovery), EC-0371 (Endocyte), VS-5584 (Verastem), PQR-401 (Piqur), PQR-316 (Piqur), PQR-311 (Piqur), PQR-309 (Piqur), PF-06465603 (Pfizer), NV-128 (Novogen), nPT-MTOR (Biotica Technology), BC-210 (Biotica Technology), WAY-600 (Biotica Technology), WYE-354 (Biotica Technology), WYE-687 (Biotica Technology), LOR-220 (Lorus Therapeutics), HMPL-518 (Hutchison China MediTech), GNE-317 (Genentech), EC-0565 (Endocyte), CC-214 (Celgene), ABTL-0812 (Ability Pharmaceuticals), and pharmaceutically acceptable salts thereof, and combinations thereof.

FIG. 1

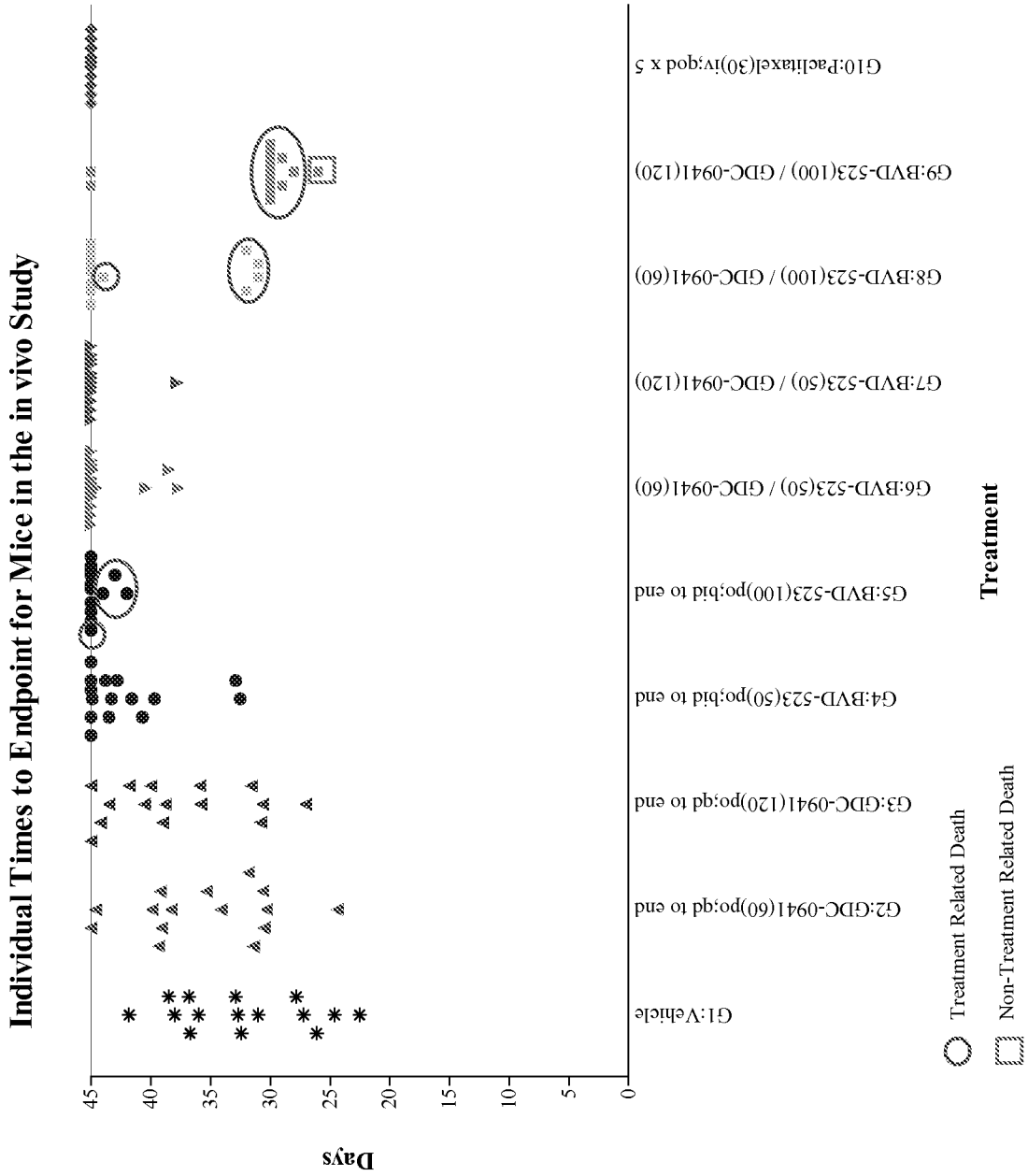
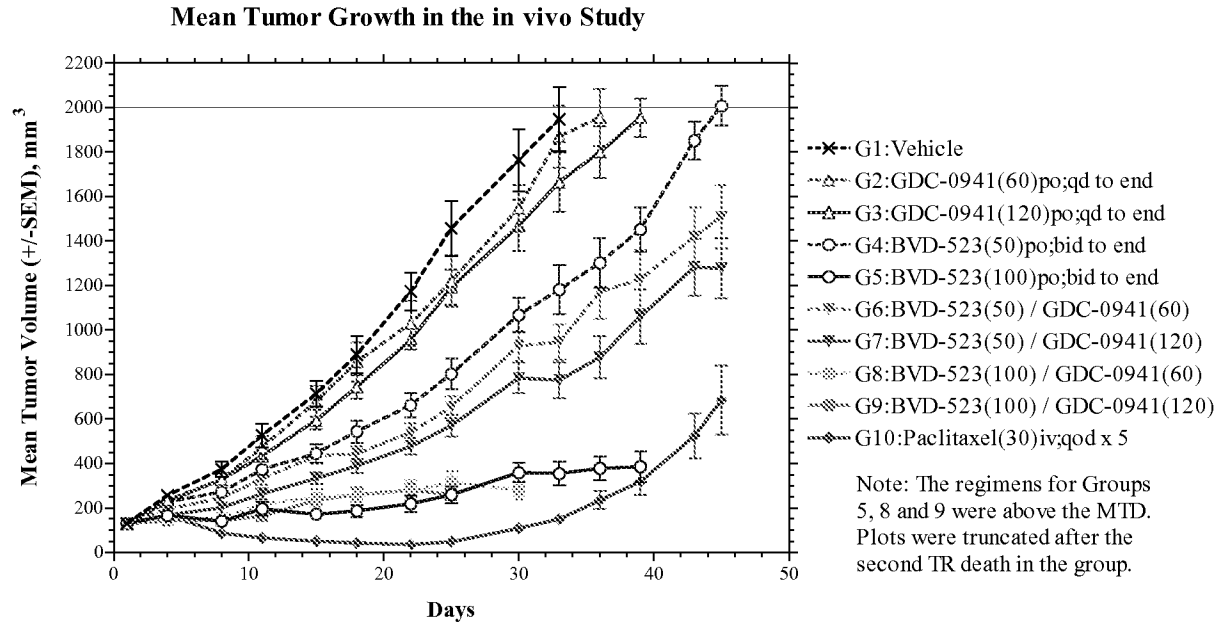

Individual Times to Endpoint for Mice in the in vivo Study
Days
0
5
10
15
20
25
30
35
40
45
G1:Vehicle
G2:GDC-0941(60)po;qd to end
G3:GDC-0941(120)po;qd to end
G4:BVD-523(50)po;bid to end
G5:BVD-523(100)po;bid to end
G6:BVD-523(50) / GDC-0941(60)
G7:BVD-523(50) / GDC-0941(120)
G8:BVD-523(100) / GDC-0941(60)
G9:BVD-523(100) / GDC-0941(120)
G10:Paclitaxel(30)iv;qod x 5
Treatment Related Death
Non-Treatment Related Death
Treatment

FIG. 2

Mean Tumor Growth and Kaplan-Meier Plot for the in vivo Study

A



B

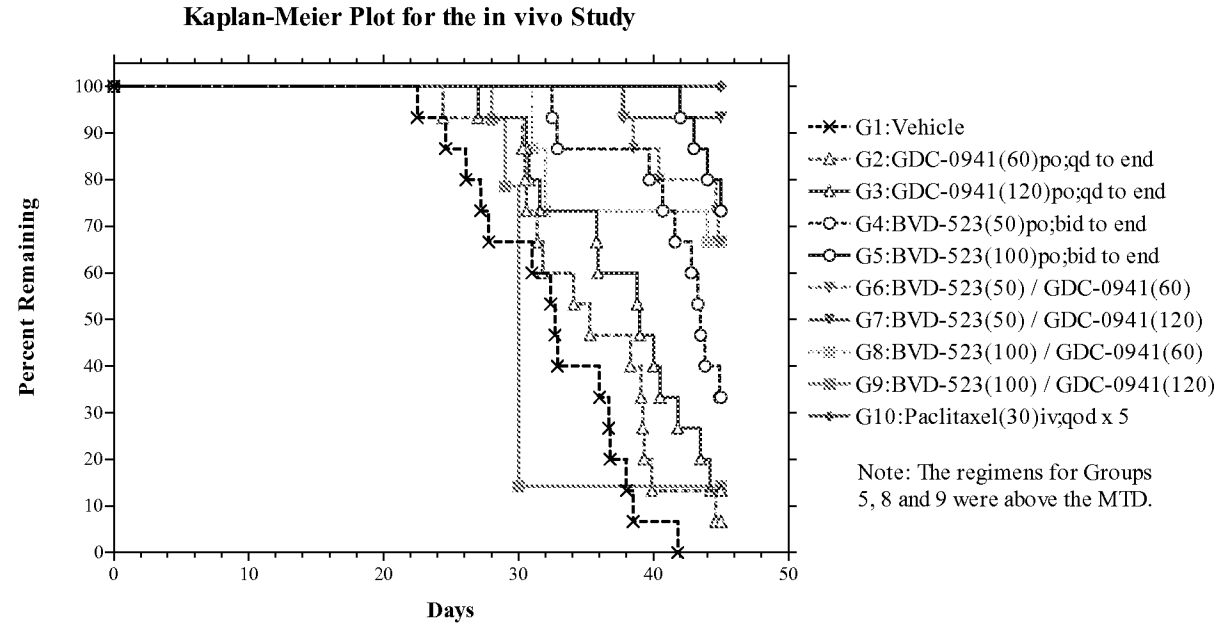


FIG. 3

Percent Mean Body Weight Changes from Day 1 in the in vivo Study

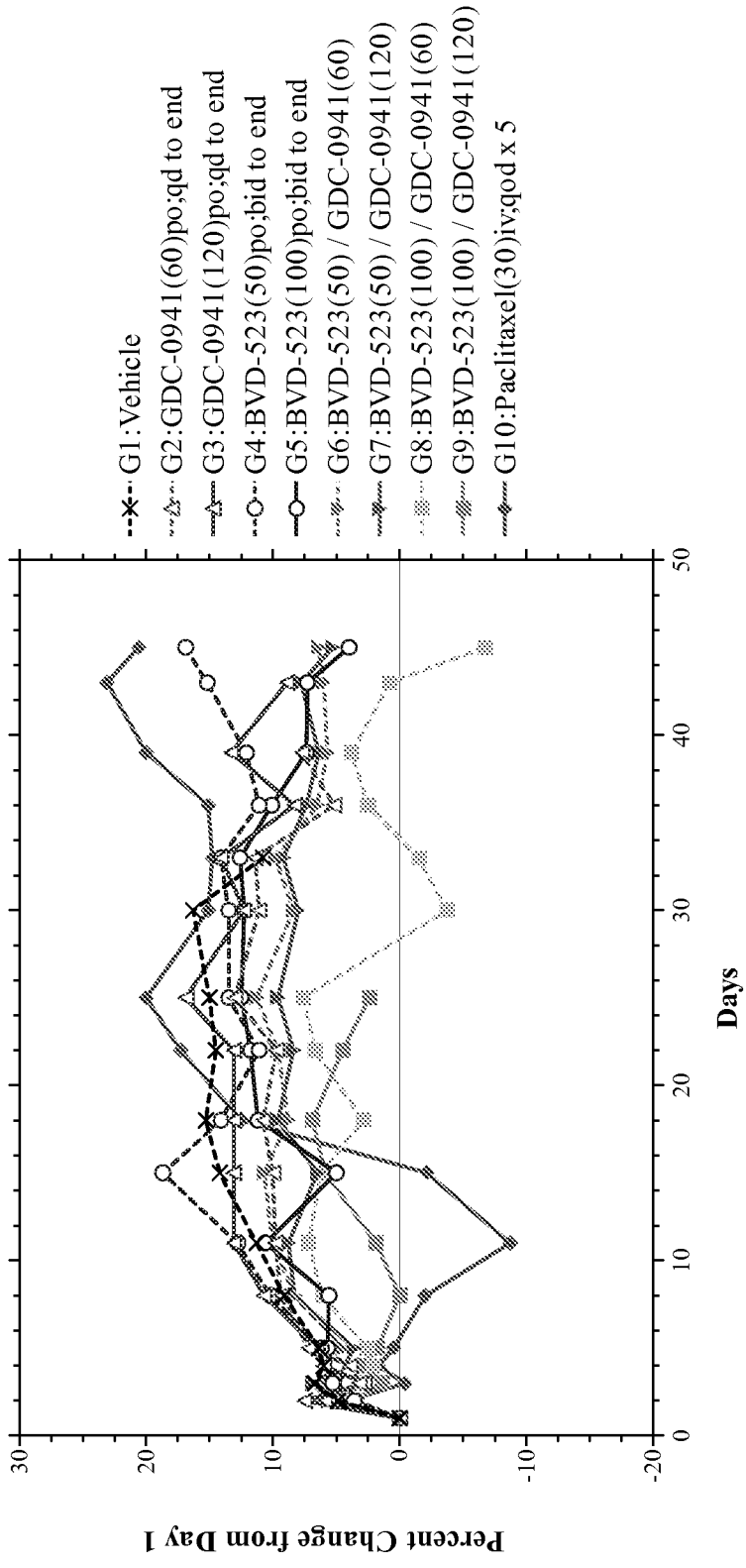


Fig. 4

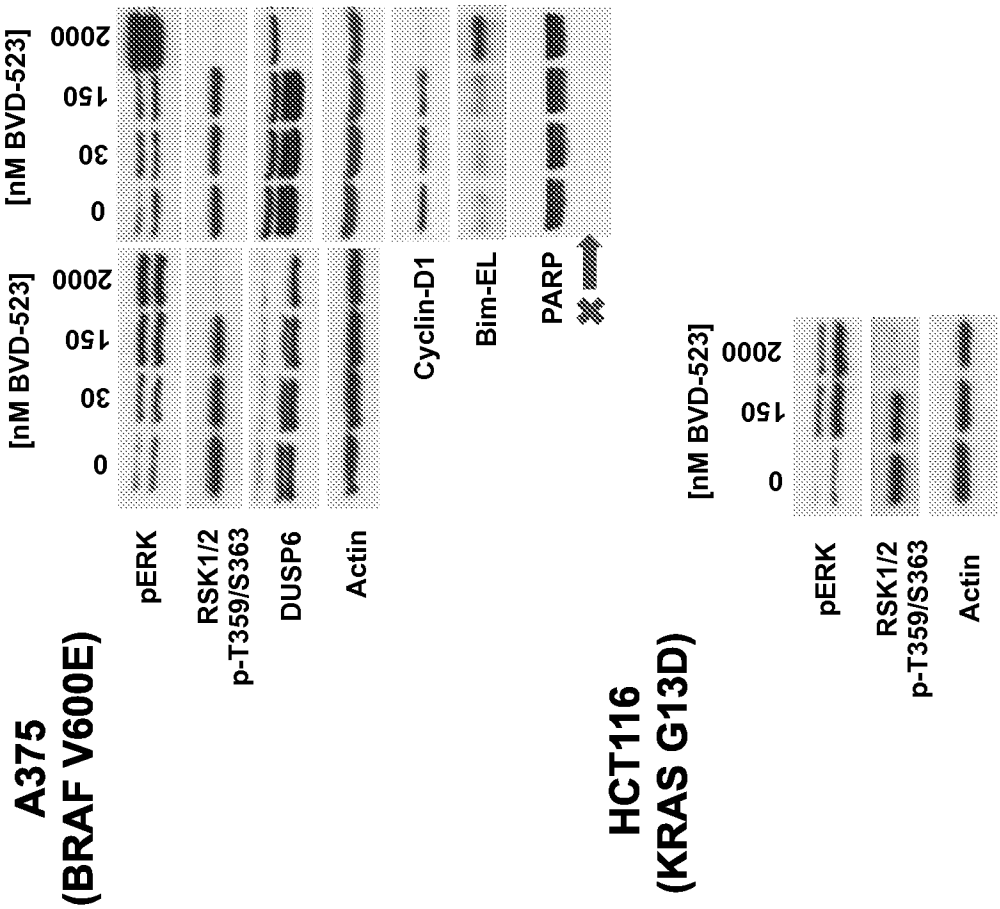

A375
(BRAF V600E)
4Hrs
24Hrs
[nM BVD-523]
0
30
150
2000
pERK
RSK1/2
p-T359/S363
DUSP6
Actin
Cyclin-D1
Bim-EL
PARP
HCT116
(KRAS G13D)
[nM BVD-523]
0
150
2000
pERK
RSK1/2
p-T359/S363
Actin

FIG. 5

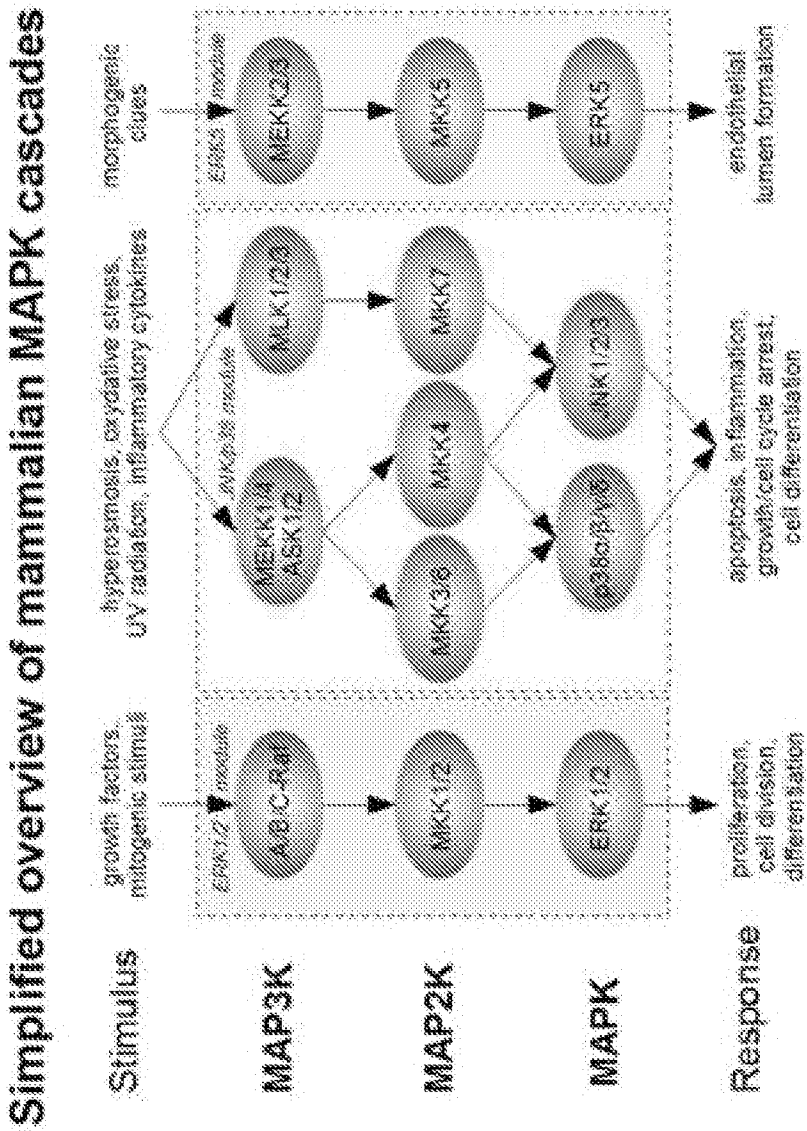

Simplified overview of mammalian MAPK cascades
Stimulus
growth factors, mitogenic stimuli
hyperosmosis, oxidative stress, UV radiation, inflammatory cytokines
morphogenic cues
MAP3K
ERK1/2 module
A-,B-,C-Raf
p38/JNK module
MEKK1/4 ASK1/2
MLK1/2/3
ERK5 module
MEKK2/3
MAP2K
MKK1/2
MKK3/6
MKK4
MKK7
MKK5
MAPK
ERK1/2
p38α/β/γ/δ
JNK1/2/3
ERK5
Response
proliferation, cell division, differentiation
apoptosis, inflammation, growth/cell cycle arrest, cell differentiation
endothelial lumen formation

FIG. 6

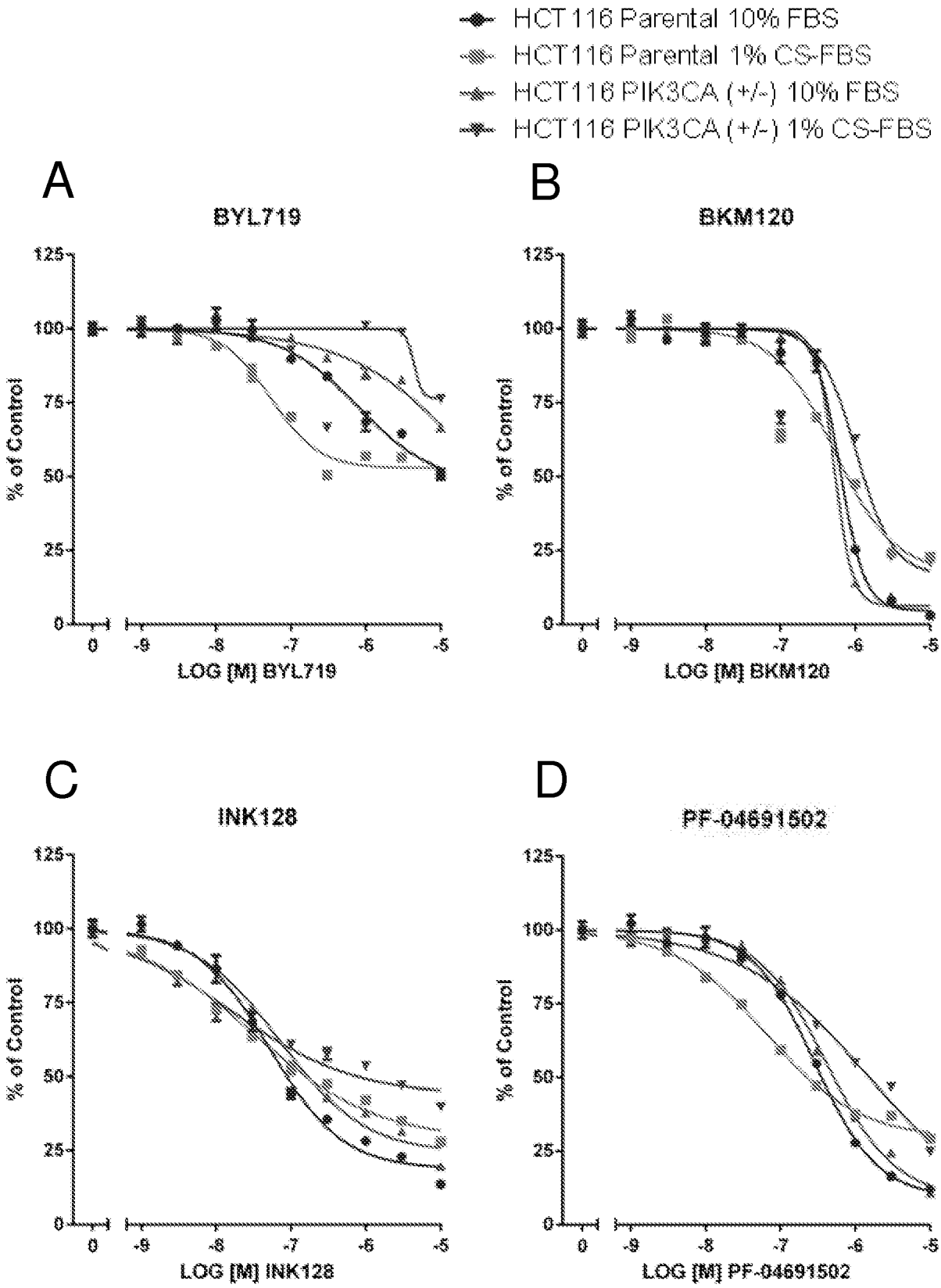

HCT116 Parental 10% FBS
HCT116 Parental 1% CS-FBS
HCT116 PIK3CA (+/-) 10% FBS
HCT116 PIK3CA (+/-) 1% CS-FBS
A
BYL719
% of Control
LOG [M] BYL719
B
BKM120
% of Control
LOG [M] BKM120
C
INK128
% of Control
LOG [M] INK128
D
PF-04691502
% of Control
LOG [M] PF-04691502

FIG. 6, Continued

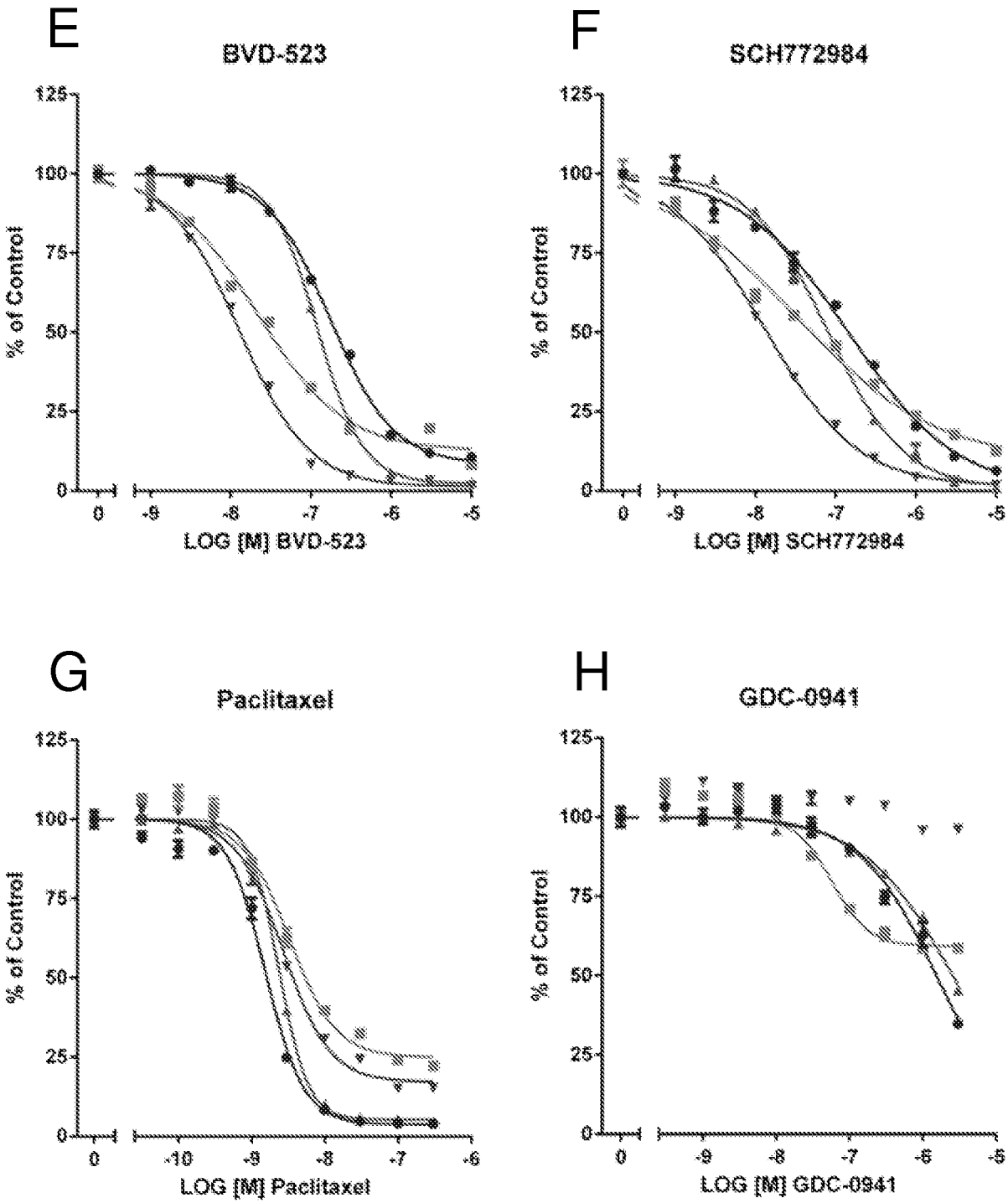


FIG. 7

A

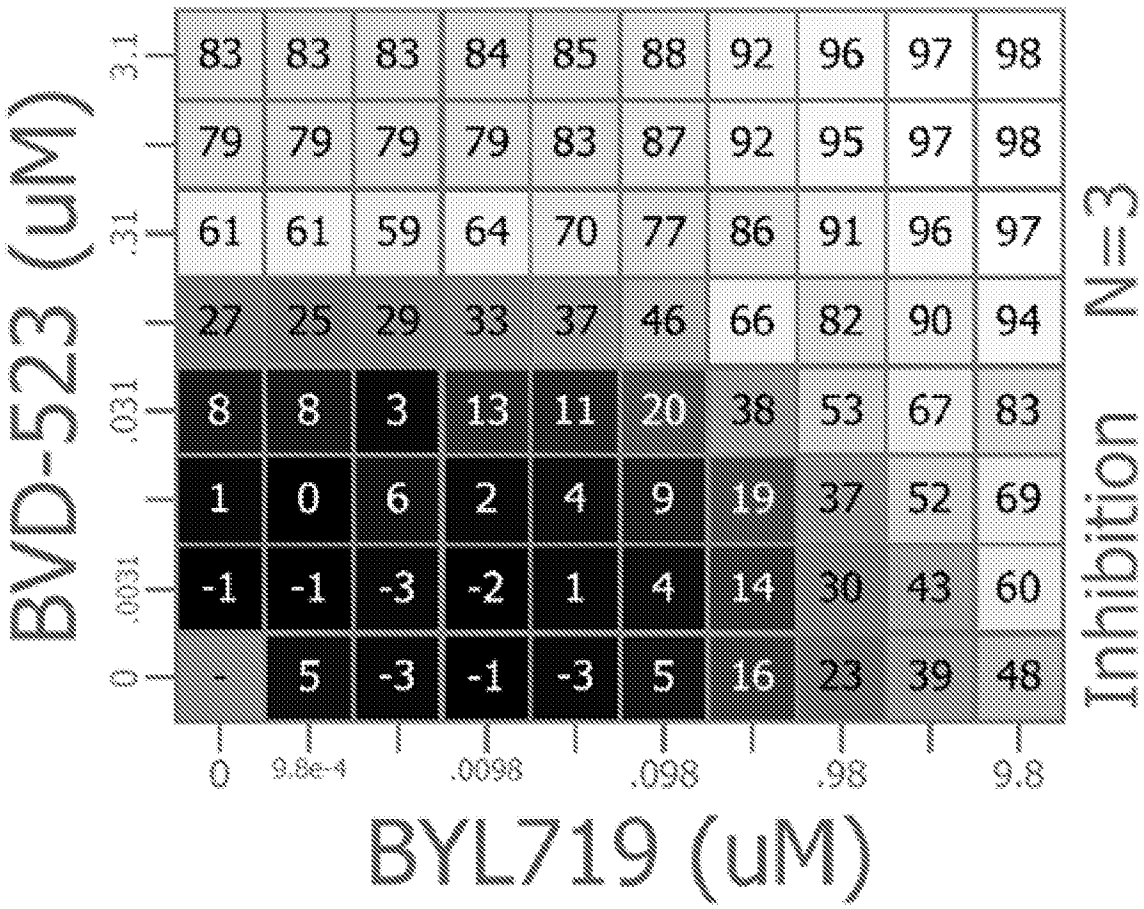

BVD-523 (uM)
3.1
.31
.031
.0031
0
83 83 83 84 85 88 92 96 97 98
79 79 79 79 83 87 92 95 97 98
61 61 59 64 70 77 86 91 96 97
27 25 29 33 37 46 66 82 90 94
8 8 3 13 11 20 38 53 67 83
1 0 6 2 4 9 19 37 52 69
-1 -1 -3 -2 1 4 14 30 43 60
- 5 -3 -1 -3 5 16 23 39 48
0
9.8e-4
.0098
.098
.98
9.8
BYL719 (uM)
Inhibition N=3

FIG. 7, Continued

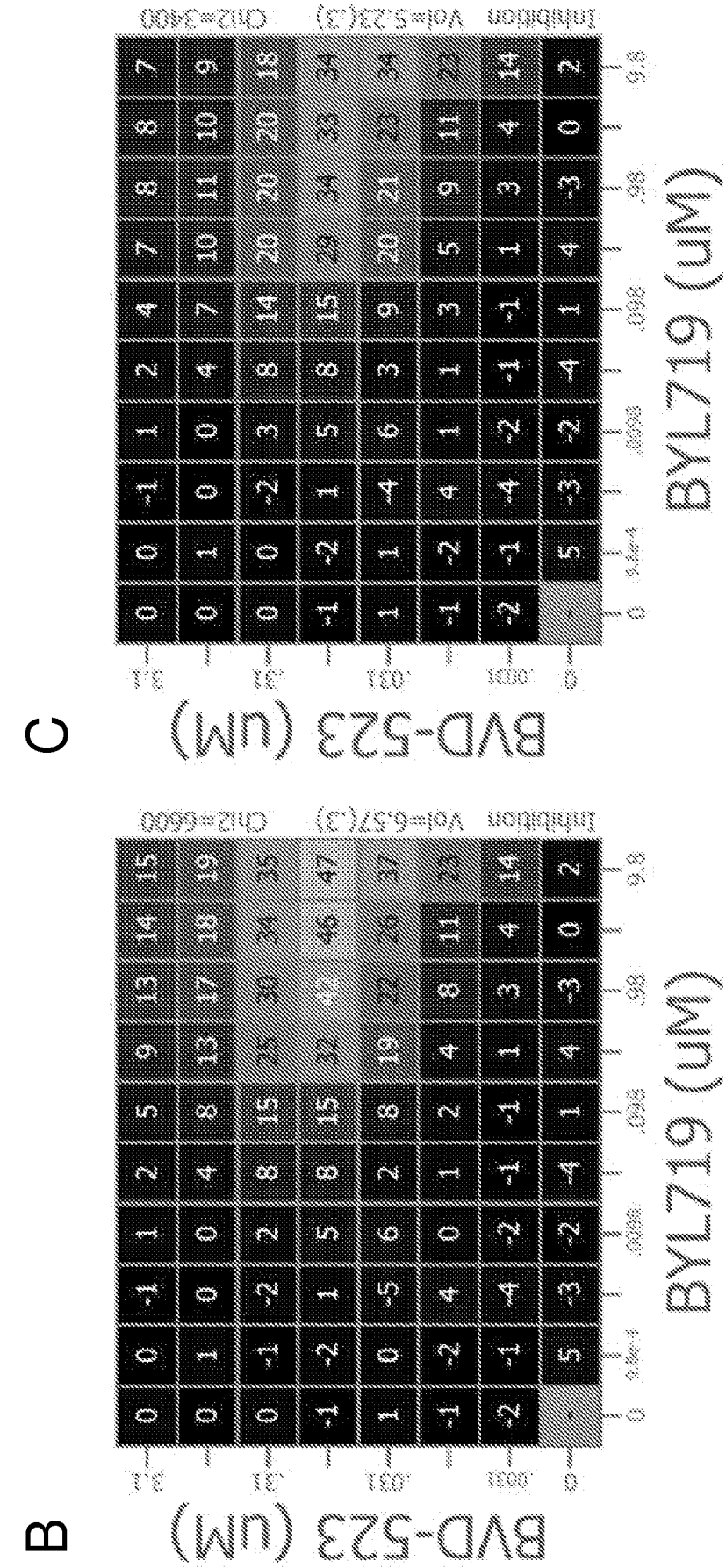


FIG. 7, Continued

D

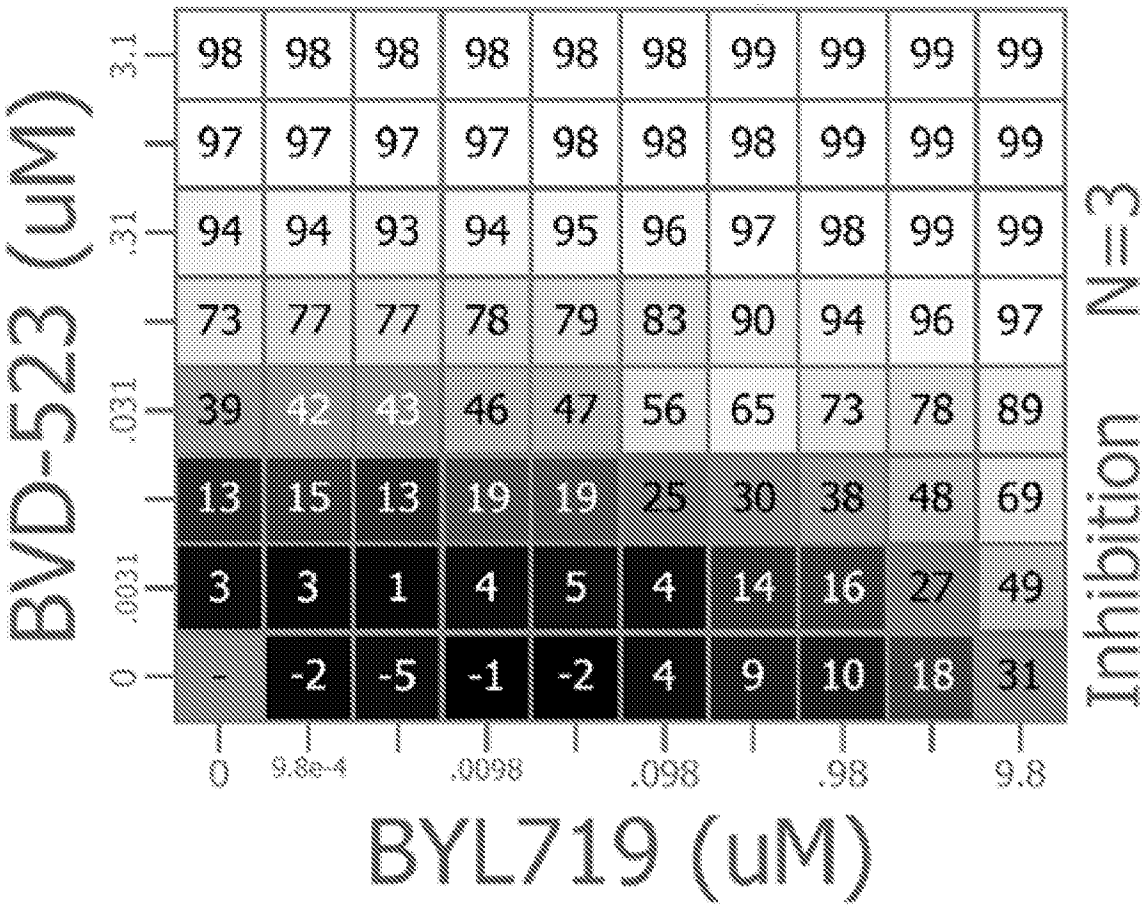


FIG. 7, Continued

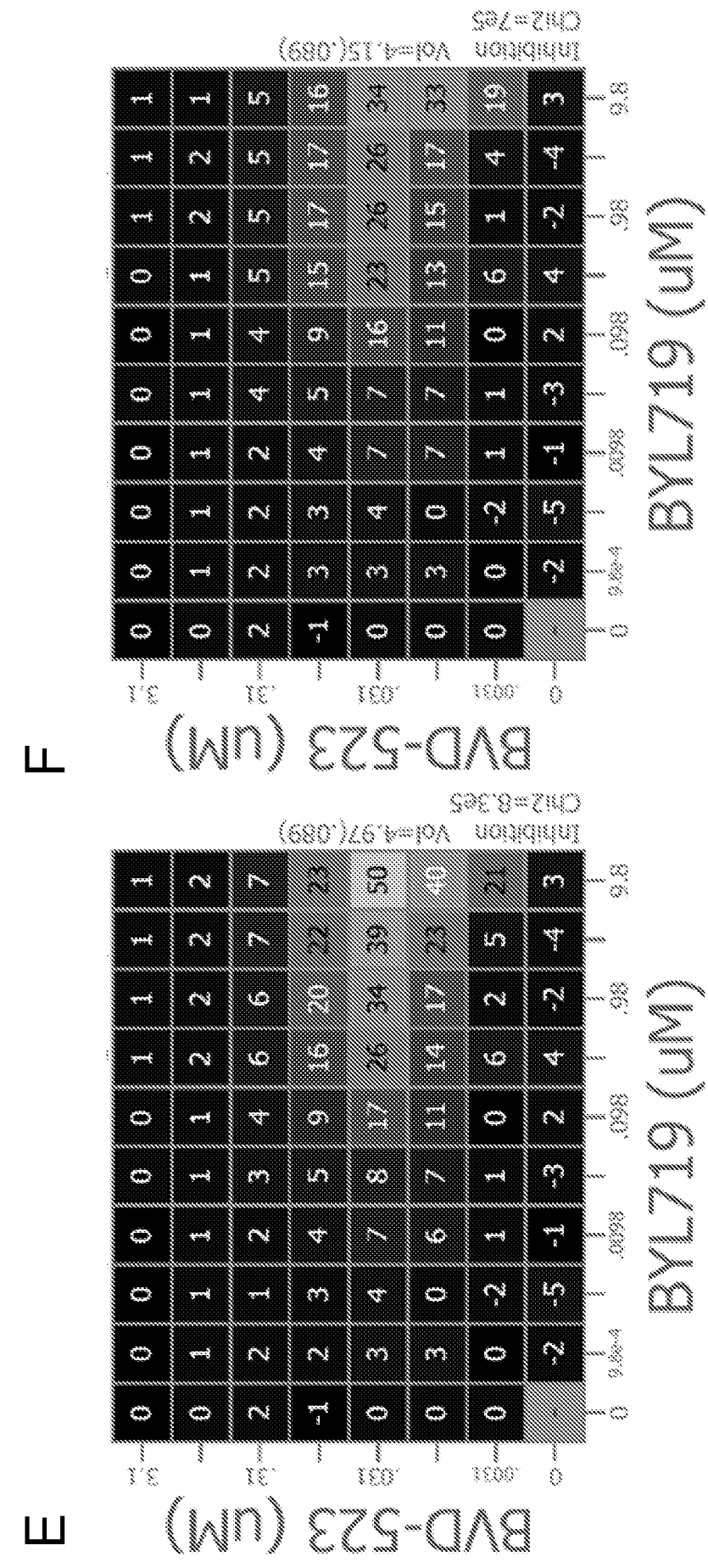
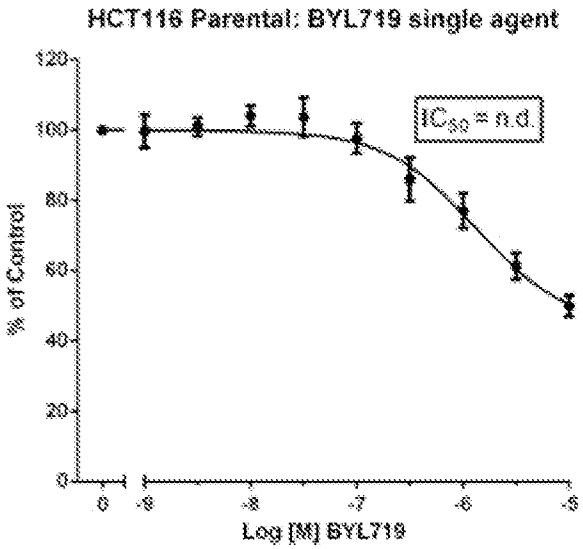
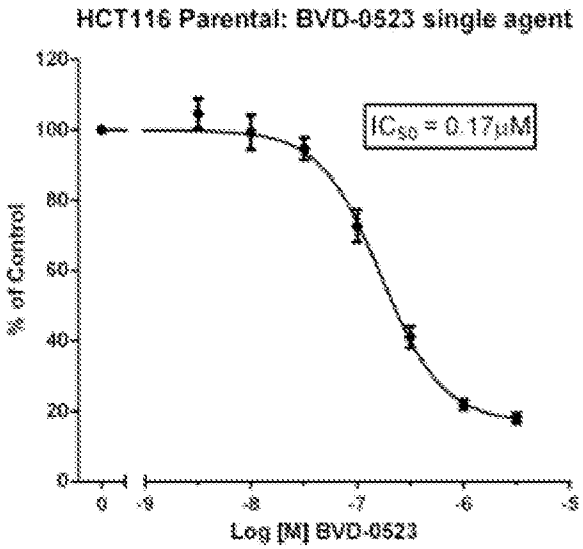


FIG. 7, Continued

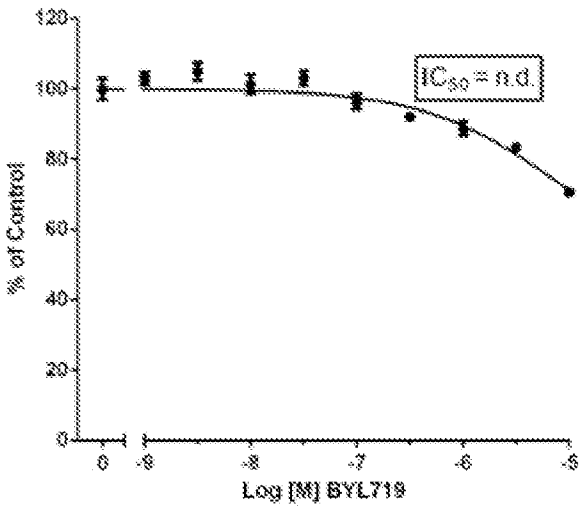
G



H



I



J

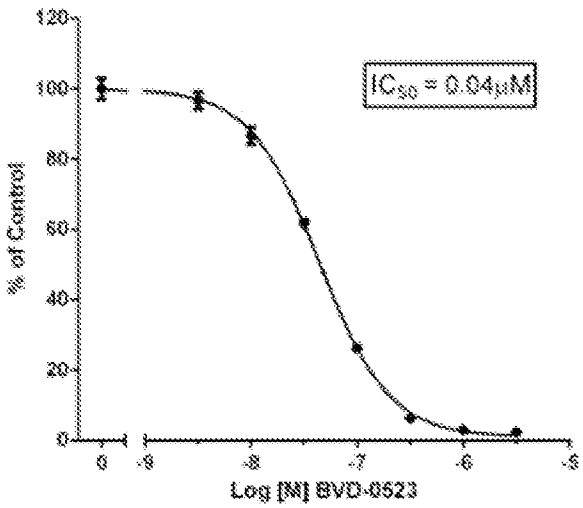


FIG. 8

A

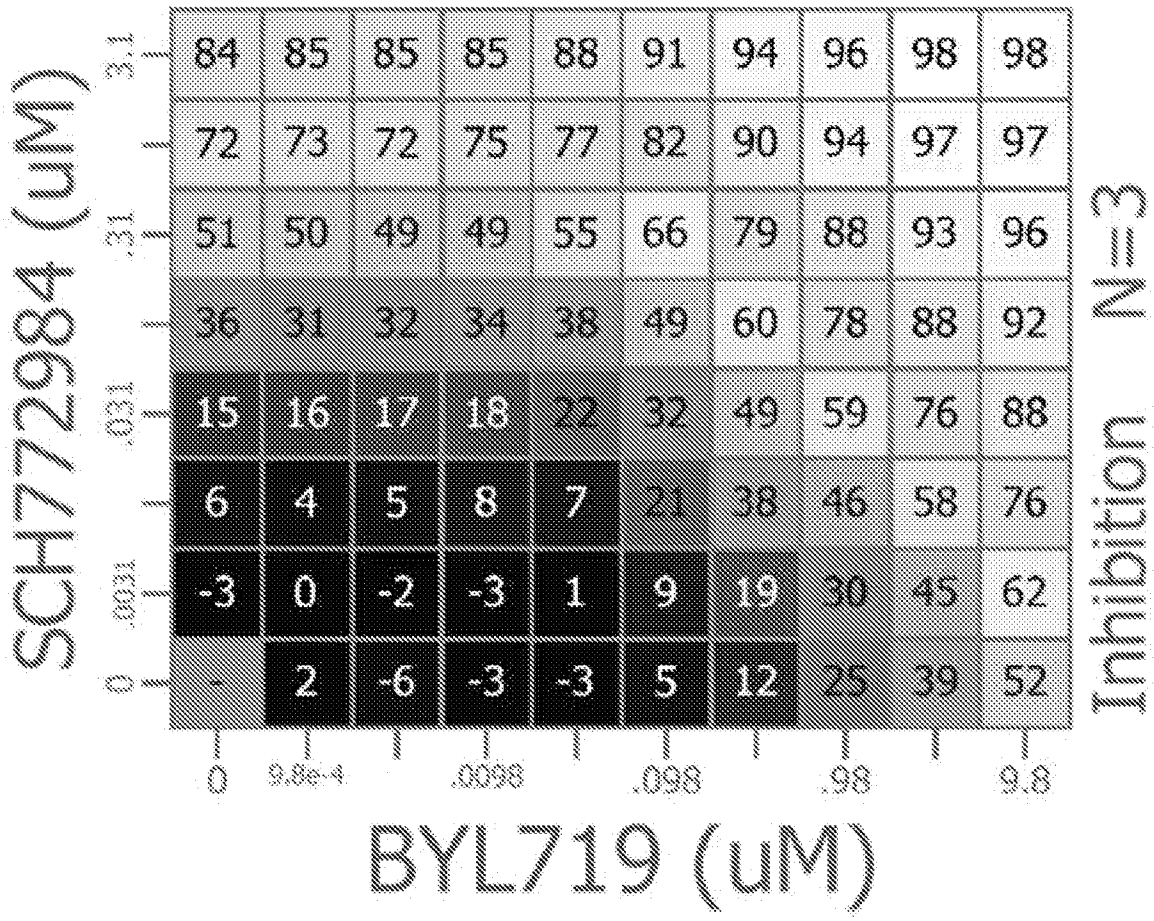

SCH772984 (uM)
3.1
.31
.031
.0031
0
84 85 85 85 88 91 94 96 98 98
72 73 72 75 77 82 90 94 97 97
51 50 49 49 55 66 79 88 93 96
36 31 32 34 38 49 60 78 88 92
15 16 17 18 22 32 49 59 76 88
6 4 5 8 7 21 38 46 58 76
-3 0 -2 -3 1 9 19 30 45 62
- 2 -6 -3 -3 5 12 25 39 52
0
9.8e-4
.0098
.098
.98
9.8
BYL719 (uM)
Inhibition N=3

FIG. 8, Continued

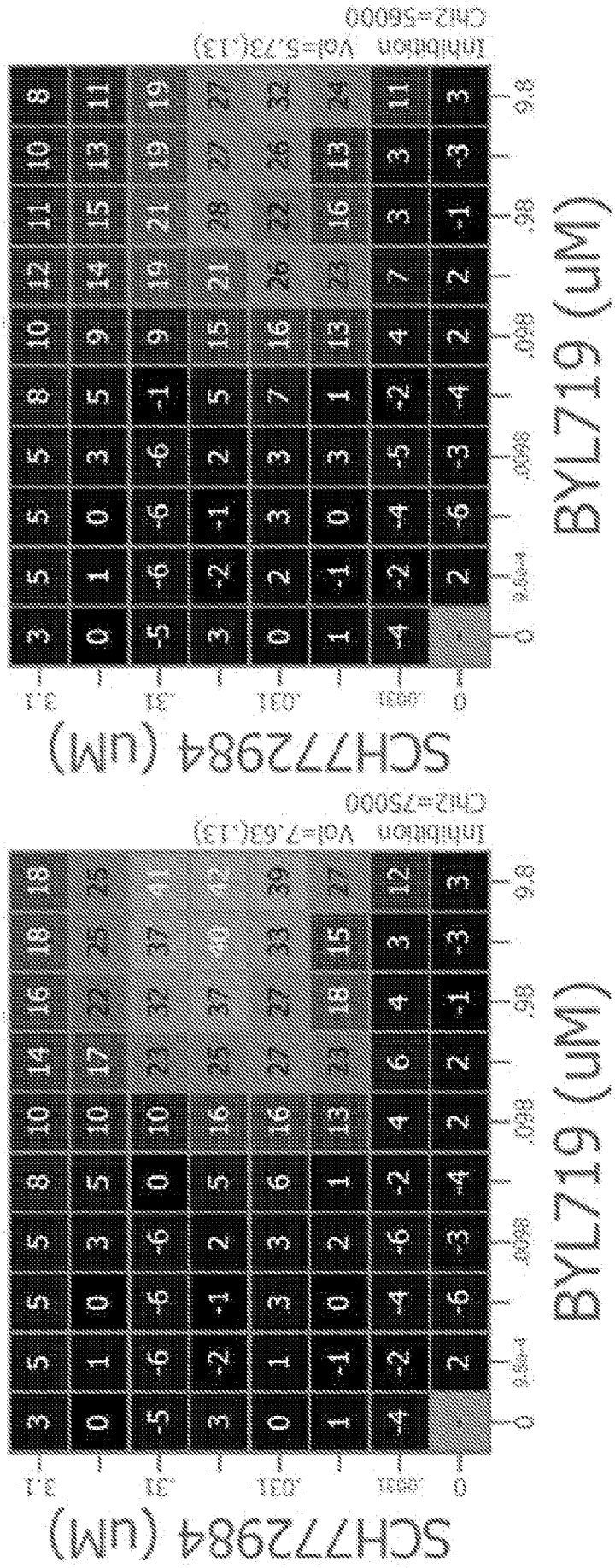


FIG. 8, Continued

D

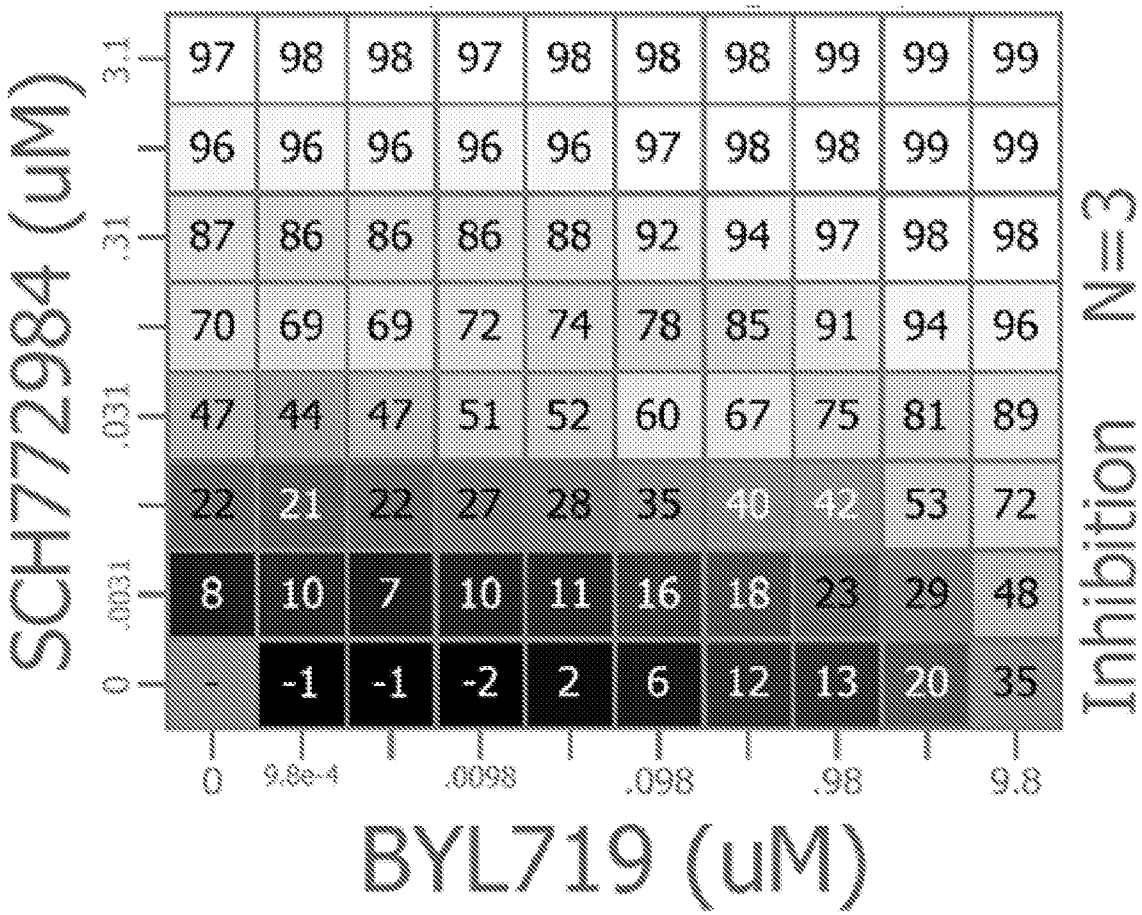
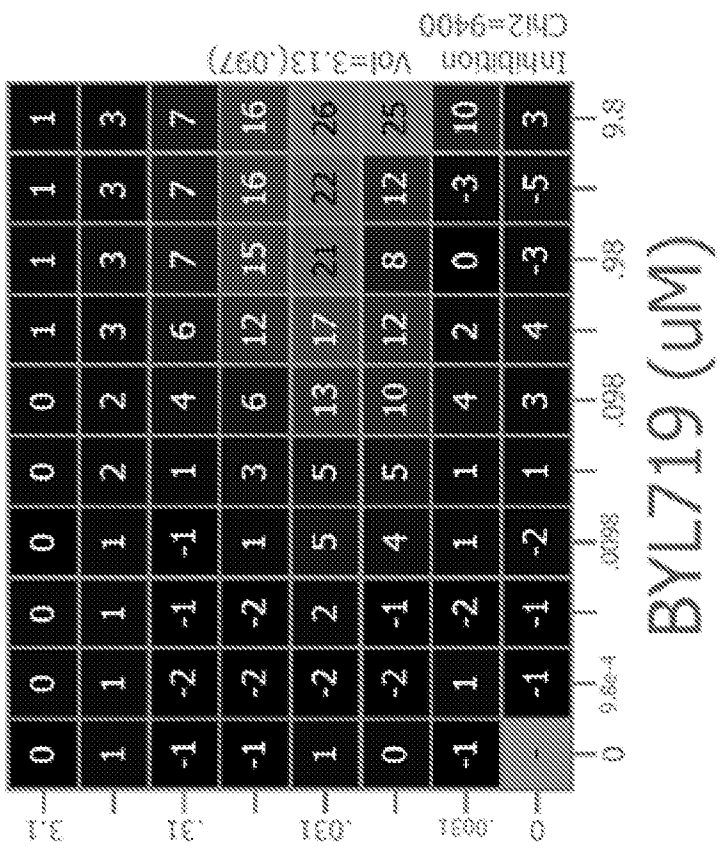


FIG. 8, Continued



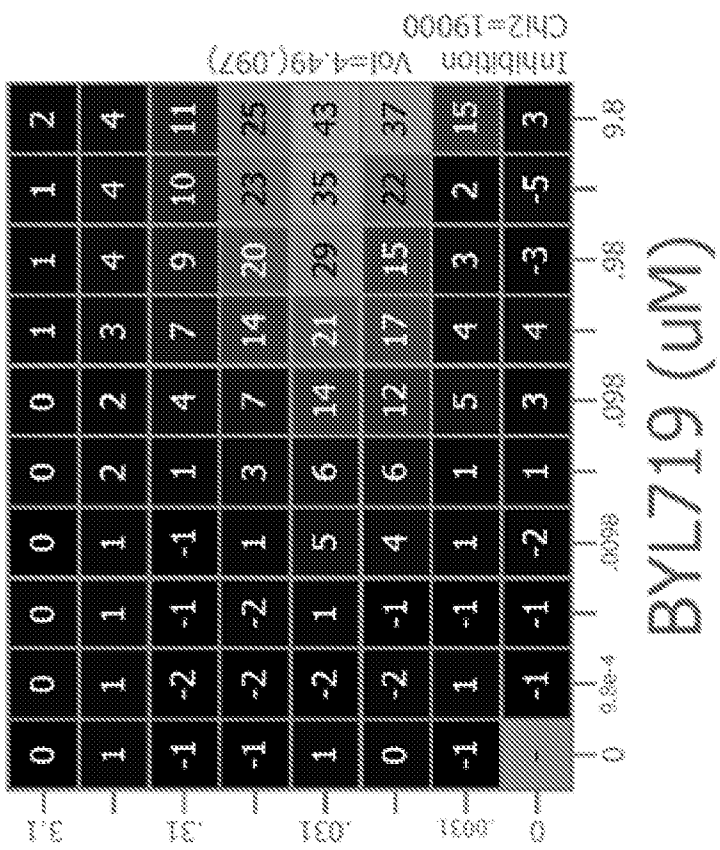
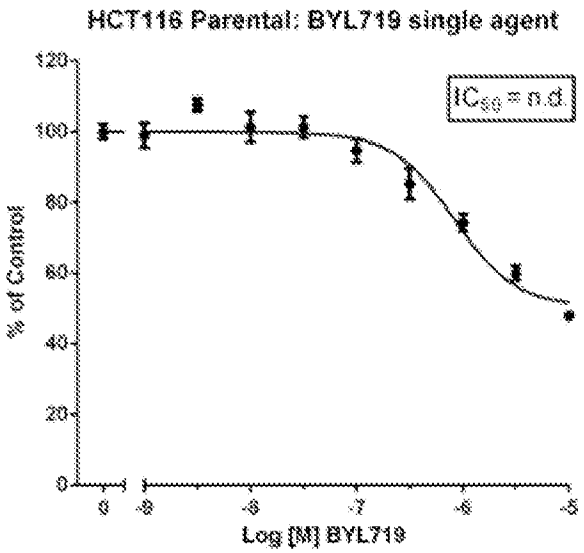
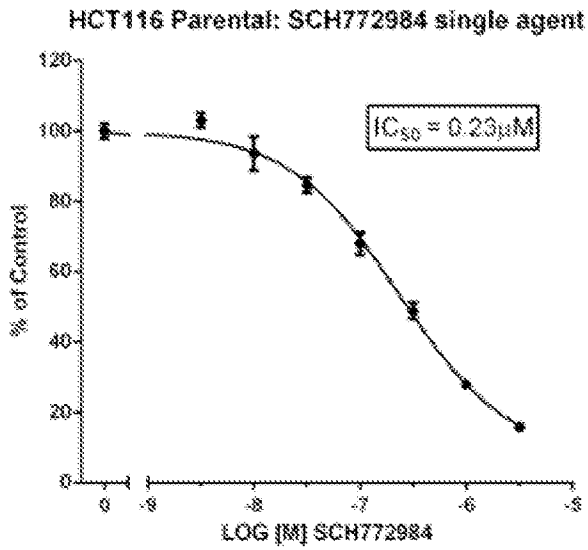


FIG. 8, Continued

G



H



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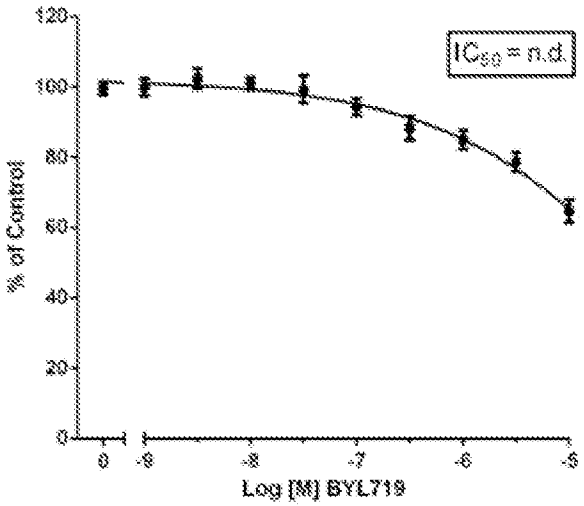

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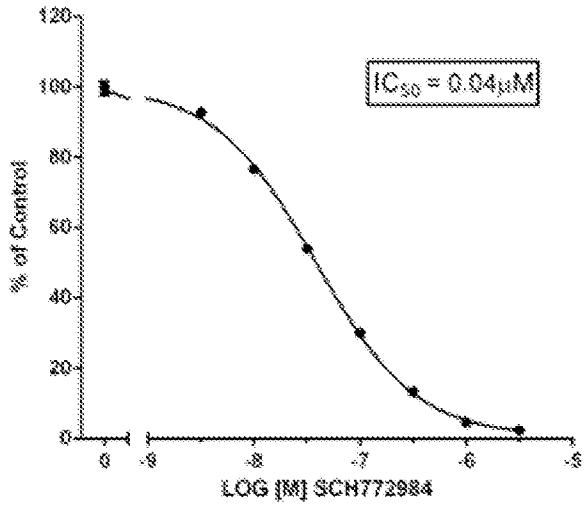
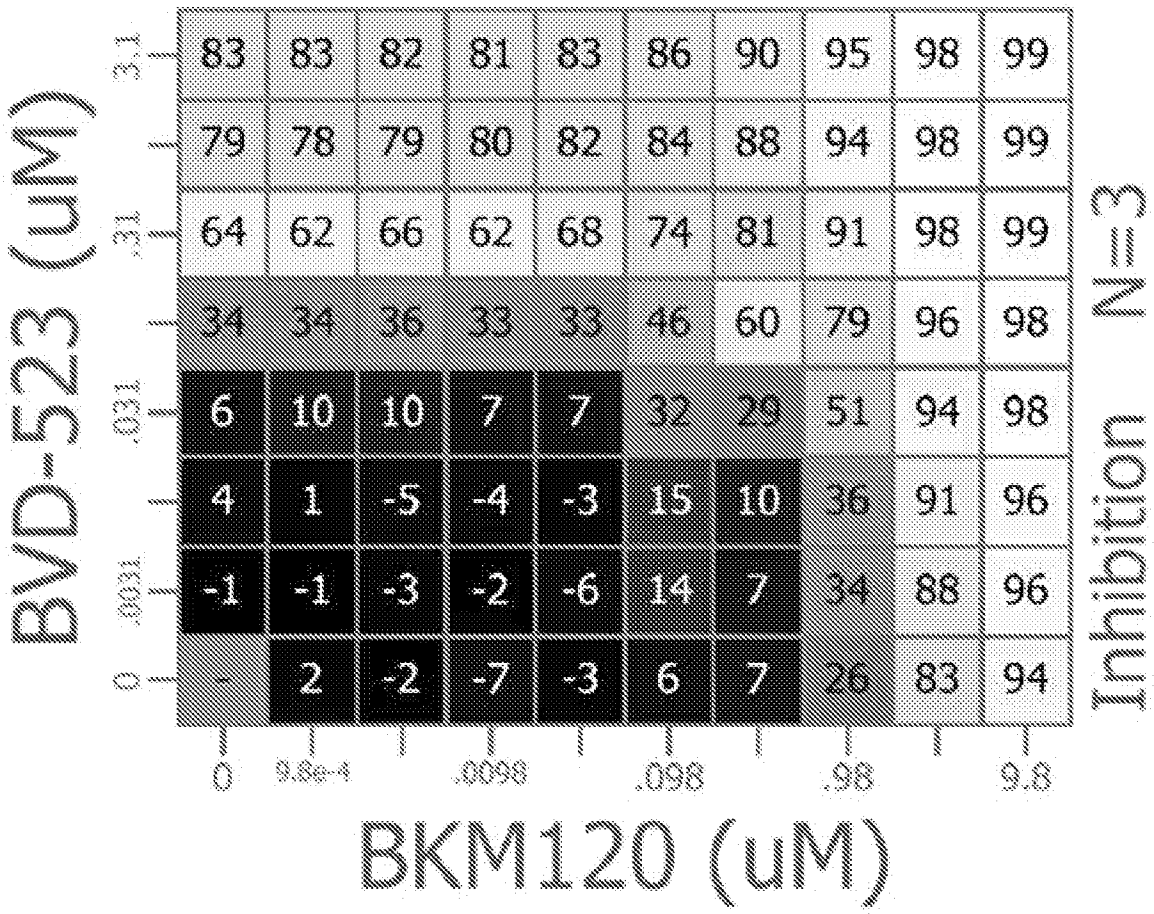


FIG. 9

A


BVD-523 (uM)
3.1
.31
.031
.0031
0
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79 78 79 80 82 84 88 94 98 99
64 62 66 62 68 74 81 91 98 99
34 34 36 33 33 46 60 79 96 98
6 10 10 7 7 32 29 51 94 98
4 1 -5 -4 -3 15 10 36 91 96
-1 -1 -3 -2 -6 14 7 34 88 96
- 2 -2 -7 -3 6 7 26 83 94
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9.8e-4
.0098
.098
.98
9.8
BKM120 (uM)
Inhibition N=3

FIG. 9, Continued

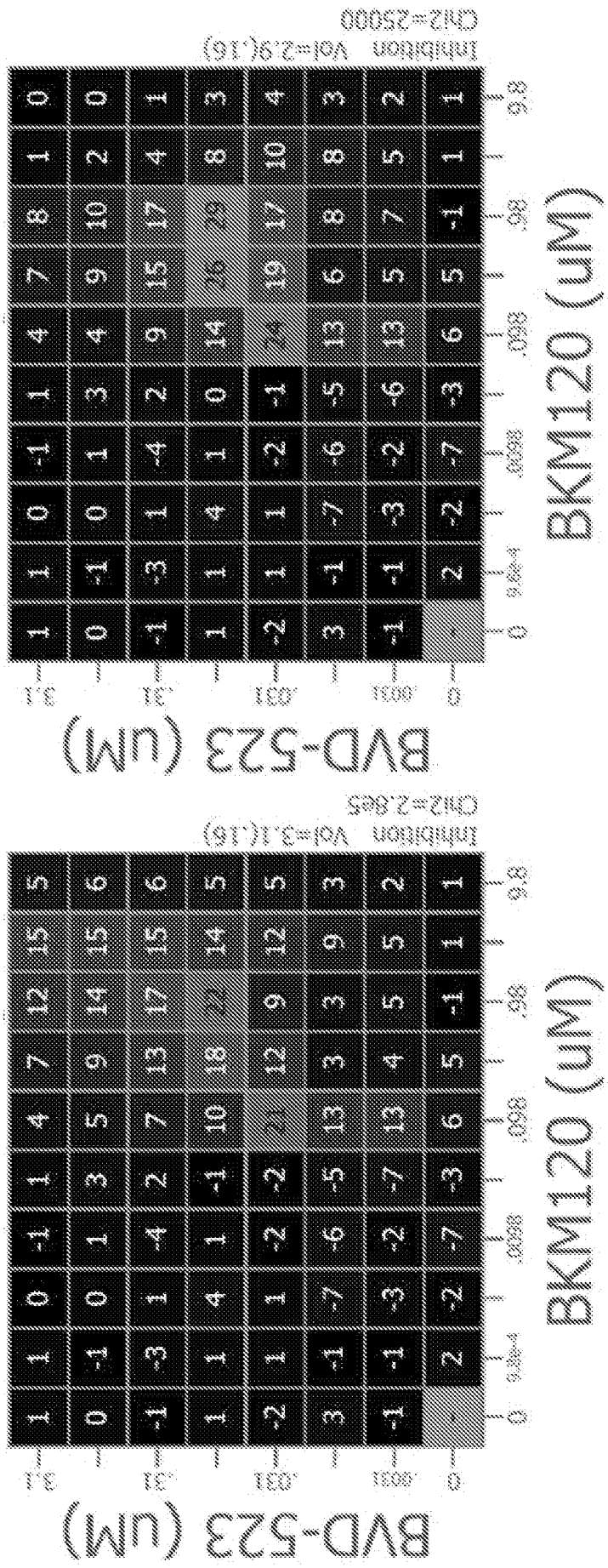


FIG. 9, Continued

D

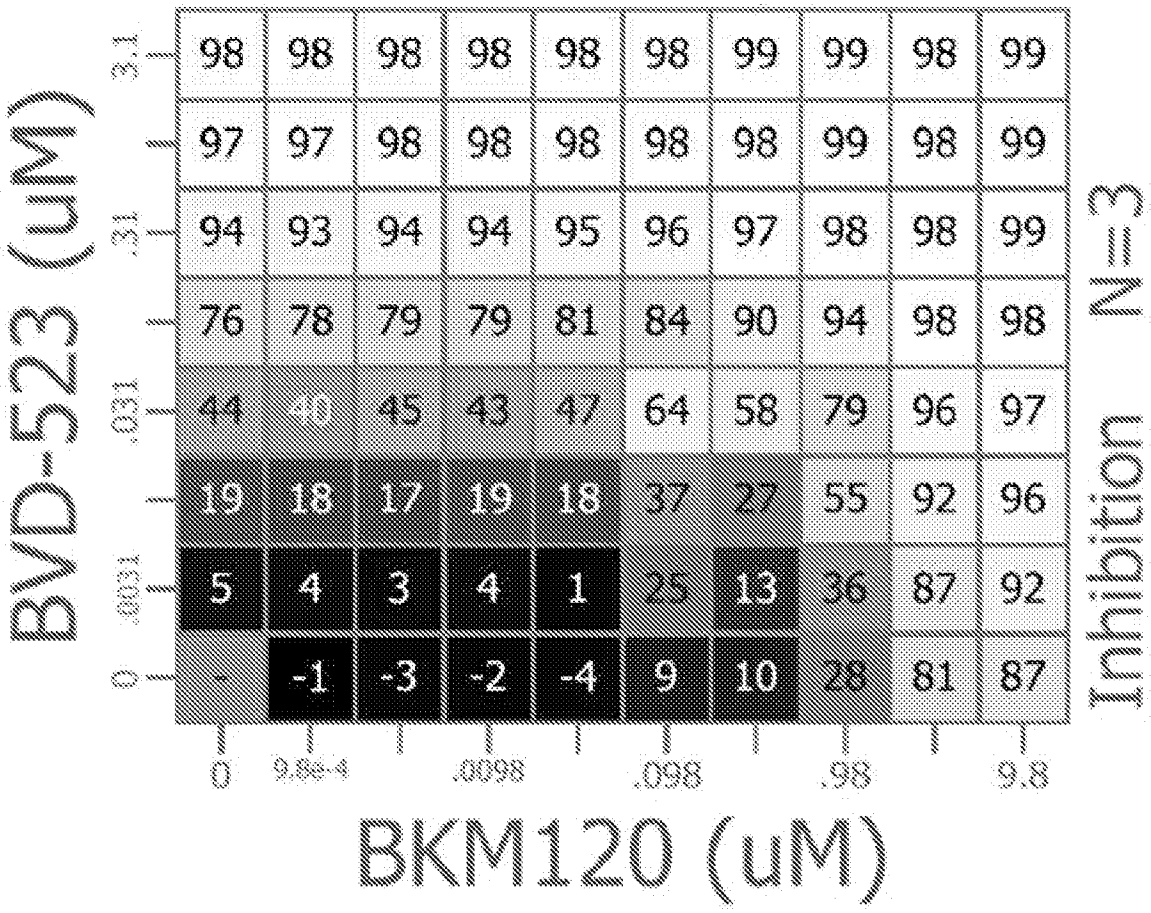
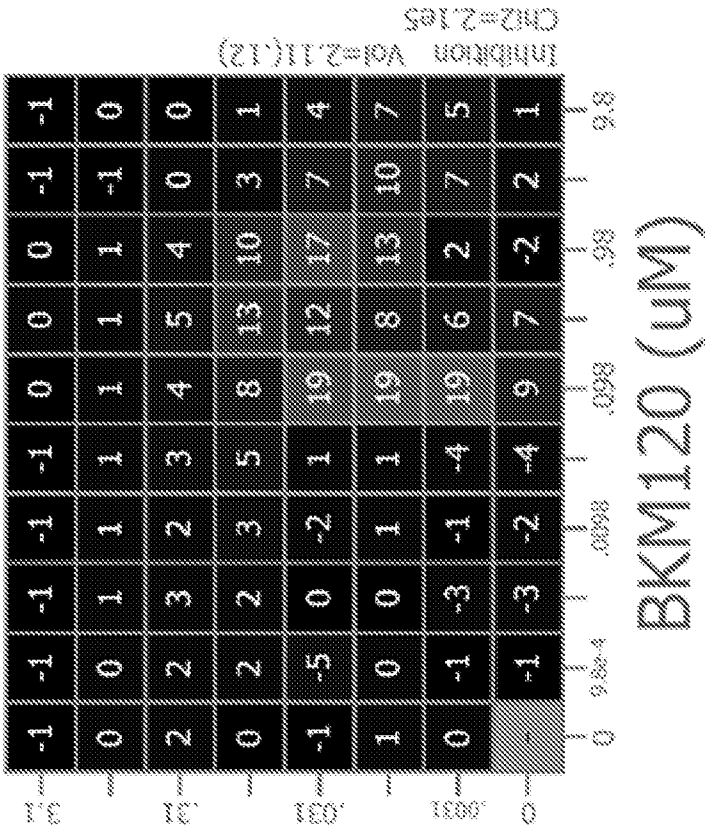


FIG. 9, Continued



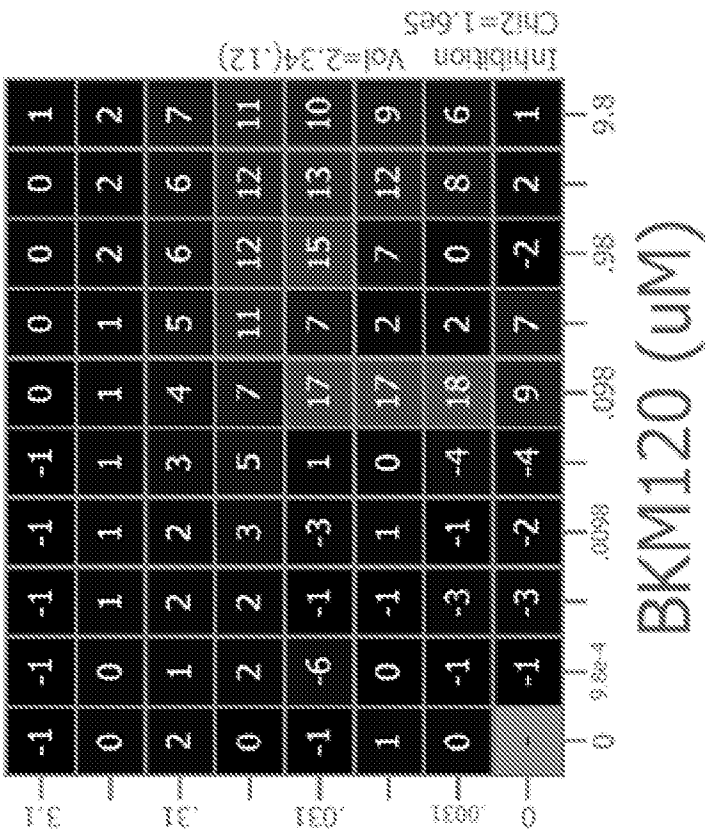
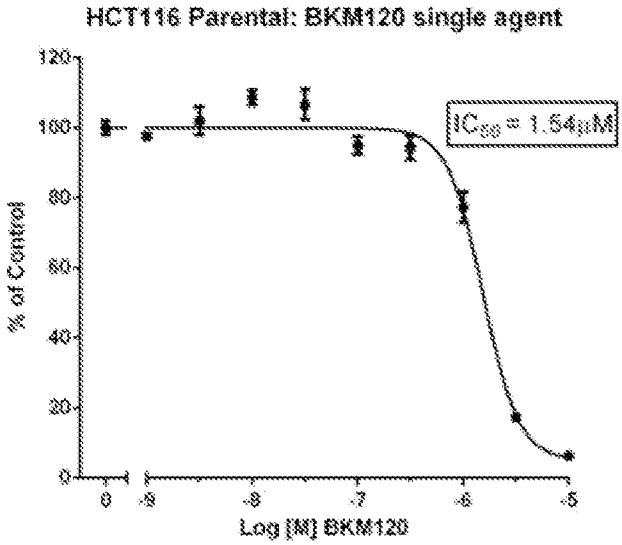


FIG. 9, Continued

G



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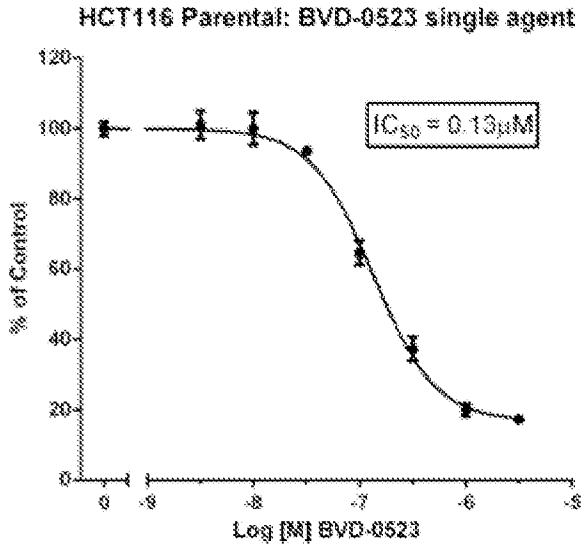

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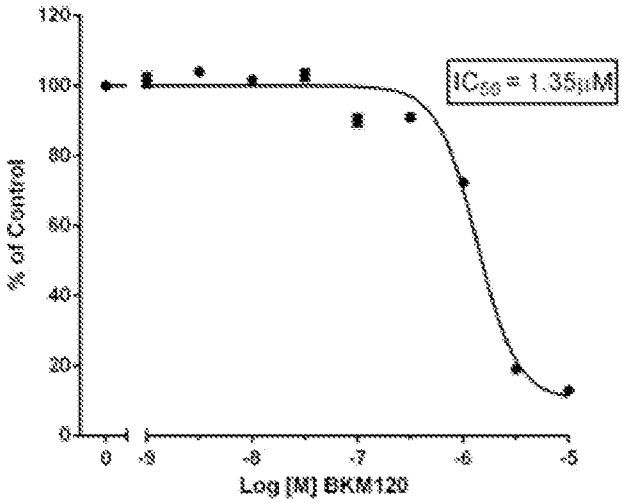

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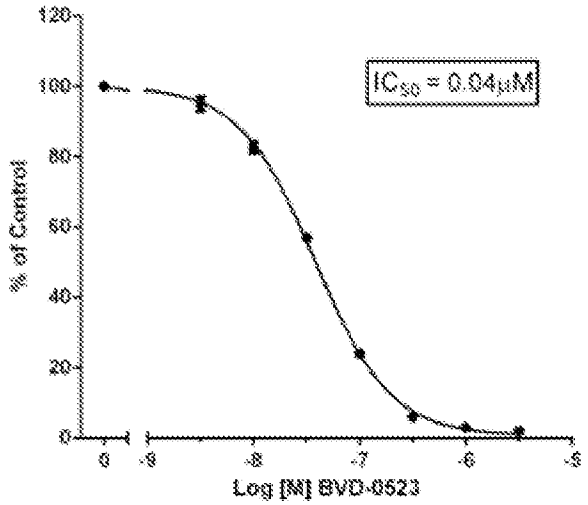


FIG. 10

A

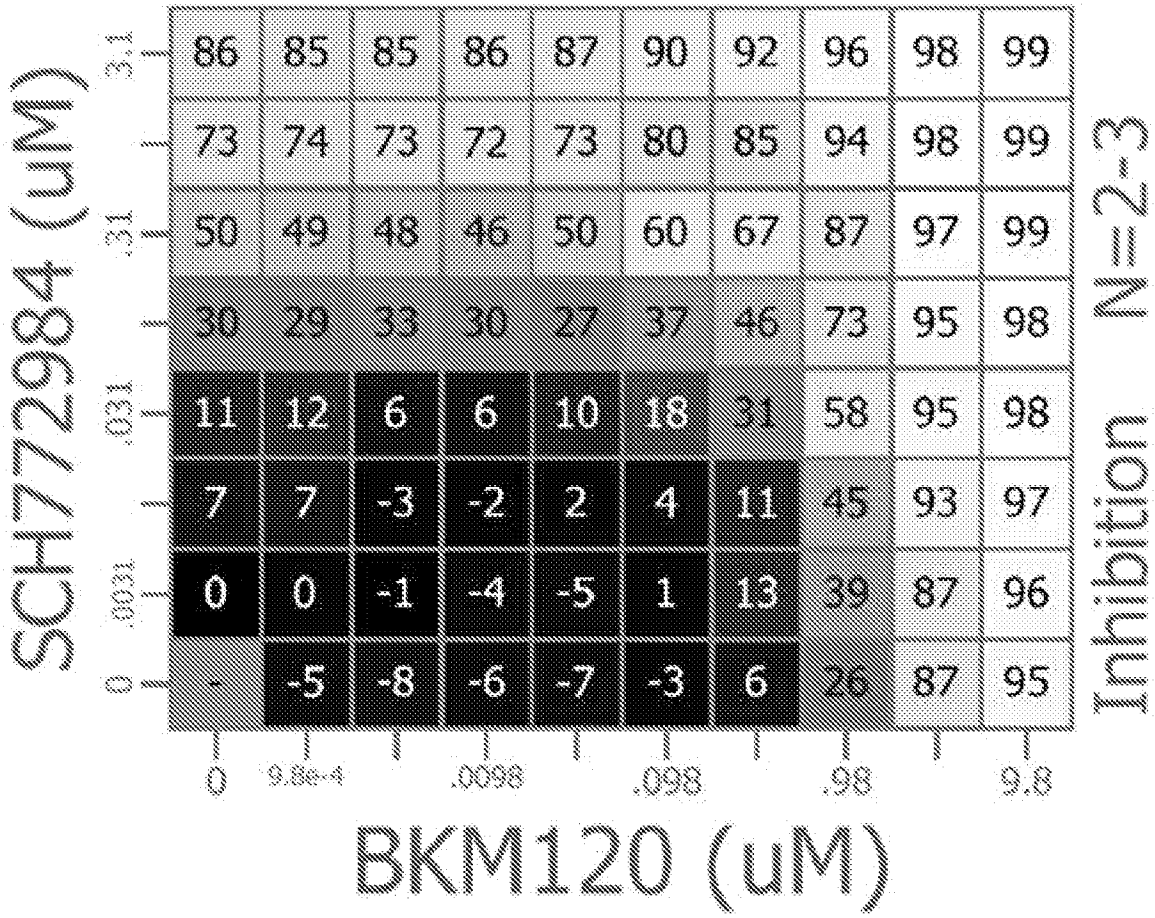

SCH772984 (uM)
3.1
.31
.031
.0031
0
86 85 85 86 87 90 92 96 98 99
73 74 73 72 73 80 85 94 98 99
50 49 48 46 50 60 67 87 97 99
30 29 33 30 27 37 46 73 95 98
11 12 6 6 10 18 31 58 95 98
7 7 -3 -2 2 4 11 45 93 97
0 0 -1 -4 -5 1 13 39 87 96
- -5 -8 -6 -7 -3 6 26 87 95
0
9.8e-4
.0098
.098
.98
9.8
BKM120 (uM)
Inhibition N=2-3

FIG. 10, Continued

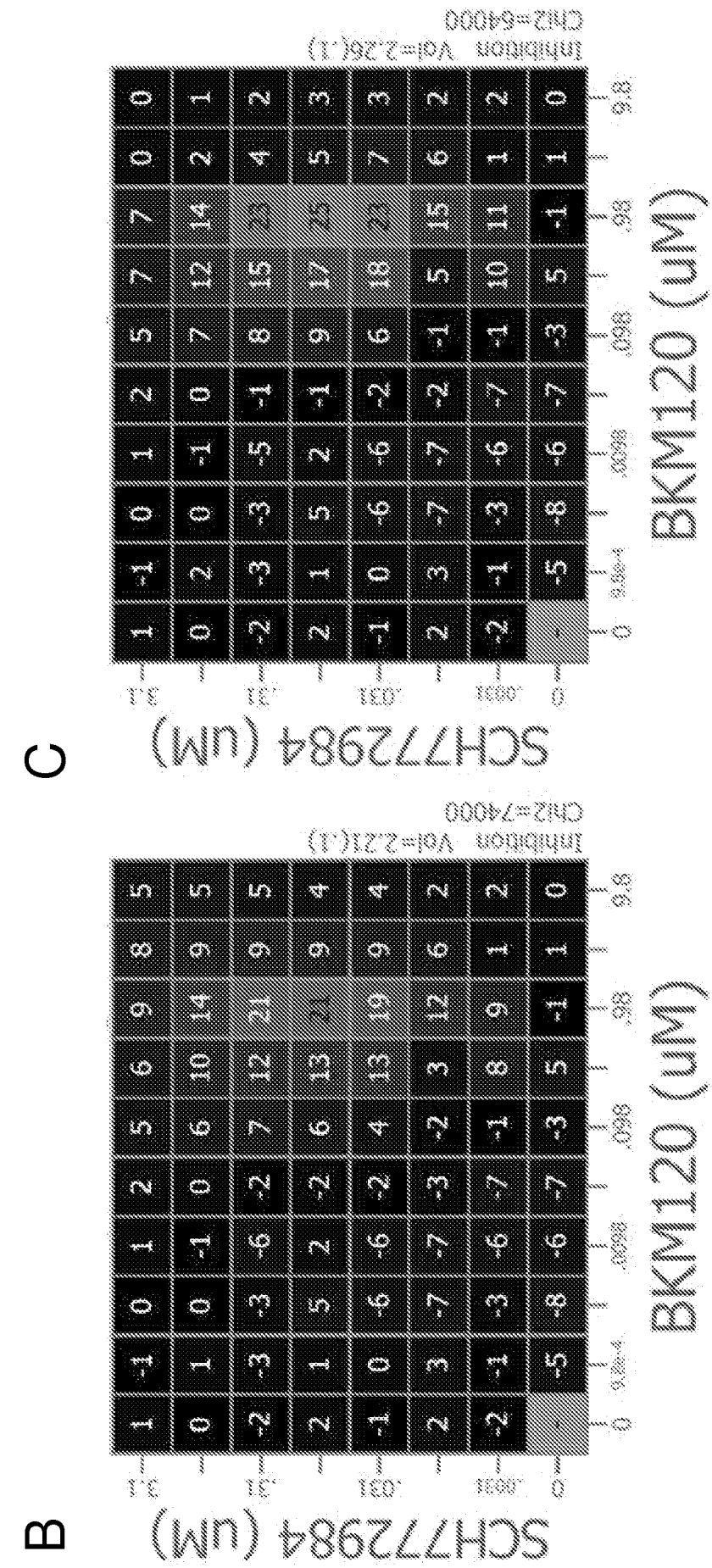


FIG. 10, Continued

D

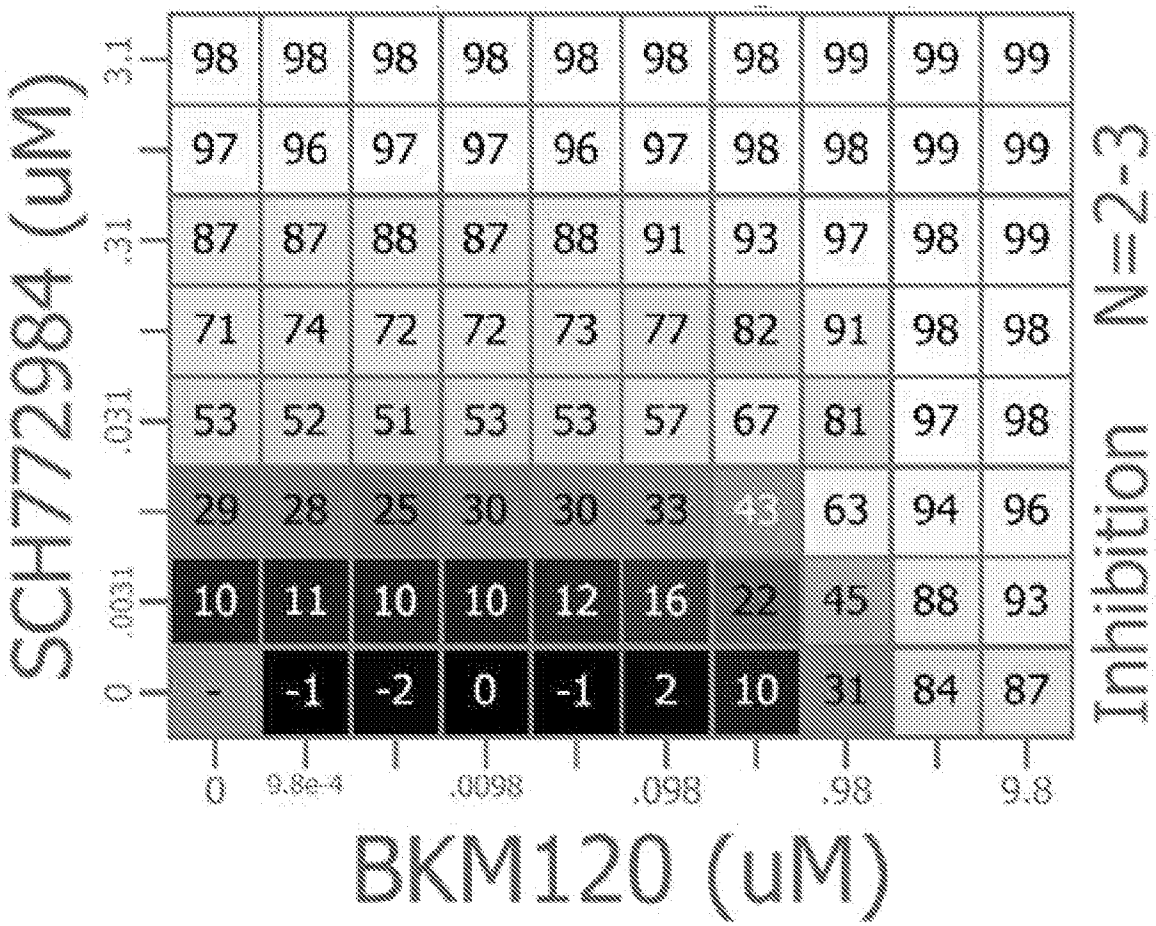


FIG. 10, Continued

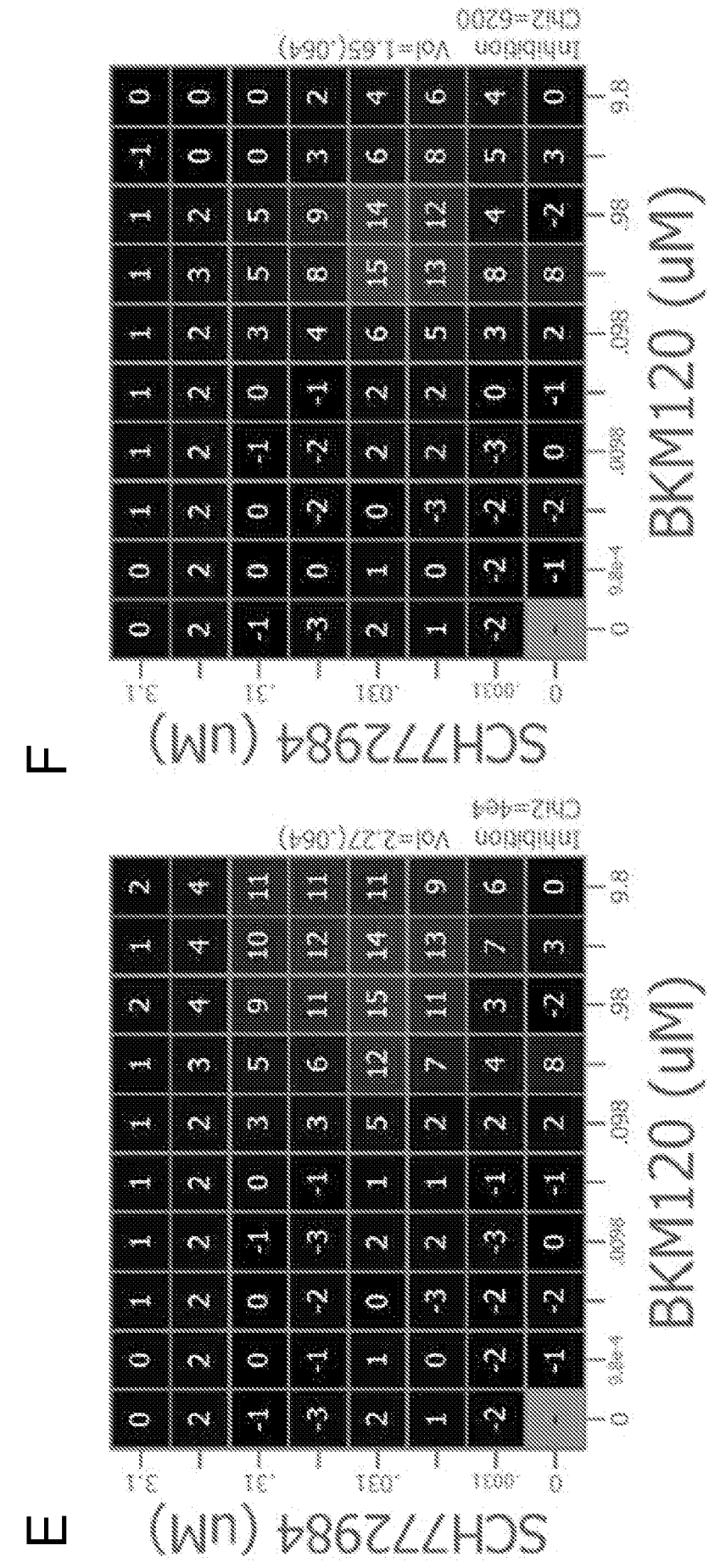
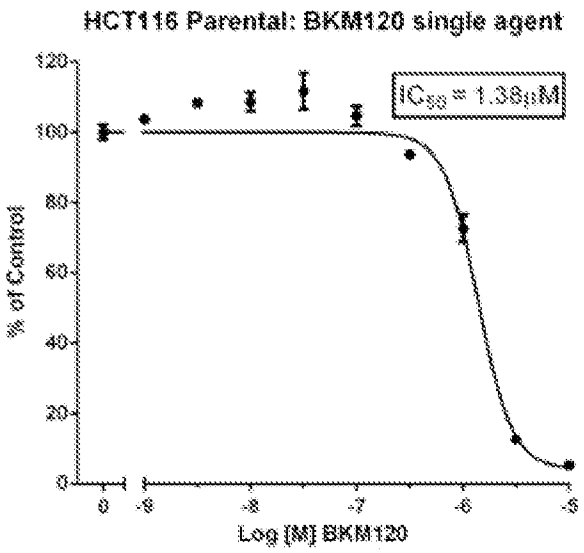
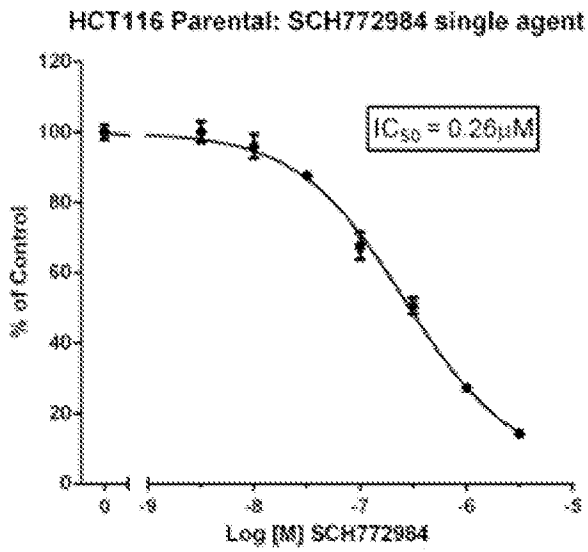


FIG. 10, Continued

G



H



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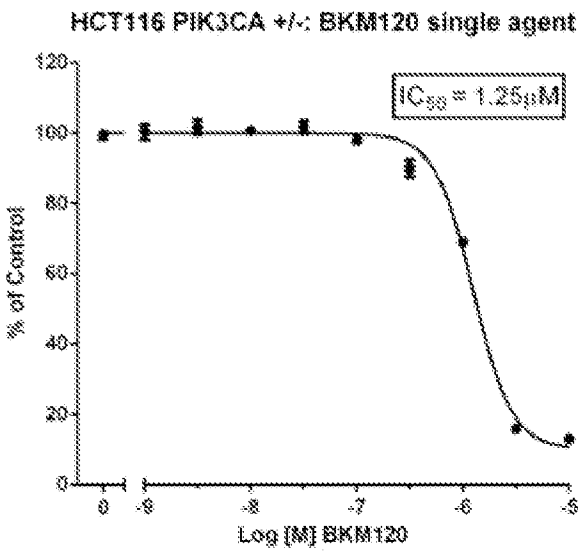

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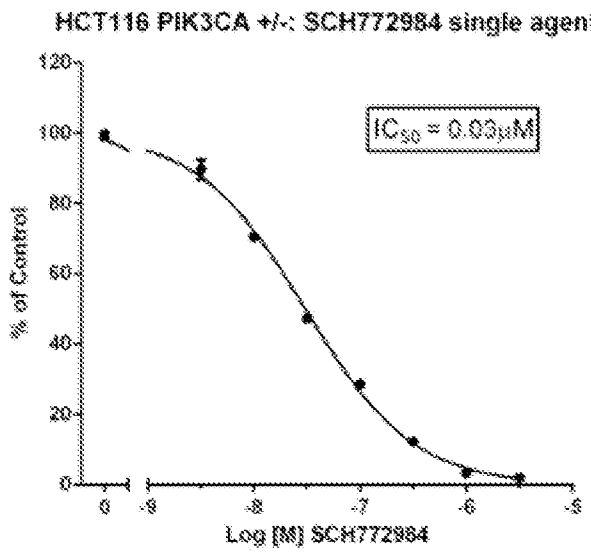
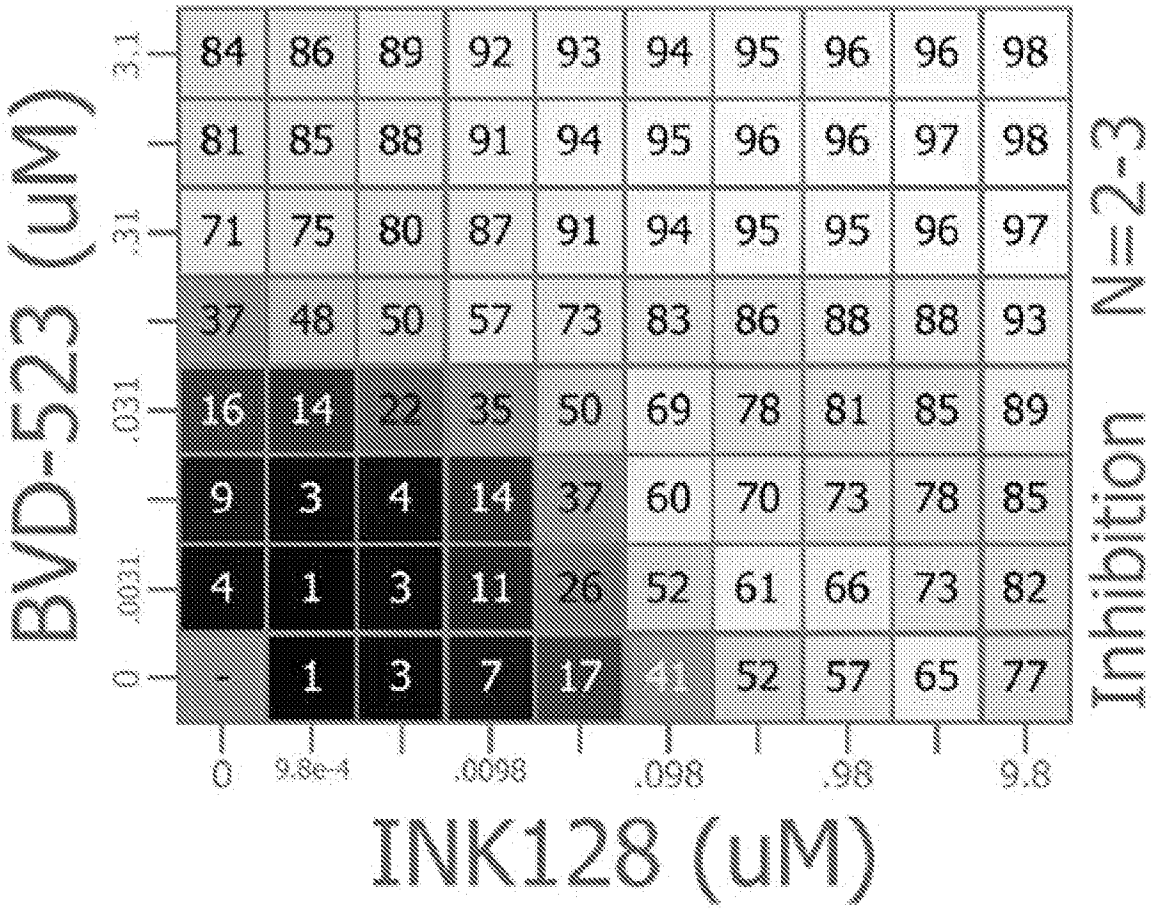


FIG. 11

A


BVD-523 (uM)
3.1
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.031
.0031
0
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81 85 88 91 94 95 96 96 97 98
71 75 80 87 91 94 95 95 96 97
37 48 50 57 73 83 86 88 88 93
16 14 22 35 50 69 78 81 85 89
9 3 4 14 37 60 70 73 78 85
4 1 3 11 26 52 61 66 73 82
1 3 7 17 41 52 57 65 77
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.098
.98
9.8
INK128 (uM)
Inhibition N=2-3

FIG. 11, Continued

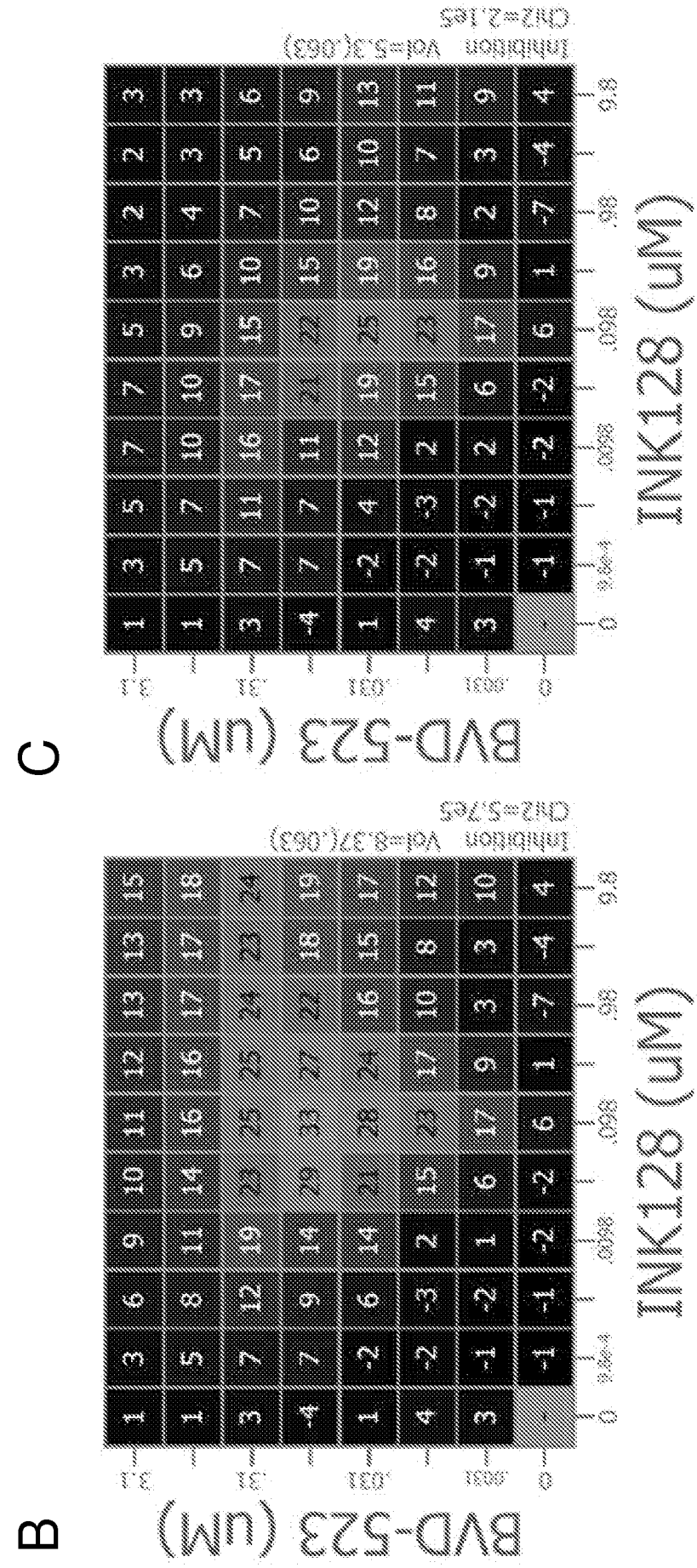


FIG. 11, Continued

D

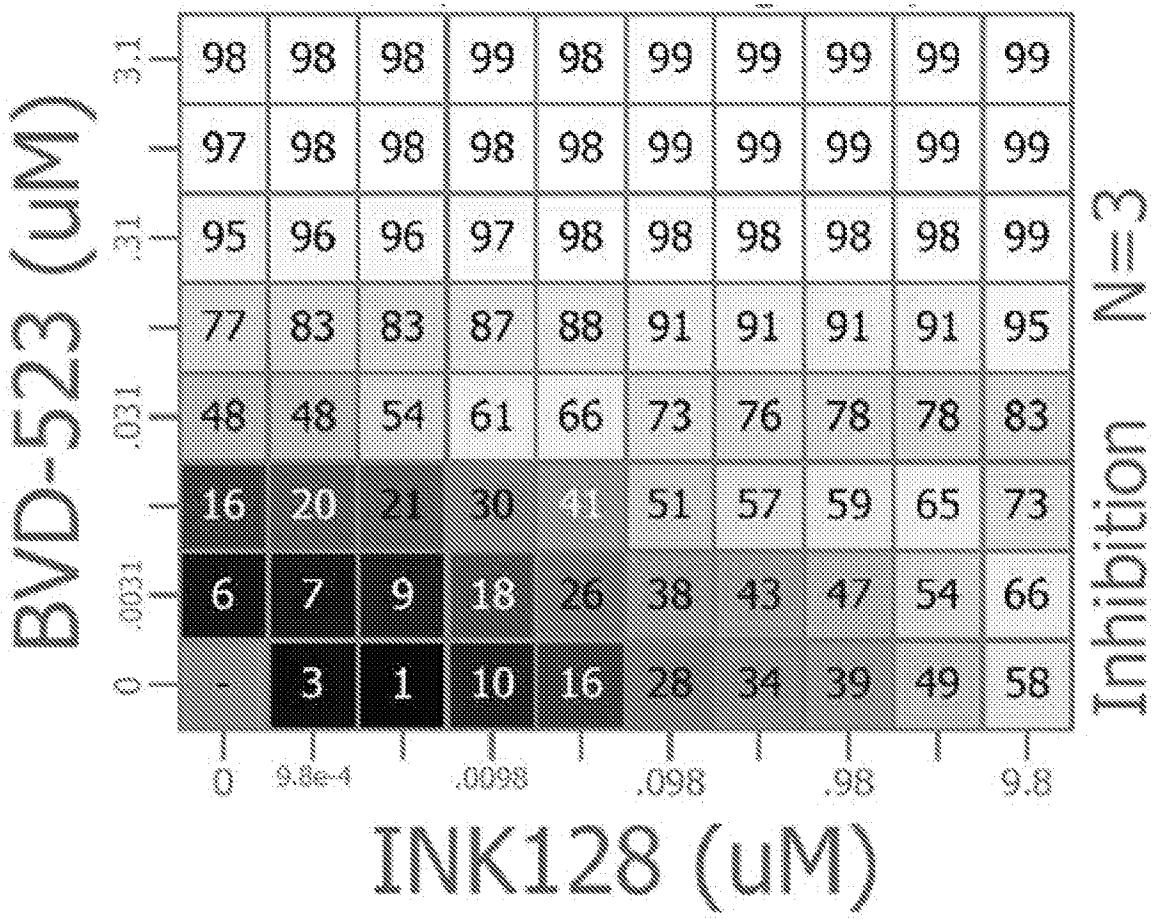
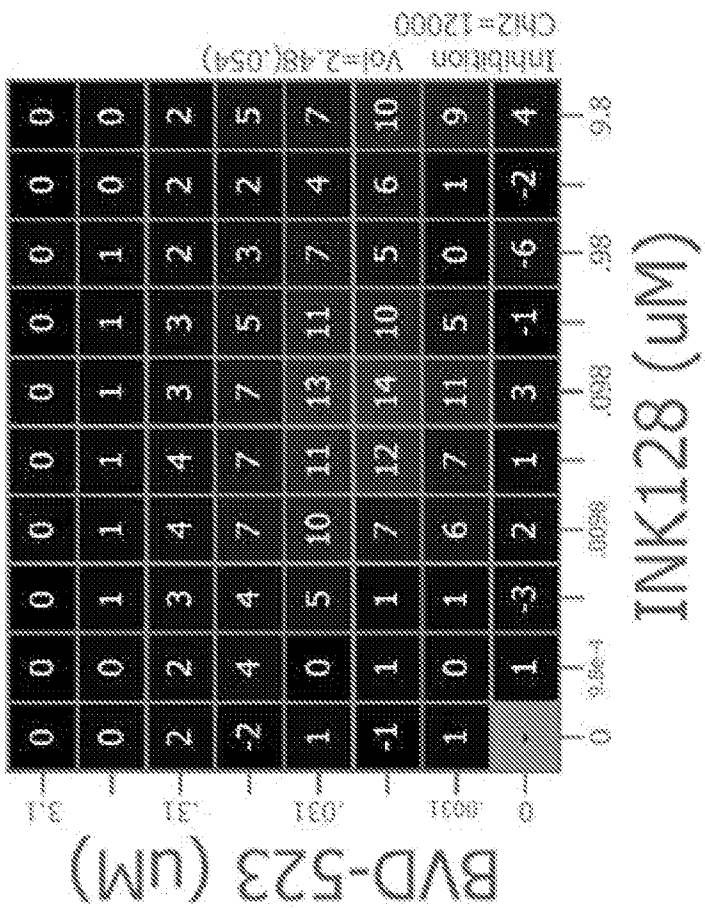


FIG. 11, Continued



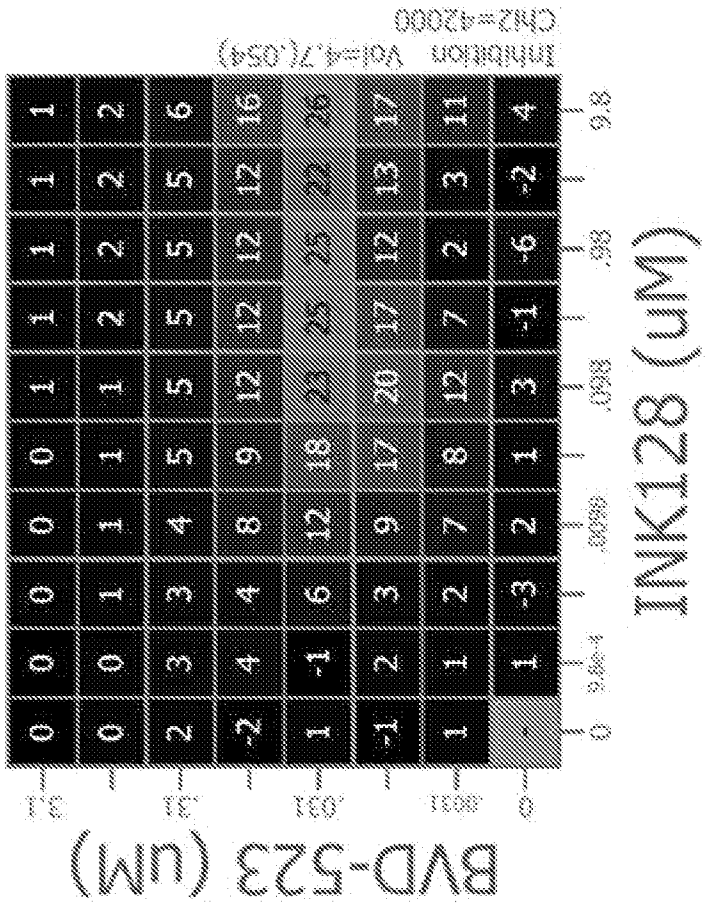
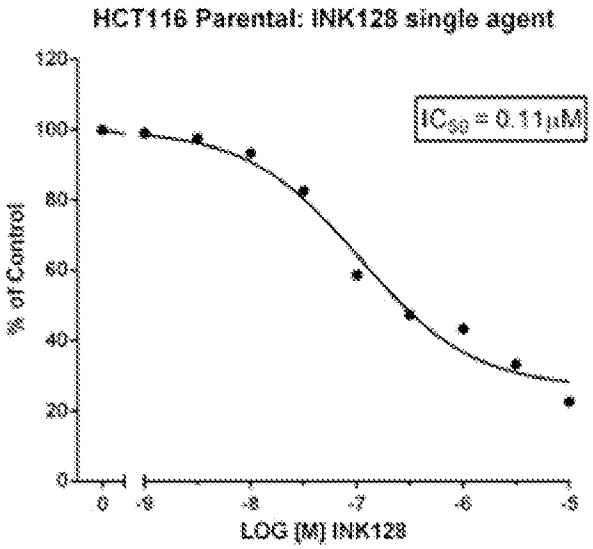


FIG. 11, Continued

G



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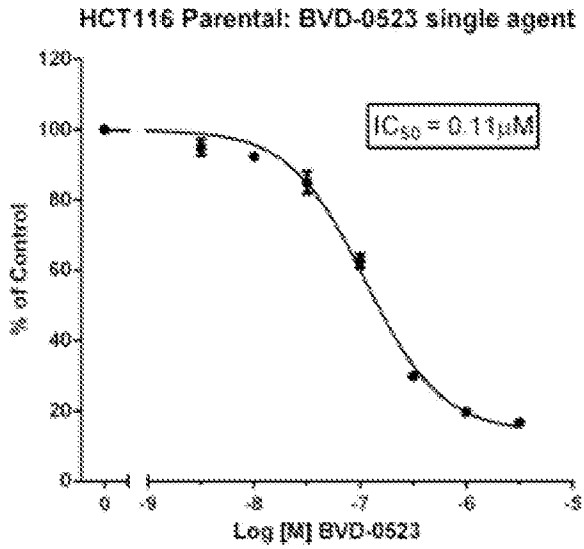

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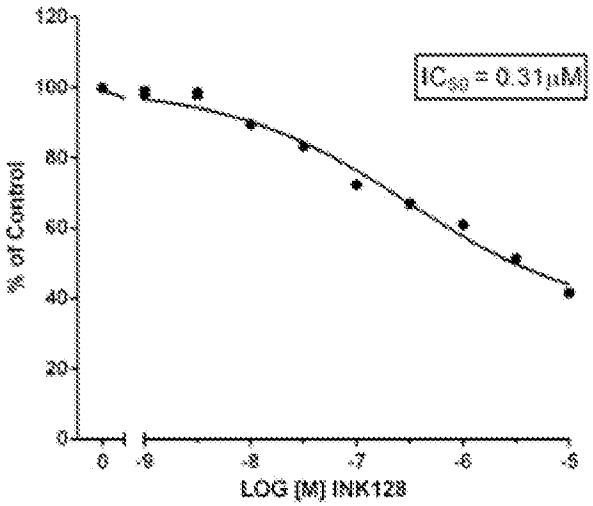

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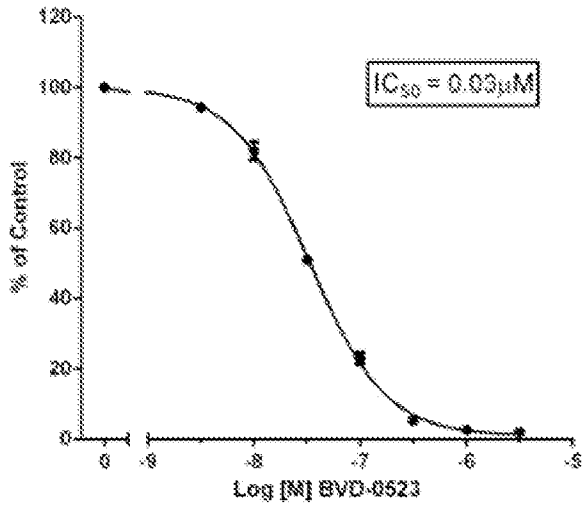
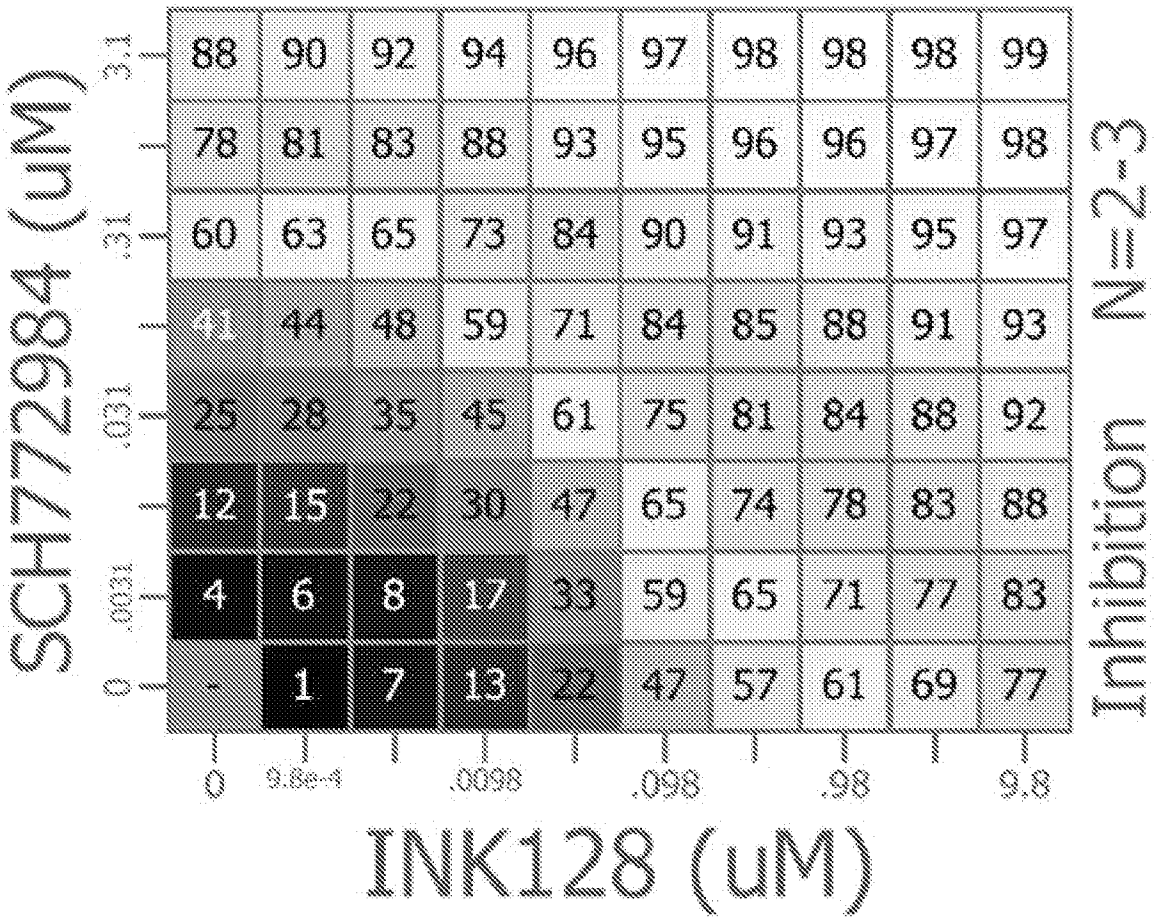


FIG. 12

A


SCH772984 (uM)
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.0031
0
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78 81 83 88 93 95 96 96 97 98
60 63 65 73 84 90 91 93 95 97
44 44 48 59 71 84 85 88 91 93
25 28 35 45 61 75 81 84 88 92
12 15 22 30 47 65 74 78 83 88
4 6 8 17 33 59 65 71 77 83
- 1 7 13 22 47 57 61 69 77
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9.8e-4
.0098
.098
.98
9.8
INK128 (uM)
Inhibition N=2-3

FIG. 12, Continued

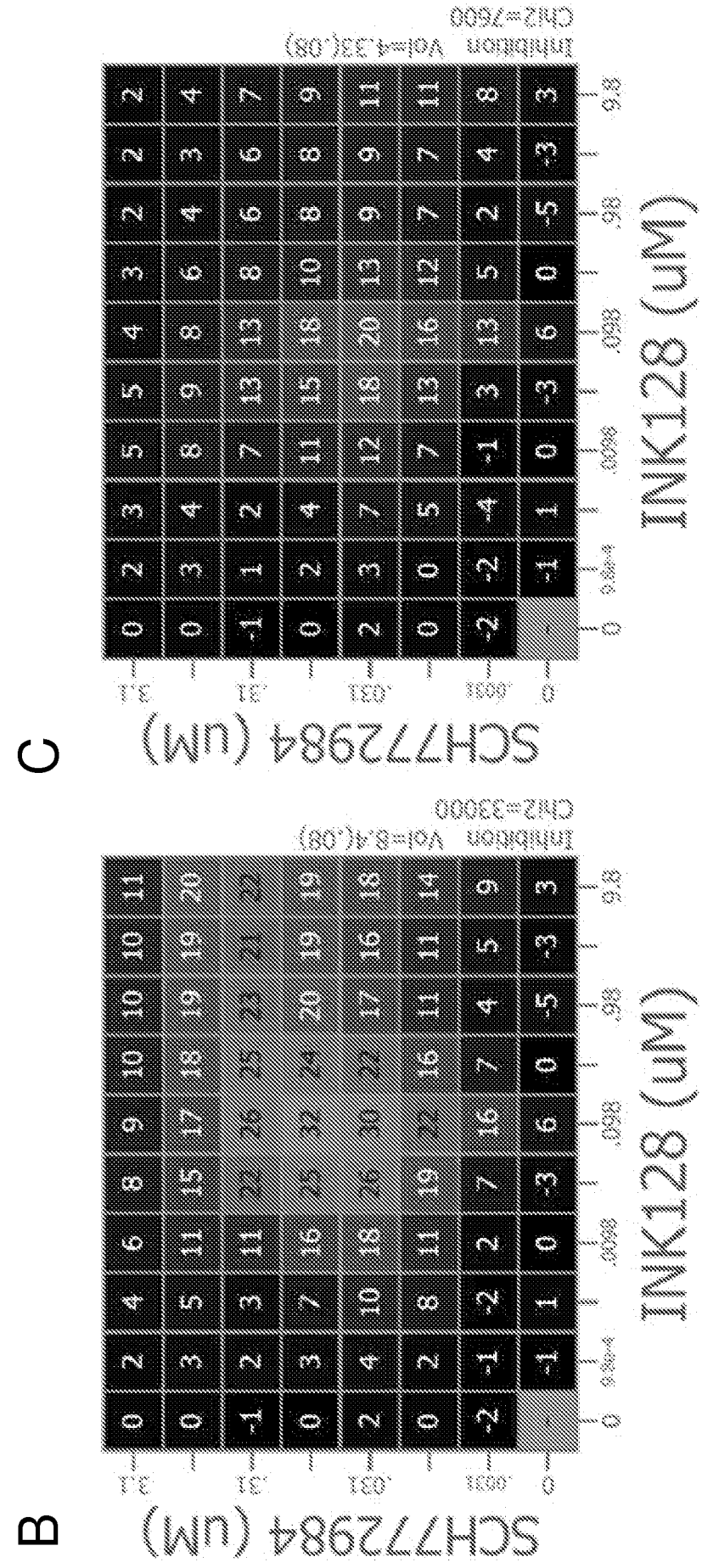


FIG. 12, Continued

D

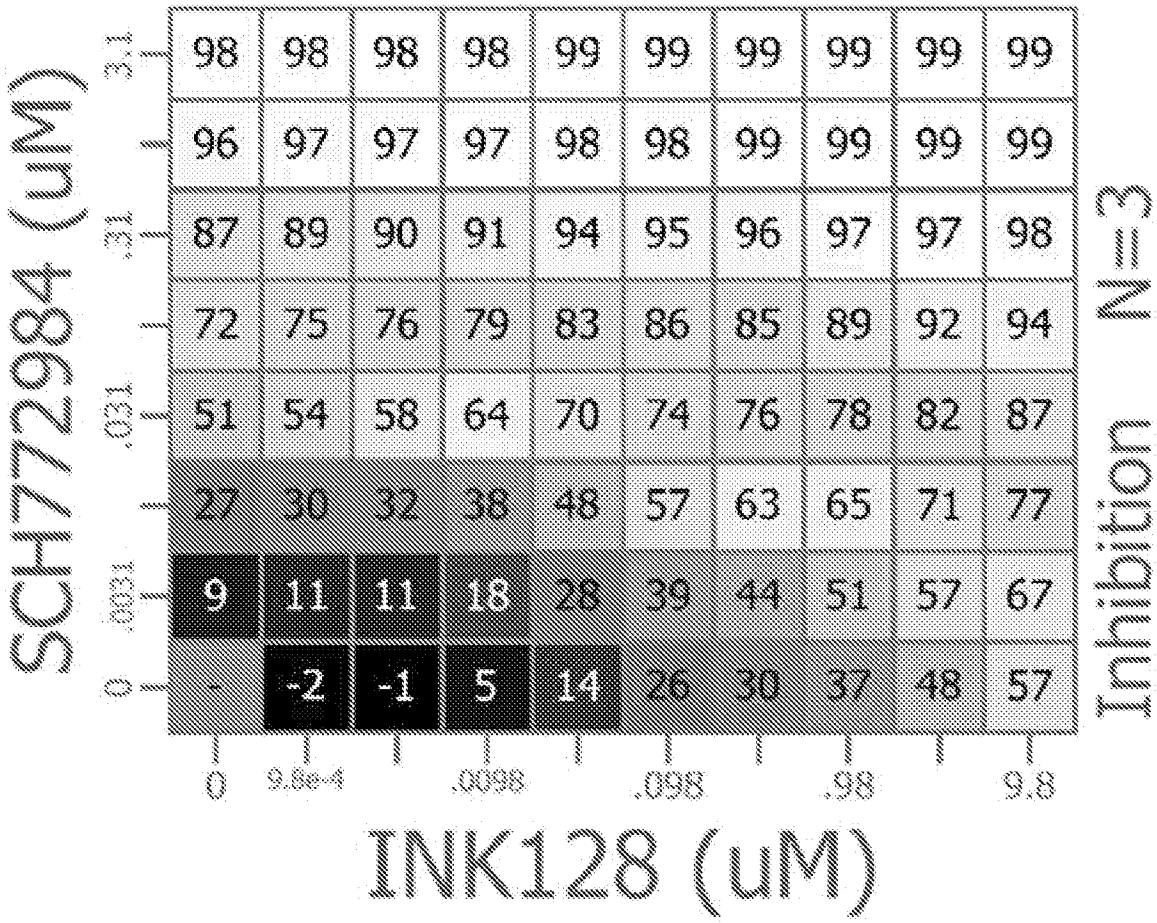


FIG. 12, Continued

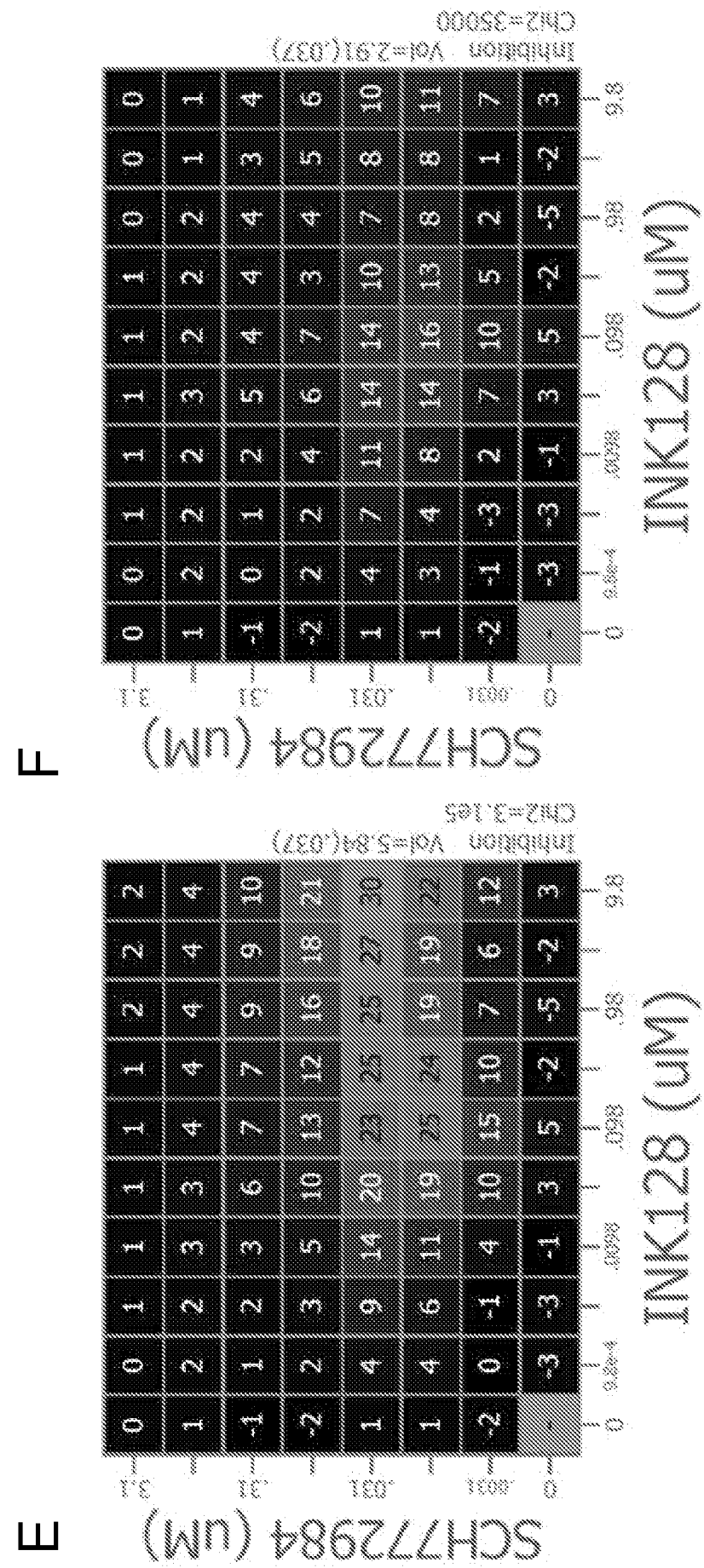
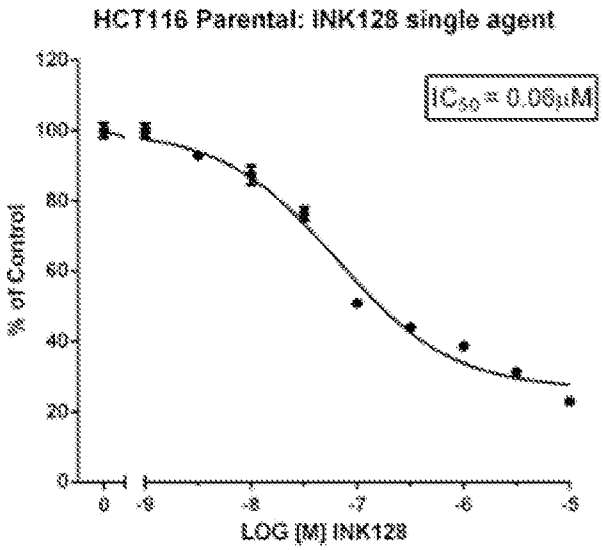


FIG. 12, Continued

G



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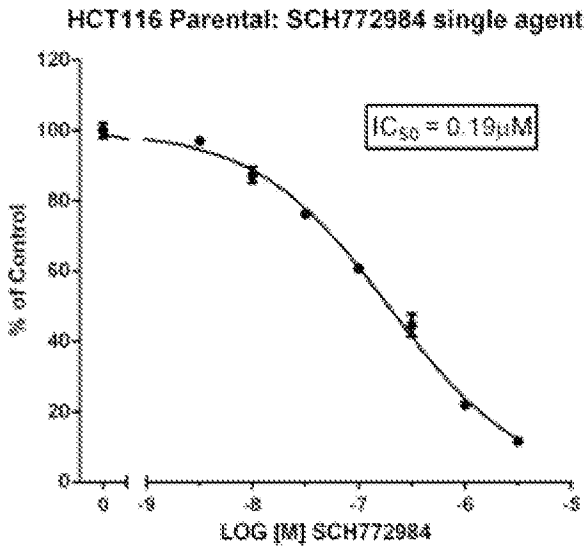

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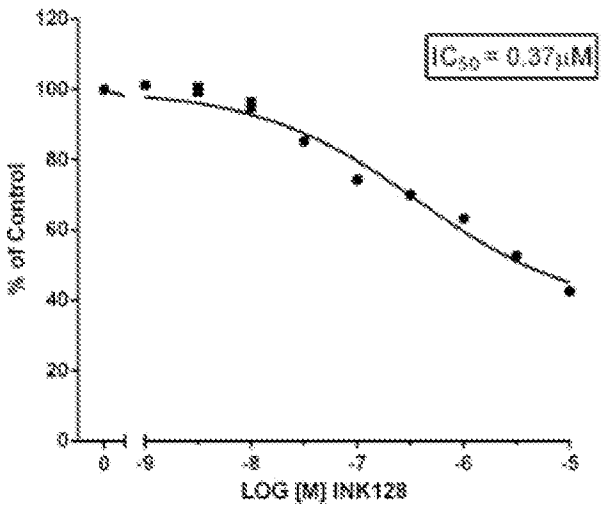

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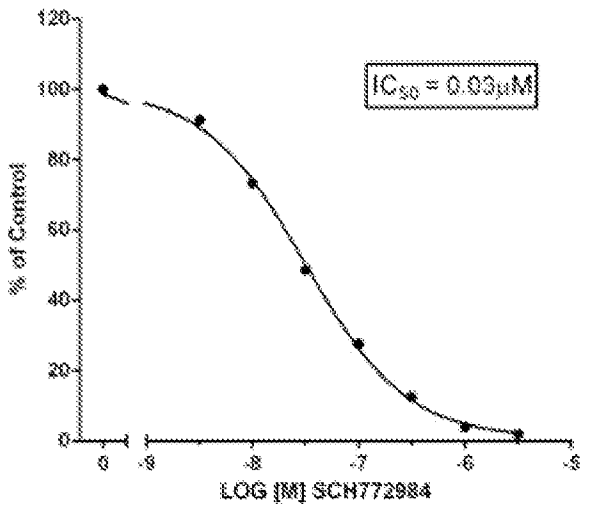
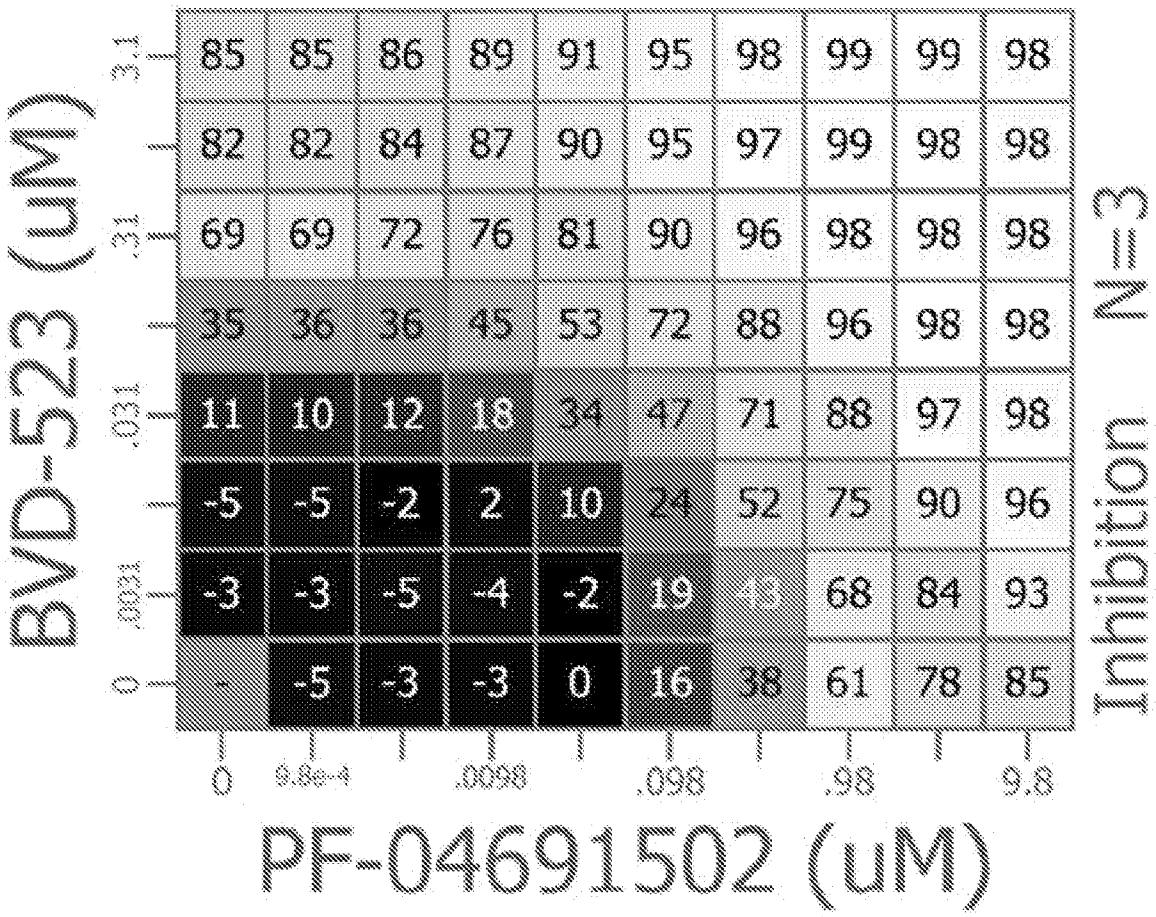


FIG. 13

A


BVD-523 (uM)
3.1
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.0031
0
85 85 86 89 91 95 98 99 99 98
82 82 84 87 90 95 97 99 98 98
69 69 72 76 81 90 96 98 98 98
35 36 36 45 53 72 88 96 98 98
11 10 12 18 34 47 71 88 97 98
-5 -5 -2 2 10 24 52 75 90 96
-3 -3 -5 -4 -2 19 43 68 84 93
- -5 -3 -3 0 16 38 61 78 85
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9.8e-4
.0098
.098
.98
9.8
PF-04691502 (uM)
Inhibition N=3

FIG. 13, Continued

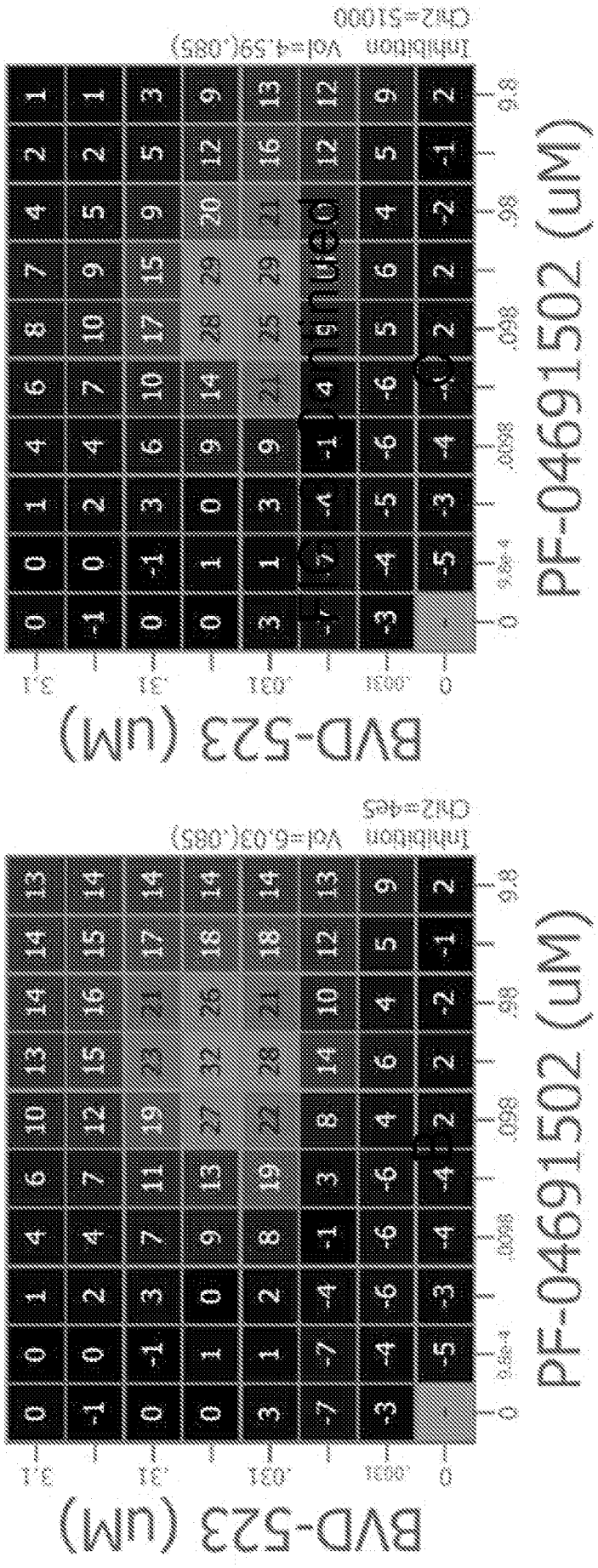


FIG. 13, Continued

D

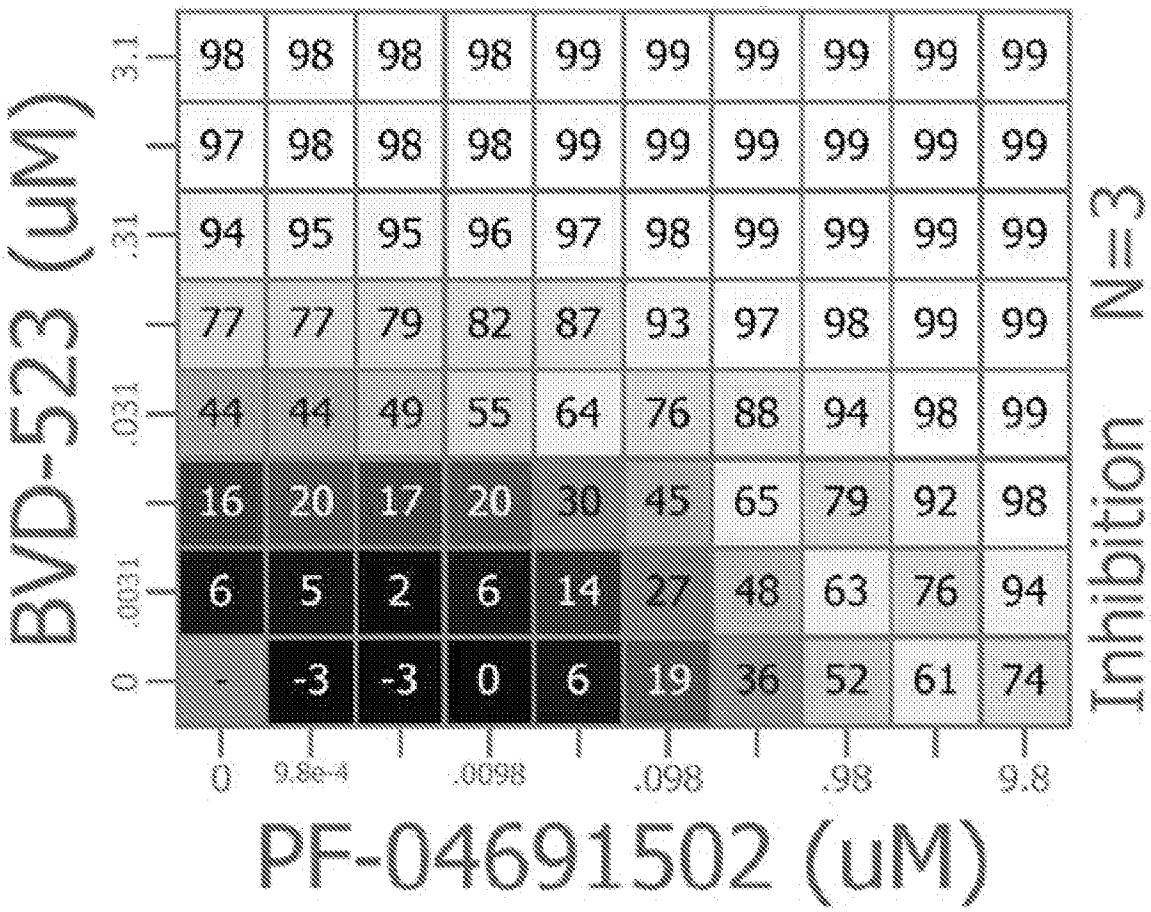


FIG. 13, Continued

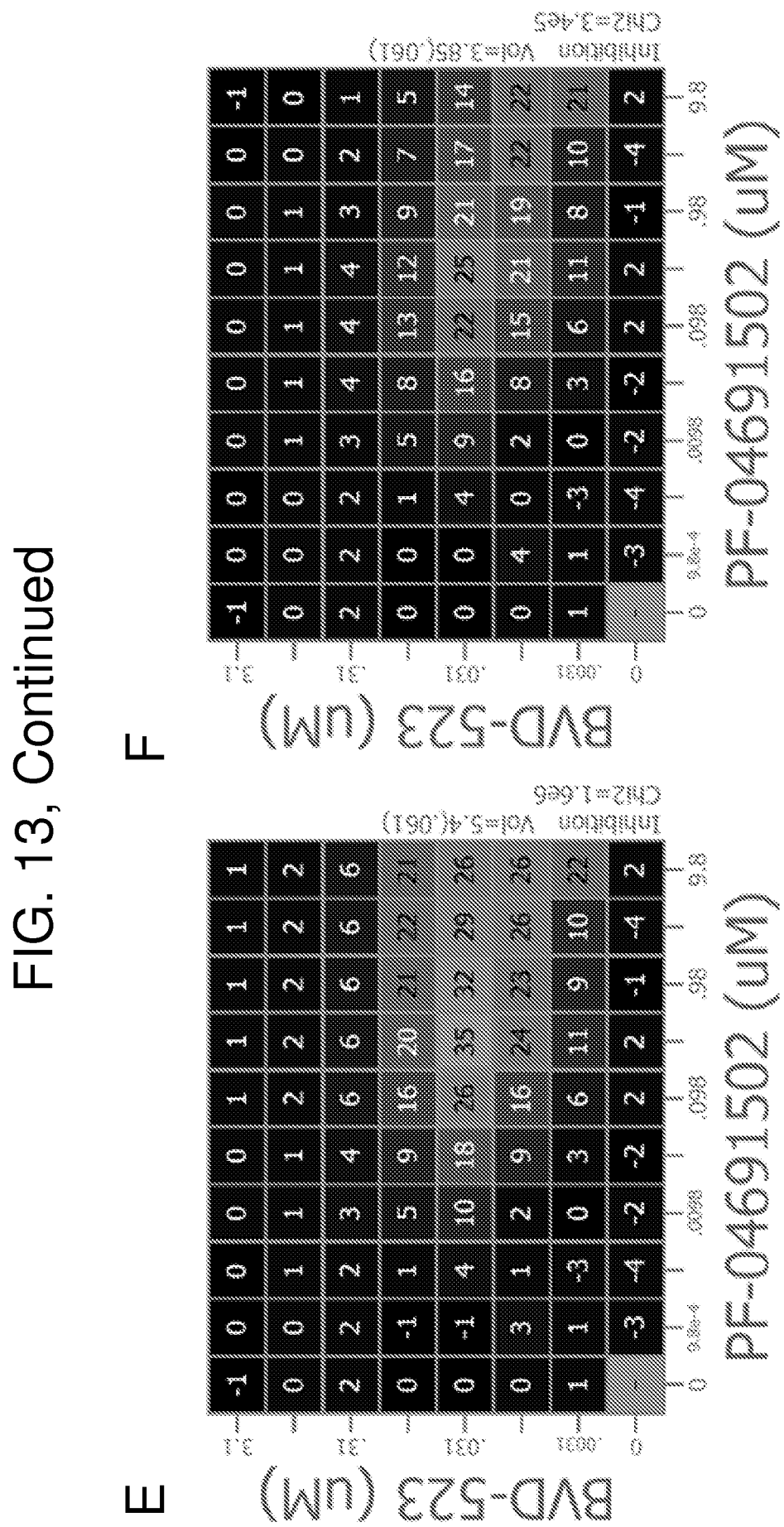
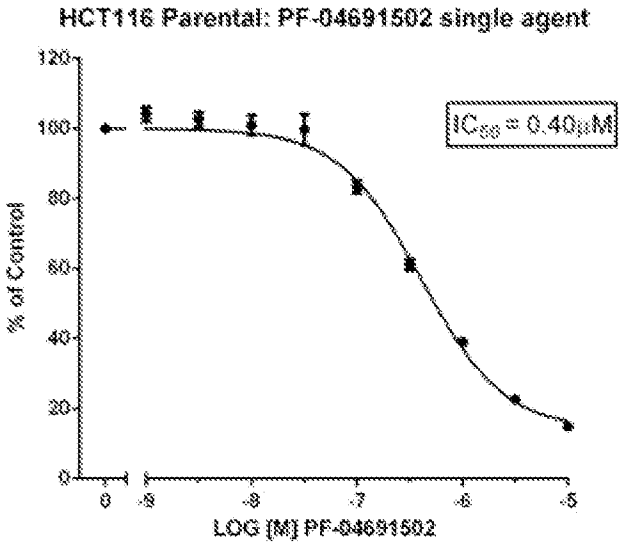
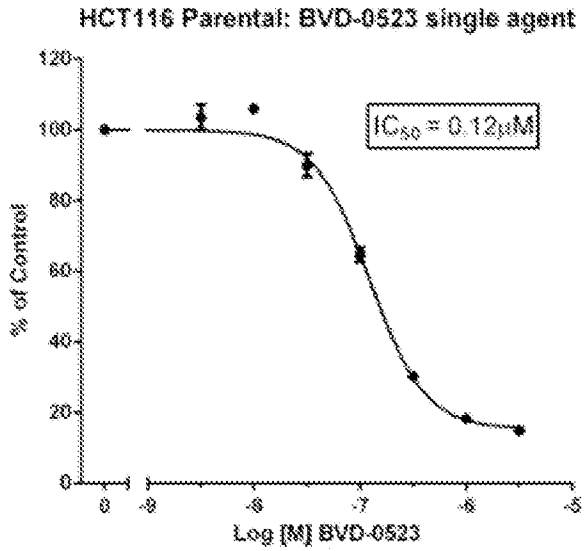


FIG. 13, Continued

G



H



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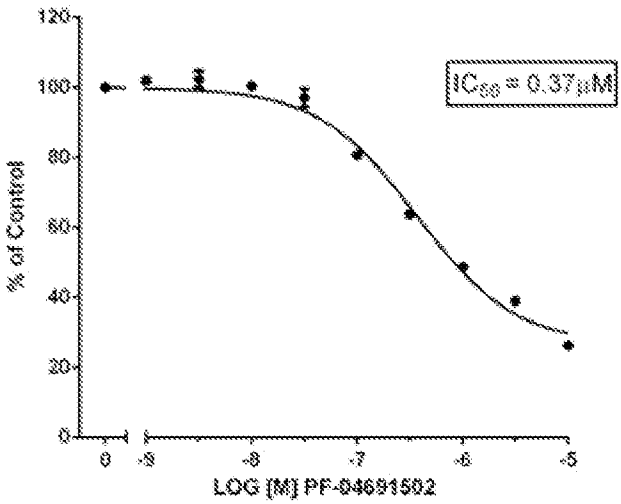


J

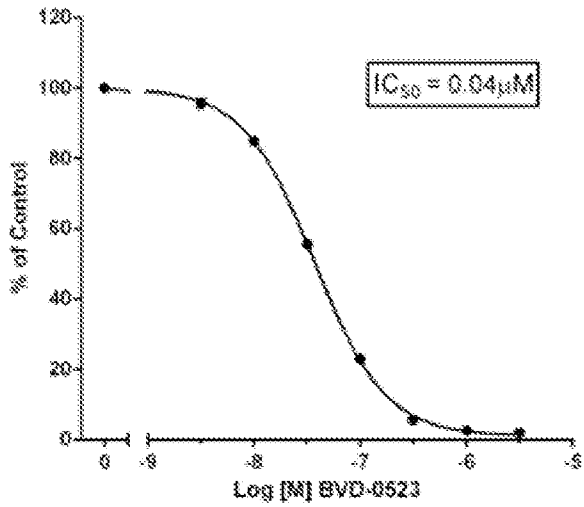
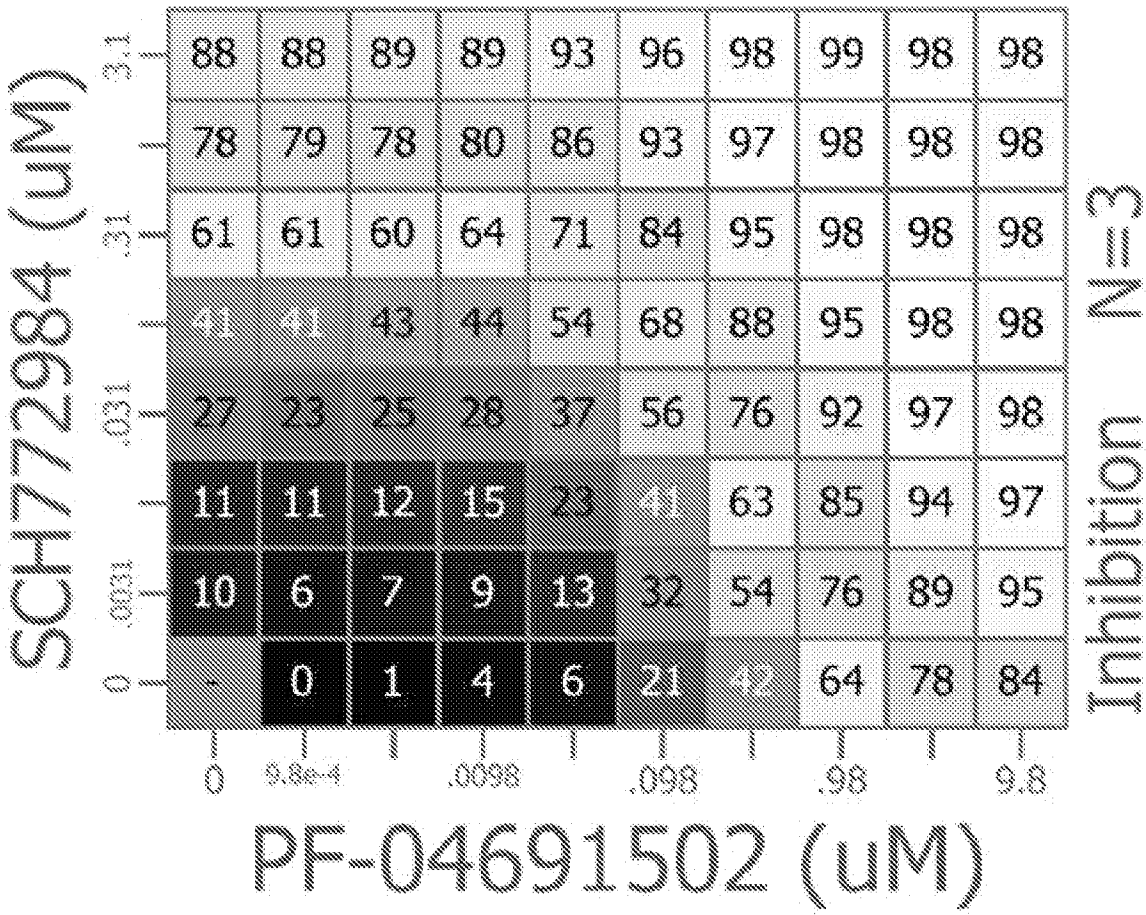


FIG. 14

A


SCH772984 (uM)
3.1
.31
.031
.0031
0
88 88 89 89 93 96 98 99 98 98
78 79 78 80 86 93 97 98 98 98
61 61 60 64 71 84 95 98 98 98
41 41 43 44 54 68 88 95 98 98
27 23 25 28 37 56 76 92 97 98
11 11 12 15 23 41 63 85 94 97
10 6 7 9 13 32 54 76 89 95
- 0 1 4 6 21 42 64 78 84
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.0098
.098
.98
9.8
PF-04691502 (uM)
Inhibition N=3

FIG. 14, Continued

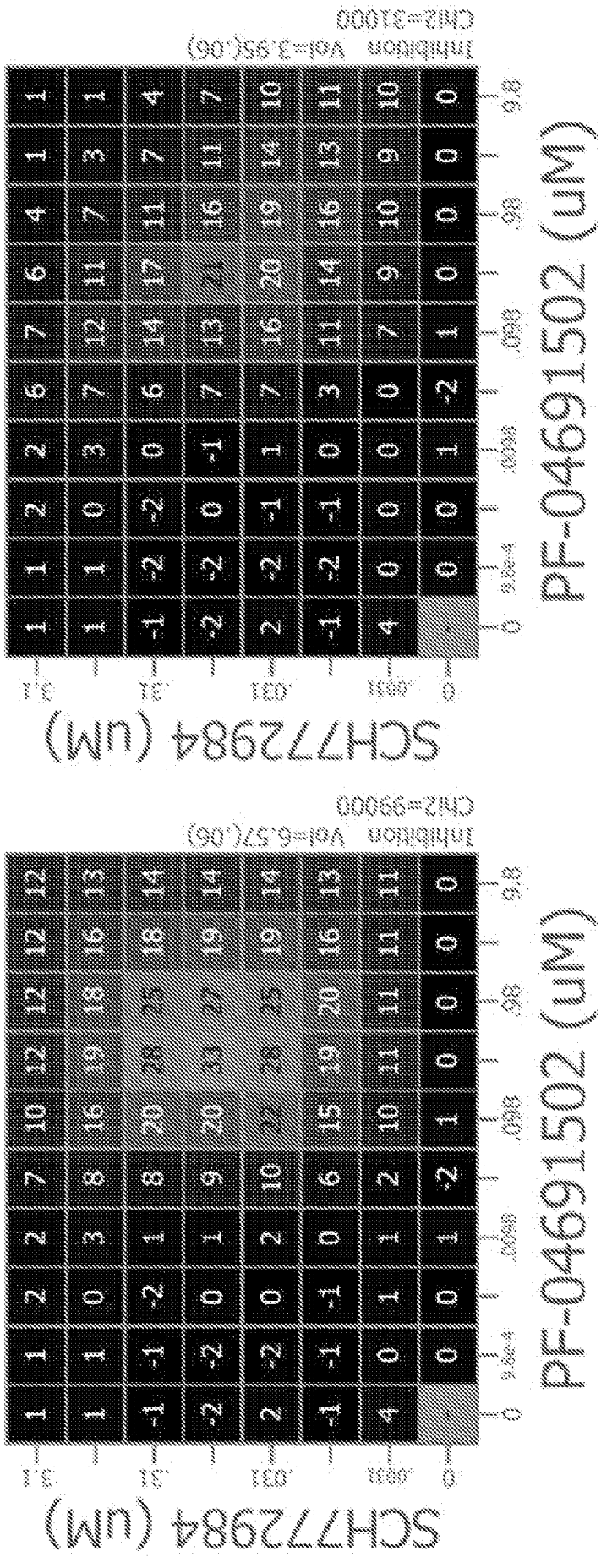


FIG. 14, Continued

D

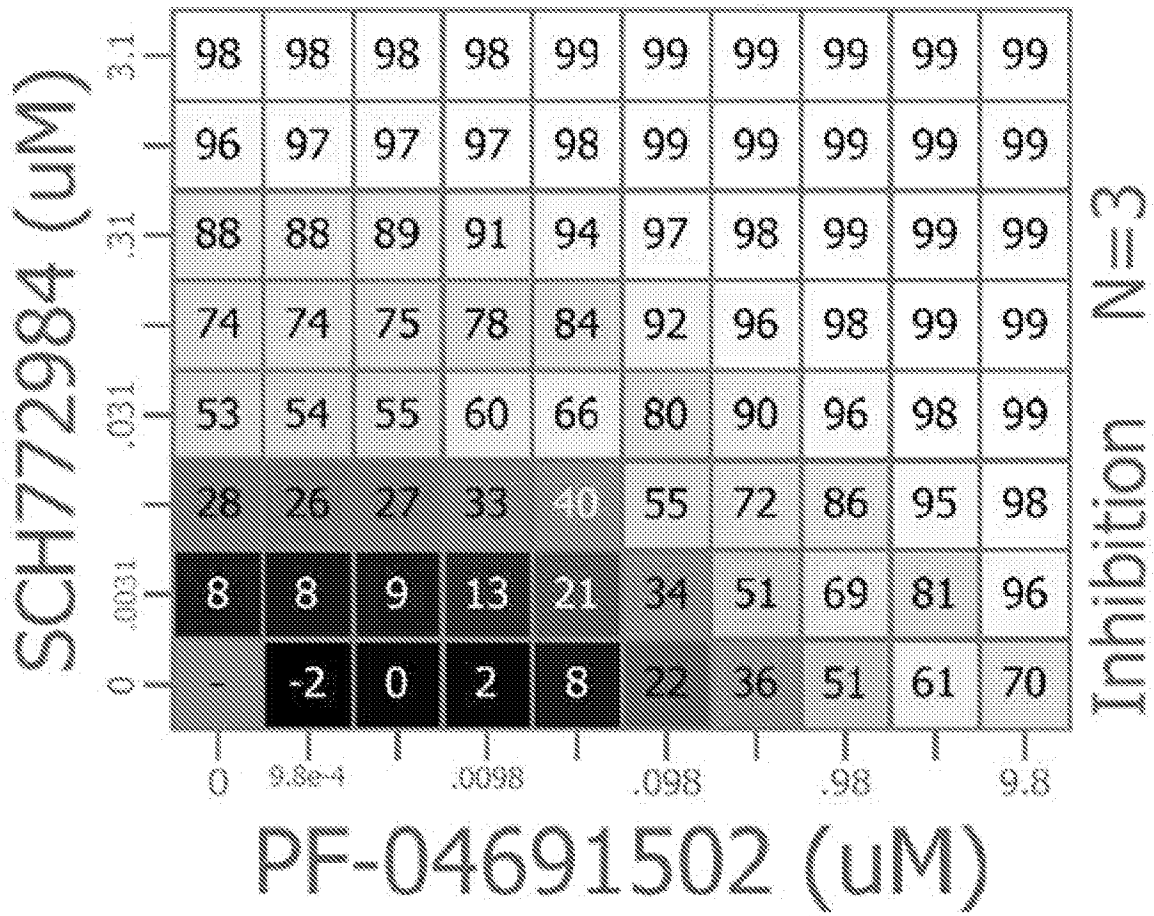


FIG. 14, Continued

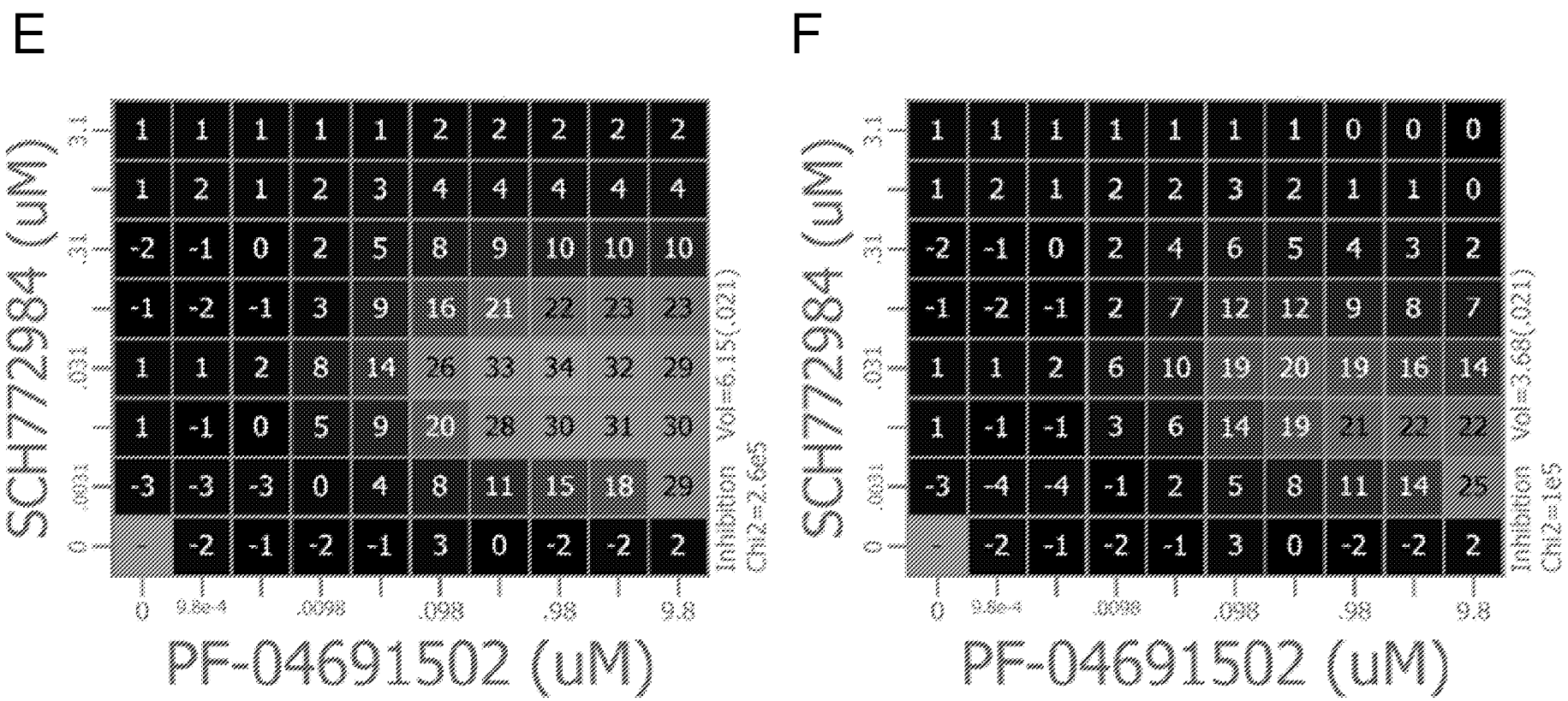
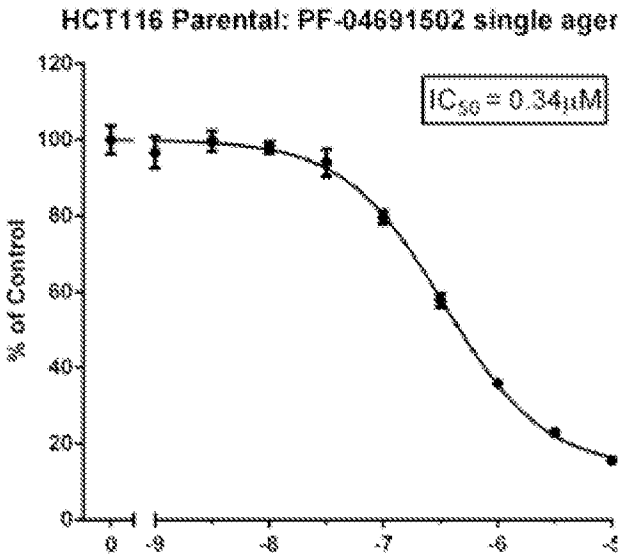
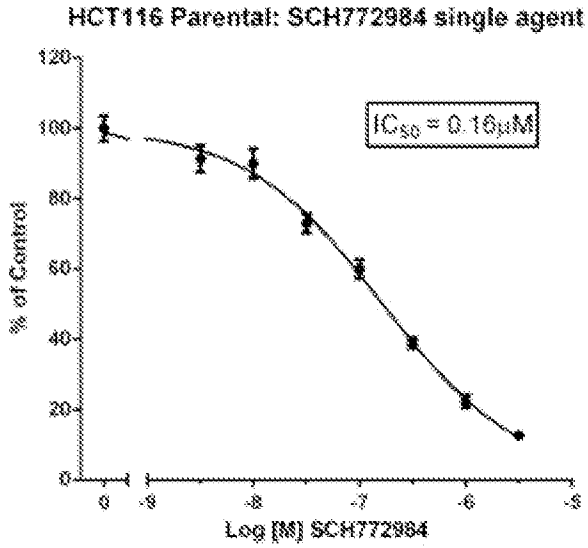


FIG. 14, Continued

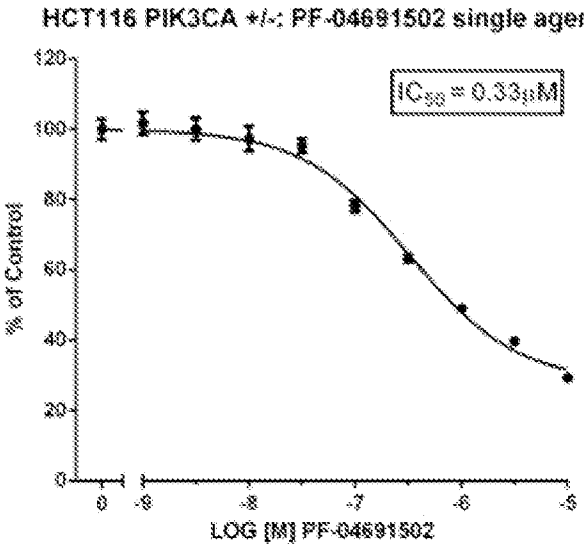
G



H



I



J

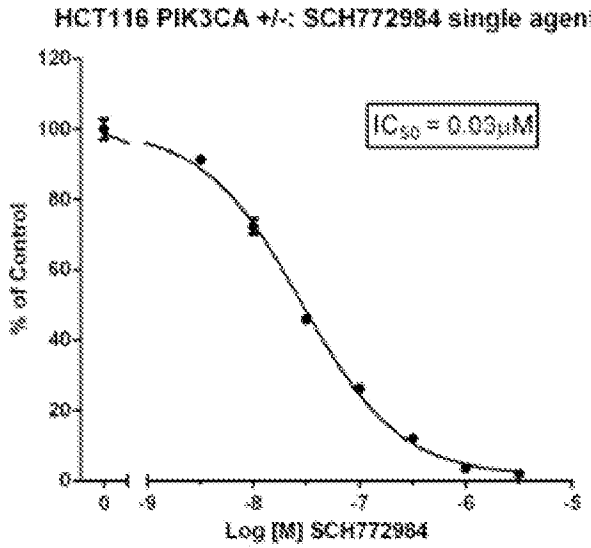


FIG. 15

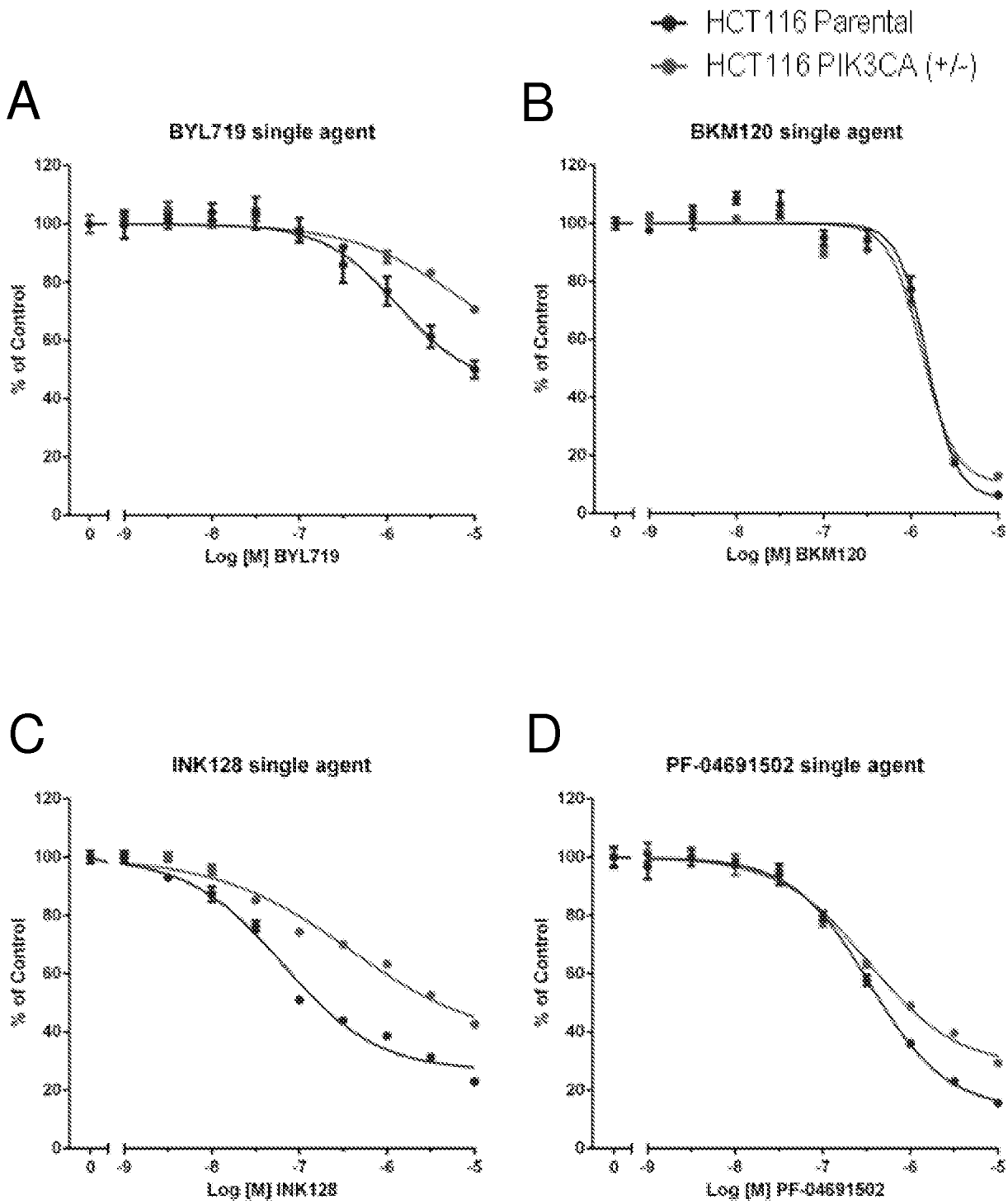
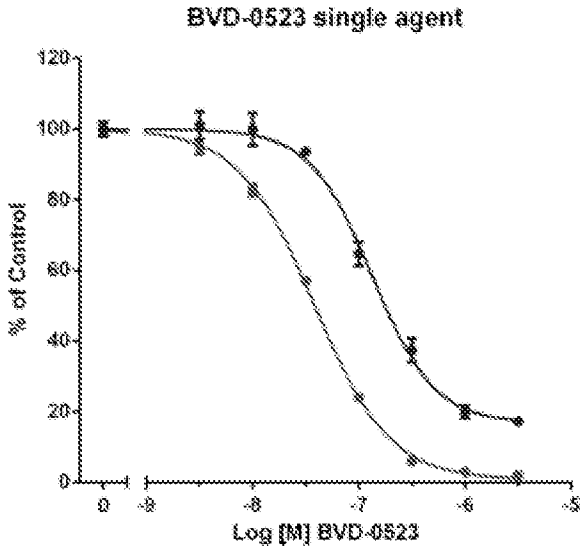

HCT116 Parental
HCT116 PIK3CA (+/-)
A
BYL719 single agent
% of Control
Log [M] BYL719
B
BKM120 single agent
% of Control
Log [M] BKM120
C
INK128 single agent
% of Control
Log [M] INK128
D
PF-04691502 single agent
% of Control
Log [M] PF-04691502

FIG. 15, Continued

E



F

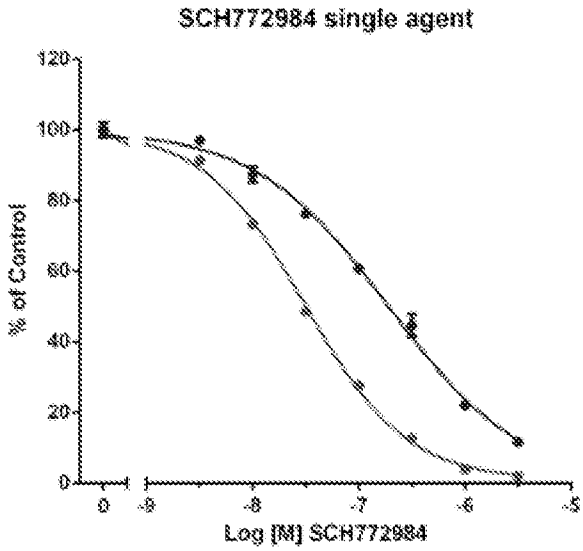


FIG. 16

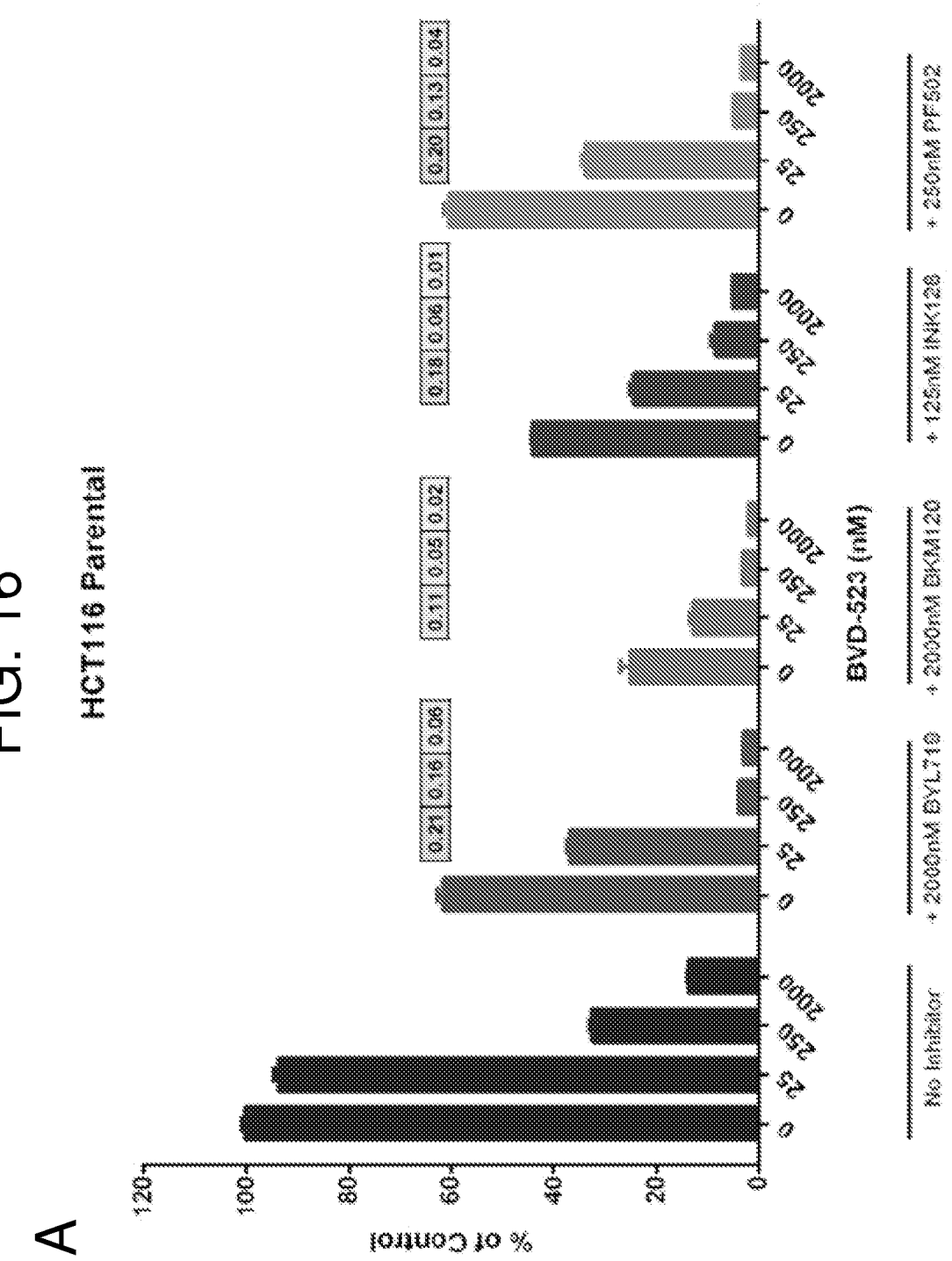

A
HCT116 Parental
% of Control
120
100
80
60
40
20
0
0.21
0.16
0.09
0.11
0.08
0.02
0.13
0.08
0.01
0.20
0.13
0.04
0
25
50
250
2000
BVD-523 (nM)
No Inhibitor
+ 2000nM BYL719
+ 2000nM BKM120
+ 125nM INK128
+ 250nM PF502

FIG. 16, Continued

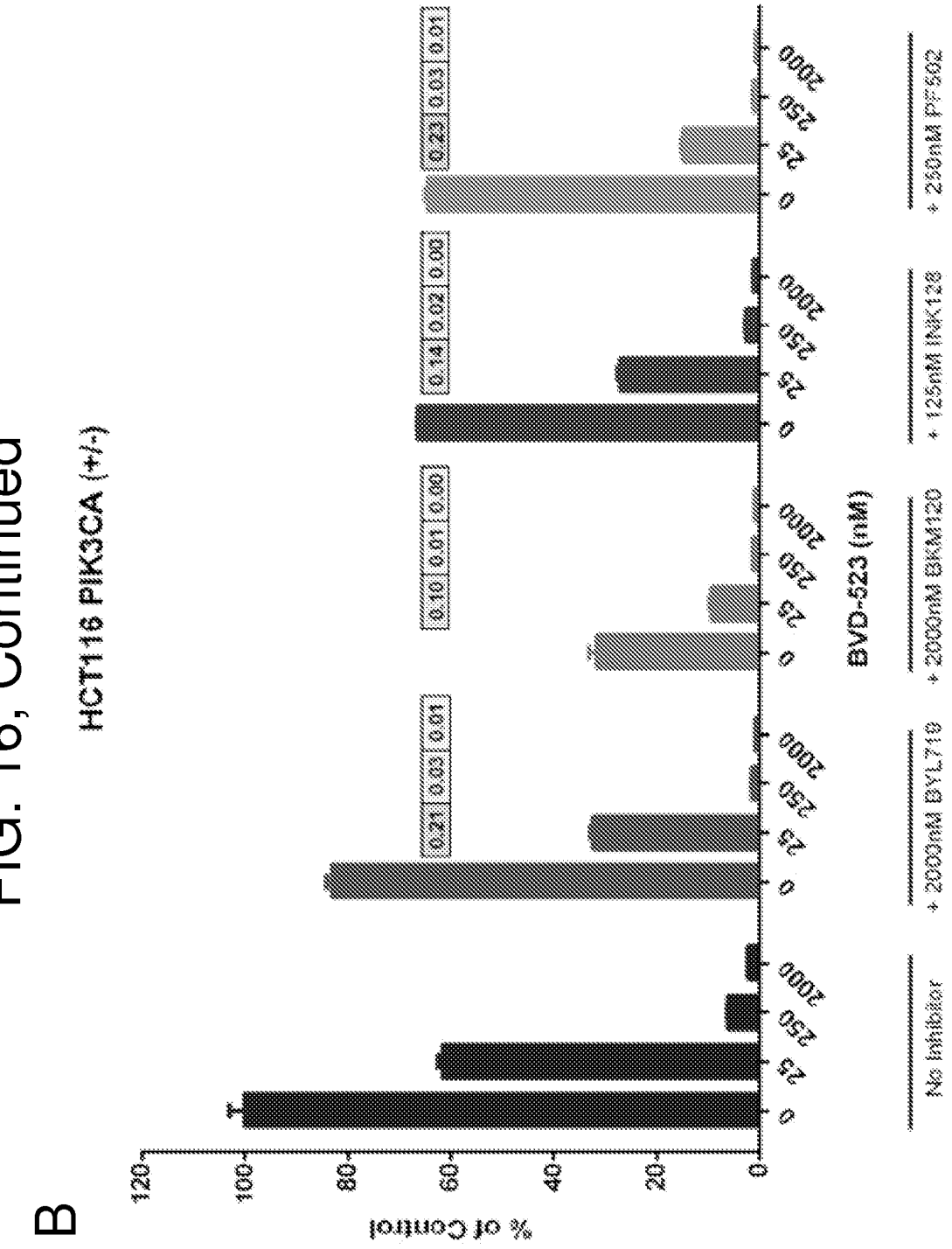


FIG. 16, Continued

C

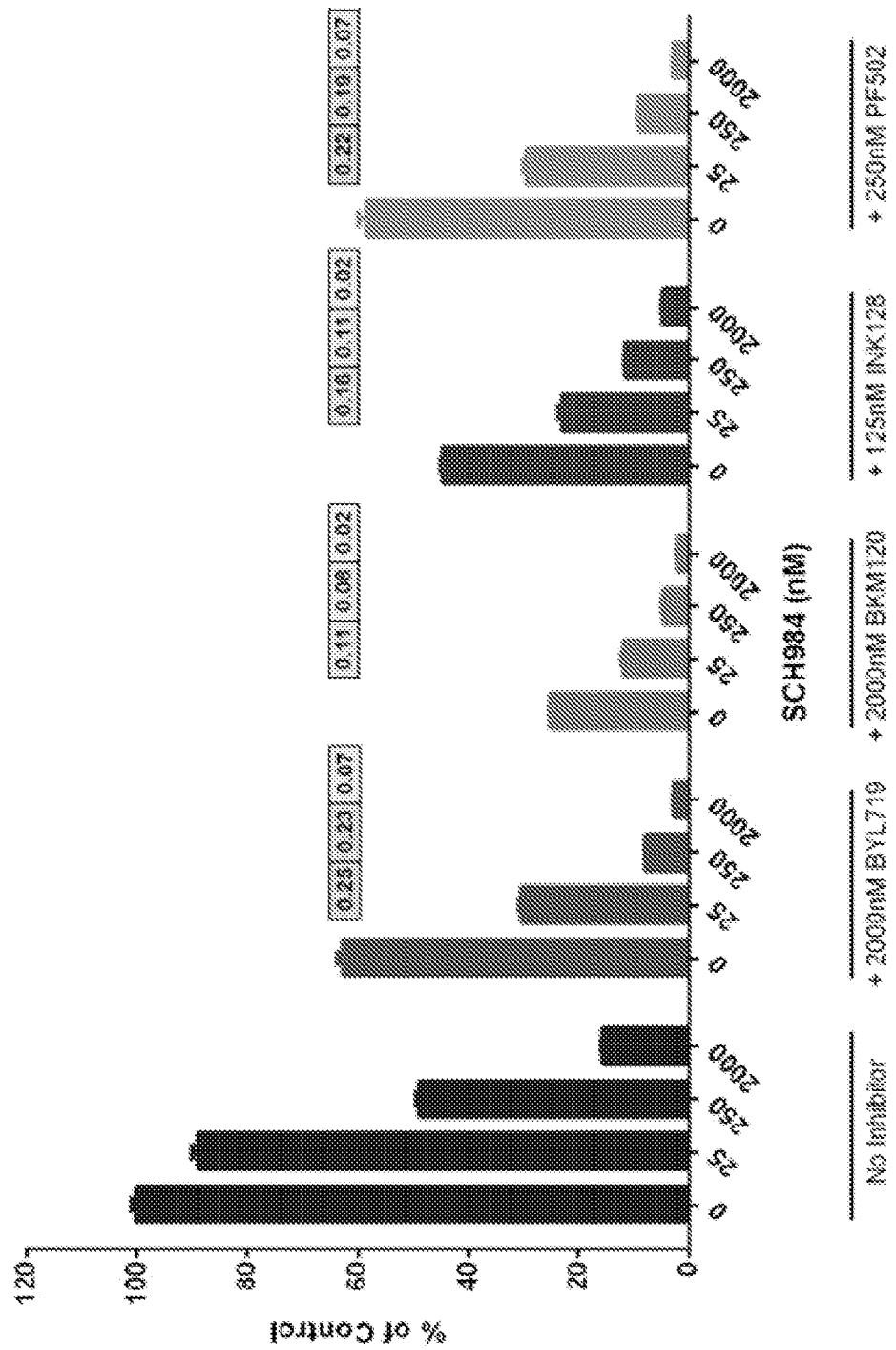


FIG. 16, Continued

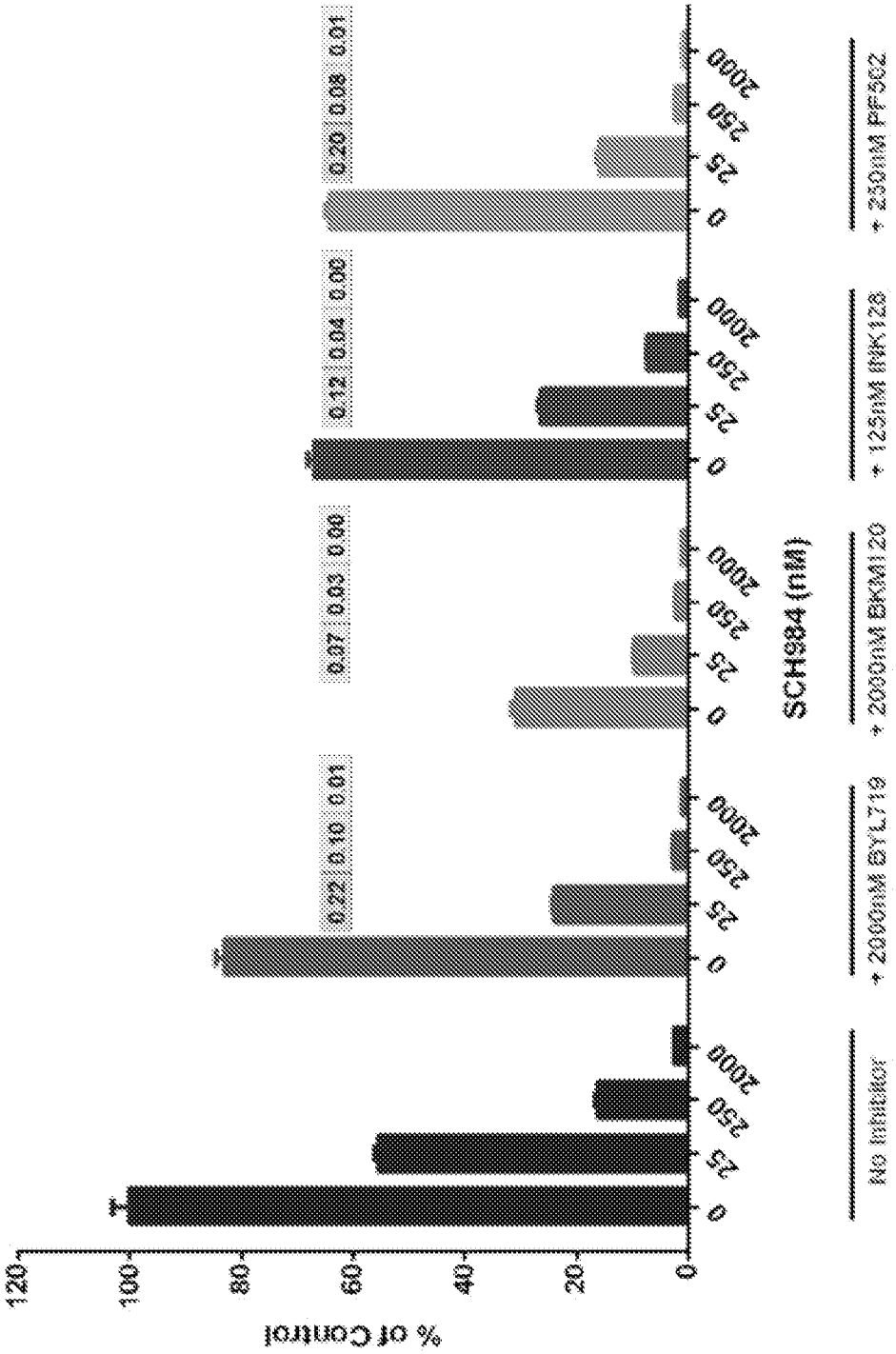


FIG. 17

A

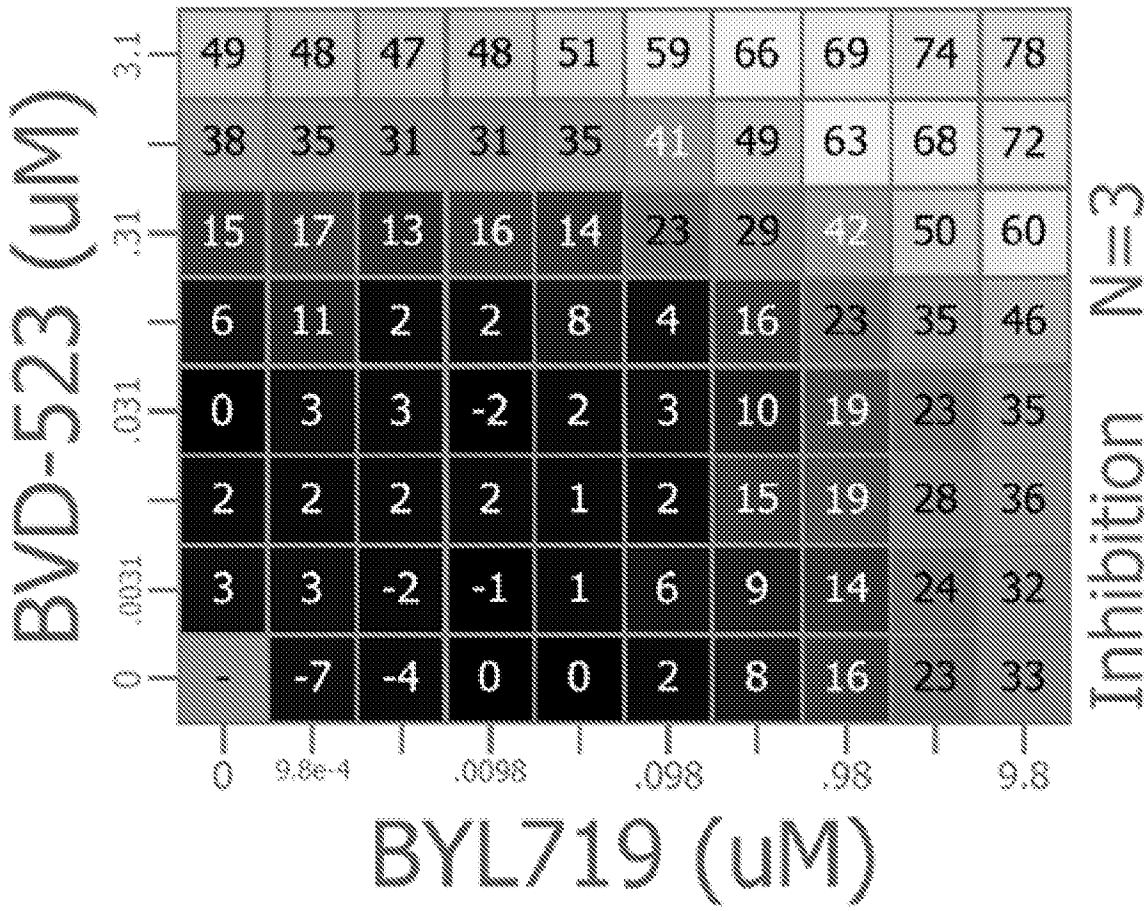
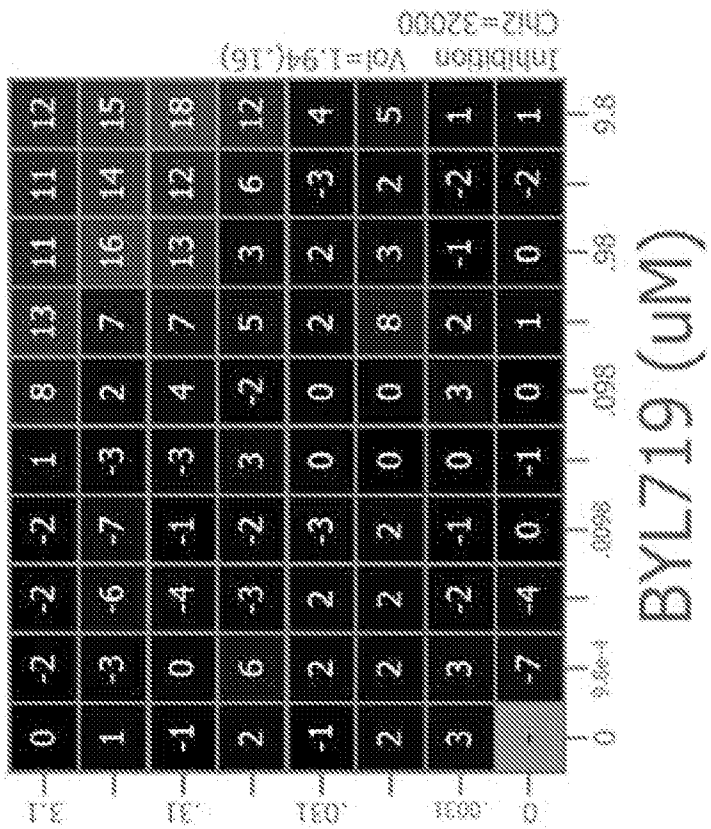

BVD-523 (uM)
3.1
.31
.031
.0031
0
49 48 47 48 51 59 66 69 74 78
38 35 31 31 35 41 49 63 68 72
15 17 13 16 14 23 29 42 50 60
6 11 2 2 8 4 16 23 35 46
0 3 3 -2 2 3 10 19 23 35
2 2 2 2 1 2 15 19 28 36
3 3 -2 -1 1 6 9 14 24 32
- -7 -4 0 0 2 8 16 23 33
0
9.8e-4
.0098
.098
.98
9.8
BYL719 (uM)
Inhibition N=3

FIG. 17, Continued



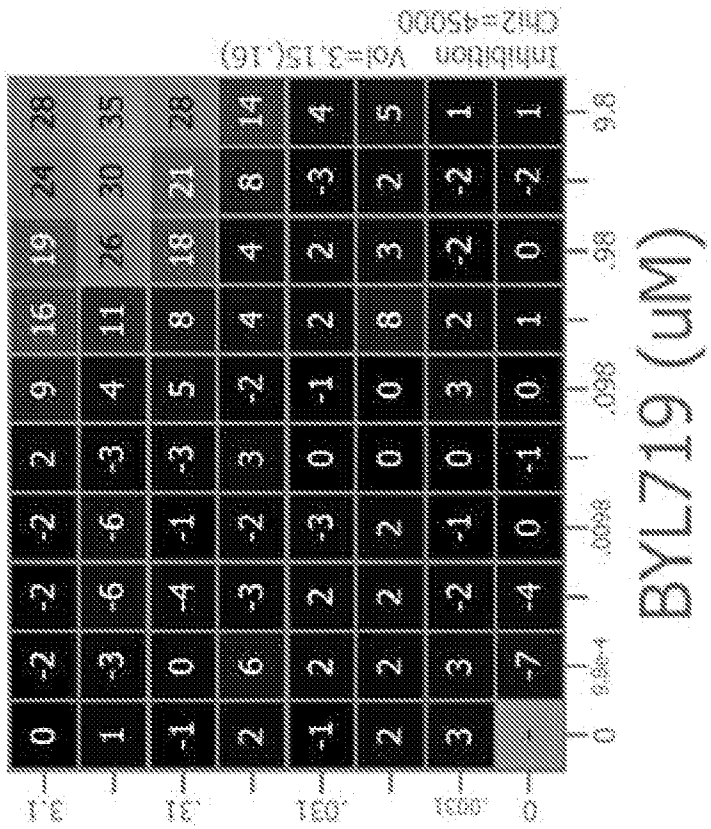


FIG. 17, Continued

D

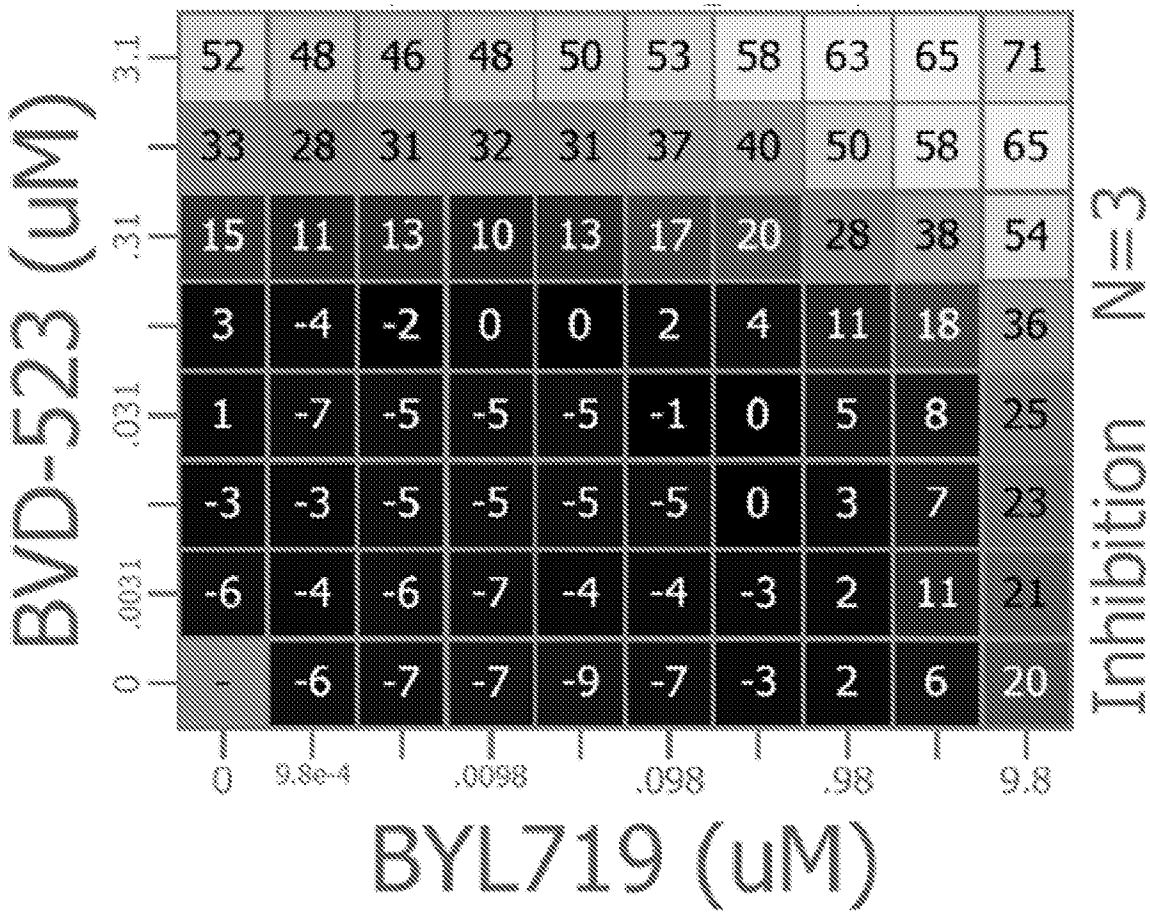
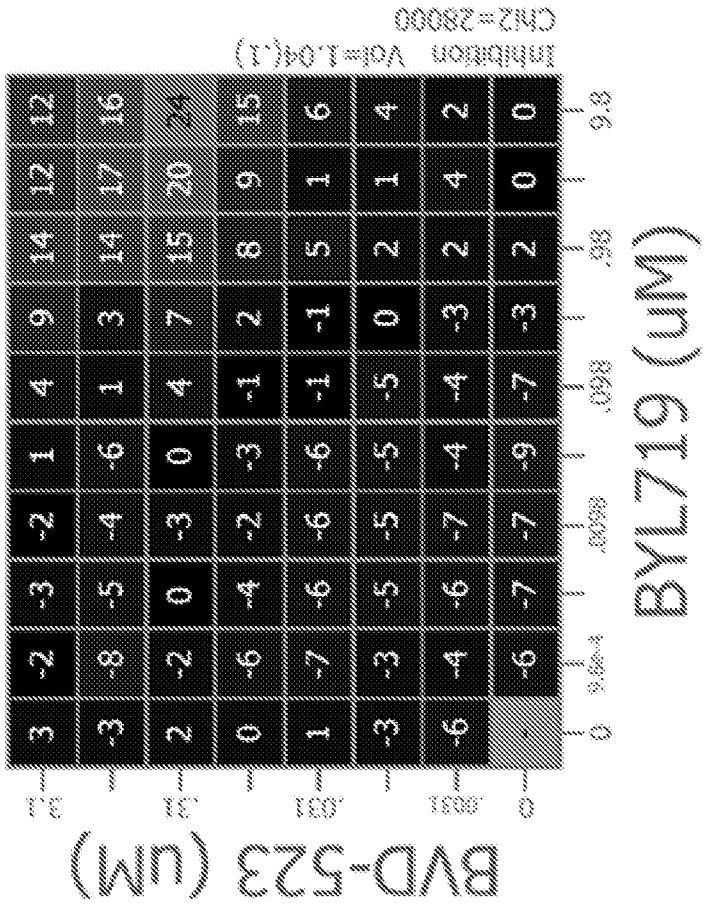


FIG. 17, Continued



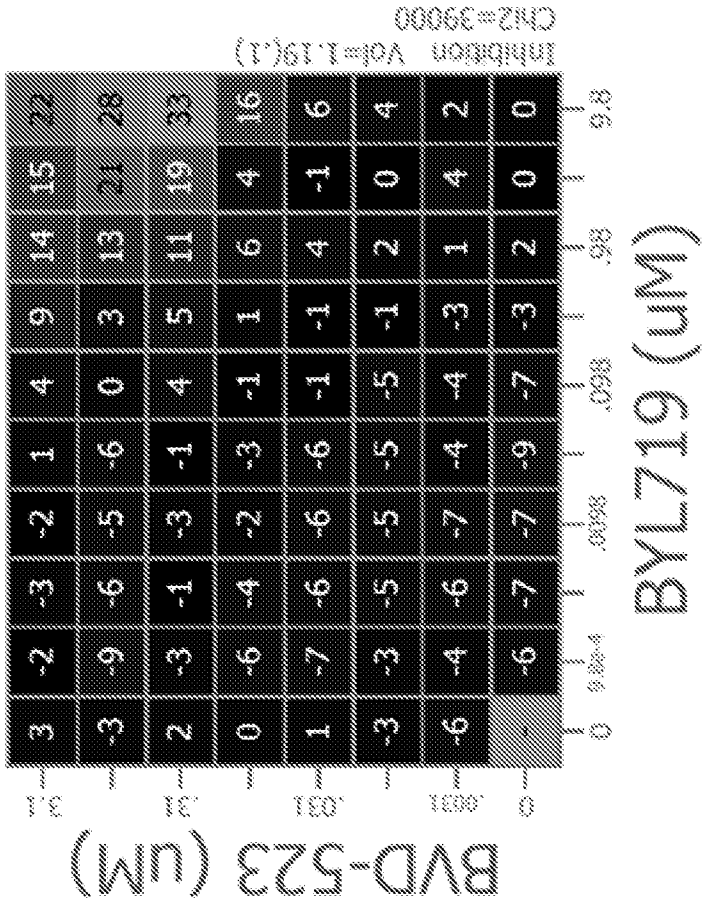
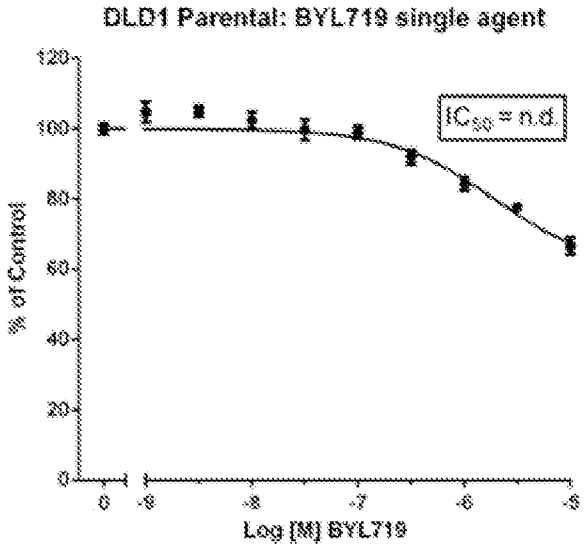
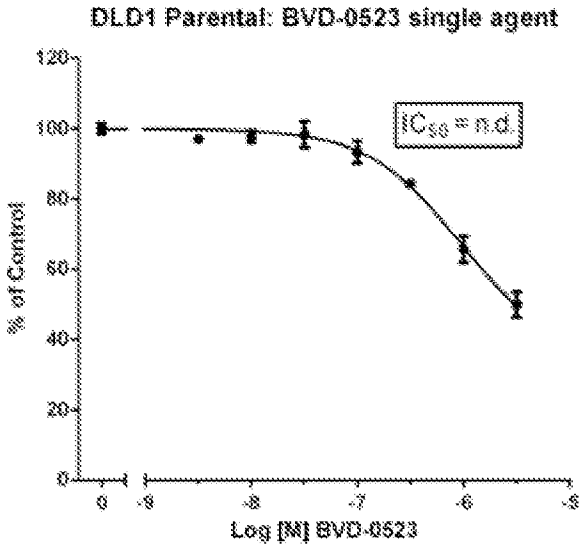


FIG. 17, Continued

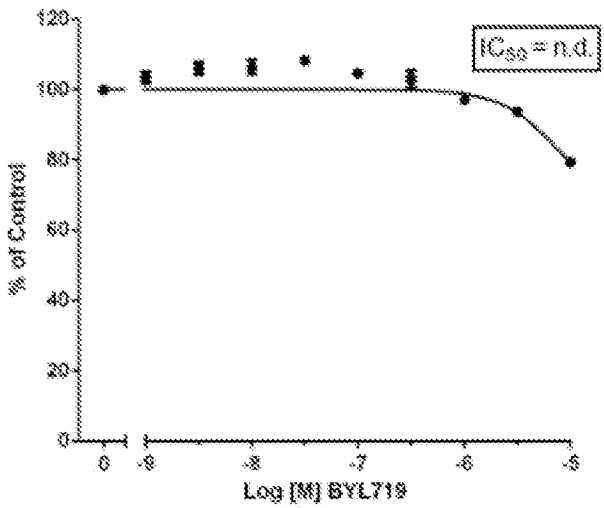
G



H



I



J

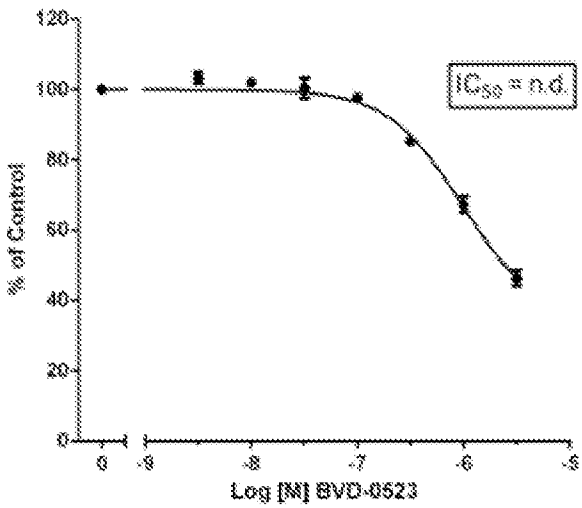


FIG. 18

A

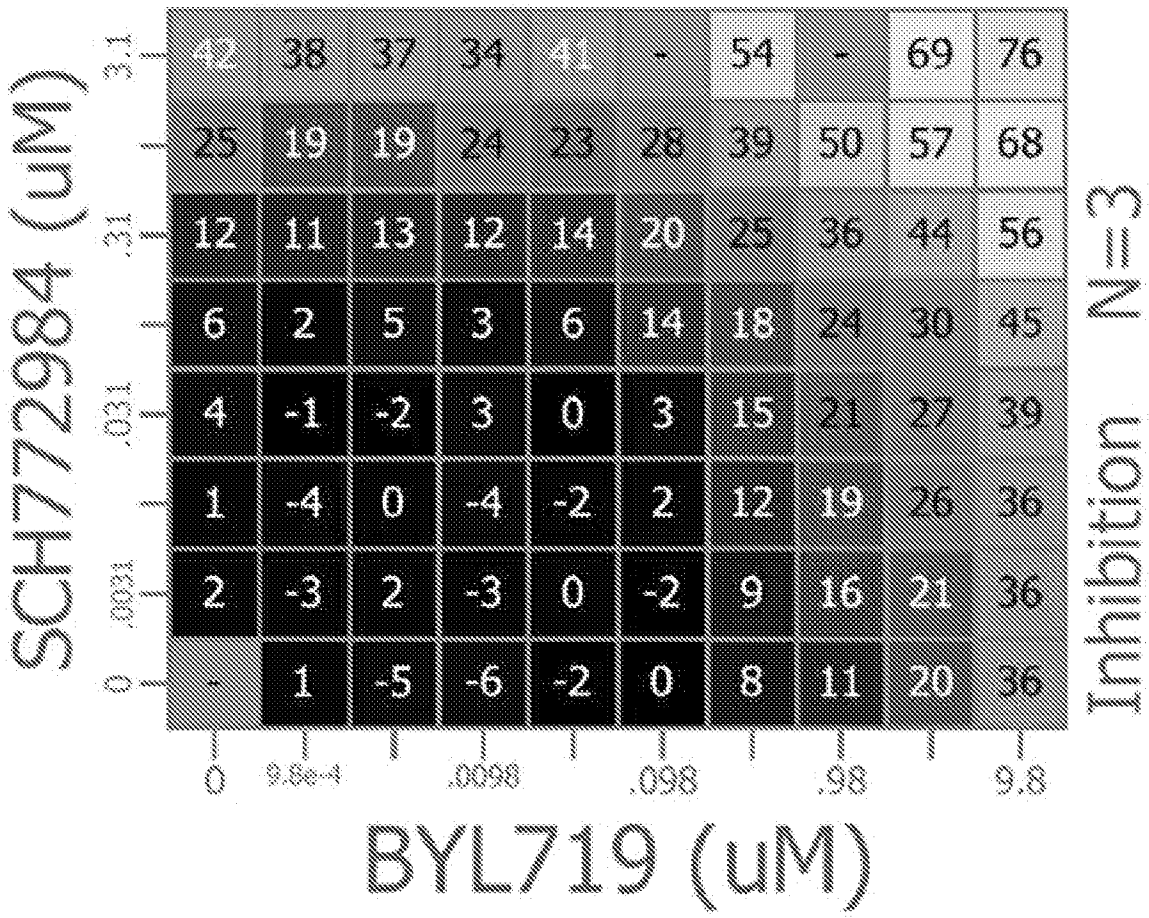

SCH772984 (uM)
3.1
.31
.031
.0031
0
42 38 37 34 41 - 54 - 69 76
25 19 19 24 23 28 39 50 57 68
12 11 13 12 14 20 25 36 44 56
6 2 5 3 6 14 18 24 30 45
4 -1 -2 3 0 3 15 21 27 39
1 -4 0 -4 -2 2 12 19 26 36
2 -3 2 -3 0 -2 9 16 21 36
- 1 -5 -6 -2 0 8 11 20 36
0
9.8e-4
.0098
.098
.98
9.8
BYL719 (uM)
Inhibition N=3

FIG. 18, Continued

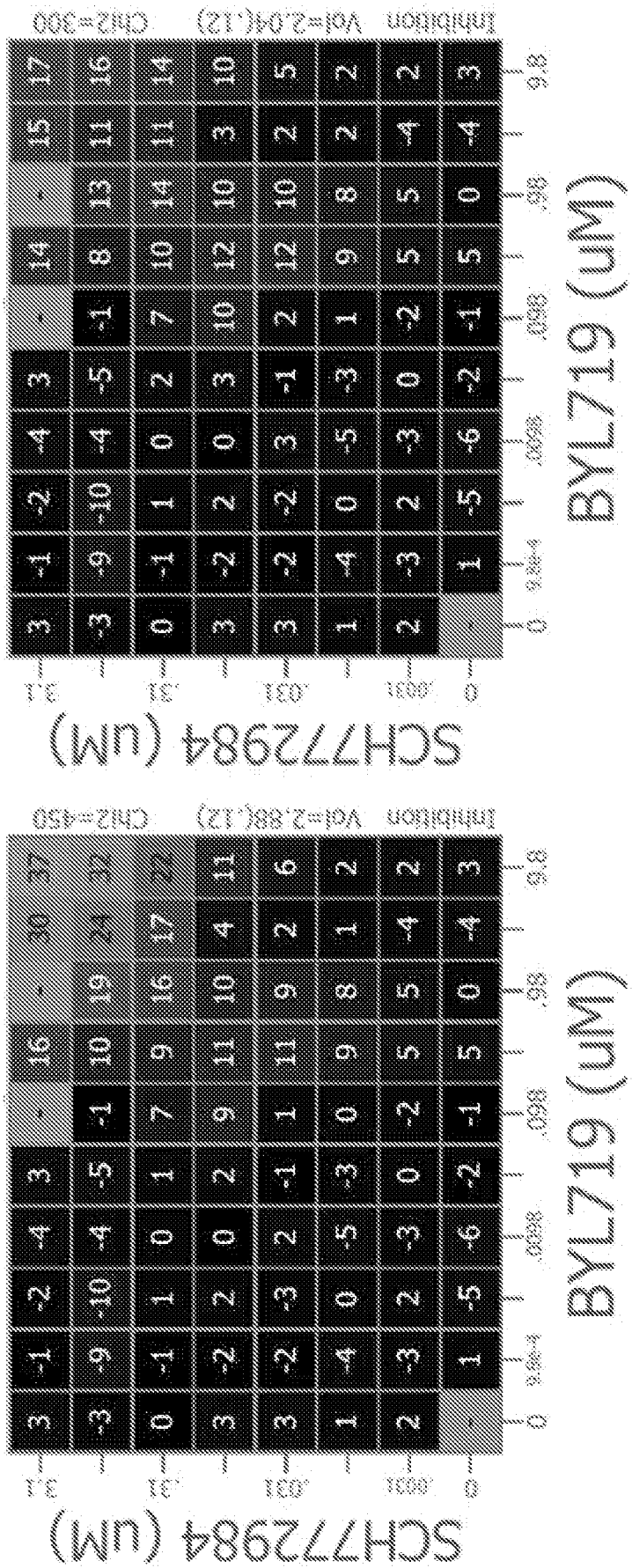


FIG. 18, Continued

D

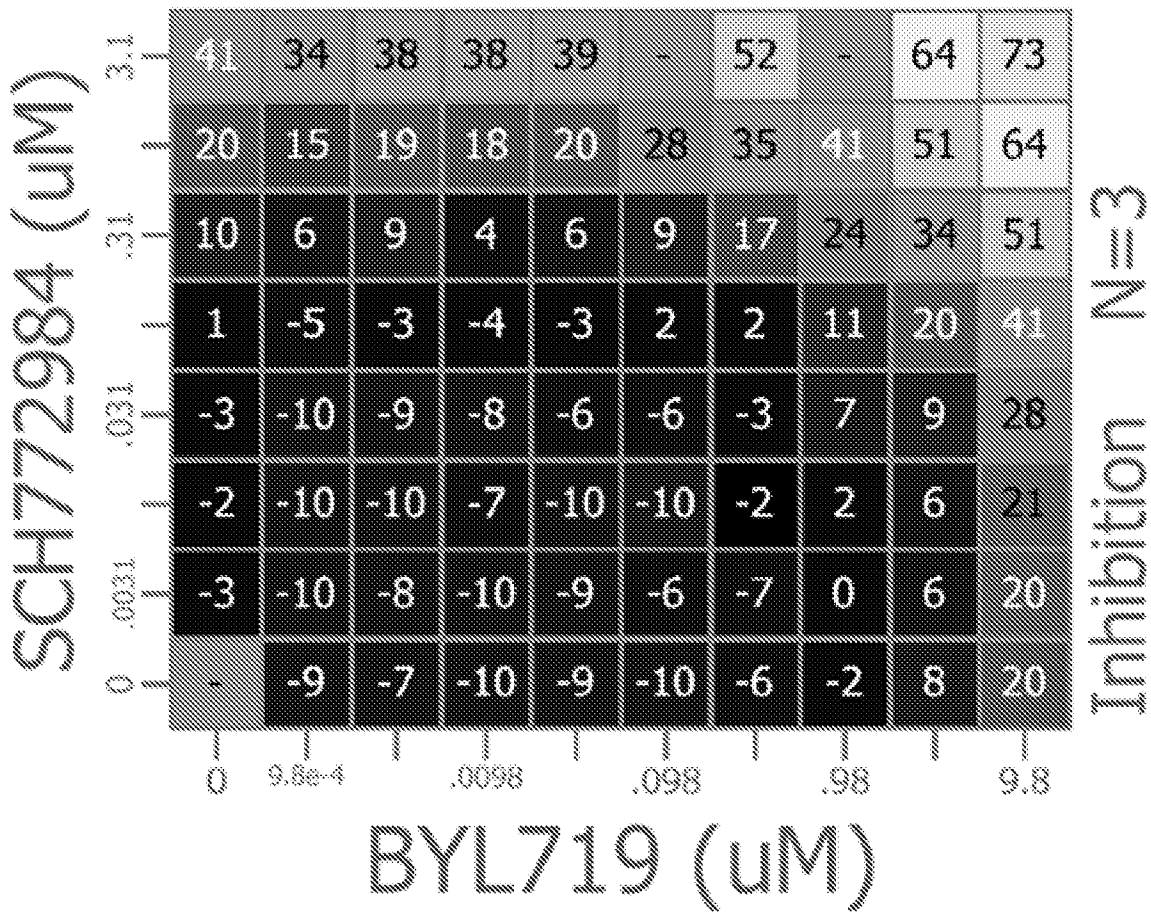


FIG. 18, Continued

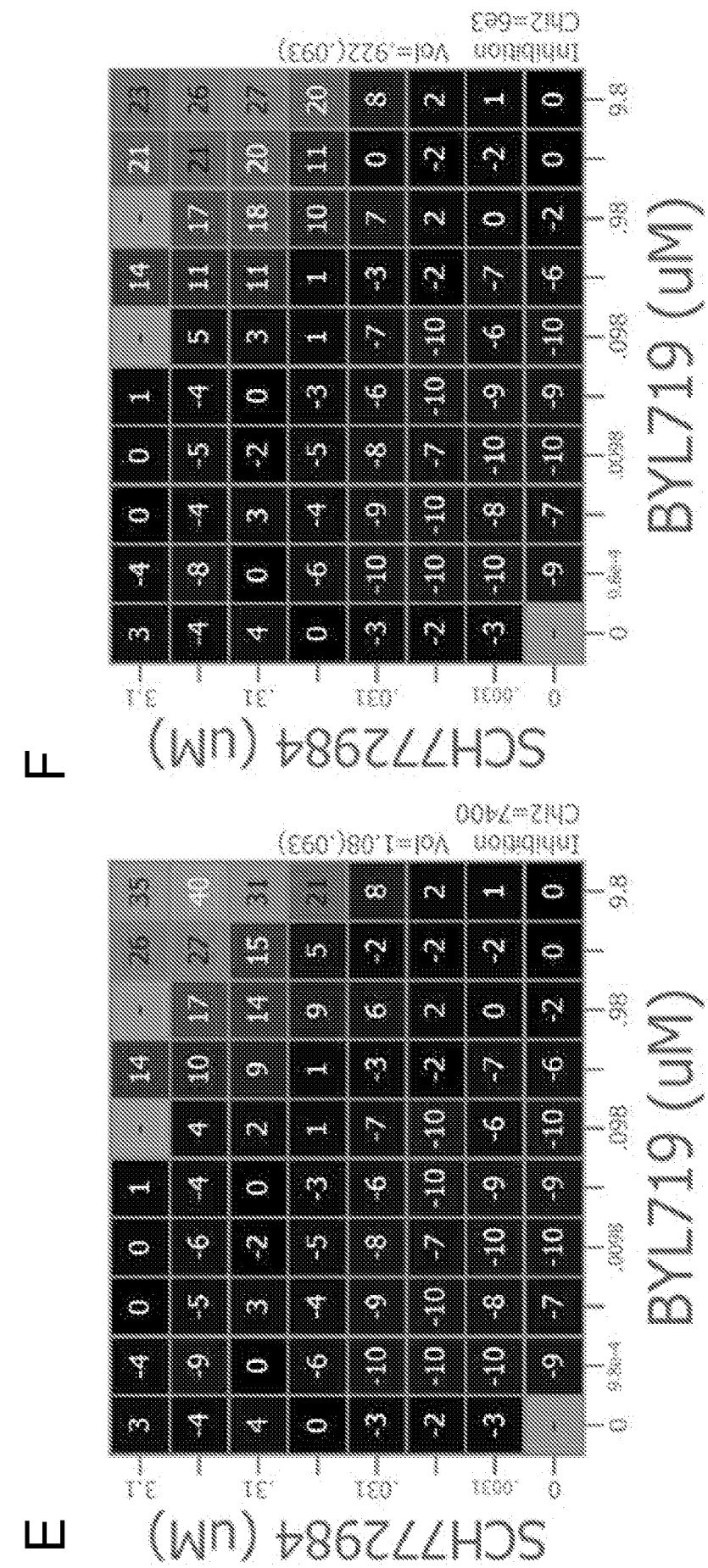
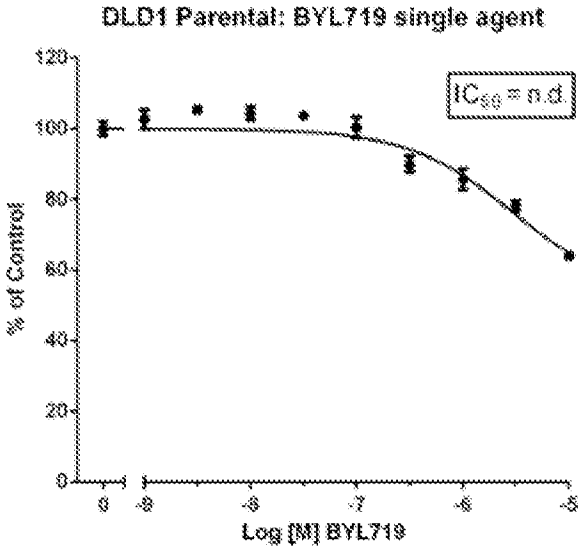
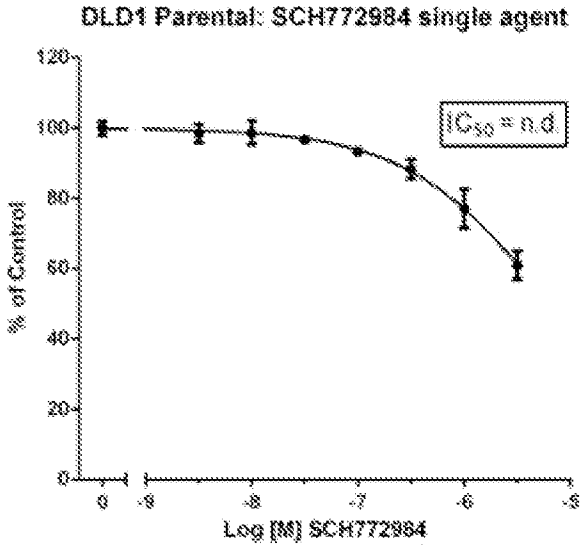


FIG. 18, Continued

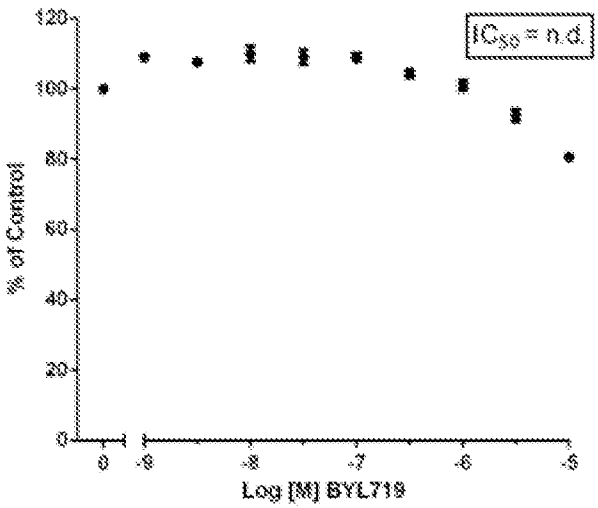
G



H



I



J

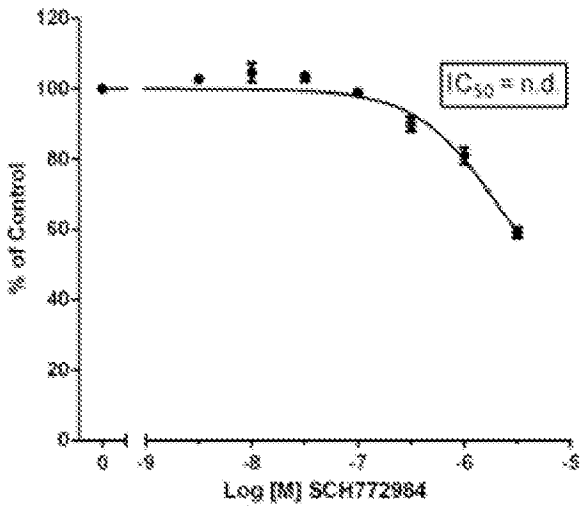


FIG. 19

A

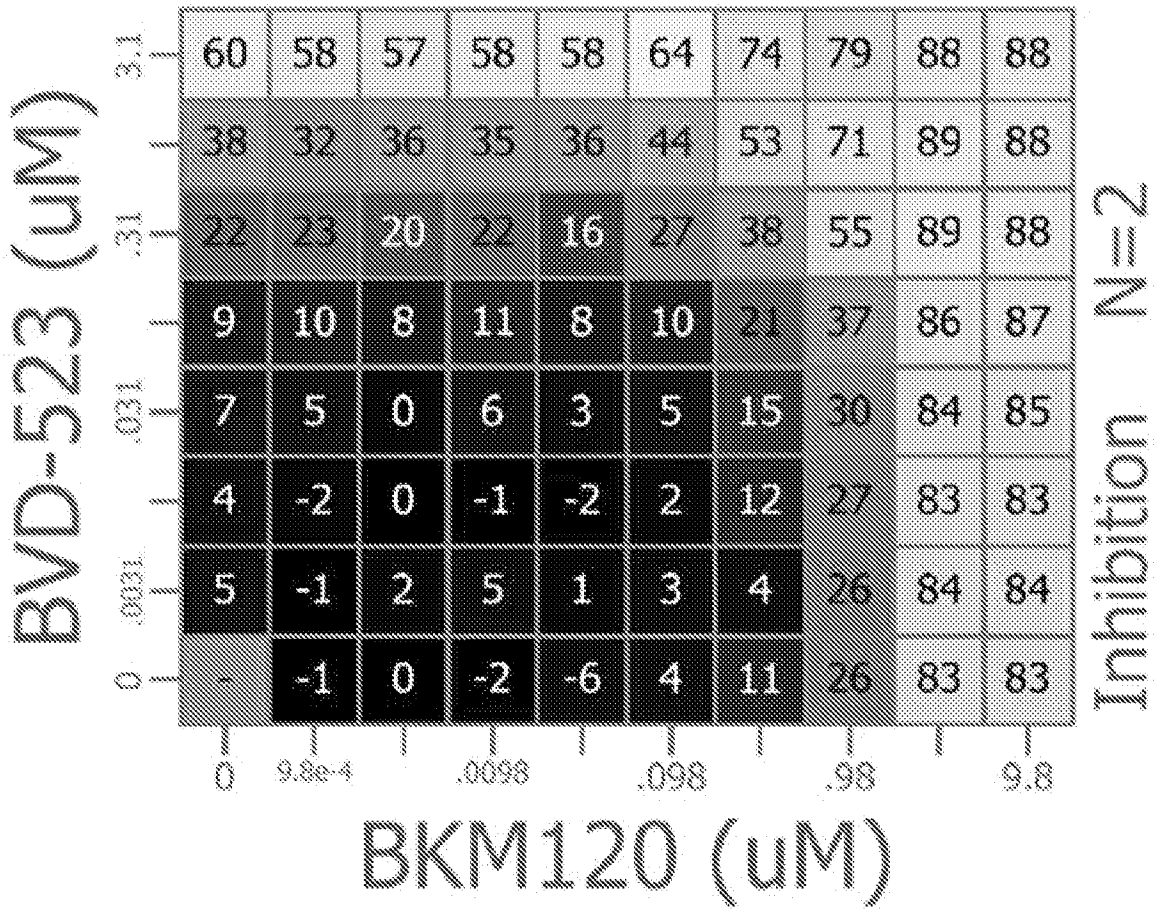
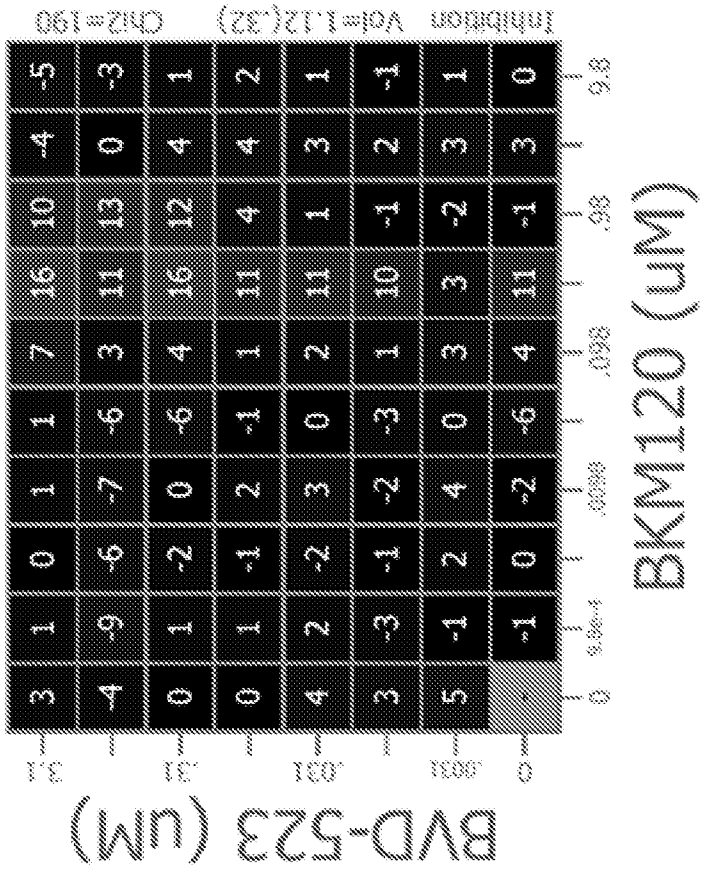

BVD-523 (uM)
3.1
.31
.031
.0031
0
60 58 57 58 58 64 74 79 88 88
38 32 36 35 36 44 53 71 89 88
22 23 20 22 16 27 38 55 89 88
9 10 8 11 8 10 21 37 86 87
7 5 0 6 3 5 15 30 84 85
4 -2 0 -1 -2 2 12 27 83 83
5 -1 2 5 1 3 4 26 84 84
- -1 0 -2 -6 4 11 26 83 83
0 9.8e-4 .0098 .098 .98 9.8
BKM120 (uM)
Inhibition N=2

FIG. 19, Continued



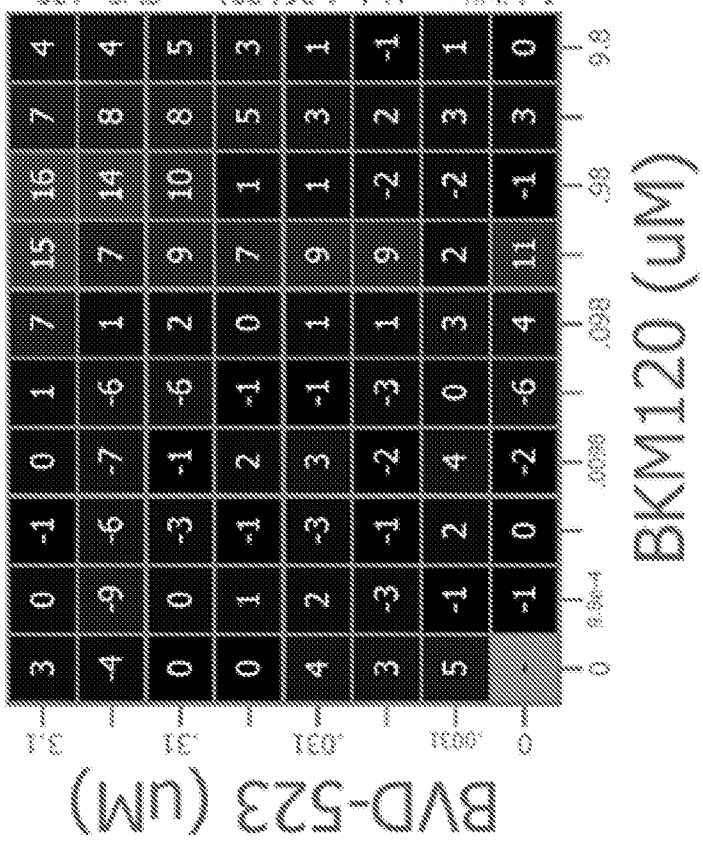


FIG. 19, Continued

D

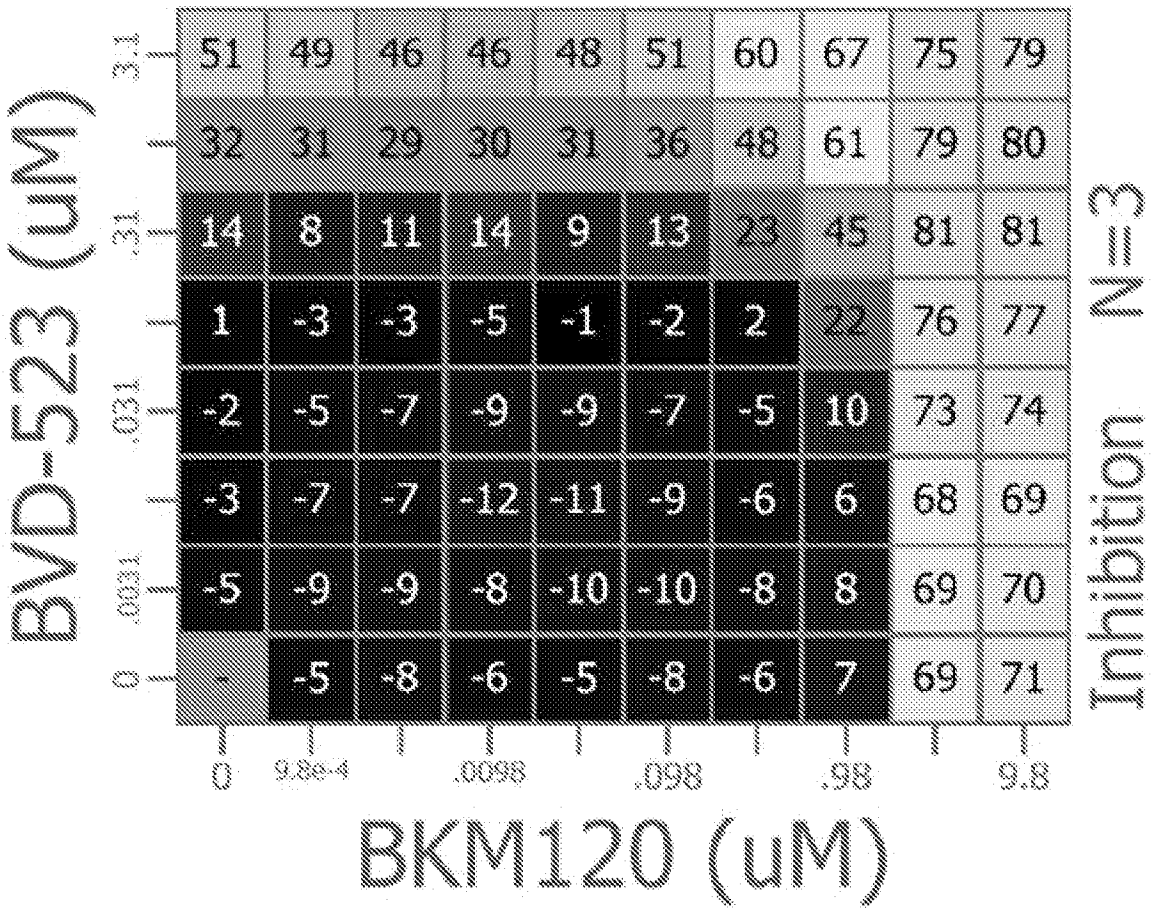
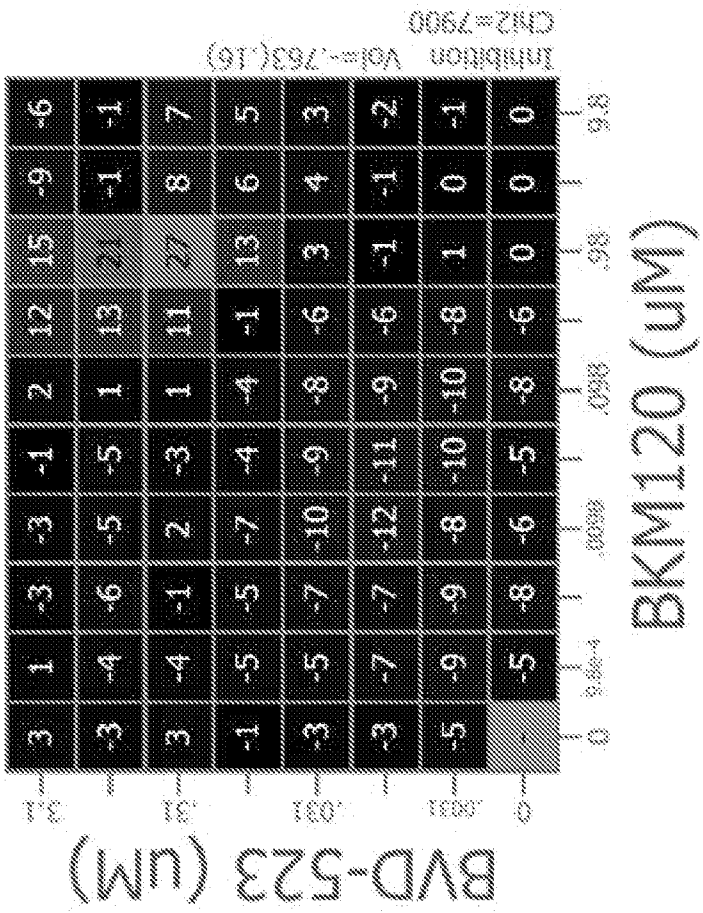


FIG. 19, Continued



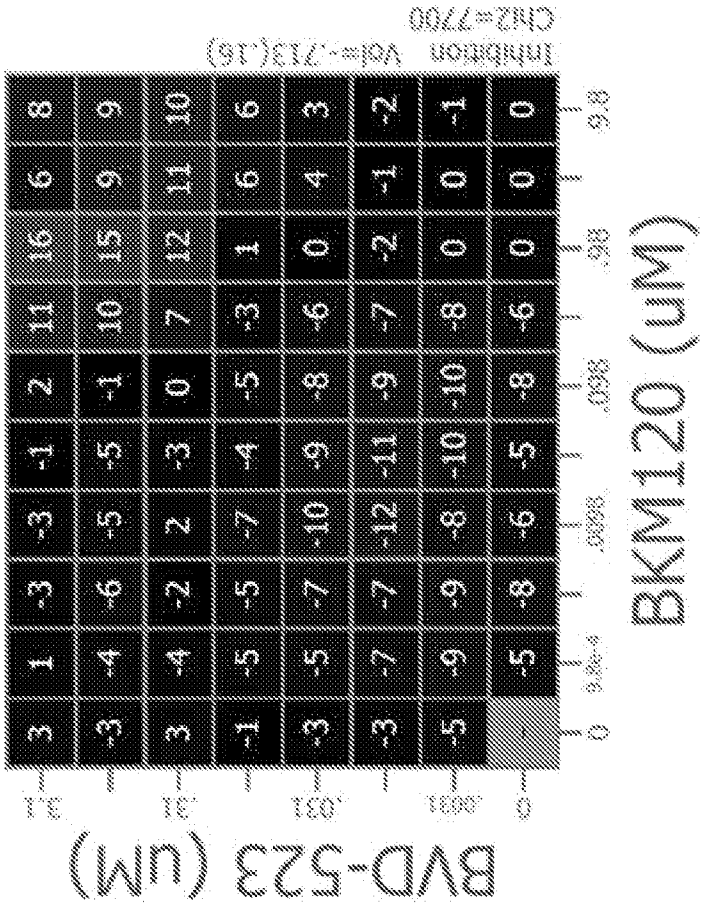
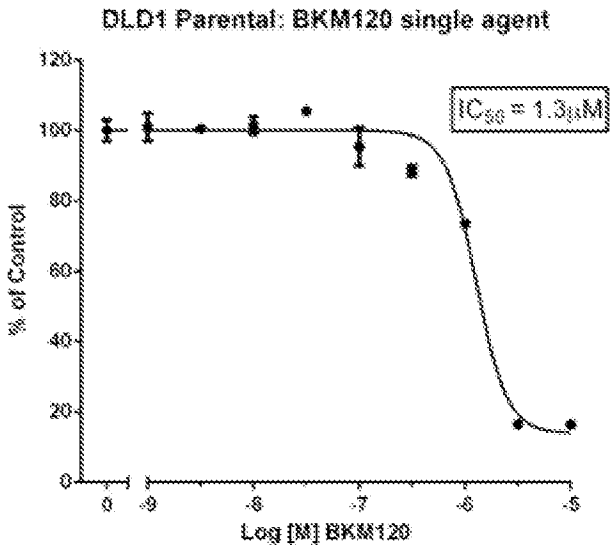
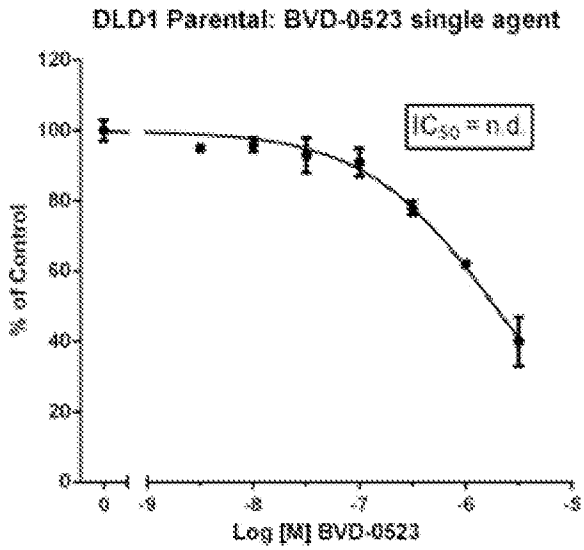


FIG. 19, Continued

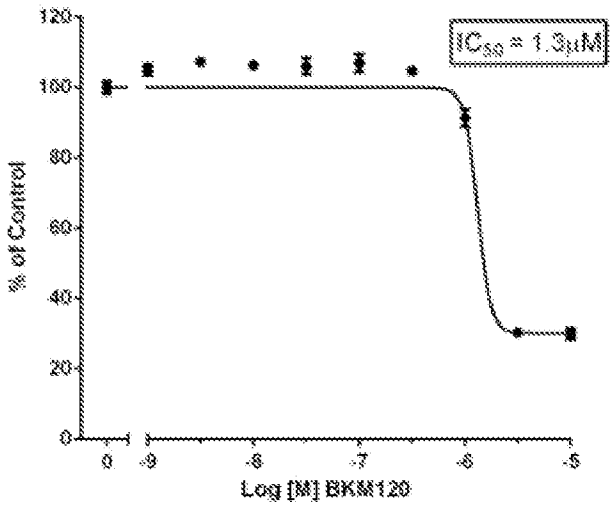
G



H



I



J

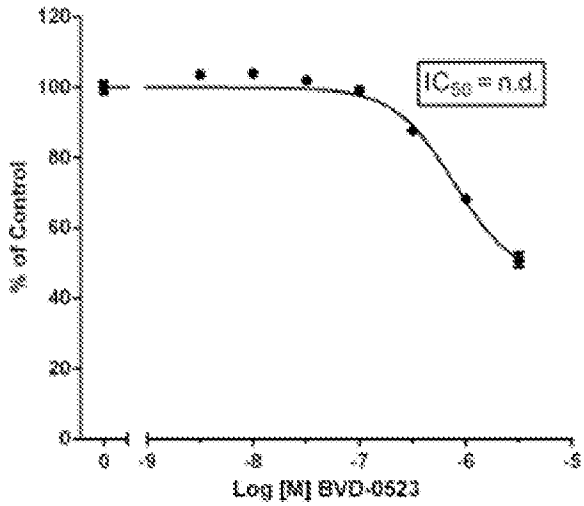


FIG. 20

A

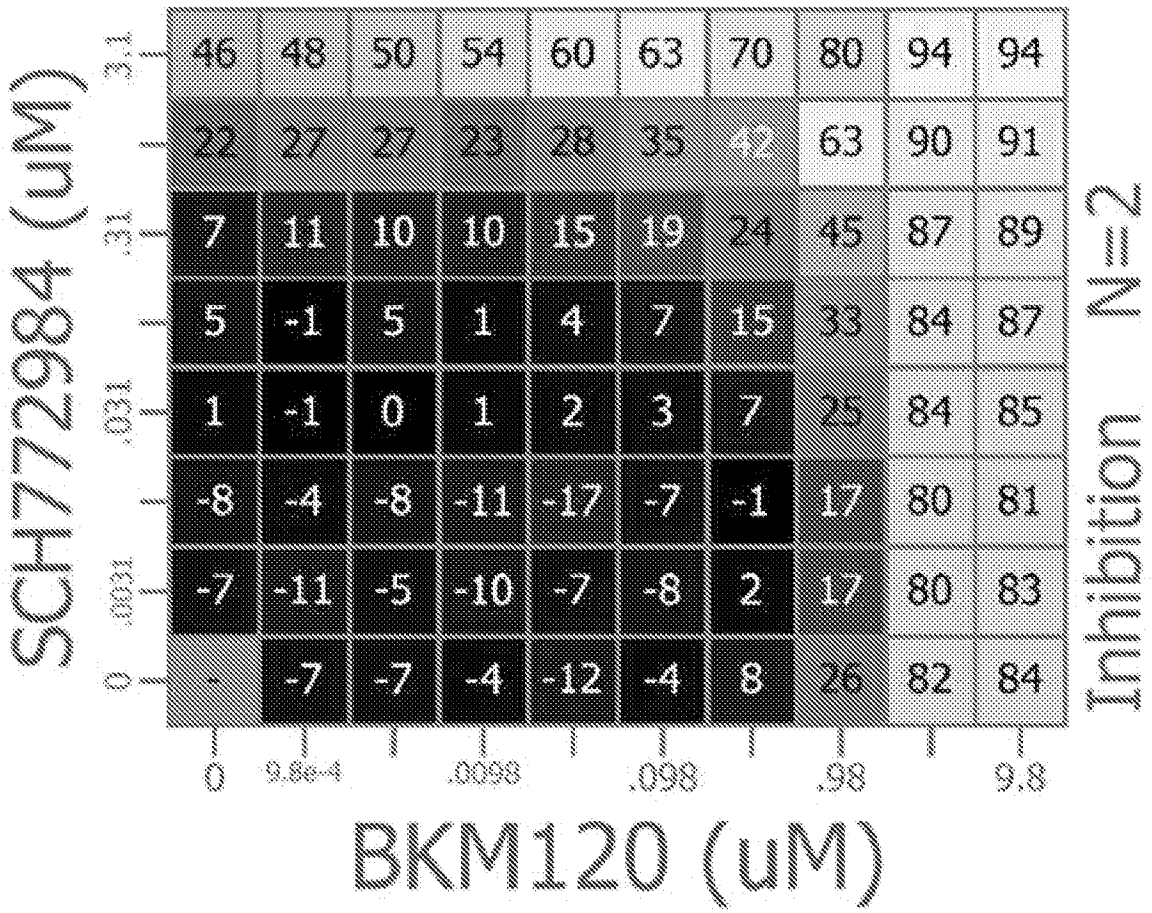

SCH772984 (uM)
3.1
.31
.031
.0031
0
46 48 50 54 60 63 70 80 94 94
22 27 27 23 28 35 42 63 90 91
7 11 10 10 15 19 24 45 87 89
5 -1 5 1 4 7 15 33 84 87
1 -1 0 1 2 3 7 25 84 85
-8 -4 -8 -11 -17 -7 -1 17 80 81
-7 -11 -5 -10 -7 -8 2 17 80 83
- -7 -7 -4 -12 -4 8 26 82 84
Inhibition N=2
0
9.8e-4
.0098
.098
.98
9.8
BKM120 (uM)

FIG. 20, Continued

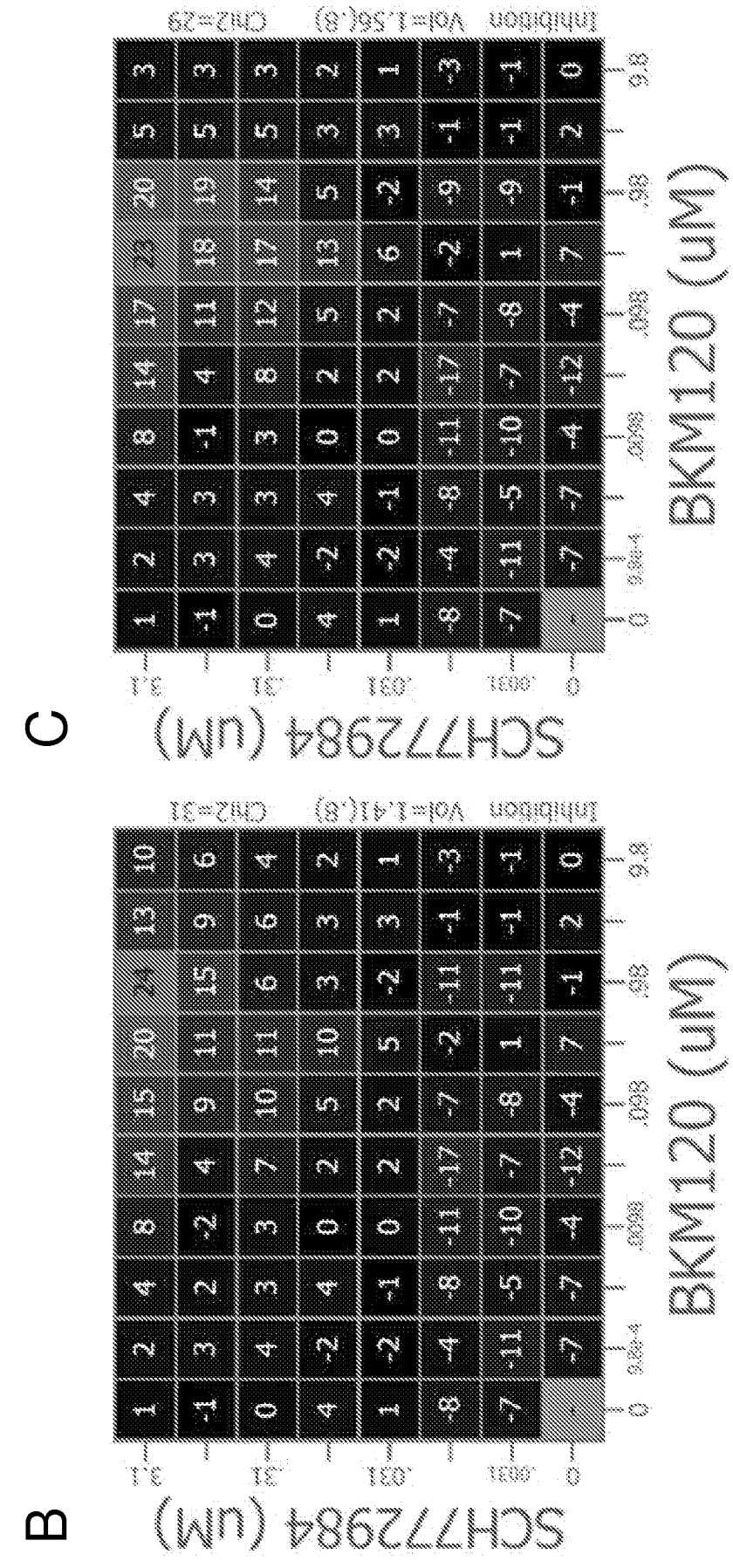


FIG. 20, Continued

D

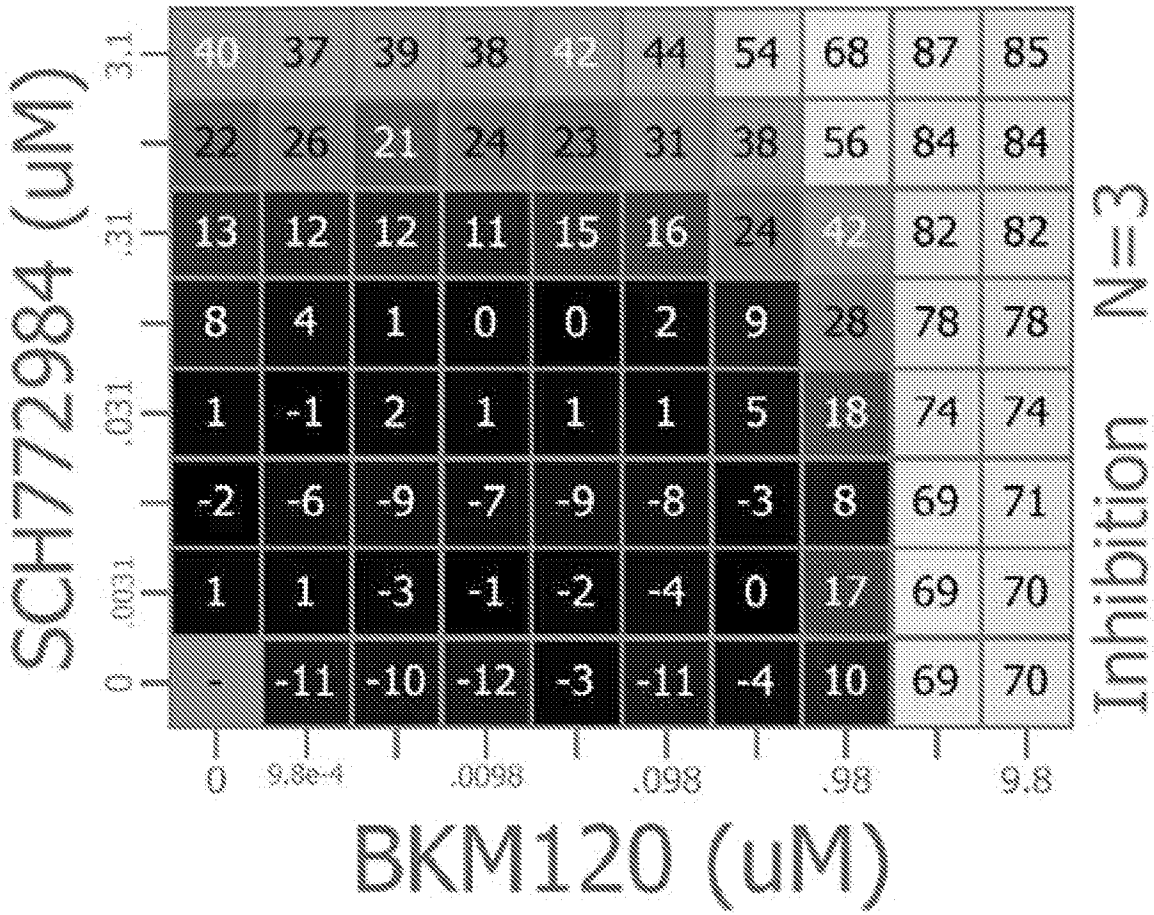
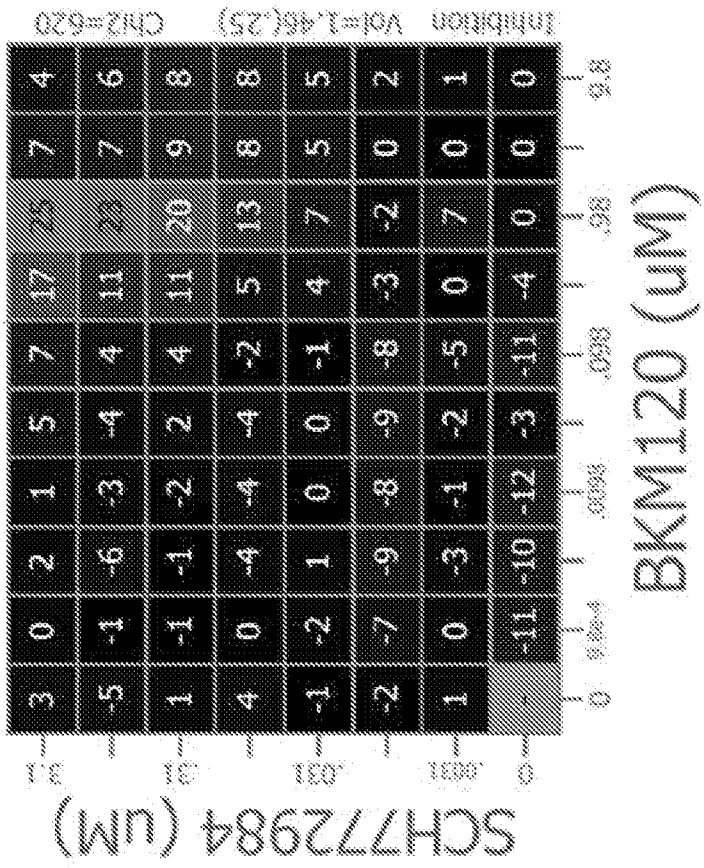


FIG. 20, Continued



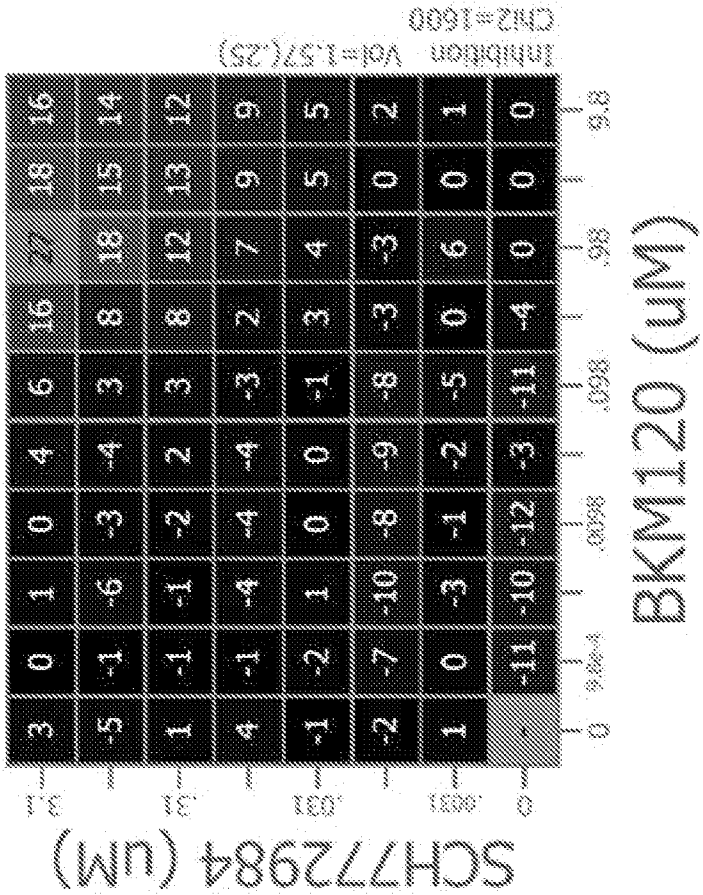
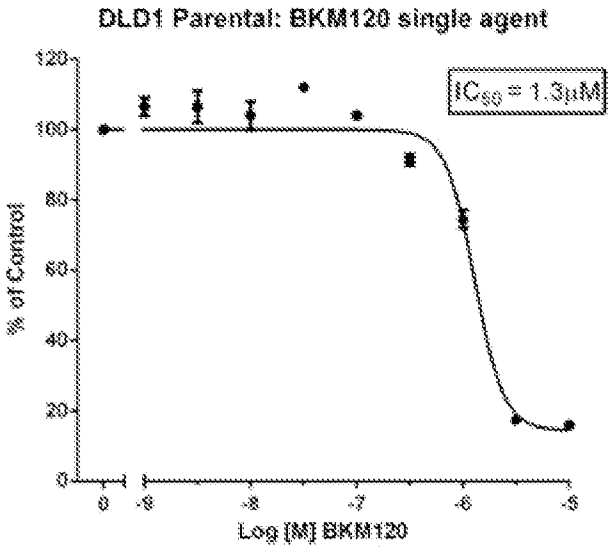
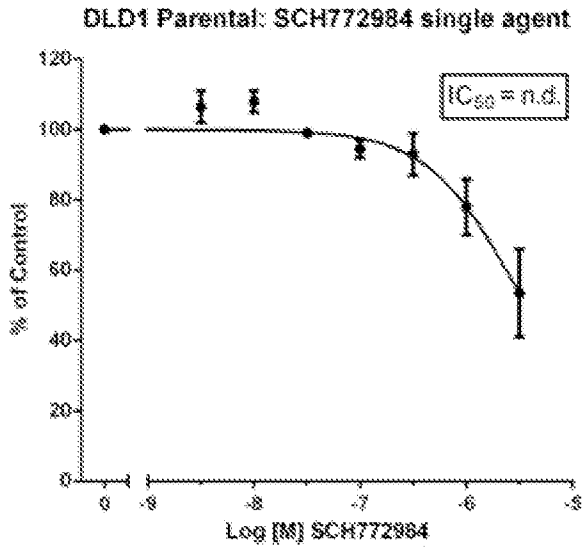


FIG. 20, Continued

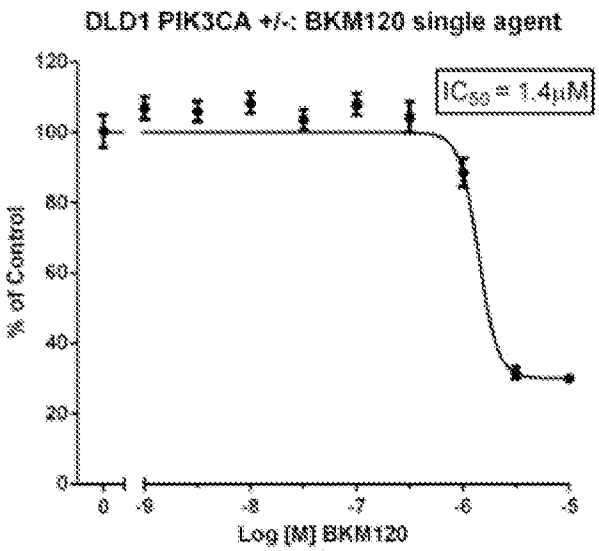
G



H



I



J

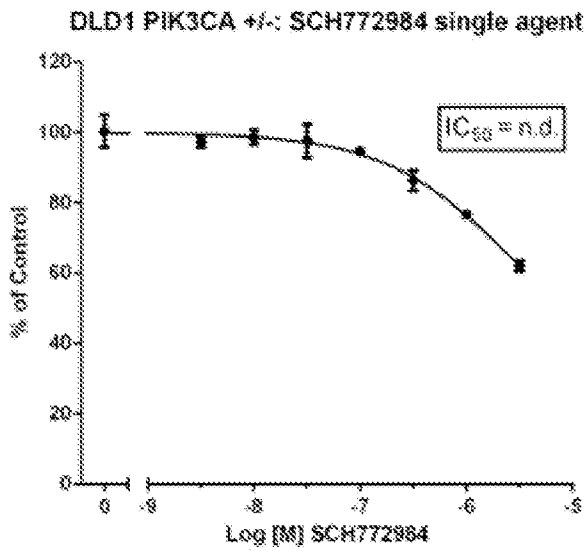


FIG. 21

A

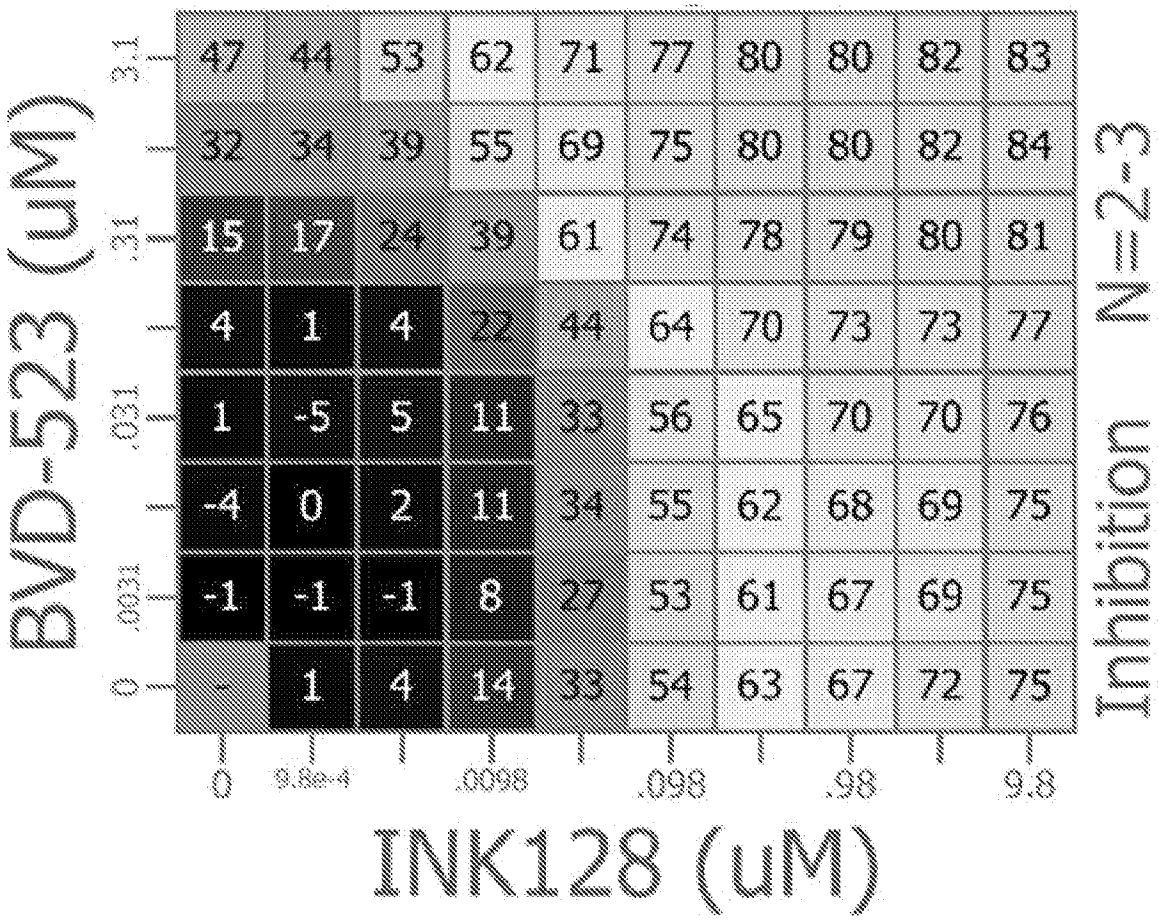

BVD-523 (uM)
3.1
.31
.031
.0031
0
47 44 53 62 71 77 80 80 82 83
32 34 39 55 69 75 80 80 82 84
15 17 24 39 61 74 78 79 80 81
4 1 4 22 44 64 70 73 73 77
1 -5 5 11 33 56 65 70 70 76
-4 0 2 11 34 55 62 68 69 75
-1 -1 -1 8 27 53 61 67 69 75
- 1 4 14 33 54 63 67 72 75
0
9.8e-4
.0098
.098
.98
9.8
INK128 (uM)
Inhibition N=2-3

FIG. 21, Continued

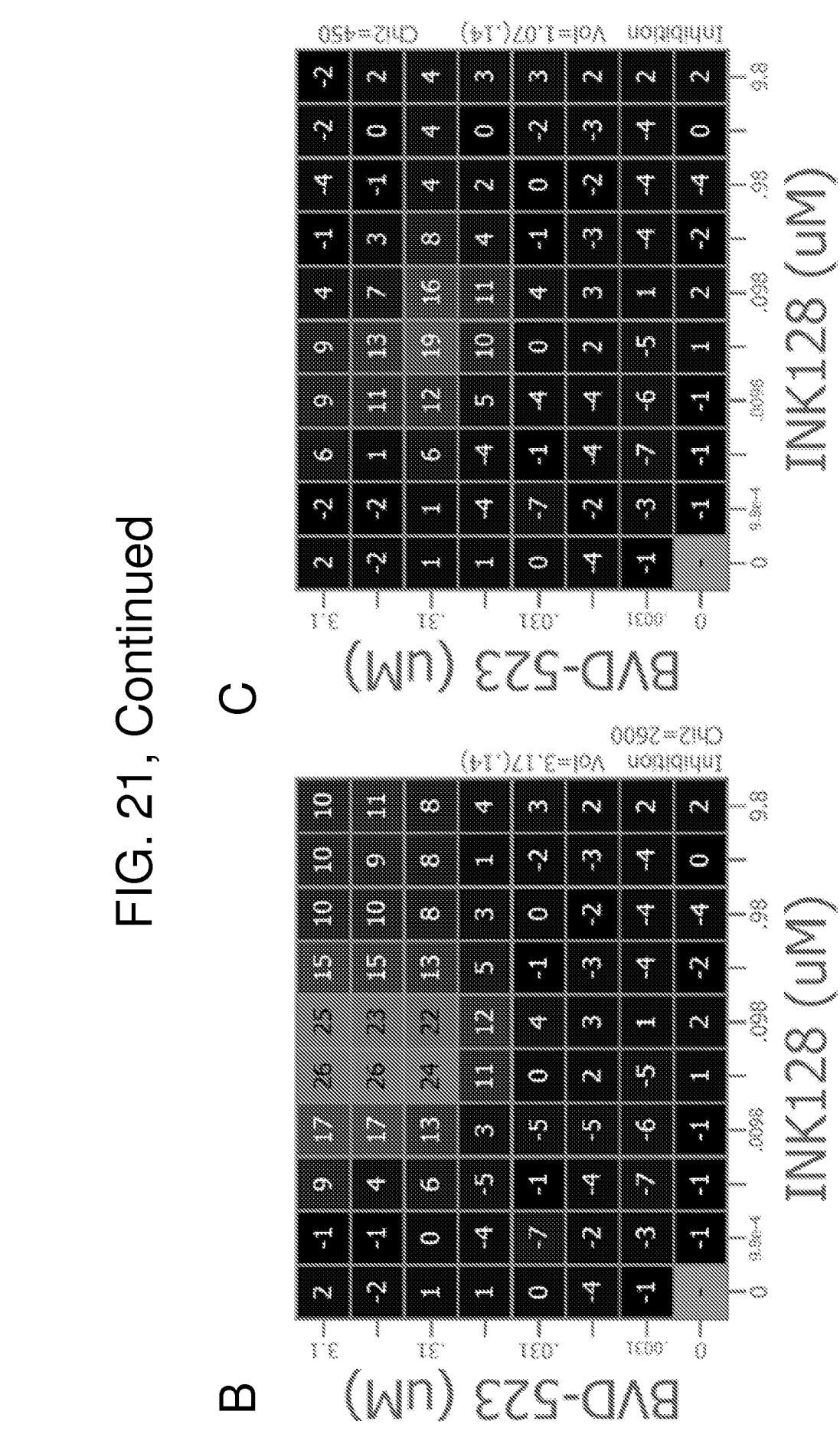


FIG. 21, Continued

D

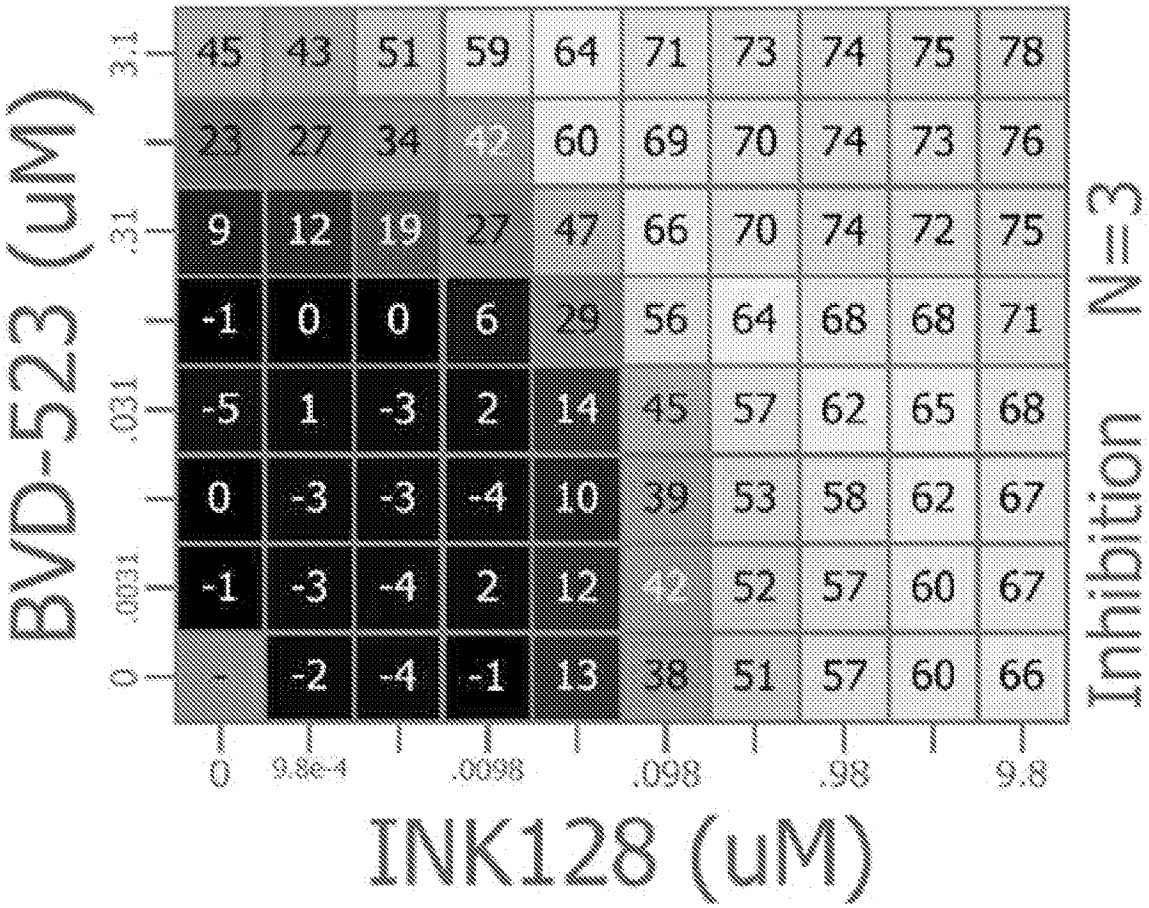
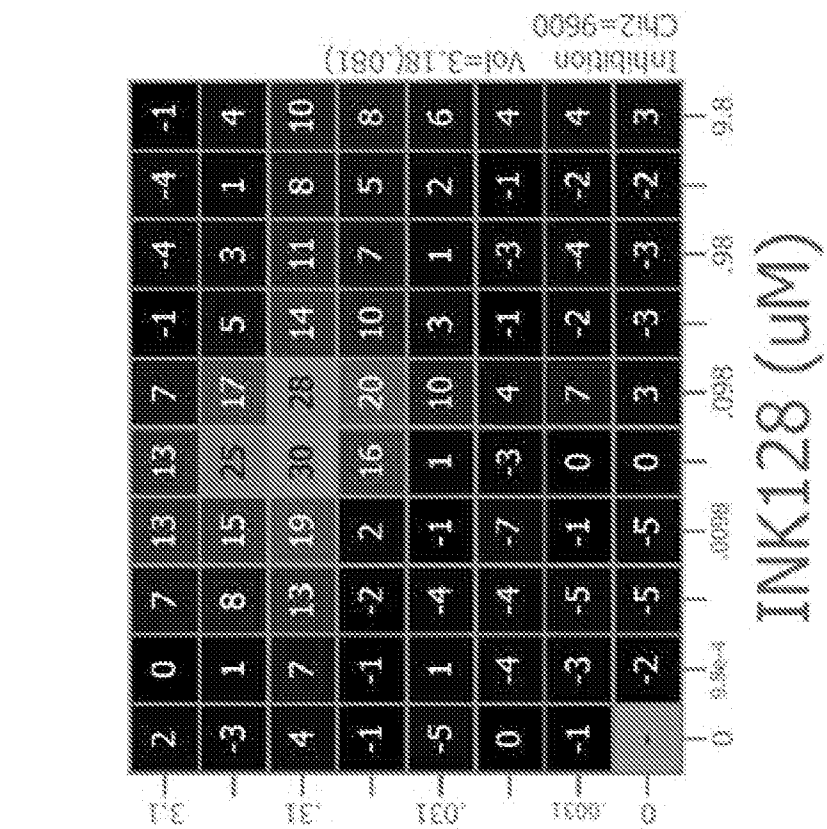


FIG. 21, Continued



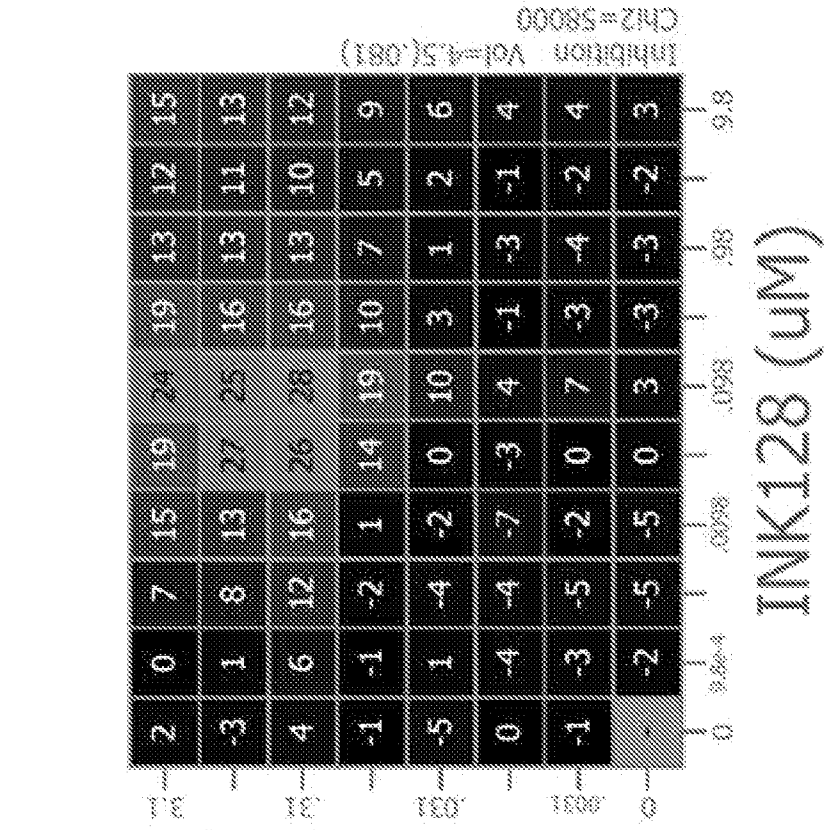
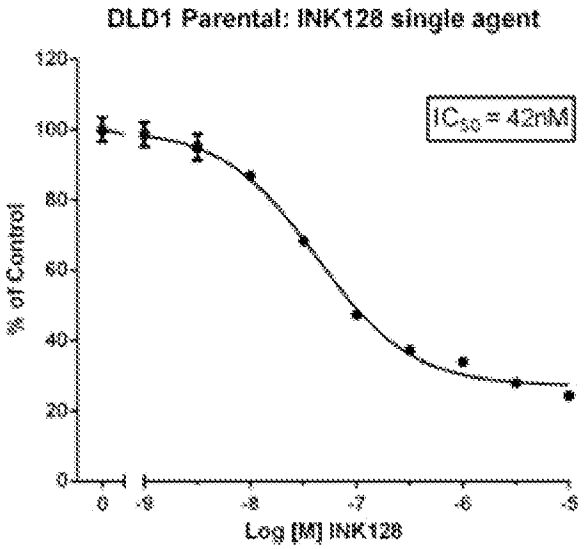
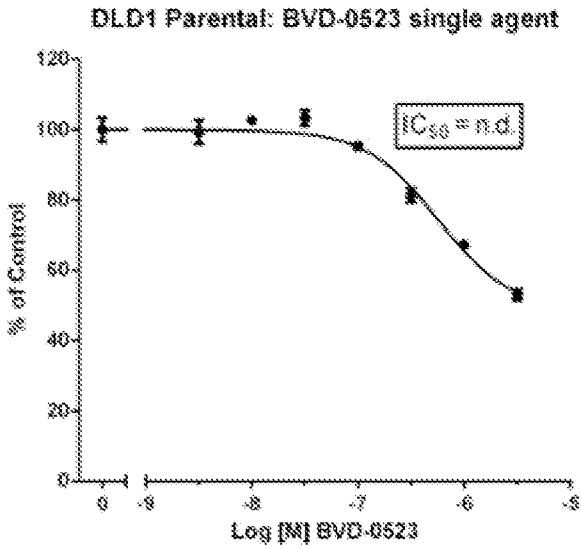


FIG. 21, Continued

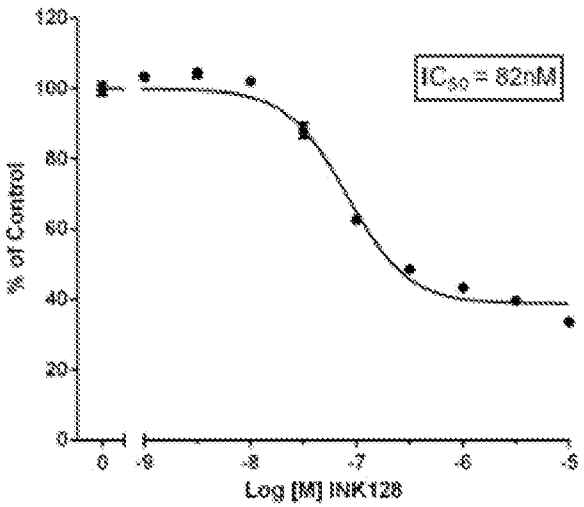
G



H



I



J

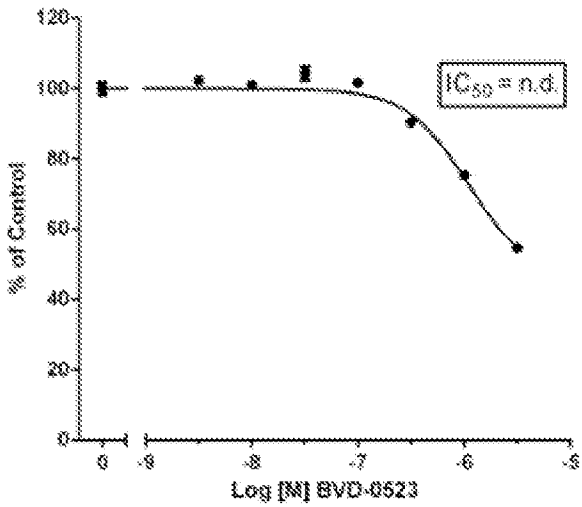


FIG. 22

A

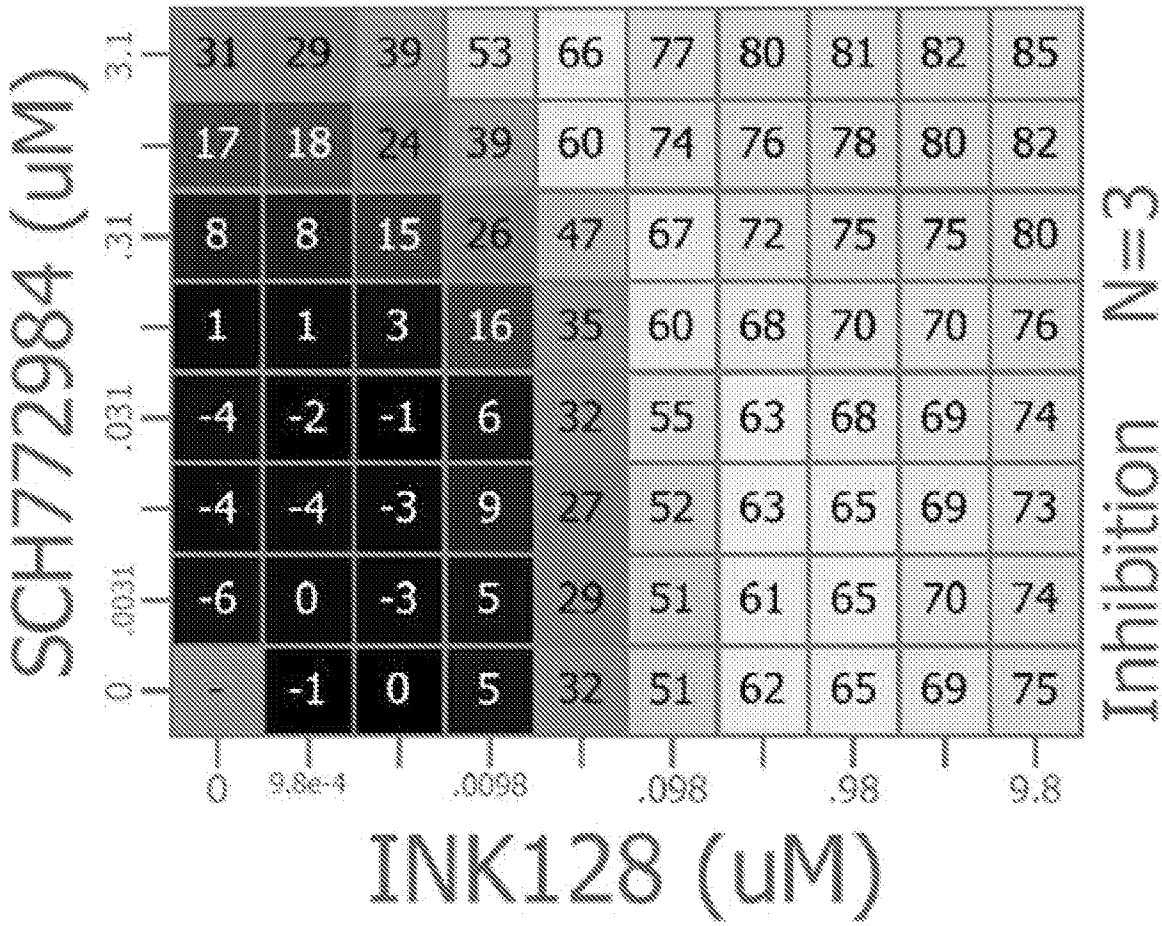

SCH772984 (uM)
3.1
.31
.031
.0031
0
31 29 39 53 66 77 80 81 82 85
17 18 24 39 60 74 76 78 80 82
8 8 15 26 47 67 72 75 75 80
1 1 3 16 35 60 68 70 70 76
-4 -2 -1 6 32 55 63 68 69 74
-4 -4 -3 9 27 52 63 65 69 73
-6 0 -3 5 29 51 61 65 70 74
- -1 0 5 32 51 62 65 69 75
Inhibition N=3
0
9.8e-4
.0098
.098
.98
9.8
INK128 (uM)

FIG. 22, Continued

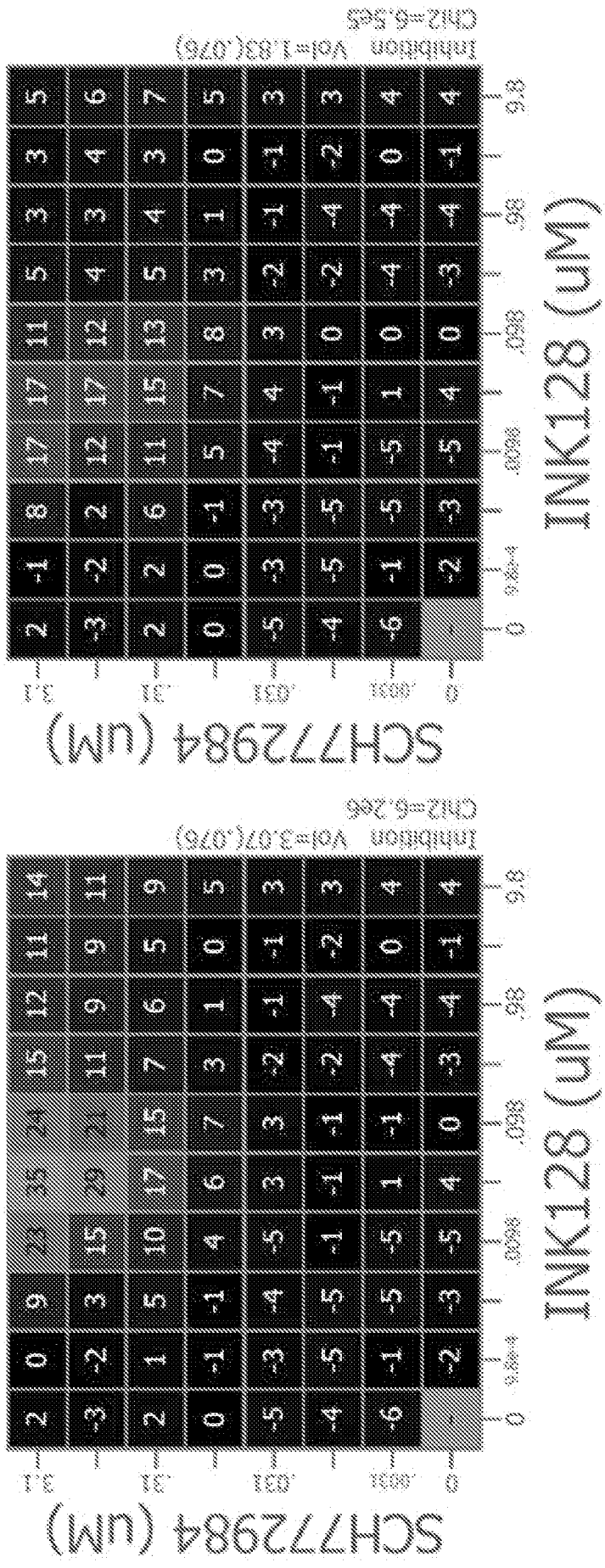


FIG. 22, Continued

D

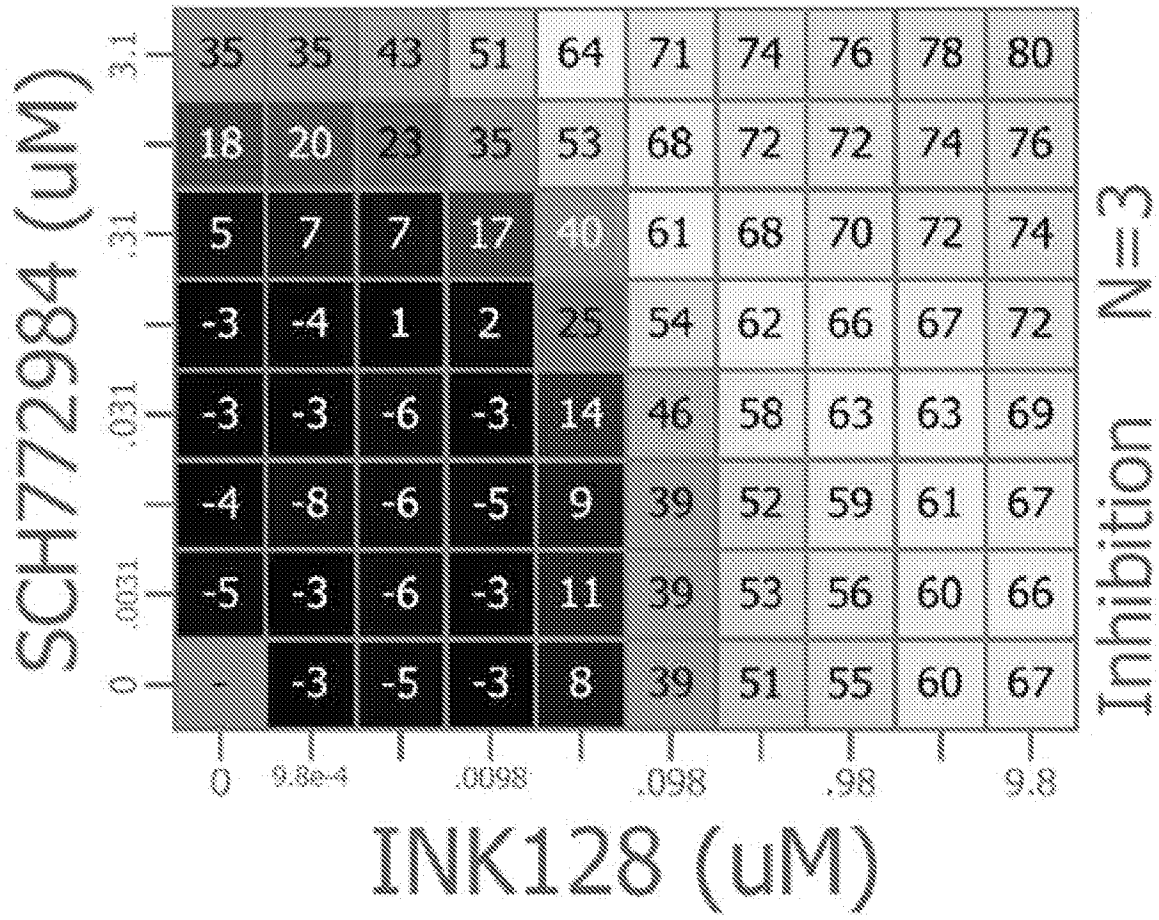


FIG. 22, Continued

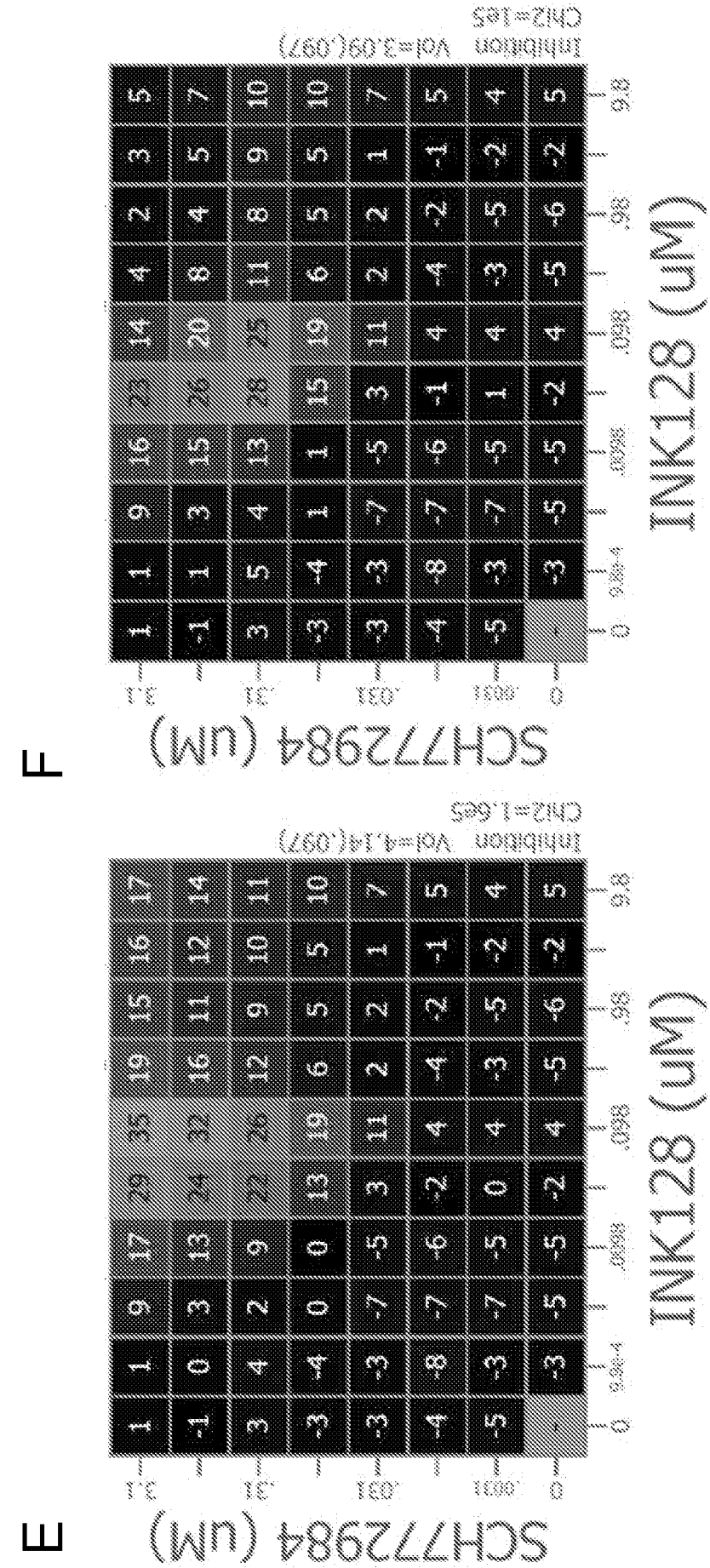
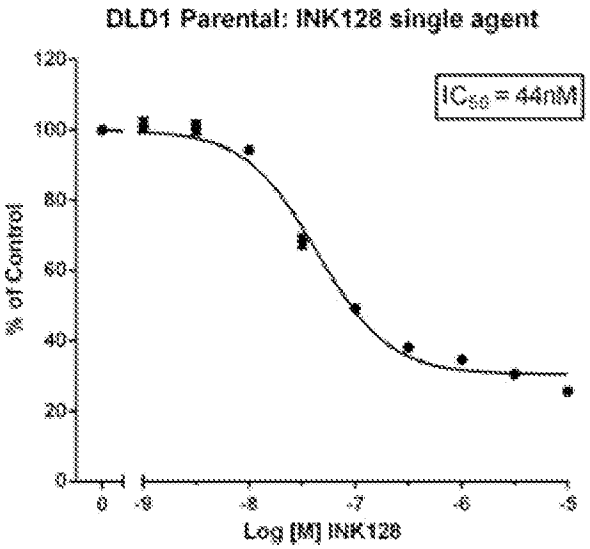
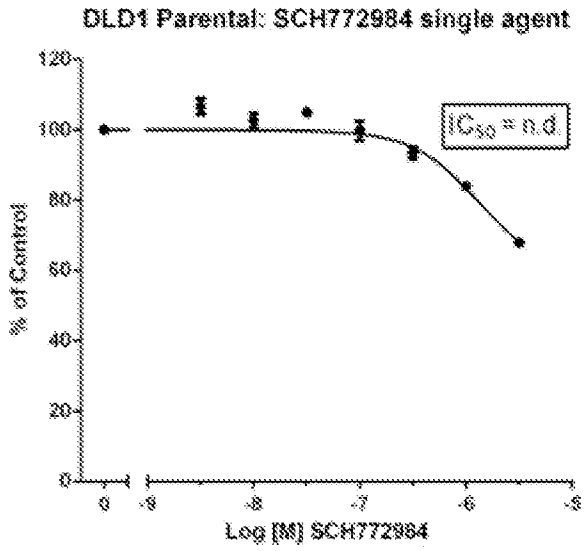


FIG. 22, Continued

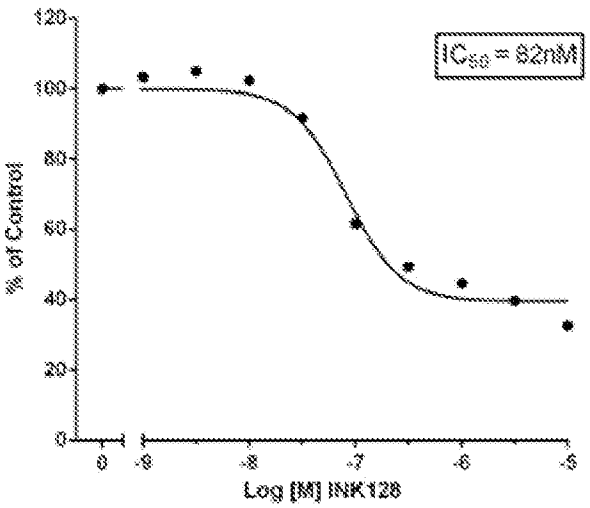
G



H



I



J

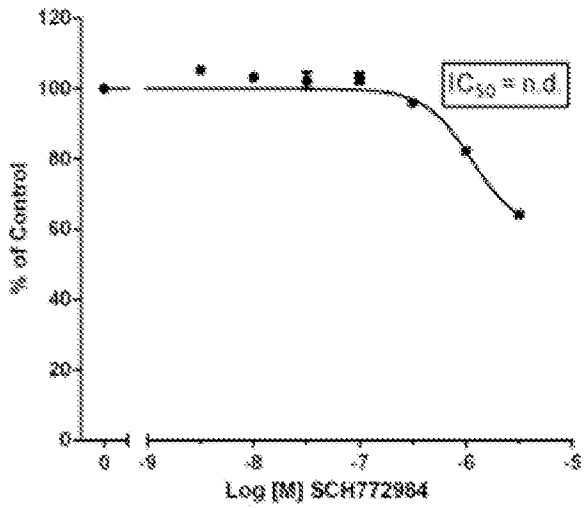


FIG. 23

A

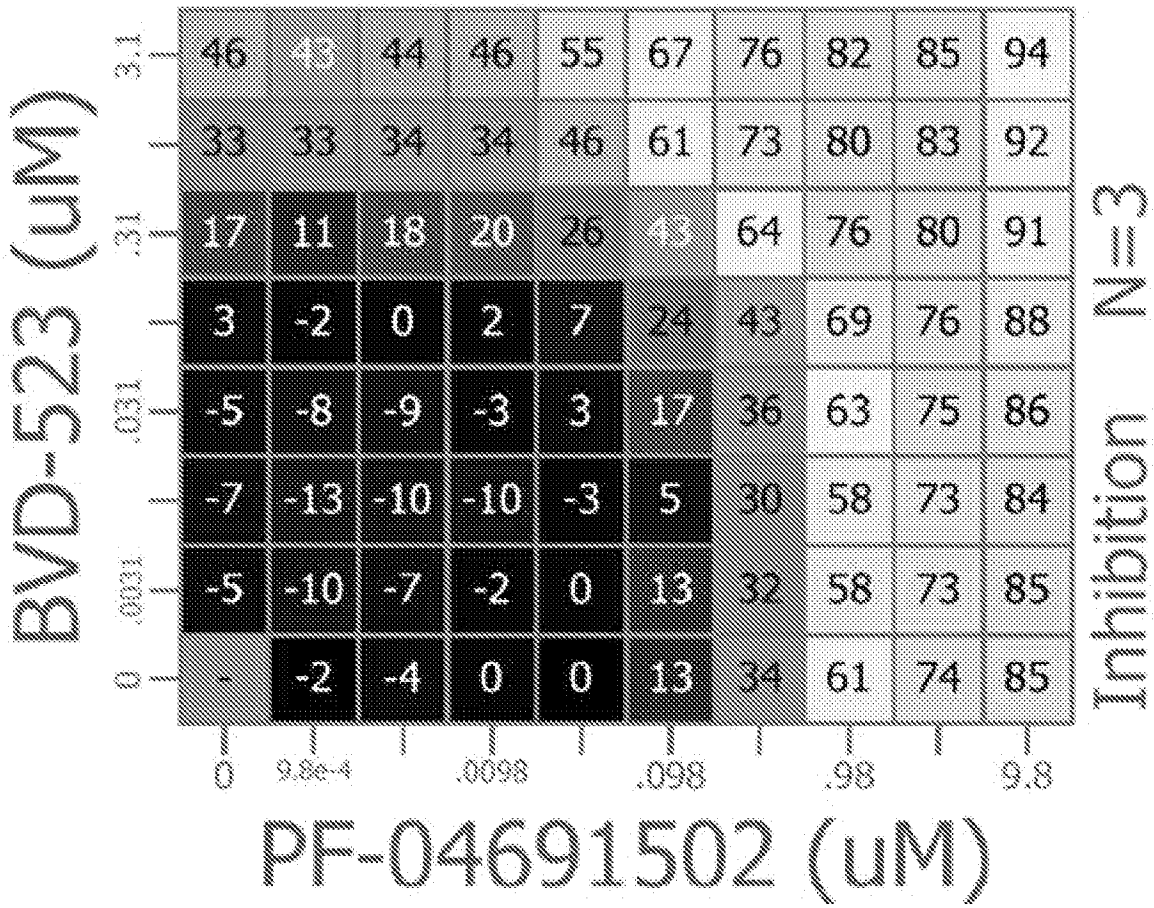

BVD-523 (uM)
3.1
.31
.031
.0031
0
46 43 44 46 55 67 76 82 85 94
33 33 34 34 46 61 73 80 83 92
17 11 18 20 26 43 64 76 80 91
3 -2 0 2 7 24 43 69 76 88
-5 -8 -9 -3 3 17 36 63 75 86
-7 -13 -10 -10 -3 5 30 58 73 84
-5 -10 -7 -2 0 13 32 58 73 85
- -2 -4 0 0 13 34 61 74 85
Inhibition N=3
0
9.8e-4
.0098
.098
.98
9.8
PF-04691502 (uM)

FIG. 23, Continued

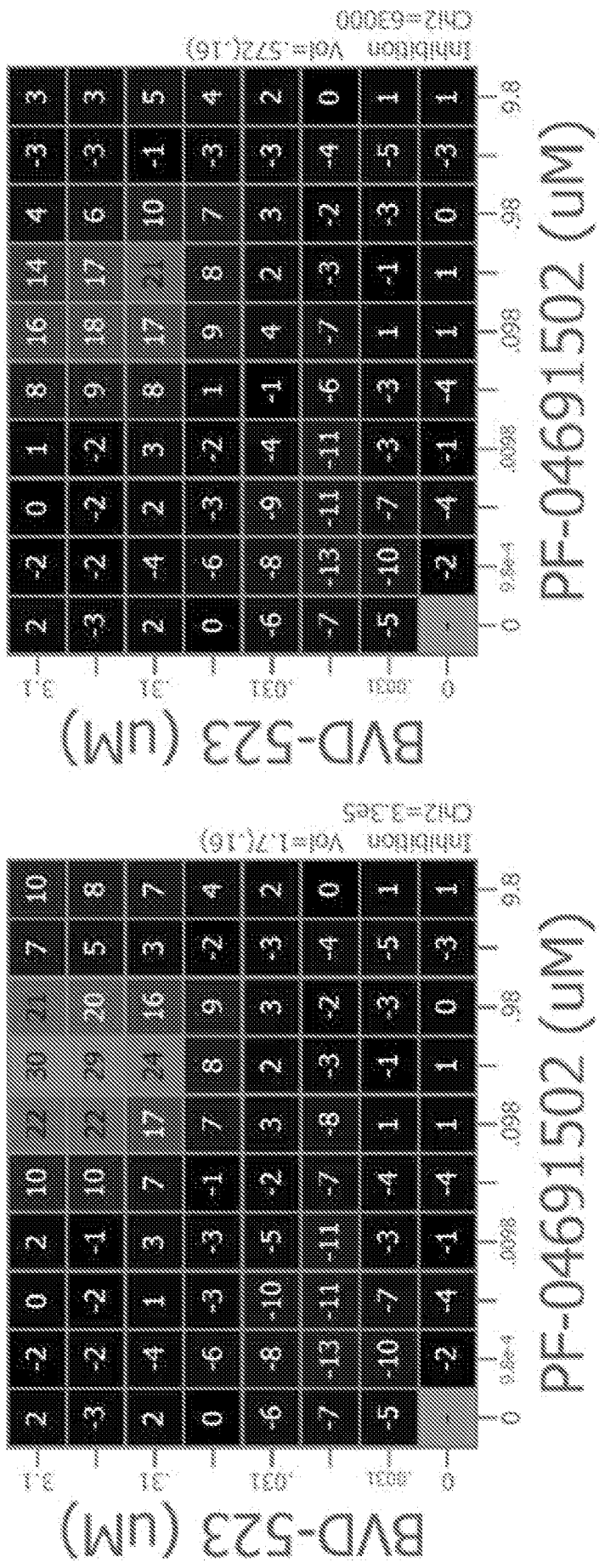


FIG. 23, Continued

D

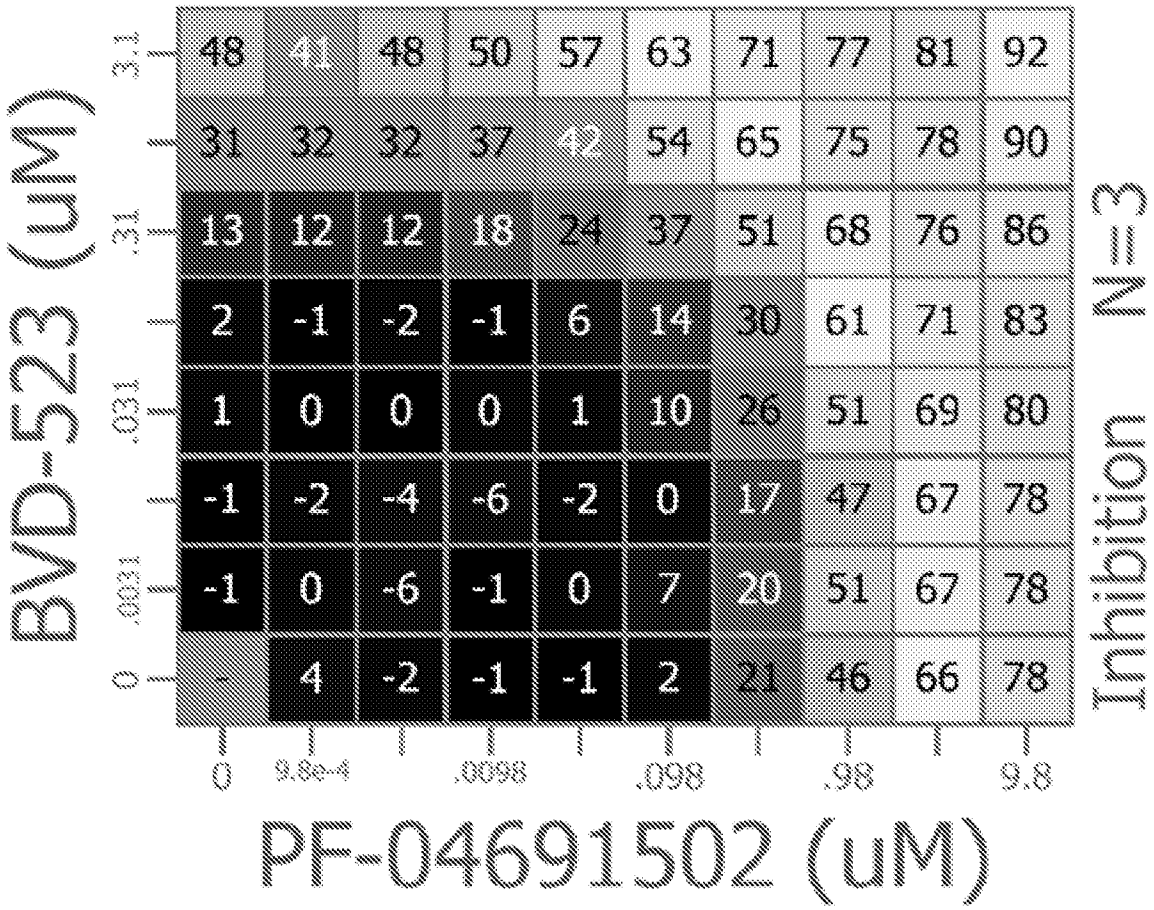
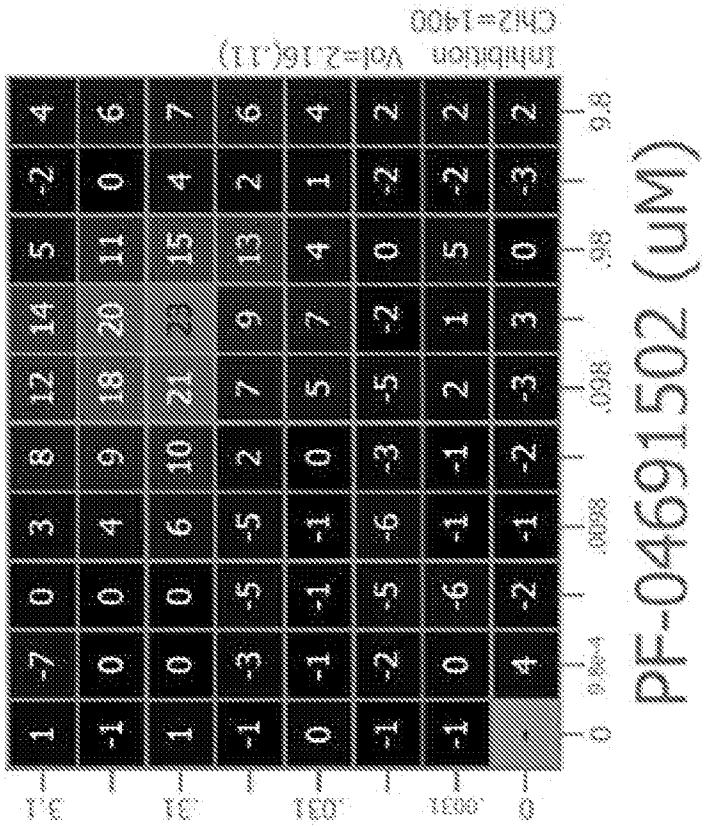


FIG. 23, Continued



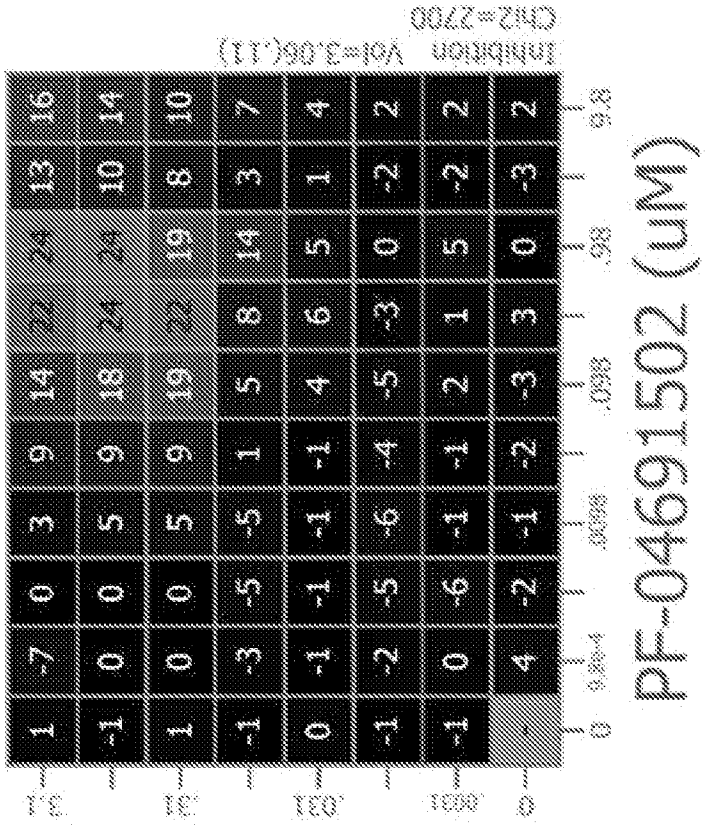
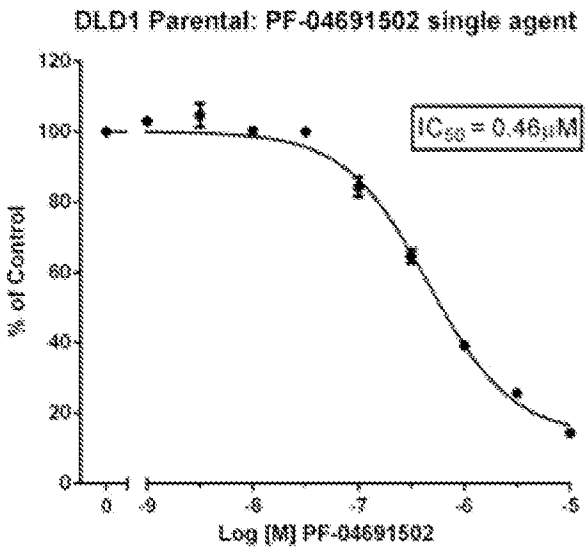
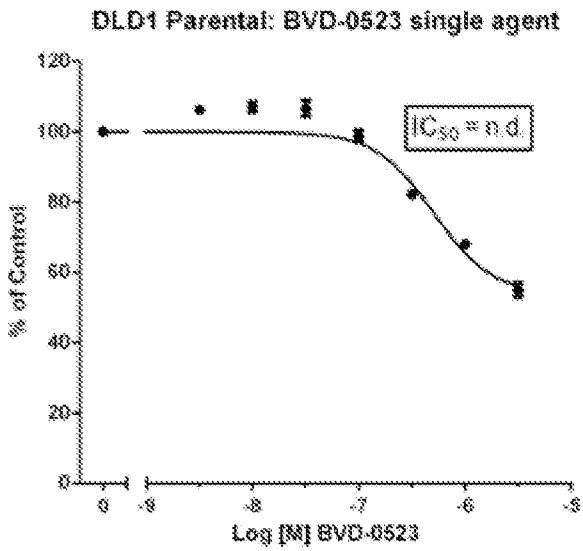


FIG. 23, Continued

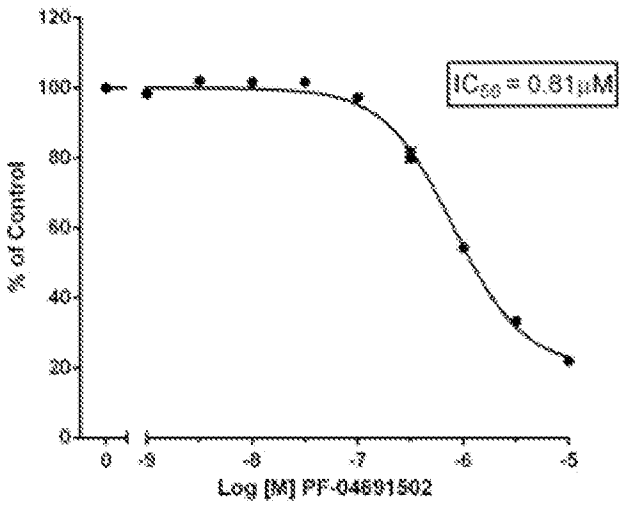
G



H



I



J

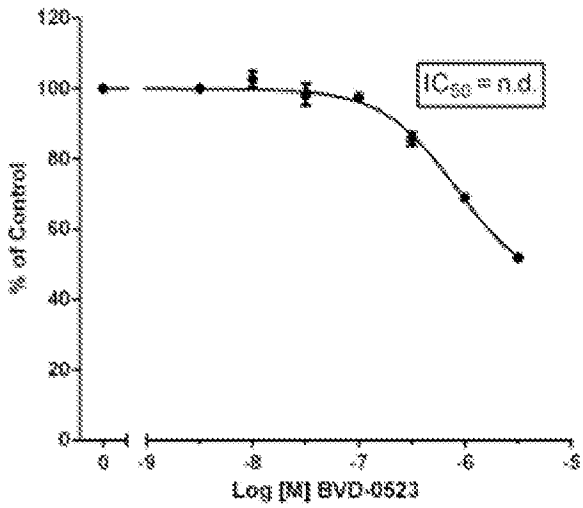


FIG. 24

A

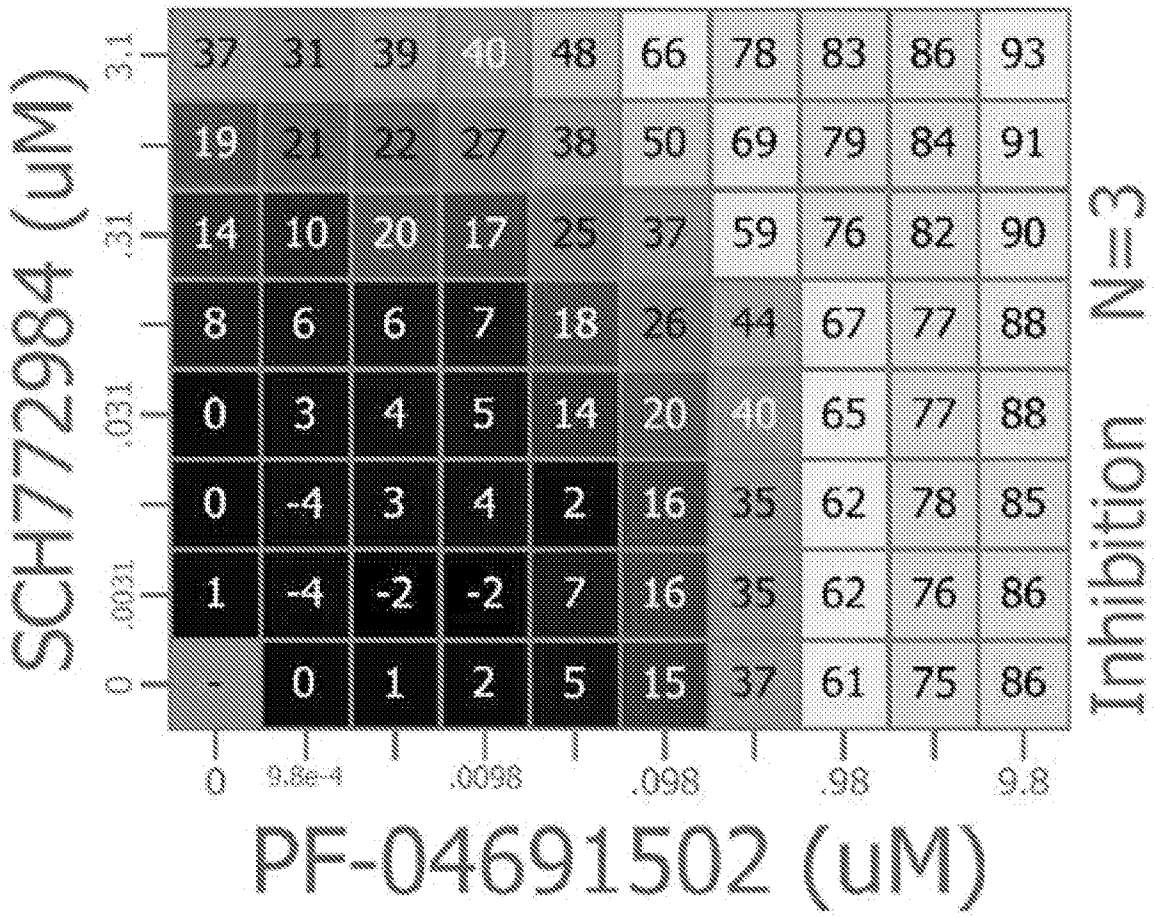

SCH772984 (uM)
3.1
.31
.031
.0031
0
37 31 39 40 48 66 78 83 86 93
19 21 22 27 38 50 69 79 84 91
14 10 20 17 25 37 59 76 82 90
8 6 6 7 18 26 44 67 77 88
0 3 4 5 14 20 40 65 77 88
0 -4 3 4 2 16 35 62 78 85
1 -4 -2 -2 7 16 35 62 76 86
- 0 1 2 5 15 37 61 75 86
Inhibition N=3
0
9.8e-4
.0098
.098
.98
9.8
PF-04691502 (uM)

FIG. 24, Continued

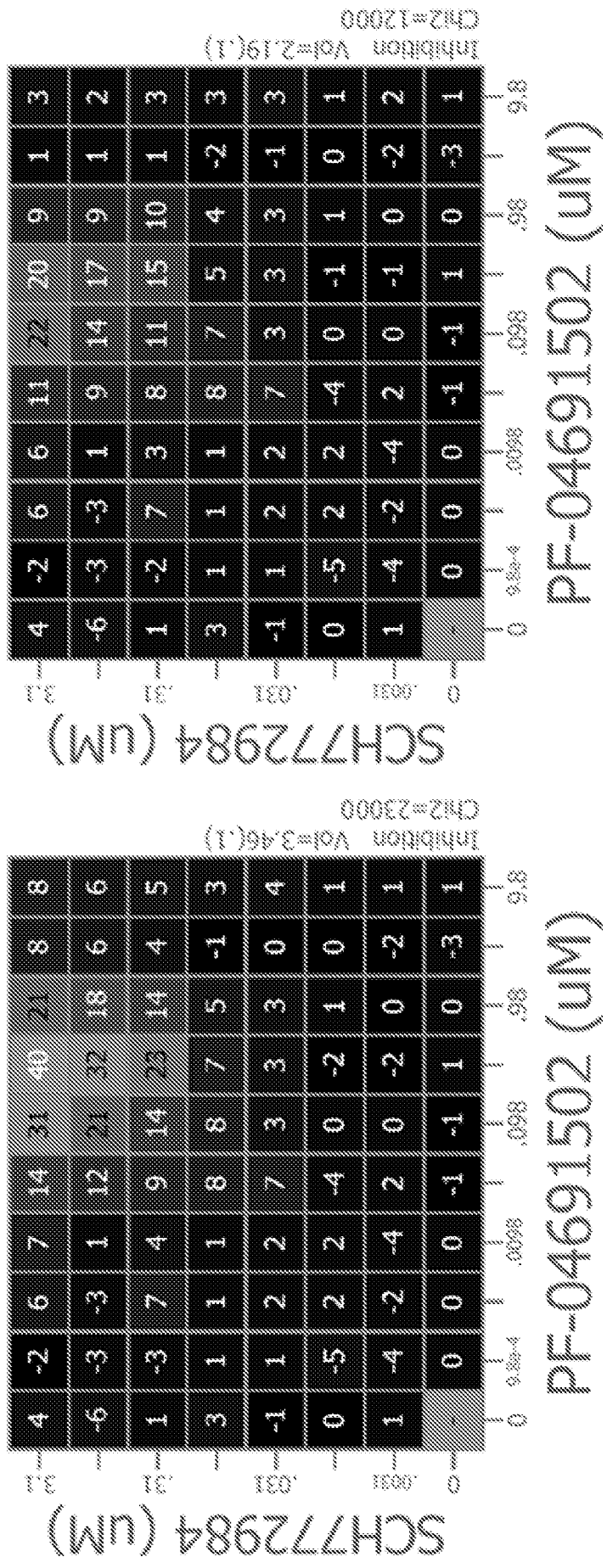


FIG. 24, Continued

D

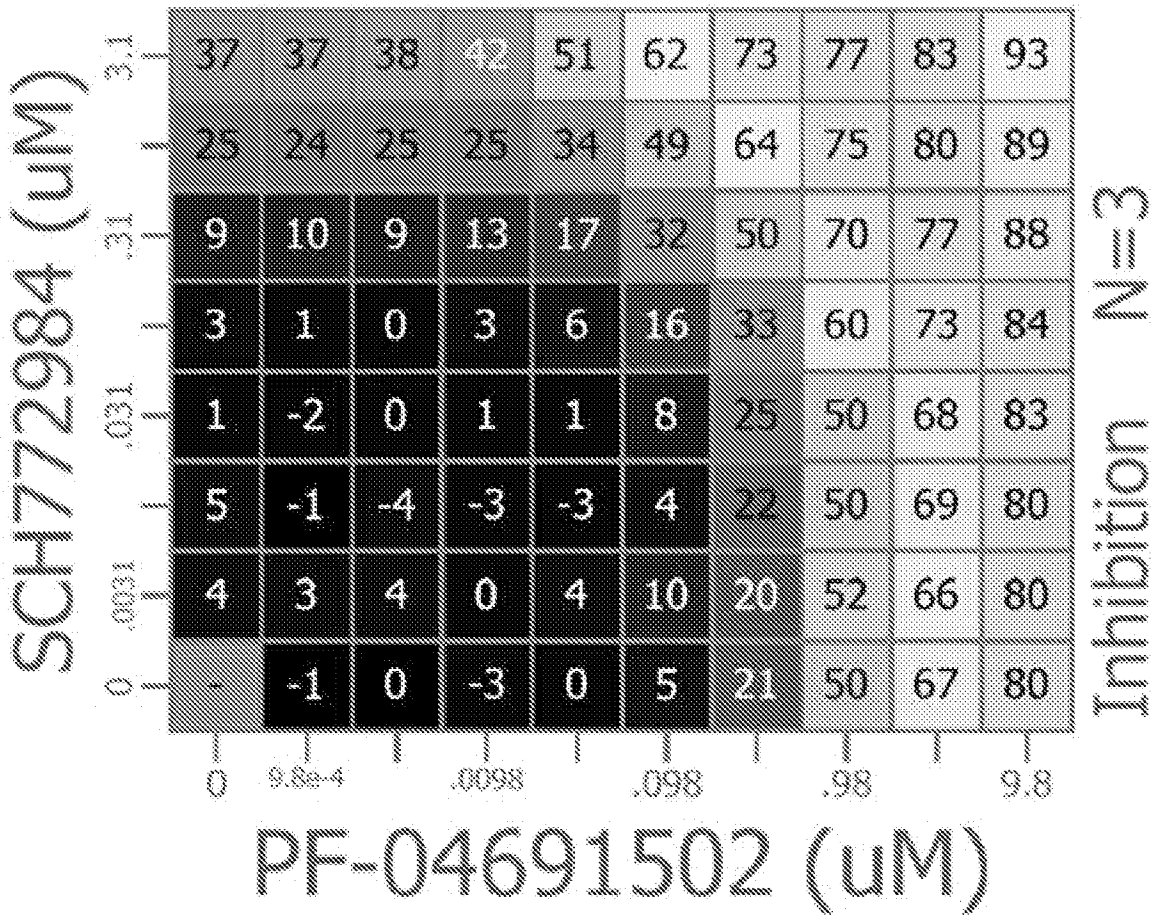
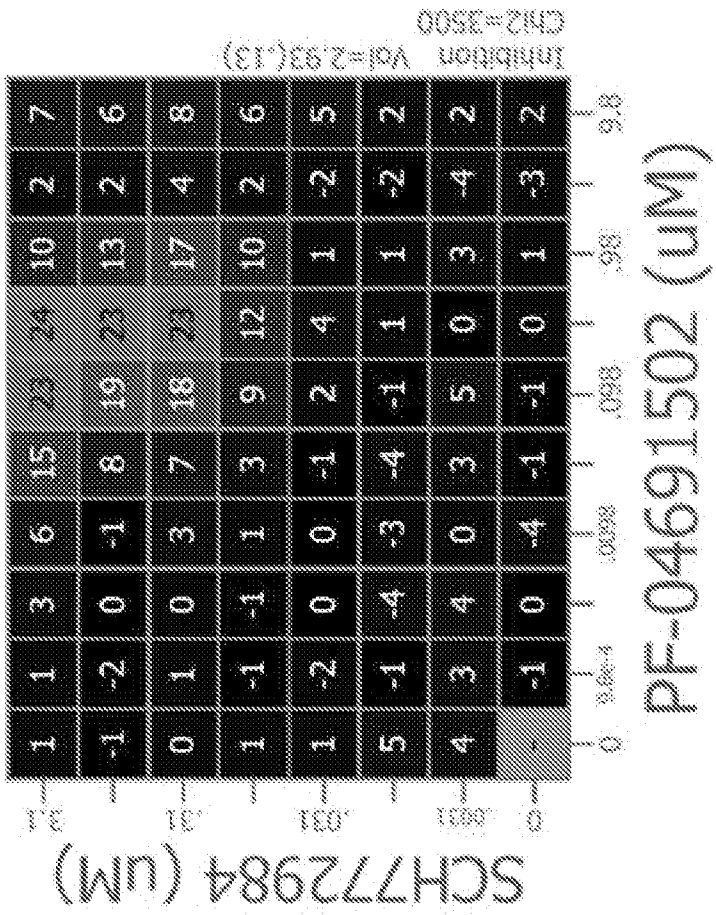


FIG. 24, Continued



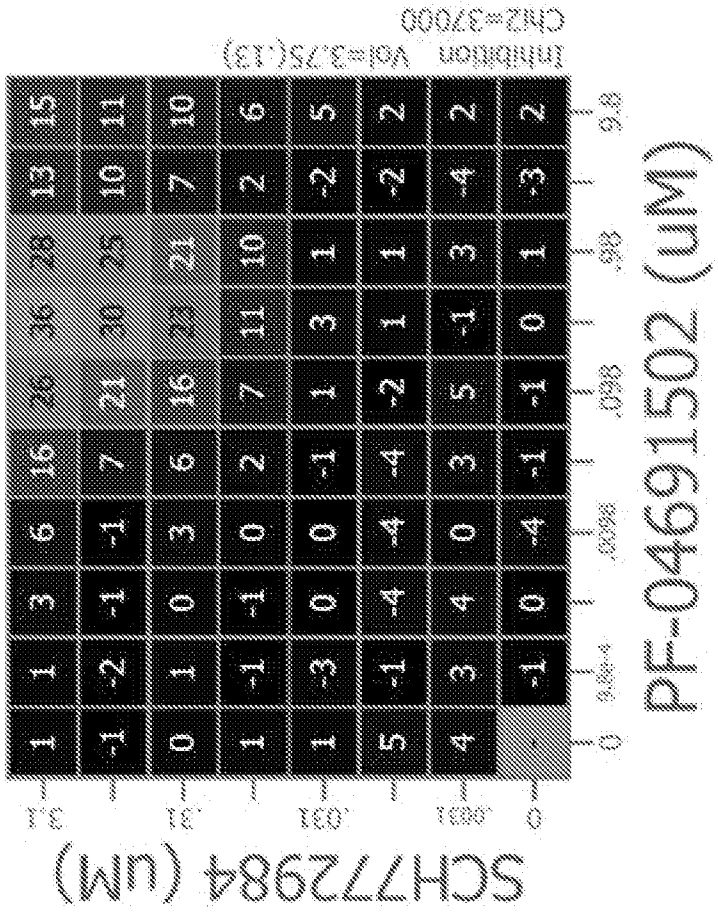
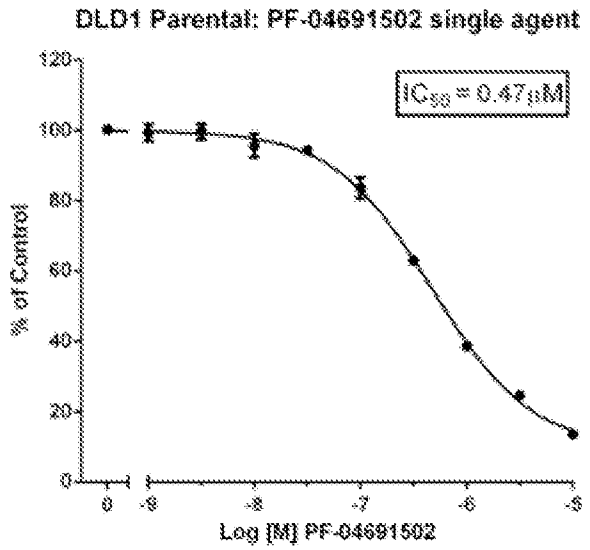
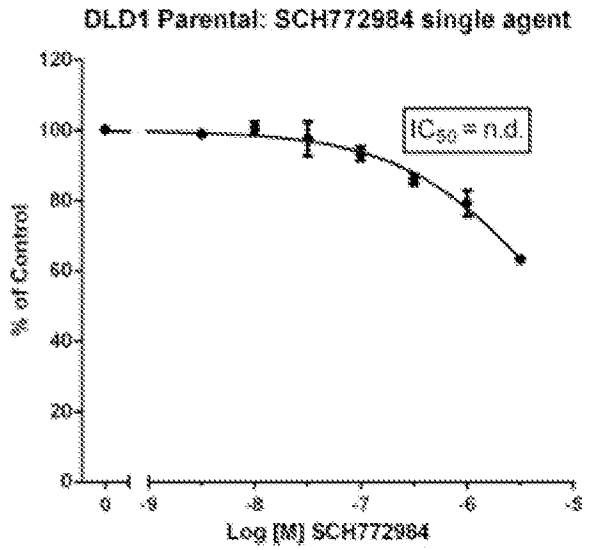


FIG. 24, Continued

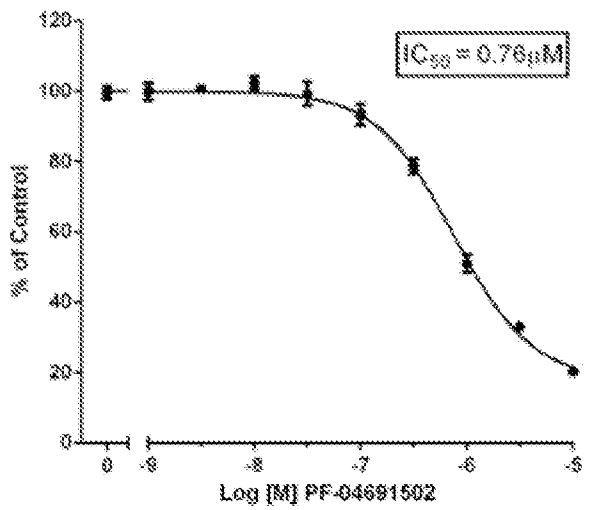
G



H



I



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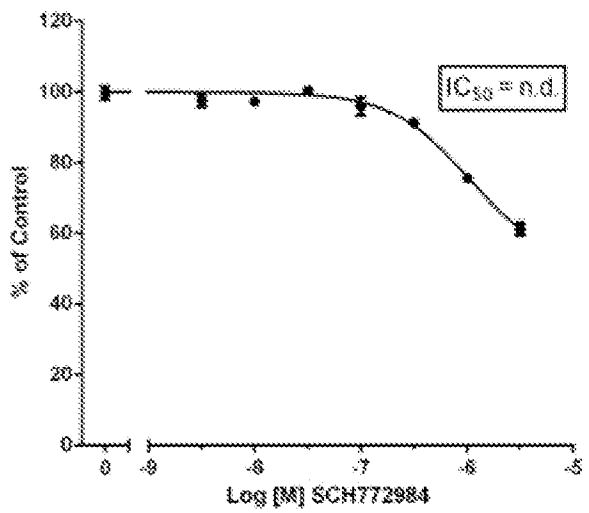


FIG. 25

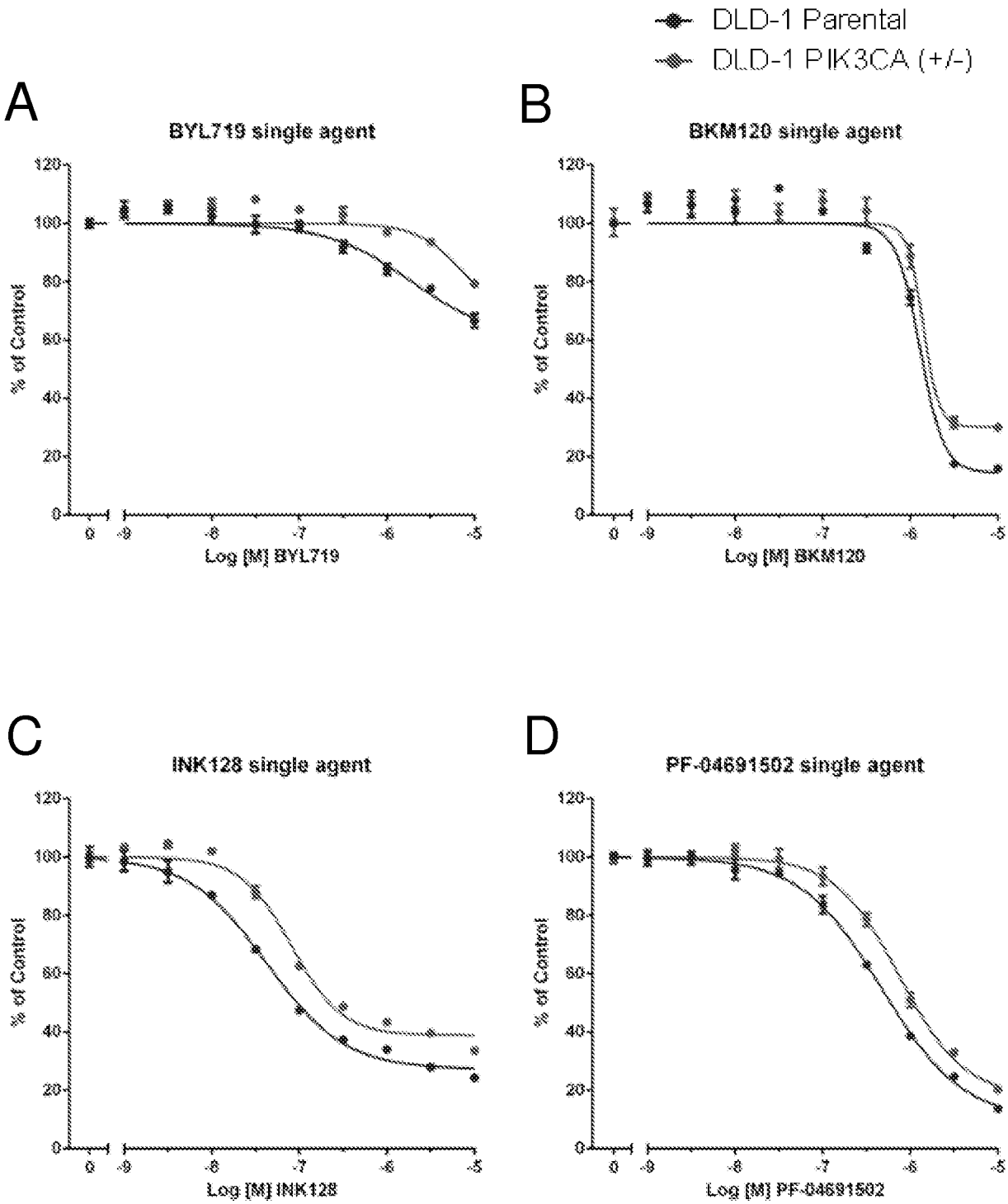
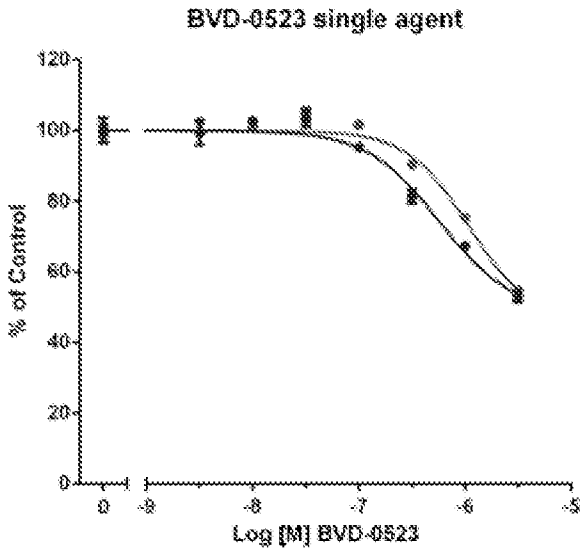

DLD-1 Parental
DLD-1 PIK3CA (+/-)
A
BYL719 single agent
% of Control
Log [M] BYL719
B
BKM120 single agent
% of Control
Log [M] BKM120
C
INK128 single agent
% of Control
Log [M] INK128
D
PF-04691502 single agent
% of Control
Log [M] PF-04691502

FIG. 25, Continued

E



F

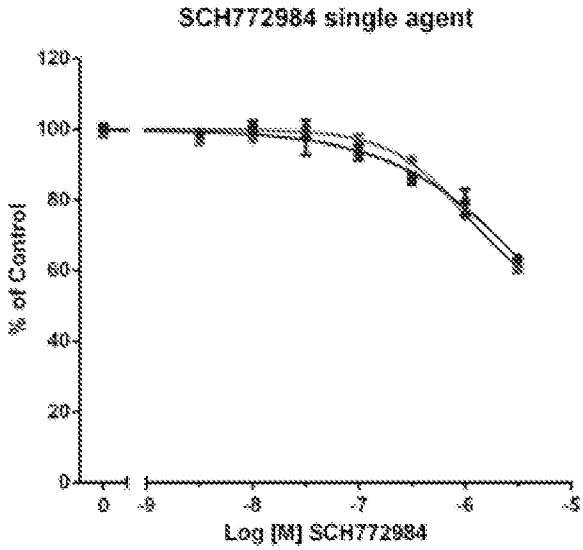


FIG. 26

A

	DLD1 Parental	DLD1 PIK3CA +/-	HCT116 Parental	HCT116 PIK3CA +/-
BKM120 x BVD-523	1.28	0.70	3.1	1.4
BKM120 x SCH772984	1.41	1.07	2.21	2.27
BVD-523 x BYL719	2.15	1.19	5.2	3.6
BVD-523 x INK128	3.17	4.5	5.6	4.7
BVD-523 x PF-04691502	1.7	3.66	4.7	5.4
BYL719 x SCH772984	2.08	1.66	4.2	3.6
INK128 x SCH772984	3.07	4.14	5.4	4.2
PF-04691502 x SCH772984	2.46	3.75	4.7	4.7

B

	DLD1 Parental	DLD1 PIK3CA +/-	HCT116 Parental	HCT116 PIK3CA +/-
BKM120 x BVD-523	1.12	0.70	2.9	1.11
BKM120 x SCH772984	1.56	1.46	2.26	1.83
BVD-523 x BYL719	1.94	1.04	4.6	3.3
BVD-523 x INK128	1.07	3.03	5.2	3.8
BVD-523 x PF-04691502	.572	2.16	4.4	3.6
BYL719 x SCH772984	2.04	.922	4.6	3.2
INK128 x SCH772984	1.83	3.09	4.7	3.6
PF-04691502 x SCH772984	2.19	2.69	4.4	3.8

FIG. 26, Continued

C

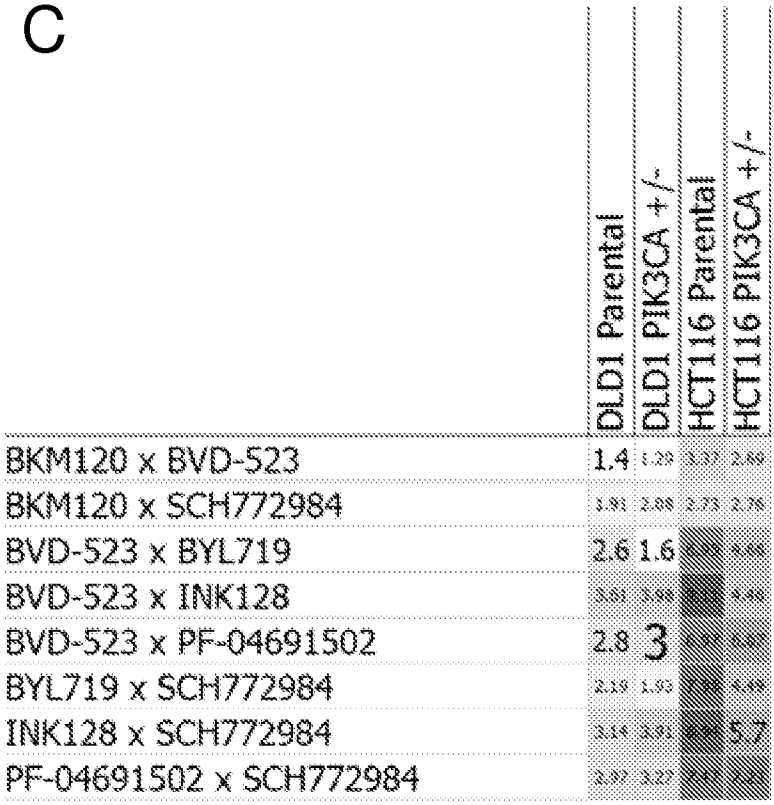
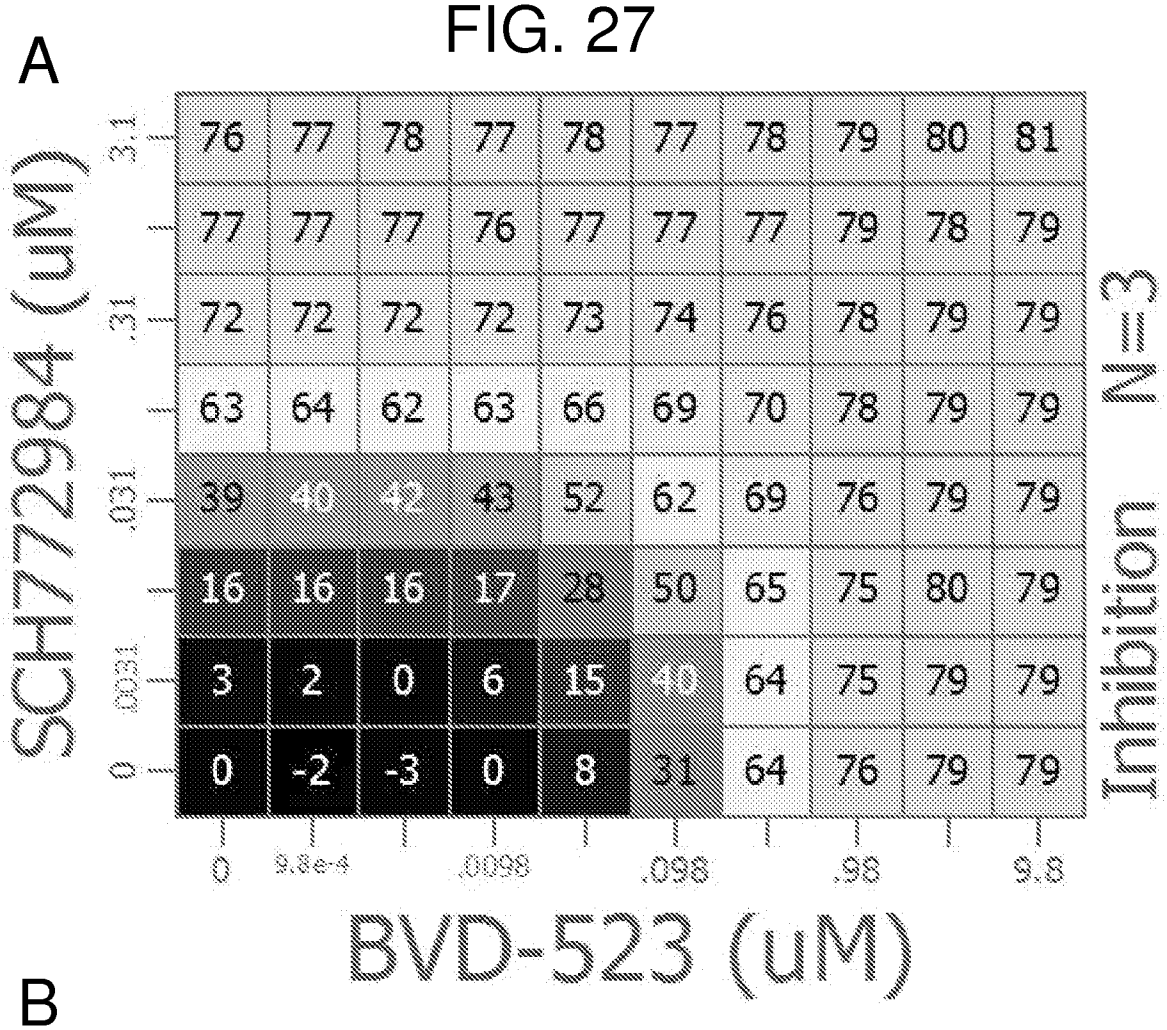
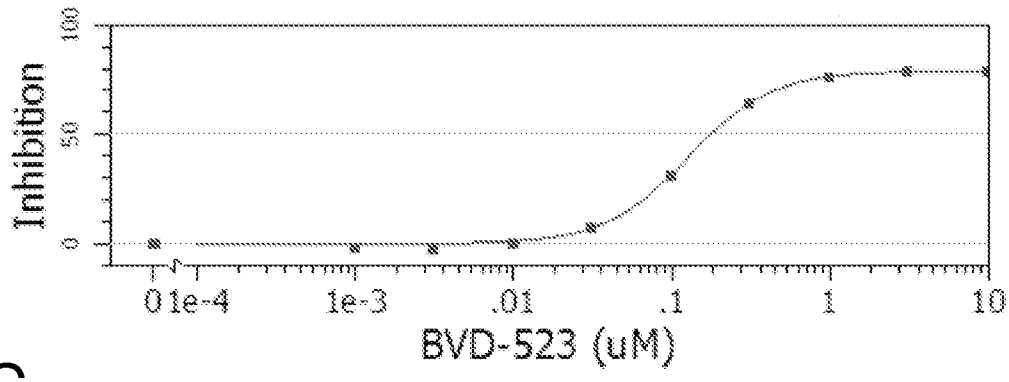


FIG. 27


A
SCH772984 (uM)
3.1
1
.31
1
.031
1
.0031
0
76 77 78 77 78 77 78 79 80 81
77 77 77 76 77 77 77 79 78 79
72 72 72 72 73 74 76 78 79 79
63 64 62 63 66 69 70 78 79 79
39 40 42 43 52 62 69 76 79 79
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
0 9.8e-4 .0098 .098 .98 9.8
BVD-523 (uM)
Inhibition N=3


B
Inhibition
100
50
0
0 1e-4 1e-3 .01 .1 1 10
BVD-523 (uM)

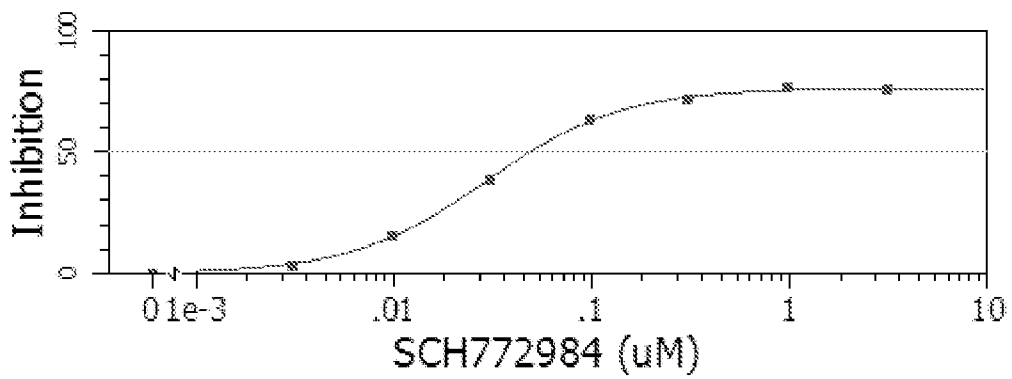
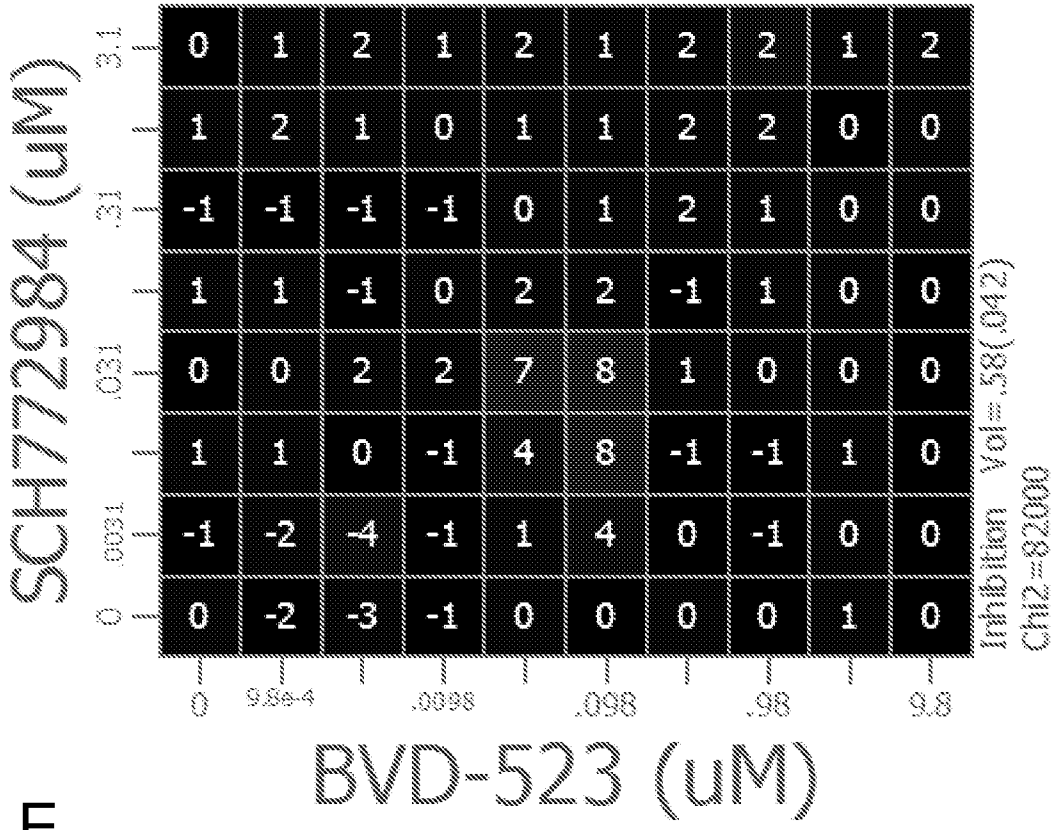
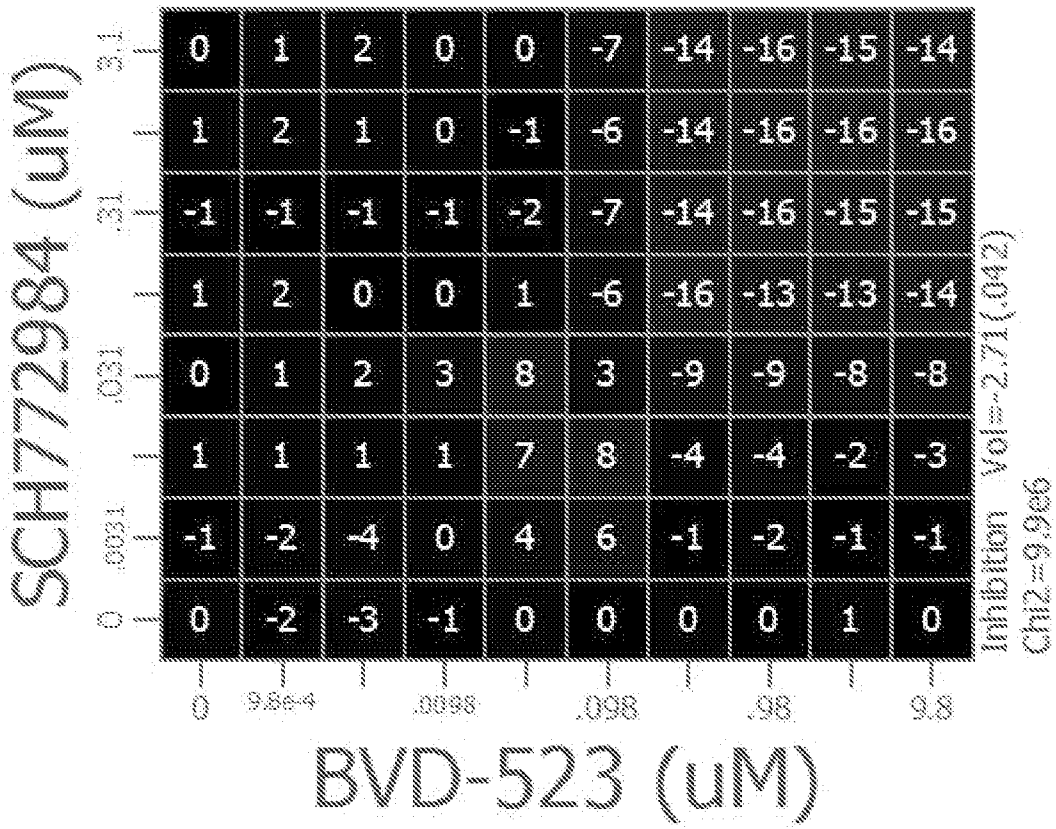

C
Inhibition
100
50
0
0 1e-3 .01 .1 1 10
SCH772984 (uM)

FIG. 27, Continued

D



E



SEQUENCE LISTING

<110> SAHA, Saurabh

<120> CANCER TREATMENTS USING COMBINATIONS OF PI3K/AKT PATHWAY AND ERK INHIBITORS

<130> C065272/0375601

<140> US61/919,638
<141> 2013-12-20

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<170> PatentIn version 3.3

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aaggcggcgg cggggccaga ggctcagcgg ctcccaggtg cgggagagag gcctgctgaa 180

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Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys
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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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Val Phe Ala Ile Asn Asn Thr Lys Ser Phe Glu Asp Ile His His Tyr
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Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr Lys
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Ser Ala Lys Thr Arg Gln Gly Val Asp Asp Ala Phe Tyr Thr Leu Val
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<213> Mus musculus

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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
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Val Phe Ala Ile Asn Asn Thr Lys Ser Phe Glu Asp Ile His His Tyr
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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 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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165 170 175

Lys Lys Lys Lys Ser Arg Thr Arg Cys Thr Val Met
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<212> DNA
<213> Oryctolagus cuniculus

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<210> 10
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<212> PRT

<213> Oryctolagus cuniculus

<400> 10

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Gln Arg Gly Glu Glu Glu Ala Gln Thr Cys Cys Gly Cys Arg Phe Pro
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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
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Leu Phe Met Leu Cys Val Ser Tyr Gln Val Asp Glu Arg Thr Cys Ile
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Gln Phe Ser Met Lys Leu Leu Tyr Phe Val Leu Ser Ala Leu Gly Leu
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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
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<213> Cavia porcellus

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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

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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
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Met Ser Lys Asp Gly Lys Lys Lys Lys Lys Lys Ser Lys Thr Lys Cys
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<213> Cavia porcellus

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<210> 14
<211> 188
<212> PRT
<213> Cavia porcellus

<400> 14

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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 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
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<212> DNA
<213> Canis lupus familiaris

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<210> 16
<211> 227
<212> PRT
<213> Canis lupus familiaris

<400> 16

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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 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
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<212> DNA
<213> Canis lupus familiaris

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<212> PRT

<213> Canis lupus familiaris

<400> 18

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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
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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
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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
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<212> DNA
<213> Felis catus

<400> 19

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<213> Felis catus

<400> 20

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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
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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
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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 Lys Thr Lys Cys Ile Ile Met
180 185

<210> 21
<211> 1512
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<213> Felis catus

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<210> 22
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<400> 22

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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
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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 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
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Ser Ala Lys Thr Arg Gln Arg Val Glu Asp Ala Phe Tyr Thr Leu Val
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Thr Pro Gly Cys Val Lys Ile Lys Lys Cys Ile Val Met Gly Val Asp
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Ile Ile Met
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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 ttttttttaa acgatgaaat gaaaaaatgt caaaatcttg agtattggct 2040

agttctcttt aacactggct aaagtaacat ttttgtaaac acttcagtac agtctggtcc 2100

attattaaga atatctaatg cttatacaat aaagtaatgc taac 2144

<210> 24
<211> 188
<212> PRT
<213> Bos taurus

<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 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> 25
<211> 1010
<212> DNA
<213> Bos taurus

<400> 25
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> 26
<211> 227
<212> PRT
<213> Bos taurus

<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

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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 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
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<210> 27
<211> 797
<212> DNA
<213> Bos taurus

<400> 27
gcggtggcgg cggcggcggc ggtggcggtg gcggttcggc cagtactccc ggcccccgcc 60

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> 28
<211> 189
<212> PRT
<213> Bos taurus

<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 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

<210> 29
<211> 1112
<212> DNA
<213> Gallus gallus

<400> 29
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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

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> 30
<211> 188
<212> PRT
<213> Gallus gallus

<400> 30

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

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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 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
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<210> 31
<211> 3724
<212> DNA
<213> Homo sapiens

<400> 31

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gagcctggaa gagccccgag cgtttctgct ttgggacaac catacatcta attccttaaa    120

gtagttttat atgtaaaact tgcaaagaat cagaacaatg cctccacgac catcatcagg    180

tgaactgtgg ggcatccact tgatgccccc aagaatccta gtagaatgtt tactaccaaa    240

tggaatgata gtgactttag aatgcctccg tgaggctaca ttaataacca taaagcatga    300

actatttaaa gaagcaagaa aataccccct ccatcaactt cttcaagatg aatcttctta    360

cattttcgta agtgttactc aagaagcaga aagggaagaa ttttttgatg aaacaagacg    420

actttgtgac cttcggcttt ttcaaccctt tttaaaagta attgaaccag taggcaaccg    480

tgaagaaaag atcctcaatc gagaaattgg ttttgctatc ggcatgccag tgtgtgaatt    540

tgatatggtt aaagatccag aagtacagga cttccgaaga aatattctga acgtttgtaa    600

agaagctgtg gatcttaggg acctcaattc acctcatagt agagcaatgt atgtctatcc    660
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tccaaatgta gaatcttcac cagaattgcc aaagcacata tataataaat tagataaagg 720

gcaaataata gtggtgatct gggtaatagt ttctccaaat aatgacaagc agaagtatac 780

tctgaaaatc aaccatgact gtgtaccaga acaagtaatt gctgaagcaa tcaggaaaaa 840

aactcgaagt atgttgctat cctctgaaca actaaaactc tgtgttttag aatatcaggg 900

caagtatatt ttaaaagtgt gtggatgtga tgaatacttc ctagaaaaat atcctctgag 960

tcagtataag tatataagaa gctgtataat gcttgggagg atgcccaatt tgatgttgat 1020

ggctaaagaa agcctttatt ctcaactgcc aatggactgt tttacaatgc catcttattc 1080

cagacgcatt tccacagcta caccatatat gaatggagaa acatctacaa aatccctttg 1140

ggttataaat agtgcactca gaataaaaat tctttgtgca acctacgtga atgtaaatat 1200

tcgagacatt gataagatct atgttcgaac aggtatctac catggaggag aacccttatg 1260

tgacaatgtg aacactcaaa gagtaccttg ttccaatccc aggtggaatg aatggctgaa 1320

ttatgatata tacattcctg atcttcctcg tgctgctcga ctttgccttt ccatttgctc 1380

tgttaaaggc cgaaagggtg ctaaagagga acactgtcca ttggcatggg gaaatataaa 1440

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tatgtcagtg attgaagagc atgccaattg gtctgtatcc cgagaagcag gatttagcta 1680

ttcccacgca ggactgagta acagactagc tagagacaat gaattaaggg aaaatgacaa 1740

agaacagctc aaagcaattt ctacacgaga tcctctctct gaaatcactg agcaggagaa 1800

agattttcta tggagtcaca gacactattg tgtaactatc cccgaaattc tacccaaatt 1860

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gcttgtgaga tttttactga agaaagcatt gactaatcaa aggattgggc acttttttctt 2160

ttggcattta aaatctgaga tgcacaataa aacagttagc cagaggtttg gcctgctttt 2220

ggagtcctat tgtcgtgcat gtgggatgta tttgaagcac ctgaataggc aagtcgaggc 2280

aatggaaaag ctcattaact taactgacat tctcaaacag gagaagaagg atgaaacaca 2340

aaaggtacag atgaagtttt tagttgagca aatgaggcga ccagatttca tggatgctct 2400

acagggcttt ctgtctcctc taaaccctgc tcatcaacta ggaaacctca ggcttgaaga 2460

gtgtcgaatt atgtcctctg caaaaaggcc actgtggttg aattgggaga acccagacat 2520

catgtcagag ttactgtttc agaacaatga gatcatcttt aaaaatgggg atgatttacg 2580

gcaagatatg ctaacacttc aaattattcg tattatggaa aatatctggc aaaatcaagg 2640

tcttgatctt cgaatgttac cttatggttg tctgtcaatc ggtgactgtg tgggacttat 2700

tgaggtggtg cgaaattctc acactattat gcaaattcag tgcaaaggcg gcttgaaagg 2760

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cttcattttg ggaattggag atcgtcacaa tagtaacatc atggtgaaag acgatggaca 2940

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acgagaacgt gtgccatttg ttttgacaca ggatttctta atagtgatta gtaaaggagc 3060

ccaagaatgc acaaagacaa gagaatttga gaggtttcag gagatgtgtt acaaggctta 3120

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tggtggctgg acaacaaaaa tggattggat cttccacaca attaaacagc atgcattgaa 3360

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ctctcagcag gcaaagaccg attgcatagg aattgcacaa tccatgaaca gcattagaat 3480

ttacagcaag aacagaaata aaatactata taatttaaat aatgtaaacg caaacagggt 3540

ttgatagcac ttaaactagt tcatttcaaa attaagcttt agaataatgc gcaatttcat 3600

gttatgcctt aagtccaaaa aggtaaactt tgaagattgt ttgtatcttt ttttaaaaaa 3660

caaaacaaaa caaaaatccc caaaatatat agaaatgatg gagaaggaaa aaaaaaaaaa 3720

aaaa 3724

<210> 32
<211> 1068
<212> PRT
<213> Homo sapiens

<400> 32

Met Pro Pro Arg Pro Ser Ser Gly Glu Leu Trp Gly Ile His Leu Met
1 5 10 15

Pro Pro Arg Ile Leu Val Glu Cys Leu Leu Pro Asn Gly Met Ile Val
20 25 30

Thr Leu Glu Cys Leu Arg Glu Ala Thr Leu Ile Thr Ile Lys His Glu
35 40 45

Leu Phe Lys Glu Ala Arg Lys Tyr Pro Leu His Gln Leu Leu Gln Asp
50 55 60

Glu Ser Ser Tyr Ile Phe Val Ser Val Thr Gln Glu Ala Glu Arg Glu
65 70 75 80

Glu Phe Phe Asp Glu Thr Arg Arg Leu Cys Asp Leu Arg Leu Phe Gln
85 90 95

```
Pro Phe Leu Lys Val Ile Glu Pro Val Gly Asn Arg Glu Glu Lys Ile
            100                 105                 110

Leu Asn Arg Glu Ile Gly Phe Ala Ile Gly Met Pro Val Cys Glu Phe
        115                 120                 125

Asp Met Val Lys Asp Pro Glu Val Gln Asp Phe Arg Arg Asn Ile Leu
    130                 135                 140

Asn Val Cys Lys Glu Ala Val Asp Leu Arg Asp Leu Asn Ser Pro His
145                 150                 155                 160

Ser Arg Ala Met Tyr Val Tyr Pro Pro Asn Val Glu Ser Ser Pro Glu
                165                 170                 175

Leu Pro Lys His Ile Tyr Asn Lys Leu Asp Lys Gly Gln Ile Ile Val
            180                 185                 190

Val Ile Trp Val Ile Val Ser Pro Asn Asn Asp Lys Gln Lys Tyr Thr
        195                 200                 205

Leu Lys Ile Asn His Asp Cys Val Pro Glu Gln Val Ile Ala Glu Ala
    210                 215                 220

Ile Arg Lys Lys Thr Arg Ser Met Leu Leu Ser Ser Glu Gln Leu Lys
225                 230                 235                 240

Leu Cys Val Leu Glu Tyr Gln Gly Lys Tyr Ile Leu Lys Val Cys Gly
                245                 250                 255

Cys Asp Glu Tyr Phe Leu Glu Lys Tyr Pro Leu Ser Gln Tyr Lys Tyr
            260                 265                 270

Ile Arg Ser Cys Ile Met Leu Gly Arg Met Pro Asn Leu Met Leu Met
        275                 280                 285

Ala Lys Glu Ser Leu Tyr Ser Gln Leu Pro Met Asp Cys Phe Thr Met
    290                 295                 300

Pro Ser Tyr Ser Arg Arg Ile Ser Thr Ala Thr Pro Tyr Met Asn Gly
305                 310                 315                 320

Glu Thr Ser Thr Lys Ser Leu Trp Val Ile Asn Ser Ala Leu Arg Ile
                325                 330                 335

Lys Ile Leu Cys Ala Thr Tyr Val Asn Val Asn Ile Arg Asp Ile Asp
            340                 345                 350

Lys Ile Tyr Val Arg Thr Gly Ile Tyr His Gly Gly Glu Pro Leu Cys
        355                 360                 365
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Asp Asn Val Asn Thr Gln Arg Val Pro Cys Ser Asn Pro Arg Trp Asn
    370                 375                 380

Glu Trp Leu Asn Tyr Asp Ile Tyr Ile Pro Asp Leu Pro Arg Ala Ala
385                 390                 395                 400

Arg Leu Cys Leu Ser Ile Cys Ser Val Lys Gly Arg Lys Gly Ala Lys
                405                 410                 415

Glu Glu His Cys Pro Leu Ala Trp Gly Asn Ile Asn Leu Phe Asp Tyr
            420                 425                 430

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

Pro His Gly Leu Glu Asp Leu Leu Asn Pro Ile Gly Val Thr Gly Ser
    450                 455                 460

Asn Pro Asn Lys Glu Thr Pro Cys Leu Glu Leu Glu Phe Asp Trp Phe
465                 470                 475                 480

Ser Ser Val Val Lys Phe Pro Asp Met Ser Val Ile Glu Glu His Ala
                485                 490                 495

Asn Trp Ser Val Ser Arg Glu Ala Gly Phe Ser Tyr Ser His Ala Gly
            500                 505                 510

Leu Ser Asn Arg Leu Ala Arg Asp Asn Glu Leu Arg Glu Asn Asp Lys
        515                 520                 525

Glu Gln Leu Lys Ala Ile Ser Thr Arg Asp Pro Leu Ser Glu Ile Thr
    530                 535                 540

Glu Gln Glu Lys Asp Phe Leu Trp Ser His Arg His Tyr Cys Val Thr
545                 550                 555                 560

Ile Pro Glu Ile Leu Pro Lys Leu Leu Leu Ser Val Lys Trp Asn Ser
                565                 570                 575

Arg Asp Glu Val Ala Gln Met Tyr Cys Leu Val Lys Asp Trp Pro Pro
            580                 585                 590

Ile Lys Pro Glu Gln Ala Met Glu Leu Leu Asp Cys Asn Tyr Pro Asp
        595                 600                 605

Pro Met Val Arg Gly Phe Ala Val Arg Cys Leu Glu Lys Tyr Leu Thr
    610                 615                 620

Asp Asp Lys Leu Ser Gln Tyr Leu Ile Gln Leu Val Gln Val Leu Lys
625                 630                 635                 640
```

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Tyr Glu Gln Tyr Leu Asp Asn Leu Leu Val Arg Phe Leu Leu Lys Lys
                645                 650                 655

Ala Leu Thr Asn Gln Arg Ile Gly His Phe Phe Phe Trp His Leu Lys
            660                 665                 670

Ser Glu Met His Asn Lys Thr Val Ser Gln Arg Phe Gly Leu Leu Leu
        675                 680                 685

Glu Ser Tyr Cys Arg Ala Cys Gly Met Tyr Leu Lys His Leu Asn Arg
    690                 695                 700

Gln Val Glu Ala Met Glu Lys Leu Ile Asn Leu Thr Asp Ile Leu Lys
705                 710                 715                 720

Gln Glu Lys Lys Asp Glu Thr Gln Lys Val Gln Met Lys Phe Leu Val
                725                 730                 735

Glu Gln Met Arg Arg Pro Asp Phe Met Asp Ala Leu Gln Gly Phe Leu
            740                 745                 750

Ser Pro Leu Asn Pro Ala His Gln Leu Gly Asn Leu Arg Leu Glu Glu
        755                 760                 765

Cys Arg Ile Met Ser Ser Ala Lys Arg Pro Leu Trp Leu Asn Trp Glu
    770                 775                 780

Asn Pro Asp Ile Met Ser Glu Leu Leu Phe Gln Asn Asn Glu Ile Ile
785                 790                 795                 800

Phe Lys Asn Gly Asp Asp Leu Arg Gln Asp Met Leu Thr Leu Gln Ile
                805                 810                 815

Ile Arg Ile Met Glu Asn Ile Trp Gln Asn Gln Gly Leu Asp Leu Arg
            820                 825                 830

Met Leu Pro Tyr Gly Cys Leu Ser Ile Gly Asp Cys Val Gly Leu Ile
        835                 840                 845

Glu Val Val Arg Asn Ser His Thr Ile Met Gln Ile Gln Cys Lys Gly
    850                 855                 860

Gly Leu Lys Gly Ala Leu Gln Phe Asn Ser His Thr Leu His Gln Trp
865                 870                 875                 880

Leu Lys Asp Lys Asn Lys Gly Glu Ile Tyr Asp Ala Ala Ile Asp Leu
                885                 890                 895

Phe Thr Arg Ser Cys Ala Gly Tyr Cys Val Ala Thr Phe Ile Leu Gly
            900                 905                 910
```

Ile Gly Asp Arg His Asn Ser Asn Ile Met Val Lys Asp Asp Gly Gln
915 920 925

Leu Phe His Ile Asp Phe Gly His Phe Leu Asp His Lys Lys Lys Lys
930 935 940

Phe Gly Tyr Lys Arg Glu Arg Val Pro Phe Val Leu Thr Gln Asp Phe
945 950 955 960

Leu Ile Val Ile Ser Lys Gly Ala Gln Glu Cys Thr Lys Thr Arg Glu
965 970 975

Phe Glu Arg Phe Gln Glu Met Cys Tyr Lys Ala Tyr Leu Ala Ile Arg
980 985 990

Gln His Ala Asn Leu Phe Ile Asn Leu Phe Ser Met Met Leu Gly Ser
995 1000 1005

Gly Met Pro Glu Leu Gln Ser Phe Asp Asp Ile Ala Tyr Ile Arg
1010 1015 1020

Lys Thr Leu Ala Leu Asp Lys Thr Glu Gln Glu Ala Leu Glu Tyr
1025 1030 1035

Phe Met Lys Gln Met Asn Asp Ala His His Gly Gly Trp Thr Thr
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Leu Phe Lys Glu Ala Arg Lys Tyr Pro Leu His Gln Leu Leu Gln Asp
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Glu Ser Ser Tyr Ile Phe Val Ser Val Thr Gln Glu Ala Glu Arg Glu
65                  70                  75                  80

Glu Phe Phe Asp Glu Thr Arg Arg Leu Cys Asp Leu Arg Leu Phe Gln
                85                  90                  95

Pro Phe Leu Lys Val Ile Glu Pro Val Gly Asn Arg Glu Glu Lys Ile
            100                 105                 110

Leu Asn Arg Glu Ile Gly Phe Val Ile Gly Met Pro Val Cys Glu Phe
        115                 120                 125

Asp Met Val Lys Asp Pro Glu Val Gln Asp Phe Arg Arg Asn Ile Leu
    130                 135                 140

Asn Val Cys Lys Glu Ala Val Asp Leu Arg Asp Leu Asn Ser Pro His
145                 150                 155                 160

Ser Arg Ala Met Tyr Val Tyr Pro Pro Asn Val Glu Ser Ser Pro Glu
                165                 170                 175

Leu Pro Lys His Ile Tyr Asn Lys Leu Asp Lys Gly Gln Ile Ile Val
            180                 185                 190

Val Ile Trp Val Ile Val Ser Pro Asn Asn Asp Lys Gln Lys Tyr Thr
        195                 200                 205

Leu Lys Ile Asn His Asp Cys Val Pro Glu Gln Val Ile Ala Glu Ala
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Ile Arg Lys Lys Thr Arg Ser Met Leu Leu Ser Ser Glu Gln Leu Lys
225                 230                 235                 240

Leu Cys Val Leu Glu Tyr Gln Gly Lys Tyr Ile Leu Lys Val Cys Gly
                245                 250                 255

Cys Asp Glu Tyr Phe Leu Glu Lys Tyr Pro Leu Ser Gln Tyr Lys Tyr
            260                 265                 270

Ile Arg Ser Cys Ile Met Leu Gly Arg Met Pro Asn Leu Met Leu Met
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Ala Lys Glu Ser Leu Tyr Ser Gln Leu Pro Ile Asp Ser Phe Thr Met
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Pro Ser Tyr Ser Arg Arg Ile Ser Thr Ala Thr Pro Tyr Met Asn Gly
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Glu Thr Ala Thr Lys Ser Leu Trp Val Ile Asn Ser Ala Leu Arg Ile
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Lys Ile Leu Cys Ala Thr Tyr Val Asn Val Asn Ile Arg Asp Ile Asp
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Lys Ile Tyr Val Arg Thr Gly Ile Tyr His Gly Gly Glu Pro Leu Cys
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Asp Asn Val Asn Thr Gln Arg Val Pro Cys Ser Asn Pro Arg Trp Asn
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Glu Trp Leu Asn Tyr Asp Ile Tyr Ile Pro Asp Leu Pro Arg Ala Ala
385                 390                 395                 400

Arg Leu Cys Leu Ser Ile Cys Ser Val Lys Gly Arg Lys Gly Ala Lys
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Glu Glu His Cys Pro Leu Ala Trp Gly Asn Ile Asn Leu Phe Asp Tyr
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Thr Asp Thr Leu Val Ser Gly Lys Met Ala Leu Asn Leu Trp Pro Val
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Pro His Gly Leu Glu Asp Leu Leu Asn Pro Ile Gly Val Thr Gly Ser
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Ser Ser Val Val Lys Phe Pro Asp Met Ser Val Ile Glu Glu His Ala
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Asn Trp Ser Val Ser Arg Glu Ala Gly Phe Ser Tyr Ser His Thr Gly
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Leu Ser Asn Arg Leu Ala Arg Asp Asn Glu Leu Arg Glu Asn Asp Lys
        515                 520                 525

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

Asp Met Val Lys Asp Pro Glu Val Gln Asp Phe Arg Arg Asn Ile Leu
130 135 140

Asn Val Cys Lys Glu Ala Val Asp Leu Arg Asp Leu Asn Ser Pro His
145 150 155 160

Ser Arg Ala Met Tyr Val Tyr Pro Pro Asn Val Glu Ser Ser Pro Glu
165 170 175

Leu Pro Lys His Ile Tyr Asn Lys Leu Asp Lys Gly Gln Ile Ile Val
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Val Ile Trp Val Ile Val Ser Pro Asn Asn Asp Lys Gln Lys Tyr Thr
195 200 205

Leu Lys Ile Asn His Asp Cys Val Pro Glu Gln Val Ile Ala Glu Ala
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Ile Arg Lys Lys Thr Arg Ser Met Leu Leu Ser Ser Glu Gln Leu Lys

225 230 235 240

Leu Cys Val Leu Glu Tyr Gln Gly Lys Tyr Ile Leu Lys Val Cys Gly
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Cys Asp Glu Tyr Phe Leu Glu Lys Tyr Pro Leu Ser Gln Tyr Lys Tyr
260 265 270

Ile Arg Ser Cys Ile Met Leu Gly Arg Met Pro Asn Leu Met Leu Met
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Ala Lys Glu Ser Leu Tyr Ser Gln Leu Pro Met Asp Cys Phe Thr Met
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Pro Ser Tyr Ser Arg Arg Ile Ser Thr Ala Thr Pro Tyr Met Asn Gly
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Glu Thr Ser Thr Lys Ser Leu Trp Val Ile Asn Ser Ala Leu Arg Ile
325 330 335

Lys Ile Leu Cys Ala Thr Tyr Val Asn Val Asn Ile Arg Asp Ile Asp
340 345 350

Lys Ile Tyr Val Arg Thr Gly Ile Tyr His Gly Gly Glu Pro Leu Cys
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Asp Asn Val Asn Thr Gln Arg Val Pro Cys Ser Asn Pro Arg Trp Asn
370 375 380

Glu Trp Leu Asn Tyr Asp Ile Tyr Ile Pro Asp Leu Pro Arg Ala Ala
385 390 395 400

Arg Leu Cys Leu Ser Ile Cys Ser Val Lys Gly Arg Lys Gly Ala Lys
405 410 415

Glu Glu His Cys Pro Leu Ala Trp Gly Asn Ile Asn Leu Phe Asp Tyr
420 425 430

Thr Asp Thr Leu Val Ser Gly Lys Met Ala Leu Asn Leu Trp Pro Val
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Pro His Gly Leu Glu Asp Leu Leu Asn Pro Ile Gly Val Thr Gly Ser
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Asn Pro Asn Lys Glu Thr Pro Cys Leu Glu Leu Glu Phe Asp Trp Phe
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Ser Ser Val Val Lys Phe Pro Asp Met Ser Val Ile Glu Glu His Ala
485 490 495

Asn Trp Ser Val Ser Arg Glu Ala Gly Phe Ser Tyr Ser His Ala Gly

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Leu Ser Asn Arg Leu Ala Arg Asp Asn Glu Leu Arg Glu Asn Asp Lys
515 520 525

Glu Gln Leu Arg Ala Ile Cys Thr Arg Asp Pro Leu Ser Glu Ile Thr
530 535 540

Glu Gln Glu Lys Asp Phe Leu Trp Ser His Arg His Tyr Cys Val Thr
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Ile Pro Glu Ile Leu Pro Lys Leu Leu Leu Ser Val Lys Trp Asn Ser
565 570 575

Arg Asp Glu Val Ala Gln Met Tyr Cys Leu Val Lys Asp Trp Pro Pro
580 585 590

Ile Lys Pro Glu Gln Ala Met Glu Leu Leu Asp Cys Asn Tyr Pro Asp
595 600 605

Pro Met Val Arg Gly Phe Ala Val Arg Cys Leu Glu Lys Tyr Leu Thr
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Asp Asp Lys Leu Ser Gln Tyr Leu Ile Gln Leu Val Gln Val Leu Lys
625 630 635 640

Tyr Glu Gln Tyr Leu Asp Asn Leu Leu Val Arg Phe Leu Leu Lys Lys
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Ala Leu Thr Asn Gln Arg Ile Gly His Phe Phe Phe Trp His Leu Lys
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Ser Glu Met His Asn Lys Thr Val Ser Gln Arg Phe Gly Leu Leu Leu
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Glu Ser Tyr Cys Arg Ala Cys Gly Met Tyr Leu Lys His Leu Asn Arg
690 695 700

Gln Val Glu Ala Met Glu Lys Leu Ile Asn Leu Thr Asp Ile Leu Lys
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Gln Glu Lys Lys Asp Glu Thr Gln Lys Val Gln Met Lys Phe Leu Val
725 730 735

Glu Gln Met Arg Arg Pro Asp Phe Met Asp Ala Leu Gln Gly Phe Leu
740 745 750

Ser Pro Leu Asn Pro Ala His Gln Leu Gly Asn Leu Arg Leu Glu Glu
755 760 765

Cys Arg Ile Met Ser Ser Ala Lys Arg Pro Leu Trp Leu Asn Trp Glu

770 775 780

Asn Pro Asp Ile Met Ser Glu Leu Leu Phe Gln Asn Asn Glu Ile Ile
785 790 795 800

Phe Lys Asn Gly Asp Asp Leu Arg Gln Asp Met Leu Thr Leu Gln Ile
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Ile Arg Ile Met Glu Asn Ile Trp Gln Asn Gln Gly Leu Asp Leu Arg
820 825 830

Met Leu Pro Tyr Gly Cys Leu Ser Ile Gly Asp Cys Val Gly Leu Ile
835 840 845

Glu Val Val Arg Asn Ser His Thr Ile Met Gln Ile Gln Cys Lys Gly
850 855 860

Gly Leu Lys Gly Ala Leu Gln Phe Asn Ser His Thr Leu His Gln Trp
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Leu Lys Asp Lys Asn Lys Gly Glu Ile Tyr Asp Ala Ala Ile Asp Leu
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Phe Thr Arg Ser Cys Ala Gly Tyr Cys Val Ala Thr Phe Ile Leu Gly
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Ile Gly Asp Arg His Asn Ser Asn Ile Met Val Lys Asp Asp Gly Gln
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Leu Phe His Ile Asp Phe Gly His Phe Leu Asp His Lys Lys Lys Lys
930 935 940

Phe Gly Tyr Lys Arg Glu Arg Val Pro Phe Val Leu Thr Gln Asp Phe
945 950 955 960

Leu Ile Val Ile Ser Lys Gly Ala Gln Glu Cys Thr Lys Thr Arg Glu
965 970 975

Phe Glu Arg Phe Gln Glu Met Cys Tyr Lys Ala Tyr Leu Ala Ile Arg
980 985 990

Gln His Ala Asn Leu Phe Ile Asn Leu Phe Ser Met Met Leu Gly Ser
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Gly Met Pro Glu Leu Gln Ser Phe Asp Asp Ile Ala Tyr Ile Arg
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Lys Thr Leu Ala Leu Asp Lys Thr Glu Gln Glu Ala Leu Glu Tyr
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Glu Ser Ser Tyr Ile Phe Val Ser Val Thr Gln Glu Ala Glu Arg Glu
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Glu Phe Phe Asp Glu Thr Arg Arg Leu Cys Asp Leu Arg Leu Phe Gln
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Pro Phe Leu Lys Val Ile Glu Pro Val Gly Asn Arg Glu Glu Lys Ile
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Leu Asn Arg Glu Ile Gly Phe Ala Ile Gly Met Pro Val Cys Glu Phe
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Asp Met Val Lys Asp Pro Glu Val Gln Asp Phe Arg Arg Asn Ile Leu
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Asn Val Cys Lys Glu Ala Val Asp Leu Arg Asp Leu Asn Ser Pro His
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Ser Arg Ala Met Tyr Val Tyr Pro Pro Asn Val Glu Ser Ser Pro Glu
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Leu Pro Lys His Ile Tyr Asn Lys Leu Asp Lys Gly Gln Ile Ile Val
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Val Ile Trp Val Ile Val Ser Pro Asn Asn Asp Lys Gln Lys Tyr Thr
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Leu Lys Ile Asn His Asp Cys Val Pro Glu Gln Val Ile Ala Glu Ala
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Cys Asp Glu Tyr Phe Leu Glu Lys Tyr Pro Leu Ser Gln Tyr Lys Tyr
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Ala Lys Glu Ser Leu Tyr Ser Gln Leu Pro Met Asp Cys Phe Thr Met
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Pro Ser Tyr Ser Arg Arg Ile Ser Thr Ala Thr Pro Tyr Met Asn Gly
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Glu Thr Ser Thr Lys Ser Leu Trp Val Ile Asn Ser Ala Leu Arg Ile
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Lys Ile Leu Cys Ala Thr Tyr Val Asn Val Asn Ile Arg Asp Ile Asp
340 345 350

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

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Leu Ser Asn Arg Leu Ala Arg Asp Asn Glu Leu Arg Glu Asn Asp Lys
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Glu Gln Leu Arg Ala Ile Cys Thr Arg Asp Pro Leu Ser Glu Ile Thr
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Glu Gln Glu Lys Asp Phe Leu Trp Ser His Arg His Tyr Cys Val Thr
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Ile Pro Glu Ile Leu Pro Lys Leu Leu Leu Ser Val Lys Trp Asn Ser
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Arg Asp Glu Val Ala Gln Met Tyr Cys Leu Val Lys Asp Trp Pro Pro
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Ile Lys Pro Glu Gln Ala Met Glu Leu Leu Asp Cys Asn Tyr Pro Asp
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Pro Met Val Arg Gly Phe Ala Val Arg Cys Leu Glu Lys Tyr Leu Thr
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Asp Asp Lys Leu Ser Gln Tyr Leu Ile Gln Leu Val Gln Val Leu Lys
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Tyr Glu Gln Tyr Leu Asp Asn Leu Leu Val Arg Phe Leu Leu Lys Lys
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Ala Leu Thr Asn Gln Arg Ile Gly His Phe Phe Phe Trp His Leu Lys
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Ser Glu Met His Asn Lys Thr Val Ser Gln Arg Phe Gly Leu Leu Leu
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Glu Ser Tyr Cys Arg Ala Cys Gly Met Tyr Leu Lys His Leu Asn Arg
690 695 700

Gln Val Glu Ala Met Glu Lys Leu Ile Asn Leu Thr Asp Ile Leu Lys
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Gln Glu Lys Lys Asp Glu Thr Gln Lys Val Gln Met Lys Phe Leu Val
725 730 735

Glu Gln Met Arg Arg Pro Asp Phe Met Asp Ala Leu Gln Gly Phe Leu
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Ser Pro Leu Asn Pro Ala His Gln Leu Gly Asn Leu Arg Leu Glu Glu
755 760 765

Cys Arg Ile Met Ser Ser Ala Lys Arg Pro Leu Trp Leu Asn Trp Glu

770 775 780

Asn Pro Asp Ile Met Ser Glu Leu Leu Phe Gln Asn Asn Glu Ile Ile
785 790 795 800

Phe Lys Asn Gly Asp Asp Leu Arg Gln Asp Met Leu Thr Leu Gln Ile
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Ile Arg Ile Met Glu Asn Ile Trp Gln Asn Gln Gly Leu Asp Leu Arg
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Met Leu Pro Tyr Gly Cys Leu Ser Ile Gly Asp Cys Val Gly Leu Ile
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Glu Val Val Arg Asn Ser His Thr Ile Met Gln Ile Gln Cys Lys Gly
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Gly Leu Lys Gly Ala Leu Gln Phe Asn Ser His Thr Leu His Gln Trp
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Phe Thr Arg Ser Cys Ala Gly Tyr Cys Val Ala Thr Phe Ile Leu Gly
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Ile Gly Asp Arg His Asn Ser Asn Ile Met Val Lys Asp Asp Gly Gln
915 920 925

Leu Phe His Ile Asp Phe Gly His Phe Leu Asp His Lys Lys Lys Lys
930 935 940

Phe Gly Tyr Lys Arg Glu Arg Val Pro Phe Val Leu Thr Gln Asp Phe
945 950 955 960

Leu Ile Val Ile Ser Lys Gly Ala Gln Glu Cys Thr Lys Thr Arg Glu
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Phe Glu Arg Phe Gln Glu Met Cys Tyr Lys Ala Tyr Leu Ala Ile Arg
980 985 990

Gln His Ala Asn Leu Phe Ile Asn Leu Phe Ser Met Met Leu Gly Ser
995 1000 1005

Gly Met Pro Glu Leu Gln Ser Phe Asp Asp Ile Ala Tyr Ile Arg
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Lys Thr Leu Ala Leu Asp Lys Thr Glu Gln Glu Ala Leu Glu Tyr
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<213> Bos taurus

<400> 45

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Glu Phe Phe Asp Glu Thr Arg Arg Leu Cys Asp Leu Arg Leu Phe Gln
                85                  90                  95

Pro Phe Leu Lys Val Ile Glu Pro Val Gly Asn Arg Glu Glu Lys Ile
            100                 105                 110

Leu Asn Arg Glu Ile Gly Phe Ala Ile Gly Met Pro Val Cys Glu Phe
        115                 120                 125

Asp Met Val Lys Asp Pro Glu Val Gln Asp Phe Arg Arg Asn Ile Leu
    130                 135                 140

Asn Val Cys Lys Glu Ala Val Asp Leu Arg Asp Leu Asn Ser Pro His
145                 150                 155                 160

Ser Arg Ala Met Tyr Val Tyr Pro Pro Asn Val Glu Ser Ser Pro Glu
                165                 170                 175

Leu Pro Lys His Ile Tyr Asn Lys Leu Asp Lys Gly Gln Ile Ile Val
            180                 185                 190

Val Ile Trp Val Ile Val Ser Pro Asn Asn Asp Lys Gln Lys Tyr Thr
        195                 200                 205

Leu Lys Ile Asn His Asp Cys Val Pro Glu Gln Val Ile Ala Glu Ala
    210                 215                 220

Ile Arg Lys Lys Thr Arg Ser Met Leu Leu Ser Ser Glu Gln Leu Lys
225                 230                 235                 240

Leu Cys Val Leu Glu Tyr Gln Gly Lys Tyr Ile Leu Lys Val Cys Gly
                245                 250                 255

Cys Asp Glu Tyr Phe Leu Glu Lys Tyr Pro Leu Ser Gln Tyr Lys Tyr
            260                 265                 270

Ile Arg Ser Cys Ile Met Leu Gly Arg Met Pro Asn Leu Met Leu Met
        275                 280                 285

Ala Lys Glu Ser Leu Tyr Ser Gln Leu Pro Met Asp Cys Phe Thr Met
    290                 295                 300
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Pro Ser Tyr Ser Arg Arg Ile Ser Thr Ala Thr Pro Tyr Met Asn Gly
305                 310                 315                 320

Glu Thr Ser Thr Lys Ser Leu Trp Val Ile Asn Ser Ala Leu Arg Ile
                325                 330                 335

Lys Ile Leu Cys Ala Thr Tyr Val Asn Val Asn Ile Arg Asp Ile Asp
            340                 345                 350

Lys Ile Tyr Val Arg Thr Gly Ile Tyr His Gly Gly Glu Pro Leu Cys
        355                 360                 365

Asp Asn Val Asn Thr Gln Arg Val Pro Cys Ser Asn Pro Arg Trp Asn
    370                 375                 380

Glu Trp Leu Asn Tyr Asp Ile Tyr Ile Pro Asp Leu Pro Arg Ala Ala
385                 390                 395                 400

Arg Leu Cys Leu Ser Ile Cys Ser Val Lys Gly Arg Lys Gly Ala Lys
                405                 410                 415

Glu Glu His Cys Pro Leu Ala Trp Gly Asn Ile Asn Leu Phe Asp Tyr
            420                 425                 430

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

Pro His Gly Leu Glu Asp Leu Leu Asn Pro Ile Gly Val Thr Gly Ser
    450                 455                 460

Asn Pro Asn Lys Glu Thr Pro Cys Leu Glu Leu Glu Phe Asp Trp Phe
465                 470                 475                 480

Ser Ser Val Val Lys Phe Pro Asp Met Ser Val Ile Glu Glu His Ala
                485                 490                 495

Asn Trp Ser Val Ser Arg Glu Ala Gly Phe Ser Tyr Ser His Ala Gly
            500                 505                 510

Leu Ser Asn Arg Leu Ala Arg Asp Asn Glu Leu Arg Glu Asn Asp Lys
        515                 520                 525

Glu Gln Leu Arg Ala Ile Cys Thr Arg Asp Pro Leu Ser Glu Ile Thr
    530                 535                 540

Glu Gln Glu Lys Asp Phe Leu Trp Ser His Arg His Tyr Cys Val Thr
545                 550                 555                 560

Ile Pro Glu Ile Leu Pro Lys Leu Leu Leu Ser Val Lys Trp Asn Ser
                565                 570                 575
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Arg Asp Glu Val Ala Gln Met Tyr Cys Leu Val Lys Asp Trp Pro Pro
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Ile Lys Pro Glu Gln Ala Met Glu Leu Leu Asp Cys Asn Tyr Pro Asp
        595                 600                 605

Pro Met Val Arg Gly Phe Ala Val Arg Cys Leu Glu Lys Tyr Leu Thr
    610                 615                 620

Asp Asp Lys Leu Ser Gln Tyr Leu Ile Gln Leu Val Gln Val Leu Lys
625                 630                 635                 640

Tyr Glu Gln Tyr Leu Asp Asn Leu Leu Val Arg Phe Leu Leu Lys Lys
                645                 650                 655

Ala Leu Thr Asn Gln Arg Ile Gly His Phe Phe Phe Trp His Leu Lys
            660                 665                 670

Ser Glu Met His Asn Lys Thr Val Ser Gln Arg Phe Gly Leu Leu Leu
        675                 680                 685

Glu Ser Tyr Cys Arg Ala Cys Gly Met Tyr Leu Lys His Leu Asn Arg
    690                 695                 700

Gln Val Glu Ala Met Glu Lys Leu Ile Asn Leu Thr Asp Ile Leu Lys
705                 710                 715                 720

Gln Glu Lys Lys Asp Glu Thr Gln Lys Val Gln Met Lys Phe Leu Val
                725                 730                 735

Glu Gln Met Arg Arg Pro Asp Phe Met Asp Ala Leu Gln Gly Phe Leu
            740                 745                 750

Ser Pro Leu Asn Pro Ala His Gln Leu Gly Asn Leu Arg Leu Glu Glu
        755                 760                 765

Cys Arg Ile Met Ser Ser Ala Lys Arg Pro Leu Trp Leu Asn Trp Glu
    770                 775                 780

Asn Pro Asp Ile Met Ser Glu Leu Leu Phe Gln Asn Asn Glu Ile Ile
785                 790                 795                 800

Phe Lys Asn Gly Asp Asp Leu Arg Gln Asp Met Leu Thr Leu Gln Ile
                805                 810                 815

Ile Arg Ile Met Glu Asn Ile Trp Gln Asn Gln Gly Leu Asp Leu Arg
            820                 825                 830

Met Leu Pro Tyr Gly Cys Leu Ser Ile Gly Asp Cys Val Gly Leu Ile
        835                 840                 845
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Glu Val Val Arg Asn Ser His Thr Ile Met Gln Ile Gln Cys Lys Gly
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Gly Leu Lys Gly Ala Leu Gln Phe Asn Ser His Thr Leu His Gln Trp
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Leu Lys Asp Lys Asn Lys Gly Glu Ile Tyr Asp Ala Ala Ile Asp Leu
                885                 890                 895

Phe Thr Arg Ser Cys Ala Gly Tyr Cys Val Ala Thr Phe Ile Leu Gly
            900                 905                 910

Ile Gly Asp Arg His Asn Ser Asn Ile Met Val Lys Asp Asp Gly Gln
        915                 920                 925

Leu Phe His Ile Asp Phe Gly His Phe Leu Asp His Lys Lys Lys Lys
    930                 935                 940

Phe Gly Tyr Lys Arg Glu Arg Val Pro Phe Val Leu Thr Gln Asp Phe
945                 950                 955                 960

Leu Ile Val Ile Ser Lys Gly Ala Gln Glu Cys Thr Lys Thr Arg Glu
                965                 970                 975

Phe Glu Arg Phe Gln Glu Met Cys Tyr Lys Ala Tyr Leu Ala Ile Arg
            980                 985                 990

Gln His Ala Asn Leu Phe Ile Asn  Leu Phe Ser Met Met  Leu Gly Ser
        995                 1000                1005

Gly Met  Pro Glu Leu Gln Ser  Phe Asp Asp Ile Ala  Tyr Ile Arg
    1010                1015                1020

Lys Thr  Leu Ala Leu Asp Lys  Thr Glu Gln Glu Ala  Leu Glu Tyr
    1025                1030                1035

Phe Met  Lys Gln Met Asn Asp  Ala His His Gly Gly  Trp Thr Thr
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Lys Met  Asp Trp Ile Phe His  Thr Ile Lys Gln His  Ala Leu Asn
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acttcaagta caaaattgaa agactttaaa atgccacccc gaccatcatc tggtgaacta 180

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<211> 1068
<212> PRT
<213> Gallus gallus

<400> 47

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Thr Leu Glu Cys Leu Arg Glu Ala Thr Leu Leu Thr Ile Lys His Glu
35 40 45

Leu Phe Lys Glu Ala Arg Lys Tyr Pro Leu Tyr Gln Leu Leu Gln Asp
50 55 60

Glu Ser Ser Tyr Ile Phe Val Ser Val Thr Gln Glu Ala Glu Arg Glu

65 70 75 80

Glu Phe Phe Asp Glu Thr Arg Arg Leu Cys Asp Leu Arg Leu Phe Gln
85 90 95

Pro Phe Leu Lys Val Ile Glu Pro Val Gly Asn Arg Glu Glu Lys Ile
100 105 110

Leu Asn Arg Glu Ile Gly Phe Ala Ile Gly Met Pro Ile Cys Glu Phe
115 120 125

Asp Met Val Lys Asp Pro Glu Val Gln Asp Phe Arg Arg Asn Ile Leu
130 135 140

Asn Val Cys Lys Glu Ala Val Asp Leu Arg Asp Ala Asn Ala Pro His
145 150 155 160

Ser Arg Ala Leu Tyr Val Cys Pro Pro Asn Val Glu Ser Ser Pro Glu
165 170 175

Leu Pro Lys His Ile Tyr Asn Lys Leu Asp Lys Gly Gln Ile Ile Val
180 185 190

Val Ile Trp Val Ile Val Ser Pro Asn Asn Asp Lys Gln Lys Tyr Thr
195 200 205

Leu Lys Ile Asn His Asp Cys Val Pro Glu Gln Val Ile Ala Glu Ala
210 215 220

Ile Arg Lys Lys Thr Arg Ser Met Leu Leu Ser Ser Glu Gln Leu Lys
225 230 235 240

Leu Cys Val Leu Glu Tyr Gln Gly Lys Tyr Ile Leu Lys Val Cys Gly
245 250 255

Cys Asp Glu Tyr Leu Leu Glu Lys Tyr Pro Leu Ser Gln Tyr Lys Tyr
260 265 270

Ile Arg Ser Cys Ile Met Leu Gly Arg Met Pro Asn Leu Met Leu Met
275 280 285

Ala Lys Glu Ser Leu Tyr Thr Gln Leu Pro Leu Asp Thr Phe Thr Met
290 295 300

Pro Ser Tyr Ser Arg Arg Ile Ser Thr Ala Thr Pro Tyr Met Asn Gly
305 310 315 320

Glu Ala Thr Ala Lys Ser Leu Trp Thr Ile Asn Ser Ala Leu Arg Ile
325 330 335

Arg Ile Leu Cys Ala Thr Tyr Val Asn Val Asn Ile Arg Asp Ile Asp

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            340                 345                 350

Lys Ile Tyr Val Arg Thr Gly Ile Tyr His Gly Gly Glu Pro Leu Cys
        355                 360                 365

Asp Asn Val Asn Thr Gln Arg Val Pro Cys Ser Asn Pro Arg Trp Asn
    370                 375                 380

Glu Trp Leu Ser Tyr Asp Met Tyr Ile Pro Asp Leu Pro Arg Ala Ala
385                 390                 395                 400

Arg Leu Cys Leu Ser Ile Cys Ser Val Lys Gly Arg Lys Gly Ala Lys
                405                 410                 415

Glu Glu His Cys Pro Leu Ala Trp Gly Asn Ile Asn Met Phe Asp Tyr
            420                 425                 430

Thr Asp Thr Leu Val Ser Gly Lys Met Ala Leu Asn Leu Trp Ala Val
        435                 440                 445

Pro His Gly Leu Glu Asp Leu Leu Asn Pro Ile Gly Val Thr Gly Ser
    450                 455                 460

Asn Pro Asn Lys Glu Thr Pro Cys Leu Glu Leu Glu Phe Asp Trp Phe
465                 470                 475                 480

Ser Asn Pro Val Lys Phe Pro Asp Met Thr Val Ile Glu Glu His Ala
                485                 490                 495

Asn Trp Thr Ile Ser Arg Glu Leu Gly Phe Asn Tyr Ser Tyr Ala Gly
            500                 505                 510

Leu Ser Asn Arg Ile Ala Arg Asp Asn Glu Leu Arg Glu Ser Asp Lys
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Glu Gln Leu Arg Ala Ile Cys Thr Arg Asp Pro Leu Ser Glu Ile Thr
    530                 535                 540

Glu Gln Glu Lys Asp Phe Leu Trp Ser His Arg His Tyr Cys Val Asn
545                 550                 555                 560

Thr Pro Glu Ile Leu Pro Lys Leu Leu Leu Ser Val Lys Trp Asn Ser
                565                 570                 575

Arg Asp Glu Val Ala Gln Met Tyr Cys Leu Val Lys Asp Trp Pro Pro
            580                 585                 590

Ile Lys Pro Glu Gln Ala Met Glu Leu Leu Asp Cys Asn Tyr Pro Asp
        595                 600                 605

Pro Met Val Arg Ala Phe Ala Val Arg Cys Leu Glu Lys Tyr Leu Thr
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610 615 620

Asp Asp Lys Leu Ser Gln Tyr Leu Ile Gln Leu Val Gln Val Leu Lys
625 630 635 640

Tyr Glu Gln Tyr Leu Asp Asn Gln Leu Val Arg Phe Leu Leu Lys Lys
645 650 655

Ala Leu Thr Asn Gln Arg Ile Gly His Phe Phe Phe Trp His Leu Lys
660 665 670

Ser Glu Met His Asn Lys Thr Val Ser Gln Arg Phe Gly Leu Leu Leu
675 680 685

Glu Ser Tyr Cys Arg Ala Cys Gly Met Tyr Leu Lys His Leu Ser Arg
690 695 700

Gln Val Glu Ala Met Glu Lys Leu Ile Asn Leu Thr Asp Ile Leu Lys
705 710 715 720

Gln Glu Lys Lys Asp Glu Thr Gln Lys Val Gln Met Lys Phe Leu Val
725 730 735

Glu Gln Met Arg Arg Pro Asp Phe Met Asp Ala Leu Gln Gly Phe Ile
740 745 750

Ser Pro Leu Asn Pro Ala His Gln Leu Gly Asn Leu Arg Leu Glu Glu
755 760 765

Cys Arg Ile Met Ser Ser Ala Lys Arg Pro Leu Trp Leu Asn Trp Glu
770 775 780

Asn Pro Asp Ile Met Ser Glu Leu Leu Phe Gln Asn Asn Glu Ile Ile
785 790 795 800

Phe Lys Asn Gly Asp Asp Leu Arg Gln Asp Met Leu Thr Leu Gln Ile
805 810 815

Ile Arg Ile Met Glu Asn Ile Trp Gln Asn Gln Gly Leu Asp Leu Arg
820 825 830

Met Leu Pro Tyr Gly Cys Leu Ser Ile Gly Asp Cys Val Gly Leu Ile
835 840 845

Glu Val Val Arg Ser Ser His Thr Ile Met Gln Ile Gln Cys Lys Gly
850 855 860

Gly Leu Lys Gly Ala Leu Gln Phe Asn Ser His Thr Leu His Gln Trp
865 870 875 880

Leu Lys Asp Lys Asn Lys Gly Glu Met Tyr Asp Ala Ala Ile Asp Leu

885 890 895

Phe Thr Arg Ser Cys Ala Gly Tyr Cys Val Ala Thr Phe Ile Leu Gly
900 905 910

Ile Gly Asp Arg His Asn Ser Asn Ile Met Val Lys Asp Asp Gly Gln
915 920 925

Leu Phe His Ile Asp Phe Gly His Phe Leu Asp His Lys Lys Lys Lys
930 935 940

Phe Gly Tyr Lys Arg Glu Arg Val Pro Phe Val Leu Thr Gln Asp Phe
945 950 955 960

Leu Ile Val Ile Ser Lys Gly Ala Gln Glu Cys Thr Lys Thr Arg Glu
965 970 975

Phe Glu Arg Phe Gln Glu Met Cys Tyr Lys Ala Tyr Leu Ala Ile Arg
980 985 990

Gln His Ala Asn Leu Phe Ile Asn Leu Phe Ser Met Met Leu Gly Ser
995 1000 1005

Gly Met Pro Glu Leu Gln Ser Phe Asp Asp Ile Ala Tyr Ile Arg
1010 1015 1020

Lys Thr Leu Ala Leu Asp Lys Thr Glu Gln Glu Ala Leu Glu Tyr
1025 1030 1035

Phe Met Lys Gln Met Asn Asp Ala His His Gly Gly Trp Thr Thr
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Lys Met Asp Trp Ile Phe His Thr Ile Lys Gln His Ala Leu Asn
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<212> DNA
<213> Homo sapiens

<400> 48
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ttataaaaa 2949

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<212> PRT
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<400> 49

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

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

Ser Val Leu Pro Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val
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Ala Arg Ser Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe
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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
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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
    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

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

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

Pro Ala Ser Asp Ser Ile Gly Pro Gln Ile Leu Thr Ser Pro Ser Pro
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Ser Lys Ser Ile Pro Ile Pro Gln Pro Phe Arg Pro Ala Asp Glu Asp
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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
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Asp Gln Gly Phe Arg Gly Asp Gly Gly Ser Thr Thr Gly Leu Ser Ala
385                 390                 395                 400

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

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

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

Ser Arg Asn Asn Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe
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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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Thr Phe Phe Thr Leu Ala Phe Cys Asp Phe Cys Arg Lys Leu Leu Phe
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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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Arg Asn Gln Phe Gly Gln Arg Asp Arg Ser Ser Ser Ala Pro Asn Val
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His Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Glu Lys Phe Pro Glu
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Val Phe Asp Phe Glu Pro Gly Pro Val Phe Arg Gly Ser Thr Thr Gly
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Ile Ala Arg Gln Thr Ala Gln Gly Met Asp Tyr Leu His Ala Lys Ser
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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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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
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Met Val Gly Arg Gly Tyr Leu Ser Pro Asp Leu Ser Lys Val Arg Ser
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Lys Arg Asp Glu Arg Pro Leu Phe Pro Gln Ile Leu Ala Ser Ile Glu
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Leu Leu Ala Arg Ser Leu Pro Lys Ile His Arg Ser Ala Ser Glu Pro
755 760 765

Ser Leu Asn Arg Ala Gly Phe Gln Thr Glu Asp Phe Ser Leu Tyr Ala
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Ser Ile Tyr Leu Glu Ala Tyr Glu Glu Tyr Thr Ser Lys Leu Asp Ala
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Leu Gln Gln Arg Glu Gln Gln Leu Leu Glu Ser Leu Val Phe Gln Asn
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Pro Thr Asp Val Ser Arg Ser Asn Pro Lys Ser Pro Gln Lys Pro Ile
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Val Arg Val Phe Leu Pro Asn Lys Gln Arg Thr Val Val Pro Ala Arg
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Cys Gly Val Thr Val Arg Asp Ser Leu Lys Lys Ala Leu Met Met Arg
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Lys Lys Pro Ile Gly Trp Asp Thr Asp Ile Ser Trp Leu Thr Gly Glu
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Glu Leu His Val Glu Val Leu Glu Asn Val Pro Leu Thr Thr His Asn
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Phe Val Arg Lys Thr Phe Phe Thr Leu Ala Phe Cys Asp Phe Cys Arg
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Lys Leu Leu Phe Gln Gly Phe Arg Cys Gln Thr Cys Gly Tyr Lys Phe
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His Gln Arg Cys Ser Thr Glu Val Pro Leu Met Cys Val Asn Tyr Asp
        195                 200                 205

Gln Leu Asp Leu Leu Phe Val Ser Lys Phe Phe Glu His His Pro Val
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Pro Gln Glu Glu Ala Ser Leu Ala Glu Thr Ala Leu Thr Ser Gly Ser
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Ser Pro Ser Ala Pro Pro Ser Asp Ser Ile Gly His Gln Ile Leu Thr
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Ser Pro Ser Pro Ser Lys Ser Ile Pro Ile Pro Gln Ser Phe Arg Pro
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Ala Asp Glu Asp His Arg Asn Gln Phe Gly Gln Arg Asp Arg Ser Ser
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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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Asp Gln Gly Phe Arg Gly Asp Gly Ala Pro Leu Asn Gln Leu Met Arg
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Cys Leu Arg Lys Tyr Gln Ser Arg Thr Pro Ser Pro Leu Leu Pro Ser
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Val Pro Ser Asp Ile Val Phe Asp Phe Glu Pro Gly Pro Val Phe Arg
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Leu Gly Arg Arg Asp Ser Ser Asp Asp Trp Glu Ile Pro Asp Gly Gln
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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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Ala Lys Ser Ile Ile His Arg Asp Leu Lys Ser Asn Asn Ile Phe Leu
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His Glu Asp Leu Thr Val Lys Ile Gly Asp Phe Gly Leu Ala Thr Val
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Lys Ser Arg Trp Ser Gly Ser His Gln Phe Glu Gln Leu Ser Gly Ser
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Ile Leu Trp Met Ala Pro Glu Val Ile Arg Met Gln Asp Lys Asn Pro
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Tyr Ser Phe Gln Ser Asp Val Tyr Ala Phe Gly Ile Val Leu Tyr Glu
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Leu Met Thr Gly Gln Leu Pro Tyr Ser Asn Ile Asn Asn Arg Asp Gln
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Leu Lys Lys Lys Arg Asp Glu Arg Pro Leu Phe Pro Gln Ile Leu Ala
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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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catcagtttg aacagttgtc tggatccatt ttgtggatgg caccagaagt aatcagaatg 1740

cgagataaaa acccatacag ttttcagtcc gatgtatatg catttgggat tgttctatat 1800

gaattgatga ctgggcagtt accctattca aatatcaaca acagggacca gataattttt 1860

atggtgggac gaggatatct atctccagat ctcagcaagg tacggagtaa ctgtccaaaa 1920

gccatgaaga ggttaatggc ggagtgcctc aaaaagaaaa gagatgagag accactcttt 1980

ccccaaattc tcgcctctat tgagctgctg gcccgctcat tgccaaaaat tcaccgcagt 2040

gcatcagaac cctccttgaa tcgggctggt ttccaaacag aggattttag tctctatgct 2100

tgtgcttctc caaaaacacc catccaggca gggggatatg gtgcgtttcc tgtccactga 2160

tgcaaattaa atgagtgaga aataaa 2186

<210> 57
<211> 719
<212> PRT
<213> Cavia porcellus

<400> 57

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

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

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

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

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

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

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

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

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

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

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

<210> 58
<211> 3229
<212> DNA
<213> Canis lupus familiaris

<400> 58
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cccgcaagat gtggagttac agtccgggac agtctaaaga aagctctgat gatgagaggt 120

ctaatcccag agtgctgtgc tgtttacaga attcaggatg gagagaagaa accgattggc 180

tgggacactg atatttcctg gctcactgga gaggaattgc atgtagaagt gttggaaaat 240

gttccgctta ccacacacaa ctttgtacgg aaaacttttt tcaccttagc attttgtgac 300

ttttgtcgaa agctgctttt ccagggtttt cgctgtcaaa catgtggtta taaatttcac 360

cagcgttgta gtacagaggt tccactgatg tgtgttaatt atgaccaact tgatttgctg 420

tttgtctcca agttctttga acaccaccca ataccacagg aggaggcctc catagcagag 480

actgccctta cgtctggatc atccccttct gctcccccct ccgattctcc tgggccccca 540

attctgacca gtccgtctcc ttcaaaatcc attccaattc cacagccttt ccgaccagca 600

gatgaagatc atcgaaatca gtttggacaa cgagaccggt cctcatcagc tccaaatgtg 660

catataaaca caatagaacc cgtcaacatt gatgacttga ttagagacca agggtttcgt 720

agtgatggag gatcaaccac aggtttgtct gccacccccc ctgcctcatt gcctggctca 780

ctcactaatg taaaagcatt acagaaatct ccaggacctc agcgggaaag aaaatcatct 840

tcatcctcag aagataggaa tcgaatgaaa acacttggta gacgggattc aagtgatgat 900

tgggagatac ctgatgggca gatcacagtg ggacagagaa ttggatccgg gtcatttggg 960

acagtctaca agggaaagtg gcatggtgac gtggcagtga aaatgttgaa tgtgacagca 1020

cccacacctc agcagttaca ggccttcaaa aatgaagtag gagtactcag gaaaactcga 1080

catgtgaata tcctactctt tatgggctat tcaacaaagc cccaactggc tattgttacc 1140

cagtggtgtg agggctccag cttatatcac catctccaca tcattgagac caaatttgag 1200

atgataaagc ttatagatat tgcacggcag actgcacagg gcatggatta cttacacgcc 1260

aagtcaatca tccacagaga cctcaagagt aataatattt ttcttcatga agacctcaca 1320

gtaaaaatag gtgattttgg tctagccaca gtgaaatctc gatggagtgg gtcccatcag 1380

tttgaacagt tgtctggatc cattttgtgg atggcaccag aagtgatccg aatgcaagac 1440

aaaaacccat atagcttcca gtcagatgta tacgcatttg ggattgttct atatgaattg 1500

atgacagggc agttacctta ttcaaacatc aacaacaggg accagataat ttttatggtg 1560

ggacgaggat atctttctcc agatctcagt aaggtacgga gtaactgtcc aaaagccatg 1620

aagagattga tggcagagtg cctaaaaaag aaaagagatg agaggccact ctttccccaa 1680

attctcgcct ctattgagct gctggcccgc tcattgccaa aaattcaccg cagtgcatca 1740

gaaccctcct tgaatcgggc tggcttccaa acagaggatt ttagtctcta tgcttgcgct 1800

tctccaaaaa cacccatcca ggcaggggga tacggagaat ttgcagcctt caagtagcca 1860

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agctggtgtg gaacagaatg gaatttccca tccaacaaaa gagggaagaa tgttttagga 2040

accagaattc tctgctgcca gtgtttcttc ttcaacacaa ataccacgtg catacaagtc 2100

tgcccactcc caggaaggaa gaggagagcc tgagttctga ccttttgatg gtcaggcatg 2160

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caagtgttgg ggatttttt ttttgccctc cacaatgtag caagttctca ggaaaataca 2700

gttaatatct tcctcctaag ctcttccagt catcaagtac ttatgtggct actttgtcca 2760

gggcacaaaa tgccatggcg gtatccaatt aaaagcctac aaaactgctt gataacagtt 2820

ttgaatgtgt gagacattta tgtaatttaa atgtaaggta caagttttaa tttctgagtt 2880

tctctattat atttttatta aaaagaaaat aattttcaga tttaattgaa ttggaataaa 2940

ataatacttc ccaccagaat tatatatcct ggaaaattgt atttttgtta tataaacaac 3000

ttttaaagaa agatcattat ccttttctct acctaaatat ggggagtctt agcataatga 3060

cagatattta taatttttaa attaatggta cttgctggat ccacactaac atctttgcta 3120

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<210> 59
<211> 617
<212> PRT
<213> Canis lupus familiaris

<400> 59

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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

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

Thr Val Lys Ser Arg Trp Ser Gly Ser His Gln Phe Glu Gln Leu Ser
450 455 460

Gly Ser Ile Leu Trp Met Ala Pro Glu Val Ile Arg Met Gln Asp Lys
465 470 475 480

Asn Pro Tyr Ser Phe Gln Ser Asp Val Tyr Ala Phe Gly Ile Val Leu
485 490 495

Tyr Glu Leu Met Thr Gly Gln Leu Pro Tyr Ser Asn Ile Asn Asn Arg

500 505 510

Asp Gln Ile Ile Phe Met Val Gly Arg Gly Tyr Leu Ser Pro Asp Leu
515 520 525

Ser Lys Val Arg Ser Asn Cys Pro Lys Ala Met Lys Arg Leu Met Ala
530 535 540

Glu Cys Leu Lys Lys Lys Arg Asp Glu Arg Pro Leu Phe Pro Gln Ile
545 550 555 560

Leu Ala Ser Ile Glu Leu Leu Ala Arg Ser Leu Pro Lys Ile His Arg
565 570 575

Ser Ala Ser Glu Pro Ser Leu Asn Arg Ala Gly Phe Gln Thr Glu Asp
580 585 590

Phe Ser Leu Tyr Ala Cys Ala Ser Pro Lys Thr Pro Ile Gln Ala Gly
595 600 605

Gly Tyr Gly Glu Phe Ala Ala Phe Lys
610 615

<210> 60
<211> 1889
<212> DNA
<213> Canis lupus familiaris

<400> 60
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ttggtgggga gcataatcca ccatcaatat atctggaggc ctatgaagaa tacaccagca 120

aactagatgc cctccaacag cgagaacaac agttattgga atccctgggg aatggaactg 180

atttttctgt ttctagctct gcatcaacgg acaccgttac atcttcttcc tcttctagcc 240

tttcagtgct accttcatct ctttcagttt ttcaaaatcc cacagatata tcacggagca 300

atcccaagtc accacaaaaa cctatcgtta gagtcttcct gcccaataaa cagaggacgg 360

tggtacccgc aagatgtgga gttacagtcc gggacagtct aaagaaagct ctgatgatga 420

gaggtctaat cccagagtgc tgtgctgttt acagaattca ggatggagag aagaaaccga 480

ttggctggga cactgatatt tcctggctca ctggagagga attgcatgta gaagtgttgg 540

aaaatgttcc gcttaccaca cacaactttg tacggaaaac ttttttcacc ttagcatttt 600

gtgacttttg tcgaaagctg cttttccagg gttttcgctg tcaaacatgt ggttataaat 660

ttcaccagcg ttgtagtaca gaggttccac tgatgtgtgt taattatgac caacttgatt 720

tgctgtttgt ctccaagttc tttgaacacc acccaatacc acaggaggag gcctccatag 780

cagagactgc ccttacgtct ggatcatccc cttctgctcc cccctccgat tctcctgggc 840

ccccaattct gaccagtccg tctccttcaa aatccattcc aattccacag cctttccgac 900

cagcagatga agatcatcga aatcagtttg gacaacgaga ccggtcctca tcagctccaa 960

atgtgcatat aaacacaata gaacccgtca acattgatga cttgattaga gaccaagggt 1020

ttcgtagtga tggaggatca accacaggtt tgtctgccac ccccccctgcc tcattgcctg 1080

gctcactcac taatgtaaaa gcattacaga aatctccagg acctcagcgg gaaagaaaat 1140

catcttcatc ctcagaagat aggaatcgaa tgaaaacact tggtagacgg gattcaagtg 1200

atgattggga gatacctgat gggcagatca cagtgggaca gagaattgga tccgggtcat 1260

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cagcacccac acctcagcag ttacaggcct tcaaaaatga agtaggagta ctcaggaaaa 1380

ctcgacatgt gaatatccta ctctttatgg gctattcaac aaagccccaa ctggctattg 1440

ttacccagtg gtgtgagggc tccagcttat atcaccatct ccacatcatt gagaccaaat 1500

ttgagatgat aaagcttata gatattgcac ggcagactgc acagggcatg gattacttac 1560

acgccaagtc aatcatccac agagacctca agagtaataa tatttttctt catgaagacc 1620

tcacagtaaa aataggtgat tttggtctag ccacagtgaa atctcgatgg agtgggtccc 1680

atcagtttga acagttgtct ggatccattt tgtggatggc accagaagtg atccgaatgc 1740

aagacaaaaa cccatatagc ttccagtcag atgtatacgc atttgggatt gttctatatg 1800

aattgatgac agggcagtta ccttattcaa acatcaacaa cagggaccag ctcagatcat 1860

gatcacggtg tcatgagatc aagccccac 1889

<210> 61
<211> 615
<212> PRT
<213> Canis lupus familiaris

<400> 61

Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu Asp Lys Phe
1 5 10 15

Gly Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala Tyr Glu Glu
20 25 30

Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln Gln Leu Leu
35 40 45

Glu Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser Ser Ala Ser
50 55 60

Thr Asp Thr Val Thr Ser Ser Ser Ser Ser Ser Leu Ser Val Leu Pro
65 70 75 80

Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Ile Ser Arg Ser Asn
85 90 95

Pro Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu Pro Asn Lys
100 105 110

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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
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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
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<210> 62
<211> 3521
<212> DNA
<213> Felis catus

<220>

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

<400> 62
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ctgggatatt ttgtgatttg ccttggccat tgtccactgt ccttgacatt gcctgaagga 120

gaaccactga tgctaatgtt gaaggtgacc tttgcaggct ctccactact cataccaaag 180

atgcggcccc ctgataatcc cagagccact gtctgcacat gggcaaaaca ggctacattc 240

tgtgcagact ggggagaaag gttccaagaa cacagtgcca tagttttggg cagagagttt 300

caacacagca tagtgtctat ggcagtatct ggatttggcc gggggaagtg cccaagagga 360

gacagtcagg ctgtgtccta cggccaagga cctgcactta tttttgcatg cagtggttta 420

gcacagggaa gagaacgaag taggaaatcg gagccatgga aacggcagag cggaggaaac 480

gtgcacgcgc gagggtgggc acgaaaggaa agaaccctcc ccagaagact gcgcgagggc 540

gctcctagga ttacgtcacg caccccgcga aaactgaaat gtactgtgtg tggtctttta 600

attgaactat cttccttatg tgcacttaan nnnnnnnnnn nnnnnnnnng cggcggcggc 660

ggtggcgcgg agcagggcca ggctctgttc aacggggaca tggagcccga agccggcgcc 720

gcggcctctt cggctgcgga ccctgccatt cccgaggagg tgtggaatat caaacaaatg 780

attaagttga cacaggaaca tatagaggcc ctattggaca aatttggtgg ggagcataat 840

ccaccatcaa tatatctaga ggcctatgaa gaatacacca gcaagctaga tgccctccaa 900

cagagagaac aacagttatt ggaatccctg gggaatggaa ctgatttttc tgtttctagc 960

tctgcatcaa cagacaccgt tacatcttcc tcctcttcta gcctttcagt gctaccttca 1020

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aaacctatcg ttagagtctt cctgcctaat aaacagagga cagtggtacc tgcaagatgt 1140

ggagttacag tccgggacag tctaaagaaa gctctgatga tgagaggtct aatccctgag 1200

tgctgtgctg tttacagaat tcaggatgga gagaagaaac caattggctg ggacactgat 1260

atctcctggc tcaccggaga ggaattgcat gtagaagtgt tggaaaatgt tccacttaca 1320

actcacaact ttgtatgtac ggaaaacgtt ttcaccttag cattttgtga cttttgtcga 1380

aagctgcttt tccaaggttt tcgctgtcaa acgtgtggtt ataaatttca ccagcgttgt 1440

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aagttctttg aacaccaccc aataccacag gaggaggcct ccatagcaga gactgcccta 1560

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Thr Val Ser Ala Leu Gly Tyr Phe Val Ile Cys Leu Gly His Cys Pro
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Leu Ser Leu Thr Leu Pro Glu Gly Glu Pro Leu Met Leu Met Leu Lys
        35                  40                  45

Val Thr Phe Ala Gly Ser Pro Leu Leu Ile Pro Lys Met Arg Pro Pro
    50                  55                  60

Asp Asn Pro Arg Ala Thr Val Cys Thr Trp Ala Lys Gln Ala Thr Phe
65                  70                  75                  80

Cys Ala Asp Trp Gly Glu Arg Phe Gln Glu His Ser Ala Ile Val Leu
                85                  90                  95

Gly Arg Glu Phe Gln His Ser Ile Val Ser Met Ala Val Ser Gly Phe
            100                 105                 110

Gly Arg Gly Lys Cys Pro Arg Gly Asp Ser Gln Ala Val Ser Tyr Gly
        115                 120                 125

Gln Gly Pro Ala Leu Ile Phe Ala Cys Ser Gly Leu Ala Gln Gly Arg
    130                 135                 140

Glu Arg Ser Arg Lys Ser Glu Pro Trp Lys Arg Gln Ser Gly Gly Asn
145                 150                 155                 160

Val His Ala Arg Gly Trp Ala Arg Lys Glu Arg Thr Leu Pro Arg Arg
                165                 170                 175

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

Lys Cys Thr Val Cys Gly Leu Leu Ile Glu Leu Ser Ser Leu Cys Ala
        195                 200                 205

Leu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gly Gly Gly Gly Gly Ala Glu
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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
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Ile Lys Gln Met Ile Lys Leu Thr Gln Glu His Ile Glu Ala Leu Leu
            260                 265                 270
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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
    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
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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
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Ser Lys Ser Ile Pro Ile Pro Gln Pro Phe Arg Pro Ala Asp Glu Asp
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His Arg Asn Gln Phe Gly Gln Arg Asp Arg Ser Ser Ser Ala Pro Asn
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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
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Thr Gln Trp Cys Glu Gly Ser Ser Leu Tyr His His Leu His Ile Ile
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Glu Thr Lys Phe Glu Met Ile Lys Leu Ile Asp Ile Ala Arg Gln Thr
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Ala Gln Gly Met Asp Tyr Leu His Ala Lys Ser Ile Ile His Arg Asp
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Leu Lys Ser Asn Asn Ile Phe Leu His Glu Asp Leu Thr Val Lys Ile
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Gly Asp Phe Gly Leu Ala Thr Val Lys Ser Arg Trp Ser Gly Ser His
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Ile Arg Met Gln Asp Lys Asn Pro Tyr Ser Phe Gln Ser Asp Val Tyr
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Ala Phe Gly Ile Val Leu Tyr Glu Leu Met Thr Gly Gln Leu Pro Tyr
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Ser Asn Ile Asn Asn Arg Asp Gln Ile Ile Phe Met Val Gly Arg Gly
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Tyr Leu Ser Pro Asp Leu Ser Lys Val Arg Ser Asn Cys Pro Lys Ala
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Met Lys Arg Leu Met Ala Glu Cys Leu Lys Lys Lys Arg Asp Glu Arg
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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

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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

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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
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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 Asp Leu Leu
        275                 280                 285

Phe Val Ser Lys Phe Phe Glu His His Pro Ile Pro Gln Glu Glu Ala
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Ser Leu Ala Glu Thr Thr Leu Pro Cys Gly Ser Ser Pro Ser Ala Pro
305                 310                 315                 320

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
    370                 375                 380

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

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

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

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

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

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

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

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

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

Asp Phe Gly Leu Ala Thr Val Lys Ser Arg Trp Ser Gly Ser His Gln
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Phe Glu Gln Leu Ser Gly Ser Ile Leu Trp Met Ala Pro Glu Val Ile
    610                 615                 620
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Arg Met Gln Asp Lys Asn Pro Tyr Ser Phe Gln Ser Asp Val Tyr Ala
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Phe Gly Ile Val Leu Tyr Glu Leu Met Thr Gly Gln Leu Pro Tyr Ser
                645                 650                 655

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

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

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

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

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

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

Pro Ile Gln Ala Gly Gly Tyr Gly Thr Phe Pro Val His
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Thr Glu Val Pro Leu Met Cys Val Asn Tyr Asp Gln Leu Asp Leu Leu
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Gly Glu His Asn Pro Pro Ser Ile Tyr Leu Glu Ala Tyr Glu Glu Tyr
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Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln Gln Leu Leu Glu
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Ser Leu Gly Asn Gly Thr Asp Phe Ser Val Ser Ser Ser Ala Ser Thr
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Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val Ser Arg Ser Asn Pro
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Lys Ser Pro Gln Lys Pro Ile Val Arg Val Phe Leu Pro Asn Lys Gln
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Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr Val Arg Asp Ser Leu
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Lys Lys Ala Leu Met Met Arg Gly Leu Ile Pro Glu Cys Cys Ala Val
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Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly Trp Asp Thr Asp
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Ile Ser Trp Leu Thr Gly Glu Glu Leu His Val Glu Val Leu Glu Asn
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Val Pro Leu Thr Thr His Asn Phe Val Arg Lys Thr Phe Phe Thr Leu
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Gln Thr Cys Gly Tyr Lys Phe His Gln Arg Cys Ser Thr Glu Val Pro
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Thr Thr Leu Pro Cys Gly Ser Ser Pro Ser Ala Pro Pro Ser Asp Ser
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Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp Asp Trp Glu Ile Pro
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Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly Ser Gly Ser Phe Gly
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Gly Ser Ser Leu Tyr His His Leu His Ile Ile Glu Thr Lys Phe Glu
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Glu Lys Asp Lys Gln Ile Leu Ala Ser Ile Glu Leu Leu Ala Arg 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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Val Leu Pro Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val Ser
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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
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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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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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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
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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
435 440 445

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

Arg Lys Thr Arg His Val Asn Ile Leu Leu Phe Met Gly Tyr Ser Thr
465 470 475 480

Lys Pro Gln Leu Ala Ile Val Thr Gln Trp Cys Glu Gly Ser Ser Leu
485 490 495

Tyr His His Leu His Ile Ile Glu Thr Lys Phe Glu Met Ile Lys Leu
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Ile Asp Ile Ala Arg Gln Thr Ala Gln Gly Met Asp Tyr Leu His Ala

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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
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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
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Ser Phe Gln Ser Asp Val Tyr Ala Phe Gly Ile Val Leu Tyr Glu Leu
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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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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
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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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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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Val Leu Pro Ser Ser Leu Ser Val Phe Gln Asn Pro Thr Asp Val Ser
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Pro Asn Lys Gln Arg Thr Val Val Pro Ala Arg Cys Gly Val Thr 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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Gly Ser Phe Gly Thr Val Tyr Lys Gly Lys Trp His Gly Asp Val Ala
465                 470                 475                 480

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Leu Phe Pro Gln Val Gly Lys Thr Leu Leu Ser Lys Arg Gln Asn Ser
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His Ser Arg His Leu Gly Leu Gln
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<400> 79

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20 25 30

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Gln Gly Phe Arg Ser Asp Gly Gly Ser Thr Thr Gly Leu Ser Ala Thr
385                 390                 395                 400
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Pro Pro Ala Ser Leu Pro Gly Ser Leu Ser Asn Val Lys Ala Leu Gln
                405                 410                 415

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Asn Ile Asn Asn Arg Asp Gln Ile Ile Phe Met Val Gly Arg Gly Tyr
            660                 665                 670
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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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Leu Phe Pro Gln Asp Leu Ser Ser His His Arg His Lys Asn Phe Arg
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Trp Leu Gln Val Tyr Met
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<400> 81

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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

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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
    130                 135                 140

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

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

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

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

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

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

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

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

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

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

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

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

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

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

His Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Asp Leu Ile Arg Asp
    370                 375                 380
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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
                405                 410                 415

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Phe Gly Ile Val Leu Tyr Glu Leu Met Thr Gly Gln Leu Pro Tyr Ser
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Lys Cys Cys Ala Arg Ala Tyr Phe Pro
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<400> 83

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Gln Gly Gln Ala Leu Phe Asn Gly Asp Met Glu Pro Glu Ala Gly Ala
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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

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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
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Val Lys Met Leu Asn Val Thr Ala Pro Thr Pro Gln Gln Leu Gln Ala
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Leu Leu Phe Met Gly Tyr Ser Thr Lys Pro Gln Leu Ala Ile Val Thr
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Asp Phe Gly Leu Ala Thr Val Lys Ser Arg Trp Ser Gly Ser His Gln
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Cys Cys Ala Val Tyr Arg Ile Gln Asp Gly Glu Lys Lys Pro Ile Gly
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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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Ser Leu Ala Glu Thr Thr Leu Pro Cys Gly Ser Ser Pro Ser Ala Pro
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His Ile Asn Thr Ile Glu Pro Val Asn Ile Asp Asp Leu Ile Arg Asp
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<400> 87

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Asp Gly Glu Lys Lys Pro Ile Gly Trp Asp Thr Asp Ile Ser Trp Leu

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Thr Gly Glu Glu Leu His Val Glu Val Leu Glu Asn Val Pro Leu Thr
35 40 45

Thr His Asn Phe Val Arg Lys Thr Phe Phe Thr Leu Ala Phe Cys Asp
50 55 60

Phe Cys Arg Lys Leu Leu Phe Gln Gly Phe Arg Cys Gln Thr Cys Gly
65 70 75 80

Tyr Lys Phe His Gln Arg Cys Ser Thr Glu Val Pro Leu Met Cys Val
85 90 95

Asn Tyr Asp Gln Leu Asp Leu Leu Phe Val Ser Lys Phe Phe Glu His
100 105 110

His Pro Ile Pro Gln Glu Glu Ala Ser Leu Ala Glu Thr Thr Leu Pro
115 120 125

Cys Gly Ser Ser Pro Ser Ala Pro Pro Ser Asp Ser Ile Gly Pro Pro
130 135 140

Ile Leu Thr Ser Pro Ser Pro Ser Lys Ser Ile Pro Ile Pro Gln Pro
145 150 155 160

Phe Arg Pro Ala Asp Glu Asp His Arg Asn Gln Phe Gly Gln Arg Asp
165 170 175

Arg Ser Ser Ser Ala Pro Asn Val His Ile Asn Thr Ile Glu Pro Val
180 185 190

Asn Ile Asp Asp Leu Ile Arg Asp Gln Gly Phe Arg Ser Asp Gly Gly
195 200 205

Ser Thr Thr Gly Leu Ser Ala Thr Pro Pro Ala Ser Leu Pro Gly Ser
210 215 220

Leu Ser Asn Val Lys Ala Leu Gln Lys Ser Pro Gly Pro Gln Arg Glu
225 230 235 240

Arg Lys Ser Ser Ser Ser Ser Glu Asp Arg Asn Arg Met Lys Thr Leu
245 250 255

Gly Arg Arg Asp Ser Ser Asp Asp Trp Glu Ile Pro Asp Gly Gln Ile
260 265 270

Thr Val Gly Gln Arg Ile Gly Ser Gly Ser Phe Gly Thr Val Tyr Lys
275 280 285

Gly Lys Trp His Gly Asp Val Ala Val Lys Met Leu Asn Val Thr Ala

290 295 300

Pro Thr Pro Gln Gln Leu Gln Ala Phe Lys Asn Glu Val Gly Val Leu
305 310 315 320

Arg Lys Thr Arg His Val Asn Ile Leu Leu Phe Met Gly Tyr Ser Thr
325 330 335

Lys Pro Gln Leu Ala Ile Val Thr Gln Trp Cys Glu Gly Ser Ser Leu
340 345 350

Tyr His His Leu His Ile Ile Glu Thr Lys Phe Glu Met Ile Lys Leu
355 360 365

Ile Asp Ile Ala Arg Gln Thr Ala Gln Gly Met Asp Tyr Leu His Ala
370 375 380

Lys Ser Ile Ile His Arg Asp Leu Lys Ser Asn Asn Ile Phe Leu His
385 390 395 400

Glu Asp Leu Thr Val Lys Ile Gly Asp Phe Gly Leu Ala Thr Val Lys
405 410 415

Ser Arg Trp Ser Gly Ser His Gln Phe Glu Gln Leu Ser Gly Ser Ile
420 425 430

Leu Trp Met Ala Pro Glu Val Ile Arg Met Gln Asp Lys Asn Pro Tyr
435 440 445

Ser Phe Gln Ser Asp Val Tyr Ala Phe Gly Ile Val Leu Tyr Glu Leu
450 455 460

Met Thr Gly Gln Leu Pro Tyr Ser Asn Ile Asn Asn Arg Asp Gln Ile
465 470 475 480

Ile Phe Met Val Gly Arg Gly Tyr Leu Ser Pro Asp Leu Ser Lys Val
485 490 495

Arg Ser Asn Cys Pro Lys Ala Met Lys Arg Leu Met Ala Glu Cys Leu
500 505 510

Lys Lys Lys Arg Asp Glu Arg Pro Leu Phe Pro Gln Val Gly Lys Thr
515 520 525

Leu Leu Ser Lys Arg Gln Asn Ser Glu Val Ile Arg Glu Lys Asp Lys
530 535 540

Gln Ile Leu Ala Ser Ile Glu Leu Leu Ala Arg Ser Leu Pro Lys Ile
545 550 555 560

His Arg Ser Ala Ser Glu Pro Ser Leu Asn Arg Ala Gly Phe Gln Thr

565 570 575

Glu Asp Phe Ser Leu Tyr Ala Cys Ala Ser Pro Lys Thr Pro Ile Gln
580 585 590

Ala Gly Gly Tyr Gly Glu Phe Ala Ala Phe Lys
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<211> 2295
<212> DNA
<213> Equus caballus

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<222> (79)..(79)
<223> n is a, c, g, or t

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gacatggaac ccggaggcnc cgcgccggcg cccgcggcct cgtcggccgc ggaccctgcc 120

attcccgagg aggtatggaa tatcaaacaa atgattaaat tgacacagga acatatagag 180

gccctattgg acaaatttgg tggggagcat aatccaccat caatatatct ggaggcctat 240

gaagaataca ccagcaagct agatgccctc caacaaagag aacaacagtt attggaatcc 300

ctggggaatg gaactgattt ttctgtttct agttctgcat caacggacac cgttacatct 360

tcttcctctt ctagcctttc agtgctacct tcatctcttt cagttttca aaatcccaca 420

gatgtgtcac ggagcaaccc taagtcacca caaaaaccta tcgttagagt cttcctgccc 480

aacaaacaga ggacagtggt acctgcaagg tgtggcgtta cagtccggga cagtctaaag 540

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ggagagaaga aaccaattgg ctgggacact gatatttcct ggctcactgg agaggaattg 660

catgtagaag tgttggagaa tgttccactt acaacacaca actttgtacg gaaaactttt 720

ttcaccttag cattttgtga cttttgtcga aagctgcttt tccagggttt ccgctgtcaa 780

acatgtggtt ataaatttca ccagcgttgt agtacagagg ttccactgat gtgtgttaat 840

tatgaccaac ttgatttgct gtttgtctcc aagttctttg aacaccaccc agtatcacag 900

gaggaggcct ccttagcaga gactgccctt acatctggat catccccttc tgcacccccc 960

tccgattcca ttgggcccca aattctcacc agtccatctc cttcaaaatc cattccaatt 1020

ccacagcctt tccgaccagc agatgaagat catcgaaatc agtttggaca acgagaccgg 1080

tcctcatcag ctccaaatgt acatataaac acaatagaac ctgtcaatat tgatgacttg 1140

attagagacc aagggtttcg tagtgatgga ggatcaacca caggtttatc tgccaccccc 1200

cctgcctcat tacctggctc actcactaat gtgaaggcat tacagaaatc tccaggacct 1260

caacgggaaa ggaaatcatc ttcatcctca gaagacagga atcgaatgaa aactcttggt 1320

agacgggatt caagtgacga ttgggagatt cctgatgggc agatcacagt gggacaaaga 1380

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ggagtactca ggaaaactcg acatgtgaat atcctactct tcatgggcta ttcaacaaag 1560

ccacaactgg ctattgttac ccagtggtgt gagggctcca gcttatatca ccatctccac 1620

atcattgaga ccaaatttga gatgatcaaa cttatagata ttgctcggca aactgcacag 1680

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cgatggagtg ggtcccatca gtttgaacag ttgtctggat ccattttgtg gatggcacca 1860

gaagtaatca gaatgcaaga taaaaacccg tatagctttc aatcagatgt atatgccttt 1920

gggattgttc tgtatgaatt gatgactgga cagttacctt attcaaacat caacaacagg 1980

gaccagataa tttttatggt gggaagagga tatctatctc cagatctcag taaggtacgg 2040

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aaaattcacc gcagtgcatc agagccctcc ttgaatcggg ctggcttcca gacagaggat 2220

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<210> 89
<211> 764
<212> PRT
<213> Equus caballus

<220>
<221> misc_feature
<222> (27)..(27)
<223> Xaa can be any naturally occurring amino acid

<400> 89

Met Lys Thr Leu Ser Gly Gly Gly Gly Gly Ala Glu Gln Gly Gln Ala
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Leu Phe Asn Gly Asp Met Glu Pro Gly Gly Xaa Ala Pro Ala Pro Ala
20 25 30

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

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

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

Glu Glu Tyr Thr Ser Lys Leu Asp Ala Leu Gln Gln Arg Glu Gln Gln

85 90 95

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

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

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

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

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

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

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

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

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

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

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

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

Val Ser Lys Phe Phe Glu His His Pro 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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        355                 360                 365

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 90
<211> 2678
<212> DNA
<213> Gallus gallus

<400> 90
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ggcgcctgct acgccgggag cggcggcggc gacccggcca tcccggagga ggtgtggaat 180

atcaaacaga tgattaaatt aacacaagaa catatagaag cgctgttaga caagtttgga 240

ggagagcata acccaccatc aatatattta gaggcctatg aggagtacac cagcaaacta 300

gatgctctac agcagagaga acagcagtta ttggaatcca tgggaaatgg aactgatttc 360

tctgtttcca gttcagcttc aacggacaca gttgcatcat cttcctcctc tagcctctct 420

gtagcacctt catccctttc agtttatcaa aatcctactg atatgtcgcg gaataaccct 480

aagtctccac agaagcctat tgttagagtc ttcctgccca acaagcaaag gactgtggtt 540

ccggcaagat gtggggtgac agtccgagac agcctgaaga aagctctgat gatgagaggt 600

cttattccag aatgctgtgc tgtttacaga atacaggatg gagagaagaa gccaattggc 660

tgggacactg acatttcctg gctaaccgga gaggagttac acgtggaggt cttggagaat 720

gtgccactca caacacacaa ttttgtacga aaaacattct tcacgttagc gttctgcgac 780

ttctgtcgaa agctgctttt ccagggattc cgatgccaga catgtggcta caaatttcac 840

cagcgctgta gcacagaagt gccactgatg tgtgttaact acgaccaact cgatttgctg 900

tttgtctcca agttctttga acatcacccc atatcgcagg aggagaccac cttaggagag 960

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aagtcaatca tccacagaga cctcaagagt aataatattt ttcttcatga agacctcaca 1920

gtaaaaatag gtgacttcgg tctggctaca gtgaaatcac gatggagtgg atctcatcaa 1980

tttgaacagt tatctggatc aattctatgg atggcaccgg aagtgatcag gatgcaagac 2040

aaaaacccat atagctttca gtcagatgtg tatgcattcg ggattgtgct ttatgaactg 2100

atgactggac agttaccata ctcaaacatc aacaacaggg accagataat ttttatggtg 2160

ggacgaggat atctatctcc agacctcagt aaagtaagaa gtaactgtcc aaaagctatg 2220

aagagactaa tggcagaatg cttgaaaaag aaaagagatg agagacctct ttttccacag 2280

attcttgcct ccattgagct tctggcccgg tcgttgccaa aaattcaccg cagtgcatct 2340

gagccgtcac taaaccgggc tggcttccag accgaggatt tcagtctgta tgcttgtgct 2400

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ggaacagctg gcaagaagaa ttagaaggta cttaaagg 2678

<210> 91
<211> 806
<212> PRT
<213> Gallus gallus

<400> 91

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Asn Gly Asp Met Glu Pro Glu Pro Pro Pro Pro Val Leu Gly Ala Cys
            20                  25                  30

Tyr Ala Gly Ser Gly Gly Gly Asp Pro Ala Ile Pro Glu Glu Val Trp
        35                  40                  45

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Pro Pro Ser Asp Ser Val Gly Pro Pro Ile Leu Pro Ser Pro Ser Pro
325 330 335

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

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

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

Asp Gln Gly Val Arg Gly Glu Gly Ala Pro Leu Asn Gln Leu Met Arg
385 390 395 400

Cys Leu Arg Lys Tyr Gln Ser Arg Thr Pro Ser Pro Leu Leu His Ser
405 410 415

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

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

Ser Leu Thr Asn Val Lys Ala Leu Gln Lys Ser Pro Gly Pro Gln Arg
450 455 460

Glu Arg Lys Ser Ser Ser Ser Ser Glu Asp Arg Asn Arg Met Lys Thr
465 470 475 480

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

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

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

Ala Pro Thr Pro Gln Gln Leu Gln Ala Phe Lys Asn Glu Val Gly Val

530 535 540

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

Thr Lys Pro Gln Leu Ala Ile Val Thr Gln Trp Cys Glu Gly Ser Ser
565 570 575

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

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

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

His Glu Asp Leu Thr Val Lys Ile Gly Asp Phe Gly Leu Ala Thr Val
625 630 635 640

Lys Ser Arg Trp Ser Gly Ser His Gln Phe Glu Gln Leu Ser Gly Ser
645 650 655

Ile Leu Trp Met Ala Pro Glu Val Ile Arg Met Gln Asp Lys Asn Pro
660 665 670

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

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

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

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

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

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

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

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

Gly Gly Phe Pro Val His

805