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(54) Title: P70 S6 KINASE INHIBITOR AND MTOR INHIBITOR COMBINATION THERAPY

(57) Abstract: The present invention provides a combination therapy comprising the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, and an mTOR inhibitor for use in the treatment of glioblastoma multiforme, adenocarcinomas of the colon, non-small-cell lung cancer, small-cell lung cancer, cisplatin-resistant small-cell lung cancer, ovarian cancer, leukemia, pancreatic cancer, prostate cancer, mammary carcinoma, renal cell carcinoma, multiple myeloma, Kaposi Sarcoma, Hodgkins lymphoma, lymphangioleiomyomatosis, Non-Hodgkins lymphoma or sarcoma.



WO 2010/056574 A1

P70 S6 KINASE INHIBITOR AND MTOR INHIBITOR COMBINATION THERAPY

BACKGROUND OF THE INVENTION

5 The phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway encompasses a number of signaling points which are critical in the control of cell growth and survival. mTOR is a serine-threonine kinase which is involved in controlling many cellular functions such as cell proliferation, cell survival, protein synthesis and transcription. It has been shown that inhibition of mTOR activity in tumor
10 cells results in G1 growth arrest caused by the disruption of translation of regulatory cell cycle proteins. P70 S6 kinase is a serine-threonine protein kinase which is a downstream effector of the PI3K/AKT/mTOR signaling pathway. P70 S6 kinase phosphorylates the ribosomal protein S6 in cells and regulates ribosome biogenesis, cell growth and cell cycle progression in response to mitogenic stimulation. P70 S6 kinase is commonly
15 activated in many solid tumors. Inhibitors of p70 S6 kinase, which are useful in the treatment of such tumors, are disclosed in WO 2006/046024 and WO 2008/075109.

 Rapamycin is a macrolide compound which is produced by the bacterium *streptomyces hygroscopicus*. Rapamycin binds to the intracellular protein FKBP-12 and forms a complex which inhibits the activity of mTOR. Analogues of rapamycin, which
20 are mTOR inhibitors and are useful in the treatment of cancers, are disclosed in EP 1 413 581, WO 95/28406 and WO 03/64383.

 There exists a need for improved therapies for the treatment of cancers. Furthermore, there is a need for therapies having greater efficacy than existing therapies. Preferred combination therapies of the present invention show greater efficacy than
25 treatment with either therapeutic agent alone. More preferred combination therapies of the present invention show greater efficacy when sub-optimal doses of each of the therapeutic agents are administered.

BRIEF SUMMARY OF THE INVENTION

30 The present invention provides a product containing the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, and an mTOR

-2-

inhibitor as a combined preparation for simultaneous, separate or sequential use in therapy.

The present invention further provides a product containing the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, and an mTOR inhibitor as a combined preparation for simultaneous, separate or sequential use in the treatment of glioblastoma multiforme, adenocarcinomas of the colon, non-small-cell lung cancer, small-cell lung cancer, cisplatin-resistant small-cell lung cancer, ovarian cancer, leukemia, pancreatic cancer, prostate cancer, mammary carcinoma, renal cell carcinoma, multiple myeloma, Kaposi's Sarcoma, Hodgkin's lymphoma, lymphangioleiomyomatosis, Non-Hodgkin's lymphoma or sarcoma.

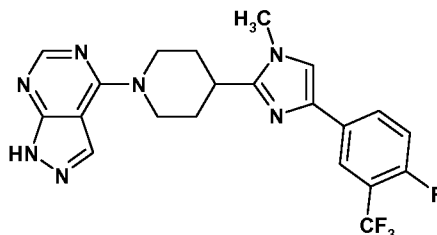
The present invention further provides the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate or sequential combination with an mTOR inhibitor in the treatment of glioblastoma multiforme, adenocarcinomas of the colon, non-small-cell lung cancer, small-cell lung cancer, cisplatin-resistant small-cell lung cancer, ovarian cancer, leukemia, pancreatic cancer, prostate cancer, mammary carcinoma, renal cell carcinoma, multiple myeloma, Kaposi's Sarcoma, Hodgkin's lymphoma, lymphangioleiomyomatosis, Non-Hodgkin's lymphoma or sarcoma.

The present invention further provides a method of treating a cancer selected from the group consisting of glioblastoma multiforme, adenocarcinomas of the colon, non-small-cell lung cancer, small-cell lung cancer, cisplatin-resistant small-cell lung cancer, ovarian cancer, leukemia, pancreatic cancer, prostate cancer, mammary carcinoma, renal cell carcinoma, multiple myeloma, Kaposi's Sarcoma, Hodgkin's lymphoma, lymphangioleiomyomatosis, Non-Hodgkin's lymphoma and sarcoma comprising administering to a patient in need thereof the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, and an mTOR inhibitor in amounts that in combination are effective.

-3-

DETAILED DESCRIPTION OF THE INVENTION

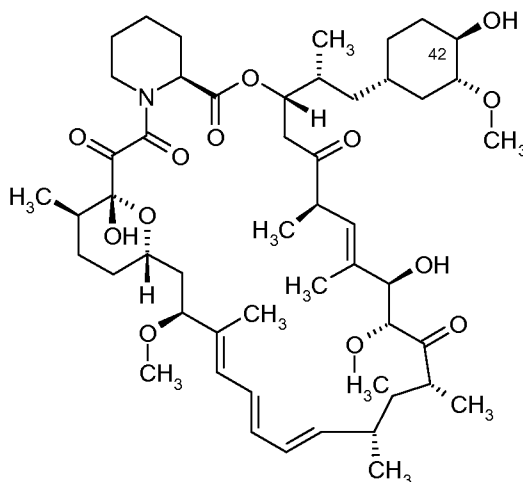
The compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine:



5 is a p70 S6 kinase inhibitor.

The compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine is a base, and accordingly will react with any of a number of organic and inorganic acids to form pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine which are substantially non-toxic to living organisms. Such salts include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2-19 (1977), which are known to the skilled artisan. The tosylate (also known as p-toluene sulfonate) and hydrochloride salts are preferred. The tosylate salt is especially preferred.

"mTOR Inhibitor" means any compound, peptide or antibody which is an inhibitor of mTOR. Preferred mTOR inhibitors include rapamycin (also known as sirolimus) and analogues thereof. Rapamycin has the following structure:



-4-

Preferred rapamycin analogues include everolimus (42-O-(2-hydroxy)ethyl-
rapamycin; disclosed in EP 1 413 581), temsirolimus (42-(3-hydroxy-2-(hydroxymethyl)-
2-methyl propanoate)-rapamycin; Torisel®; disclosed in WO 95/28406) and deforolimus
(42-(dimethylphosphinate)rapamycin; disclosed in WO 03/64383). Especially preferred
5 rapamycin analogues are everolimus and temsirolimus. Certain rapamycin analogues are
also rapamycin prodrugs because they are metabolized *in-vivo* to form rapamycin.

The term “combination therapy” refers to treatment comprising the administration
of the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-
yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt
10 thereof, and an mTOR inhibitor (the “therapeutic agents”) in combination. The
therapeutic agents may be administered simultaneously, separately or sequentially.

The term “treating” or “treatment” includes the slowing, interrupting, arresting,
controlling, stopping, reducing, or reversing the progression or severity of a symptom,
disorder, condition or disease.

15 The term “amounts that are in combination effective” means the amount of the
compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-
piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt
thereof, and the amount of the mTOR inhibitor which are effective in treating the
disorders described herein when administered in combination. The amount of each
20 therapeutic agent which is effective in combination may be equal to the amount which is
effective when the therapeutic agent is administered on its own or it may be less than the
amount which is effective when the therapeutic agent is administered on its own (i.e. it
may be a sub-optimal dose).

The combination therapy described herein may be used in the treatment of
25 proliferative disorders such as cancer and in the inhibition of angiogenesis in mammals.
In all embodiments of the present invention, it is preferred that the cancer to be treated is
selected from glioblastoma multiforme, adenocarcinomas of the colon, non-small-cell
lung cancer, small-cell lung cancer, cisplatin-resistant small-cell lung cancer, ovarian
cancer, leukemia, pancreatic cancer, prostate cancer, mammary carcinoma, renal cell
30 carcimoma, multiple myeloma, Kaposi’s Sarcoma, Hodgkin’s lymphoma,
lymphangi leiomyomatosis, Non-Hodgkin’s lymphoma and sarcoma. It is especially

-5-

preferred that the cancer to be treated is renal cell carcinoma or glioblastoma multiforme. It is preferred that the mammal to be treated is a human.

In an alternative embodiment of the present invention, an mTOR inhibitor can be used in simultaneous, separate or sequential combination with the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, in the treatment of cancer, in particular, the cancers described above.

The compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, can be used in the manufacture of a medicament for use in combination therapy for treating cancer, in particular, the cancers described above, wherein said medicament is to be administered in combination with an mTOR inhibitor.

In a further alternative embodiment of the present invention, an mTOR inhibitor can be used in the manufacture of a medicament for use in combination therapy for treating cancer, in particular, the cancers described above, wherein said medicament is to be administered in combination with the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof.

In a further alternative embodiment, there is provided a pharmaceutical formulation comprising the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, and an mTOR, in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

The compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, and the mTOR inhibitor can be administered by a variety of routes. They may be administered by the same route or by different routes. Preferably, the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, is administered orally. The mTOR inhibitor everolimus is preferably administered orally. The mTOR inhibitor temsirolimus is preferably administered intravenously.

-6-

The optimum dosage regimens for each of the therapeutic agents used in the combination therapy of the present invention may vary depending on, for example, the route of administration, the disease being treated and the mTOR inhibitor used. For example, the dose of the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, may be in the range 100 mg to 2000 mg per day. Preferred doses are in the range 600 mg to 1600 mg per day. In a preferred embodiment, the compound is administered twice daily and each dose is in the range 300 mg to 800 mg. The dose of the mTOR inhibitor everolimus may be in the range 2 mg to 20 mg per day. Preferred doses of everolimus are 5 mg or 10 mg per day. The dose of the mTOR inhibitor temsirolimus may be in the range 12.5 mg to 50 mg per week. A preferred dose of temsirolimus is 25 mg per week.

The combination therapy may be administered for a single fixed period of time, for example, 6 months. The combination therapy may be administered according to a cyclical schedule, where there are alternating treatment and non-treatment periods. Alternatively, the combination therapy may be administered continuously. It is preferred that the combination therapy is administered continuously (until disease progression or unacceptable toxicity).

In one embodiment, the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, and the mTOR inhibitor are administered separately. When administered separately, the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, and the mTOR inhibitor may be administered according to different dosing regimens and by different routes of administration.

In another embodiment, the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, and the mTOR inhibitor are administered sequentially. In this embodiment either therapeutic agent may be administered first. It is preferred that the time between a dose of one therapeutic agent and a dose of the other is

-7-

less than 8 hours. More preferably, less than 4 hours and even more preferably, less than 1 hour.

In yet another embodiment, the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a
5 pharmaceutically acceptable salt thereof, and the mTOR inhibitor are administered simultaneously. In this embodiment, the agents may be administered in the same formulation or simultaneously via different routes of administration.

The therapeutic agent 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine tosylate is preferably
10 administered orally. It is further preferred that two doses of 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine tosylate are administered per day over the course of the treatment and that each dose is in the range 300 mg to 800 mg.

In one embodiment, the therapeutic agents used in the combination therapy are 4-
15 [4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine tosylate and everolimus. It is preferred that 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine tosylate is administered orally according to the preferred dosing schedule described above. In this embodiment, it is preferred that everolimus is
20 also administered orally. It is further preferred that one dose of everolimus is administered per day and that each dose is 10 mg. In this embodiment, it is preferred that the combination therapy is administered continuously.

In another embodiment, the therapeutic agents used in the combination therapy are 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-
25 1H-pyrazolo[3,4-d]pyrimidine tosylate and temsirolimus. It is preferred that 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine tosylate is administered orally according to the preferred dosing schedule described above. In this embodiment, it is preferred that temsirolimus is administered intravenously. It is further preferred that one dose of temsirolimus is
30 administered per week and that each dose is 25 mg. In this embodiment, it is preferred that the combination therapy is administered continuously.

-8-

The compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, and pharmaceutically acceptable salts thereof, may be prepared according to the methods described below.

5 Preparation of the Intermediate 4-Chloro-1H-pyrazolo[3,4-d]pyrimidine

To a solution of allopurinol (20 g; 146.94 mmoles) in toluene (205.71 mL), add phosphoryl chloride (68.27 mL; 734.68 mmoles) and diisopropylethylamine (56.38 mL; 323.26 mmoles) and heat the mixture at 80°C for 2 hours. Remove the solvent *in vacuo* to half and pour the mixture into 2 M potassium phosphate, dibasic (734.68 mL; 1.47 moles) in water at 4°C. Stir the mixture overnight at room temperature (RT). Filter off the precipitate through a pad of Celite® and wash it subsequently with EtOAc. Separate the filtrate, wash the aqueous layer with more EtOAc, join the organic layers, dry it over MgSO₄, filter and concentrate *in vacuo* to afford the title compound (16 g; 70.45% yield) as a yellow solid. MS (APCI): $m/z = 155.1$ [M + H].

15

Preparation of 4-{4-[4-(4-Fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine hydrochloride

Add methenamine (1.10 equiv; 231.55 mmoles; 32.46 g) to a solution of 4-fluoro-3-(trifluoromethyl)phenacyl bromide (60.00 g; 1.00 equiv; 210.50 mmoles) in ethyl acetate (450 mL; 4.60 moles). Stir the mixture at RT overnight. Remove the solvent *in vacuo* and triturate the solid in methyl tert-butyl ether (MTBE). Filter and dry under reduced pressure. Add ethanol (450 mL; 7.73 moles), followed by hydrogen chloride (150 mL; 8.30 equiv; 1.75 moles) and stir the mixture at RT overnight. Remove the solvent *in vacuo* and dry the solid *in vacuo* at 50 °C for a week to obtain 2-Amino-1-(4-fluoro-3-trifluoromethyl-phenyl)-ethanone hydrochloride (54.23 g; 100% yield) as a white solid.

Add N-methylmorpholine (3 equiv; 631.52 mmoles; 69.66 mL) to a solution of piperidine-1,4-dicarboxylic acid mono-tert-butyl ester (1.20 equiv; 252.61 mmoles; 57.92 g) in tetrahydrofuran (THF) (400 mL). Cool the mixture to -10 °C with a dry ice-acetone bath. Add isobutyl chloroformate (1.1 equiv ; 231.56 mmoles; 30.26 mL) dropwise while maintaining the temperature below -5 °C. After 30 min at -5 °-10 °C, add 2-amino-1-(4-fluoro-3-trifluoromethyl-phenyl)-ethanone hydrochloride (54.23 g; 1.00 equiv; 210.51

-9-

mmoles) suspended in THF (300 mL) and stir the mixture in the bath at -5 °C for 20 min. Stir for 1 hour at RT. Add water and EtOAc, then wash the organic layer with water and saturated aqueous sodium chloride. Dry over MgSO₄, filter and remove solvent *in vacuo*. Suspend the crude in MTBE and stir for 2 hours. Filter the solid and dry *in vacuo* to give
5 1-[2-(4-Fluoro-3-trifluoromethyl-phenyl)-2-oxo-ethylcarbamoyl]-piperidine-4-carboxylic acid tert-butyl ester (64.44 g; 70.79% yield).

Add ammonium acetate (15 equiv; 1.02 moles; 78.61 g) to a solution of 1-[2-(4-fluoro-3-trifluoromethyl-phenyl)-2-oxo-ethylcarbamoyl]-piperidine-4-carboxylic acid tert-butyl ester (29.4 g; 1.00 equiv; 67.99 mmoles) in 1-butanol (150 mL; 1.64 moles),
10 then add triethylamine (1 equiv ; 67.99 mmoles; 9.48 mL). Stir the mixture at 160 °C in a sealed tube for 3 h. Add EtOAc and water, then wash the organic layer with more water and saturated aqueous sodium chloride and concentrated *in vacuo*. Triturate the crude in MTBE, filter and dry under reduced pressure to give 4-[4-(4-Fluoro-3-trifluoromethyl-phenyl)-1*H*-imidazol-2-yl]-piperidine-1-carboxylic acid tert-butyl ester (18.23 g; 44.10
15 mmoles, 64.86% yield) as a white solid.

Add 4-[4-(4-Fluoro-3-trifluoromethyl-phenyl)-1*H*-imidazol-2-yl]-piperidine-1-carboxylic acid tert-butyl ester (16.03 g; 1.00 equiv; 38.77 mmoles) in 40 mL of dimethyl sulfoxide (DMSO) to a solution of potassium hydroxide (1.5 equiv ; 58.16 mmoles; 3.26 g) in 200 mL of DMSO. After 5 min at RT, add methyl iodide (1.1 equiv; 42.65 mmoles;
20 2.66 mL) in one portion. Stir at RT for two hours, then pour the mixture into ice water. Filter the solid, wash with water, and dry under reduced pressure. Triturate the solid in hot heptane, filter and dried under reduced pressure to give 4-[4-(4-Fluoro-3-trifluoromethyl-phenyl)-1-methyl-1*H*-imidazol-2-yl]-piperidine-1-carboxylic acid tert-butyl ester (8.7 g; 52.49% yield) as a white solid.

Add hydrogen chloride (4.00 equiv; 81.41 mmoles; 20.35 mL) to a solution of 4-[4-(4-Fluoro-3-trifluoromethyl-phenyl)-1-methyl-1*H*-imidazol-2-yl]-piperidine-1-carboxylic acid tert-butyl ester (8.7 g; 1.00 equiv; 20.35 mmoles) in dichloromethane (101.77 mL), at RT. Stir the solution at RT for 1 hour. Remove the solvent under reduced pressure, and dissolve the crude in isopropyl alcohol (101.77 mL). Add 4-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidine (1.65 equiv; 33.58 mmoles; 5.19 g) and
30 triethylamine (10 equiv; 203.54 mmoles; 28.37 mL). Stir the mixture at reflux for 1 hour. Remove the solvent under reduced pressure and triturate the crude in water overnight.

-10-

Filter the solid and triturate in hot acetonitrile, filter and dry *in vacuo*. 4-{4-[5-(4-Fluoro-3-trifluoromethyl-phenyl)-3-methyl-1*H*-imidazol-2-yl]-piperidin-1-yl}-1*H*-pyrazolo[3,4-*d*]pyrimidine (8.42 g; 18.86 mmol; 92.66% yield) is obtained as a light yellow solid.

Add hydrogen chloride (1.1 equiv; 18.52 mmol; 4.63 mL) to a suspension of 4-{4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1*H*-imidazol-2-yl]-piperidin-1-yl}-1*H*-pyrazolo[3,4-*d*]pyrimidine (7.5 g; 1.00 equiv; 16.84 mmol) in dichloromethane (50 mL), and stir the mixture for 1 hour at RT. Remove the solvent *in vacuo*, and triturate the crude in MTBE for 1 hour. Filter the solid and dry *in vacuo* overnight to give 4-{4-[4-(4-Fluoro-3-trifluoromethyl-phenyl)-3-methyl-1*H*-imidazol-2-yl]-piperidin-1-yl}-1*H*-pyrazolo[3,4-*d*]pyrimidine hydrochloride (7.99 g; 16.58 mmol; 98.47% yield) as a white solid. ¹H-NMR (300 MHz, DMSO): δ 14.01-13.99 (m, 1H), 8.57-8.54 (m, 2H), 8.26-8.19 (m, 3H), 7.72-7.63 (m, 1H), 5.23-5.20 (m, 2H), 3.89 (s, 3H), 3.41 (m, 2H), 2.15-2.07 (m, 3H), 1.10 (s, 2H).

15 Preparation of 4-{4-[4-(4-Fluoro-3-trifluoromethyl-phenyl)-1-methyl-1*H*-imidazol-2-yl]-piperidin-1-yl}-1*H*-pyrazolo[3,4-*d*]pyrimidine p-toluenesulfonate

Cool a solution of 4-fluoro-3-(trifluoromethyl)phenacyl bromide (93% pure by HPLC, 1000 g; 3.51 moles) and THF (5 L) to <5 °C in an ice bath. Add a solution of sodium azide (239 g; 3.68 moles, 1.05 eq) in water (800 mL) drop wise over one hour at < 5 °C. After stirring at < 5 °C for one hour, separate and discard the aqueous layer. While still cold, add the organic layer slowly over 3 hours to a solution of triphenylphosphine (920.2g, 3.51 moles, 1.0 eq), p-toluenesulfonic acid monohydrate (1335g; 7.02 moles; 2.0 eq), and THF (5L). Maintain the temperature at < 15 °C throughout this addition and solids precipitate during the addition.

25 Stir the reaction mixture at <20 °C for 2 hours and then filter the solid, wash with THF (3 x 2 L), and dry at 50 °C under vacuum to give 1167.4g (85%, 92% corrected for starting material purity) of 2-amino-1-(4-fluoro-3-trifluoromethyl-phenyl)-ethanone p-toluenesulfonate as a white crystalline solid.

Combine 2-amino-1-(4-fluoro-3-trifluoromethyl-phenyl)-ethanone p-toluenesulfonate (1133 g; 2.88 moles), 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (795 g; 3.47 moles; 1.20 eq), THF (3450 mL), and ethyl acetate (7500 mL) to form a thin white slurry. Cool the slurry to < 5 °C in ice bath and add 2-propanephosphonic acid

-11-

anhydride (T₃P) (50% solution in EtOAc) (2385 g; 3.75 moles, 1.3 eq). Then add N-methylmorpholine (795 mL; 7.21 moles; 2.5 eq) over 1 hour, maintaining the temperature < 10°C. Warm the resulting slurry to ambient temperature and stir for 2 hours.

Quench the reaction by addition of water. Separate the organic phase, then wash
5 with aqueous NaHCO₃, aqueous NaCl. Warm the organic phase to 50 °C on a rotary evaporator and add n-heptane. Distill solvent under vacuum until the final slurry volume is approximately 5 L. Cool the slurry to RT and filter the solids, wash with n-heptane (2 x 1L) and then dry in a vacuum oven at 50°C overnight, resulting in 1-[2-(4-fluoro-3-trifluoromethyl-phenyl)-2-oxo-ethylcarbamoyl]-piperidine-4-carboxylic acid tert-butyl
10 ester (1124.8g, 90%) as a white solid.

Combine 1-[2-(4-fluoro-3-trifluoromethyl-phenyl)-2-oxo-ethylcarbamoyl]-piperidine-4-carboxylic acid tert-butyl ester (100 g, 231 mmoles), ammonium acetate (178.3 g; 2.31 moles; 10 eq), and methanol (1000 mL). The reactor used for this transformation is a coiled 1/16" I.D. stainless steel tube (total internal volume of tubing in
15 oven is 541 mL). Heat the reactor in an oven to 140°C. Control the back pressure in this tube at 250 psig by a regulator to allow super-heating of the solution above its normal boiling point. Pump the solution prepared above continuously through the heated tube under pressure at 6.01 mL/min (affording a total residence time in the heated tube of 90 minutes). As the solution exits the oven, cool it back to 20°C in a tube-in-tube heat
20 exchanger. Once the entire solution process through the reactor (8 hours total processing time), concentrate the resulting orange solution under vacuum at 30°C to a total volume of 600 mL. Add acetonitrile (200 mL) and heat the solution to 50 °C. Add water (700 mL) drop wise with seeding over 2 hours to crystallize the product. Cool the resulting slurry to 20°C and filter the solid, then wash with 20% MeOH in water (2 x 200 mL).
25 Dry the resulting solid under vacuum at 50 °C. Re-slurry the solid in acetonitrile (200 mL) at 50 °C. Cool the slurry to ambient temperature, filter the solid and wash with acetonitrile (100 mL) to afford 4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1*H*-imidazol-2-yl]-piperidine-1-carboxylic acid tert-butyl ester (54.43g; 132 mmoles; 57%) as an off white solid.

30 Dissolve 4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1*H*-imidazol-2-yl]-piperidine-1-carboxylic acid tert-butyl ester (80.02 g; 183.69 mmoles) in DMSO (1060 mL). Add KOH (18.47 g; 279.82 mmoles; 1.5 eq) in one portion. Add methyl iodide (27.74 g;

-12-

- 193.48 mmoles; 1.05 eq) over 30 minutes at 25 °C. Stir the solution at 25 °C for 1 hour. Add a mixture of 4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1*H*-imidazol-2-yl]-piperidine-1-carboxylic acid tert-butyl ester seed crystals (0.17 g) and water (80 mL) over 5 minutes to the solution. Stir the resulting thin slurry at 25 °C for 30 minutes. Add
- 5 additional water (240.73 mL) over 30 minutes at 25 °C. Filter the solid and wash with 20% DMSO in water (2 x 120 mL) and then water (120 mL). Dry the solid under vacuum at 60 °C. Dissolve the resulting dried solids in ethanol (480 mL) at 50 °C. Add water (240 mL) over 5 minutes. Then add 4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1*H*-imidazol-2-yl]-piperidine-1-carboxylic acid tert-butyl ester seed (0.038 g) and
- 10 more water (240 mL) over 30 minutes. Cool the resulting slurry to 25 °C over 2 hours. Filter the solids and wash the cake with 20% EtOH in water. Dry the solid under vacuum at 60 °C affording 4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1*H*-imidazol-2-yl]-piperidine-1-carboxylic acid tert-butyl ester (72.36g, 92%) as a white solid.
- 15 Prepare an anhydrous HCl solution by slow addition of acetyl chloride (193.14 mL; 2.71 moles; 4.00 eq) to methanol (1160 mL) over 45 minutes at < 5°C. Add the resulting solution to a separate flask containing a solution of 4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1*H*-imidazol-2-yl]-piperidine-1-carboxylic acid tert-butyl ester (290 g; 678.46 mmoles) in methanol (2320 mL) over 90 minutes at 20 °C. Stir
- 20 the reaction mixture at 20 °C overnight. Concentrate the reaction mixture under vacuum at 30 °C. Add DMSO (1080 mL; 15.20 moles; 1.08 L; 1.19 kg) and the distillation continues until the internal temperature reaches 50 °C at a pressure of 20 mm Hg. Add DMSO until the total volume is 2030 mL. Then add triethylamine (473 mL; 3.39 moles; 5 eq) via addition funnel over 30 minutes. Charge solid 4-chloro-1*H*-pyrazolo[3,4-
- 25 *d*]pyrimidine (110.29 g; 713.58 mmoles; 1.05 eq) in equal portions equally spaced over 30 minutes. Stir the resulting slurry at 20 °C overnight. Heat the slurry to 80 °C. Add water (229 mL) to afford a clear solution. Seed the reaction and add more water (1273 mL) slowly over 4 hours to fully crystallize the product. Cool the slurry to 50 °C and filter the solid. Wash the cake with 30% water in DMSO (2 x 290mL), then water (290
- 30 mL). Dry the solids under vacuum at 60 °C to afford 4-{4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1*H*-imidazol-2-yl]-piperidin-1-yl}-1*H*-pyrazolo[3,4-*d*]pyrimidine (301g, 99%) as an off white solid.

-13-

Dissolve 4-{4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1*H*-imidazol-2-yl]-piperidin-1-yl}-1*H*-pyrazolo[3,4-*d*]pyrimidine (20g, 44.9 mmols) in a 20:1 H₂O:acetone mixture (360 mL). Add a solution of p-toluenesulfonic acid monohydrate (10.25g; 53.9 mmols; 1.2 eq) in a 20:1 H₂O:acetone mixture (40 mL) to the reaction over
 5 20 minutes at 20 °C. Heat the reaction mixture to 55 °C, hold for 1 hour, then cool to 25 °C over 1 hour. Filter the solid and wash the cake with water (40 mL). Drying under vacuum at 50 °C affords 4-{4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1*H*-imidazol-2-yl]-piperidin-1-yl}-1*H*-pyrazolo[3,4-*d*]pyrimidine p-toluenesulfonate (23.9g; 86%) as a white solid.

10

Preparation of Crystalline 4-{4-[4-(4-Fluoro-3-trifluoromethyl-phenyl)-1-methyl-1*H*-imidazol-2-yl]-piperidin-1-yl}-1*H*-pyrazolo[3,4-*d*]pyrimidine p-toluenesulfonate

To a 1-L round bottom flask with overhead stirrer charge with 60.12g of 4-{4-[4-(4-Fluoro-3-trifluoromethyl-phenyl)-1-methyl-1*H*-imidazol-2-yl]-piperidin-1-yl}-1*H*-
 15 pyrazolo[3,4-*d*]pyrimidine (prepared according to either of the above preparations without the final salt formation step), followed by 250 mL of 5% aq. MeOH. Stir the resulting slurry and add p-toluenesulfonic acid monohydrate (26.88 g) followed by a rinse forward with the remaining 50 mL of 5% aq. MeOH. Stir the resulting slurry and cool the crystals to 5 °C. After 1 h at 5 °C, stop stirring and filter the slurry on a Buchner
 20 funnel. Rinse the flask out with 75mL of cold 5% aq. MeOH and use this rinse to wash the filter cake. Transfer the solids to a weighing dish and dry at 50 °C *in vacuo* all day and all night, with a slow air bleed. The final weight is 71.44 g.

X-ray powder diffraction analysis is performed with a D4 Endeavor diffractometer, equipped with a CuK α source ($\lambda=1.54056$ Å) operating at 40 kV and 50
 25 mA. The sample is scanned from 4° to 40° in 2 θ , with a step size of 0.009 in 2 θ and a scan rate of ≥ 1.5 sec per step.

Angle 2-theta ($\pm 0.1^\circ$)	Intensity %	Angle 2-theta ($\pm 0.1^\circ$)	Intensity %
6.826	12	23.485	14
10.256	24	23.615	17
12.984	24	23.866	22
13.131	61	24.024	20
13.431	25	24.667	11
13.688	100	24.795	11

-14-

Angle 2-theta ($\pm 0.1^\circ$)	Intensity %	Angle 2-theta ($\pm 0.1^\circ$)	Intensity %
14.062	24	25.029	8
15.745	6	25.552	9
17.121	15	26.234	5
18.599	5	26.556	10
18.919	21	27.031	6
19.38	29	27.693	11
20.603	14	27.97	5
21.661	6	28.352	6
21.962	14	28.428	5
22.108	9	38.232	5

Determination of In Vivo Efficacy

U87MG human glioblastoma cells (5×10^6) are subcutaneously implanted into the flank of female athymic nude mice in 0.2 mL of matrigel. Approximately 1 week post-implantation when the tumor size is approximately 100 mg, mice are randomized into groups of 10 and dosed orally once daily at 3 mg/kg 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine tosylate (the p70 S6 kinase inhibitor; formulated in 35% PEG300/10%HPBCD/10%PS80 in H₂O; concentration of inhibitor is 0.38 mg/mL) or 3 mg/kg rapamycin (formulated in NaCMC Tween 80; concentration of rapamycin is 2.5 mg/mL) or in combination (3 mg/kg of the p70 S6 kinase inhibitor and 3 mg/kg of rapamycin). The vehicle group is given the 2 vehicles (NaCMC Tween 80 and 35% PEG300/10%HPBCD/10%PS80 in H₂O) in combination (0.1 mL of each). Treatment is continued for 23 days. Tumor volumes are measured using standard technique twice weekly and reported. Tumor size and body weight are recorded and analyzed bi-weekly. Tumor volume is estimated by using the formula: $v = l \times w^2 \times 0.536$ where l = larger of measured diameter and w = smaller of perpendicular diameter. The analysis uses SAS software version 8.2 (SAS Institutes Inc, Cary, NC) to analyze the log tumor volume data using a repeated measures ANOVA model with a spatial power covariance structure. For each time point taken, treatment groups are compared to the vehicle control group. Tumor volumes are given as means \pm standard errors for each treatment group determined from a repeated measures ANOVA on each group. (SAS for Mixed Models, 2nd Ed., Littell *et al.*, 2006, SAS Institutes Inc, Cary, NC).

-15-

The results of this study are shown in the table below. n (the number of mice) is 10 for all the data, except for the data from day 27 onwards in the rapamycin only group and the data from day 23 onwards in the combination group when it is 9. The data in the column headed Signif. indicates whether the difference relative to the vehicle group is statistically significant: NS = Not Significant ($p > 0.05$); * = $0.01 < p \leq 0.05$; ** = $0.001 < p \leq 0.01$; *** = $p \leq 0.001$. The rapamycin only treatment group is not significantly different from the vehicle group throughout.

	Vehicle		Rapamycin Only		p70 S6 Kinase Inhibitor Only			p70 S6 Kinase Inhibitor and Rapamycin in Combination		
Day	Mean	SE	Mean	SE	Mean	SE	Signif.	Mean	SE	Signif.
7	48.1	5.4	43.1	6.2	43.8	4.0	NS	51.3	6.8	NS
10	70.4	7.9	65.6	9.5	79.6	7.2	NS	78.4	10.4	NS
13	119.4	13.3	121.9	17.6	118.7	10.8	NS	118.0	15.7	NS
16	237.4	26.4	220.4	31.9	159.0	14.4	*	133.9	17.8	**
20	334.0	37.2	311.5	45.0	233.6	21.2	*	118.8	15.8	***
23	648.3	72.2	606.0	87.6	539.1	48.9	NS	277.0	37.2	***
27	1037.9	115.6	879.7	129.2	928.6	84.2	NS	465.3	63.3	***
30	1301.4	145.0	1160.8	172	1158.5	105.0	NS	625.6	85.7	***
34	1486.4	165.6	1429.5	213.6	1256.6	113.9	NS	532.7	73.4	***

The results show that 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine tosylate inhibits the growth of U87MG glioblastoma cancer xenografts in nude mice in combination with rapamycin. 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine tosylate was dosed at 3 mg/kg once a day and rapamycin was dosed at 3 mg/kg once a day. These doses were sub-optimal doses for each agent. At these doses, the combination showed enhanced efficacy relative to treatment with

-16-

either agent alone. The combination is statistically different ($p < 0.001$) from the vehicle, whereas the individual treatment groups are not significantly different from the vehicle group.

-17-

WE CLAIM:

1. A product containing the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, and an mTOR inhibitor as a combined preparation for simultaneous, separate or sequential use in therapy.
2. A product containing the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, and an mTOR inhibitor as a combined preparation for simultaneous, separate or sequential use in the treatment of glioblastoma multiforme, adenocarcinomas of the colon, non-small-cell lung cancer, small-cell lung cancer, cisplatin-resistant small-cell lung cancer, ovarian cancer, leukemia, pancreatic cancer, prostate cancer, mammary carcinoma, renal cell carcinoma, multiple myeloma, Kaposi's Sarcoma, Hodgkin's lymphoma, lymphangi leiomyomatosis, Non-Hodgkin's lymphoma or sarcoma.
3. The product according to claim 2 wherein the combined preparation is for simultaneous, separate or sequential use in the treatment of renal cell carcinoma or glioblastoma multiforme.
4. The product according to any one of claims 1 to 3 wherein the mTOR inhibitor is everolimus or temsirolimus.
5. The product according to any one of claims 1 to 4 wherein the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, is 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine tosylate.
6. The product according to any one of claims 1 to 5 wherein the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-

-18-

1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, is to be administered orally.

7. The compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate or sequential combination with an mTOR inhibitor in the treatment of glioblastoma multiforme, adenocarcinomas of the colon, non-small-cell lung cancer, small-cell lung cancer, cisplatin-resistant small-cell lung cancer, ovarian cancer, leukemia, pancreatic cancer, prostate cancer, mammary carcinoma, renal cell carcinoma, multiple myeloma, Kaposi's Sarcoma, Hodgkin's lymphoma, lymphangioleiomyomatosis, Non-Hodgkin's lymphoma or sarcoma.
8. The compound according to claim 7, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate or sequential combination with an mTOR inhibitor wherein the use is in the treatment of renal cell carcinoma or glioblastoma multiforme.
9. The compound according to claim 7 or claim 8, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate or sequential combination with an mTOR inhibitor wherein the mTOR inhibitor is everolimus or temsirolimus.
10. The compound according to any one of claims 7 to 9 wherein the compound is 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine tosylate.
11. The compound according to any one of claims 7 to 10, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate or sequential combination with an mTOR inhibitor wherein the compound is to be administered orally.

-19-

12. A method of treating a cancer selected from the group consisting of glioblastoma multiforme, adenocarcinomas of the colon, non-small-cell lung cancer, small-cell lung cancer, cisplatin-resistant small-cell lung cancer, ovarian cancer, leukemia, pancreatic cancer, prostate cancer, mammary carcinoma, renal cell carcinoma, multiple myeloma, Kaposi's Sarcoma, Hodgkin's lymphoma, lymphangioleiomyomatosis, Non-Hodgkin's lymphoma and sarcoma comprising administering to a patient in need thereof the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, and an mTOR inhibitor in amounts that in combination are effective.
13. The method according to claim 12 wherein the cancer is renal cell carcinoma or glioblastoma multiforme.
14. The method according to claim 12 or claim 13 wherein the mTOR inhibitor is everolimus or temsirolimus.
15. The method according to any one of claims 12 to 14 wherein the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, is 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine tosylate.
16. The method according to any one of claims 12 to 15 wherein the compound 4-[4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1-methyl-1H-imidazol-2-yl]-piperidin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, or a pharmaceutically acceptable salt thereof, is administered orally.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/063188

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/436 A61K31/519 A61K45/06
ADD. A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	BAUMANN P ET AL: "Myeloma cell growth inhibition is augmented by synchronous inhibition of the insulin-like growth factor-1 receptor by NVP-AEW541 and inhibition of mammalian target of rapamycin by Rad001" ANTI-CANCER DRUGS 200904 GB, vol. 20, no. 4, April 2009 (2009-04), pages 259-266, XP8118887 ISSN: 0959-4973 abstract	1-16
Y,P	WO 2008/140947 A1 (LILLY CO ELI) 20 November 2008 (2008-11-20) page 72, line 26 - page 73, line 1; claims 1, 5, 6, 9, 11; examples 6, 7, 55, 57, 58 ----- -/--	1-16



Further documents are listed in the continuation of Box C.



See patent family annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/063188

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	<p>IKEZOE T ET AL: "The antitumor effects of sunitinib (formerly SU11248) against a variety of human hematologic malignancies: Enhancement of growth inhibition via inhibition of mammalian target of rapamycin signaling" MOLECULAR CANCER THERAPEUTICS 200610 US, vol. 5, no. 10, October 2006 (2006-10), pages 2522-2530, XP002568287 ISSN: 1535-7163 page 2529, right-hand column</p>	1-16
A	<p>WO 2007/047754 A2 (LIOTTA LANCE A) 26 April 2007 (2007-04-26) page 4; claims 1, 14, 16, 18, 19, 23-25, 27, 28, 45; figure 11; example III page 14, paragraph 4 - page 15, paragraph 1</p>	1-16
A	<p>WO 2005/117909 A2 (EXELIXIS INC) 15 December 2005 (2005-12-15) page 42; claims</p>	1-16
A	<p>WO 2006/071819 A1 (EXELIXIS INC) 6 July 2006 (2006-07-06) pages 5-6, 59, paragraph 142; claims</p>	1-16
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Information on patent family members

International application No

PCT/US2009/063188

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