

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
27 September 2007 (27.09.2007)

PCT

(10) International Publication Number
WO 2007/109275 A2

(51) International Patent Classification:

A61K 31/506 (2006.01) A61K 31/337 (2006.01)

(21) International Application Number:

PCT/US2007/006920

(22) International Filing Date: 20 March 2007 (20.03.2007)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/784,954 20 March 2006 (20.03.2006) US

(71) Applicant (for all designated States except US): **BAYER PHARMACEUTICALS CORPORATION** [US/US];
400 Morgan Lane, West Haven, Connecticut 06516 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BHARGAVA, Ajay** [IN/US]; 106 North Racebrook Road, Woodbridge, Connecticut 06525 (US). **CARTER, Christopher** [US/US]; 48 Blue Hills Drive, Guilford, Connecticut 06437 (US). **BRANDS, Michael** [DE/DE]; Kinderbusch 6b, 42329 Wuppertal (DE).

(74) Agents: **GRAY, William, F.** et al.; Bayer Pharmaceuticals Corporation, 400 Morgan Lane, West Haven, Connecticut 06516 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

- without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PACLITAXEL COMBINATION

(57) Abstract: This invention relates to a novel combination of compounds and processes for its preparation, methods of treating diseases, particularly cancer, comprising administering said combination, and methods of making said pharmaceutical composition for the treatment or prevention of disorders, particularly cancer.



WO 2007/109275 A2

Paclitaxel combination

This invention relates to a novel combination of compounds and processes for its preparation, methods of treating diseases, particularly cancer, comprising administering said combination, and methods of making said pharmaceutical composition for the
5 treatment or prevention of disorders, particularly cancer.

Cancer is a disease resulting from an abnormal growth of tissue. Certain cancers have the potential to invade into local tissues and also metastasize to distant organs. This disease can develop in a wide variety of different organs, tissues and cell types. Therefore,
10 the term "cancer" refers to a collection of over a thousand different diseases.

Over 4.4 million people worldwide were diagnosed with breast, colon, ovarian, lung, or prostate cancer in 2002 and over 2.5 million people died of these devastating diseases (Globocan 2002 Report). In the United States alone, over 1.25 million new cases and over 500,000 deaths from cancer were expected in 2005. The majority of these new
15 cases will be cancers of the colon (~100,000), lung (~170,000), breast (~210,000) and prostate (~230,000). Both the incidence and prevalence of cancer is predicted to increase by approximately 15% over the next ten years, reflecting an average growth rate of 1.4% (American Cancer Society, Cancer Facts and Figures 2005).

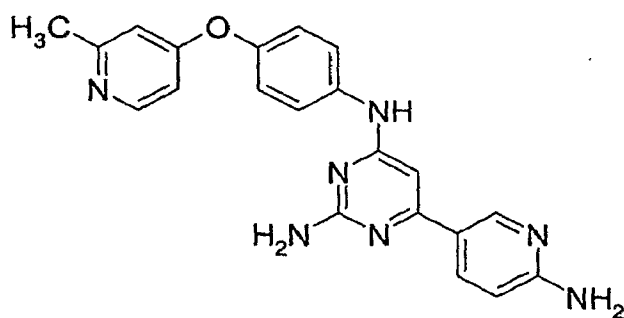
Cancer treatments are of two major types, either curative or palliative. The main
20 curative therapies for cancer are surgery and radiation. These options are generally successful only if the cancer is found at an early localized stage. Once the disease has progressed to locally advanced cancer or metastatic cancer, these therapies are less effective and the goal of therapy aims at symptom palliation and maintaining good quality of life. The most prevalent treatment protocols in either treatment mode involve a
25 combination of surgery, radiation therapy and/or chemotherapy.

Cytotoxic drugs (also known as cytoreductive agents) are used in the treatment of cancer, either as a curative treatment or with the aim of prolonging life or palliating symptoms. Cytotoxics may be combined with radiotherapy and/or surgery, as neo-
adjuvant treatment (initial chemotherapy aimed at shrinking the tumor, thereby rendering
30 local therapy such as surgery and radiation more effective) or as adjuvant chemotherapy (used in conjunction or after surgery and/or localized therapy). Combinations of different

drugs are frequently more effective than single drugs: they may provide an advantage in certain tumors of enhanced response, reduced development of drug resistance and/or increased survival. It is for these reasons that the use of combined cytotoxic regimens in the treatment of many cancers is very common.

5 Cytotoxic agents in current use employ different mechanisms to block proliferation and induce cell death. One group of such agents are the microtubule modulators that interfere with the polymerization or depolymerization of microtubules. Taxol® (Paclitaxel), chemical name benzenepropanoic acid, beta-(benzoylamino)-alpha-hydroxy-, 6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-
 10 4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca(3,4)benz(1,2-b)oxet-9-ylester, (2aR-(2aalpha,4beta,4abeta,6beta,9alpha(alphaR*,betaS*), 11alpha,12alpha,12aalpha,12balphalpha)), or tax-11-en-9-one,5beta,20-epoxy-1,2alpha,4,7beta,10beta,13alpha-hexahydroxy-, 4,10-diacetate 2-benzoate,13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine, Chemical Abstracts Service Registry Number
 15 [33069-62-4], Orange Book application No. 020262 by Bristol Myers Squibb, hereinafter referred to as Paclitaxel, is such a microtubule modulator.

In one embodiment, the present invention provides a combination of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine:



with Paclitaxel.

Unless otherwise stated, the following definitions apply for the technical expressions used
 25 throughout this specification and claims:

Combination refers to the result or product of combining two or more individual units,

ingredients or compounds. In a first meaning, combination refers to a spatial relationship. These units, ingredients or compounds can remain unchanged in the combination, or they can to a lesser or greater extent react or interact. Also, they can be physically brought and blended together to form one mixture, or they can be brought together into a container
5 without blending. Combination also refers to the result or product of combining said ingredients, if they are further processed or treated after having been combined. For example, an example of a combination is cookie dough, which consists of several ingredients being mixed together. If the cookie dough in above example is baked and covered with frosting, it still remains a combination. In another example, combination
10 refers to the product of combining two or more pharmaceutical ingredients, such as pharmaceutically active compounds, and also refers to this product if it is further processed and packaged, such as two pharmaceutically active compounds being brought together to form a mixture, the mixture then being pressed into a tablet, the tablet then subsequently being coated and packaged. The tablet still remains a combination.

15 In a second meaning, combination refers to a temporal relationship, i.e. two or more acts are performed simultaneously or in temporal proximity. Acts are performed simultaneously, when they are done at the same point in time or in overlapping time periods. For example, a tv set simultaneously transmits sound and picture and thus transmits
20 a combination of the two.

Two or more acts can also be performed in temporal proximity, i.e. after one another, to form a combination. What counts as temporal proximity is dependent on the totality of circumstances; one indicator being that the acts are being performed to achieve a certain purpose; another that the acts are being performed shortly after one another on a timescale
25 relevant for the observed system.

For example, a sequence of chess moves is often referred to as a combination, while the moves are being done one after the other with the opponent making his intermittent moves. They are done with the purpose of eventually defeating the opponent.

The actual time elapsed between the acts performed in a combination can thus be
30 irrelevant.

In another example of a combination as acts being performed in temporal proximity, combination refers to a drug regimen, wherein a patient is administered two or more drugs to treat a disease. Depending on the disease or disorder, the exact circumstances of

administering the drug can vary, but would still represent a combination. For example, when treating an acute bacterial infection, a physician might consider to administer two antibacterial drugs to the patient, where administering these drugs within an interval of several minutes to hours or even a few days would be considered a combination. For a
5 chronic disease, administration of two drugs within an interval of days or weeks could be considered a combination, as long as it is done by the physician as parts of a treatment, that is with the intention of treating the respective disease.

To combine refers to the act of bringing two or more individual units, ingredients or
10 compounds into close relationship. They can be brought together in a spatial sense, e.g. combined into one mixture, also referred to as intermixing or blending. For example, to prepare a cookie dough several ingredients are being mixed together. This can happen by filling them all into a container and mixing them, or by placing one ingredient in a container and subsequently, while mixing, adding the remaining ingredients.

15 In the example described above, one can bring two or more pharmaceutical ingredients together, form a mixture, press the mixture into a tablet, then subsequently coat and package the tablet. By bringing the ingredients together one combines them within the meaning of the present invention.

In a second meaning, 'to combine' refers to a temporal relationship, i.e. two or more acts
20 are performed simultaneously or in temporal proximity, as discussed above under Combination.

Throughout this document, for the sake of simplicity, the use of singular language is given preference over plural language, but is generally meant to include the plural language if not
25 otherwise stated. E.g., the expression "A method of treating a disease in a patient, comprising administering to a patient an effective amount of a compound of claim 1" is meant to include the simultaneous treatment of more than one disease as well as the administration of more than one compound of claim 1.

30 In another embodiment, the present invention provides a process for preparing a combination of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine with Paclitaxel, comprising combining 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine and

Paclitaxel. For example, this process can be performed using techniques known to the person skilled in the pharmaceutical art.

In another embodiment, the present invention provides a pharmaceutical
5 composition comprising a combination of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine with Paclitaxel; and a process for preparing a pharmaceutical composition comprising a combination of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine with Paclitaxel, comprising combining 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-
10 yl)oxy]phenyl}pyrimidine-2,4-diamine and Paclitaxel. and converting them into a suitable pharmaceutical composition. For example, this process can be performed using techniques known to the person skilled in the pharmaceutical art.

In yet another embodiment, the present invention provides a pharmaceutical
15 composition comprising a combination of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine with Paclitaxel and a pharmaceutically acceptable carrier; and a process for preparing a pharmaceutical composition comprising a combination of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine with Paclitaxel and a
20 pharmaceutically acceptable carrier, comprising combining 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine with Paclitaxel and a pharmaceutically acceptable carrier.

In yet another embodiment, the present invention provides a pharmaceutical
25 composition comprising a combination of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine with Paclitaxel and a pharmaceutically acceptable carrier, wherein said pharmaceutical composition is suitable for parenteral administration.

Parenteral administration can be carried out by avoiding an absorption step (e.g. by
30 intravenous, intraarterial, intracardial, intraspinal or intralumbar administration) or by including absorption (e.g. by intramuscular, subcutaneous, intracutaneous or intraperitoneal administration). Suitable parenteral administration forms are for example injection and infusion formulations in the form of solutions, suspensions, emulsions,

lyophilisates and sterile powders. Such parenteral pharmaceutical compositions are described in Part 8, Chapter 84 of Remington's Pharmaceutical Sciences, 18th ed. 1990, Mack Publishing Group, Enolo.

5 In one embodiment, the invention relates to intravenous (i.v.) application of the active compounds, e.g. as bolus injection (that is as single dose, e.g. per syringe), infusion over a short period of time (e.g. for up to one hour) or infusion over a long period of time (e.g. for more than one hour). The application can also be done by intermittent dosing. The applied volume can vary dependent on the conditions and usually is 0.5 to 30, or 1 to 20
10 ml for bolus injection, 25 to 500, or 50 to 250 ml for infusion over a short period of time and 50 to 1000, or 100 to 500 ml for infusion over a long period of time. Thus, in yet another embodiment, the present invention provides a pharmaceutical composition suitable for intravenous administration over a short or long period of time.

15 The application forms should be sterile and free of pyrogens. They can be based on aqueous solvents or mixtures of aqueous and organic solvents. Examples are ethanol, polyethyleneglycol (PEG) 300 or 400, aqueous solutions containing cyclodextrins or emulsifiers, such as lecithin, Pluronic F68®, Solutol HS15® or Cremophor®. Aqueous solutions are preferred.

20 For intravenous application the solutions are generally isotonic and euhydic, for example with a pH of 3 to 11, 6 to 8 or about 7.4.

Glass or plastic containers can be employed as packaging for i.v.-solutions, e.g. rubber seal vials. They can contain liquid volumes of 1 to 1000, or 5 to 50 ml. The solution can directly be withdrawn from the vial to be applied to the patient. For this purpose, it can be
25 advantageous to provide the active compound in solid form (e.g. as lyophilisate) and dissolve by adding the solvent to the vial directly before administration.

Solutions for infusion can advantageously be packaged in containers made from glass or plastic, for example bottles or collapsible containers such as bags. They can contain liquid volumes of 1 to 1000, or 50 to 500 ml.

30

In yet another embodiment, the present invention provides a pharmaceutical composition comprising 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-

yl)oxy]phenyl}pyrimidine-2,4-diamine, Paclitaxel, purified Cremophor EL and dehydrated ethyl alcohol.

In yet another embodiment, the present invention provides a packaged pharmaceutical composition, comprising a container comprising a combination of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine with Paclitaxel and a pharmaceutically acceptable carrier and instructions for using the pharmaceutical composition to treat a disease in a patient; and a packaged pharmaceutical composition, wherein the container is a bottle or collapsible bag.

In yet another embodiment, the present invention provides a kit-of-parts, comprising a plurality of containers comprising 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine and Paclitaxel or both, optionally further comprising instructions for using the kit-of-parts to treat a disease in a patient.

In yet another embodiment, the present invention provides a process for preparing a combination of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine with Paclitaxel, comprising combining 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine with Paclitaxel, purified Cremophor EL and dehydrated ethyl alcohol.

In another embodiment, the present invention provides a method for treating a disorder, comprising administering to a patient a pharmaceutically effective amount of a combination of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine with Paclitaxel; or a method for treating a disorder, comprising administering to a patient a pharmaceutically effective amount of a pharmaceutical composition comprising a combination of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine with Paclitaxel and a pharmaceutically acceptable carrier; or said method, wherein the is suitable for intravenous administration; or wherein the intravenous administration is intravenous administration over a short or long period of time; or said pharmaceutical composition suitable for intravenous administration; or a method for treating a disorder, comprising administering to a patient a pharmaceutically effective amount of a pharmaceutical

composition comprising a combination of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine, Paclitaxel, purified Cremophor EL and dehydrated ethyl alcohol.

5 In yet another embodiment, the present invention provides said method for treating a disorder, wherein said disorder is cancer. In yet another embodiment, the present invention provides a method for treating cancer, wherein said cancer is small cell lung cancer.

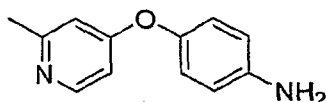
10 In yet another embodiment, the present invention provides a method for treating a disorder, comprising administering to a patient a pharmaceutically effective amount of a combination of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine with Paclitaxel, wherein 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine and Paclitaxel are
15 administered simultaneously or in temporal proximity, such as within 24 hours.

In yet another embodiment, the present invention provides a method for treating a disorder, comprising administering to a patient a pharmaceutically effective amount of a combination of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine with Paclitaxel, wherein 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine together with 6mg
20 Paclitaxel, 527 mg of purified Cremophor® EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol per ml are diluted in 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP, or 5%
25 Dextrose in Ringer's Injection and administered into a vein (intravenous infusion, optionally further by administering certain premedications to reduce or prevent the chance of having a severe allergic reaction.

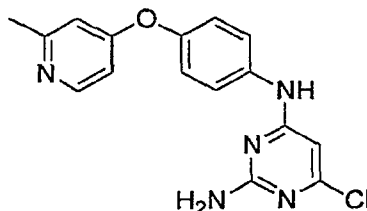
In yet another embodiment, the present invention provides a method for treating a
30 disorder, comprising administering to a patient a pharmaceutically effective amount of a combination of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine with Paclitaxel, wherein less than the maximum tolerated dose is administered or patient weight loss is minimized.

Examples

Paclitaxel is commercially available or can be prepared similarly to known processes. 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine is a dry powder with a color ranging from white to ivory or light yellow and can be prepared as follows:

Step 1: Preparation of {4-[(2-Methylpyridin-4-yl)oxy] phenyl} amine

- 4-aminophenol (44.9 g, 410 mmol) was added to the 1L 3-neck flask and dissolved with *N,N*-dimethylacetamide (600 mL). The stirred mixture was then cooled to 9 °C and potassium *t*-butoxide (46.18 g, 410 mmol) was added portionwise; the solution turned green and solidified before potassium *t*-butoxide addition was completed. Stirring was reestablished and a solution containing the 4-chloro-2-picoline (50 g, 390 mmol) in *N,N*-dimethylacetamide (400 mL) was slowly added and the mixture was heated at 90 °C for 17 h. The mixture was then allowed to cool to 45 °C, filtered and concentrated to near dryness in *vacuo* to leave brown residue. The residue was slowly added to vigorously stirred water (1L) and the suspension was stirred for 1hr. The solids were then collected by suction filtration and washed with small amount of isopropanol, ether and dried to afford {4-[(2-Methylpyridin-4-yl) oxy] phenyl} amine (49.9 g, 64%) as light tan solid. ¹H NMR (DMSO-*d*₆) δ 8.21 (d, 1H), 6.78 (d, 2H), 6.57-6.63 (m, 4H), 5.10 (s, 2H), 2.35 (s, 3H); MS ES 201 (M+H)⁺, calcd 201, RT = 1.04 min.

Step 2: Preparation of 6-chloro-N⁴-(4-{[2-methylpyridin-4-yl]oxy}phenyl)pyrimidine-2,4-diamine

{4-[(2-Methylpyridin-4-yl) oxy] phenyl} amine (47.5 g, 237 mmol) and 2-amino-4,6-

dichloropyrimidine (40.8 g, 249 mmol) were suspended in water (900 mL) and 2-propanol (300 mL). 2M aqueous hydrochloric acid solution (23.7 mL) was then added and the mixture was then heated at 95 °C for 17 h. The mixture was then allowed to come to rt and solids were collected by suction filtration and washed with small amount of isopropanol.

5 The solids were then resuspended in DMF and heated at 90 °C. Triethylamine (20 mL) was then added and the mixture was stir for additional 10 min at 90 °C. Water was then added in excess until cloudiness persisted at temperature. This was cooled to about 5 °C and precipitate formed were collected by suction filtration, washed with water and dried in vacuum oven at 40 °C to afford desired product (50 g, 64%) as light tan solid. ¹H NMR (DMSO-*d*₆) δ 9.40 (s, 1H), 8.27 (d, 1H), 7.76 (d, 2H), 7.06 (d, 2H), 6.75 (brs, 2H), 6.72 (d, 1H), 6.66 (s, 1H), 5.98 (s, 1H); MS ES 328 (M+H)⁺, calcd 328, RT = 1.45 min.

Step 3: Preparation of . 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine

15 To a mixture of 6-chloro-N⁴-(4-[[2-methylpyridin-4-yl]oxy]phenyl)pyrimidine-2,4-diamine (2.0 g, 6.1 mmol) and 2-Amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.6 g, 7.3 mmol) in DMF (30 mL) was added aqueous Na₂CO₃ (2 M, 9.0 mL) and 1,1'-bis(diphenylphosphino)ferrocenepalladium (II) chloride (223 mg, 0.3 mmol).
20 The resulting mixture was degassed for 10 min before it was heated at 80 °C overnight. The resulting mixture was cooled to rt before it was concentrated under vacuo and dissolved in EtOAc. The resulting mixture was washed with water and brine and the organic layer was dried over Na₂SO₄. Removal of the solvent under vacuo gave the crude material, which was purified with 40 M biotage eluting with 100% EtOAc first and then
25 with 95% CH₂Cl₂ and 5% 2 N ammonia in MeOH to provide the title compound as an off-white solid (1340 mg, 57%): ¹H NMR (DMSO-*d*₆): δ 9.20 (s, 1H), 8.51 (dd, 1H), 8.27 (d, 1H), 7.81-7.88 (m, 3H), 7.03-7.06 (m, 2H), 6.72 (d, 1H), 6.68 (dd, 1H), 6.47 (dd, 1H), 6.33 (s, 1H), 6.32 (s, 2H), 6.23 (s, 2H), 2.39 (s, 3H) ppm; MS ES 386 (M+H)⁺, RT = 1.06 min.

A. Physiological activity

The utility of the compounds of the present invention can be illustrated, for example, by their activity *in vitro* in the *in vitro* tumor cellular proliferation assay described below. The link between activity in tumor cell proliferation assays *in vitro* and anti-tumor activity in the clinical setting has been very well established in the art. For example, the therapeutic utility of taxol (Silvestrini et al. *Stem Cells* 1993, 11(6), 528-35), taxotere (Bissery et al. *Anti Cancer Drugs* 1995, 6(3), 339), and topoisomerase inhibitors (Edelman et al. *Cancer Chemother. Pharmacol.* 1996, 37(5), 385-93) were demonstrated with the use of *in vitro* tumor proliferation assays.

The *in vitro* effect of the compounds according to the invention can be demonstrated in the following Cellular Proliferation Assay:

Tumor cells are seeded on Day 0 at subconfluent densities in RPMI growth medium with 10% FBS and incubated at 37 °C in a humidified incubator containing 5% CO₂. On Day 1, cultures are treated with various concentrations of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine and Paclitaxel (0 – 10 µM, 0.1% final DMSO (dimethylsulfoxide) concentration) for 72 hours. Cell viability is assessed using Alamar Blue staining per the manufacturer's protocol (Trek Diagnostic Systems, Inc., Cleveland, Ohio) or measuring the ATP content using the CellTiter-Glo Assay (Promega, Wisconsin, USA).

The *in vivo* effect of the compounds according to the invention can be demonstrated in the NCI-H460 NSCLC xenograft model:

Animals

Ncr *nu/nu* female mice (Taconic Farms, Germantown, NY, USA) were used for all *in vivo* studies. The mice were housed and maintained within the Comparative Medicine Department at Bayer Corporation, West Haven, CT in accordance with Bayer IACUC, State, and Federal guidelines for the humane treatment and care of laboratory animals. Mice received food and water *ad libitum*.

Compounds

6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine (here called Compound 1) was stored in the dark until used.

5 Clinical grade Paclitaxel (Bristol Myers Squibb, USA) came supplied as a dry powder. It was stored at room temperature as indicated on the package insert.

Vehicles

10 Cremophor EL /Ethanol (50:50) (Sigma Cremophor EL Cat.# C-5135; 500g, 95% Ethyl Alcohol), was prepared as a stock solution, wrapped with aluminum foil, and stored at room temperature. Paclitaxel was formulated at 4-fold (4X) of the highest dose in this Cremophor EL/Ethanol (50:50) solution. This 4X stock solution was prepared fresh daily. Final dosing solutions were prepared by dilution to 1X with endotoxin screened distilled H₂O (GIBCO, Cat.# 15230-147) and mixed by vortexing immediately prior to dosing.

15 Solutol HS15 /Ethanol (50:50) (BAXF Solutol HS15, 95% ethyl alcohol) was prepared as a stock solution, wrapped with aluminum foil, and stored at room temperature. Compound 1 was formulated at 5-fold (5X) of the highest dose in this Solutol/Ethanol (50:50) solution. This 5X stock solution was prepared fresh daily. Final dosing solutions were prepared by dilution to 1X with 0.9% saline and mixed by vortexing immediately
20 prior to dosing.

Tumor Lines

25 The NCI-H460 human non-small-cell lung carcinoma line was obtained from the American Type Tissue Culture Collection Repository. NCI-H460 cells were maintained and passaged *in vitro* using DMEM (GIBCO cat. # 11995-065; 500 mls) supplemented with 10% heat inactivated fetal bovine serum (JRH Biosciences cat.# 12106-500M), 2mM L-glutamine (GIBCO cat. # 25030-81), 10mM HEPES buffer (GIBCO cat # 15630-080) and penicillin-streptomycin (GIBCO cat. # 15140-122; 5 mls/ 50 mls DMEM). Cells were
30 maintained at 37°C and 5% CO₂ in a Fisher Scientific 610 CO₂ incubator.

Tumor Xenograft Experiments

Studies with the NCI-H460 cells were initiated by harvesting cells from an *in vitro*

culture by adding Trypsin-EDTA (GIBCO cat#25200-056) for 2 minutes followed by centrifugation of the cells into a pellet and resuspension in HBSS (GIBCO cat# 14025-092) to a final cell count of 5×10^7 viable cells/ml. A volume of 0.1ml of the cell suspension was injected s.c. in the right flank of each mouse. All treatment was initiated when all mice in the experiment had established tumors ranging in size from 100 to 150 mg. The general health of mice was monitored and mortality was recorded daily. Tumor dimensions and body weights were recorded two to three times a week starting with the first day of treatment. Animals were euthanized according to Bayer IACUC guidelines. The maximum tolerated dose (MTD) is defined as the highest dose that produces less than 20% lethality and/or 20% net body weight loss.

Compound 1 was administered i.v. on a q4d x 3 schedule and paclitaxel was administered i.v on a q2d x 5 schedule. On days when both compounds were administered, compound 1 was dosed first and paclitaxel was administered 4 h later. Both agents were dosed up to their respective MTD (maximum tolerated dose). Tumor weights (mg) were calculated using the equation $(l \times w^2)/2$, where l and w refer to the larger and smaller dimensions collected at each measurement. There were 10 mice per group.

Results

An evaluation endpoint of three tumor mass doublings was used to evaluate the anti-tumor efficacy of the combination of these agents at their MTDs to the efficacy of the corresponding single agents as represented in Table 1. The tumor growth delay produced by each individual therapy was approximately 8 days (median time to reach the evaluation endpoint in the control groups was 7 days and 15 days for both compound 1 and paclitaxel. The tumor growth delay produced by the combination therapy was approximately 14 days (the time to reach the evaluation endpoint in the combination therapy group was 21 days). There was no lethality on any treatment. The average tumor weight at each day of measurement (mean $\pm$ standard error of the mean, SEM) for each group is summarized in Table 1.

	Mean Tumor Weight (mg $\pm$ SEM on each day post-implant)							
	Day 6	Day 10	Day 12	Day 14	Day 17	Day 20	Day 24	Day 28
Control	135 $\pm$ 6	428 $\pm$ 23	794 $\pm$ 50	1234 $\pm$ 79	1768 $\pm$ 110			
Vehicles	126 $\pm$ 5	409 $\pm$ 39	762 $\pm$ 67	1193 $\pm$ 115	1873 $\pm$ 162			
compound 1 (40 mg/kg) + vehicle	124 $\pm$ 5	239 $\pm$ 37	295 $\pm$ 50	351 $\pm$ 72	464 $\pm$ 80	802 $\pm$ 144	1466 $\pm$ 253	
vehicle + Paclitaxel (15 mg/kg)	124 $\pm$ 4	263 $\pm$ 44	326 $\pm$ 53	366 $\pm$ 87	528 $\pm$ 131	962 $\pm$ 289		
compound 1 (40 mg/kg) + Paclitaxel (15 mg/kg)	129 $\pm$ 5	176 $\pm$ 22	172 $\pm$ 24	147 $\pm$ 27	132 $\pm$ 24	221 $\pm$ 55	526 $\pm$ 155	1229 $\pm$ 286

Table 1: Effect of compound 1 and paclitaxel on growth of H460 xenografts in NCr mice

B. Operative examples relating to pharmaceutical compositions

The compounds according to the invention can be converted into pharmaceutical preparations as follows:

5

Solution for intravenous administration 1:

Composition: 1 mg 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine, 1 mg Paclitaxel, 15 g polyethylenglykol 400 and 250 g water optionally with up to 15 % Cremophor EL, and optionally up to 15% ethyl
10 alcohol, and optionally up to 2 equivalents of a pharmaceutically suitable acid such as citric acid or hydrochloric acid.

Preparation:

1 mg 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-
15 diamine, 1 mg Paclitaxel, and the polyethylenglykol 400 are dissolved in the water with stirring. The solution is sterile filtered (pore size 0.22 µm) and filled into heat sterilized infusion bottles under aseptical conditions. The infusion bottles are being sealed with rubber seals.

20 **Solution for intravenous administration 2:**

Composition: 1 mg 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine, 1 mg Paclitaxel, saline solution, optionally with up to 15 % by weight of Cremophor EL, and optionally up to 15% by weight of ethyl alcohol, and optionally up to 2 equivalents of a pharmaceutically suitable acid such as
25 citric acid or hydrochloric acid.

Preparation:

1 mg 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-
diamine and 1 mg Paclitaxel are dissolved in the saline solution with stirring. Optionally
30 Cremophor EL, ethyl alcohol or acid are added. The solution is sterile filtered (pore size 0.22 µm) and filled into heat sterilized infusion bottles under aseptical conditions. The infusion bottles are being sealed with rubber seals.

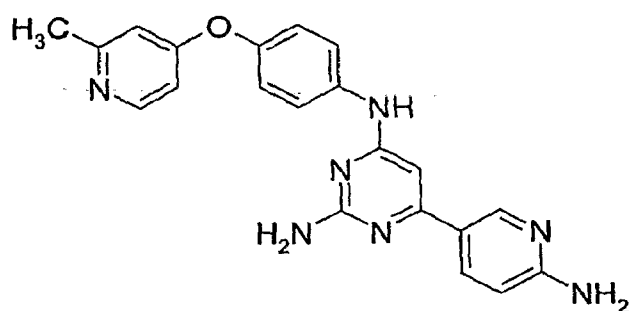
Solution for intravenous administration 3:

Composition: 1 mg 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine, 6 mg Paclitaxel, 527 mg of purified Cremophor EL, 49.7% (v/v) dehydrated ethyl alcohol USP per mL solution, dilution with a in 0.9%

- 5 Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP, or 5% Dextrose in Ringer's Injection.

Claims

1. A combination of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine



with Paclitaxel.

2. A process for preparing a combination of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine with Paclitaxel, comprising combining 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine and Paclitaxel.

3. A pharmaceutical composition comprising a combination of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine with Paclitaxel.

4. The composition of claim 3, wherein the composition is suitable for parenteral administration.

5. The composition of claim 4, wherein the parenteral administration is intravenous administration.

6. The composition of claim 3, further comprising purified Cremophor EL and dehydrated ethyl alcohol.

7. A packaged pharmaceutical composition, comprising a container comprising a combination of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine with Paclitaxel and a pharmaceutically acceptable carrier and instructions for using the pharmaceutical composition to treat a disease in a patient
8. A process for preparing a pharmaceutical composition comprising a combination of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine with Paclitaxel, comprising combining 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine and Paclitaxel and converting them into a suitable pharmaceutical composition.
9. A kit-of-parts, comprising a plurality of containers comprising 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine and Paclitaxel or both, optionally further comprising instructions for using the kit-of-parts to treat a disease in a patient.
10. A method for treating a disorder, comprising administering to a patient a pharmaceutically effective amount of a combination of 6-(6-aminopyridin-3-yl)-N⁴-{4-[(2-methylpyridin-4-yl)oxy]phenyl}pyrimidine-2,4-diamine with Paclitaxel.
11. The method of claim 10, wherein the disorder is cancer.
12. The method of claim 11, wherein the disorder is non small cell lung cancer.
13. The method of claim 10, further comprising the steps of administering purified Cremophor[®] EL, ethyl alcohol and an Injection selected from the group consisting of 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP, and 5% Dextrose in Ringer's Injection.

Paclitaxel combination