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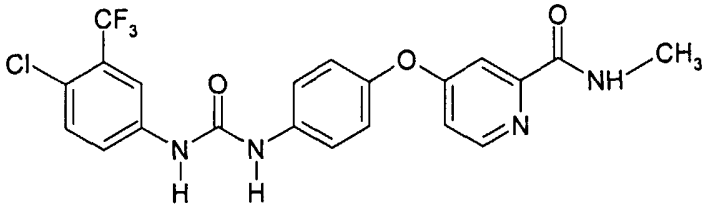
(54) **Title:** NEW PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF CANCER



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(57) **Abstract:** This invention relates to novel pharmaceutical compositions comprising a solid dispersion of the compound of Formula (I), to processes for preparing these novel pharmaceutical compositions and to their use for treating hyper-proliferative disorders, such as cancer, either as a sole agent or in combination with other therapies.

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New Pharmaceutical Compositions for the Treatment of Cancer

This application claims the benefit of the filing date of U.S. Provisional Application Serial No. 60/604,753 filed August 27, 2004, which is incorporated by reference herein.

Field of the Invention

This invention relates to novel pharmaceutical compositions, to processes for preparing these novel pharmaceutical compositions and to their use for treating hyper-proliferative disorders, such as cancer, either as a sole agent or in combination with other therapies.

Background of the Invention

Diarylureas are a class of serine-threonine kinase inhibitors as well as tyrosine kinase inhibitors known in the art. The following publications illustrate their utility as active ingredient in pharmaceutical compositions for the treatment of hyper-proliferative diseases, such as cancer:

Smith et al., *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2775-2778.

Lowinger et al., *Clin. Cancer Res.* **2000**, *6(suppl.)*, 335.

Lyons et al., *Endocr.-Relat. Cancer* **2001**, *8*, 219-225.

Riedl et al., *Book of Abstracts, 92nd AACR Meeting, New Orleans, LA, USA, abstract 4956.*

Khire et al., *Book of Abstracts, 93rdAACR Meeting, San Francisco, CA, USA, abstract 4211.*

Lowinger et al., *Curr. Pharm. Design* **2002**, *8*, 99-110.

Carter et al., *Book of Abstracts, 92ndAACR Meeting, New Orleans, LA, USA, abstract 4954.*

Vincent et al., *Book of Abstracts, 38th ASCO Meeting, Orlando, FL, USA, abstract 1900.*

Hilger et al., *Book of Abstracts, 38th ASCO Meeting, Orlando, FL, USA, abstract 1916.*

Moore et al., *Book of Abstracts, 38th ASCO Meeting, Orlando, FL, USA, abstract 1816.*

Strumberg et al., *Book of Abstracts, 38th ASCO Meeting, Orlando, FL, USA, abstract 121.*

Omega-Carboxyaryl diphenyl ureas are disclosed in WO00/42012 (published July 20, 2000), WO00/41698 (published July 20, 2000), and in the following published U.S. applications:

US2002-0165394-A1, published November 7, 2002,
US2001-003447-A1, published October 25, 2001,
US2001-0016659-A1, published August 23, 2001,
US2002-013774-A1, published September 26, 2002,

and copending U.S. applications:
09/758,547, filed January 12, 2001,
09/889,227, filed July 12, 2001,
09/993,647, filed November 27, 2001,
10/042,203, filed January 11, 2002 and
10/071,248, filed February 11, 2002

In particular, it has been discovered that the diphenyl urea of Formula I, also referred as "BAY 43-9006" or 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide, is a potent inhibitor of raf, VEGFR-2, p38, and PDGFR kinases. These enzymes are all molecular targets of interest for the treatment of hyper-proliferative diseases, including cancer. Therefore, the compound of Formula I will be used as medicine for the treatment of the above mentioned diseases.

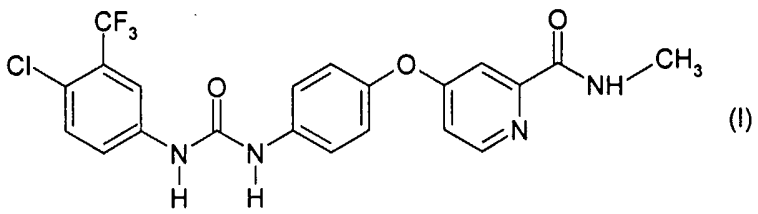
A preferred route of drug administration is through the oral cavity. This route provides great comfort and convenience of dosing. The bioavailability achieved after oral administration is a measure for the potential usefulness of an oral dosage form of a drug. Bioavailability after oral application depends on several factors, such as

solubility of the active in aqueous media, dose strength, dissolution of the dosage form, absorption throughout the gastrointestinal tract and first pass effect.
Therefore solid pharmaceutical compositions for oral application containing the compound of Formula I, which result in improved dissolution, absorption and exposure in mammals, improved inter-patient variability, and overall improved efficacy in the clinic are desired.

Description of the Invention

Pharmaceutical compositions comprising a solid dispersion of the compound of Formula I below are provided.

Formula I is as follows:



(I)

The term "the compound of Formula I", or "the compound of this invention" does not only refer to 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide as depicted in Formula I, but also refers to its solvates, hydrates, pharmaceutically acceptable salts, or a combination thereof.

The present invention pertains to

(i) novel pharmaceutical compositions containing the compound of Formula I in the form of a solid dispersion, which includes solid solutions, glass solutions, glass suspensions, amorphous precipitations in a crystalline carrier, eutectics or monotecics, compound or complex formation and combinations thereof,

(ii) processes for preparing these novel pharmaceutical compositions, and

(iii) the use of these compositions for the treatment of hyper-proliferative diseases, such as cancer, either as a sole agent, or in combination with other anti-cancer therapies.

In the following, the different types of solid dispersions (solid solutions, glass solutions, glass suspensions, amorphous precipitations in a crystalline carrier, eutectics or monotecics, compound or complex formation and combinations thereof) are collectively referred to as "solid dispersion."

A pharmaceutical composition according to this invention comprises of a solid dispersion comprising at least the compound of Formula I and a pharmaceutically acceptable matrix.

The term "matrix" or "matrix agents" as used herein refers to both polymeric excipients, non-polymeric excipients and combinations thereof, capable of dissolving or dispersing the compound of formula I.

An aspect of the invention of particular interest is a pharmaceutical composition comprising a solid dispersion, wherein the matrix comprises a pharmaceutically acceptable polymer, such as polyvinylpyrrolidone, vinylpyrrolidone/vinylacetate copolymer, polyalkylene glycol (i.e. polyethylene glycol), hydroxyalkyl cellulose (i.e. hydroxypropyl cellulose), hydroxyalkyl methyl cellulose (i.e. hydroxypropyl methyl cellulose), carboxymethyl cellulose, sodium carboxymethyl cellulose, ethyl cellulose, polymethacrylates, polyvinyl alcohol, polyvinyl acetate, vinyl alcohol/vinyl acetate copolymer, polyglycolized glycerides, xanthan gum, carrageenan, chitosan, chitin, poyldextrin, dextrin, starch, proteins or combinations thereof.

Another aspect of the invention is a pharmaceutical composition comprising a solid dispersion, wherein the matrix comprises a sugar and/or sugar alcohol and/or cyclodextrin, for example sucrose, lactose, fructose, maltose, raffinose, sorbitol, lactitol, mannitol, maltitol, erythritol, inositol, trehalose, isomalt, inulin, maltodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutyl ether cyclodextrin or combinations thereof.

An aspect of the invention of particular interest is a pharmaceutical composition comprising a solid dispersion which is an amorphous co-precipitate of a compound of Formula I and polyvinylpyrrolidone.

Additional suitable excipients that are useful in the formation of the matrix of the solid dispersion include, but are not limited to alcohols, organic acids, organic bases, amino acids, phospholipids, waxes, salts, fatty acid esters, polyoxyethylene sorbitan fatty acid esters, and urea.

The solid dispersion of the compound of Formula I in the matrix may contain certain additional pharmaceutical acceptable ingredients, such as carriers, surfactants, fillers, disintegrants, recrystallization inhibitors, plasticizers, defoamers, antioxidants, detackifier, pH-modifiers, glidants and lubricants.

A carrier according to this invention is an excipient, which becomes loaded with a mixture, comprised of at least the matrix agent and the compound of this invention, during the manufacturing process of the solid dispersion, for example by hot melt extrusion, hot melt coating, prilling, congealing, solvent evaporation processes (e.g. layering, coating, granulation), and thus becomes an integral part of the solid dispersion.

In an embodiment of this invention, the matrix comprises a water soluble polymer.

In another embodiment, at least one from the group of polyvinylpyrrolidone, copovidone, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyethylene glycol and polyethylene oxide is used as matrix agent in the solid dispersion.

In another embodiment, polyvinylpyrrolidone is used as matrix agent.

Another embodiment comprises hydroxypropyl cellulose as matrix agent.

Another aspect of the invention of particular interest are solid dispersions containing croscarmellose sodium, sodium starch glycollate, crospovidone, low substituted

hydroxypropyl cellulose (L-HPC), starch, microcrystalline cellulose or a combination thereof as carrier or disintegrant.

In an embodiment, the solid dispersion comprises polyvinylpyrrolidone and croscarmellose sodium.

In another embodiment, the solid dispersion comprises polyvinylpyrrolidone and sodium starch glycollate.

In another embodiment, the solid dispersion comprises polyvinylpyrrolidone, croscarmellose sodium and microcrystalline cellulose.

In another embodiment, the solid dispersion comprises hydroxypropyl cellulose and croscarmellose sodium.

In yet another embodiment, the solid dispersion comprises hydroxypropyl cellulose and at least one excipient, which is a sugar, sugar alcohol, cyclodextrin or combination thereof.

The solid dispersion of the invention is prepared according to methods known to the art for the manufacture of solid dispersions, such as fusion/melt technology, hot melt coating, prilling, congealing, solvent evaporation (e.g. freeze drying, spray drying, vacuum drying, layering of powders of granules, powders or pellets an fluid bed granulation), coprecipitation, supercritical fluid technology and electrostatic spinning method.

Hot melt extrusion or solvent evaporation techniques are suitable processes for preparation of solid dispersion formulations of this invention.

A solvent suitable for manufacture of solid dispersions by solvent evaporation processes such as spray-drying, layering and fluid-bed granulation can be any

compound, wherein the compound of Formula I can be dissolved. Preferred solvents include alcohols (e.g. methanol, ethanol, n-propanol, isopropanol, and butanol), ketones (e.g. acetone, methyl ethyl ketone and methyl isobutyl ketone), esters (e.g. ethyl acetate and propyl acetate) and various other solvents such as acetonitrile, methylene chloride, choroform, hexane, toluene, tetrahydrofuran, cyclic ethers, and 1,1,1-trichloroethane. Lower volatility solvents, such as dimethyl acetamide or dimethylsulfoxide can also be used. Mixtures of solvents, can also be used, as can mixtures with water as long as the drug and if necessary the matrix agent are sufficiently soluble to make the process practicable.

An aspect of the invention of particular interest is a pharmaceutical composition in which the compound of Formula I is substantially amorphous.

Another aspect of the invention of particular interest is a solid dispersion of the compound of Formula I, wherein the matrix is a polyvinylpyrrolidone polymer.

Another aspect of the invention of particular interest is a solid dispersion of the compound of Formula I, wherein the matrix is a hydroxypropylcellulose polymer.

Another aspect of this invention which is of particular interest is a novel pharmaceutical composition comprising a co-precipitate of a compound of formula I and a matrix.

This pharmaceutical composition will be utilized to achieve the desired pharmacological effect by oral administration to a patient in need thereof, and will be advantageous to a conventional formulation in terms of drug release, bioavailability, and/or interpatient variability in mammals. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or disease, including prophylactic treatment.

For oral administration, the solid dispersion described herein can be formulated into solid or liquid preparations such as powder, granules, pellets, tablets, capsules, dragées, chewable tablets, dispersible tables, troches, lozenges, melts, solutions,

suspensions, or emulsions, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. For this purpose the solid dispersion may be compounded with conventional excipients, for example binders, fillers, lubricants, disintegrants, solvents, surfactants, thickeners and stabilizers, coating materials as well as flavoring agents, sweeteners, flavoring and coloring agents.

It is believed that one skilled in the art, utilizing the preceding information, can utilize the present invention to its fullest extent. The oral formulation of the compound of Formula I refers to a wide range of dosages such as 1 mg, 10 mg, 100 mg, or even 1 g daily dosing and beyond. This would be accomplished, for example, by modifying the composition and size of the tablet or capsule, and/or by administering multiple tablets or capsules per day to the patient in need thereof. Alternatively, the solid dispersion formulation may also be dosed in forms such as powders, granules, chewable or dispersible tablets, or by dispersions of any adequate solid formulation in a suitable liquid prior to use, for example if the optimal dose regimen was no longer consistent with a feasible tablet or capsule size.

Method of treating hyper-proliferative disorders

The present invention also relates to a method for using a new oral pharmaceutical composition of the compound of Formula I to treat mammalian hyper-proliferative disorders, including cancer. This method comprises administering the pharmaceutical composition in the form of a solid dispersion to a mammal in need thereof, including a human, an amount which is effective to treat the disorder. The term "hyper-proliferative disorders" and/or "cancer" not only refers to solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases, but also includes lymphomas, sarcomas, and leukemias.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma *in situ*, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small intestine, and salivary gland cancers.

Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, and urethral cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Head-and-neck cancers include, but are not limited to laryngeal / hypopharyngeal / nasopharyngeal / oropharyngeal cancer, and lip and oral cavity cancer.

Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, fibrosarcoma, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

These disorders have been well characterized in humans, but also exist with a similar etiology in other mammals, and can be treated by administering the pharmaceutical compositions of the present invention.

The total amount of the active ingredient (compound of Formula I) to be administered via the oral route using the pharmaceutical composition of the present invention will generally range from about 0.01 mg/kg to about 50 mg/kg body weight per day. Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of hyper-proliferative disorders, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the pharmaceutical compositions of this invention can readily be determined by those skilled in the art. The amount of the administered active ingredient can vary widely according to such considerations as the particular compound and dosage unit employed, the mode and time of administration, the period of treatment, the age, sex, and general condition of the patient treated, the nature and extent of the condition treated, the rate of drug metabolism and excretion, the potential drug combinations and drug-drug interactions, and the like.

The pharmaceutical compositions of this invention can be administered as the sole agent or in combination with one or more other therapies where the combination causes no unacceptable adverse effects. For example, they can be combined with cytotoxic agents, signal transduction inhibitors, or with other anti-cancer agents or therapies, as well as with admixtures and combinations thereof.

In one embodiment, the pharmaceutical compositions of the present invention can be combined with cytotoxic anti-cancer agents. Examples of such agents can be found in

the 11th Edition of the *Merck Index* (1996). These agents include, by no way of limitation, asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Other cytotoxic drugs suitable for use with the pharmaceutical compositions of the invention include, but are not limited to, those compounds acknowledged to be used in the treatment of neoplastic diseases in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition, 1996, McGraw-Hill). These agents include, by no way of limitation, aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2', 2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

Other cytotoxic anti-cancer agents suitable for use in combination with the compositions of the invention also include newly discovered cytotoxic principles such as oxaliplatin, gemcitabine, capecitabine, epothilone and its natural or synthetic derivatives, temozolomide (Quinn et al., *J. Clin. Oncology* **2003**, *21*(4), 646-651), tositumomab (Bexxar), trabedectin (Vidal et al., *Proceedings of the American Society for Clinical Oncology* **2004**, *23*, abstract 3181), and the inhibitors of the kinesin spindle protein Eg5 (Wood et al., *Curr. Opin. Pharmacol.* **2001**, *1*, 370-377).

In another embodiment, the pharmaceutical compositions of the present invention can be combined with other signal transduction inhibitors. Of particular interest are signal

transduction inhibitors which target the EGFR family, such as EGFR, HER-2, and HER-4 (Raymond et al., *Drugs* **2000**, *60* (Suppl.1), 15-23; Harari et al., *Oncogene* **2000**, *19* (53), 6102-6114), and their respective ligands. Examples of such agents include, by no way of limitation, antibody therapies such as Herceptin (trastuzumab), Erbitux (cetuximab), and pertuzumab. Examples of such therapies also include, by no way of limitation, small-molecule kinase inhibitors such as ZD-1839 / Iressa (Baselga et al., *Drugs* **2000**, *60* (Suppl. 1), 33-40), OSI-774 / Tarceva (Pollack et al. *J. Pharm. Exp. Ther.* **1999**, *291*(2), 739-748), CI-1033 (Bridges, *Curr. Med. Chem.* **1999**, *6*, 825-843), GW-2016 (Lackey et al., *92nd AACR Meeting, New Orleans, March 24-28, 2001, abstract 4582*), CP-724,714 (Jani et al., *Proceedings of the American Society for Clinical Oncology* **2004**, 23, abstract 3122), HKI-272 (Rabindran et al., *Cancer Res.* **2004**, *64*, 3958-3965), and EKB-569 (Greenberger et al., *11th NCI-EORTC-AACR Symposium on New Drugs in Cancer Therapy, Amsterdam, November 7-10, 2000, abstract 388).*

In another embodiment, the pharmaceutical compositions of the present invention can be combined with other signal transduction inhibitors targeting receptor kinases of the split-kinase domain families (VEGFR, FGFR, PDGFR, flt-3, c-kit, c-fms, and the like), and their respective ligands. These agents include, by no way of limitation, antibodies such as Avastin (bevacizumab). These agents also include, by no way of limitation, small-molecule inhibitors such as STI-571 / Gleevec (Zvelebil, *Curr. Opin. Oncol., Endocr. Metab. Invest. Drugs* **2000**, *2*(1), 74-82), PTK-787 (Wood et al., *Cancer Res.* **2000**, *60*(8), 2178-2189), SU-11248 (Demetri et al., *Proceedings of the American Society for Clinical Oncology* **2004**, *23*, abstract 3001), ZD-6474 (Hennequin et al., *92nd AACR Meeting, New Orleans, March 24-28, 2001, abstract 3152*), AG-13736 (Herbst et al., *Clin. Cancer Res.* **2003**, *9*, 16 (suppl 1), abstract C253), KRN-951 (Taguchi et al., *95th AACR Meeting, Orlando, FL, 2004, abstract 2575*), CP-547,632 (Beebe et al., *Cancer Res.* **2003**, *63*, 7301-7309), CP-673,451 (Roberts et al., *Proceedings of the American Association of Cancer Research* **2004**, *45*, abstract 3989), CHIR-258 (Lee et al., *Proceedings of the American Association of Cancer Research* **2004**, *45*, abstract 2130), MLN-518 (Shen et al., *Blood* **2003**, *102*, 11, abstract 476), and AZD-2171 (Hennequin et al., *Proceedings of the American Association of Cancer Research* **2004**, *45*, abstract 4539).

In another embodiment, the pharmaceutical compositions of the present invention can be combined with inhibitors of the Raf/MEK/ERK transduction pathway (Avruch et al., *Recent Prog. Horm. Res.* **2001**, *56*, 127-155), or the PKB (akt) pathway (Lawlor et al., *J. Cell Sci.* **2001**, *114*, 2903-2910). These include, by no way of limitation, PD-325901 (Sebolt-Leopold et al., *Proceedings of the American Association of Cancer Research* **2004**, *45*, abstract 4003), and ARRY-142886 (Wallace et al., *Proceedings of the American Association of Cancer Research* **2004**, *45*, abstract 3891).

In another embodiment, the pharmaceutical compositions of the present invention can be combined with inhibitors of histone deacetylase. Examples of such agents include, by no way of limitation, suberoylanilide hydroxamic acid (SAHA), LAQ-824 (Ottmann et al., *Proceedings of the American Society for Clinical Oncology* **2004**, *23*, abstract 3024), LBH-589 (Beck et al., *Proceedings of the American Society for Clinical Oncology* **2004**, *23*, abstract 3025), MS-275 (Ryan et al., *Proceedings of the American Association of Cancer Research* **2004**, *45*, abstract 2452), and FR-901228 (Piekarz et al., *Proceedings of the American Society for Clinical Oncology* **2004**, *23*, abstract 3028).

In another embodiment, the pharmaceutical compositions of the present invention can be combined with other anti-cancer agents such as proteasome inhibitors, and m-TOR inhibitors. These include, by no way of limitation, bortezomib (Mackay et al., *Proceedings of the American Society for Clinical Oncology* **2004**, *23*, Abstract 3109), and CCI-779 (Wu et al., *Proceedings of the American Association of Cancer Research* **2004**, *45*, abstract 3849).

Generally, the use of cytotoxic and/or cytostatic anti-cancer agents in combination with the pharmaceutical compositions of the present invention will serve to:

(1) yield better efficacy in reducing the growth of a tumor or even eliminate the tumor as compared to administration of either agent alone,

(2) provide for the administration of lesser amounts of the administered agents,

(3) provide for a chemotherapeutic treatment protocol that is well tolerated in the patient with fewer deleterious pharmacological complications than observed with single agent chemotherapies and certain other combined therapies,

(4) provide for treating a broader spectrum of different cancer types in mammals, especially humans,

(5) provide for a higher response rate among treated patients,

(6) provide for a longer survival time among treated patients compared to standard chemotherapy treatments,

(7) provide a longer time for tumor progression, and/or

(8) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other cancer agent combinations produce antagonistic effects.

It is believed that one skilled in the art, using the preceding information and information available in the art, can utilize the present invention to its fullest extent.

It should be apparent to one of ordinary skill in the art that changes and modifications can be made to this invention without departing from the spirit or scope of the invention as it is set forth herein.

All publications, applications and patents cited above and below are incorporated herein by reference.

Example 1 refers to a preparation of the compound used in this invention. Representative solid dispersion formulations of the compound of this invention are described in Examples 2, 3, and 4.

Examples

Example 1: Preparation of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide

A method of preparing BAY 43-9006 (4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide) is described in Bankston et al. "A Scaleable Synthesis of BAY 43-9006: A Potent Raf Kinase Inhibitor for the Treatment of Cancer" *Org. Proc. Res. Dev.* **2002**, 6(6), 777-781.

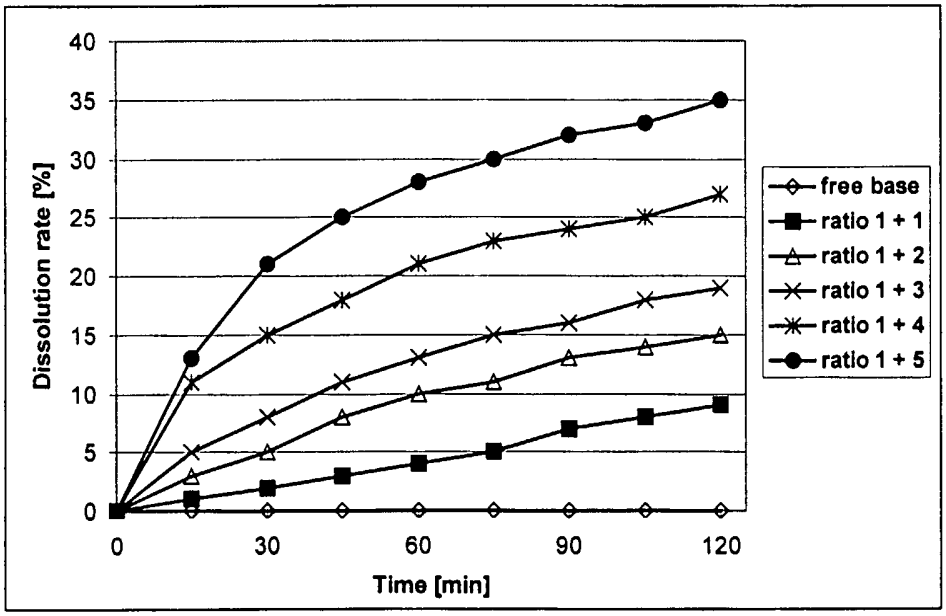
Example 2: Preparation of 1:1, 1:2, 1:3, 1:4, and 1:5 solid dispersion of the compound of Example 1 with polyvinylpyrrolidone.

In an uncapped vial, one part of the compound of Example 1 as a free base was mixed with one, two, three, four, or five parts polyvinylpyrrolidone (PVP-25 / Kollidon 25) respectively. The mixture was dissolved in a sufficient amount of a 5 to 1 mixture of acetone and ethanol, until all powders were in solution. The uncapped vial was placed into a vacuum oven set at 40°C, and let dry for at least 24 hours.

The *in vitro* dissolution properties of the pharmaceutical compositions of Example 2 are compared with those of the free base of Example 1 as depicted in the dissolution profile below.

Based on this data, it can be assumed that the oral administration of the compound of the present invention, as a solid dispersion, will result in an improved absorption and bioavailability in humans, compared with a conventional formulation.

Dissolution Profile



In vitro dissolution profiles of solid dispersions of the compound of the present invention in various amounts of polyvinylpyrrolidone (ratios ranging from 1:1 to 1:5).

Example 3: Preparation of a 1:3 solid dispersion of the compound of Example 1 with hydroxypropyl cellulose.

In a heat-resistant vessel, one part of the compound of Example 1 as a free base was thoroughly mixed with three parts of hydroxypropyl cellulose (HPC-L), melted together at a temperature of > 200°C on a heating plate, then cooled back to room temperature.

Example 4: Preparation of a 1:5 solid dispersion of the compound of Example 1 with starch and polyethylene glycol.

In a heat-resistant vessel, one part of the compound of Example 1 as a free base was thoroughly mixed with 4 parts of starch and one part of polyethylene glycol (PEG 6000), melted together at a temperature of > 200 °C on a heating plate, and then cooled to room temperature.

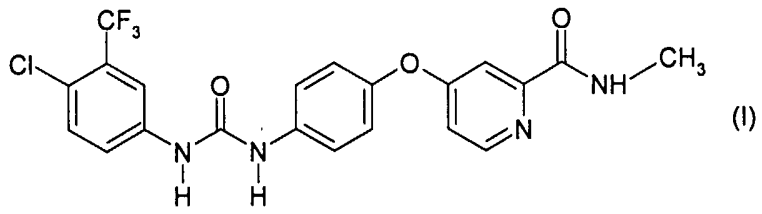
It is believed that this new type of pharmaceutical composition, comprising a solid dispersion of the compound of Formula I, will result in improved bioavailability, improved inter-patient variability, and overall superior efficacy for the treatment of hyper-proliferative diseases, including cancer.

Based on these findings it can be assumed that this new type of pharmaceutical composition, comprising a solid dispersion of the compound of Formula I, will result in improved absorption and exposure, reduced inter-patient variability, and overall superior efficacy for the treatment of hyper-proliferative disorders, including cancer.

What is Claimed is :

1. A composition containing 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide and/or salts, hydrates, solvates thereof in the form of a solid dispersion.

2. A composition comprising a solid dispersion comprising at least the compound of Formula I and a pharmaceutically acceptable matrix.



(I)

3. A composition according to claim 2, wherein the matrix comprises polymeric excipients or non-polymeric excipients capable of dissolving or dispersing the compound of Formula I.

4. A composition according to claim 2, wherein the matrix comprises a combination of polymeric excipients and non-polymeric excipients capable of dissolving or dispersing the compound of Formula I.

5. A composition according to claim 2, wherein the matrix comprises a water soluble polymer.

6. A compositions according to claim 5, wherein the matrix comprises at least one polymer from the group consisting of polyvinylpyrrolidone, copovidone, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyethylene glycole or polyethylene oxide.

7. A composition according to claim 6, wherein the matrix comprises polyvinylpyrrolidone .

8. A composition according to claim 7, wherein the weight ratio of the compound of Formula I calculated as solvent-free base to polyvinylpyrrolidone is between 1:0.5 and 1:20.

9. A composition according to claim 6, wherein the matrix comprises hydroxypropyl cellulose.

10. A composition according to claim 9, wherein the weight ratio of the compound of Formula I calculated as solvent-free base to hydroxypropyl cellulose is between 1:0.5 and 1:20.

11. A composition according to any of the proceeding claims, wherein the solid dispersion comprises croscarmellose sodium, sodium starch glycolate, crospovidone, low substituted hydroxypropyl cellulose, starch, microcrystalline cellulose or a combination thereof.

12. A composition according to claim 8, wherein the solid dispersion comprises polyvinylpyrrolidone and croscarmellose sodium.

13. A composition according to claim 8, wherein the solid dispersion comprises polyvinylpyrrolidone and sodium starch glycolate.

14. A composition according to claim 8, wherein the solid dispersion comprises polyvinylpyrrolidone, croscarmellose sodium and microcrystalline cellulose.

15. A composition according to claim 10, wherein the solid dispersion comprises hydroxypropyl cellulose and croscarmellose sodium.

16. A composition according to claim 10, wherein the solid dispersion comprises hydroxypropyl cellulose and at least one excipient which is a sugar, sugar alcohol, cyclodextrin.

17. A composition according to any of the proceeding claims, wherein the solid dispersion is substantially homogeneous.
18. A composition according to any of the proceeding claims, which contains the compound of Formula I in substantially amorphous form.

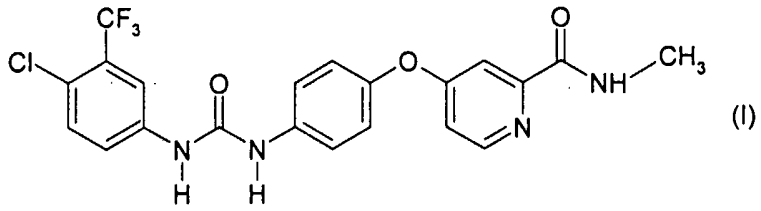
19. A composition as claimed in any one of the proceeding claims, which is a pharmaceutical composition for oral application.

20. A composition as claimed in any one of the proceeding claims, which is a pharmaceutical composition in the form of a tablet.

21. A composition as claimed in any one of the proceeding claims, which is a pharmaceutical composition in the form of a capsule.

22. A composition as claimed in any one of the proceeding claims, which is a pharmaceutical composition in the form of a powder, granulate or sachet.

23. A process for the preparation of a solid dispersion of the compound of Formula I



(I)

which comprises simultaneously exposing the compound of Formula I and at least one matrix to hot melt extrusion, hot melt coating, prilling, congealing, solvent evaporation techniques or a combination thereof.

24. A process according to claim 23, wherein the solid dispersion is prepared by exposing the compound of Formula I and at least one matrix agent to hot melt extrusion.

25. A process according to claim 23, wherein the solid dispersion is prepared by exposing the compound of Formula I and at least one matrix agent to solvent evaporation techniques.
26. A process as claimed in claim 23 to 25 wherein the solid dispersion is further treated with at least one additional processing step, which is milling, sieving, roller compaction, grinding, screening, mixing or a combination thereof.

27. A process as claimed in claim 23 to 26 comprising the additional step of compounding the solid dispersion with one or more pharmaceutical acceptable excipients to form a mixture and shaping this mixture into tablets, filled capsules or sachets.

28. A pharmaceutical composition, produced by a process of claims 23 to 27.

29. A method for treatment of hyper-proliferative disorders comprising administering a pharmaceutical composition according to any of the claims 1 to 22 and 28 to a mammal, including a human, either as sole agent or in combination with other therapies.

30. A method for treatment of cancer comprising administering a pharmaceutical composition according to any of the claims 1 to 22 and 28 to a mammal, including a human, either as sole agent or in combination with other therapies.

31. A method for treatment of cancer comprising administering a pharmaceutical composition according to any of the claims 1 to 22 and 28 to a mammal, including a human, either as sole agent or in combination with radio therapy.

32. A method for treatment of cancer comprising administering a pharmaceutical composition according to any of the claims 1 to 22 and 28 to a human patient, in combination with a cytotoxic therapy.

33. A method for treatment of cancer comprising administering a pharmaceutical composition according to any of the claims 1 to 22 and 28 to a human patient, in combination with another anti-cancer therapy targeting either VEGFR, PDGFR,

src, abl flt-3, EGFR, HER-2, aurora, raf, MEK, ERK, PI-3 kinase, AKT, mTOR, or HDAC.

INTERNATIONAL SEARCH REPORT

International Application No
US2005/030542

A. CLASSIFICATION OF SUBJECT MATTER
A61K9/14

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, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/068228 A (BAYER CORPORATION, U.S.A.) 21 August 2003 (2003-08-21) claims example B page 25, line 9 - page 29, line 31	1-33
A	US 2003/144278 A1 (B. RIEDL ET AL.) 31 July 2003 (2003-07-31) claims paragraphs '0040! - '0048! tables 4,entry,42	1-33
A	US 2003/207872 A1 (B. RIEDL ET AL.) 6 November 2003 (2003-11-06) claims tables 4,entry,55 paragraphs '0040! - '0048!	1-33

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 2006	26/01/2006

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

tional Application No
/US2005/030542

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/047523 A (ONYX PHARM. INC., U.S.A.) 12 June 2003 (2003-06-12) claims figure 2 page 4, line 17 - page 7, line 16	1-33

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

ırnational application No.
PCT/US2005/030542

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 29-33 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

tional Application No
/US2005/030542

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03068228 A	21-08-2003	AU 2003209116 A1	04-09-2003
		CA 2475703 A1	21-08-2003
		EP 1478358 A1	24-11-2004
		JP 2005522448 T	28-07-2005
US 2003144278 A1	31-07-2003	NONE	
US 2003207872 A1	06-11-2003	NONE	
WO 03047523 A	12-06-2003	AU 2002365899 A1	17-06-2003
		CA 2466762 A1	12-06-2003
		EP 1578346 A2	28-09-2005
		JP 2005526008 T	02-09-2005