METHOD OF TREATING PROLIFERATIVE DISORDERS AND OTHER PATHOLOGICAL CONDITIONS MEDIATED BY BCR-ABL, C-KIT, DDR1, DDR2 OR PDGF-R KINASE ACTIVITY

The present invention relates to a regimen for the administration of a pyrimidyl-aminobenzamide of formula (I) wherein the radicals as defined herein, or of a pharmaceutically acceptable salt thereof, for the treatment of proliferative disorders, particularly solid and liquid tumors, and other pathological conditions mediated by the Bcr-Ab1 oncoprotein, the cell transmembrane tyrosine kinase receptor c-Kit, DDR1 (discoidin domain receptor 1), DDR2 (discoidin domain receptor 2) or PDGF-R (platelet derived growth factor receptor) kinase activity, wherein the pyrimidylaminobenzamide of formula I and, optionally, pharmaceutically acceptable carriers, are dispersed in a fruit preparation.

The patent application is classified under the International Patent Classification (IPC) codes A61K 31/506 (2006.01) and A61K 9/00 (2006.01).

Priority data includes an application filed on November 17, 2009 (17.1.2009) in the United States.

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Additional designations include: AIP (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), and OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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METHOD OF TREATING PROLIFERATIVE DISORDERS AND OTHER PATHOLOGICAL CONDITIONS MEDIATED BY BCR-ABL, C-KIT, DDR1, DDR2 OR PDGF-R KINASE ACTIVITY

The present invention relates to a regimen for the administration of a pyrimidylaminobenzamide of formula I

\[
\begin{array}{c}
\text{Py} \\
\text{N} \\
\text{N} \\
\text{NH} \\
\text{R4} \\
\text{R1} \\
\text{R2} \\
\end{array}
\]

(I)

wherein

(a) Py denotes 3-pyridyl,

\( R_1 \) represents hydrogen, lower alkyi, lower alkoxy-lower alkyi, acyloxy-lower alkyi, carboxy-lower alkyi, lower alkoxy carbonyl-lower alkyi, or phenyl-lower alkyi;

\( R_2 \) represents hydrogen, lower alkyi, optionally substituted by one or more identical or different radicals \( R_3 \), cycloalkyl, benzocycloalkyl, heterocyclyl, an aryl group, or a mono- or bicyclic heteroaryl group comprising zero, one, two or three ring nitrogen atoms and zero or one oxygen atom and zero or one sulfur atom, which groups in each case are unsubstituted or mono- or polysubstituted; and

\( R_3 \) represents hydroxy, lower alkoxy, acyloxy, carboxy, lower alkoxy carbonyl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, amino, mono- or disubstituted amino, cycloalkyl, heterocyclyl, an aryl group, or a mono- or bicyclic heteroaryl group comprising zero, one, two or three ring nitrogen atoms and zero or one oxygen atom and zero or one sulfur atom, which groups in each case are unsubstituted or mono- or polysubstituted;

or wherein \( R_1 \) and \( R_2 \) together represent alkylene with four, five or six carbon atoms optionally mono- or disubstituted by lower alkyi, cycloalkyl, heterocyclyl, phenyl, hydroxy, lower alkoxy, amino, mono- or disubstituted amino, oxo, pyridyl, pyrazinyl or pyrimidinyl; benzalkylene with four or five carbon atoms; oxaalkylene with one oxygen and three or four carbon atoms; or azaalkylene with one nitrogen and three or four carbon atoms
wherein nitrogen is unsubstituted or substituted by lower alkyl, phenyl-lower alkyl, lower alkoxy carbonyl-lower alkyl, carboxy-lower alkyl, carbamoyl-lower alkyl, N-mono- or N,N-disubstituted carbamoyl-lower alkyl, cycloalkyl, lower alkoxy carbonyl, carboxy, phenyl, substituted phenyl, pyridinyl, pyrimidinyl, or pyrazinyl;

R₄ represents hydrogen, lower alkyl, or halogen;

or

(b) Py denotes 5-pyrimidyl, R₁ is hydrogen, R₂ is \([(3S)-3-(dimethylamino)-1-pyrrolidinyl]-methyl\)-3-(trifluoromethyl)phenyl and R₄ is methyl;

or of a pharmaceutically acceptable salt thereof,

for the treatment of proliferative disorders, particularly solid and liquid tumors, and other pathological conditions mediated by the Bcr-Abl oncoprotein, the cell transmembrane tyrosine kinase receptor c-Kit, DDR1 (discoidin domain receptor 1), DDR2 (discoidin domain receptor 2) or PDGF-R (platelet derived growth factor receptor) kinase activity.

The compound of formula 1, wherein Py denotes 3-pyridyl, R₁ represents hydrogen, R₂ represents 5-(4-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)phenyl and R₄ represents methyl, is known under the International Non-proprietary Name "nilotinib". Nilotinib (4-methyl-3-[4-(3-pyridinyl)-2-pyrimidinyl]amino]-N-[5-(4-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)phenyl] benzamide) is approved and marketed in the form of its monohydrochloride monohydrate salt under the brand name Tasigna™. Nilotinib is an ATP-competitive inhibitor for Bcr-Abl and also inhibits c-Kit, DDR1, DDR2 and PDGF-R kinase activity at clinically relevant concentrations. Tasigna™ is available as 200 mg hard gelatin capsule for oral administration for the treatment of Philadelphia-positive chronic myeloid leukaemia (CML) in the chronic phase (CP) and accelerated phase (AP) in patients resistant to or intolerant of at least one prior therapy including imatinib. For the treatment of CML a daily dose of 800 mg of nilotinib is applied in two doses of 400 mg each.

The effect of food on the pharmacokinetic parameters of 400 mg oral dose of nilotinib in the capsule formulation mentioned above was studied in human subjects. The concomitant administration of nilotinib with food significantly increased subjects exposure. In said study the total exposure (AUC₀₋₅₅) was 82 % and Cₐₕₕ was 112 % after a high fat breakfast, whereas the increase in total exposure (AUC₀₋₅₅) was 29 % and Cₜₖₕ was 55 % after a light breakfast given 30 minutes prior to dosing. In view of these findings, it is recommended that nilotinib shall not be taken with a meal in order to minimize the effect of
food on nilotinib bioavailability. A statement in this regard is, for instance, included in sections 4.2, 4.4 and 4.5 of the SPC (Summary of Product Characteristics) of the marketing authorization for Tasigna™ issued by the European Medicines Agency (EMEA). Concurrent intake of grapefruit juice also resulted in a modest increase in nilotinib absorption; $C_{\text{max}}$ increased by 60% and AUC increased by 29% (Yin OQ, Gallagher N, Li A, et al. J Clin Pharmacol. 2010; 50:188-194).

Certain patients, for instance elderly patients and pediatric patients, sometimes have difficulties to swallow hard gelatin capsules as a whole. For those patients, suffering from a proliferative disorder, particularly a solid and liquid tumor disorder, or other pathological conditions mediated by Bcr-Abl, c-Kit, DDR1, DDR2 or PDGF-R kinase activity, an alternative dosage form for nilotinib is required. For pediatric patients also dosage flexibility is desirable in order to allow dosage adjustment in accordance with body weight.

It was now surprisingly found that the problem described above can be resolved by oral administration of nilotinib dispersed in a fruit preparation.

More specifically, as shown in the Examples, a single oral administration of 400 mg nilotinib (contents of two 200 mg nilotinib capsules), each dispersed in one teaspoon of applesauce is bioequivalent to a single oral administration of 400 mg nilotinib given as intact capsules. However, the same amount dispersed in plain non-fat yogurt is not found to be bioequivalent.

Hence, the present invention relates to a method of treating a proliferative disorder or other pathological conditions mediated by Bcr-Abl, c-Kit, DDR1, DDR2 or PDGF-R kinase activity comprising oral administration of an effective dose of a pyrimidyiaminobenzamide of formula I
wherein the radicals have the meanings as provided above, or of a pharmaceutically acceptable salt thereof, and, optionally, other pharmaceutically acceptable carriers, dispersed in a fruit preparation, to a human patient in need thereof.

The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated:

The prefix "lower" denotes a radical having up to and including a maximum of 7, especially up to and including a maximum of 4 carbon atoms, the radicals in question being either linear or branched with single or multiple branching.

Where the plural form is used for compounds, salts, and the like, this is taken to mean also a single compound, salt, or the like.

Lower alkyl is preferably alkyl with from and including 1 up to and including 7, preferably from and including 1 to and including 4, and is linear or branched; preferably, lower alkyl is butyl, such as n-butyl, sec-butyl, isobutyl, tert-butyl, propyl, such as n-propyl or isopropyl, ethyl or methyl. Preferably lower alkyl is methyl, propyl or tert-butyl.

Lower acyl is preferably formyl or lower alky carbonyl, in particular acetyl.

An aryl group is an aromatic radical which is bound to the molecule via a bond located at an aromatic ring carbon atom of the radical. In a preferred embodiment, aryl is an aromatic radical having 6 to 14 carbon atoms, especially phenyl, naphthyl, tetrahydronaphthyl, fluorenyl or phenanthrenyl, and is unsubstituted or substituted by one or more, preferably up to three, especially one or two substituents, especially selected from
amino, mono- or disubstituted amino, halogen, lower alkyl, substituted lower alkyl, lower alkenyl, lower alkynyl, phenyl, hydroxy, etherified or esterified hydroxy, nitro, cyano, carbonyl, esterified carboxy, alkanoyl, benzoyl, carboxamoyl, N-mono- or N,N-disubstituted carboxamoyl, amidino, guanidino, ureido, mercapto, sulfo, lower alkylthio, phenylthio, phenyl-lower alkylthio, lower alkylphenylthio, lower alkylsulfinyl, phenylsulfinyl, phenyl-lower alkylsulfinyl, lower alkylphenylsulfinyl, lower alkylsulfonyl, phenylsulfonyl, phenyl-lower alkylsulfonyl, lower alkylphenylsulfonyl, halogen-lower alkylmercaptop, halogen-lower alkylsulfanyl, such as especially trifluoromethanesulfanyl, dihydroxybora \((-\text{B(OH)}_2\)) \(_2\), heterocycyl, a mono- or bicyclic heteroaryl bound and lower alkyylene dioxy bound at adjacent C-atoms of the ring, such as methylene dioxy. Aryl is more preferably phenyl, naphthyl or tetrahydronapthyl, which in each case is either unsubstituted or independently substituted by one or two substituents selected from the group comprising halogen, especially fluorine, chlorine, or bromine; hydroxy; hydroxy etherified by lower alkyl, e.g. by methyl, by halogen-lower alkyl, e.g. trifluoromethyl, or by phenyl; lower alkyylene dioxy bound to two adjacent C-atoms, e.g. methylenedioxy, lower alkyl, e.g. methyl or propyl; halogen-lower alkyl, e.g. trifluoromethyl; hydroxy-lower alkyl, e.g. hydroxymethyl or 2-hydroxy-2-propyl; lower alkoxy-lower alkyl; e.g. methoxymethyl or 2-methoxyethyl; lower alkoxy carbonyl-lower alkyl, e.g. methoxy carbonylmethyl; lower alkynyl, such as 1-propynyl; esterified carboxy, especially lower alkoxy carbonyl, e.g. methoxy carbonyl, n-propanoyl carbonyl or iso-propanoyl carbonyl; N-monosubstituted carbamoyl, in particular carbamoyl monosubstituted by lower alkyl, e.g. methyl, n-propyl or iso-propyl; amino; lower alkylamino, e.g. methylamino; di-lower alkylamino, e.g. dimethylamino or diethylamino; lower alkyleneco amino, e.g. pyrrolidino or piperidino; lower oxalkylene amino, e.g. morpholino, lower azalkylene amino, e.g. pyrrolidino, acylamino, e.g. acetylamino or benzoylamino; lower alkylsulfonyl, e.g. methylsulfonyl; sulfamoyl; or phenylsulfonyl.

A cycloalkyl group is preferably cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl, and may be unsubstituted or substituted by one or more, especially one or two, substituents selected from the group defined above as substituents for aryl, most preferably by lower alkyl, such as methyl, lower alkoxy, such as methoxy or ethoxy, or hydroxy, and further by oxo or fused to a benzo ring, such as in benzocyclopentyl or benzocyclohexyl.

Substituted alkyl is alkyl as last defined, especially lower alkyl, preferably methyl; where one or more, especially up to three, substituents may be present, primarily from the
group selected from halogen, especially fluorine, amino, N-lower alkylamino, N,N-di-lower alkylamino, N-lower alkanoylamino, hydroxy, cyano, carboxy, lower alkoxy carbonyl, and phenyl-lower alkoxy carbonyl. Trifluoromethyl is especially preferred.

Mono- or disubstituted amino is especially amino substituted by one or two radicals selected independently of one another from lower alkyl, such as methyl; hydroxy-lower alkyl, such as 2-hydroxyethyl; lower alkoxy lower alkyl, such as methoxy ethyl; phenyl-lower alkyl, such as benzyl or 2-phenylethyl; lower alkanoyl, such as acetyl; benzoyl; substituted benzyol, wherein the phenyl radical is especially substituted by one or more, preferably one or two, substituents selected from nitro, amino, halogen, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxy carbonyl, lower alkanoyl, and carbamoyl; and phenyl-lower alkoxy carbonyl, wherein the phenyl radical is unsubstituted or especially substituted by one or more, preferably one or two, substituents selected from nitro, amino, halogen, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxy carbonyl, lower alkanoyl, and carbamoyl; and is preferably N-lower alkylamino, such as N-methylamino, hydroxy-lower alkylamino, such as 2-hydroxyethylamino or 2-hydroxypropyl, lower alkoxy lower alkyl, such as methoxy ethyl, phenyl-lower alkylamino, such as benzylamino, N,N-di-lower alkylamino, N-phenyl-lower alkyl-N-lower alkylamino, N,N-di-lower alkylphenylamino, lower alkanoylamino, such as acetylamino, or a substituent selected from the group comprising benzoylamino and phenyl-lower alkoxy carbonylamino, wherein the phenyl radical in each case is unsubstituted or especially substituted by nitro or amino, or also by halogen, amino, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxy carbonyl, lower alkanoyl, carbamoyl or aminocarbonylamino. Disubstituted amino is also lower alkylene-amino, e.g. pyrrolidino, 2-oxopyrrolidino or piperidino; lower oxalkylene-amino, e.g. morpholino, or lower azaalkylene-amino, e.g. piperazino or N-substituted piperazino, such as N-methylpiperazino or N-methoxycarbonylpiperazino.

Halogen is especially fluorine, chlorine, bromine, or iodine, especially fluorine, chlorine, or bromine.

Etherified hydroxy is especially C₆-C₂alkyloxy, such as n-decyloxy, lower alkoxy (preferred), such as methoxy, ethoxy, isopropoxy, or tert-butyloxy, phenyl-lower alkoxy, such as benzyloxy, phenyloxy, halogen-lower alkoxy, such as trifluoromethoxy, 2,2,2-
trifluoroethoxy or 1,1,2,2-tetrafluoroethoxy, or lower alkoxy which is substituted by mono- or bicyclic heteroaryl comprising one or two nitrogen atoms, preferably lower alkoxy which is substituted by imidazolyl, such as 1H-imidazol-1-yl, pyrrolyl, benzimidazolyl, such as 1-benzimidazolyl, pyridyl, especially 2-, 3- or 4-pyridyl, pyrimidinyl, especially 2-pyrimidinyl, pyrazinyl, isoquinolinyl, especially 3-isoquinolinyl, quinolinyl, indolyl orthiazolyl.

Esterified hydroxy is especially lower alkanoyloxy, benzoxyloxy, lower alkoxy carboxyloxy, such as tert-butoxycarboxyloxy, or phenyl-lower alkoxy carboxyloxy, such as benzylxycarboxyloxy.

Esterified carboxy is especially lower alkoxy carbonyl, such as tert-butoxycarbonyl, isopropoxy carbonyl, methoxycarbonyl or ethoxycarbonyl, phenyl-lower alkoxy carbonyl, or phenyloxycarbonyl.

Alkanoyl is primarily alkylcarbonyl, especially lower alkanoyl, e.g. acetyl.

N-Mono- or N,N-disubstituted carbamoyl is especially substituted by one or two substituents independently selected from lower alkyl, phenyl-lower alkyl and hydroxy-lower alkyl, or lower alkyne, oxa-lower alkyne or aza-lower alkyne optionally substituted at the terminal nitrogen atom.

A mono- or bicyclic heteroaryl group comprising zero, one, two or three ring nitrogen atoms and zero or one oxygen atom and zero or one sulfur atom, which groups in each case are unsubstituted or mono- or polysubstituted, refers to a heterocyclic moiety that is unsaturated in the ring binding the heteroaryl radical to the rest of the molecule in formula I and is preferably a ring, where in the binding ring, but optionally also in any annealed ring, at least one carbon atom is replaced by a heteroatom selected from the group consisting of nitrogen, oxygen and sulfur; where the binding ring preferably has 5 to 12, more preferably 5 or 6 ring atoms; and which may be unsubstituted or substituted by one or more, especially one or two, substituents selected from the group defined above as substituents for aryl, most preferably by lower alkyl, such as methyl, lower alkoxy, such as methoxy or ethoxy, or hydroxy. Preferably the mono- or bicyclic heteroaryl group is selected from 2H-pyrrolyl, pyrrolyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, purinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 4H-quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalyl,
quinazolinyl, quinnolinyl, pteridinyl, indolizinyl, 3H-indolyl, indolyl, isoindolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, furazanyl, benzo[d]pyrazolyl, thieryl and furanyl. More preferably the mono- or bicyclic heteroaryl group is selected from the group consisting of pyrrolyl, imidazolyl, such as 1H-imidazol-1-yl, benzimidazolyl, such as 1-benzimidazolyl, indazolyl, especially 5-indazolyl, pyridyl, especially 2-, 3- or 4-pyridyl, pyrimidinyl, especially 2-pyrimidinyl, pyrazinyl, isoquinolinyl, especially 3-isoquinolinyl, quinolinyl, especially 4- or 8-quinolinyl, indolyl, especially 3-indolyl, thiazolyl, benzo[d]pyrazolyl, thieryl, and furanyl. In one preferred embodiment of the invention the pyridyl radical is substituted by hydroxy in ortho position to the nitrogen atom and hence exists at least partially in the form of the corresponding tautomer which is pyridin-(1H)2-one. In another preferred embodiment, the pyrimidinyl radical is substituted by hydroxy both in position 2 and 4 and hence exists in several tautomeric forms, e.g. as pyrimidine-(1H, 3H)2,4-dione.

Heterocyclyl is especially a five, six or seven-membered heterocyclic system with one or two heteroatoms selected from the group comprising nitrogen, oxygen, and sulfur, which may be unsaturated or wholly or partly saturated, and is unsubstituted or substituted especially by lower alkyl, such as methyl, phenyl-lower alkyl, such as benzyl, oxo, or heteroaryl, such as 2-piperazinyl; heterocyclyl is especially 2- or 3-pyrrolinyl, 2-oxo-5-pyrrolidinyl, piperidinyl, N-benzyl-4-piperidinyl, N-lower alkyl-4-piperidinyl, N-lower alkyl-piperazinyl, morpholinyl, e.g. 2- or 3-morpholinyl, 2-oxo-1H-azepin-3-yl, 2-tetrahydrofuran-1-yl, or 2-methyl-1,3-dioxolan-2-yl.

Pyrimidylaminobenzamides within the scope of formula I, wherein py is 3-pyridyl and the process for their manufacture are disclosed in WO 04/005281, which is hereby incorporated into the present application by reference.

The pyrimidylaminobenzamide of formula I wherein Py denotes 5-pyrimidyl, \( R_1 \) is hydrogen, \( R_2 \) is \([[(3S)-3-(dimethylamino)-1-pyrrolidinyl]methyl]-3-(trifluoromethyl)phenyl \) and \( R_4 \) is methyl is also known as INNO-406. The compound, its manufacture and pharmaceutically compositions suitable for its administration are disclosed in EP1533304A.

Pharmacetically acceptable salts of pyrimidylaminobenzamides of formula I, wherein py is 3-pyridyl, are especially those disclosed in WO2007/015871. In one preferred
embodiment nilotinib is employed in the form of its monohydrochloride monohydrate. WO2007/015870 discloses certain polymorphs of nilotinib and pharmaceutically acceptable salts thereof useful for the present invention. A suitable formulation for the administration of nilotinib monohydrochloride monohydrate is described in WO2008/037716.

As used herein, the expression "a proliferative disorder or other pathological conditions mediated by Bcr-Abl, c-Kit, DDR1, DDR2 or PDGF-R kinase activity" activity means melanoma, especially melanoma harboring c-KIT mutations, breast cancer, cancer of the colon, lung cancer, cancer of the prostate or Kaposi's sarcoma, gastrointestinal stromal tumors (GIST), acute myeloid leukemia (AML), leukemia which responds to an inhibition of the Abl tyrosine kinase activity, such as chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL), mesothelioma, systemic mastocytosis, hypereosinophilic syndrome (HES), fibrosis, especially hepatic fibrosis and renal fibrosis, rheumatoid arthritis, polyarthritis, scleroderma, lupus erythematosus, graft-versus-host diseases, neurofibromatosis, pulmonary hypertension, especially, pulmonary arterial hypertension, Alzheimer's disease, seminomas and dysgerminomas and psoriasis. Preferably, the regime described herein is applied in the following disorders and conditions: GIST, CML, Ph+ ALL, systemic mastocytosis, HES, fibrosis, scleroderma, neurofibromatosis and pulmonary arterial hypertension.

In one embodiment of the present invention the disorder is selected from CML and Ph+ ALL, more preferably CML.

In another embodiment of the present invention the disorder is selected from GIST and melanoma, especially melanoma harboring c-KIT mutations.

In another embodiment of the present invention the disorder is selected from systemic mastocytosis and HES.

In a further embodiment of the present invention the disorder is selected from systemic scleroderma, neurofibromatosis and pulmonary arterial hypertension.

As used herein, the expression "$C_{\text{max}}$" means maximum peak concentration in plasma.
As used herein, the expression "AUC" means area under the plasma concentration curve.

The language "oral administration of a pyrimidylaminobenzamide of formula I dispersed in a fruit preparation" as used herein preferably means that the compound of formula I alone or together with at least one suitable pharmaceutical carrier is dispersed in a fruit preparation and administered, preferably manually, to the mouth of the human patient with a suitable device, e.g. a spoon. If desired, 100 to 250 ml of water can be consumed together with the fruit preparation.

As used herein, the term "fruit preparation" means a juice, sauce or puree prepared from fruits, more preferably from apples, pears or peaches, most preferably apples. In one preferred embodiment of the invention, the fruit preparation employed is applesauce. Suitable applesauce is available under the brands Andros® applesauce, Mott's® applesauce and Odenwald Apfelmus (Odenwald-Fruchte GmbH, Germany). Grapefruit is known to affect the kinetics of drug up-take in human patients. Hence, the term "fruit preparation" does not encompass any juice, sauce or puree prepared from grapefruit.

For the purposes of the present invention, the total daily dose of nilotinib can be adjusted to the needs of the patients depending, in particular on the disease to be treated and the disease status of the patient under treatment, but in any event will not exceed a total daily dose of 800 mg.

In one embodiment of the invention, the content of two 200 mg nilotinib capsules as disclosed in WO2008/037716 are each dispersed in one teaspoon of applesauce resulting in a single oral administration of 400 mg nilotinib.

Preferably, the mixture of the compound of formula I dispersed in fruit preparation should be taken immediately after its preparation, wherein "immediately" for the purpose of the present invention means within a time frame of 30 minutes, preferably within 15 minutes, more preferably within 5 minutes and most preferably within 2 minutes after preparation.
The present invention further provides a commercial package containing a pyrimidylaminobenzamide of formula \( I \), e.g. nilotinib, as defined herein together with instructions to disperse the pyrimidylaminobenzamide of formula \( I \), e.g. nilotinib, in a fruit preparation.

In a further aspect, the instant invention relates to a pyrimidylaminobenzamide of formula \( I \)

![Chemical Structure](image)

wherein

(a) \( \text{Py} \) denotes 3-pyridyl,

\( R_1 \) represents hydrogen, lower alkyl, lower alkoxy-lower alkyl, acyloxy-lower alkyl, carboxy-lower alkyl, lower alkoxy carbonyl-lower alkyl, or phenyl-lower alkyl;

\( R_2 \) represents hydrogen, lower alkyl, optionally substituted by one or more identical or different radicals \( R_3 \), cycloalkyl, benzocycloalkyl, heterocyclyl, an aryl group, or a mono- or bicyclic heteroaryl group comprising 0-, 1-, 2- or 3-ring nitrogen atoms and 0 or 1 oxygen atom and 0 or 1 sulfur atom, which groups in each case are unsubstituted or mono- or poly-substituted; and

\( R_3 \) represents hydroxy, lower alkoxy, acyloxy, carboxy, lower alkoxy carbonyl, carbamoyl, \( N \)-mono- or \( \text{N}^1/\text{N}^2 \)-di-substituted carbamoyl, amino, mono- or di-substituted amino, cycloalkyl, heterocyclyl, an aryl group, or a mono- or bi-cyclic heteroaryl group comprising 0-, 1-, 2- or 3-ring nitrogen atoms and 0 or 1 oxygen atom and 0 or 1 sulfur atom, which groups in each case are unsubstituted or mono- or poly-substituted; or

\( R_1 \) and \( R_2 \), together, represent alkylene with 4, 5 or 6 carbon atoms optionally mono- or di-substituted by lower alkyl, cycloalkyl, heterocyclyl, phenyl, hydroxy, lower alkoxy, amino, mono- or di-substituted amino, oxo, pyridyl, pyrazinyl or pyrimidinyl; benzalkylene with 4 or 5 carbon atoms; oxalkylene with 1 oxygen and 3 or 4 carbon atoms; or azaalkylene with 1 nitrogen and 3 or 4 carbon atoms, wherein nitrogen is unsubstituted or substituted by lower alkyl, phenyl-lower alkyl, lower alkoxy carbonyl-lower alkyl, carboxy-lower alkyl, carbamoyl-
lower alkyl, W-mono- or N,A/-di-substituted carbamoyl-lower alkyl, cycloalkyl, lower alkoxycarbonyl, carboxy, phenyl, substituted phenyl, pyridinyl, pyrimidinyl or pyrazinyl; 
R₄ represents hydrogen, lower alkyl or halogen; 
or 
(b) Py denotes 5-pyrimidyl, R₁ is hydrogen, R₂ is [[(3S)-3-(dimethylamino)-1-pyrrolidinyl]-methyl]-3-(trifluoromethyl)phenyl and R₄ is methyl; 
or a pharmaceutically acceptable salt thereof, for the treatment of a proliferative disorder or other pathological conditions mediated by Bcr-Abl, c-Kit, DDR1, DDR2 or PDGF-R kinase activity, wherein the compound of formula (I) or a pharmaceutically acceptable salt thereof and, optionally, pharmaceutically acceptable carriers, are dispersed in a fruit preparation, 

Furthermore, the instant invention pertains to the use of a pyrimidylaminobenzamide of formula I

![Chemical Structure](image)

wherein 
(a) Py denotes 3-pyridyl, 
R₁ represents hydrogen, lower alkyl, lower alkoxy-lower alkyl, acyloxy-lower alkyl, carboxylower alkyl, lower alkoxycarbonyl-lower alkyl, or phenyl-lower alkyl; 
R₂ represents hydrogen, lower alkyl, optionally substituted by one or more identical or different radicals R₃, cycloalkyl, benzycycloalkyl, heterocyclyl, an aryl group, or a mono- or bicyclic heteroaryl group comprising 0-, 1-, 2- or 3-ring nitrogen atoms and 0 or 1 oxygen atom and 0 or 1 sulfur atom, which groups in each case are unsubstituted or mono- or polysubstituted; and 
R₃ represents hydroxy, lower alkoxy, acyloxy, carboxy, lower alkoxycarbonyl, carbamoyl, N-mono- or N,V-di-substituted carbamoyl, amino, mono- or di-substituted amino, cycloalkyl, heterocyclyl, an aryl group, or a mono- or bi-cyclic heteroaryl group comprising 0-, 1-, 2- or
3-ring nitrogen atoms and 0 or 1 oxygen atom and 0 or 1 sulfur atom, which groups in each case are unsubstituted or mono- or poly-substituted; or

R₁ and R₂, together, represent alkylene with 4, 5 or 6 carbon atoms optionally mono- or di-substituted by lower alkyl, cycloalkyl, heterocyclyl, phenyl, hydroxy, lower alkoxy, amino, mono- or di-substituted amino, o xo, pyridyl, pyrazinyl or pyrimidinyl; benzalkylene with 4 or 5 carbon atoms; oxalkylene with 1 oxygen and 3 or 4 carbon atoms; or azaalkylene with 1 nitrogen and 3 or 4 carbon atoms, wherein nitrogen is unsubstituted or substituted by lower alkyl, phenyl-lower alkyl, lower alkoxy carbonyl-lower alkyl, carboxy-lower alkyl, carbamoyl-lower alkyl, A/-mono- or AV-di-substituted carbamoyl-lower alkyl, cycloalkyl, lower alkoxy carbonyl, carboxy, phenyl, substituted phenyl, pyridinyl, pyrimidinyl or pyrazinyl;

R₄ represents hydrogen, lower alkyl or halogen; or

(b) Py denotes 5-pyrimidyl, R₁ is hydrogen, R₂ is [((3S)-3-(dimethylamino)-1-pyrrolidinyl]-methyl]-3-(trifluoromethyl)phenyl and R₄ is methyl;

or a pharmaceutically acceptable salt thereof,

for the manufacture of a medicament for the treatment of a proliferative disorder or other pathological conditions mediated by Bcr-Abl, c-Kit, DDR1, DDR2 or PDGF-R kinase activity, wherein the medicament is designated to be dispersed in a fruit preparation, optionally together with pharmaceutically acceptable carriers, and orally administered to a human patient in need thereof.

EXAMPLES

Example 1: In vitro stability tests

The content of nilotinib capsules prepared as disclosed in WO2008/037716 is dispersed in yogurt or applesauce. It is shown that nilotinib is stable at room temperature for 15 minutes with mean nilotinib recovery between 97.6 to 99.9 %.

Example 2: Randomized, open label, three-period crossover single-center study in 48 healthy subjects comparing the bioavailability of nilotinib when administered as intact capsule or the capsule content mixed with yogurt or applesauce in healthy volunteers (HV)
The HV between 18 and 65 years obtain under fasted conditions either a single oral administration of 400 mg nilotinib with two intact 200 mg nilotinib capsules (treatment A); a single oral administration of 400 mg nilotinib with the content of two 200 mg nilotinib capsules each dispersed in one teaspoon of non-fat plain yogurt (treatment B); or a single oral administration of 400 mg nilotinib with the content of two 200 mg nilotinib capsules each dispersed in one teaspoon of applesauce (treatment C). Serial blood samples for serum nilotinib concentration determination are collected for up to 72 hours after each nilotinib administration. All treatments were administered with 240 ml of water, in the morning, after an overnight fast of at least 10 hours. Subjects continued to fast until 4 hours after administration. Standardized meals were served at 4 hours (lunch) and 10 hours (dinner) after nilotinib administration. Consumption of grapefruit, grapefruit juice, or any caffeinated beverages within 48 hours of study initiation was prohibited.

Serum nilotinib concentrations were determined from blood samples collected at pre-dose (0 hour) and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, and 72 hours post-nilotinib administration on days 1, 13, and 25. At each time point, 2.5 mL of whole blood was drawn using a Serum Separator Vacutainer® (Becton, Dickinson and Company, Franklin Lakes, New Jersey, USA) tube. The tube was allowed to stand vertically at room temperature for 30 minutes prior to centrifugation at 5°C for 10 minutes at 1100 g. Immediately after centrifugation, the upper serum sample was transferred and stored frozen at ≤-15°C until shipped to the analytical site for sample analyses.

Serum concentrations of nilotinib were measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay as described previously, with slight modifications (Larson RA, le Coutre PD, Reiffers J et al. J Clin Oncol 28:7s, 2010 (suppl; abstr 6501)). Nilotinib and the internal standard, [M+4]nilotinib, were extracted from a 100 µL serum sample with 700 pL of methyl tertiary-butyl ether (MTBE). The MTBE layer was transferred, evaporated to dryness, and reconstituted with 400 µL of an acetonitrile and 0.2% formic acid mixture (40:60, v/v). Chromatography was carried out using a Phenomenex Synergi™ Polar-RP column (particle size 4 µm, 50 mm x 2 mm i.d.) (Phenomenex, Inc, Torrance, California) held at room temperature. Elution of the analytes was performed using an isocratic elution at a flow rate of 0.5 ml/min with mobile phases of 0.2% formic acid in 10 mM aqueous ammonium formate : 0.2% formic acid in acetonitrile (60:40, v/v). Detection was performed by MS/MS in positive ion mode on a Sciex API4000 mass spectrometer.
(Applied Biosystem, USA) with multiple reaction monitoring of m/z 530→289 for nilotinib and 534→293 for the internal standard. The lower limit of quantification for nilotinib was 2.50 ng/mL using a 100 µL serum sample. Precision of the assay at each QC level was <11% and the accuracy ranged from 95.2% to 104.3%.

Following the administration of a single oral dose of 400-mg nilotinib as two 200-mg intact capsules, the peak serum concentration of nilotinib occurred at a median time (t_{\text{max}}) of 4.0 hours, and the C_{\text{max}} values averaged 398 ng/mL. The mean t_{\text{1/2}} of nilotinib was found to be 19.8 hours. These results are in agreement with those observed in previous studies in healthy volunteers who received a same 400-mg oral dose of nilotinib as intact capsules.

Compared with the administration of 400-mg nilotinib as two 200-mg intact capsules (Treatment A), the systemic exposure of nilotinib was found to be generally higher following the administration of nilotinib as two capsule contents (400 mg) mixed with yogurt (Treatment B). The geometric mean values of C_{\text{max}}, AUC_{0\text{-tail}}, and AUC_{0\text{-inf}} of nilotinib were increased by 31%, 11%, and 8% respectively. The 90% CIs of the geometric mean ratio (Treatment B vs A) of nilotinib C_{\text{max}}, AUC_{0\text{-t}}, and AUC_{0\text{-inf}} were 1.22-1.41, 1.05-1.06, and 1.02-1.15, respectively.

Administration of the contents of two nilotinib capsules (400 mg) dispersed in applesauce (Treatment C), showed similar exposure compared with administration of nilotinib as intact capsules (Treatment A). The geometric mean ratio (Treatment C vs A) of nilotinib C_{\text{max}}, AUC_{0\text{-t}}, and AUC_{0\text{-inf}} was 0.95, 0.99, and 0.97 respectively, and the corresponding 90% CIs were 0.88-1.02, 0.94-1.04, and 0.90-1.03 respectively.

The results are summarized in Table 1.

**Table 1: Study Results**

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<td>Treatment A</td>
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<td>(intact capsule)</td>
<td>(mixed with yogurt)</td>
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<td>t_{\text{max}} (h)</td>
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<td>C_{\text{max}} (ng/mL)</td>
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The studies allow the following conclusions:

- Single oral administration of 400 mg niotinib, with two 200 mg niotinib capsules content, each dispersed in one teaspoon of non-fat plain yogurt is not bioequivalent to a single oral administration of 400 mg niotinib given as intact capsules.

- Single oral administration of 400 mg niotinib, with two 200 mg niotinib capsules content, each dispersed in one teaspoon of applesauce is bioequivalent to a single oral administration of 400 mg niotinib given as intact capsules.

The studies also show that the administration of niotinib in a fruit preparation is safe and well tolerated by human subjects.
We claim:

1. A method of treating a proliferative disorder or other pathological conditions mediated by Bcr-Abl, c-Kit, DDR1, DDR2 or PDGF-R kinase activity comprising oral administration of an effective dose of a pyrimidylaminobenzamide of formula (I):

![Chemical Structure](image)

wherein

(a) Py denotes 3-pyridyl,

R₁ represents hydrogen, lower alkyi, lower alkoxy-lower alkyi, acyloxy-lower alkyi, carboxy-lower alkyi, lower alkoxy carbonyl-lower alkyi, or phenyl-lower alkyi;

R₂ represents hydrogen, lower alkyi, optionally substituted by one or more identical or different radicals R₃, cycloalkyl, benzycloalkyl, heterocyclyl, an aryl group, or a mono- or bicyclic heteroaryl group comprising 0-, 1-, 2- or 3-ring nitrogen atoms and 0 or 1 oxygen atom and 0 or 1 sulfur atom, which groups in each case are unsubstituted or mono- or poly-substituted; and

R₃ represents hydroxy, lower alkoxy, acyloxy, carboxy, lower alkoxy carbonyl, carbamoyl, N-mono- or A/A'-di-substituted carbamoyl, amino, mono- or di-substituted amino, cycloalkyl, heterocyclyl, an aryl group, or a mono- or bi-cyclic heteroaryl group comprising 0-, 1-, 2- or 3-ring nitrogen atoms and 0 or 1 oxygen atom and 0 or 1 sulfur atom, which groups in each case are unsubstituted or mono- or poly-substituted; or

R₁ and R₂, together, represent alkyene with 4, 5 or 6 carbon atoms optionally mono- or di-substituted by lower alkyi, cycloalkyl, heterocyclyl, phenyl, hydroxy, lower alkoxy, amino, mono- or di-substituted amino, oxo, pyridyl, pyrazinyl or pyrimidinyl; benzalkylene with 4 or 5 carbon atoms; oxaaalkylene with 1 oxygen and 3 or 4 carbon atoms; or azaalkylene with 1 nitrogen and 3 or 4 carbon atoms, wherein nitrogen is unsubstituted or substituted by lower alkyi, phenyl-lower alkyi, lower alkoxy carbonyl-lower alkyi, carboxy-lower alkyi, carbamoyl-lower alkyi, /V-mono- or N./V-di-substituted carbamoyl-lower alkyi, cycloalkyl,
lower alkoxy carbonyl, carboxy, phenyl, substituted phenyl, pyridinyl, pyrimidinyl or pyrazinyl;

R_4 represents hydrogen, lower alkyl or halogen;
or

(b) Py denotes 5-pyrimidyl, R_1 is hydrogen, R_2 is [[(3S)-3-(dimethylamino)-1-pyrrolidinyl]-methyl]-3-(trifluoromethyl)phenyl and R_4 is methyl;
or a pharmaceutically acceptable salt thereof, and, optionally, pharmaceutically acceptable carriers, dispersed in a fruit preparation, to a human patient in need thereof.

2. The method according to claim 1, wherein the pyrimidylaminobenzamide is 4-methyl-3-[4-(3-pyridinyl)-2-pyrimidinyl]amino]-N-[5-(4-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)-phenyl] benzamide.

3. The method according to claim 2, wherein the pyrimidylaminobenzamide is employed in the form of its hydrochloride monohydrate.

4. The method according to any one of claims 1 to 3, wherein the proliferative disorder or other pathological condition is selected from melanoma, breast cancer, cancer of the colon, lung cancer, cancer of the prostate or Kaposi’s sarcoma, gastrointestinal stromal tumors (GIST), acute myeloid leukemia (AML), leukemia which responds to an inhibition of the Abl tyrosine kinase activity, mesothelioma, systemic mastocytosis, hypereosinophilic syndrome (HES), fibrosis, rheumatoid arthritis, polyarthritis, scleroderma, lupus erythematosus, graft-versus host diseases, neurofibromatosis, pulmonary hypertension, Alzheimer’s disease, seminomas and dysgerminomas and psoriasis.

5. The method according to any one of claims 1 to 3, wherein the proliferative disorder or other pathological condition is selected from GIST, CML, Ph+ ALL, systemic mastocytosis, HES, fibrosis, scleroderma, neurofibromatosis and pulmonary arterial hypertension.

6. The method according to claim 1, wherein the human patient is a elderly or a pediatric patient.
7. The method according to claim 1, wherein the fruit preparation is a juice, sauce or puree prepared from fruits.

8. The method according to claim 1, wherein the fruit preparation is applesauce.

9. A commercial package containing a pyrimidylaminobenzamide of formula I

\[
\begin{align*}
\text{Py} & \quad N \\
N & \quad \text{R4} \\
& \quad \text{R1} \\
& \quad \text{R2} \\
& \quad \text{N} \\
& \quad \text{O}
\end{align*}
\]

wherein
  (a) Py denotes 3-pyridyl,
  \(R_1\) represents hydrogen, lower alkyl, lower alkoxy-lower alkyl, acyloxy-lower alkyl, carboxy-lower alkyl, lower alkoxy carbonyl-lower alkyl, or phenyl-lower alkyl;
  \(R_2\) represents hydrogen, lower alkyl, optionally substituted by one or more identical or different radicals \(R_3\), cycloalkyl, benz cycloalkyl, heterocyclic, an aryl group, or a mono- or bicyclic heteroaryl group comprising zero, one, two or three ring nitrogen atoms and zero or one oxygen atom and zero or one sulfur atom, which groups in each case are unsubstituted or mono- or polysubstituted; and
  \(R_3\) represents hydroxy, lower alkoxy, acyloxy, carboxy, lower alkoxy carbonyl, carbamoyl, \(N\)-mono- or \(N,N\)-disubstituted carbamoyl, amino, mono- or disubstituted amino, cycloalkyl, heterocyclic, an aryl group, or a mono- or bicyclic heteroaryl group comprising zero, one, two or three ring nitrogen atoms and zero or one oxygen atom and zero or one sulfur atom, which groups in each case are unsubstituted or mono- or polysubstituted; and
  or wherein \(R_1\) and \(R_2\) together represent alkylene with four, five or six carbon atoms optionally mono- or disubstituted by lower alkyl, cycloalkyl, heterocyclic, phenyl, hydroxy, lower alkoxy, amino, mono- or disubstituted amino, oxo, pyridyl, pyrazinyl or pyrimidinyl; benzalkylene with four or five carbon atoms; ox aalkylene with one oxygen and three or four carbon atoms; or azaalkylene with one nitrogen and three or four carbon atoms wherein nitrogen is unsubstituted or substituted by lower alkyl, phenyl-lower alkyl, lower alkoxy carbonyl-lower alkyl, carboxy-lower alkyl, carbamoyl-lower alkyl, \(N\)-monob- or \(N,N\)-
disubstituted carbamoyl-lower alkyi, cycloalkyi, lower alkoxy carbonyl, carboxy, phenyl, substituted phenyl, pyridinyl, pyrimidinyl, or pyrazinyl.

R₄ represents hydrogen, lower alkyi, or halogen;

wherein the prefix "lower" denotes a radical having up to and including a maximum of 7 carbon atoms,

or

(b) Py denotes 5-pyrimidyl, R₁ is hydrogen, R₂ is [[[(3S)-3-(dimethylamino)-1-pyrrolidinyl]-methyl]-3-(trifluoromethyl)phenyl and R₄ is methyl;

or a pharmaceutically acceptable salt thereof, respectively,

together with instructions to disperse the compound of formula I or a pharmaceutically acceptable salt thereof in a fruit preparation.

10. A pyrimidylaminobenzamide of formula I

\[
\text{Py} \quad \text{N} \quad \text{NH} \\
\quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \qua
R₁ and R₂, together, represent alkylene with 4, 5 or 6 carbon atoms optionally mono- or di-substituted by lower alkyl, cycloalkyl, heterocyclyl, phenyl, hydroxy, lower alkoxy, amino, mono- or di-substituted amino, oxo, pyridyl, pyrazinyl or pyrimidinyl; benzalkylene with 4 or 5 carbon atoms; oxalkylene with 1 oxygen and 3 or 4 carbon atoms; orazaalkylene with 1 nitrogen and 3 or 4 carbon atoms, wherein nitrogen is unsubstituted or substituted by lower alkyl, phenyl-lower alkyl, lower alkoxy carbonyl-lower alkyl, carboxy-lower alkyl, carbamoyl-lower alkyl, A-/mono- or A//V-di-substituted carbamoyl-lower alkyl, cycloalkyl, lower alkoxy carbonyl, carboxy, phenyl, substituted phenyl, pyridinyl, pyrimidinyl or pyrazinyl;
R₄ represents hydrogen, lower alkyl or halogen;

or

(b) Py denotes 5-pyrimidyl, R₁ is hydrogen, R₂ is [[(3S)-3-(dimethylamino)-1-pyrrolidinyl]-methyl]-3-(trifluoromethyl)phenyl and R₄ is methyl;
or a pharmaceutically acceptable salt thereof, for the treatment of a proliferative disorder or other pathological conditions mediated by Bcr-Abl, c-Kit, DDR1, DDR2 or PDGF-R kinase activity, wherein the compound of formula (I) or a pharmaceutically acceptable salt thereof and, optionally, pharmaceutically acceptable carriers, are dispersed in a fruit preparation.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A61K31/506 A61P35/00 A61K9/00

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

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, BIOSIS, CHEM ABS Data, EMBASE, WPI Data, BEILSTEIN Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of Box C. See patent family 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
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*"I" 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 to involve an inventive step when the document is taken alone

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"A" document member of the same patent family

Date of the actual completion of the international search: 10 February 2011

Date of mailing of the international search report: 21/02/2011

Authorized officer: Garabatos-Perera, J

Form PCT/ISA/2010 (second sheet) (April 2005)
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