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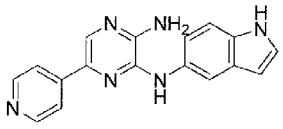

(I)

(57) Abstract: The present invention relates to a compound according to formula (I) in crystalline form and a process for making said crystalline form. The invention also concerns a method of making the compound according to formula (I) in amorphous form, said amorphous form may be used as a starting material for making the crystalline form of the compound of formula (I).

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PROCESSES FOR MANUFACTURING OF A KINASE INHIBITOR

TECHNICAL FIELD

The present invention relates to a novel process for the manufacture of the compound N-3-(1 H-indol-5-yl)-5-pyridin-4-yl-pyrazine-2,3-diamine, useful in large scale production. The present invention also relates to N-3-(1H-indol-5-yl)-5-pyridin-4-yl-pyrazine-2,3-diamine in crystalline form, a method for producing said crystalline form and uses thereof.

BACKGROUND OF THE INVENTION

Protein kinases are involved in the regulation of cellular metabolism, proliferation, differentiation and survival. The FLT-3 (fms-like tyrosine kinase) receptor is a member of the class III subfamily of receptor tyrosine kinases and has been shown to be involved in various disorders such as haematological disorders, proliferative disorders, autoimmune disorders and skin disorders.

In order to function effectively as an inhibitor, a kinase inhibitor needs to have a certain profile regarding its target specificity and mode of action. Depending on factors such as the disorder to be treated, mode of administration etc. the kinase inhibitor will have to be designed to exhibit suitable properties. For instance, compounds exhibiting a good plasma stability are desirable since this will provide a pharmacological effect of the compounds extending over time. Another example is oral administration of the inhibitor which may require that the inhibitor is transformed into a prodrug in order to improve the bioavailability.

WO 2009/095399 discloses pyrazine compounds acting as inhibitors of protein kinases, especially FTL3, useful in the treatment of haematological disorders, proliferative disorders, autoimmune disorders and skin disorders. This document discloses methods for manufacturing such compounds. However these methods are not suitable for large scale processes and the chemical yields are moderate. Furthermore, the compounds obtained by these methods are in amorphous form.

Pharmaceutical solids can exist in different forms, such as crystalline, amorphous, or glass and also in solvated or hydrated forms. A polymorph is a solid crystalline phase of a

compound resulting from the possibility of at least two crystalline arrangements of the molecules of that compound in the solid state.

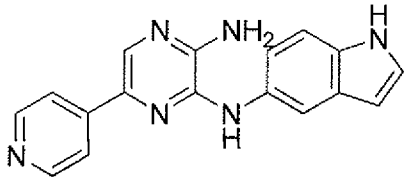
It is a well-known fact that different forms of the same drug may provide differences in certain pharmaceutically important physicochemical properties, such as stability, solubility, dissolution rate, crystal habit and tableting behavior. Changes in certain of these physiochemical properties may ultimately affect the bioavailability of the drug.

BRIEF DESCRIPTION OF THE FIGURE

Figure 1 shows an X-ray powder diffraction (XRPD) spectrum of the compound according to formula (I) in crystalline form.

DETAILED DESCRIPTION

In one aspect of the invention, there is provided a process for preparing a compound of formula (I)



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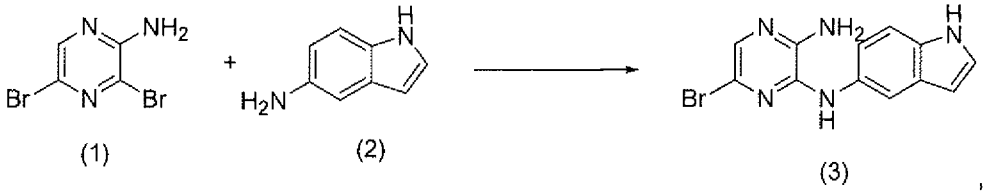
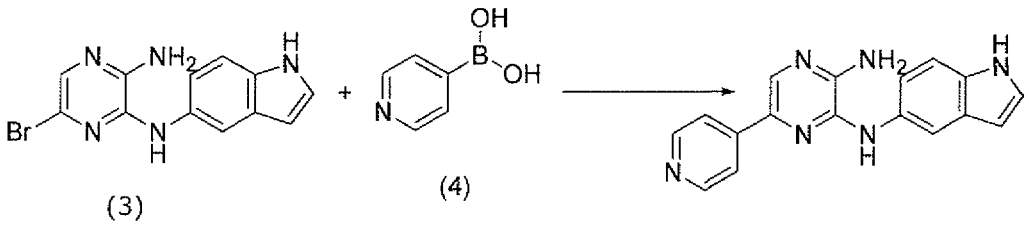
said process comprises the steps of:

a) reacting a compound of formula (1) with a compound of formula (2) in an inert solvent and in the presence of an $(C_{1-6}alkyl)_3amine$, providing a compound of formula (3):



(1) (2) (3)

b) Suzuki coupling of a compound of formula (3) and a compound of formula (4) in an inert solvent and in the presence of a palladium catalyst and a base, providing a crude product comprising a compound of formula (I) and palladium



(3) (4) (I)

and

c) removing the palladium from the crude product in step b).

In one aspect of the invention, there is provided a process as described herein, wherein step c) comprises treatment of the crude product with a palladium scavenger comprising thiol groups.

In one aspect of the invention, there is provided a process as described herein, wherein the palladium scavenger comprises L-cysteine.

In one aspect of the invention, there is provided a process as described herein, wherein the palladium scavenger comprises trithiocyanuric acetic acid.

In one aspect of the invention, there is provided a process as described herein, wherein the palladium scavenger comprises charcoal.

In one aspect of the invention, there is provided a process as described herein, wherein the palladium scavenger comprises trithiocyanuric acetic acid and 3-mercaptopropyl ethyl sulfide silica. These scavengers allow for removing virtually all palladium in the crude product of N-3-(1H-indol-5-yl)-5-pyridin-4-yl-pyrazine-2,3-diamine formed in the process described herein.

In one aspect of the invention, there is provided a process as described herein, wherein the palladium scavenger comprises L-cysteine, trithiocyanuric acetic acid and 3-mercaptopropyl ethyl sulfide silica.

In one aspect of the invention, there is provided a process as described herein, wherein the palladium scavenger comprises trithiocyanuric acetic acid, 3-mercaptopropyl ethyl sulfide silica and 2-mercaptoethyl ethyl sulfide silica.

In one aspect of the invention, there is provided a process as described herein, wherein the palladium catalyst comprises $Pd(OAc)_2$.

In one aspect of the invention, there is provided a process as described herein, wherein the palladium catalyst comprises $Pd(OAc)_2$ and DTP-PPS.

In one aspect of the invention, there is provided a process as described herein, wherein the palladium catalyst comprises Pd(dppf).

In one aspect of the invention, there is provided a process as described herein, wherein the solvent in step a) is 1-ethyl-2-pyrrolidone (NEP). The use of NEP as solvent allows for obtaining the compound of formula (3) in high yield and high purity. An advantage of using NEP is also that it is highly compatible with triethylamine.

In one aspect of the invention, the solvent in step a) is DMSO.

In one aspect of the invention, there is provided a process as described herein, wherein the base in step a) is triethyl amine (TEA).

In one aspect of the invention, there is provided a process as described herein, wherein the solvent in step b) is DMA. The use of DMA has the advantage that it is compatible with the palladium scavenger L-cysteine.

in one aspect of the invention, the solvent in step b) is DMF.

In one aspect of the invention, there is provided a process as described herein, wherein the base in step b) is K_2C0_3.

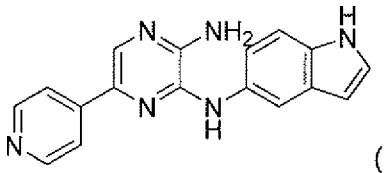
In one aspect of the invention, there is provided a process as described herein, further comprising a step d) subsequent to step c) wherein the crude product is filtered. For instance, filtering may take place using hyflo super cel.

In an embodiment of the invention, there is provided a method as described herein wherein step a) is performed in NEP using triethylamine as base and $Pd(OAc)_2$ x

DTB-PPS as catalyst, and step b) is performed in DMA using K_2C0_3 as base. Heating may take place in step a) and/or step b).

In an embodiment of the invention, there is provided a method as described herein wherein step a) is performed in DMSO using triethyiamine as base and Pd(dppf) as catalyst, and step b) is performed in DMF using K_2C0_3 as base. Heating may take place in step a) and/or step b).

In a further aspect of the invention, there is provided a crystalline form of a compound according to formula (I),



(I).

The compound of formula (I) has the chemical name N-3-{1 H-indol-5-yl)-5-pyridin-4-yl-pyrazine-2,3-diamine.

In a further aspect of the invention, there is provided a crystalline form of a compound according to formula (1) as described herein, characterized in that said crystalline form has an XRPD pattern with at least one peak at about 25.5 º 2Θ.

In a further aspect of the invention, there is provided a crystalline form of a compound according to formula (I) as described herein, characterized in that said crystalline form has an XRPD pattern with at least two peaks at about 25.5 º 2Θ and about 18.7 º 2Θ.

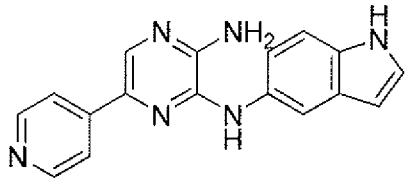
In a further aspect of the invention, there is provided a crystalline form of a compound according to formula (I) as described herein, characterized in that said crystalline form has an XRPD pattern with at least three peaks at about 25.5 º 2Θ and about 18.7 º 2Θ and about 23.4 º 2Θ.

In a further aspect of the invention, there is provided a crystalline form of a compound according to formula (I) as described herein, characterized in that said

crystalline form has an XRPD pattern with at least four peaks at about 25.5 ^{0} 2Θ and about 18.7 ^{0} 2Θ and about 23.4 ^{0} 2Θ and about 9.8 ^{0} 2Θ.

In a further aspect of the invention, there is provided a crystalline form of a compound according to formula (i) as described herein, characterized by the XRDP pattern essentially shown in Figure 1.

In an aspect of the invention, there is provided a process for preparing a compound according to formula (I)



(I)

in crystalline form wherein said process comprises the step of:

i) adding a compound according to formula (I) in amorphous form to acetic acid;

ii) adding potassium hydroxide to the mixture formed in i) thereby precipitating the compound of formula (I) in crystalline form, and

iii) removing the crystalline form of the compound according to formula (I) from the mixture of step ii).

in yet an aspect of the invention, there is provided a compound according to formula (I) in crystalline form as described herein for use in therapy.

In yet an aspect of the invention, there is provided a compound according to formula (1) in crystalline form as described herein for use in the treatment of haematological diseases, proliferative disorders, cancer, autoimmune disorders and skin disorders.

In yet an aspect of the invention, there is provided a compound according to formula (I) in crystalline form as described herein for use in the prophylaxis of haematological diseases, proliferative disorders, cancer, autoimmune disorders and skin disorders.

In yet an aspect of the invention, there is provided a compound according to formula (I) in crystalline form as described herein for use in the treatment of haematoiogical diseases.

In yet an aspect of the invention, there is provided a compound according to formula (I) in crystalline form as described herein for use in the prophylaxis of haematoiogical diseases.

In yet an aspect of the invention, there is provided a compound according to formula (I) in crystalline form as described herein for use in the treatment of leukemia such as such as acute myeloic leukemia (AML), mixed lineage leukemia (MLL), T-cell type acute lymphocytic leukemia (T-ALL), B-cell type acute lymphocytic leukemia (B_ALL) and chronic myelomonocytic leukemia (CMML), the proliferative disorder is cancer, and the autoimmune disorder is selected from psoriasis and atopic dermatitis.

In yet an aspect of the invention, there is provided a compound according to formula (I) in crystalline form as described herein for use in the prophylaxis of leukemia such as acute myeloic leukemia (AML), mixed lineage leukemia (MLL), T-cell type acute lymphocytic leukemia (T-ALL), B-cell type acute lymphocytic leukemia (B_ALL) and chronic myelomonocytic leukemia (CMML), the proliferative disorder is cancer, and the autoimmune disorder is selected from psoriasis and atopic dermatitis..

In yet an aspect of the invention, there is provided a compound according to formula (I) in crystalline form as described herein for use in the treatment of acute myeloid leukemia

In yet an aspect of the invention, there is provided a compound according to formula (I) in crystalline form as described herein for use in the prophylaxis of acute myeloid leukemia

In yet an aspect of the invention, there is provided a compound according to formula (1) in crystalline form as described herein for the manufacture of a medicament for use in the treatment of haematoiogical diseases, proliferative disorders, cancer, autoimmune disorders and skin disorders.

In yet an aspect of the invention, there is provided a compound according to formula (I) in crystalline form as described herein for the manufacture of a medicament for use in the prophylaxis of haematologicai diseases, proliferative disorders, cancer, autoimmune disorders and skin disorders.

In yet an aspect of the invention, there is provided a compound according to formula (I) in crystalline form as described herein for the manufacture of a medicament fo use in the treatment of haematologicai diseases.

In yet an aspect of the invention, there is provided a compound according to formula (I) in crystalline form as described herein for the manufacture of a medicament fo use in the prophylaxis of haematologicai diseases.

In yet an aspect of the invention, there is provided a compound according to formula (I) in crystalline form as described herein for the manufacture of a medicament for use in the treatment of leukemia such as acute myeloic leukemia (AML), mixed lineage leukemia (MLL), T-cell type acute lymphocytic leukemia (T-ALL), B-cell type acute lymphocytic leukemia (B_ALL) and chronic myeiomonocytic leukemia (CMML), the proliferative disorder is cancer, and the autoimmune disorder is selected from psoriasis and atopic dermatitis.

In yet an aspect of the invention, there is provided a compound according to formuia (I) in crystalline form as described herein for the manufacture of a medicament for use in the prophylaxis of leukemia such as acute myeloic leukemia (AML), mixed lineage leukemia (MLL), T-cell type acute lymphocytic leukemia (T-ALL), B-cell type acute lymphocytic leukemia (B_ALL) and chronic myeiomonocytic leukemia (CMML), the proliferative disorder is cancer, and the autoimmune disorder is selected from psoriasis and atopic dermatitis.

In yet an aspect of the invention, there is provided a compound according to formula (I) in crystalline form as described herein for the manufacture of a medicament for use in the treatment of acute myeloid leukemia

In yet an aspect of the invention, there is provided a compound according to formula (I) in crystalline form as described herein for the manufacture of a medicament for use in the prophylaxis of acute myeloid leukemia

In still a further aspect, there is provided a method for treating haematological diseases, proliferative disorders, cancer, autoimmune disorders and skin disorders in a patient, comprising administering to said patient in need of such treatment a therapeutic effective amount of a compound according to formula (I) in crystalline form as described herein.

In still a further aspect, there is provided a method for preventing haematological diseases, proliferative disorders, cancer, autoimmune disorders and skin disorders in a patient, comprising administering to said patient in need of such prevention a therapeutic effective amount of a compound according to formula (I) in crystalline form as described herein.

In still a further aspect, there is provided a method for treating of haematological diseases in a patient, comprising administering to said patient in need of such treatment a therapeutic effective amount of a compound according to formula (I) in crystalline form as described herein.

In still a further aspect, there is provided a method for preventing haematological diseases in a patient, comprising administering to said patient in need of such prevention a therapeutic effective amount of a compound according to formula (I) in crystalline form as described herein.

In still a further aspect, there is provided a method as described herein, wherein the haematological disease is leukemia such as acute myeloic leukemia (AWL), mixed lineage leukemia (MLL), T-cell type acute lymphocytic leukemia (T-ALL), B-cell type acute lymphocytic leukemia (B__ALL) and chronic myelomonocytic leukemia (CMML), the proliferative disorder is cancer, and the autoimmune disorder is selected from psoriasis and atopic dermatitis.

In still a further aspect, there is provided a method as described herein, wherein the haematological disease is acute myeloid leukemia.

In still a further aspect, there is provided a method as described herein further comprising administering of at least one anti-cancer compound.

In still a further aspect, there is provided a method as described herein, wherein the compound of formula (I) in crystalline form is administered simultaneously as the at least one anti-cancer compound.

In still a further aspect, there is provided a method as described herein, wherein the compound of formula **(I)** in crystalline form is administered after the administration of the at least one anti-cancer compound.

In still a further aspect, there is provided a method as described herein, wherein the compound of formula **(1)** in crystalline form is administered before the administration of the at least one anti-cancer compound.

In still a further aspect, there is provided a method as described herein, wherein the at least one anti-cancer compound is cytarabine.

In still a further aspect, there is provided a method as described herein, wherein the at least one anti-cancer compound is daunorubicin.

In still an aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula **(I)** in crystalline form as described herein in admixture with a pharmaceutically acceptable adjuvant, diluent and/or carrier.

In still an aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula **(I)** in crystalline form as described herein. The pharmaceutical composition may further comprise at least one anti-cancer compound. The pharmaceutical composition may comprise pharmaceutically acceptable adjuvants, diluents and/or carriers.

The term "composition" is intended to include the formulation of the active component or a pharmaceutically acceptable salt with a pharmaceutically acceptable carrier. For example this invention may be formulated by means known

in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols or nebulisers for inhalation, and for parenteral use (including intravenous, intramuscular or infusion sterile aqueous or oily solutions or suspensions or sterile emulsions.

The pharmaceuticai compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oiiy suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs.

In an aspect of the invention, there is provided a combination of a compound of formula (I) in crystalline form as described herein and at least one anti-cancer compound.

In an aspect of the invention, there is provided a combination as described herein, wherein the combination is a fix combination.

As used herein, a fix combination is understood to mean a combination or fixed-dose combination in which two or more drugs are combined in a single dosage form. The drugs may be combined in certain fixed doses. Examples of dosage forms suitable in fix combinations include pharmaceutical formulations and two-compartment systems.

In an aspect of the invention, there is provided a combination as described herein, wherein the at least one anti-cancer compound is cytarabine.

In an aspect of the invention, there is provided a combination as described herein, wherein the at least one anti-cancer compound is daunorubicin.

In an aspect of the invention, there is provided a combination as described herein for use in therapy.

In an aspect of the invention, there is provided a combination as described herein, for treating of haematoiogical diseases, proliferative disorders, cancer, autoimmune disorders and skin disorders.

In an aspect of the invention, there is provided a combination as described herein, for preventing haematoiogical diseases, proliferative disorders, cancer, autoimmune disorders and skin disorders.

In an aspect of the invention, there is provided a combination as described herein, for treating haematoiogical diseases.

In an aspect of the invention, there is provided a combination as described herein, for preventing haematoiogical diseases.

In an aspect of the invention, there is provided a combination as described herein, for treating leukemia such as acute myeloic leukemia (AML), mixed lineage leukemia (MLL), T-cell type acute lymphocytic leukemia (T-ALL), B-celf type acute lymphocytic leukemia (B_ALL) and chronic myeiomonocytic leukemia (CMML), the proliferative disorder is cancer, and the autoimmune disorder is selected from psoriasis and atopic dermatitis.

In an aspect of the invention, there is provided a combination as described herein, for preventing leukemia such as acute myeloic leukemia (AML), mixed lineage leukemia (MLL), T-ceil type acute lymphocytic leukemia (T-ALL), B-cell type acute lymphocytic leukemia (B_ALL) and chronic myeiomonocytic leukemia (CMML), the proliferative disorder is cancer, and the autoimmune disorder is selected from psoriasis and atopic dermatitis.

In an aspect of the invention, there is provided a combination as described herein, for treating acute myeloic leukemia.

In an aspect of the invention, there is provided a combination as described herein, for preventing acute myeloic leukemia.

In an aspect of the invention, there is provided a combination as described herein, for the manufacture of a medicament for use in treating of haematologicai diseases, proliferative disorders, cancer, autoimmune disorders and skin disorders.

In an aspect of the invention, there is provided a combination as described herein, for the manufacture of a medicament for use in preventing haematologicai diseases, proliferative disorders, cancer, autoimmune disorders and skin disorders.

In an aspect of the invention, there is provided a combination as described herein, for the manufacture of a medicament for use in treating of haematologicai diseases.

In an aspect of the invention, there is provided a combination as described herein, for the manufacture of a medicament for use in preventing haematologicai diseases.

In an aspect of the invention, there is provided a combination as described herein, for the manufacture of a medicament for use in treating leukemia such as acute myeloic leukemia (AML), mixed lineage leukemia (MLL), T-cell type acute lymphocytic leukemia (T-ALL), B-cell type acute lymphocytic leukemia (B_ALL) and chronic myelomonocytic leukemia (CMML), the proliferative disorder is cancer, and the autoimmune disorder is selected from psoriasis and atopic dermatitis.

In an aspect of the invention, there is provided a combination as described herein, for the manufacture of a medicament for use in preventing leukemia such as acute myeloic leukemia (AML), mixed lineage leukemia (MLL), T-cell type acute lymphocytic leukemia (T-ALL), B-ceil type acute lymphocytic leukemia (B_ALL) and chronic myelomonocytic leukemia (CMML), the proliferative disorder is cancer, and the autoimmune disorder is selected from psoriasis and atopic dermatitis.

In an aspect of the invention, there is provided a combination as described herein, for the manufacture of a medicament for use in treating acute myeloic leukemia.

in an aspect of the invention, there is provided a combination as described herein, for the manufacture of a medicament for use in preventing acute myeloic leukemia.

In still a further aspect, there is provided a method for treating haematological diseases, proliferative disorders, cancer, autoimmune disorders and skin disorders in a patient, comprising administering to said patient in need of such treatment a therapeutic effective amount of a combination as described herein.

In still a further aspect, there is provided a method for preventing haematological diseases, proliferative disorders, cancer, autoimmune disorders and skin disorders in a patient, comprising administering to said patient in need of such prevention a therapeutic effective amount of a combination as described herein.

The term patient is understood to comprise a warm-blooded animal such as a human.

In still a further aspect, there is provided a method for treating of haematological diseases in a patient, comprising administering to said patient in need of such treatment a therapeutic effective amount of a combination as described herein.

In still a further aspect, there is provided a method for preventing haematological diseases in a patient, comprising administering to said patient in need of such prevention a therapeutic effective amount of a combination as described herein.

In still a further aspect, there is provided a method for treating leukemia in a patient, comprising administering to said patient in need of such treatment a therapeutic effective amount of a combination as described herein.

In still a further aspect, there is provided a method for preventing leukemia in a patient, comprising administering to said patient in need of such treatment a therapeutic effective amount of a combination as described herein.

In still a further aspect, there is provided a method for treating acute myeloid leukemia in a patient, comprising administering to said patient in need of such treatment a therapeutic effective amount of a combination as described herein.

In still a further aspect, there is provided a method for preventing acute myeloid leukemia in a patient, comprising administering to said patient in need of such treatment a therapeutic effective amount of a combination as described herein,

In yet an aspect of the invention, there is provided a kit of parts comprising:

(i) a compound of formula (I) in crystalline form as described herein, and

(ii) at least one anti-cancer drug, or a derivative thereof.

In yet an aspect of the invention, there is provided a kit of parts as described herein for use in therapy.

In yet an aspect of the invention, there is provided a kit of parts as described herein for use in the treatment of haematological diseases, proliferative disorders, cancer, autoimmune disorders and skin disorders.

In yet an aspect of the invention, there is provided a kit of parts as described herein for use in the prevention of haematological diseases, proliferative disorders, cancer, autoimmune disorders and skin disorders.

In yet an aspect of the invention, there is provided a kit of parts as described herein for use in the treatment of haematological diseases.

In yet an aspect of the invention, there is provided a kit of parts as described herein for use in the prevention of haematological diseases.

In yet an aspect of the invention, there is provided a kit of parts as described herein for use in the treatment of leukemia such as acute myeloic leukemia (AML), mixed lineage leukemia (MLL), T-cefl type acute lymphocytic leukemia (T-ALL), B-cell type acute lymphocytic leukemia (B_ALL) and chronic myelomonocytic leukemia (CMML), the proliferative disorder is cancer, and the autoimmune disorder is selected from psoriasis and atopic dermatitis.

In yet an aspect of the invention, there is provided a kit of parts as described herein for use in the prevention of leukemia such as acute myeloic leukemia (AML), mixed

lineage leukemia (MLL), T-cell type acute lymphocytic leukemia (T-ALL), B-cell type acute lymphocytic leukemia (B__ALL) and chronic myelomonocytic leukemia (CMML), the proliferative disorder is cancer, and the autoimmune disorder is selected from psoriasis and atopic dermatitis.

In yet an aspect of the invention, there is provided a kit of parts as described herein for use in the treatment of leukemia such as acute myeloic leukemia (AML).

In yet an aspect of the invention, there is provided a kit of parts as described herein for use in the prevention of leukemia such as acute myeloic leukemia (AML).

In yet an aspect of the invention, there is provided a kit of parts as described herein for the manufacture of a medicament for use in the treatment of haemato!ogical diseases, proliferative disorders, cancer, autoimmune disorders and skin disorders.

In yet an aspect of the invention, there is provided a kit of parts as described herein for the manufacture of a medicament for use in the prevention of haematological diseases, proliferative disorders, cancer, autoimmune disorders and skin disorders.

In yet an aspect of the invention, there is provided a kit of parts as described herein for the manufacture of a medicament for use in the treatment of haematological diseases.

In yet an aspect of the invention, there is provided a kit of parts as described herein for the manufacture of a medicament for use in the prevention of haematological diseases.

In yet an aspect of the invention, there is provided a kit of parts as described herein for the manufacture of a medicament for use in the treatment of from leukemia such as acute myeloic leukemia (AML), mixed lineage leukemia (MLL), T-cell type acute lymphocytic leukemia (T-ALL), B-cell type acute lymphocytic leukemia (B_ALL) and chronic myelomonocytic leukemia (CMML), the proliferative disorder is cancer, and the autoimmune disorder is selected from psoriasis and atopic dermatitis.

In yet an aspect of the invention, there is provided a kit of parts as described herein for the manufacture of a medicament for use in the prevention of from leukemia such as acute myeloic leukemia (AML), mixed lineage leukemia (MLL), T-ceil type acute lymphocytic !eukemia (T-ALL), B-cell type acute lymphocytic leukemia (B_ALL) and chronic myelomonocytic leukemia (CMML), the proliferative disorder is cancer, and the autoimmune disorder is selected from psoriasis and atopic dermatitis.

in yet an aspect of the invention, there is provided a kit of parts as described herein for the manufacture of a medicament for use in the treatment of from acute myeloic leukemia.

In yet an aspect of the invention, there is provided a kit of parts as described herein for the manufacture of a medicament for use in the prevention of from acute myeloic leukemia.

In yet an aspect of the invention, there is provided a kit of parts as described herein, wherein the compound of formula (I) in crystalline form is administered simultaneously as the at least one anti-cancer compound.

In yet an aspect of the invention, there is provided a kit of parts as described herein, wherein the compound of formula (I) in crystalline form is administered after the administration of the at least one anti-cancer compound.

In yet an aspect of the invention, there is provided a kit of parts as described herein, wherein the compound of formula (I) in crystalline form is administered before the administration of the at least one anti-cancer compound.

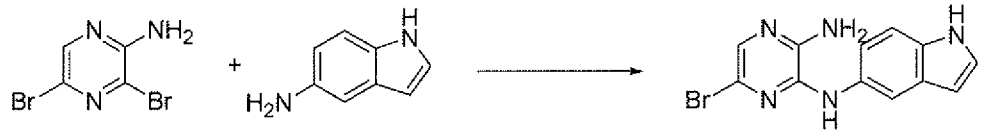
In yet an aspect of the invention, there is provided a kit of parts as described herein, wherein the at least one anti-cancer drug is cytarabine.

In yet an aspect of the invention, there is provided a kit of parts as described herein, wherein the at least one anti-cancer drug is daunorubicin.

Methods of preparation

The compound of formula (I) may be obtained in amorphous or crystalline form using the processes outlined below.

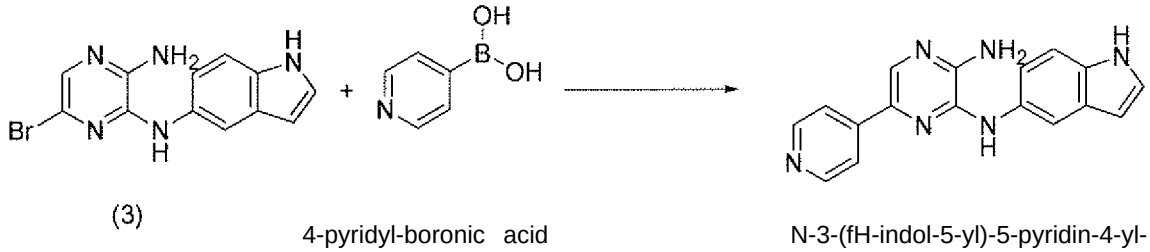
Step 1:



2-Amino-3,5-dibromopyrazine (1) 5-aminoindole (2) 5-Bromo-/V-3-(i/-/-indol-5-yi)-pyrazine-2,3-diamine (3)

Reaction of 2-amino-3,5-dibromopyrazine (1) and 5-aminoindole (2) in a nucleophilic substitution reaction in the presence of a C^alkyiamine and an inert po!ar solvent yields 3-bromo-/V-3-(7H-indol-5-yl)-pyrazine-2,3-diamine (3). Examples of inert polar solvents are DMSO, water and NEP. Examples of (d-ealkyl^amine are triethylamine, trimethyiamine and tributylamine. The reaction may be performed at reflux temperature or at about 100-130°C.

Step 2:



(3) 4-pyridyl-boronic acid (4) N-3-(fH-indol-5-yl)-5-pyridin-4-yl-pyrazine-2,3-diamine (I)

A Suzuki coupling of 3-bromo-/V-3-(i/-/-indol-5-yl)-pyrazine-2,3-diamine) (3) and 4-pyridyl-boronic acid (4) in an inert polar solvent in the presence of a palladium catalyst and a base yields N-3-(1 H-indol-5-yi)-5-pyridin-4-yl-pyrazine-2,3-diamine (I) in amorphous form. Examples of inert solvents are DMF, water and DMA. Examples of palladium catalysts are Pd(dppf) and $Pd(OAc)_2$-DTB-PPS. Example of a base is K_2C0_3 The reaction may be performed under inert and oxygen-free atmosphere such as nitrogen or argon.

Heating may take place during step 1 and/or step 2. Steps 1 and 2 may be performed at reflux or in a temperature range of from 100 to 140°C, such as from 105 to 135°C, such as from 110 to 130°C, such as from 130-135 °C, such as from 110-115 °C.

Step 3:

A compound of formula (I), also denominated N-3-(1 H-indo!-5-yl)-5-pyridin-4-yl-pyrazine-2,3-diamine, in amorphous form may be dissolved in acetic acid (HOAc) after which potassium hydroxide (KOH) is added. The compound of formula (I) in amorphous form may be obtained from the process outlined in steps 1 and 2. Alternatively, the compound of formula (I) may be obtained according to the process described in WO 2009/095399. The obtained crystalline form is removed from the slurry by, for instance, filtration. Step 3 may be repeated. Step 3 may be performed at a temperature of about 40°C followed by cooling to room temperature.

The process for preparing a compound according to formula (1) may comprise an additional step (step i) between step 2 and step 3 in order to remove palladium from the crude product of the compound of formula (I). The step comprises; forming a slurry comprising an acid and the compound according to formula (I) in a solvent, adding a si!oxane compound to said slurry, removing the solvent from the slurry and adding an organic solvent, such as DMF and/or toluene, to the solid formed whereby a mixture is formed and then potassium hydroxide is added to the formed mixture, Alternattvely, palladium may be removed from the crude product comprising (1) using a palladium scavenger such as TMT and/or 3-mercaptopropyl ethyl sulfide silica.

The crystalline form of the compound according to formula (I) may also be prepared from an amorphous form of the compound according to formula (I) by dissolving said amorphous form of the compound in a solvent mixture of dichloromethane/methanol followed by evaporation of the solvent in a rotary evaporator. The amorphous form of the compound of formula (I) may obtained using the process disclosed in WO 2009/095399.

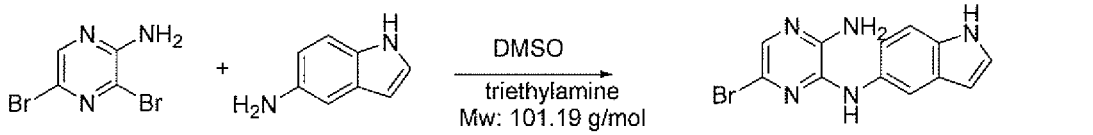
The invention is further illustrated by the following non-limiting examples.

Examples

Abbreviations

M	Molar
$Pd(dppf)Cl_2$	1,1'-Bis(diphenylphosphino)ferrocene]-dichloropalladium(ll)
K_2C0_3	Potassium carbonate
DMF	N,N-Dimethylformamide
DMA	N, N-Dimethylacetamide
DMSO	Dimethyl sulfoxide
eq.	equivalents
aq.	aqueous
L Litre	
HOAc	acetic acid
Me-THF	2- Methyltetrahydrofuran
TEA	Triethylamine
KOH	potassium hydroxide
mL	miliilitre
HPLC	high-performance liquid chromatography
NEP	1-ethy[-2-pyrrolidone
DTB-PPS	3-(di-tert-butylphosphino)propane-1 -sulfonic acid

Example 1. Preparation of 5-Bromo-W-3-(iH-indoi-5-y!)-pyrazine-2,3-diamine (compound 3)



2-Amino-3,5-dibromopyrazine
Mw: 252.89 g/mol
(1)

5-aminoindole
Mw: 132.16 g/mol
(2)

5-Bromo-N-3-(1 H-indol-5-yl)-pyrazine-2,3-diamine
(3)
Mw: 304.15 g/mol

DMSO (10 L, 11 kg), 2-amino-3,5-dibromopyrazine **(1)** (4.5 kg, 17.8 mol, 1 eq.), 5-amino indole **(2)** (3.06 kg, 23.15 mol, 1.3 eq.) and triethylamine (7.4 L, 5.4 kg, 53.36 mol, 3 eq.) were charged to a reactor. The reaction mixture was heated to 95°C while agitated. After 12 hours, the heating was discontinued and the conversion was 88% of 2-amino-3,5-dibromopyrazine. The reaction was heated again to 95°C and

agitated for an additional 2.5 hours. There was no improvement in conversion. The reaction mixture was agitated at ambient temperature overnight. Triethylamine (3.5 kg) was removed under vacuum and the remaining reaction mixture was transferred to a stainless steel container from which it was charged into another reactor. Subsequently, 18.4 kg of 50% acetic acid (aq.) was introduced over a period of 20 minutes under agitation, followed by purified water (61 L) charged over a period time of 60 minutes. The slurry was then filtered and the isolated material was washed with 2 x 20 L of 1% acetic acid (aq.).

The isolated 3-bromo-/V-3-(7H-indol-5-yl)-pyrazine-2,3-diamine) **(3)** was transferred to a drying cabinet and dried to invariable weight at 40 ±3˚C, (19 hours), to afford 4.36 kg, 14.34 mol, 81 % yield, with a purity of 96% by HPLC.

The reaction temperature in the batch record was set to be 130-135˚C. However, at 95¨C the reaction mixture was at reflux.

Example 2. Preparation of W-3-(iH-indol-5-yl)-5-pyndin-4-yl-pyrazine-2,3-diamine (compound I)

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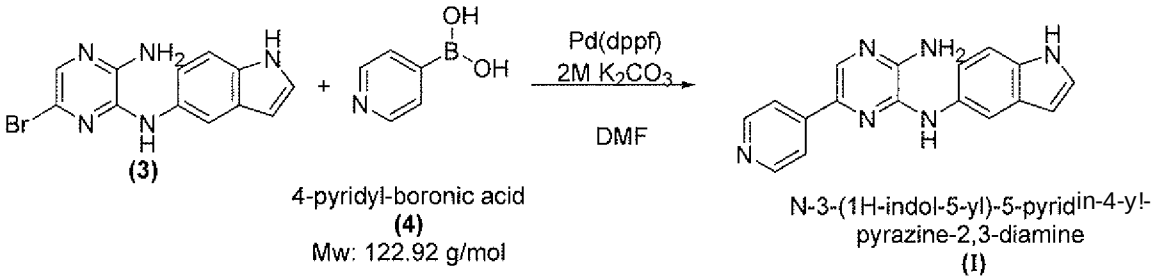


To a reactor was charged /V,A/-dimethylformamide (46.7 L, 45 kg), 4-pyridylboronic acid **(4)** (2.64 kg, 21.5 mol, 1.5 eq.) and 5-bromo-A/-3-(7H-indol-5-yl)-pyrazine-2,3-diamine **(3)** (4.36 kg, 14.3 mol). The reactor was then flushed with nitrogen prior to the charging of Pd(dppf)Cl_2-catalyst (0.47 kg, 0.55 mol, 0.04 eq.). To reactor was then charged, over a period of 20 minutes, 24.9 kg of a 2 M solution of potassium carbonate (aq.). The reactor was flushed with nitrogen and heated under agitation to 110-115˚C for 1.5 hours, after which 98.3% conversion of **(3)** was showed. The reaction mixture was quenched by addition of purified water (180 L) under vigorous agitation. The precipitated material was isolated on a hastalloy filter and washed

with purified water (50 L), The isolated material was transferred to a drying cabinet and dried to invariable weight at 40 ±3°C (18 hours), to afford a compound of formula (5), i.e. a compound of formula (I) also denominated A/-3-(iH-Indol-5-yl)-5-pyhdin-4-yl-pyra2ine-2,3-diamine, (3.64 kg, 12.1 mol, 85 % yield).

During the process precipitated material was observed in the solutions, after the reactions, in both steps not previously seen in lab-scale. These impurities were not removed.

Example 3. Purification and crystallisation

In order to remove residual solvents from the material, two consecutive re-precipitations of the material from acetic acid were performed. This also gave crystallinity of the isolated substance. The purification is performed in order to remove palladium.

Purification

To a 1 L round bottomed flask was added 37.8 g of a compound according to formula (I) followed by 600 mL 2 M HOAc (aq.). The material was stirred at RT until a clear, dark red solution was obtained. To the solution was added 30 g Hyflo Super Celite and the slurry was filtered. The filter cake was washed with 25 mL 2 M HOAc (aq) and 2x35 mL purified water. The obtained filtrate was transferred to a 2 L round bottomed flask containing 950 mL of Me-THF. The mixture was then stirred and heated to 40°C for 30 minutes. To the solution was then added 290 mL 8 M KOH (aq.) at 40°C and pH in the solution was 14.

The aqueous phase was removed and the organic phase washed with 2x100 mL of purified water. The remaining organic phase was then transferred to a 2 L round bottomed flask, followed by 95 mL of DMF, 20 g scavenger 3-Mercaptopropyl ethyl sulphide silica, Phosphonics LTD and 20 g scavenger 2-Mercaptoethyl ethyl sulfide silica purchased from Phosphonics LTD. The solution was vigorously stirred and heated at 60°C. A sample was withdrawn from the slurry after 12 hours, and showed 6 ppm of palladium remaining in the solution. The mixture was allowed to cool and was then filtered to remove the scavenger. The round bottomed flask and filter were rinsed with a mixture of 90 mL Me-THF and 10 mL DMF. Me-THF was then removed on a rotary evaporator and the remaining slurry was azeotropically dried

with two portions of 100 mL toluene. To the remaining slurry was then added 85 mL of DMF to a total of 185 mL DMF (5ml DMF/g substance). To the clear solution was then added, slowly, while agitated, 1500 mL of toluene which produced a heavy precipitate. The slurry was filtered off and washed with 2x50 mL of toluene where after the material was dried overnight at *35°C* under vacuum to afford 30.9 g of a compound according to formula (I) in a yield of 82%.

Crystallisation:

Example i

1. First re-precipitation

The A/-3-(i/-/-indol-5-yl)-5-pyridin-4-yl-pyrazine-2,3-diamine material (30.9 g) was added to a 1 L round bottomed flask and 450 mL 2 M HOAc (aq.) was added. The slurry was agitated and heated to 40°C for 1 hour, until the material had dissolved. To the solution was then added 158 mL 8 M KOH (aq.) at 40°C. The pH in the solution was 11.4. The slurry was then allowed to cool to 25°C and filtered. The filter cake was washed with 3x 80 mL of purified water and the material was dried overnight at 95°C under vacuum to afford 28.7g A/-3-(iW-indol-5-yl)-5-pyridin-4-yl-pyrazine-2,3-diamine in a yield of 93%.

2. Second re-precipitation

A/-3-(7/-/-indol-5-yl)-5-pyridin-4-yi-pyrazine-2,3-diamine material (28.7 g) was added to a 1L round bottomed flask and 430 mL 2 M HOAc (aq) was added. The slurry was agitated and heated to 40°C for 1 hour, until the material had dissolved. To the solution was then added 15 mL 8M KOH (aq) at 40°C. The pH in the solution was 12.3. The slurry was then allowed to cool to 25°C and filtered. The filter cake was washed with 5x50 mL of purified water, and the solid was then dried overnight at 95°C under vacuum to afford 28.3 g A/-3-(i/-/-indol-5-yl)-5-pyridin-4-yi-pyrazine-2,3-diamine in a yield of 99%.

Example ii

The jV-S-iiH-indol-S-yO-S-pyridin^-yi-pyrazine^^-diamine material (2. 1 kg, 7 mol) was added to a reactor, followed by 2M HOAc (aq.) (59.6 L, 60.2 kg) . The solution in the reactor was then heated to 40°C and stirred for 20 minutes. To the clear solution was then charged, slowly, 30% KOH (aq.) (25 kg) under vigorous agitation. The slurry was agitated for 15 minutes. pH in the solution was 6.2, and a total of 1.5

kg 30% KOH (aq.) was then added to the solution to give pH 12.1 . The precipitated material was isolated on a Hastelloy filter and washed with purified water (5x30 L). The solid was then transferred to a drying cabinet and dried to invariable weight at 85 ±3°C under vacuum (16 hours; a sample was withdrawn after 16 hours, showing 1400 ppm HOAc and 75 ppm DMF), to afford W-3-(7H-indol-5-yi)-5-pyridin-4-yl-pyrazine-2,3-diamine (2.0 kg, 7 mol, 95 % yield).

Hence, A/-3-(i/-/-indol-5-y!)-5-pyridin-4-yl-pyrazine-2,3-diamine is obtained in an uniform crystalline form, which was achieved by precipitating the product from aqueous acetic acid by introduction of aqueous potassium hydroxide.

Example 4. Characterization of the compound according to formula (I) in crystalline form

X-Ray Powder Diffraction (XRPD)

X-Ray Powder Diffraction (XRPD) experiments were run on an X'Pert Pro diffractometer (PANanalyticai, Netherlands) set in Bragg-Brentano geometry. The diffractometer was equipped with a Ge(1 11) primary monochromator and PiXcell detector. A representative sample was placed on a zero background quarts single crystal specimen support (Siltronix, France).

Experiments were run using Cu $K_{\alpha 1}$ radiation (45kV and 40 mA) at ambient temperature and humidity. Scans were run in continues scan mode in the range 2-50 ° 2Θ using automatic divergence and antiscatter slits with observed length of 10 mm, a step size of 0.01 31° 2Θ and a common counting time of 97.920 seconds. The sample holder was spinned with a revolution time of 2 seconds.

Data collections were done with the application software X'Pert Data Collector version 2.2d and instrument control software version 1.9D, and pattern analysis and profile refinement was done with X'Pert HighScore Plus version 2.2.3. Ail software's comes from PANanalyticai B.V., Netherlands.

TABLE 1 Selected peaks of the crystalline form of the compound according to formula (I). The XRPD pattern (Cu K_α) was obtained when measuring using radiation with a wavelength of about 40 mA.

Peak	Measured angle [° 2θ]
1	6.4 ± 0.3
2	9.8 ± 0.3
3	18.7 ± 0.3
4	23.4 ± 0.3
5	25.5 ± 0.3

Dynamic Vapour Sorption (DVS)

The hygroscopicity of the samples was studied by Dynamic Vapor Sorption Gravimetry (DVS) using a DVS-1 (Surface Measurement Ltd., UK). Approximately 10 mg of the substance was weighed into a glass cup. The relative weight was recorded at 20 second interval, when the target relative humidity (RH) over the sample was increased stepwise from 0% to 90%, and then similarly decreased back to 0% RH, with 10% RH per step. Each sample was run in three consecutive full cycles. The condition to proceed to the next level of RH was a weight increase below or equal to 0.001% within 15 minutes, with a maximum total time per step of 24 hours. The temperature was kept at 25°C.

Thermogravimetry (TG)

Thermogravimetry (TG) was performed on a Seiko TG/DTA 6200 and open 90 µl Pt-pans with ca 10 mg of sample and a nitrogen flow of 200 mL/min. The temperature program was ambient (20°C) to 500°C with a heating rate of 10 °C/min. A blank was subtracted and the TG data was normalized with respect to sample size and analyzed using the Muse Standard Analysis software, version 6.1 U.

Example 5. Synthesis of 5-Bromo-W-3-(fH-indol-5-yl)-pyrazine-2,3-diamrne (compound 3)

2-Amino-3,5-dibromopyrazine (45 g, 1.0 eq.), 5-aminoindole (30,6 g, 1.3 eq.), 67.5 mL NEP, i.e. 1-ethyl-2-pyrrolidone, and 74.5 mL triethyiamine were added to a 250 mL reactor. The jacket temperature was set to 130°C and the reaction mixture was stirred for 22 h. HPLC after 22 h showed 87% conversion of the 2-amino-3,5-dibromopyrazine. After 24 h HPLC showed 92% conversion and the reaction slurry was cooled to 80°C and quenched by addition of addition of 50% HOAc(aq) and water. The obtained slurry was then allowed to cool to room temperature over night while agitated. The material was isolated on a glass filter funnel and was washed with water. The materia! was dried at 80 °C under vacuum until dry to afford 71% of the compound 5-bromo-A/-3-(7H-indol-5-yl)-pyrazine-2,3-diamine as a dark brown powder. The purity was 99.8% as measured by HPLC.

Example 6. Synthesis of W-3-(iH-indol-5-yl)-5-pyridin-4-yl-pyrazine-2,3-diamine (Compound I)

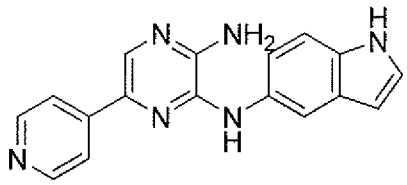
5-Bromo-W-3-(iH-indo!-5-yl)-pyrazine-2,3-diamine (15.0 g, 49 mmol, 1.0 eq.), 4-pyridyl boronic acid (6.6 g, 59 mmol, 1.2 eq.), $Pd(OAc)_2$ (166 mg, 0.74 mmol, 0.015 eq.), DTB-PPS, i.e. 3-(di-tert-butyiphosphino)propane-1-sulfonic acid, (199 mg, 0.74 mmol, 0.015 eq.), and DMA, i.e. *N*,/V-dimethylacetamide, (75 mL) were added to a three-necked round-bottomed fiask equipped with a mechanical stirrer, thermometer, and a nitrogen atmosphere. Through a septa was added 2M K_2C0_3 (aq) (27 ml, 54 mmol, 1.1 eq.) with a syringe. The temperature was increased to 100 °C. Samples for HPLC-analysis of the conversion were drawn and when the conversion had reached 100% the temperature was cooled to 25 °C. At that temperature a water solution of 0.5 M L-cysteine (150 ml) was added by a syringe pump over 1 hour with a rate of 2.5 mL/minute. After 3 hours maturing time at room temperature the material was isolated on a glass filter funnel and was washed with water. The material was dried at 40 °C under vacuum over the weekend, and 15 grams of /V-3-(7/-/-indol-5-yl)-5-pyridin-4-yl-pyrazine-2,3-diamine (101%) were obtained as a brown powder.

Example 7. Purification of W-3-(fH-indol-5-yl)-5-pyridin-4-yl-pyrazine-2,3-diamine (Compound I)

The crude (7.0 g, 23 mmol) and 2M HOAc (98 mL) was added to a 250 mL round-bottomed flask. To this was added TMT, i.e. trithiocyanuric acid, (1.4 g) and SPM32, i.e. 3-mercaptopropyi ethyl sulfide silica, (1.4 g). The mixture was stirred in room temperature for 24 hours. After 24 hour a polish filtration through hyflo super cei was performed. To the clear filtrate was added 50 mL 5 M $KOH_{(aq)}$ under 15 minutes to precipitate the product. After 18 hours maturing time at room temperature the material was isolated on a glass filter funnel and was washed with 2x20 mL water. The first was being a slurry wash and the second a displacement wash. The materiai was dried at 40 °C under vacuum over the weekend, and 3.9 grams (56%) was obtained as a light yellow powder. The Pd content was 3.7 ppm.

CLAIMS

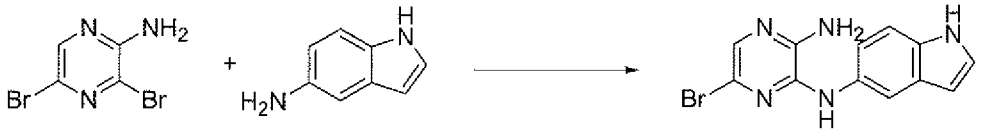
1. A process for preparing a compound of formula (I)



(I)

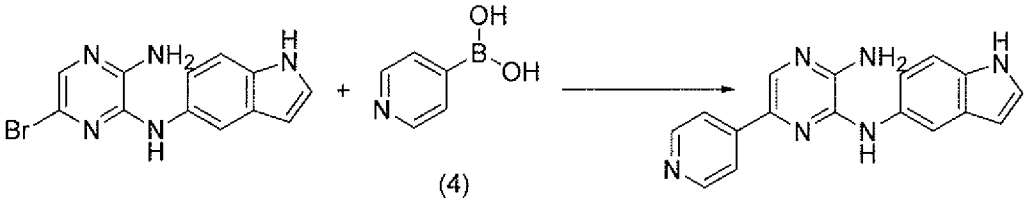
said process comprising the steps of:

a) reacting a compound of formula (1) with a compound of formula (2) in an inert solvent and in the presence of an **(C_{1-6}alkyl)$_3$**amine, providing a compound of formula (3) :



(1) (2) (3)

b) Suzuki coupling of a compound of formula (3) and a compound of formula (4) in an inert solvent and in the presence of a palladium catalyst and a base, providing a crude product comprising a compound of formula (I) and palladium



(3) (4) (I)

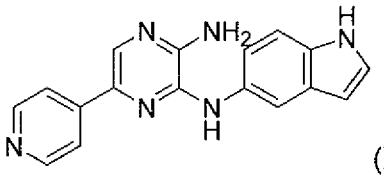
and

c) removing the palladium from the crude product in step b).

2. A process according to claim 1, wherein removal of palladium in step c) comprises treatment of the crude product with a palladium scavenger comprising thiol groups.

3. A process according to claim 2, wherein the palladium scavenger comprises trithiocyanuric acetic acid and/or 3-mercaptopropyl ethyl sulfide siiica.

4. A crystalline form of a compound according to formula (I),



(I).

5. A crystalline form according to claim 4, characterized in that said form has an XRPD pattern with at least one peak at about 25.5 º 2Θ.

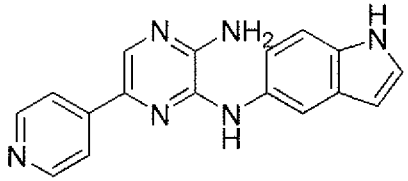
6. A crystalline form according to claim 4, characterized in that said form has an XRPD pattern with at least two peaks at about 25.5 º 20 and about 18.7 º 20.

7. A crystalline form according to claim 4, characterized in that said form has an XRPD pattern with at least three peaks at about 25.5 º 2Θ and about 18.7 º 20 and about 23.4 º 2Θ.

8. A crystalline form according to claim 4, characterized in that said form has an XRPD pattern with at least four peaks at about 25.5 º 2Θ and about 18.7 º 2Θ and about 23.4 º 2Θ and about 9.8 º 2Θ.

9. A crystalline form of a compound according to claim 4, characterized by the XRDP pattern essentially as shown in Figure 1.

10. A process for preparing a compound according to formula (I)



(I)

in crystalline form, wherein said process comprises the step of:

i) adding a compound according to formula (I) in amorphous form to acetic acid;

ii) adding potassium hydroxide to the mixture formed in i) thereby precipitating the compound of formula (I) in crystalline form, and

iii) removing the crystalline form of the compound according to formula (1) from the mixture of step ii).

11. A crystalline form according to any one of claims 4 to 9 for use in therapy.

12. A crystalline form according to any one of claims 4 to 9 for use in the treatment of haemato!ogical diseases, proliferative disorders, cancer, autoimmune disorders and skin disorders.

13. A crystalline form according to claim 12 for use in the treatment of haematologicai diseases.

14. A crystalline form according to any one of claims 4 to 9 for use in the manufacture of a medicament for use in the treatment of haematologicai diseases, proliferative disorders, cancer, autoimmune disorders and skin disorders.

15. A crystalline form according to claim 13 for use in the manufacture of a medicament for the treatment of haematologicai diseases.

16. A crystalline form according to claim 13 or 15, wherein the haematologicai disease is acute myeloic leukemia.

17. A combination comprising a compound of formula (1) in crystalline form according to any one of claims 4 to 9 and at least one anti-cancer compound.

18. A kit of parts comprising:

(i) a compound of formula (I) in crystalline form according to any one of claims 4 to 9, and

(ii) at least one anti-cancer drug, or a derivative thereof.

19. A kit of parts according to claim 18, wherein the compound of formula (I) and the at least one anti-cancer compound are administered simultaneously or sequentially.

20. A method for the treatment of haematologicai diseases, proliferative disorders, cancer, autoimmune disorders and skin disorders in a patient comprising administering to said patient in need of such treatment a therapeutic effective

amount of a crystalline form of a compound according to formula (I) according to any one of claims 4 to 9.

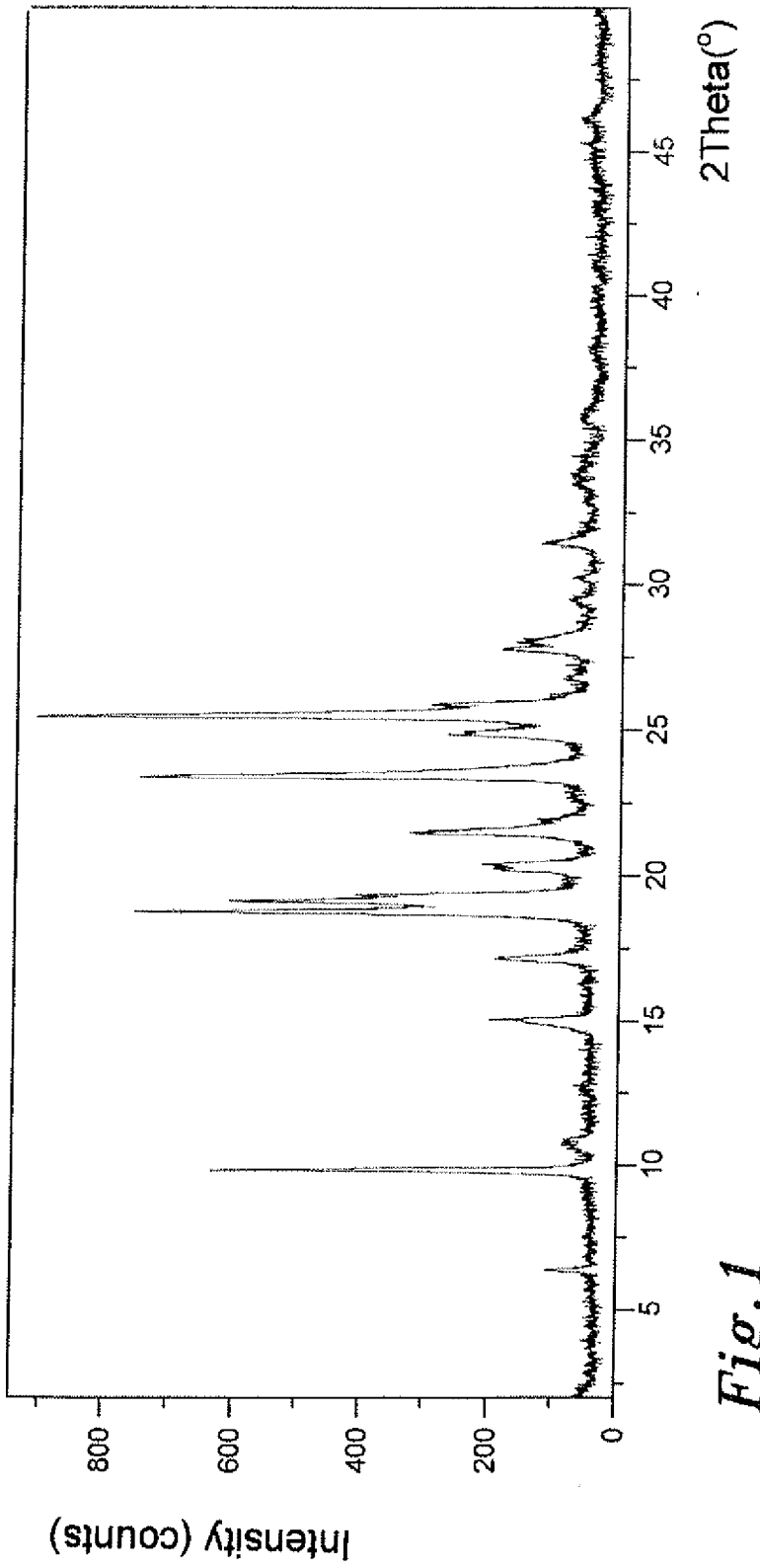

Intensity (counts)
0
200
400
600
800
5
10
15
20
25
30
35
40
45
2Theta(°)

Fig. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE201 2/051 4 1 1

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

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)

IPC: A61 K, A61 P, C07D

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

SE, DK, Fl, NO classes as above

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

EPO-Internal, PAJ, WPI data, CHEM ABS Data, Registry, Reaxys

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009095399 A2 (BIOVITRUM AB PUBL ET AL), 6 August 2009 (2009-08-06); page 4, line 1 - line 19; page 19, line 16 - page 20, line 14; claims 1, 4-1 5, 24	4-20
Y	--	1-3
Y	US 20060091 067 A 1 (FAN YUNYING ET AL), 4 May 2006 (2006-05-04); page 7, column 2, paragraph [0057] - page 8, column 2, paragraph [0060]; page 9, column 2, paragraph [0063] - page 12, column 1, paragraph [0070]; claims; Example 4-5, 7-1 1	1-3
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I_I Further documents are listed in the continuation of Box C. ☒ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international fding date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier application or patent but published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

Date of the actual completion of the international search	Date of mailing of the international search report
25-03-201 3	26-03-201 3
Name and mailing address of the ISA/SE Patent- och registreringsverket Box 5055 S-1 02 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Niclas Sandstrom Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE201 2/051 4 11

Box No. 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. ☒ Claims Nos.: 20
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 20 relates to a method for treatment of the human or animal body by surgery or by therapy, as well as diagnostic methods, see PCT rule 39.1 (iv).

.../...

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 No. Ill 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:

The following separate inventions were identified:

1: Claims 1-3 directed to a work up procedure of the crude product from the synthesis of N-3-(1 H-indol-5-y)-5-pyridin-4-yl-pyrazine-2,3-diamine.

2: Claims 4-20 directed to a crystalline form of N-3-(1 H-indol-5-y)-5-pyridin-4-yl-pyrazine-2,3-diamine and its use in treatment of haematological diseases, proliferative disorders, cancer, autoimmune disorders and skin disorders.

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 additional fees, this Authority did not invite payment of additional fees.

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 and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

Continuation of: Box No. II

Nevertheless, a search has been made for this claim. The search has been directed to the technical content of the claim.

Continuation of: second sheet

International Patent Classification (IPC)

C07D 401/14 (2006.01)
***A61K* 37/4565** (2006.01)
A61P 17/00 (2006.01)
A61P 35/00 (2006.01)

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				US	201 1009831 0	A 1	28/04/201 1
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				CN	10 1094836	A	26/1 2/2007
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				ZA	200704350	A	27/08/2008