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(54) Title: PROCESSES FOR THE PREPARATION OF RUXOLITINIB PHOSPHATE

(57) Abstract: The present invention relates to processes for the preparation of ruxolitinib and ruxolitinib phosphate. The present invention also provides a compound of Formula IV, processes for its preparation, and its use for the preparation of ruxolitinib and ruxolitinib phosphate. The present invention provides ruxolitinib phosphate having a chiral purity of 99.96% and the compound of Formula IV having a chiral purity of 99.95%.

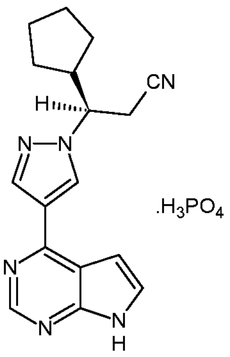
PROCESSES FOR THE PREPARATION OF RUXOLITINIB PHOSPHATE

Field of the Invention

The present invention relates to processes for the preparation of ruxolitinib and ruxolitinib phosphate. The present invention also provides a compound of Formula IV, processes for its preparation, and its use for the preparation of ruxolitinib and ruxolitinib phosphate.

Background of the Invention

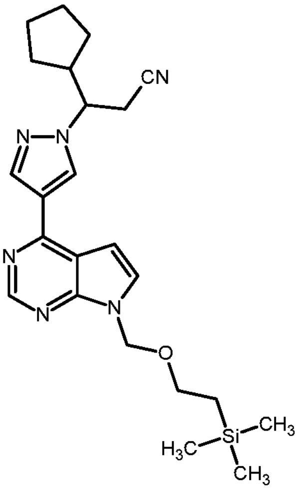
Ruxolitinib phosphate chemically is (i?)-3-(4-(7*H*-pyrrolo[2,3-<f]pyrimidin-4-yl)-l*H*-pyrazol-l-yl)-3-cyclopentylpropanenitrile phosphate, represented by Formula I.



Formula I

Ruxolitinib is indicated for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis.

U.S. Patent No. 7,598,257 describes a process for the preparation of ruxolitinib, wherein 3-cyclopentyl-3-[4-(7-[2-(trimethylsilyl)ethoxymethyl]-7 *H*-pyrrolo[2,3-£/]-pyrimidin-4-yl)-l *H*-pyrazol-l-yl]propanenitrile of Formula Ila,



Formula Ila

on separation by preparative high- performance liquid chromatography (HPLC) gives an enantiomer, (3i?)-3-cyclopentyl-3-[4-(7-[2-(trimethylsilyl)ethoxymethyl]-7 *H*-pyrrolo[2,3-£/]-pyrimidin-4-yl)-l*H*-pyrazol-l-yl]propanenitrile, which is deprotected to give ruxolitinib.

U.S. Patent No. 8,722,693 provides a process for the preparation of ruxolitinib phosphate.

U.S. Patent No. 8,410,265 describes a process for the preparation of (3i?)-3-cyclopentyl-3-[4-(7-[2-(trimethylsilyl)ethoxymethyl]-7 *H*-pyrrolo[2,3-£/]-pyrimidin-4-yl)-l*H*-pyrazol-l-yl]propanenitrile by resolution of the compound of Formula Ila with (+)-2,3-dibenzoyl-D-tartaric acid to predominantly obtain of *(2S,3S)-2,3*-bis(benzoyloxy)succinic acid-(3i?)-3-cyclopentyl-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl }-7*H*-pyrrolo[2,3-*d*\-pyrimidin-4-yl)- l*H*-pyrazol- 1-yl]propanenitrile (1:1) and its subsequent treatment with a base. It further provides a process for the preparation of ruxolitinib phosphate from (3i?)-3-cyclopentyl-3-[4-(7-[2-(trimethylsilyl)ethoxymethyl] -7*H*-pyrrolo[2,3-*d*\-pyrimidin-4-yl)- l*H*-pyrazol- 1-yl]propanenitrile. The present inventors have observed that the ruxolitinib phosphate obtained has a chiral purity of 68.59%.

There is still a need in the art to develop a new process for the preparation of ruxolitinib phosphate having high chiral purity.

Summary of the Invention

The present invention relates to processes for the preparation of ruxolitinib and ruxolitinib phosphate. The present invention also provides a compound of Formula IV, processes for its preparation, and its use for the preparation of ruxolitinib and ruxolitinib phosphate. The present invention provides ruxolitinib phosphate having a chiral purity of 99.96% and the compound of Formula IV having a chiral purity of 99.95%.

Brief Description of the Drawings

Figure **1**: High Performance Liquid Chromatography (HPLC) chromatogram of chiral purity of (25',35)-2,3-bis(benzoyloxy)butanedioic acid - (3i?)-3-cyclopentyl-3-[4-(7*H* -pyrrolo[2,3-£/|pyrimidin-4-yl)-l*H* -pyrazol-l-yl]propanenitrile (Formula IV), obtained as per Example 3.

Figure 2: HPLC chromatogram of chiral purity of ruxolitinib phosphate, obtained as per Example 5.

Figure 3: HPLC chromatogram of chiral purity of ruxolitinib phosphate, obtained as per Reference Example.

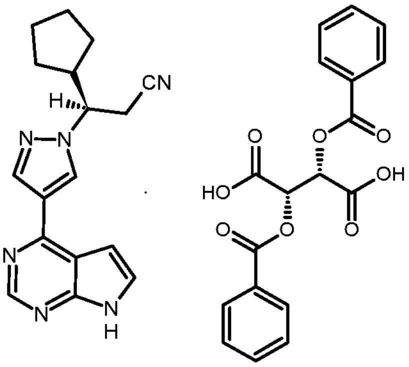
Detailed Description of the Invention

The present inventors have developed a process for the preparation of ruxolitinib phosphate having a chiral purity of about 99.96%.

The term "about," as used herein, refers to any value which lies within the range defined by a number up to ±**10**% of the value.

The term "room temperature," as used herein, refers to a temperature in the range of 25°C to 35°C.

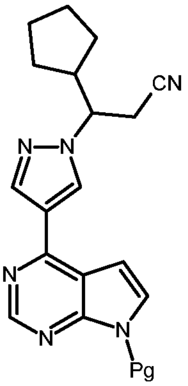
A first aspect of the present invention provides a process for the preparation of a compound of Formula IV,



Formula IV

wherein the process comprises:

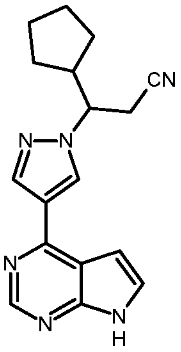
a) deprotecting a compound of Formula II



Formula II

wherein Pg is a protecting group selected from benzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, *t*-butoxycarbonyl, 2-(trimethylsilyl)ethoxymethyl, *N*-pivaloyloxymethyl, benzyloxymethyl, cyclohexyloxycarbonyl, 2-(4-trifluoromethylphenylsulfonyl)ethoxycarbonyl, vinyl, 2-chloroethyl, 2-phenylsulfonylethyl, allyl, benzyl, methoxymethyl, t-butoxymethyl, 2-tetrahydropyranyl, and 1,1-diethoxymethyl,

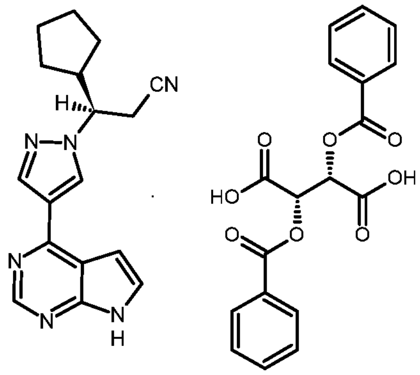
in the presence of a deprotecting agent to obtain a compound of Formula III; and



Formula III

b) treating the compound of Formula III with (+)-2,3-dibenzoyl-D-tartaric acid to obtain the compound of Formula IV.

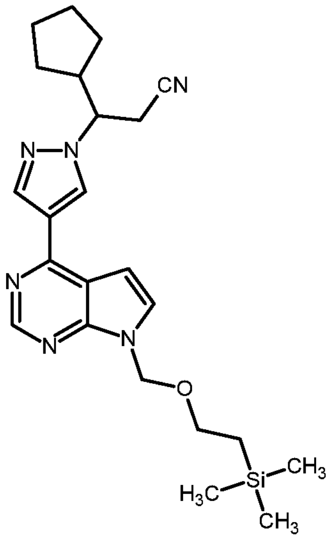
A second aspect of the present invention provides a process for the preparation of a compound of Formula IV,



Formula IV

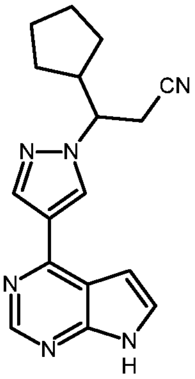
wherein the process comprises:

a) deprotecting a compound of Formula IIa



Formula IIa

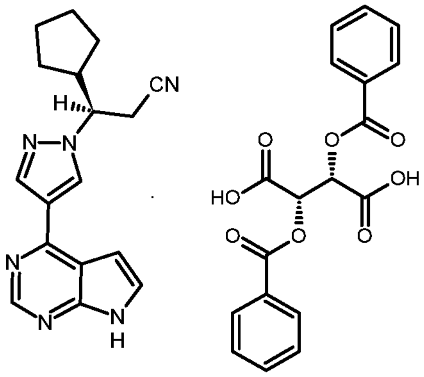
in the presence of a deprotecting agent to obtain a compound of Formula III; and



Formula III

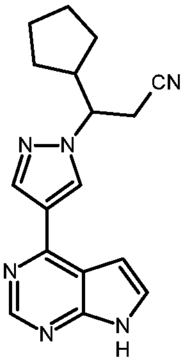
b) treating the compound of Formula III with (+)-2,3-dibenzoyl-D-tartaric acid to obtain the compound of Formula IV.

A third aspect of the present invention provides a process for the preparation of a compound of Formula IV,



Formula IV

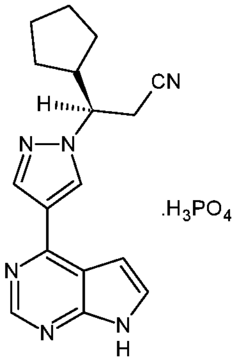
wherein the process comprises treating a compound of Formula III



Formula III

with (+)-2,3-dibenzoyl-D-tartaric acid.

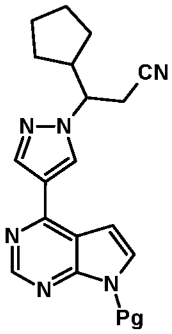
A fourth aspect of the present invention provides a process for the preparation of ruxolitinib phosphate of Formula I,



Formula I

wherein the process comprises:

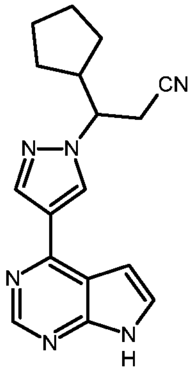
a) deprotecting a compound of Formula II



Formula II

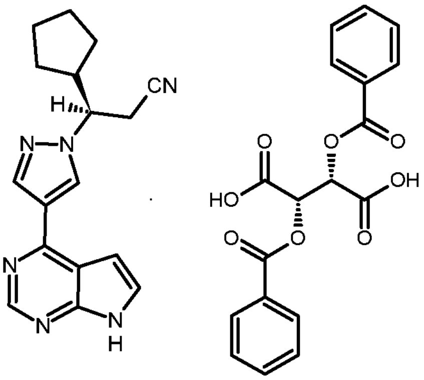
wherein Pg is a protecting group selected from a group consisting of benzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, i-butoxycarbonyl, 2-(trimethylsilyl)ethoxymethyl, *N*-pivaloyloxymethyl, benzyloxymethyl, cyclohexyloxycarbonyl, 2-(4-trifluoromethylphenylsulfonyl)ethoxycarbonyl, vinyl, 2-chloroethyl, 2-phenylsulfonylethyl, allyl, benzyl, methoxymethyl, t-butoxymethyl, 2-tetrahydropyranyl, and 1,1-diethoxymethyl,

in the presence of a deprotecting agent to obtain a compound of Formula III;



Formula III

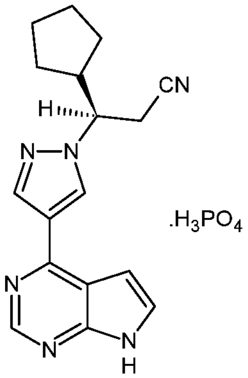
b) treating the compound of Formula III with (+)-2,3-dibenzoyl-D-tartaric acid to obtain a compound of Formula IV; and



Formula IV

c) converting the compound of Formula IV to ruxolitinib phosphate of Formula I.

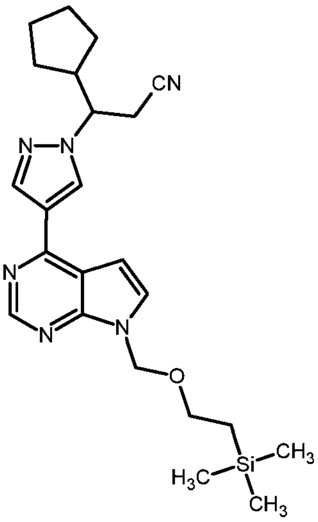
A fifth aspect of the present invention provides a process for the preparation of ruxolitinib phosphate of Formula I,



Formula I

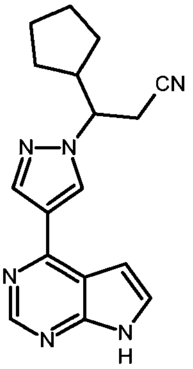
wherein the process comprises:

a) deprotecting a compound of Formula Ila



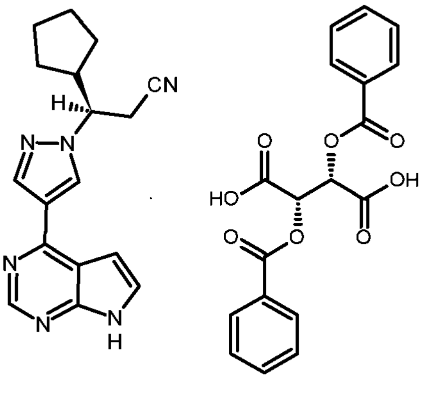
Formula Ila

in the presence of a deprotecting agent to obtain a compound of Formula HI;



Formula III

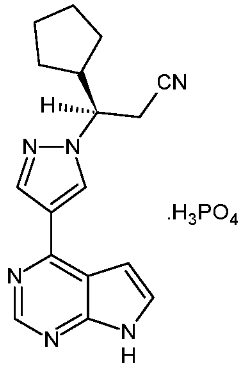
b) treating the compound of Formula III with (+)-2,3-dibenzoyl-D-tartaric acid to obtain a compound of Formula IV; and



Formula IV

c) converting the compound of Formula IV to ruxolitinib phosphate of Formula I.

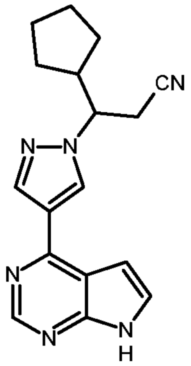
A sixth aspect of the present invention provides a process for the preparation of ruxolitinib phosphate of Formula I,



Formula I

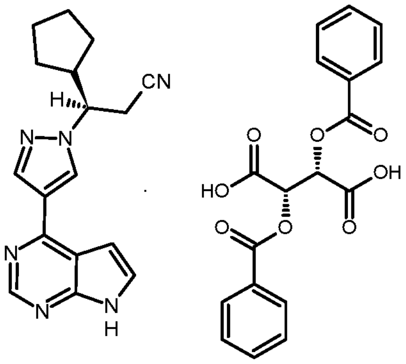
wherein the process comprises:

a) treating a compound of Formula III



Formula III

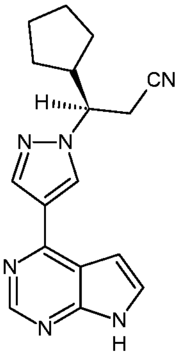
with (+)-2,3-dibenzoyl-D-tartaric acid to obtain a compound of Formula IV; and



Formula IV

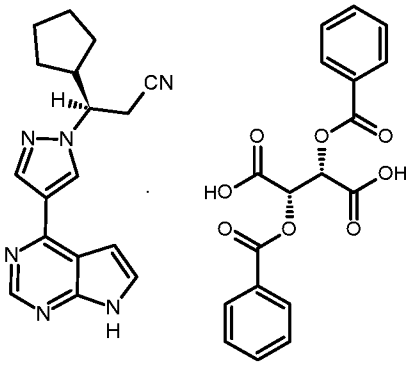
b) converting the compound of Formula IV to ruxolitinib phosphate of Formula I.

A seventh aspect of the present invention provides a process for the preparation of ruxolitinib of Formula V,



Formula V

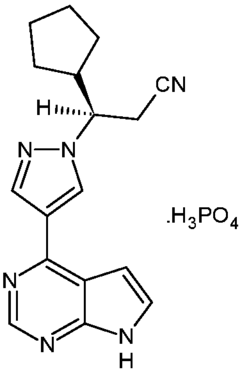
wherein the process comprises treating a compound of Formula IV



Formula IV

with abase.

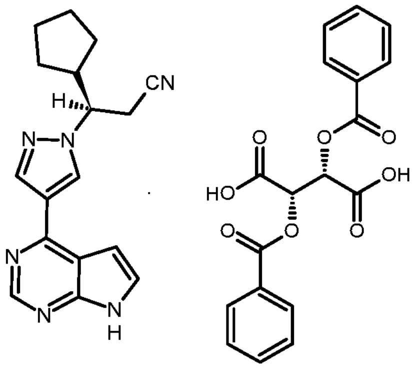
An eighth aspect of the present invention provides a process for the preparation of ruxolitinib phosphate of Formula I,



Formula I

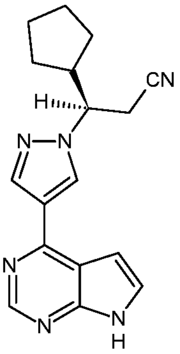
wherein the process comprises:

a) treating a compound of Formula IV



Formula IV

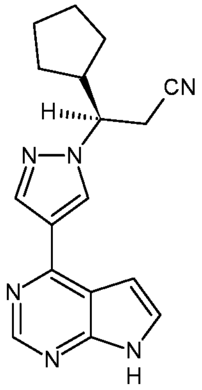
with a base to obtain ruxolitinib of Formula V; and



Formula V

b) converting the ruxolitinib of Formula V to ruxolitinib phosphate of Formula I.

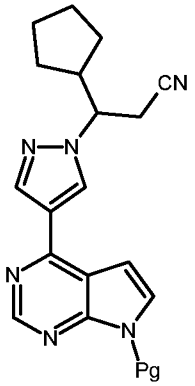
A ninth aspect of the present invention provides a process for the preparation of ruxolitinib of Formula V,



Formula V

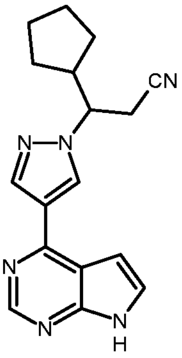
wherein the process comprises:

a) deprotecting a compound of Formula II



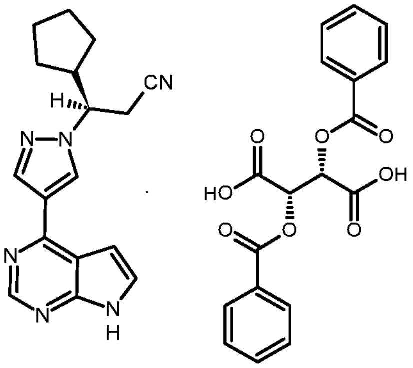
Formula II

wherein Pg is a protecting group selected from benzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, *t*-butoxycarbonyl, 2-(trimethylsilyl)ethoxymethyl, *N*-pivaloyloxymethyl, benzyloxymethyl, cyclohexyloxycarbonyl, 2-(4-trifluoromethylphenylsulfonyl)ethoxycarbonyl, vinyl, 2-chloroethyl, 2-phenylsulfonylethyl, allyl, benzyl, methoxymethyl, t-butoxymethyl, 2-tetrahydropyranyl, and 1,1-diethoxymethyl, in the presence of a deprotecting agent to obtain a compound of Formula HI:



Formula III

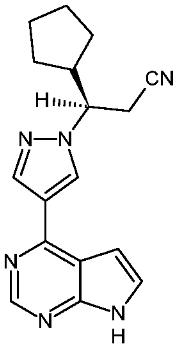
b) treating the compound of Formula III with (+)-2,3-dibenzoyl-D-tartaric acid to obtain a compound of Formula IV; and



Formula IV

c) treating the compound of Formula IV with a base to obtain ruxolitinib of Formula V.

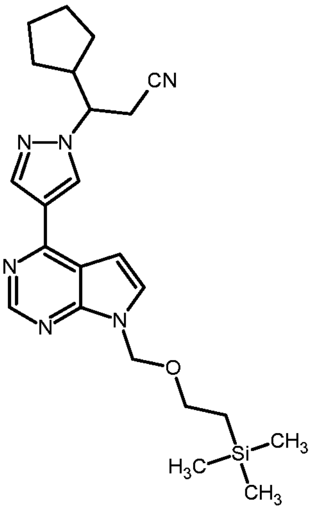
A tenth aspect of the present invention provides a process for the preparation of ruxolitinib of Formula V,



Formula V

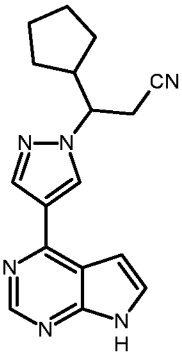
wherein the process comprises:

a) deprotecting a compound of Formula Ila



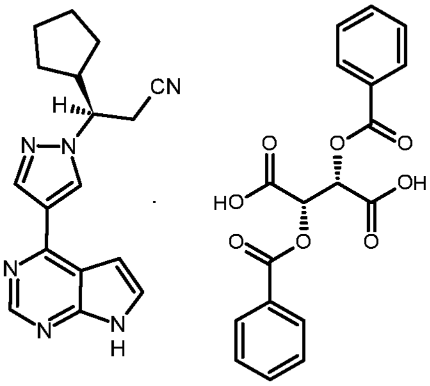
Formula Ila

in the presence of a deprotecting agent to obtain a compound of Formula HI;



Formula III

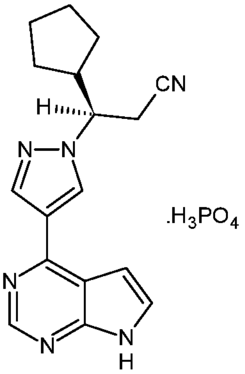
b) treating the compound of Formula III with (+)-2,3-dibenzoyl-D-tartaric acid to obtain a compound of Formula IV; and



Formula IV

c) treating the compound of Formula IV with a base to obtain ruxolitinib of Formula V.

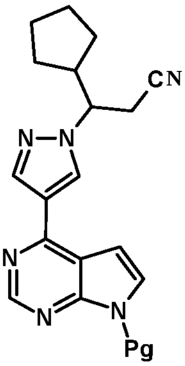
An eleventh aspect of the present invention provides a process for the preparation of ruxolitinib phosphate of Formula I,



Formula I

wherein the process comprises:

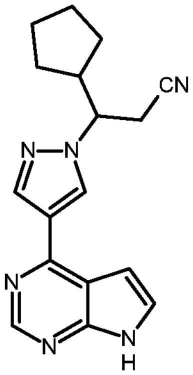
a) deprotecting a compound of Formula II



Formula II

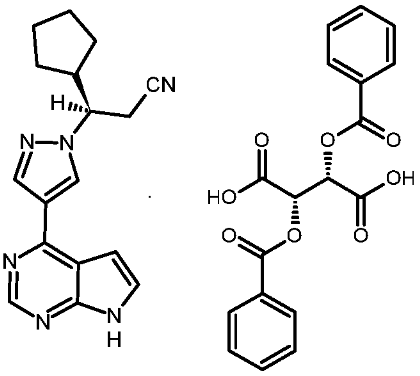
wherein Pg is a protecting group selected from benzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, *t*-butoxycarbonyl, 2-(trimethylsilyl)ethoxymethyl, *N*-pivaloyloxymethyl, benzyloxymethyl, cyclohexyloxycarbonyl, 2-(4-trifluoromethylphenylsulfonyl)ethoxycarbonyl, vinyl, 2-chloroethyl, 2-phenylsulfonylethyl, allyl, benzyl, methoxymethyl, t-butoxymethyl, 2-tetrahydropyranyl, and 1,1-diethoxymethyl,

in the presence of a deprotecting agent to obtain a compound of Formula III;



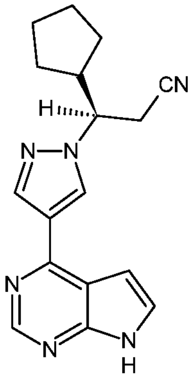
Formula III

b) treating the compound of Formula III with (+)-2,3-dibenzoyl-D-tartaric acid to obtain a compound of Formula IV;



Formula IV

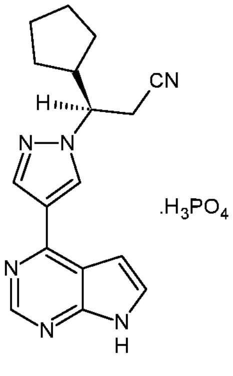
c) treating the compound of Formula IV with a base to obtain ruxolitinib of Formula V; and



Formula V

d) converting the ruxolitinib of Formula V to ruxolitinib phosphate of Formula I.

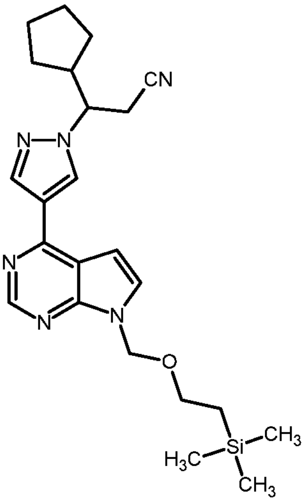
A twelfth aspect of the present invention provides a process for the preparation of ruxolitinib phosphate of Formula I,



Formula I

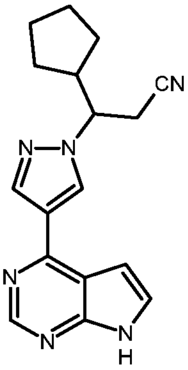
wherein the process comprises:

a) deprotecting a compound of Formula Ila



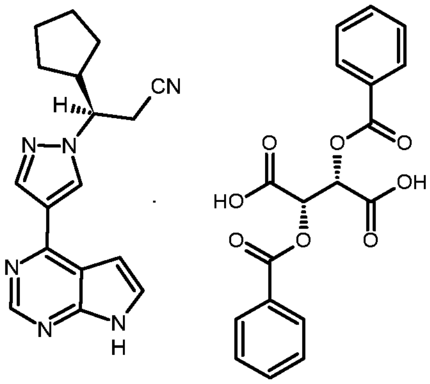
Formula Ila

in the presence of a deprotecting agent to obtain a compound of Formula HI;



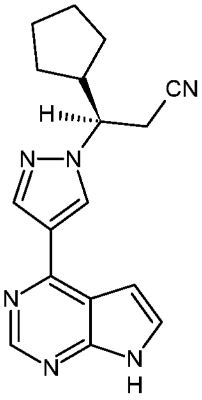
Formula III

b) treating the compound of Formula III with (+)-2,3-dibenzoyl-D-tartaric acid to obtain a compound of Formula IV;



Formula IV

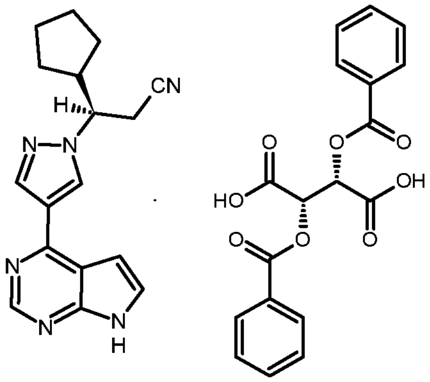
c) treating the compound of Formula IV with a base to obtain ruxolitinib of Formula V; and



Formula V

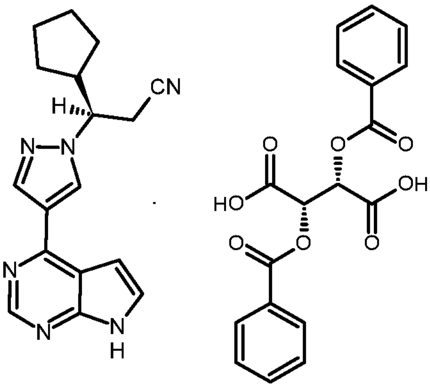
d) converting the ruxolitinib of Formula V to ruxolitinib phosphate of Formula I.

A thirteenth aspect of the present invention provides a compound of Formula IV.



Formula IV

A fourteenth aspect of the present invention provides the use of a compound of Formula IV



Formula IV

for the preparation of ruxolitinib phosphate.

The compound of Formula II or Formula Ila may be prepared by methods known in the art, for example, the methods described in U.S. Patent No. 7,598,257, or by following the method described herein. The compound of Formula II or Formula Ila may be isolated or the reaction mixture containing the compound of Formula II or Formula Ila may be used as such for the next step.

The deprotection of the compound of Formula II or Formula Ila to give the compound of Formula III is carried out in the presence of a deprotecting agent in a solvent.

The deprotecting agent is selected from the group consisting of boron trifluoride etherate, lithium tetrafluoroborate, and stannic chloride.

The solvent is selected from the group consisting of nitriles and halogenated hydrocarbons. An example of anitrile is acetonitrile. Examples of halogenated hydrocarbons include dichloroethane, dichloromethane, chloroform, and carbon tetrachloride.

The deprotection of the compound of Formula II is carried out for about 2 hours to about 8 hours, for example, for about 4 hours to about 5 hours.

The deprotection of the compound of Formula II is carried out at a temperature of about 10°C to about 50°C, for example, about 25°C to about 40°C.

The compound of Formula III may be isolated or the reaction mixture containing the compound of Formula III may be used as such for the next step.

The compound of Formula III may be isolated by filtration, decantation, extraction, distillation, evaporation, chromatography, precipitation, concentration, crystallization, centrifugation, or recrystallization. The compound of Formula III may be dried using conventional techniques, for example, drying, drying under vacuum, spray drying, freeze drying, and agitated thin film drying.

The treatment of the compound of Formula III with (+)-2,3-dibenzoyl-D-tartaric acid to give the compound of Formula IV is carried out in a solvent.

The solvent is selected from the group consisting of ethers, ketones, nitriles and mixtures thereof. Examples of ethers include tetrahydrofuran, diisopropylether, 1,4-dioxane, and methyl *tert*-butyl ether. Examples of ketones include acetone, methyl vinyl ketone, methyl isobutyl ketone, and methylethyl ketone. An example of a nitrile is acetonitrile.

The treatment of the compound of Formula III with (+)-2,3-dibenzoyl-D-tartaric acid to give the compound of Formula IV is carried out for about 15 minutes to about 5 hours, for example, for about 30 minutes to about 2 hours.

The treatment of the compound of Formula III with (+)-2,3-dibenzoyl-D-tartaric acid to give the compound of Formula IV is carried out at a temperature of about 20°C to about 75°C, for example, about 25°C to about 70°C.

The compound of Formula IV may optionally be isolated by filtration, decantation, extraction, distillation, evaporation, chromatography, precipitation, concentration, crystallization, centrifugation, or recrystallization. The compound of Formula IV may be dried using conventional techniques, for example, drying, drying under vacuum, spray drying, freeze drying, and agitated thin film drying.

The compound of Formula IV is treated with a base in a solvent to give ruxolitinib of Formula V.

The base is an inorganic or an organic base. Examples of inorganic bases include sodium carbonate, lithium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide, potassium hydroxide, and lithium hydroxide. Examples of organic bases include triethylamine, pyridine, *N,N* -diisopropylethylamine, and 1,8-diazabicylo [5 .4. 0]undec-7-ene .

The solvent is selected from the group consisting of water, esters, halogenated hydrocarbons, ketones, and mixtures thereof. Examples of esters include ethyl acetate, methyl acetate, propyl acetate, and butyl acetate. Examples of halogenated hydrocarbons include dichloromethane, dichloroethane, chloroform, and carbon tetrachloride. Examples of ketones include acetone, methyl vinyl ketone, methyl isobutyl ketone, butanone, 2-pentanone, and 3-pentanone.

The treatment of the compound of Formula IV with the base is carried out for about 5 minutes to about one hour.

The treatment of the compound of Formula IV with the base is carried out at a temperature of about 15°C to about 35°C, for example, about 20°C to about 25°C.

Ruxolitinib of Formula V may be isolated or the reaction mixture containing ruxolitinib of Formula V may be used as such for the next step.

Ruxolitinib of Formula V may be isolated by filtration, decantation, extraction, distillation, evaporation, chromatography, precipitation, concentration, crystallization, centrifugation, or recrystallization. Ruxolitinib of Formula V may be dried using conventional techniques, for example, drying, drying under vacuum, spray drying, freeze drying, and agitated thin film drying.

Further, ruxolitinib of Formula V may be converted into ruxolitinib phosphate of Formula I by following a process described in the art, for example, in U.S. Patent Nos. 8,722,693 or 8,410,265, or by following the method described herein.

While the present invention has been described in terms of its specific aspects and embodiments, certain modifications and equivalents will be apparent to those skilled in the art, and are intended to be included within the scope of the present invention.

Methods

NMR spectrum was recorded using a Bruker® AVANCE III (400 MHz) NMR spectrometer.

Chiral purity was determined by HPLC using a Waters® Alliance® HPLC e2695 Separations Module. The HPLC Column used was a CHIRALCEL® OD-H (250 x 4.6 mm) 5 μm.

Chromatographic purity was determined using an Acquity® UPLC, H-Class System, Model ChA. The column used was an HSS C-18 (100 x 2.1 mm) 1.8 μιη.

IR was recorded using a Perkin Elmer® Spectrum One FTIR Spectrometer.

The following examples are for illustrative purposes only and should not be construed as limiting the scope of the invention in any way.

EXAMPLES

Reference Example:

Preparation of ruxolitinib phosphate (Formula I) as per procedure disclosed in U.S. Patent No. 8.410.265

Step a: Preparation of **(2*S*,3*S*)-2,3**-bis(benzoyloxy)succinic acid **-(3i?)-3**-cyclopentyl **-3-[4**-(7-**{[2**-(trimethylsilyl)ethoxy]methyl}-7 ***H***-pyrrolo **[2,3-i**/]-pyrimidin **-4**-yl)**-l *H***-pyrazol **-l** -yl]propanenitrile

The title compound was prepared by following the procedure disclosed at column 163, lines 1-27 of U.S. Patent No. 8,410,265.

Step b: Preparation of **(3i?)-3**-cyclopentyl **-3-[4**-(7-**[2**-(trimethylsilyl)ethoxymethyl]-7***H***-pyrrolo **[2,3-i**/|-pyrimidin **-4**-yl)**-l *H***-pyrazol **-l** -yl]propanenitrile

The title compound was prepared by following the procedure disclosed at column 163, lines 36-59 of U.S. Patent No. 8,410,265.

Step c: Preparation of **(i?)-3-(4**-(7***H***-pyrrolo **[2,3**-^pyrimidin **-4**-yl)**-l *H***-pyrazol **-l** -yl)**-3-**cyclopentylpropanenitrile (Formula V)

The title compound was prepared by following the procedure disclosed at column 149, lines 16-58 of U.S. Patent No. 8,410,265.

Step d: Preparation of ruxolitinib phosphate (Formula **I)**

The title compound was prepared by following the procedure disclosed at column 152, lines 1-24 of U.S. Patent No. 8,410,265.

Chiral purity: 68.59 %

Example 1: Preparation of 3-cvclopentyl-3-r4-(7-r2-(trimethylsilyl)ethoxymethyll-7 *H*-pyrrolor2.3-Jl-pyrimidin-4-yl)-l *H*-pyrazol-l-yllpropanenitrile (Formula Ila or Formula II. when Pg is 2-(trimethylsilyl)ethoxymethyl)

Step a: Preparation of 4-chloro-7-{[2-(trimethylsilyl)ethoxy]methyl }-7*H*-pyrrolo[2,3-i/|pyrimidine

4-Chloro-7*H*-pyrrolo[2,3-<f]pyrimidine (100 g) was dissolved in dimethylacetamide (700 inL) at -10°C to 0°C to obtain a solution. The solution was added drop-wise to a mixture of sodium hydride (60%, 31.26 g) in dimethylacetamide (200 mL) to obtain a reaction mixture. The reaction mixture was stirred for 1 hour at 0°C to -2°C. 2-(Trimethylsilyl)ethoxymethyl chloride (119.37 g) was added drop-wise to the reaction mixture at 0°C to -10°C and the reaction mixture was stirred for 2 hours at 0°C to 5°C. After completion of the reaction, deionized (DI) water (1000 mL) and methyl fert-butyl ether (1000 mL) were added to the reaction mixture and the reaction mixture was stirred for 10 minutes at 20°C to 25°C. The layers obtained were separated and the aqueous layer was extracted with methyl *tert*-butyl ether (500 mL). The combined organic layers were washed with DI water (2 × 500 mL) and concentrated under reduced pressure at 40°C to 45°C to obtain the title compound, which was used as such for next step.

Step b: Preparation of 4-(l*H*-pyrazol-4-yl)-7-{[2-(trimethylsilyl)ethoxy]methyl }-7*H*-pyrrolo[2,3-*d*]pyrimidine

Nitrogen gas was purged through a mixture of 4-chloro-7- {[2-(trimemylsilyl)ethoxy]memyl}-7 *H*-pyIrolo[2,3-<f]pyrm^dine (as prepared in Step a), denaturated spirit (DNS) (1.85 L) and 4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-l *H*-pyrazole (176.96 g) for 15 minutes to 20 minutes. Aqueous potassium carbonate solution (269.96 g of potassium carbonate dissolved in 925 mL of DI water) was added to the mixture under nitrogen at 25°C to 30°C. Purging of nitrogen gas was continued for 20 minutes to 30 minutes at 25°C to 30°C. Tetrakis-triphenyl phosphine palladium (0) (15 g) was added to the reaction mixture under nitrogen atmosphere and the temperature of the reaction mixture was raised to 50°C to 60°C. Nitrogen purging was stopped and the reaction mixture was refluxed at 78°C to 80°C for 14 hours to 15 hours. The reaction mixture was cooled to room temperature and DI water (3700 mL) was added slowly at 25°C to 30°C. The reaction mixture was stirred for 1 hour and the solid obtained was filtered and dried in an air oven at 55°C to 60°C. Methyl *tert*-butyl ether (370 mL) was

added to the dried solid (230 g) and the mixture was stirred at 25°C to 30°C for 30 minutes. The solid obtained was filtered, washed with methyl *tert*-butyl ether (2 × 92.5 mL), and then dried under vacuum at 40°C to 45°C for 10 hours to 12 hours to obtain title compound.

Yield: 166.4 g

Step c: Preparation of 3-cyclopentyl-3-[4-(7-[2-(trimethylsilyl)ethoxymethyl]-7*H*-pyrrolo[2,3-i/|-pyrimidin-4-yl)-l *H*-pyrazol-l-yl]propanenitrile

3-Cyclopentylacrylonitrile (76.06 g) (prepared as per the procedure disclosed in U.S. Patent No. 7,598,257) was added to a mixture of 4-(l*H*-pyrazol-4-yl)-7-{[2-(trimethylsilyl)ethoxy]methyl}-7*H*-pyrrolo[2,3-£/]pyrimidine (165 g, as prepared in Step b) in dimethylsulfoxide (825 mL). Powdered potassium carbonate (16.58 g) was added to the reaction mixture and the temperature of the reaction mixture was raised to 43°C to 45°C. The reaction mixture was stirred for 24 hours. The reaction mixture was cooled to 20°C to 25°C and DI water (3300 mL) was added to the reaction mixture at 10°C to 25°C. The aqueous layer was extracted with ethyl acetate (825 mL) and the organic layer was collected. The aqueous layer was again extracted with ethyl acetate (825 mL) and the organic layer was collected. The combined organic layers were washed with DI water (825 mL) and concentrated under reduced pressure at 45°C to 50°C to obtain title compound, which was used as such for next step.

Example 2: Preparation of 3-(4-(7*H*-pyrrolo[2.3-J]pyrimidin-4-yl)-l *H*-pyrazol-l-yl)-3-cvclopentylpropanenitrile (Formula III)

Boron trifluoride etherate solution (185.56 g) was added to a solution of 3-cyclopentyl-3-[4-(7-[2-(trimethylsilyl)ethoxymethyl]-7 *H*-pyrrolo[2,3-£/]-pyrimidin-4-yl)-l*H*-pyrazol-l-yl]propanenitrile (Formula IIa or II, as prepared in Step c of Example 1) in acetonitrile (1.32 L) at 10°C to 20°C. The reaction mixture was stirred for 4 hours to 5 hours at 20°C to 25°C. DI water (330 mL) was added to the reaction mixture and the reaction mixture was stirred for 30 minutes at 25°C to 30°C. Ammonia solution (28%, 231 mL diluted with DI water (462 mL)) was added to the reaction mixture and the reaction mixture was stirred for 30 minutes at 25°C to 30°C. Ethyl acetate (825 mL) and sodium chloride (20%, 825 mL) were added to the reaction mixture and the reaction mixture was stirred for 10 minutes. The layers were separated and the aqueous layer was extracted with ethyl acetate (495 mL). The combined organic layers were washed with

1M sodium bicarbonate solution (825 mL) followed by hot DI water (2 × 825 mL). The organic layer was separated and treated with carbon at 60°C to 65°C for 1 hour. The mixture was cooled, filtered through a Hyflo®, and then washed with ethyl acetate (165 mL). The filtrate was concentrated under reduced pressure at 45°C to 50°C to obtain a residue. Toluene (330 mL) was added to the residue and the mixture was concentrated under reduced pressure at 45°C to 50°C to obtain the title compound, which was used as such for the next step.

Example 3: Preparation of (2^·.3^)-2.3-bis(benzoyloxy)butanedioic acid - (3i?)-3-cvclopentyl-3-r4-(7*H*-pyrrolor2.3-J|pyrimidin-4-yl)-l *H*-pyrazol-l-yllpropanenitrile (Formula IV)

3-(4-(7*H*-Pyrrolo[2,3-t/]pyrimidin-4-yl)-l *H*-pyrazol-l-yl)-3-cyclopentylpropanenitrile (59.5 g, Formula III, as prepared in Example 2) was dissolved in acetonitrile (1190 mL) and the temperature of the reaction mixture was raised to 50°C. (+)-2,3-Dibenzoyl-D-tartaric acid (34.79 g) was added to the reaction mixture at 50°C and the reaction mixture was stirred for 15 minutes. The reaction mixture was cooled to 25°C gradually, and then stirred for 1 hour to 2 hours at 20°C to 25°C. The reaction mixture was again heated to 68°C to 70°C and the reaction mixture was stirred for 30 minutes. The reaction mixture was cooled to 25°C gradually, and then stirred for 1 hour to 2 hours at 20°C to 25°C to obtain a solid. The solid was filtered and washed with acetonitrile (100 mL). The wet solid thus obtained was purified further three times with acetonitrile (3 × 600 mL) and three times with acetonitrile: acetone :tetrahydrofuran (300 mL (225:37.5:37.5); 220 mL (165:27.5:27.5); and 188 mL (141:23.5:23.5)). The wet solid obtained was dried under reduced pressure at 40°C to 42°C to obtain the title compound.

Yield: 9 g

Chiral purity: 99.95%

Chromatographic purity: 99.91%

^{1}H NMR (DMSO d_6, 400 MHz): δ 14.0 (brs, IH), 12.16 (s, IH), 8.79 (s, IH), 8.67 (s, IH), 8.36 (s, IH), 8.01 (d, 4H), 7.75-7.71 (m, 2H), 7.62-7.58 (m, 5H), 6.98-6.97 (m, IH), 5.87 (s, 2H), 4.54-4.53 (m, IH), 3.32-3.16 (m, 3H), 2.49-2.41 (m, IH), 1.81-1.60 (m, IH), 1.58-1.20 (m, 7H)

IRAmax (KBr): 3117.04, 3071.08, 1726.06, 1627.60, 1599.62, 816.72, 713.20 cm^{-1}

Example 4: Preparation of (j?)-3-(4-(7*H*-pyrrolor2.3-Jlpyrimidin-4-yl)-l *H*-pyrazol-l-yl)-3-cvclopentylpropanenitrile (Formula V)

A solution of sodium hydroxide (10%, 18 mL) was added to a mixture of *(2S,3S)*-2,3-bis(benzoyloxy)butanedioic acid - (3i?)-3-cyclopentyl-3-[4-(7*H*-pyrrolo[2,3-<f]pyrimidin-4-yl)-l*H*-pyrazol-l-yl]propanenitrile (12 g, Formula IV, as prepared in Example 3), ethyl acetate (240 mL), and DI water (60 mL) at 20°C to 25°C to adjust the pH to 9.5 to 10. The reaction mixture was stirred for 10 minutes to 15 minutes at 20°C to 25°C. The layers were separated and the aqueous layer was extracted with ethyl acetate (120 mL). The combined organic layers were washed with DI water (60 mL) and concentrated under reduced pressure at 40°C to 45°C to obtain the title compound, which was used as such in next step.

Example 5: Preparation of ruxolitinib phosphate (Formula I)

A mixture of (i?)-3-(4-(7*H*-pyrrolo[2,3-ii|pyrimidin-4-yl)-l *H*-pyrazol-l-yl)-3-cyclopentylpropanenitrile (Formula V, as prepared in Example 4) and isopropyl alcohol (84 mL) was heated to 60°C to 65°C for 10 minutes to 15 minutes. A solution of phosphoric acid (2. 1 g dissolved in 16.8 mL isopropyl alcohol) was added drop-wise to the reaction mixture at 60°C to 65°C. The reaction mixture was heated to 75°C and stirred for 1 hour at the same temperature. The reaction mixture was cooled to 25°C over 1.5 hours to 2 hours. The slurry obtained was stirred at 20°C to 25°C for 15 hours. The solid obtained was filtered, washed with isopropyl alcohol (12 mL), and then dried under reduced pressure at 40°C to 45°C to obtain the title compound.

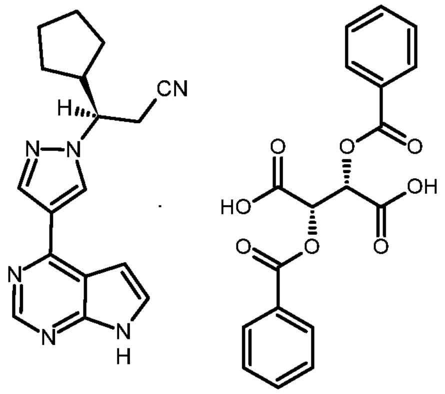
Yield: 6.4 g

Chiral purity: 99.96%

Chromatographic purity: 99.93 %

We claim

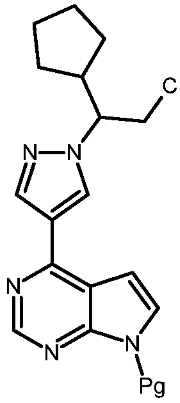
1. A process for the preparation of a compound of Formula IV,



Formula IV

wherein the process comprises:

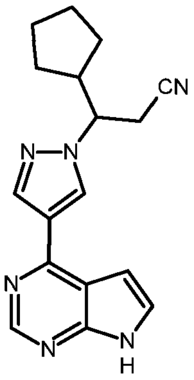
a) deprotecting a compound of Formula II



Formula II

wherein Pg is a protecting group selected from benzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, *t*-butoxycarbonyl, 2-(trimethylsilyl)ethoxymethyl, *N*-pivaloyloxymethyl, benzyloxymethyl, cyclohexyloxycarbonyl, 2-(4-trifluoromethylphenylsulfonyl)ethoxycarbonyl, vinyl, 2-chloroethyl, 2-phenylsulfonylethyl, allyl, benzyl, methoxymethyl, t-butoxymethyl, 2-tetrahydropyranyl, and 1,1-diethoxymethyl,

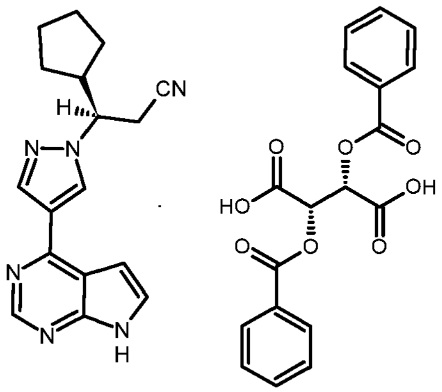
in the presence of a deprotecting agent to obtain a compound of Formula III; and



Formula III

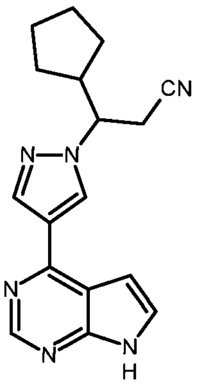
b) treating the compound of Formula III with (+)-2,3-dibenzoyl-Z)-tartaric acid to obtain the compound of Fonnula **IV.**

2. A process for the preparation of a compound of Formula **IV,**



Formula IV

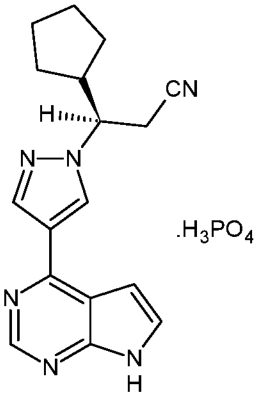
wherein the process comprises treating a compound of Formula III



Formula III

with (+)-2,3-dibenzoyl-D-tartaric acid.

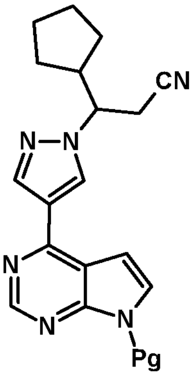
3. A process for the preparation of ruxolitinib phosphate of Formula I,



Formula I

wherein the process comprises:

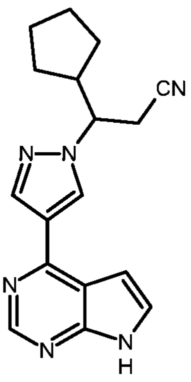
a) deprotecting a compound of Formula II



Formula II

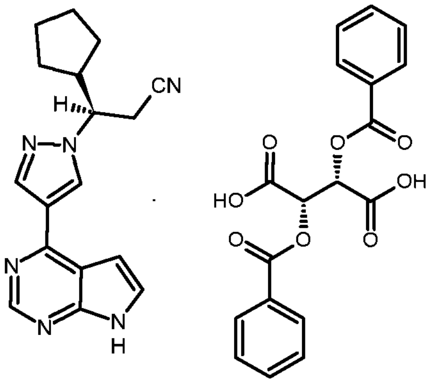
wherein Pg is a protecting group selected from benzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, *t*-butoxycarbonyl, 2-(trimethylsilyl)ethoxymethyl, *N*-pivaloyloxymethyl, benzyloxymethyl, cyclohexyloxycarbonyl, 2-(4-trifluoromethylphenylsulfonyl)ethoxycarbonyl, vinyl, 2-chloroethyl, 2-phenylsulfonylethyl, allyl, benzyl, methoxymethyl, t-butoxymethyl, 2-tetrahydropyranyl, and 1,1-diethoxymethyl,

in the presence of a deprotecting agent to obtain a compound of Formula **III**;



Formula III

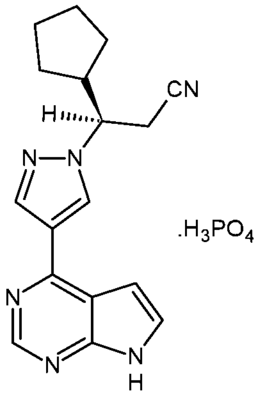
b) treating the compound of Formula **III** with (+)-2,3-dibenzoyl-Z)-tartaric acid to obtain a compound of Formula **IV; ** and



Formula IV

c) converting the compound of Formula **IV** to ruxolitinib phosphate of Formula **I**.

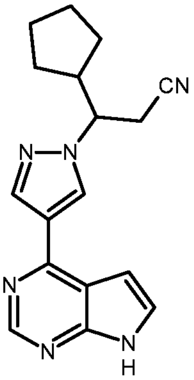
4. A process for the preparation of ruxolitinib phosphate of Formula **I**,



Formula I

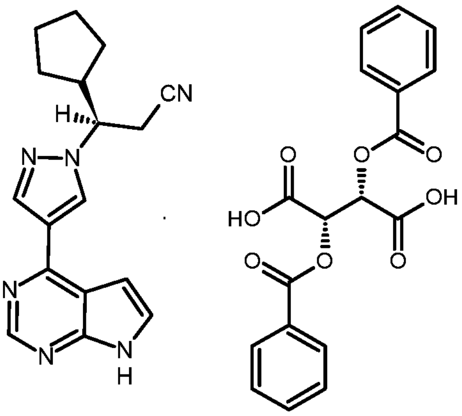
wherein the process comprises:

a) treating a compound of Formula **III**



Formula III

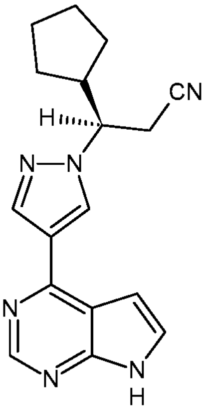
with (+)-2,3-dibenzoyl-D-tartaric acid to obtain a compound of Formula IV; and



Formula IV

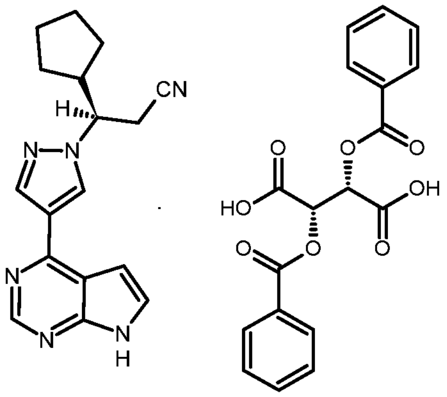
b) converting the compound of Formula IV to ruxolitinib phosphate of Formula I.

5. A process for the preparation of ruxolitinib of Formula V



Formula V

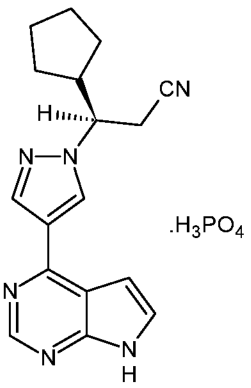
wherein the process comprises treating a compound of Formula IV



Formula IV

with abase.

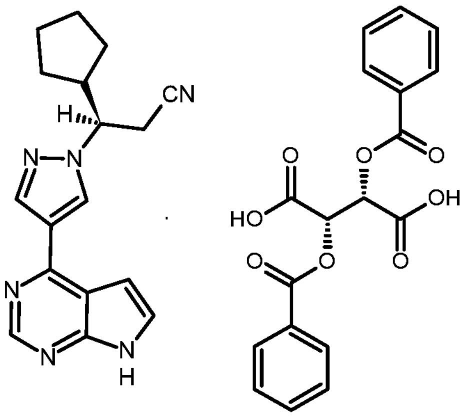
6. A process for the preparation of ruxolitinib phosphate of Formula I,



Formula I

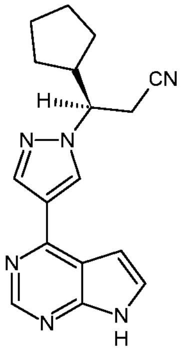
wherein the process comprises:

a) treating a compound of Formula IV



Formula IV

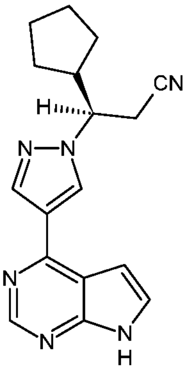
with a base to obtain ruxolitinib of Formula V; and



Formula V

b) converting the ruxolitinib of Formula V to ruxolitinib phosphate of Formula I.

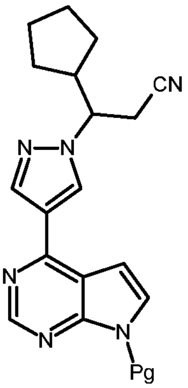
7. A process for the preparation of ruxolitinib of Formula V,



Formula V

wherein the process comprises:

a) deprotecting a compound of Formula II

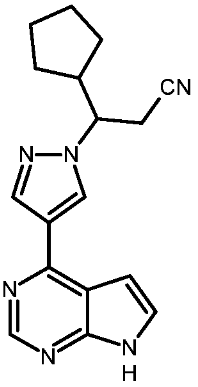


Formula II

wherein Pg is a protecting group selected from benzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, *t*-

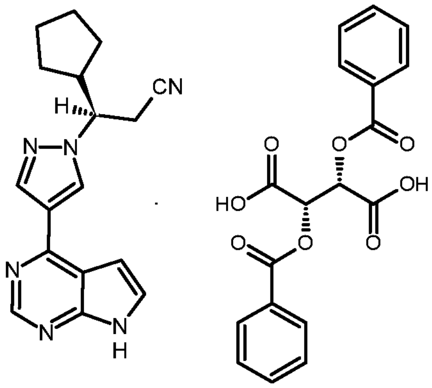
butoxycarbonyl, 2-(trimethylsilyl)ethoxymethyl, *N*-pivaloyloxymethyl, benzyloxymethyl, cyclohexyloxycarbonyl, **2-(4-**trifluoromethylphenylsulfonyl)ethoxycarbonyl, vinyl, 2-chloroethyl, 2-phenylsulfonylethyl, allyl, benzyl, methoxymethyl, t-butoxymethyl, 2-tetrahydropyranyl, and 1,1-diethoxymethyl,

in the presence of a deprotecting agent to obtain a compound of Formula III;



Formula III

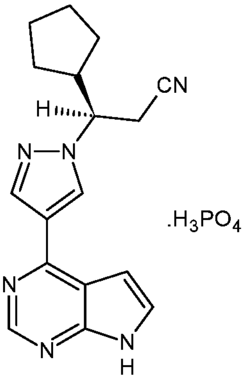
b) treating the compound of Formula III with (+)-2,3-dibenzoyl-D-tartaric acid to obtain a compound of Formula IV; and



Formula IV

c) treating the compound of Formula IV with a base to obtain ruxolitinib of Formula V.

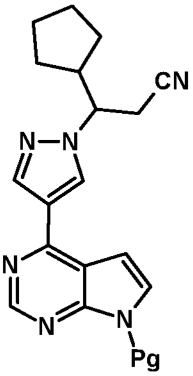
8. A process for the preparation of ruxolitinib phosphate of Formula I,



Formula I

wherein the process comprises:

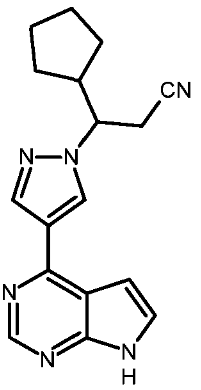
a) deprotecting a compound of Formula II



Formula II

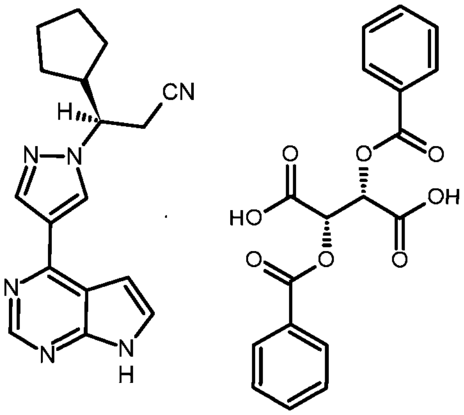
wherein Pg is a protecting group selected from benzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, *t*-butoxycarbonyl, 2-(trimethylsilyl)ethoxymethyl, *N*-pivaloyloxymethyl, benzyloxymethyl, cyclohexyloxycarbonyl, 2-(4-trifluoromethylphenylsulfonyl)ethoxycarbonyl, vinyl, 2-chloroethyl, 2-phenylsulfonylethyl, allyl, benzyl, methoxymethyl, t-butoxymethyl, 2-tetrahydropyranyl, and 1,1-diethoxymethyl,

in the presence of a deprotecting agent to obtain a compound of Formula III;



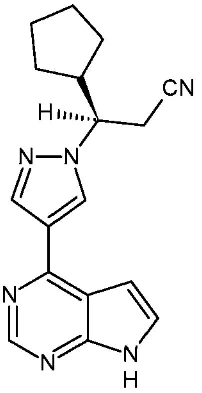
Formula III

b) treating the compound of Formula III with (+)-2,3-dibenzoyl-D-tartaric acid to obtain a compound of Formula IV;



Formula IV

c) treating the compound of Fonnula IV with a base to obtain nixolitinib of Fonnula V; and



Formula V

d) converting the ruxolitinib of Formula V to ruxolitinib phosphate of Fonnula I.

9. The process according to claim 1, 3, 7, or 8, wherein the compound of Formula II is deprotected in the presence of a deprotecting agent in a solvent.

10. The process according to claim 1, 3, 7, or 8, wherein the deprotecting agent is selected from the group consisting of boron trifluoride etherate, lithium tetrafluoroborate, and stannic chloride.

11. The process according to claim 9, wherein the solvent is selected from the group consisting of nitriles and halogenated hydrocarbons.

12. The process according to claim 11, wherein the nitrile is acetonitrile.

13. The process according to claim 11, wherein the halogenated hydrocarbons are selected from the group consisting of dichloroethane, dichloromethane, chloroform, and carbon tetrachloride.

14. The process according to claim 1, 2, 3, 4, 7, or 8, wherein the compound of Formula III is treated with (+)-2,3-dibenzoyl-D-tartaric acid in a solvent.

15. The process according to claim 14, wherein the solvent is selected from the group consisting of ethers, ketones, nitriles and mixtures thereof.

16. The process according to claim 15, wherein ethers are selected from the group consisting of tetrahydrofuran, diisopropylether, 1,4-dioxane, and methyl *tert*-butyl ether.

17. The process according to claim 15, wherein ketones are selected from the group consisting of acetone, methyl vinyl ketone, methyl isobutyl ketone, and methylethyl ketone.

18. The process according to claim 15, wherein the nitrile is acetonitrile.

19. The process according to claim 5, 6, 7, or 8, wherein the compound of Formula IV is treated with a base in a solvent.

20. The process according to claim 5, 6, 7, or 8, wherein the base is selected from an inorganic or an organic base.

21. The process according to claim 20, wherein the inorganic base is selected from the group consisting of sodium carbonate, lithium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide, potassium hydroxide, and lithium hydroxide; and the organic base is selected from the group consisting of triethylamine, pyridine, *N,N'*-diisopropylethylamine, and l,8-diazabicyclo[5.4.0]undec-7-ene.

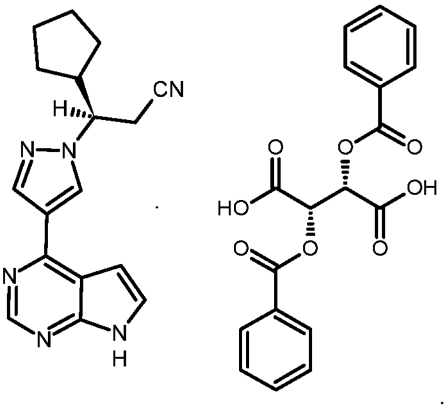
22. The process according to claim 20, wherein the solvent is selected from the group consisting of water, esters, halogenated hydrocarbons, ketones, and mixtures thereof.

23. The process according to claim 22, wherein the esters are selected from the group consisting of ethyl acetate, methyl acetate, propyl acetate, and butyl acetate.

24. The process according to claim 22, wherein the halogenated hydrocarbons are selected from the group consisting of dichloromethane, dichloroethane, chloroform, and carbon tetrachloride.

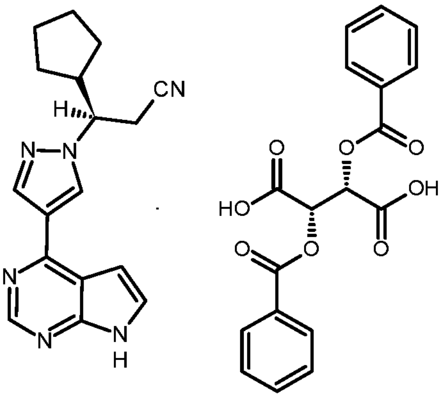
25. The process according to claim 22, wherein the ketones are selected from the group consisting of acetone, methyl vinyl ketone, methyl isobutyl ketone, butanone, 2-pentanone, and 3-pentanone.

26. A compound of Formula IV



Formula IV

27. Use of a compound of Formula IV



Formula IV

for the preparation of ruxolitinib phosphate.

Figure 1

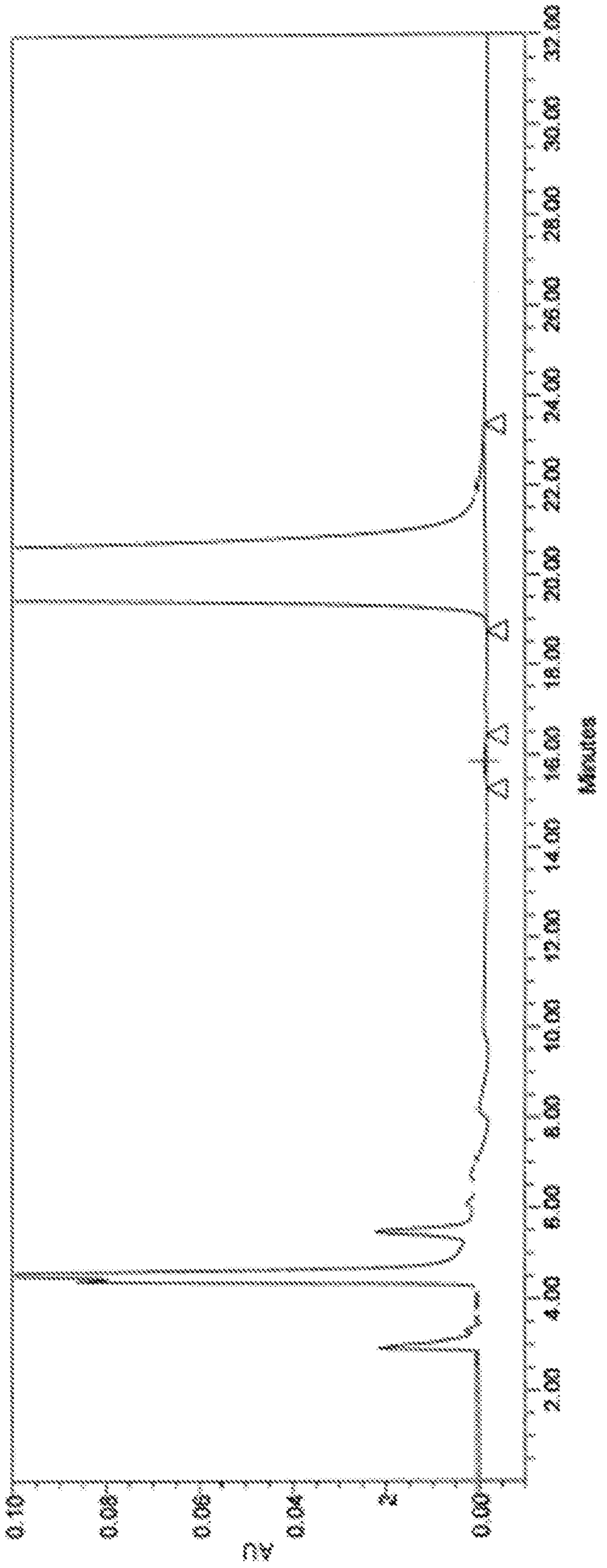

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Figure 2

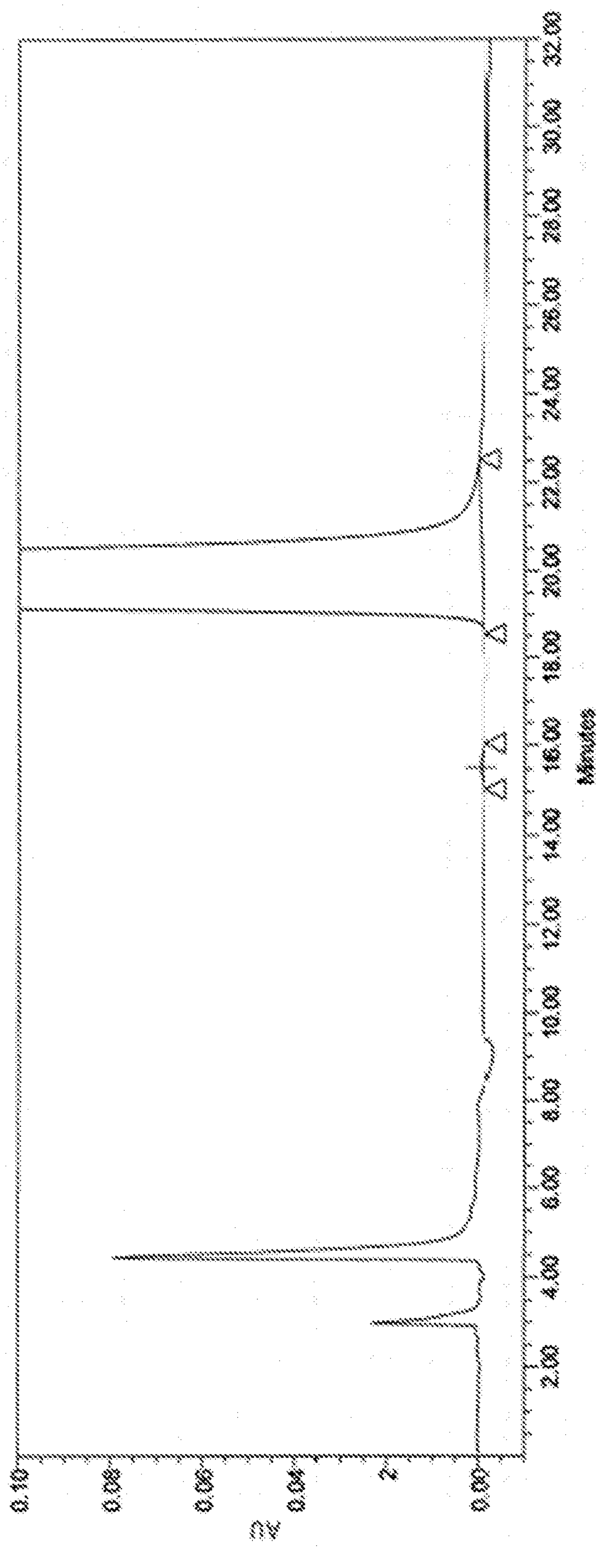
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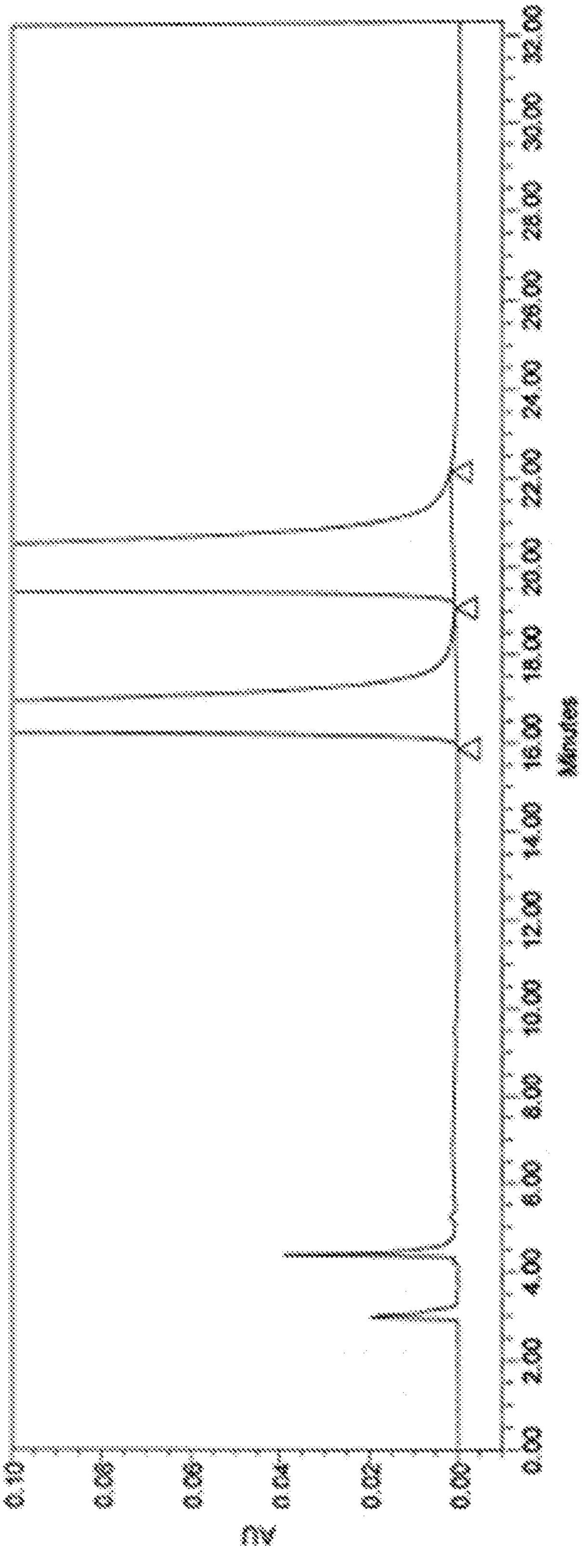
Figure 3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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2015/056642

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07D 403/14 (2015.01)

CPC - C07D 403/14 (2015.10)

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(8) - C07D 403/14, 487/04 (2015.01)
CPC - C07D 403/14, 487/04 (2015.10)

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

USPC - 544/280; IPC(8) - C07D 403/14, 487/04 (2015.01); CPC - C07D 403/14, 487/04 (2015.10) (keyword delimited)

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

Orbit, STN, PubChem, Google Scholar.
Search terms used: ruxolitnib, phosphate, tartaric, pyrrol*, pyrimidin*, pyrazol*, cyclopent*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2013/0253190 A1 (ZHOU) 26 September 2013 (26.09.2013) entire document	1-27
A	US 2012/0214825 A1 (VANNUCCHI et al) 23 August 2012 (23.08.2012) entire document	1-27
A	US 2008/0312259 A1 (RODGERS et al) 18 December 2008 (18.12.2008) entire document	1-27

☐ 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 application or patent but published on or after the international filing date

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

18 November 2015

Date of mailing of the international search report

28 DEC 2015

Name and mailing address of the ISA/

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