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Process for the preparation of (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile fumarate

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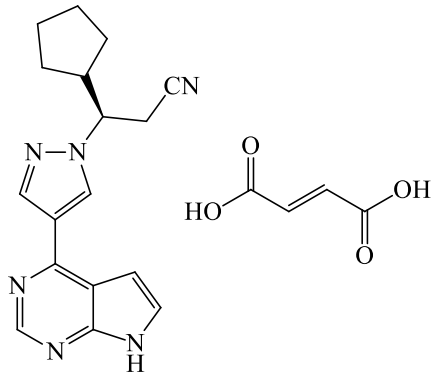
Process for the preparation of (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile fumarate

Abstract:

Process for the preparation of crystal modification 1 of (R)-3-(4-(7Hpyrrolo[2,3-d] pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile fumarate of formula-1a, which is represented by the following structural formula:



Formula-1a

Introduction:

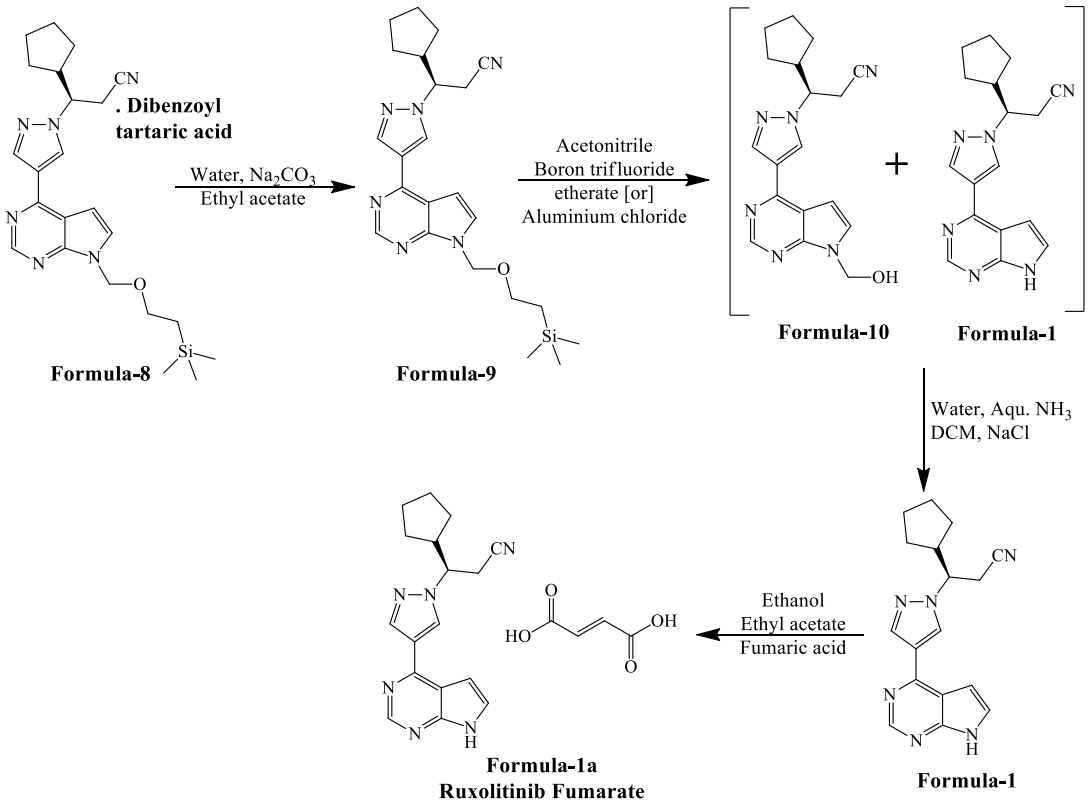
(R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropane nitrile is commonly known as Ruxolitinib, which is a selective inhibitor of Janus Associated Kinase 1 (JAK1) and JAK2 which mediates the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function.

Ruxolitinib phosphate is approved under the brand name Jakafi in the USFDA and Jakavi in Europe for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, postpolycythemia vera myelofibrosis and postessential thrombocythemia myelofibrosis.

(R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropane nitrile or a pharmaceutically acceptable salt is disclosed in US7598257 B2.

WO2017125097 A1 discloses crystal modification 1 of Ruxolitinib fumarate and process for its preparation.

The present invention involves process for the preparation of crystal modification 1 of (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile fumarate of formula-1a, schematically as mentioned below:



Experimental Section:

Example-1: Preparation of (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile fumarate.

Water (200 ml) and ethyl acetate (400 ml) was added to (R)-3-cyclopentyl-3-(4-(7-((2-(trimethylsilyl)ethoxy)methyl)-7Hpyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl) propanenitrile dibenzoyl tartaric acid (100 gms) at 25-30°C and stirred for 15 minutes. Adjusted the pH of the mixture to 3.0-4.0 using aqueous sodium carbonate solution at 25-30°C and stirred for 15 minutes. Layers were separated and aqueous layer was extracted using ethyl acetate. Combined the total organic layers. Water was added to the organic layer at 25-30°C and stirred for 20 minutes. Layers were separated and extracted the aqueous layer using ethyl acetate. Combined the organic layers. Distilled off the solvent from the organic layer under reduced pressure and co-distilled with acetonitrile.

Acetonitrile (450 ml) was added to the obtained compound at 25-30°C. Cooled the mixture to 10-15°C. Boron trifluoride etherate (35.95 gms) was slowly added to the mixture at 10-15°C. Raised the temperature of the mixture to 25-30°C and stirred for 5 hours. Cooled the mixture to 10-15°C. Water was added to the mixture. Raised the temperature of the mixture to 25-30°C and stirred for 2 hours. Cooled the mixture to 10-15°C. Aqueous ammonia solution was slowly added to the mixture at 10-15°C. Raised the temperature of the mixture to 25-30°C

and stirred for 30 hours. Water was added to the mixture and stirred for 10 minutes. Dichloromethane (800 ml) was added to the mixture at 25-30°C and stirred for 30 minutes. Layers were separated and extracted the aqueous layer with dichloromethane. Combined the organic layers and washed with aqueous sodium chloride solution. Layers were separated. Distilled off the solvent completely from the organic layer and co-distilled with ethyl acetate. To the obtained compound, ethyl acetate (180 ml) was added at 25-30°C. Raised the temperature of the mixture to 60-65°C and stirred for 15 minutes at the same temperature. Carbon (3.0 gms) was added to the mixture at 60-65°C and stirred for 30 minutes. Filtered the mixture through hyflow bed and washed the bed with ethyl acetate.

Fumaric acid (10.95 gms) was added to the above filtrate at 25-30°C and stirred for 45 minutes. Raised the temperature of the mixture to 70-75°C and stirred for 90 minutes. Cooled the mixture to 25-30°C and stirred for 4 hours at the same temperature. Filtered the precipitated solid, washed with ethyl acetate. To the obtained compound, ethyl acetate (144 ml) was added at 25-30°C. Raised the temperature of the mixture to 70-75°C and stirred for 90 minutes. Cooled the mixture to 25-30°C and stirred for 4 hours. Filtered the precipitated solid, washed with ethyl acetate and dried. Ethanol (144 ml) was added to the obtained compound at 25-30°C. Raised the temperature of the mixture to 75-80°C and stirred for 45 minutes. Filtered the mixture through hyflow bed and washed the bed with ethanol. The obtained filtrate was stirred for 4 hours at 25-30°C. Filtered the precipitated solid, washed with ethanol and dried to get the title compound. Yield: 29.0 gms.

Fumaric acid content: 15.5% w/w; Melting point by DSC: 169.38°C.

The PXRD of the obtained compound was depicted in figure-1.

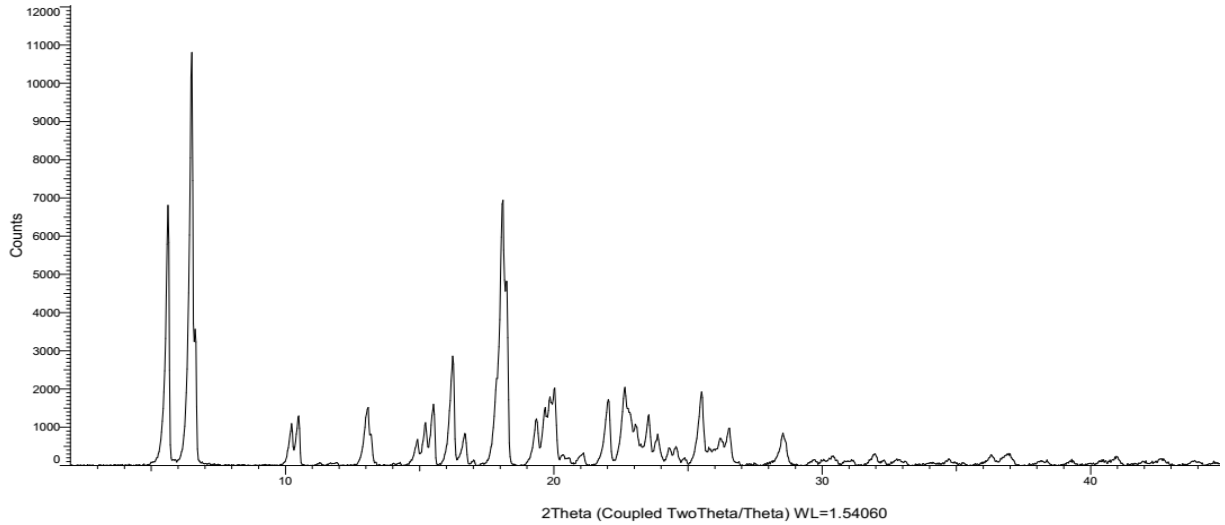


Figure-01

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