FORM 2

THE PATENTS ACT, 1970

(39 of 1970)

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The Patents Rules, 2003

COMPLETE SPECIFICATION

(Section 10 and Rule 13)

AN IMPROVED PROCESS FOR THE PREPARATION OF UPADACITINIB

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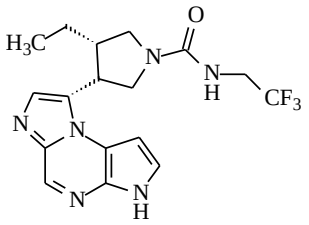
The following specification particularly describes the invention and the manner in which it is to be performed.

FIELD OF THE INVENTION

The present invention relates to an improved process for the preparation of Upadacitinib and its intermediates.

BACKGROUND OF THE INVENTION

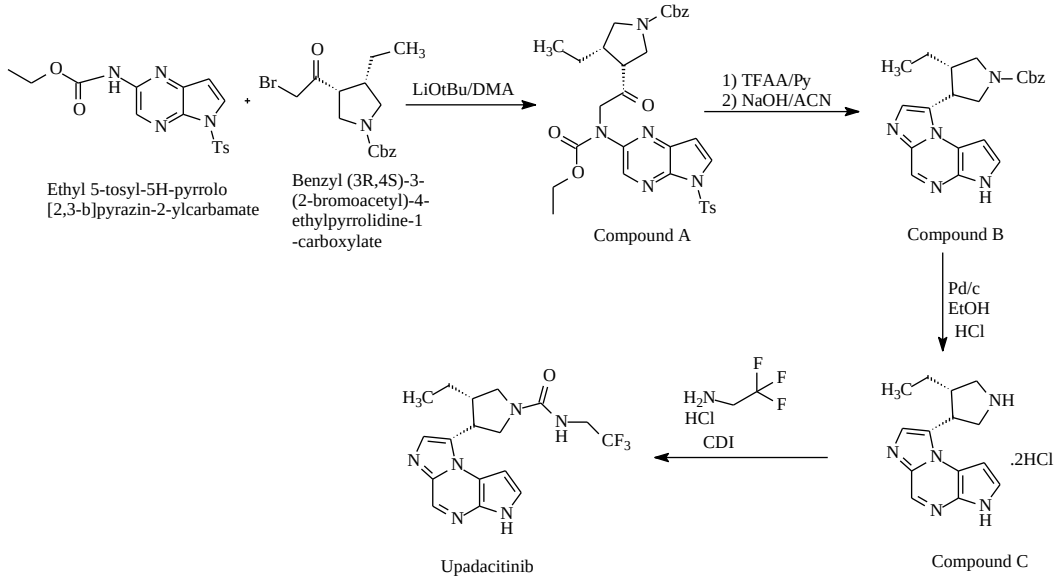
Upadacitinib is chemically known as (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide as shown below a Compound of Formula (1). It is developed by AbbVie and marketed under the brand name of Rinvoq®. Upadacitinib is a JAK1-selective inhibitor developed for the treatment of adult patients with moderate to severe rheumatoid arthritis.



Formula (1)

PCT application WO 2017/066775A1 describes a synthetic method of Upadacitinib comprising reacting ethyl-5-tosyl-5H-pyrrolo[2,3-b]pyrazin-2-ylcarbamate with benzyl (3R,4S)-3-(2-bromoacetyl)-4-ethylpyrrolidin-1-carboxylate in the presence of lithium tert-butoxide in dimethyl acetamide (DMA) to produce a Compound (A), which is treated with trifluoroacetic anhydride (TFAA), pyridine in acetonitrile to produce compound (B). The resulting compound is treated with Pd/C and hydrochloric acid to produce hydrochloride salt compound (C), which is treated with 2,2,2-trifluoroethylamine in the presence of *N*,*N*-carbonyldiimidazole to give Upadacitinib.

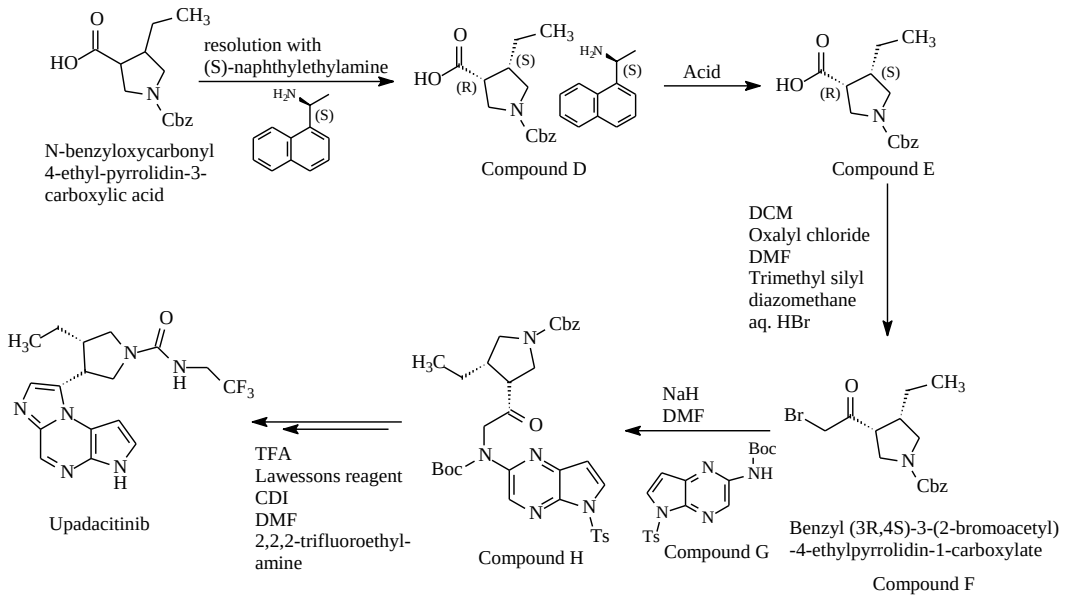
The process is as shown in Scheme-I below:



Scheme-I

During the preparation of compound A, 10-15% unreacted bromo compound was observed and due to this, compound B was synthesized in low yields. It involved tedious work up conditions and resulted in unwanted N-alkylated products during the preparation of compound C.

Further, PCT application WO 2019/016745 discloses a synthesis of Upadacitinib, which is described below. N-benzyloxycarbonyl-4-ethyl-pyrrolidine-3-carboxylic acid is treated with an optically active compound to produce an optically active salt of N-benzyloxycarbonyl 4-ethyl-pyrrolidine-3-carboxylic acid (compound D), which is treated with acid to produce an optically active N-benzyloxycarbonyl-4-ethyl-pyrrolidine-3-carboxylic acid (compound E). The resulting acid is treated with oxalyl chloride in the presence of trimethyl silyl diazomethane to produce compound F, which is further reacted with compound G to produce Upadacitinib as shown in Scheme-II below.



Scheme-II

It is observed that during the preparation of compound H, rigorous reaction conditions were used like the use of silyl reagents and moisture sensitive reagents which are difficult to handle in commercial scale. Also, the condensation of Boc intermediate (compound G) with bromo compound (compound F) in the presence of sodium hydride was leading to unwanted impurities.

Moreover, the prior art processes do not disclose a process of Upadacitinib, substantially free from impurities. The removal of the impurities from the API is essential as the compound is known to have impurities.

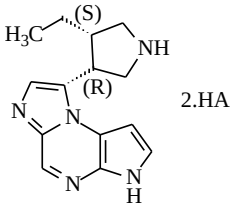
In view of this, our inventors have developed the present invention, which is surprisingly found advantageous over the reported processes.

OBJECTIVE OF THE INVENTION

The main objective of the present invention is an improved process for the preparation of Upadacitinib via preparation of novel salts of intermediate compound of formula (8) to obtain the product in high purity and good yield on a commercial scale.

SUMMARY OF THE INVENTION

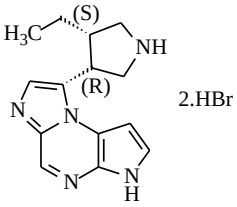
In one embodiment, the present invention provides a novel acid addition salt of compound of formula (3) and a process for the preparation thereof.



Formula (3)

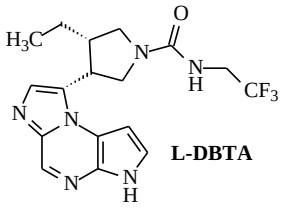
Wherein, HA is hydrobromic acid or an organic acid which comprises oxalic acid, maleic acid, citric acid, acetic acid, trifluoroacetic acid, propionic acid, malonic acid, succinic acid, fumaric acid, methane sulfonic acid, L-dibenzoyl tartaric acid, L-di-p-toluoyl tartaric acid and the likes.

In one embodiment, the present invention provides a novel crystalline dihydrobromide salt of compound of formula (3a) and a process for the preparation thereof.



Formula (3a)

In another embodiment, the present invention provides a novel crystalline L-dibenzoyl tartaric acid (L-DBTA) salt of Upadacitinib of formula (2) and a process for the preparation thereof.

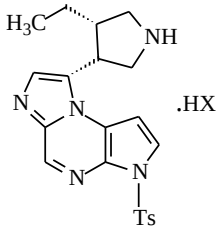


Formula (2)

In another embodiment, the present invention provides a process for the preparation of Upadacitinib (1) comprising the use of crystalline dihydrobromide salt of compound of formula (3a).

In another embodiment, the present invention provides a process for the preparation of Upadacitinib (1) comprising the use of crystalline L-DBTA salt of Upadacitinib (2).

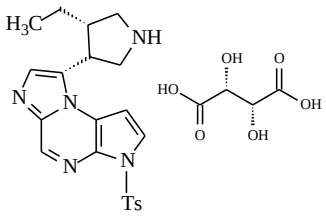
In another embodiment, the present invention provides a novel acid addition salt of compound of formula (8)



Formula (8)

Wherein, HX is an acid which comprises hydrochloric acid, hydrobromic acid, oxalic acid, maleic acid, citric acid, acetic acid, trifluoroacetic acid, propionic acid, malonic acid, succinic acid, fumaric acid, methane sulfonic acid, L-tartaric acid, L-dibenzoyl tartaric acid, L-di-p-toluoyl tartaric acid and the likes.

In another embodiment, the present invention provides a novel crystalline L-tartrate salt of compound of formula (8a) and a process for the preparation thereof.

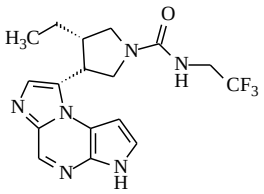


Formula (8a)

In another embodiment, the present invention provides a process for the preparation of Upadacitinib (1) comprising the use of crystalline L-tartrate salt of compound of formula (8a).

DETAILED DESCRIPTION OF THE INVENTION

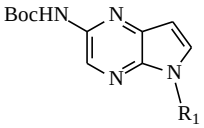
The present invention provides an improved process for the preparation of Upadacitinib (1):



Formula (1)

which comprises:

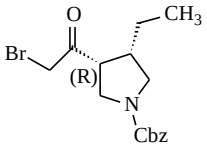
(i) reacting a compound of formula (7);



Formula (7)

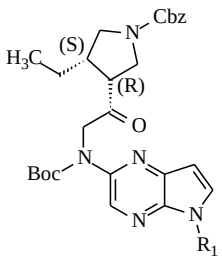
Wherein R_1 is an amino protecting group which comprises of p-toluene sulfonyl, pivaloyloxymethyl, benzyloxycarbonyl, allyl, benzyl, methoxymethyl, tert-butoxymethyl, benzyloxymethyl, p-methoxybenzyl, hydroxymethyl and/or tert-butoxycarbonyl.

with a compound of formula (6);



Formula (6)

in the presence of a base, to produce a compound of formula (5);

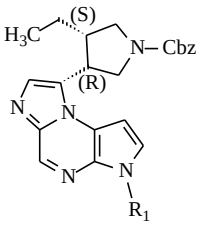


Formula (5)

Wherein R_1 is an amino protecting group described above.

(ii) Purifying the compound of formula (5) using ethanol, methanol, isopropanol (IPA), water or a mixture thereof;

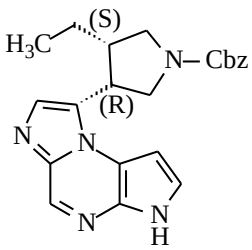
(iii) Cyclizing the compound of formula (5) with TFAA in the presence of organic or inorganic base to give compound of formula (4);



Formula (4)

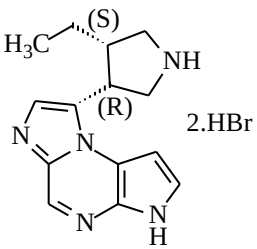
Wherein R_1 is an amino protecting group described above.

Further hydrolyzing the compound of formula (4) to give compound of formula (4b)



Formula (4b)

(iv) Deprotecting the compound of formula (4b) followed by reaction with hydrobromic acid to give a crystalline dihydrobromide salt of compound of formula (3a)



Formula (3a)

(v) Reacting the compound of formula (3a) with 2,2,2-trifluoroethylamine hydrochloride in the presence of suitable reagent(s) to give Upadacitinib (1).

The step (i) reaction is carried out in the presence of a base and a solvent at a temperature ranging from 0 to 80°C, more preferably at 20-50°C.

The step (iii) reaction is carried out in the presence of a base and solvent at a temperature ranging from 0 to 80°C, more preferably at 20-50°C. Wherein, the base is selected from pyridine, DMAP or 2-methoxy pyridine, more preferably DMAP.

The step (iv) reaction is carried out in the presence of a suitable catalyst and solvent. Wherein, the catalyst is selected from Pd/C, $Pd(OH)_2$.

The step (iv) deprotection is carried out in the presence of hydrogen atmosphere.

The deprotected compound obtained in step (iv) is treated with hydrobromic acid in alcohol solvents comprising of methanol, ethanol, isopropanol etc., to give dihydrobromide salt in a crystalline form resulting in improved purity of compound of formula (3a).

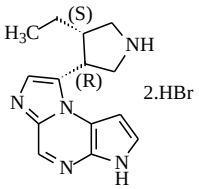
The step (iv) deprotection is carried out using hydrobromic acid in an alcoholic solvent to give compound of formula (3a).

The deprotected compound in step (iv) is treated with an organic acid comprising of oxalic acid, maleic acid, citric acid, acetic acid, trifluoroacetic acid, propionic acid, malonic acid, succinic acid, fumaric acid, methane sulfonic acid, L-dibenzoyl tartaric acid, L-di-p-toluoyl tartaric acid and the likes.

The step (v) reaction is carried out in the presence of 1,1'-carbonyldiimidazole (CDI), base and solvent(s).

The step (v) reaction is carried out in a solvent(s) which comprises THF, 2-Me-THF, dioxane, dimethoxyethane, ethyl acetate etc.

The present invention provides a process for the preparation of crystalline dihydrobromide salt of formula (3a).



Formula (3a)

which comprises:

(a) deprotecting compound of formula (4) in a suitable solvent; and

(b) adding hydrobromic acid to compound obtained from step (a);

(c) isolating the crystalline dihydrobromide salt of formula (3a).

The present invention further provides a process for the preparation of crystalline dihydrobromide salt of formula (3a), which comprises:

(a) deprotecting the compound of formula (4b);

(b) adding aq. hydrobromic acid to the solution obtained in step (a);

(c) isolating the crystalline dihydrobromide salt of formula (3a).

The present invention further provides a process for the preparation of crystalline dihydrobromide salt of formula (3a), which comprises:

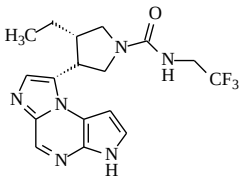
(a) dissovling the compound of formula (4b) in a suitable solvent;

(b) adding aq. hydrobromic acid to the solution obtained in step (a);

(c) isolating the crystalline dihydrobromide salt of formula (3a).

The crystalline dihydrobromide salt of formula (3a) is characterized by PXRD with characteristic peaks at 9.6, 14.2, 14.6, 14.8, 15.6, 16.2, 18.2, 18.7, 19.3, 19.8, 20.3, 21.7, 22.6, 24.2, 24.6, 25.2, 25.5, 26.1, 26.7, 27.0, 27.3 ± 0.2° (2θ).

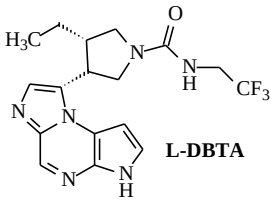
The present invention provides a process for preparation of Upadacitinib (1):



Formula (1)

which comprises:

(a) reacting compound of formula (3a) with 2,2,2-trifluoroethyl imidazole carboxamide in the presence of a base in a solvent or a mixture of solvents to give Upadacitinib which on further reacting with L-dibenzoyl tartaric acid in the presence of an organic solvent to give crystalline Upadacitinib L-dibenzoyl tartarate salt of compound of formula (2);



L-DBTA

Formula (2)

(b) further, reacting compound of formula (2) with a base in the presence of a solvent to give Upadacitinib (1).

The crystalline L-dibenzoyl tartrate salt of Upadacitinib is prepared in a solvent or a mixture of solvents comprising of THF, dioxane, ethyl acetate, acetonitrile, ethanol, methanol, n-butanol, isopropanol, isopropyl acetate, water or a mixture thereof.

The crystalline dibenzoyl tartrate salt of formula (2) is characterized by PXRD with characteristic peaks at 5.2, 6.4, 7.6, 8.6, 9.2, 9.6, 10.8, 12.2, 12.9, 13.6, 14.0, 14.3, 15.3, 16.4, 17.2, 18.6, 19.4, 19.8, 20.4, 21.6, 23.8, 24.6, 25.6, 26.2, 29.0, 30.7, 33.4, 35.6, 36.4, 37.3 ± 0.2° (2θ).

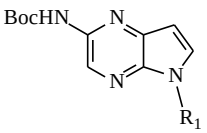
The isolation of crystalline Compound of Formula (2) results in improved purity of Upadacitinib by elimination of unwanted impurities carried over from previous steps.

The present invention provides a process for the preparation of Upadacitinib which comprises:

a) suspending crystalline Upadacitinib dibenzoyl tartrate in a solvent selected from THF, dioxane, ethyl acetate, ethanol, methanol, isopropanol, isopropyl acetate, water or a mixture thereof.
b) adjusting the pH between 9.0 to 9.5 using a suitable base selected from sodium hydroxide, potassium hydroxide, sodium carbonate or sodium bicarbonate.
c) separating the organic layer and treating with charcoal and
d) isolating Upadacitinib in a non-polar solvent.

The invention provides a process for the preparation of Upadacitinib (1) which comprises:

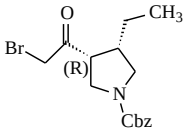
(i) reacting a compound of formula (7);



Formula (7)

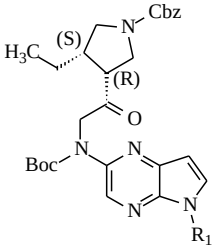
wherein R_1 is an amino protecting group described above.

with a compound of formula (6);



Formula (6)

in the presence of a base, to produce a compound of formula (5);

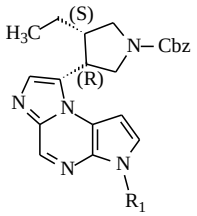


Formula (5)

wherein R_1 is an amino protecting group described above.

(ii) purifying the compound of formula (5) using ethanol, methanol, isopropanol (IPA), water or a mixture thereof;

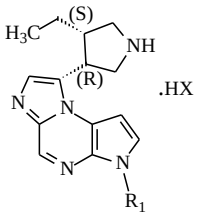
(iii) cyclizing the compound of formula (5) with TFAA in the presence of organic or inorganic base to give compound of formula (4);



Formula (4)

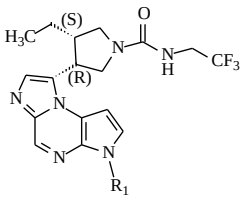
wherein R_1 is an amino protecting group described above.

(iv) deprotecting the compound of formula (4) using suitable reagent in the presence of a solvent followed by reaction with an acid to give corresponding salt of formula (8).



Formula (8)

(v) reacting the compound of formula (8) with 2,2,2-trifluoroethanamine hydrochloride in the presence of a suitable reagent to give compound of formula (9)



Formula (9)

(vi) deprotecting the compound of formula (9) to give Upadacitinib (1).

In still another embodiment, HX is an acid which comprises hydrochloric acid, hydrobromic acid or an organic acid which comprises oxalic acid, maleic acid, citric acid, acetic acid, trifluoroacetic acid, propionic acid, malonic acid,

succinic acid, fumaric acid, methane sulfonic acid, L-tartaric acid, L-dibenzoyl tartaric acid, L-di-p-toluoyl tartaric acid and the likes.

In step (iv), the suitable reagent used for Cbz deprotection is selected from Pd/C, Pd $(OH)_2$, hydrochloric acid or hydrobromic acid.

The base(s) used in the present invention comprises of inorganic bases like "alkali metal hydroxides" such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; "alkali metal carbonates" such as sodium carbonate, potassium carbonate, lithium carbonate and the like; "alkali metal bicarbonates" such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate and the like; "alkali metal hydrides" such as sodium hydride, potassium hydride, lithium hydride and the like; ammonia; and organic bases such as "alkali metal alkoxides" such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium methoxide, potassium ethoxide, potassium tert-butoxide and the like; triethyl amine, methylamine, ethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo(4.3.0)non-5-ene (DBN), lithium diisopropylamide (LDA), n-butyllithium, tribenzylamine, isopropylamine, diisopropylamine, diisopropylethylamine, N-methyl-2- pyrrolidone (NMP), N-methylmorpholine, N-ethylmorpholine, piperidine, 4-dimethylaminopyridine (DMAP), morpholine, pyridine, 2,6-lutidine, 2,4,6-collidine, imidazole, 1-methylimidazole, 1,2,4-triazole, 1,4-diazabicyclo[2.2.2]octane (DABCO) or mixtures thereof.

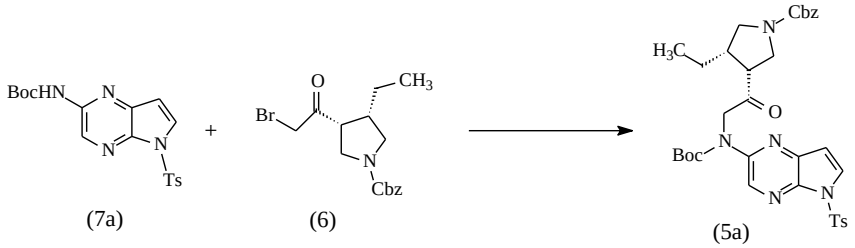
The solvent(s) used in present invention comprises of esters selected from ethyl acetate, and isopropyl acetate; aliphatic hydrocarbons selected from cyclohexane, n-hexane, n-heptane, and pentane; aromatic hydrocarbons selected from toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons selected from dichloromethane, chloroform, and ethylene dichloride; dialkyl formamides selected from dimethyl formamide; ethers selected from methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether, dimethyl ether, and methyl butyl ether; cyclic ethers selected from tetrahydrofuran, and 1,4-dioxane;

substituted cyclic ethers selected from 2-methyl tetrahydrofuran; alcohols selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, and diethylene glycol; ketones selected from acetone, methyl ethyl ketone, and methyl isobutyl ketone; dialkylsulfoxides selected from dimethyl sulfoxide; dialkylacetamides selected from N,N-dimethyl acetamide; nitriles selected from acetonitrile, and propionitrile; water and/or mixtures thereof.

The invention is illustrated with the following example, which is provided by way of illustration only and should not be construed to limit the scope of invention in any manner whatsoever.

EXAMPLES:

Example 1: Preparation of Compound (5a):

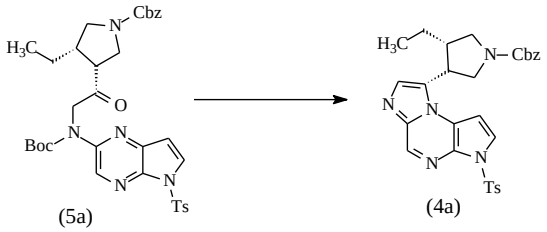


(7a) (6) (5a)

Tert-butyl-5-tosyl-5H-pyrrole [2, 3-b] pyrazine-2-yl-carbamate (**7a**) (100 g) was suspended in N, N-dimethylformamide (350 ml) at room temperature. The reaction mass was stirred to get clear solution. Later, potassium carbonate (177.80 g) was added and it was stirred for 120±10 min. The reaction mass was cooled to 0-10°C and (3R, 4S)-3-(2-bromoacetyl)-4-ethyl-1-pyrrolidine carboxylic acid phenyl methyl ester (**6**) (104.62 g) was added in 4 lots at 0-10°C. The reaction mass was stirred for 5 hours at 0-10°C. After completion of the reaction, the reaction mass was filtered and the filtration bed was washed with N, N-dimethylformamide. The filtrate was suspended into water (2000 ml) at room temperature and the reaction mass was stirred for 60±10 min. The resultant product was filtered and washed with water (100 ml X 2). The above wet filtered mass (~600g) was suspended in water (500ml) and stirred for 60±10 min at room temperature. The product was filtered and washed with water (100ml x 1) & methanol (100ml x 1). The wet filtered mass (~315g) was suspended in methanol

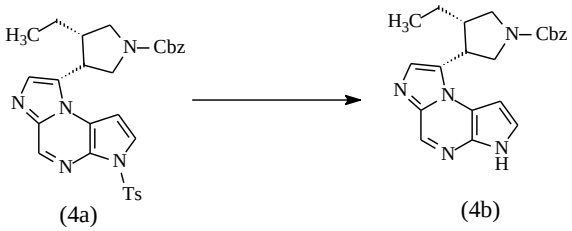
(1000ml) and stirred at 40-45°C for 60±10min. Later, the reaction mass was cooled to 20-30°C and stirred for 12±1h. The product was filtered and washed with methanol (100ml x 2). The wet filtered mass (~185 g) was dried under reduced pressure (~20 mm Hg) for 2 h±15 min to give desired compound (5a).

Example 2: Preparation of Compound (4a):



Compound (**5a**) (100 g) was suspended in acetonitrile (400 ml) at room temperature under nitrogen atmosphere. The reaction mass was stirred for 15 min to obtain clear solution. After obtaining clear solution, dimethyl-amino pyridine (1.85 g) was added and stirred for 10 min. The reaction mass was cooled to 0-10°C and trifluoro acetic anhydride (95.30 g) was added into it. Later reaction temperature was raised to 60-65°C and stirred for next 6 to 7 hours. After completion of the reaction, the reaction mass was concentrated below 55°C under reduced pressure (100-200 mm Hg). Further, it was cooled to room temperature and 2-Methyl THF (500 ml) added into it. The reaction mass was stirred to get uniform solution, diluted with water (500 ml) and stirred for 20±5 min. The layers were separated and organic layer was taken as such for next step.

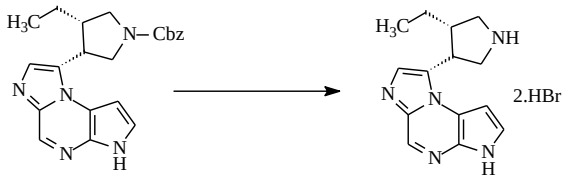
Example 3: Preparation of Compound (4b):



300 ml aqueous sodium hydroxide solution (20% w/v) was added to 2-methyl THF solution of compound (**4a**) at room temperature. The temperature was raised to 50-55°C and stirred for 4 to 5 hours. The reaction mass was cooled

to 10-20°C and pH was adjusted to 7.0-7.5 by slowly adding con. Hydrochloric acid. The reaction temperature was raised to 20-30°C and stirred for 25±5 min. The layers were separated. The separated organic layer was concentrated under reduced pressure (100-200 mm Hg) to one-fourth of its volume and proceeded to the next step.

Example 4: Preparation of crystalline Compound (3a):



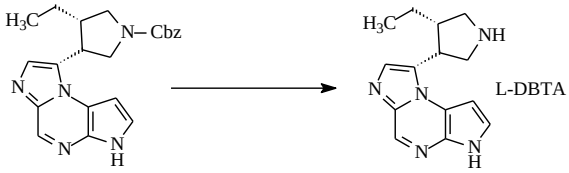
(4b) (3a)

Compound (4b) layer from the previous step was taken in ethanol into an autoclave. 10% w/w Palladium on carbon (11g) suspended in ethanol was charged into autoclave. To this ethanol (250 ml) was added under nitrogen atmosphere at 20-30°C. The autoclave was flushed with nitrogen. It was later evacuated and hydrogen gas was filled to maintain pressure at 10.0±0.5 Kg / cm^2. The reaction temperature was raised to 50-55°C, while maintaining hydrogen pressure. The stirring was continued for four hours at 50-55°C, while maintaining hydrogen pressure of 5.0±0.5 Kg. Thereafter, the reaction mass was cooled to 20-30°C and hydrogen from autoclave was displaced with nitrogen and catalyst was removed by filtration under nitrogen atmosphere. The residue was washed with ethanol (2 x 100 ml) under nitrogen atmosphere. To the above filtrate, aq. hydrobromic acid (51.50 g, 47% w/w) was slowly added and stirring was continued for 30 min. The reaction mass was concentrated up to ~100ml at a temperature below 55°C under reduced pressure. The reaction mass was cooled to 20-30°C and later ethyl acetate (300 ml) was added. The stirring was continued for 2 h±30 min and after stirring, the product was filtered and washed with ethyl acetate (50ml x 2). The wet filtered mass (100g) was kept for drying under reduced pressure (~20 mm Hg) for 2 h±15 min to give desired compound (3a).

Example 4A: Preparation of crystalline Compound (3a) using alternative approach.

Compound (4b) was dissolved in Isopropanol (200 ml) and aq. HBr (130 g) was added at room temperature. The temperature of reaction mixture was slowly raised to 80-85°C and refluxed for around 10h to complete the debenzylation. After completion of reaction, solvent was removed by distillation and the resulting residue was crystallized with ethylacetate to give Compound (3a).

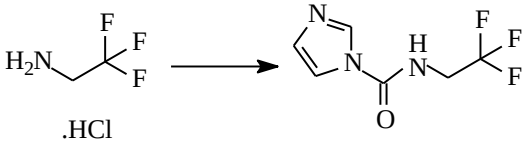
Example 4B: Preparation of crystalline Compound (3b).



(4b) (3b)

Compound (4b) (100 g) was dissolved in isopropanol (1000 ml), ammonium formate (40 g) was added and 5% palladium on charcoal (20 g) was added. The reaction mass was heated to 60-65°C and maintained for 2h. After completion of reaction, the reaction mass was cooled to 25-30°C. The catalyst was separated by filtration and solvent was removed by distillation and the resulting residue was dissolved in methyl isobutyl ketone (500 ml) and L-Dibenzoyl tartaric acid (54 g) was added at 25-30°C. The reaction mass was stirred for 8h at 25-30°C, filtered the product and washed and dried to give 98 g of crystalline compound (3b).

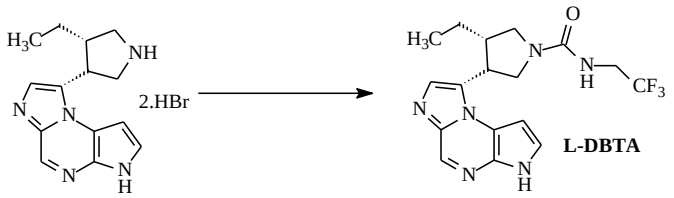
Example-5: Preparation of 2,2,2-trifluoro ethyl imidazole carboxamide:



2,2,2-trifluoroethylamine hydrochloride (52.6g) was suspended in Dichloromethane (750 ml) and 1,1-carbonyldiimidazole (58.6 g) was added at 0-10°C in two equal lots after 30min interval. The reaction was stirred for 30±5 min

after addition of second lot. To this reaction mass triethyl amine (42g) was slowly added and stirred at 10-20ºC for ~3h. A clear solution was obtained which is taken as such for the next step.

Example 6: Preparation of dibenzoyl L-(+) tartrate of Upadacitinib (2):

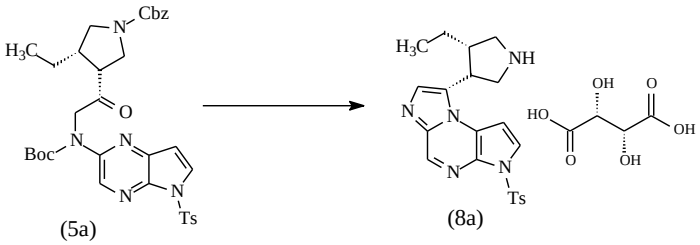


(3a) (2)

Compound (3a) (100g) was suspended in a mixture of tetrahydrofuran (500 ml) and DM water (250 ml) at 20-30°C. The reaction mass was stirred for 15 min to obtain a clear solution. Later, potassium phosphate dibasic (45.9 g) was added to the reaction mass and stirring continued for 30 min. The pH of the reaction mass was adjusted to 8.0 ± 0.2 with 10% w/v aqueous potassium hydroxide at 20-30°C followed by addition of tetrahydrofuran solution of 2,2,2-trifluoro ethyl imidazole carboxamide. The combined reaction mass was stirred for an hour. 20% w/v aqueous citric acid (500 ml) was added to the above reaction mass and stirred for 1h ± 10 min at room temperature. Ethyl acetate (500 ml) was added into it and continued to stir for 15 min. The layers were separated. The organic layer was charged with 15% w/v aqueous potassium dihydrogen phosphate (500 ml) and stirred for 25±5 min. The layers were separated. The organic layer was washed with 5% aqueous sodium bicarbonate & 10% aqueous sodium chloride solution. Later organic layer was concentrated at 40-50°C under reduced pressure (400-20 mm Hg) to get residue. Isopropyl acetate (300 ml) was added to the above residue and stirred for 15 min at room temperature. The reaction mass was diluted with isopropyl alcohol (100 ml) and DM water (75 ml) and stirred for 15 min at room temperature and later at 50-55°C. Isopropyl acetate solution of dibenzoyl L-(+)-tartaric acid (~ 1800 ml, prepared by dissolving dibenzoyl L-(+) tartaric acid (85.6 g) in 1700 ml isopropyl acetate at 25-30°C and stirred to clear solution) was added to the above reaction mass and stirred for

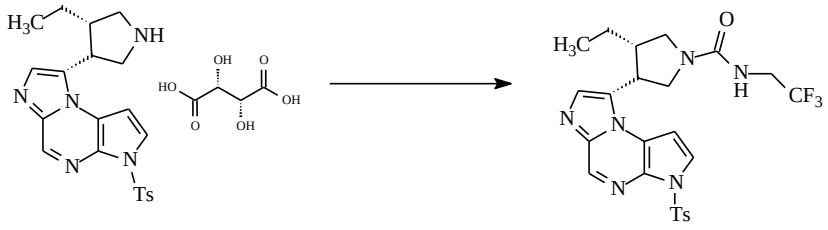
3h±30 min at 50-55°C. The precipitated product was cooled at room temperature and stirring was continued for 2h±15min. The product was filtered and washed with isopropyl acetate (150ml x 2). The wet filtered mass (~190 g) was dried at 45-50°C under reduced pressure (10-20 mm Hg) till loss on drying is ≤1% w/w (determined on 1 g at 105°C for 2h) to give desired compound (2). Weight of Upadacitinib dibenzoyl L-(+) tartrate: 160 g. Purity: (99.5%)

Example 7: Preparation of Compound of formula (8a) where R_1 is tosyl and HX is L-tartaric acid:



Compound (5a) 100g obtained from example-1 was dissolved in acetonitrile at 20-30ºC and cooled to 0-10ºC. To the cooled mixture, sodium bicarbonate (29.2g) and TFAA (190.4g) were added and raised the temperature to 50-60ºC and maintained for ~8h (monitored by HPLC). After the completion of reaction, the reaction mixture was cooled to room temperature and con. HCl (800 ml) was added at 20-40ºC (exothermic). The reaction mixture was then gradually heated to 50-60ºC and maintained for ~8h (monitored by HPLC). The reaction mixture was allowed to cool to room temperature and slowly added water (700ml) and n-heptane (400 ml) and separated the aqueous layer. Dichloromethane (500 ml) was added to the aqueous layer and cooled to 2-10ºC. The pH of the mixture was adjusted between 7.0-7.5 using 30% sodium hydroxide solution at 2- 20ºC. The organic layer was separated and washed with sodium bicarbonate solution (200ml X 2). To this organic layer, water (20ml), IPA (60ml) and L-tartaric acid (19.2g) were added and stirred at 20-30ºC for 45± 10min. Acetone (300 ml) was added to the reaction mass when the product started crystallizing out and was stirred for 2h ± 15min. It was then filtered and washed with acetone to give 74g of crystalline compound of formula (8a). Purity 99.57%.

Example 8: Preparation of compound of Formula (9a) where R_1 is tosyl:



(8a) (9a)

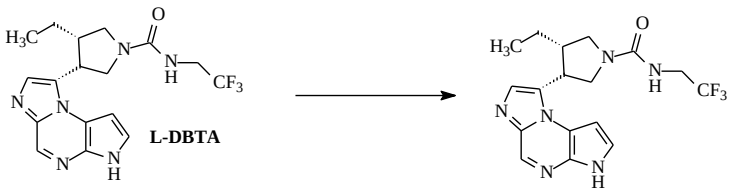
Compound (8a) 150g was suspended in DCM (1950ml) and water (450ml). To this suspension 7% aqueous sodium bicarbonate solution was added (2400ml) and stirred the reaction mixture for 20± 5min at 20-30ºC maintaining the pH not less than 7.5. The stirring was continued for ~2h and the organic layer was separated. The aqueous layer was washed with DCM (300ml) and the combined organic layer was washed with sodium chloride solution. The separated organic layer was concentrated partially up to 70% of the actual volume. This organic layer was slowly added to a solution containing 2,2,2-trifluoroethyl imidazole carboxamide (as prepared in example-5) at 10-20ºC to obtain a clear solution. This reaction mass was stirred for ~5h at 10-20ºC (monitored by HPLC). After completion of reaction water (750ml) was added to the reaction mass and stirred for 20±5 min. The organic layer was separated and washed with sodium chloride solution and concentrated upto ~150ml. To this DMF (450ml) was added and distilled to remove most of methylene chloride from concentrated mass. The concentrated mass was cooled to 20-30ºC and water (4500ml) was added slowly until the compound precipitated out. The precipitated compound was filtered and washed with water to give compound (9a) (300g wet compound).

Example 9: Preparation of Upadacitinib (1):

Compound (9a) (300g wet) obtained from example 8 was suspended in acetonitrile (525ml) to give a hazy mass. To this aqueous sodium hydroxide solution (920ml) was added at 20-30ºC. The reaction mixture was heated to 35-40ºC and maintained for ~4h (monitored by HPLC). After completion of reaction, the reaction mass was cooled to room temperature and adjusted the pH between

7.0-8.0 using 4% hydrochloric acid solution. To this Isopropyl acetate was added and stirred for 20±5 min. The organic layer was separated and washed with sodium chloride solution. The organic layer was concentrated and isolated in acetone to give Upadacitinib (1) 67.5g

Example 10: Preparation of Upadacitinib (1)

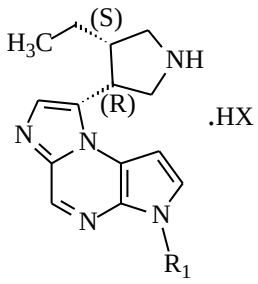


(2) (1)

Compound (2) (160 g) was suspended in DM water (800 ml) and ethyl acetate (1600 ml) and stirred for 10±5 min at room temperature. The pH was adjusted to 9.0±0.2 by adding 10% w/v aqueous sodium carbonate (500 ml) and stirring was continued at 25-30°C for 30±5 min. Layers were separated. The organic layer was concentrated till it results into solid residue. Methanol (200 ml) was added to the residue and concentrated it below 50°C under reduced pressure. Later, methanol (800 ml) was added to residue at room temperature and stirred for 30 min to get clear solution. After clear solution was obtained, carbon enoanticromos (4.0 g) was added and stirred for 25±5 min. The carbon was filtered through hyflo and was washed with methanol (100 ml). The filtrate was concentrated at a temperature below 50°C under reduced pressure (100-200 mm Hg) till it results into solid residue. n-Heptane (200 ml) was added to the residue and n-heptane was distilled out below 50°C under reduced pressure (100-200 mm Hg) to remove the traces of methanol. Again n-heptane (1000 ml) was charged to the reaction mass and stirred at room temperature for 12h ±15 min. The product was precipitated, later, it was filtered and washed with n-heptane. The obtained product (Upadacitinib-wet filtered mass, 220 g) was dried under reduced pressure till loss on drying is ≤1% w/w.

WE CLAIM:

1. Acid addition salt of compound of Formula (8)

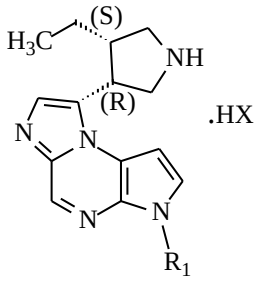


Formula (8).

Wherein, R_1 is an amino protecting group selected from p-toluene sulfonyl, pivaloyloxymethyl, benzyloxycarbonyl, allyl, benzyl, methoxymethyl, tert-butoxymethyl, benzyloxymethyl, p-methoxybenzyl, hydroxymethyl and/or tert-butoxycarbonyl.

Wherein, HX is an acid selected from hydrochloric acid, hydrobromic acid, oxalic acid, maleic acid, citric acid, acetic acid, trifluoroacetic acid, propionic acid, malonic acid, succinic acid, fumaric acid, methane sulfonic acid, L-tartaric acid, L-dibenzoyl tartaric acid, L-and di-p-toluoyl tartaric acid.

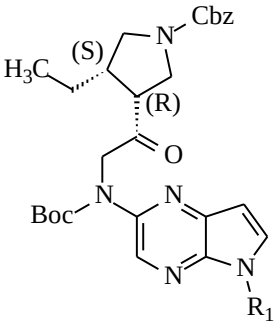
2. A process for the preparation of compound of formula (8)



Formula (8).

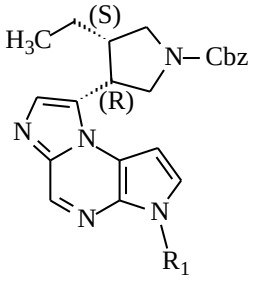
wherein, R_1 and HX are as described above, which comprises:

a) converting the compound of Formula (5);



Formula (5)

to compound of Formula (4)

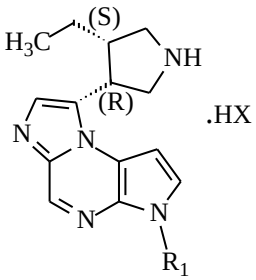


Formula (4)

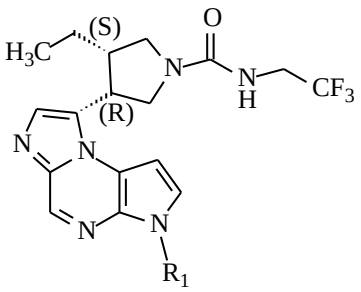
b) deprotecting the compound of formula (4) selectively with a suitable reagent in the presence of a solvent and treating the resulting compound with an acid to give compound of formula (8).

3. A process for the preparation of Upadacitinib (1) which comprises:

a) converting the compound of formula (8) into compound of formula (9)



Formula (8).



Formula (9)

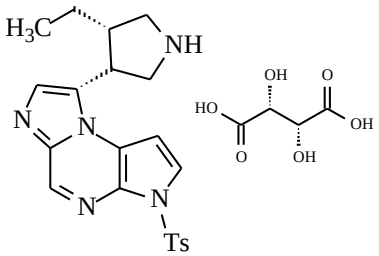
Wherein R_1 is as described above.

b) deprotecting the compound of formula (9) to give Upadacitinib (1).

4. The process as claimed in claim 2, wherein, step (a) is carried out using trifluoroacetic anhydride in the presence of a base selected from sodium carbonate, sodium bicarbonate, potassium carbonate and potassium bicarbonate, triethylamine, 4-dimethylaminopyridine (DMAP), pyridine, 2,6-lutidine.

5. The process as claimed in claim 2, wherein, the acid used in step (b) is selected from hydrochloric acid, hydrobromic acid or an organic acid which comprises oxalic acid, maleic acid, citric acid, acetic acid, trifluoroacetic acid, propionic acid, malonic acid, succinic acid, fumaric acid, methane sulfonic acid, L-tartaric acid, L-dibenzoyl tartaric acid, L-di-p-toluoyl tartaric acid.

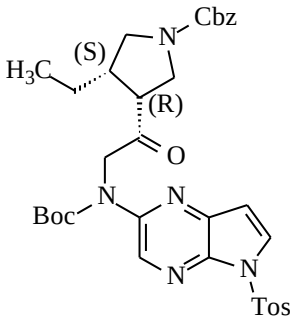
6. A process for the preparation of compound of formula (8a)



Formula (8a)

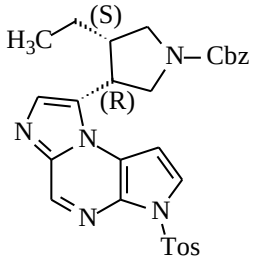
which comprises:

a) reacting the compound of formula (5a)



Formula (5a)

with trifluoroacetic anhydride in the presence of sodium bicarbonate to give compound of Formula (4a).

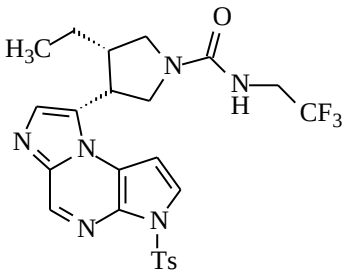


Formula (4a)

b) treating the compound of formula (4a) with hydrochloric acid in acetonitrile followed by neutralization of reaction and further reacting with L-tartaric acid in isopropyl alcohol to give crystalline L –tartrate salt compound of formula (8a)

7. The process as claimed in claim 5, further comprises:

c) treating the compound of formula (8a) with 2,2,2-trifluoroethylamine hydrochloride using a suitable reagent in the presence of a base to give tosyl protected Upadacitinib of compound of formula (9a)



Formula (9a)

d) deprotecting the compound of formula (9a) using aqueous sodium hydroxide solution in acetonitrile to give Upadacitinib (1).

Dated this 25 day of February 2023

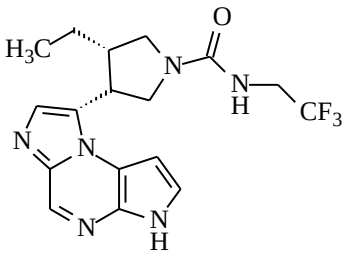
For Aurobindo Pharma Limited

Dr. M. Sivakumaran
Director

ABSTRACT

AN IMPROVED PROCESS FOR THE PREPARATION OF UPADACITINIB

The present invention relates to an improved process for the preparation of highly pure Upadacitinib via novel crystalline salts of intermediates.



Formula (1)