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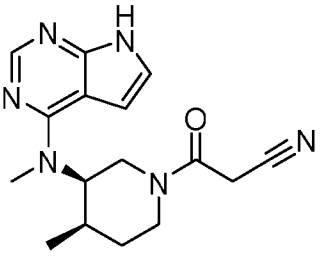
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(54) Titre : PROCEDE DE PREPARATION DE TOFACITINIB ET SON SEL PHARMACEUTIQUEMENT ACCEPTABLE
(54) Title: PROCESS FOR PREPARATION OF TOFACITINIB AND PHARMACEUTICALLY ACCEPTABLE SALT THEREOF



(I)

(57) Abrégé/Abstract:
The present invention relates to an improved process for preparation of tofacitinib (I) and pharmaceutically acceptable salt thereof.
(I)

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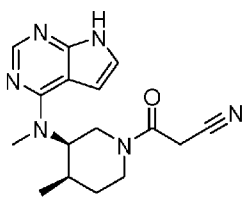
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(54) Title: PROCESS FOR PREPARATION OF TOFACITINIB AND PHARMACEUTICALLY ACCEPTABLE SALT THEREOF

(57) Abstract: The present invention relates to an improved process for preparation of tofacitinib (I) and pharmaceutically acceptable salt thereof. (I)



(I)

WO 2020/183295 A1

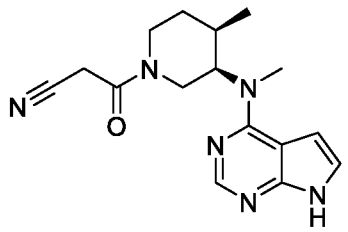
PROCESS FOR PREPARATION OF TOFACITINIB AND PHARMACEUTICALLY ACCEPTABLE SALT THEREOF

RELATED APPLICATION

This application is related to Indian Provisional Application No. IN 201921009802 filed on 13th March, 2020 and is incorporated herein in its entirety.

FIELD OF THE INVENTION

The present invention relates to an improved process for preparation of tofacitinib (I) and pharmaceutically acceptable salt thereof.



(I)

BACKGROUND OF THE INVENTION

The following discussion of prior art is intended to present the invention in appropriate technical context and allow its significance to be properly appreciated. Unless clearly indicated to the contrary, however reference to any prior-art in this specification should be construed as an admission that such art is widely known or forms part of common general knowledge in the field.

"Tofacitinib" is inhibitor of the enzyme Janus kinase 1 (JAK1) and Janus kinase 3 (JAK3), it interferes with the JAK-STAT signaling pathway. Tofacitinib is chemically known as (3R,4R)-4-methyl-3-(methyl-7H-pyrrolo [2,3-d]pyrimidin-4-ylamino)-ß-oxo-1- piperidinepropanenitrile, 2-hydroxy-1,2,3-propanetricarboxylate (1:1). Its empirical formula is $C_{16}H_{20}N_6O \cdot C_6H_8O_7$.

US Patent No. RE41783, US7265221 and US7301023 discloses (3R,4R)-4-methyl-3-(methyl-7H-pyrrolo [2,3-d]pyrimidin-4-ylamino)-ß-oxo-1-piperidinepropanenitrile and process for its preparation.

The WO2007/012953 A2 discloses process for preparation of tofacitinib wherein chiral purity of intermediate is very poor (84% cis isomer, having 68% ee), and also the process is silent about the chirality of the final tofacitinib citrate produced by this intermediate.

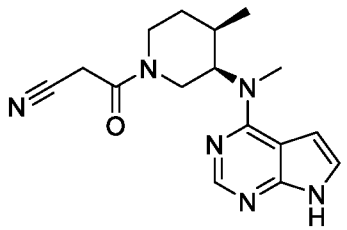
WO2014/195978 A2 discloses use of acetic acid in debenzylation step of process for preparation of tofacitinib and pharmaceutically acceptable salt thereof.

Org. Process Res. Dev. **2014**, *18* (12), pp 1714–1720 discloses process for preparation of tofacitinib.

In view of the above, it is therefore, desirable to provide an efficient, more economical, less hazardous and eco-friendly process for the preparation of tofacitinib and pharmaceutically acceptable salt thereof.

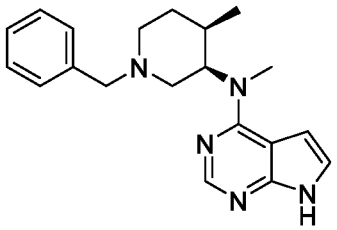
OBJECTS OF THE INVENTION

The main object of present invention is to provide an improved process for preparation of tofacitinib (I) and pharmaceutically acceptable salt thereof.



(I)

wherein, process comprises debenzylation of intermediate of formula (III) in presence of metal catalyst and pivalic acid.



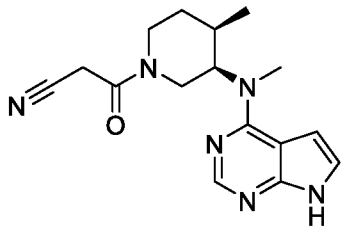
(III)

Another object of the present invention is to provide an improved process for preparation of tofacitinib citrate having dihydro impurity less than 0.2%.

Yet another object of the present invention is to provide process for preparation of tofacitinib citrate using substantially pure intermediate of formula (II).

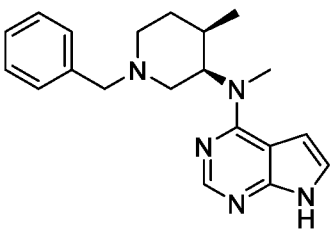
SUMMARY OF THE INVENTION

In one aspect the present invention provides an improved process for preparation of tofacitinib (I) or its pharmaceutically acceptable salt

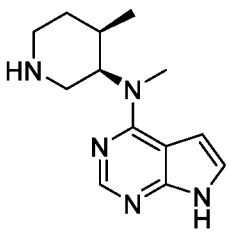


(I)

comprising, debenzylation of *N*-((3*R*,4*R*)-1-benzyl-4-methylpiperidin-3-yl)-*N*-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine intermediate of formula (III) in presence of metal catalyst and pivalic acid.



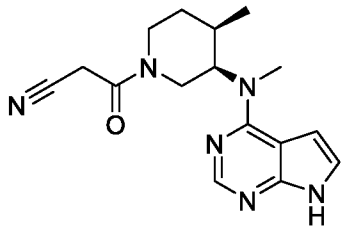
(III)



(II)

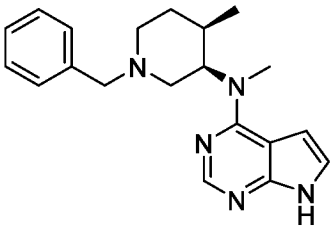
converting the resultant intermediate of formula (II) to tofacitinib citrate.

In another aspect the present invention provides an improved process for preparation of tofacitinib or its salt;

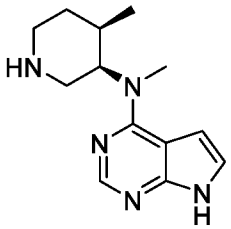


(I)

comprising, debenzylation of *N*-((3*R*,4*R*)-1-benzyl-4-methylpiperidin-3-yl)-*N*-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine intermediate of formula (III) in presence of palladium catalyst and pivalic acid.



(III)

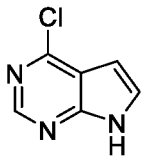


(II)

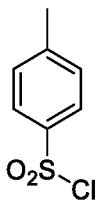
converting the resultant intermediate of formula (II) to tofacitinib citrate.

Yet another aspect of present invention is to provide a process for preparation of substantially pure tofacitinib citrate which comprises:

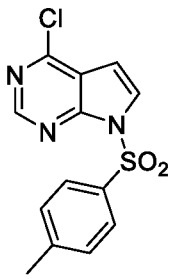
a) reacting compound of formula (VIII) with compound of formula (VII) to obtain compound of formula (VI);



(VIII)

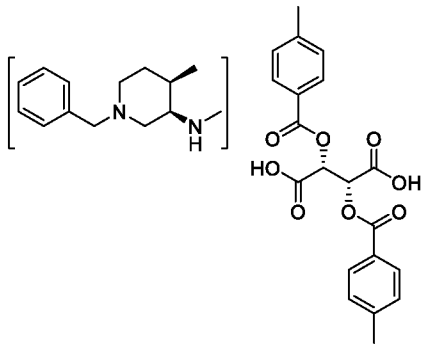


(VII)

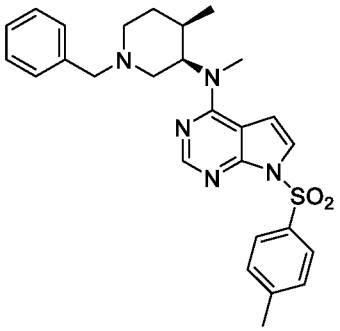


(VI)

b) reacting intermediate of formula (VI) and formula (V) in presence of water and alkali to obtain compound of formula (IV)

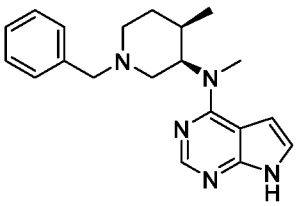


(V)



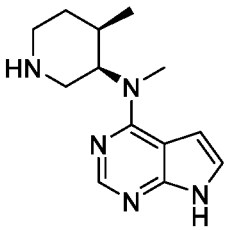
(IV)

c) converting compound of formula (IV) to compound of formula (III)



(III)

d) debenzylating compound of formula (III) in presence of pivalic acid and palladium catalyst to obtain compound of formula (II); and

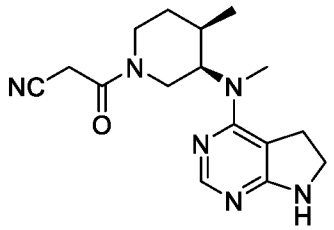


(II)

e) converting resultant compound of formula (II) to tofacitinib citrate

f) optionally purifying to obtain substantially pure tofacitinib citrate.

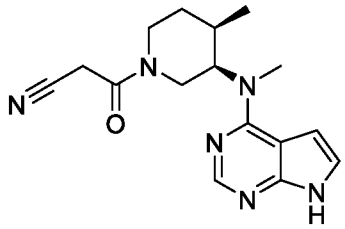
Yet another aspect of the present invention is to provide a process for preparation of substantially pure tofacitinib citrate having dihydro impurity (A) less than 0.2%, preferably less than 0.05%.



(A)

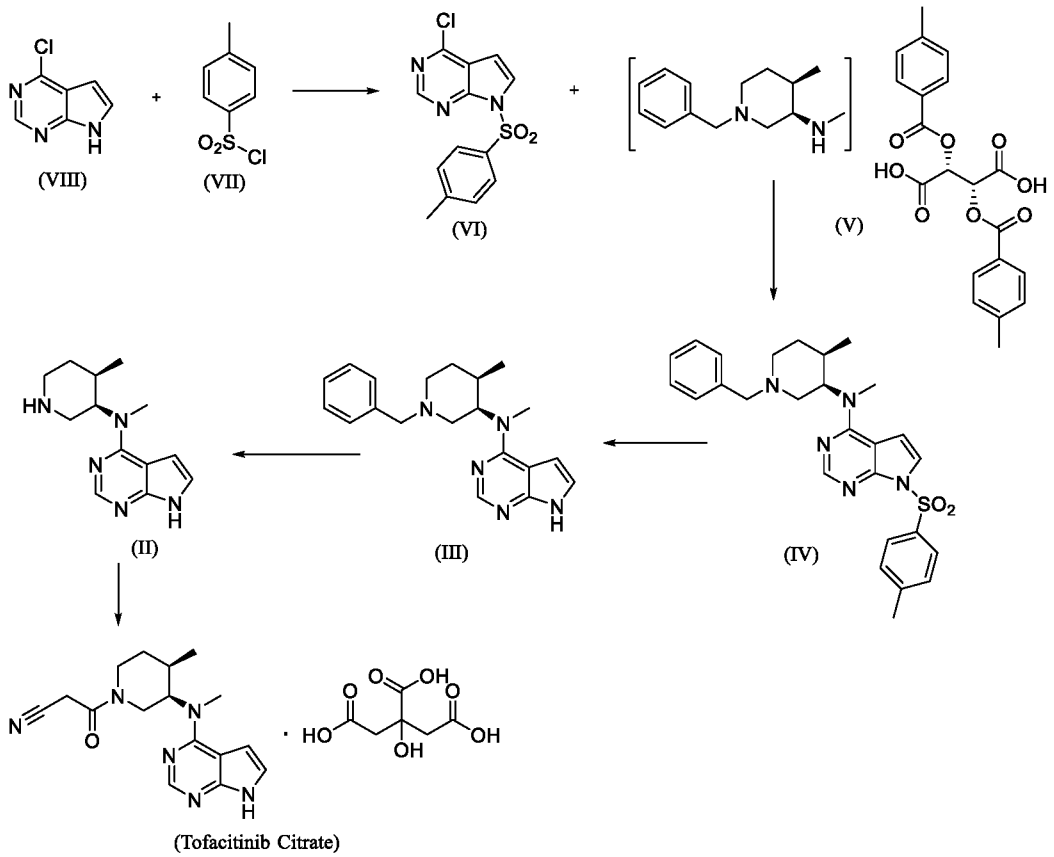
DETAILED DESCRIPTION OF THE INVENTION

The main embodiment of present invention provides a process for preparation of tofacitinib citrate;



(I)

accordingly, the complete process of present invention can be represented by following scheme.



Scheme 1

For the purpose of present invention intermediate of formula (VI) can be prepared by reacting compound of formula (VII) with compound of formula (VIII) as represented in stage I of above mentioned scheme. Which is further reacted with compound of formula (V) to obtain compound of formula (IV).

Compound of formula (IV) is hydrolyzed using alkali and water to obtain compound of formula (III), which is debenzylated by metal catalysts in presence of pivalic acid to obtain compound of formula (II). Wherein the metal catalyst can be selected from any suitable catalyst like palladium, platinum ruthenium or like. Preferably debenzylation is carried out in presence of palladium catalyst.

In an embodiment the process for preparation of intermediate of formula (II) wherein, said process is carried out in presence of pivalic acid.

The process for preparation of compound of formula (II) can be carried out in presence of suitable solvent such as aromatic hydrocarbon, alkanols or water. Suitably the reaction is carried out in presence of isopropanol, toluene, n-butanol, ethanol, water or mixture thereof.

The intermediate of formula (VI) obtained from stage I can be further converted to intermediate of formula (III) by any process known in the art. For the purpose of present invention the intermediate of formula (III) can be subjected to debenzylation in presence pivalic acid metal catalyst such as palladium. The reaction can be carried out in presence of any suitable solvent such as n-butanol, water. The intermediate of formula (II) obtained after debenzylation is converted to tofacitinib citrate. The crude tofacitinib citrate can be isolated from the reaction mixture by filtration and recrystallized to obtain substantially pure tofacitinib citrate.

Table 1: Summary of Debenzylation process of Tofacitinib

Sr. No	Acid (Volume)	Solvent-1 (Volume)	Solvent-2 (Volume)	Catalyst		Temp. (°C)	Pressure	Dihydro impurity by HPLC
				Type	Loading			
1.	Acetic acid (0.35)	Water (5)	-	10% Pd/C	20%	50°C	10	0.41
2.	Pivalic acid (0.35)	Water (5)	-	10% Pd/C	20%	50°C	10	0.05
3.	Acetic acid (0.35)	Water (5)	-	20% $Pd(OH)_2$	20%	50°C	10	0.17
4.	Pivalic acid (0.35)	Water (5)	-	20% $Pd(OH)_2$	20%	50°C	10	0.04
5.	Acetic acid (0.18)	Water (5)	-	10% Pd/C	20%	50°C	10	0.66
6.	Pivalic acid (0.18)	Water (5)	-	10% Pd/C	20%	50°C	10	0.06
7.	Pivalic acid (0.70)	Water (5)	-	10% Pd/C	20%	50°C	10	0.10
8.	Pivalic acid (0.35)	Water (5)	-	10% Pd/C	20%	55°C	10	0.19

9.	Pivalic acid (0.35)	Water (5)	-	10% Pd/C	20%	45°C	10	0.02
10.	Pivalic acid (0.35)	Water (5)	-	10% Pd/C	20%	60°C	10	0.46
11.	Trifluoro acetic acid (0.35)	Water (5)	-	10% Pd/C	20%	50°C	10	2.82%
12.	Acetic acid (0.2)	Water (10)	IPA (15)	20% $Pd(OH)_2$	15%	50°C	3-5	0.50
13.	Pivalic acid (0.2)	Water (5)	IPA (7.5)	20% $Pd(OH)_2$	15%	50°C	10	0.17

EXAMPLES

Example 1: 4-chloro-7-tosyl-7*H* pyrrolo[2,3-*d*]pyrimidine (VI)

In a three neck round bottom flask equipped with mechanical stirrer, thermometer and addition funnel, 4-methylbenzenesulfonyl chloride (86.9gm) in acetone (300ml) was added to the reaction mixture of 4-chloro-7*H* pyrrolo[2,3-*d*]pyrimidine (50gm), sodium hydroxide (19.6gm) and purified water (400ml). The resultant reaction mixture was stirred for completion of reaction and filtered. Resulting wet-cake was washed and dried at 40-50°C under vacuum to obtained 4-chloro-7-tosyl-7*H* pyrrolo[2,3-*d*]pyrimidine (VI).

Example 2: *N*-((3*R*,4*R*)-1-benzyl-4-methylpiperidin-3-yl)-*N*-methyl-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (IV)

In a three neck round bottom flask equipped with mechanical stirrer, thermometer and addition funnel, 4-chloro-7-tosyl-7*H* pyrrolo[2,3-*d*]pyrimidine (60gm) was added to the mixture of potassium carbonate (140gm) in purified water (780ml) and Bis-(3R,4R)-(1-benzyl-4-methyl-piperidine-3-yl)-methylamine di-p-toluoyl-L-tartarate. The reaction mixture thus obtained was heated up to 90-100°C. After completion of the reaction, reaction mixture was cooled, filtered and washed with purified water. Wet-cake thus obtained was purified with methanol (390ml) and dried under vacuum to obtain *N*-((3*R*,4*R*)-1-benzyl-4-methylpiperidin-3-yl)-*N*-methyl-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine.

Example 3: *N*-((3*R*,4*R*)-1-benzyl-4-methylpiperidin-3-yl)-*N*-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (III)

In a three neck round bottom flask equipped with mechanical stirrer, thermometer and addition funnel, *N*-((3*R*,4*R*)-1-benzyl-4-methylpiperidin-3-yl)-*N*-methyl-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (7gm) was added to aqueous solution of Sodium hydroxide (39.16gm). Reaction mixture was heated to 95-100°C and stirred. After completion of reaction, reaction mixture was cooled to 25-30°C and filtered. Resulting wet-cake was washed with water and dried under vacuum to obtain *N*-((3*R*,4*R*)-1-benzyl-4-methylpiperidin-3-yl)-*N*-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine.

Example 4: *N*-methyl-*N*-((3*R*,4*R*)-4-ethylpiperidin-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (II)

In a three neck round bottom flask equipped with mechanical stirrer, thermometer and addition funnel, *N*-((3*R*,4*R*)-1-benzyl-4-methylpiperidin-3-yl)-*N*-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (10gm) and catalytic amount of pivalic acid was added to purified water (50ml), to the reaction mixture 10% Pd/C was added. The

resulting reaction mixture was treated with hydrogen. After completion of reaction catalyst was filtered and washed with water. Filtrate thus obtained was basified with aqueous sodium hydroxide and product was extracted with n-butanol to obtain *N*-methyl-*N*-((3*R*,4*R*)-4-ethylpiperidin-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine.

Example 5: Tofacitinib citrate (crude)

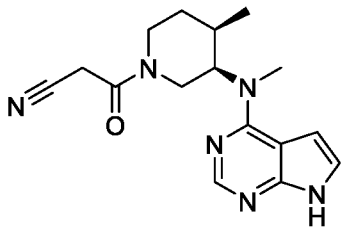
In a three neck round bottom flask equipped with mechanical stirrer, thermometer and addition funnel, *N*-methyl-*N*-((3*R*,4*R*)-4-ethylpiperidin-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (9.5gm) was added to n-butanol (45ml). To the resulting solution ethyl cyanoacetate (13gm) and 1,8-diazabicyclo[5.4.0]undec-7-ene (6gm) were added and maintained at 40-50°C. After completion of reaction aqueous citric acid solution was added and stirred. Solid thus obtained was cooled and washed with n-butanol then dried to obtain tofacitinib citrate.

Example 6: Tofacitinib citrate (purification)

In a three neck round bottom flask equipped with mechanical stirrer, thermometer and addition funnel, Tofacitinib crude thus obtained (10gm) was dissolved in water (300ml) at 80-90°C. Charcoal (0.5gm) was added to the reaction mixture and stirred for 30min. Charcoal was filtered and washed with hot water. Filtrate thus obtained was cooled to room temperature for 5-6 hr. and filtered. Solid thus obtained was washed with acetone and dried to obtain substantially pure tofacitinib citrate.

We Claim:

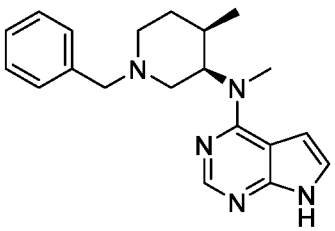
1. A process for preparation of tofacitinib (I) and pharmaceutically acceptable salt thereof



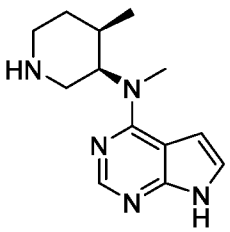
(I)

comprising:

a) debenzylation of *N*-((3*R*,4*R*)-1-benzyl-4-methylpiperidin-3-yl)-*N*-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine intermediate of formula (III) in presence of metal catalyst and pivalic acid to obtain intermediate of formula (II); and



(III)



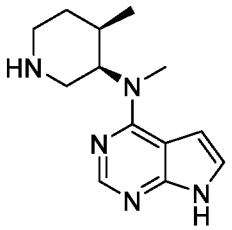
(II)

b) converting the compound of formula (II) to tofacitinib or its salt.

2. The process according to claim 1, wherein metal catalyst is selected from a group comprising palladium, platinum, ruthenium.

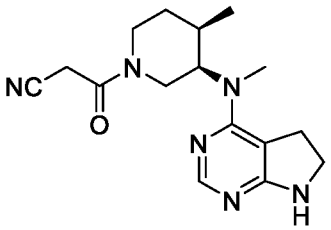
3. The process according to claim 1, comprising

a) debenzylating compound of formula (III) in presence of pivalic acid and metal catalyst to obtain a compound of formula (II); and



(II)

b) converting compound of formula (II) to tofacitinib having impurity of formula (A) less than 0.2%.

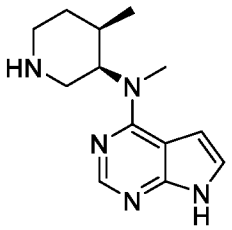


(A)

4. The process according to claim 3 wherein the tofacitinib is having impurity of formula (A) less than 0.05%.

5. The process according to claim 1, comprising:

a) debenzylating compound of formula (III) in presence of pivalic acid and metal catalyst to obtain a compound of formula (II)



(II)

b) converting compound of formula (II) to tofacitinib having less than 0.2% of impurity of formula (A); and

c) reacting tofacitinib with citric acid to obtain citrate salt of tofacitinib.

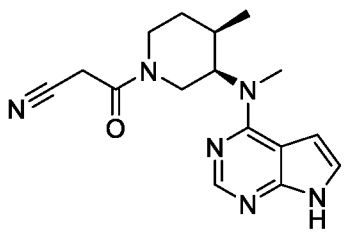
6. The process according to claim 1, comprising;
a) debenzylating compound of formula (III) in presence of metal catalyst and pivalic acid to obtain compound of formula (II); and
b) reacting compound of formula (II) with Ethyl cyanoacetate and citric acid to obtain tofacitinib citrate having impurity of formula (A) less than 0.2%.

7. The process according to claim 1, wherein the debenzylation is carried out in the presence of solvent selected from aromatic hydrocarbons, alkanols, water and mixture thereof.

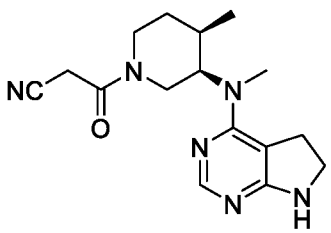
8. The process according to claim 7, wherein the solvent is selected from toluene, xylene, isopropanol, n-butanol, methanol, ethanol and water or mixture thereof.

9. The process according to claim 1, wherein tofacitinib or pharmaceutically acceptable salt thereof is having dihydro impurity of formula (A) less than 0.2%, more preferably less than 0.05%.

10. A tofacitinib or its pharmaceutically acceptable salt (I) having dihydro impurity (A) less than 0.2%

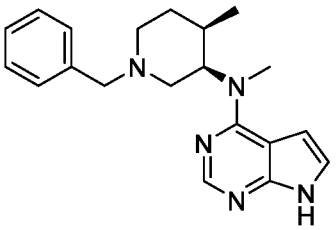


(I)

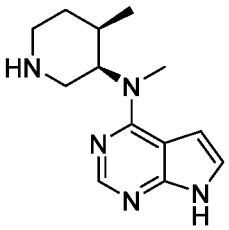


(A)

wherein the process comprises;
a) debenzylating compound of formula (III) in presence of pivalic acid and palladium catalyst to obtain a compound of formula (II)



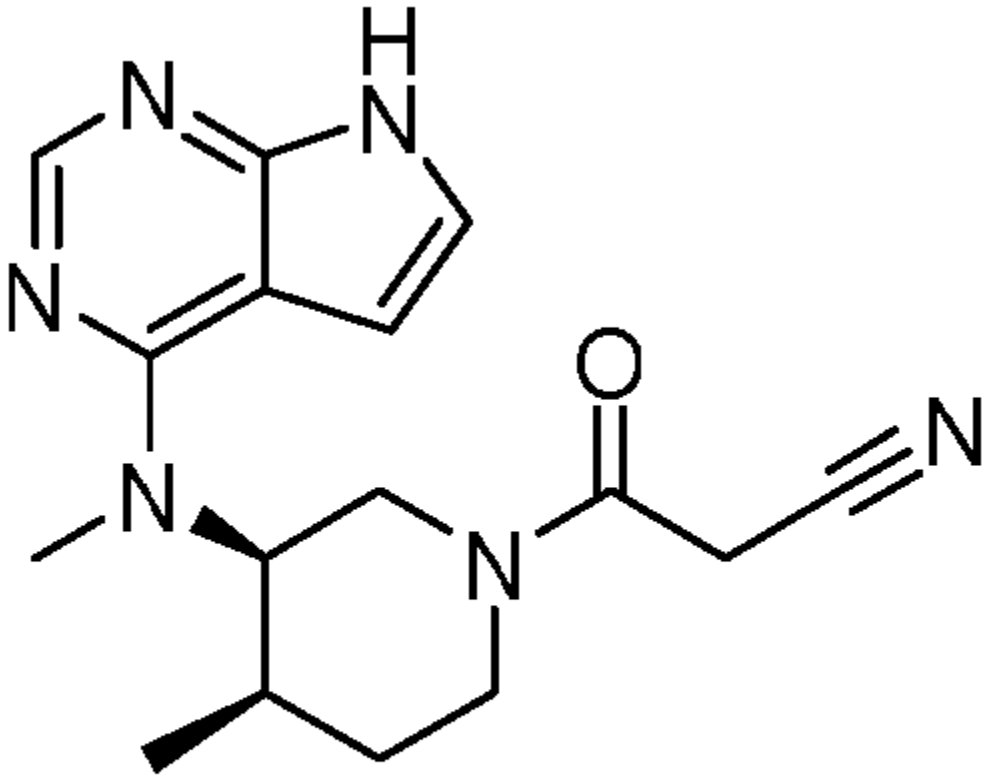
(III)



(II)

b) converting compound of formula (II) to tofacitinib having less than 0.2% of impurity of formula (A); and

c) reacting tofacitinib with citric acid to obtain citrate salt of tofacitinib.



(I)