IN THE UNITED STATED PATENT AND TRADEMARK OFFICE

Applicant : SATHE ET AL. Group Art Unit: 1625

Appln. No. : 15/868,331 Examiner: DAVID K. O'DELL

Filing Date : January 11, 2018 Confirmation No.: 9681

Attorney Docket No.: 008495.00006\US

Title: PROCESS FOR THE PREPARATION OF (3R,4R)-(1-BENZYL-4-METHYLPIPERIDIN-3-YL)-METHYLAMINE

AMENDMENT AND REPLY UNDER 37 CFR 1.111

MS Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Dear Honorable Commissioner,

This communication is responsive to the Non-Final office Action dated April 11, 2019 concerning the above-referenced patent application. No extension of time is necessary because this response is being filed by the due date of July 11, 2019.

Amendments to the Claims are reflected in the listing of claims which begin on page 2 of this document.

Remarks begin on page 8 of this document.

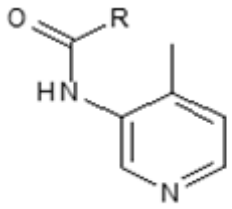
AMENDMENT TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of claims

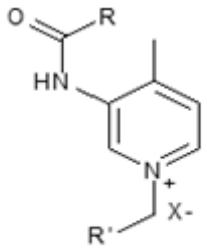
1. (Currently Amended) A process for preparation of 3-{(3R,4R)-4-methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl}-3-oxo-propanenitrile or a salt thereof comprising:

(i) N-acylation of 3-amino-4-methyl pyridine with alkyl, aryl or substituted aryl acid chloride or acid anhydride to prepare a compound of Formula IVa and optionally isolating the compound of Formula IVa;



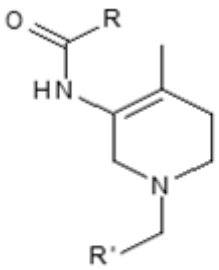
Formula IVa

(ii) quarternization of the nitrogen of the pyridine group in the compound of Formula IVa, with benzyl or substituted benzyl halide in a first solvent comprising a first organic solvent to prepare a compound of Formula Va and optionally isolating the compound of Formula Va;



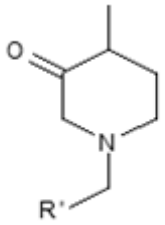
Formula Va

(iii) partial reduction of the compound of the Formula Va in presence of a first reducing agent in a second solvent at ambient temperature to produce a compound of the Formula VIa having a 1,2,5,6- tetrahydropyridine system;



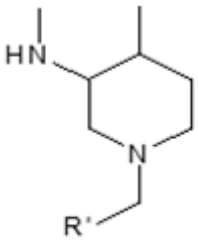
Formula VIa

(iv) hydrolysis of the 1,2,5,6-tetrahydropyridine system of the compound of Formula VIa in presence of an acid or mixture of acids to prepare a compound of the Formula VIIa;



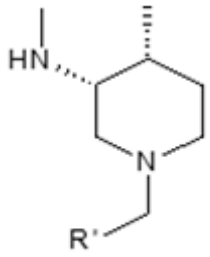
Formula VIIa

(v) reductive amination of the compound of Formula VIIa with methylamine in presence of a Lewis acid, in a third solvent comprising a third organic solvent, water, or mixture thereof; followed by reduction with a second reducing agent at an ambient temperature, to prepare a compound of Formula VIIIa;



Formula VIIIa

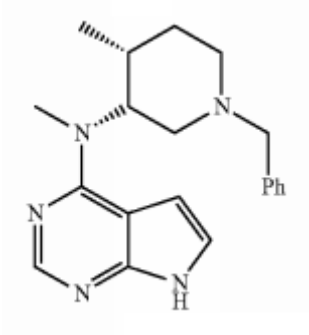
(vi) resolution of a compound of Formula VIIIa in presence of a resolving agent, in a fourth solvent comprising a fourth organic solvent, water, or mixture thereof; to prepare a compound of Formula IIa; and



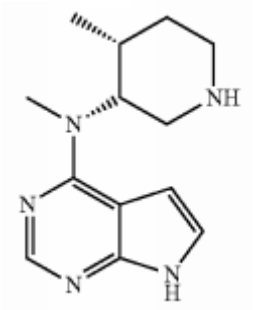
Formula IIa

(vii) conversion of the compound of Formula IIa into 3-{(3R,4R)-4-methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl}-3-oxo-propanenitrile, wherein said conversion comprises the steps of;

condensation of the compound of Formula IIa with 4-Chloropyrrolo[2,3-d]pyrimidine to produce (3R,4R)-(1-benzyl-4-methylpiperidin-3-yl)methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine of the following formula:

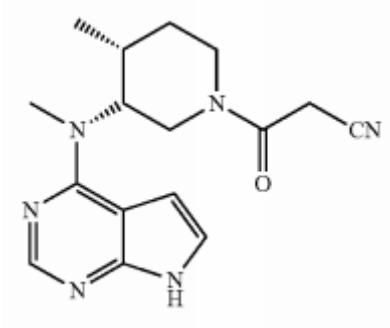


debenzylatioin of the (3R,4R)-(1-benzyl-4-methylpiperidin-3-yl)methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine to produce (3R,4R)-(4-methylpiperidin-3-yl)methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine of the following formula:



condensation of the (3R,4R)-(4-methylpiperidin-3-yl)methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine with cyano acetic acid derivative to produce 3-{(3R,4R)-4-

methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl}-3-oxo-propanenitrile of the following formula:



wherein R is selected from hydrogen, alkyl, aryl or substituted aryl; R' is a phenyl or a substituted phenyl group; and X represents a halide selected from chloro, bromo, and iodo.

2. (Original) The process of claim 1, wherein the N-acylation of part (i) is with a C_{1-10} acid anhydride.

3. (Original) The process of claim 1, wherein the N-acylation of part (i) is with a C_{1-10} acid chloride.

4. (Original) The process of claim 1, wherein the quaternization of part (ii) is with benzyl chloride, benzyl bromide, substituted benzyl chloride or substituted benzyl bromide.

5. (Original) The process of claim 1, wherein the first organic solvent comprises one or more of an aromatic solvent, a polar aprotic solvent, a non-polar solvents solvent, an ether solvent, an ester solvent, or a ketone solvent, and the first solvent optionally comprises water.

6. (Original) The process of claim 5, wherein the first organic solvent is selected from the group consisting of toluene, a xylene, cyclohexane and a mixture of two or more thereof.

7. (Original) The process of claim 6, wherein the first organic solvent is selected from toluene, xylene and a mixture thereof.

8. (Original) The process of claim 1, wherein the first and second reducing agents are independently selected from the group consisting of sodium borohydride, sodium cyanoborohydride, and sodium triacetoxyborohydride.

9. (Original) The process of claim 1, wherein the second solvent is selected from the group consisting of water, C_1-C_5 alcohol, diisopropyl ether, methyl tertiary butyl ether, toluene, xylene and mixtures of two or more thereof.

10. (Original) The process of claim 1, wherein the acid or mixture of acids of part (iv) is selected from hydrochloric acid, sulfuric acid, phosphoric acid, trifluoroacetic acid, trichloroacetic acid, substituted halo acetic acid, acetic acid, HI, HBr, mineral acids, organic acids, aqueous solutions thereof, or a mixture of two or more thereof.

11. (Original) The process of claim 1, wherein the Lewis acid of part (v) is selected from the group consisting of aluminium trichloride, ferric chloride, zinc chloride, indium chloride, and titanium(IV) tetraisopropoxide.

12. (Original) The process of claim 1, wherein the resolving agent of part (vi) is selected from the group consisting of dibenzoyl tartaric acid, ditoluoyl tartaric acid, tartaric acid, mandelic acid, and camphor sulphonic acid.

13. (Original) The process of claim 1, wherein the hydrolysis in part (iv) is carried out at a temperature in the range of from 40° C. to 110° C.

14. (Original) The process of claim 1, wherein the third organic solvent comprises methanol, ethanol, diisopropyl ether, methyl tertiary butyl ether, toluene, xylene or a mixture of two or more thereof, and the third solvent optionally comprising water.

15. (Currently Cancelled)

16. (Original) The process of claim 1 further comprising isolating the compound of Formula IVa.

17. (Original) The process of claim 1, further comprising isolating the compound of Formula Va.

18. (Currently Cancelled)

REMARKS

I. Status of the Application

With this amendment, Claims 1-14 and 16-17 are pending in this application. Claims 1 to 18 stand rejected based on prior art ground. Claim 1 has been amended to define the steps for converting compound of Formula IIa into 3-{(3R,4R)-4-methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl}-3-oxo-propanenitrile. Basis for this amendment can be found on page 1 of the Applicant's published specification. Claims 15 and 18 have been cancelled herein. No new claim has been added herein. No new matter is being added to the application.

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the following reasons.

II. Response to the 35 U.S.C. §112 Rejections

The Office Action rejects Claims 1-18 as indefinite under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA) second paragraph.

With this response, claim 1 has been amended to recite that R' is a phenyl or a substituted phenyl group, rendering its indefiniteness rejection moot.

Because claims 2-14 and 16-17 refer to or depend from independent claim 1, the amendments to claim 1 are believed to obviate the rejection as to these dependent claims as well.

III. Response to the 35 U.S.C. §102 Rejections

The Office Action rejects Claim 18 under 35 U.S.C. 102(a)(1), as being anticipated by "Flanagan" US 6,965,027.

Claim 18 has been cancelled and thus the novelty objection raised against this claim no longer applies.

The Office Action also rejects Claim 1-14 and 16-17 under 35 U.S.C. 102(a)(1), as being anticipated by Sathe WO2015087201A1. Applicant respectfully disagrees.

The present application was filed on Jan. 11, 2018, well before the Issue Notification of the prior parent application no. US14/891,028 issued on 24 April 2018. Therefore, the present application is a continuation of the prior application no. US14/891,028 claiming priority to Indian Patent Application No. 3843/MUM/2013 filed Dec. 09, 2013. Applicant therefore respectfully submits that claims 1-14 and 16-17 of the present application are entitled to the priority date of Dec. 09, 2013. Further, it is kindly submitted that paragraph [0001] of the specification filed for the present application duly provides a detailed 'Cross reference to related applications' which include the prior US application 14/891,028, the International PCT application PCT/IB2014/066510 (WO2015087201A1) and the Indian priority application 3843/MUM/2013.

As the priority date of the present application is Dec. 09, 2013, the cited reference Sathe WO2015087201A1, published on June 18, 2015, cannot be regarded as destroying the novelty of the present claims 1-14 and 16-17.

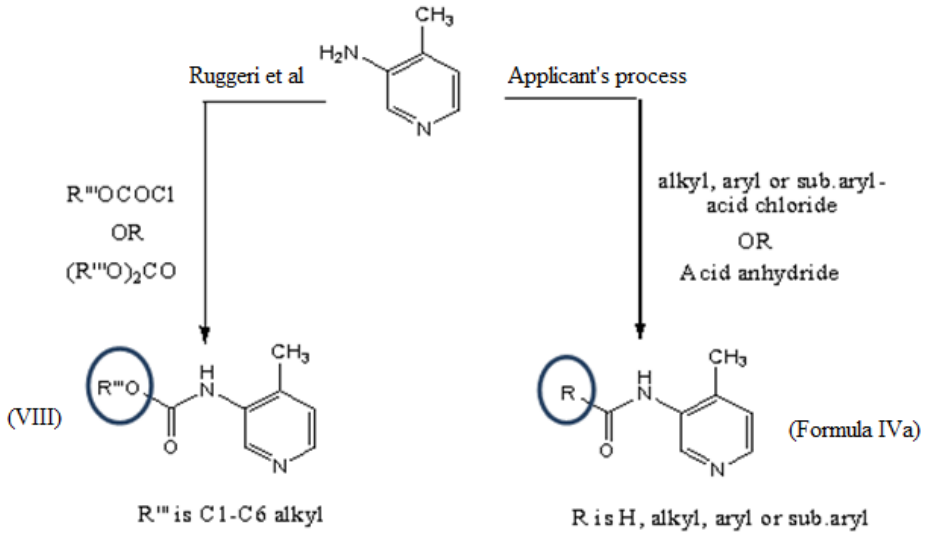
Therefore, reconsideration and withdrawal of the anticipation rejection is respectfully requested.

IV. Response to the 35 U.S.C. §103 Rejections

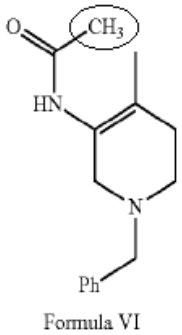
Claims 1-17 stand rejected under 35 U.S.C.§103 as allegedly being unpatentable over Brown Ripin "Development of a scalable route for the production of cis-N-Benzyl-3-methylamino-4-methylpiperidine" Organic Process Research & development 2003, 7, 115-120 hereinafter referred to as "**Brown Ripin**", Ruggeri U.S. 8,232,394 hereinafter referred to as "**Ruggeri**" AND Flanagan U.S. 6,965,027 hereinafter referred to as "**Flanagan**", in view of Cai "Investigation of practical routes for the kilogram-scale production of cis-3-Methylamino-4-methylpiperidines" Organic process Research and Development 2005, 9, 51-56 hereinafter referred to as "**Cai**", Greene and Wuts, Protective Groups in Organic Synthesis 3rd edition Wiley: New York, 1999 pages 494-615 hereinafter referred to as "**Greene and Wuts**", Jones J. Chem. Soc. Perkin Trans. I 1987, 2585-2592 hereinafter referred to as

"**Jones**", in further view of Baxter "Reductive Aminations of Carbonyl Compounds with Borohydride and Borane Reducing Agents." Chapter 1, Organic Reactions 2002, 59, 1-714 hereinafter referred to as "**Baxter**". The Applicant respectfully traverses the rejection for the following reasons.

The Office Action states that Ruggeri teaches steps (i), (ii) and (iii) of the process as set forth in Applicant's claim 1. Applicant respectfully disagrees. Ruggeri does not disclose the (1) claimed process or (2) a process that yields "enamide" intermediate compounds of formula IVa, Va and VIa. In Scheme I, Ruggeri merely discloses a conversion of 3-aminopicoline into a corresponding enecarbamate ester by reaction with alkylchloroformate or dialkyl carbonate (column 13 and 14). In contrast, the instant invention prepares a novel and inventive "enamide" intermediate of formula IVa by reacting 3-amino-4-methylpyridine with an acid chloride or acid anhydride. The applicant provides below the chemical structures and synthetic routes of the instant invention and the compounds depicted in Ruggeri to demonstrate difference between the claimed formula IVa and compound VIII of Ruggeri, and preparation methods thereof.

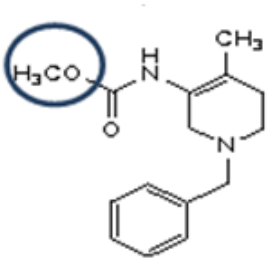


Clearly, the process disclosed in Ruggeri is quite different than the claimed process (i.e. step i) and does not yield the same result. In Example 2, Ruggeri teaches preparation of 1-benzyl-4-methyl-1,2,5,6-tetrahydro-pyridin-3-yl)-carbamic acid methyl ester (an enecarbamate ester) which is structurally different from the claimed "enamide" compound of formula VIa. This difference is demonstrated below in comparing the exemplary enamide compound of Applicant's Formula VI with the enecarbamate ester compound of Ruggeri et al.



Formula VI

Applicant's Formula VI

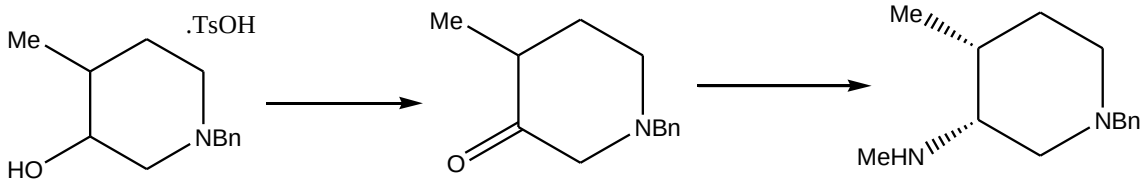


Ruggeri et al.'s Example-2

The Applicant therefore respectfully contends the "enamide" intermediate compounds of formula IVa, Va and VIa of the instant invention as set forth in claim 1 are completely different from the enecarbamate ester compounds as disclosed in Ruggeri, and cannot be considered to be homologs or analogs of formula VIII and Example-2 of the Ruggeri reference.

Further, as shown hereinabove, the cited reference Ruggeri has a fixed, essential element in its enecarbamate ester compounds for which no degree of freedom is disclosed. This fixed element (-NH-CO-O"'R) is different from the present -NH-CO-R substituent of the compounds IVa, Va and VIa of the instant invention. Further, there is no disclosure or suggestion in Ruggeri that would lead one of ordinary skill in the art to modify the reacion scheme or to make changes in substituents of the enecarbamate compounds disclosed therein in order to arrive at the "enamide" intermediates (i.e. the compounds of formula IVa, Va and VIa) of the instant invention. Thus, the primary reference Ruggeri does not teach, suggest or render obvious the reaction steps (i), (ii) and (iii) of the instant invention as set forth in Applicant's claim 1.

With regard to Brown Ripin, this reference teaches a process for preparing compound 5 according to the following scheme.



4. TsOH **8** **5**

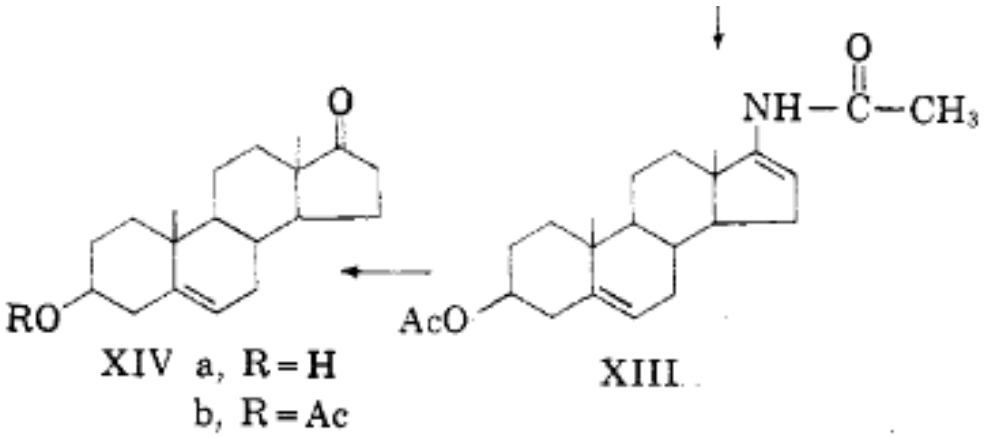
Compounds 8 and 5 of Brown Ripin may correspond to formula VIIa and VIIIa of the Applicant's claimed process, respectively. However, Brown Ripin does not disclose or suggest a method comprising the use of novel and inventive intermediate compounds of formula IVa, Va and VIa for the preparation of compound of formula VIIa (i.e. compound 8 of Brown Ripin).

In Brown Ripin, compound 8 (i.e. applicant's formula VIIa) is synthesized by oxidizing tosylic acid addition salt of compound 4. In contrast, applicant's process involves preparation of compound of formula VIIa (i.e. compound 8 of Brown Ripin) by hydrolysis of a novel intermediate compound VIa. Thus, the applicant's claimed process is completely different and does not involve preparation of compound 4 (or 4.TsOH) in its synthetic route.

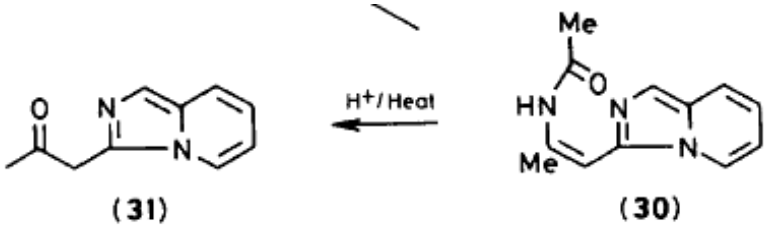
Examples 1-3 of Flanagan merely disclose resolution of racemic (1-benzyl-4-methylpiperidine-3-yl)-methylamine compound (i.e. applicant's formula VIIIa) using optical resolving agents. However, Flanagan is not directed towards the preparation of compound of formula VIIIa, and does not disclose or even suggest a method comprising the use of novel and inventive intermediate compounds of formula IVa, Va and VIa as instantly claimed.

With regard to the hydrolysis step (iv) as set forth in Applicant's claim 1, the Office Action makes reference to Rosenkranz (Journal of Organic Chemistry 1956, 21, 520-522, XIII to XIV page 521 “extreme case of hydrolysis (dilute acid, 0^{o})”) and Jones (J. Chem. Soc. Perkin Trans. I 1987, 2585-2592, page 2587 30 to 31) and alleges that enamides and enecarbamates are both N-protected imines, and readily reveal ketones upon acidic hydrolysis. Applicant respectfully disagrees.

On page 21, Rosenkranz et.al. discloses conversion of XIII to XVI:



On page 2587, Jones et al. discloses conversion of 30 to 31:



(31) (30)

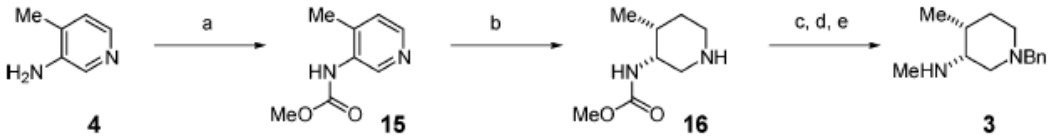
However, there exist numerous structural differences when compared to the claimed intermediate of formula VIa that render Rosenkranz and Jones quite remote. More particularly, the backbone to which the acetamide side chain is attached in both Rosenkranz and Jones is a fused cyclic system. In contrast, the instantly claimed intermediate of formula VIa is a mono heterocyclic system. Further, there is no teaching or suggestion in Rosenkranz or Jones that would lead one of ordinary skill in the art to modify the synthetic methodology disclosed therein in order to arrive at the keto derivative of formula VIIa of the instant invention. It is to be appreciated herein that chemistry is predominantly an unpredictable art and even a small change in bonding or adding an atom or a molecule to a chemical structure may yield substantially different results.

Therefore, the person of ordinary skill in the art would have no incentive or no driving force to prepare the desired product, i.e. formula VIIa (from formula VIa) by modifying the process disclosed in Rosenkranz or Jones with a reasonable expectation of success, as there is no straightforward and unambiguous direction in Rosenkranz or Jones towards the present substituent pattern.

Further, Greene and Wuts is a very generic study on the protective groups in organic synthesis, and the person of ordinary skill does not find any hint in this reference suggesting acylation of amino group of 3-amino-4-methyl pyridine. Applicant respectfully submits that selection of a suitable protecting group is very crucial for the success of a chosen method for synthesis of chemical compounds, particularly in light of the low skill in chemical arts.

The Office Action states that Cai has a related route where the starting material is the same as that of instant claim 1, i.e. 3-amino-4-picoline, displayed in Scheme 5.

Scheme 5. **Pyridine hydrogenation route to 3[a]**



[a] Reaction conditions: a) KOtBu, $(MeO_2C)_2O$, THF, 61%; b) 5% Rh/C (type 23), AcOH, H_2, 75%; c) PhCHO, $NaHB(OAc)_3$, CH_2Cl_2, HOAc, 68%; d) $LiAlH_4$, THF; e) HCl, EtOH, 47%, 2 steps.

However, Cai does not cure the deficiencies of the primary references Brown Ripin, and Ruggeri. Cai discloses a process for preparation of a compound of formula 3 (i.e. applicant's formula VIIIa) wherein 3-aminopicoline (compound 4) is first converted into an enecarbamate ester (compound 15) which is then converted into formula 16 by catalytic reduction. Methyl amine is introduced to formula 16 by further steps to obtain formula 3. Thus, Cai discloses a completely different process than the process claimed in the instant application. Some of the more important differences are discussed below and assist in confirming the non-obviousness of the claimed process.

According to Applicant's claimed process, the nitrogen in the pyridine ring is protected by a benzyl group in step (ii) before subjecting the intermediate compound to reduction step. However, the enecarbamate ester (compound 15) in Cai is directly subjected to catalytic reduction without protecting the nitrogen atom in the pyridine ring (see, "step b"). While Cai subjects the pyridine moiety (i.e. compound 15) to complete reduction, the instant invention involves partial reduction of the pyridine moiety in step (iii). Thus, the applicant's claimed process is completely different and does not prepare compound 16 in its synthetic route. Furthermore, the applicant's claimed process involves novel intermediate compound of formula IVa, which enamide compound is more than simple homolog or analog of the enecarbamate ester compound 15 disclosed in Cai.

Thus, the secondary reference Cai involves a completely different process and different intermediate compounds--which are contrary to applicant's invention and cannot be combined in any reasonable fashion with the primary references Ruggeri and Brown Ripin to render obvious the claimed invention.

Baxter merely discloses Lewis acids that facilitate imine formation in reductive aminations with sodium cyanoborohydride, which in no way renders the present invention obvious.

Thus, the Applicant respectfully contends that the prior art combination of Ruggeri, Brown Ripin, Flanagan, Greene and Wuts, Jones, Cai and Baxter would not disclose, teach or suggest the limitations and features of the independent claim 1. In particular, these references, whether applied alone or in combination, do not disclose or teach the novel and inventive intermediate compounds of formula IVa, Va and VIa, where R is H, alkyl, aryl or substituted ary group, for the preparation of 3-{(3R,4R)-4-methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl}-3-oxo-propanenitrile (**Tofacitinib**). Therefore, the Applicant respectfully contends that the synthetic route as recited in claim 1 is neither taught nor suggested by the prior art combination and hence is patentable over the prior art references.

Claims 2-14 and 16-17 refer to or depend from independent claim 1, and accordingly incorporate all of the features thereof and are patentable over the prior art combination for at least the same reasons as independent claim 1.

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the obviousness rejections.

Claim 15 has been rejected under 35 U.S.C. §103 as allegedly being unpatentable over Sathe WO2015087201A1 and Flanagan US 6,965,027.

With this response, claim 15 has been cancelled and thus the obviousness objection raised against this claim no longer applies.

V. Formal Matters and Conclusion

In view of the foregoing, the Applicant submits that claims 1-14 and 16-17, all the claims presently pending in the application, are patentably distinct from the prior art of record and are in condition for allowance. The Examiner is respectfully requested to pass the above application to issue at the earliest possible time.

Should the Examiner find the application to be other than in condition for allowance, the Examiner is requested to contact the undersigned at the local telephone number listed below to discuss any other changes deemed necessary. Please charge any deficiencies and credit any overpayments to Attorney's Deposit Account Number XXX.

Respectfully submitted,

Date XX, 2019

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Attorney for Applicant