

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : SATHE ET AL.

Group Art Unit: 1626

Appln. No. : 16/609,232

Examiner: JOSEPH KOSACK

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Title: Novel process to prepare n-[2-[(1s)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulphonyl)ethyl]-1, 3-dioxo-2,3-dihydro-1h-isoindol-4-yl]acetamide

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 July 02, 2020 concerning the above-referenced patent application. No extension of time is necessary because this response is being filed by the due date of October 02, 2020.

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

Remarks begin on page 5 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 to prepare Apremilast form B comprising steps of;
 - i. hydrogenation of 3-nitrobenzene-1, 2-dicarboxylic acid (Formula-II) in presence of suitable reducing agent and acetone as a solvent at a suitable temperature to prepare 3-aminobenzene-1, 2-dicarboxylic acid (Formula -III);
 - ii. cyclization and acetylation of 3-aminobenzene-1, 2-dicarboxylic acid (Formula -III) obtained in step i) with acetic anhydride at suitable temperature to prepare N-(1, 3-dioxo-1, 3-dihydro-2-benzofuran-4-yl) acetamide (Formula-IV);
 - iii. condensation of (1S)-1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethylamine (Formula-V) and N-(1, 3-dioxo-1, 3-dihydro-2-benzofuran-4-yl) acetamide (Formula-IV) in presence of methyl isobutyl ketone (MIBK) and acetic acid mixture, wherein MIBK and acetic acid is in the ratio of 11:4 to 12:4.5 to prepare N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulphonyl) ethyl]-1, 3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide (Formula-I);
 - iv. crystallization of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulphonyl) ethyl]-1, 3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide (Formula-I) prepared in step iii using a suitable solvent to obtain Apremilast Form B.

- 2) (CURRENTLY AMENDED) A process for preparation of Apremilast (Formula I) having less than 0.15% w/w of Des-acetyl impurity, the process comprising steps of:
 - i. hydrogenation of 3-nitrobenzene-1, 2-dicarboxylic acid (Formula - II) in presence of suitable catalyst and acetone as a solvent to prepare 3-aminobenzene-1, 2-dicarboxylic acid (Formula -III);
 - ii. cyclization and acetylation of 3-aminobenzene-1, 2-dicarboxylic acid (Formula - III) obtained in step i) with acetic anhydride to prepare N-(1, 3-dioxo-1, 3-dihydro-2-benzofuran-4-yl) acetamide (Formula-IV); and

- iii. condensation of (1S)-1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethylamine (Formula-V) and N-(1, 3-dioxo-1, 3-dihydro-2-benzofuran-4-yl)acetamide (Formula-IV) in presence of methyl isobutyl ketone and acetic acid mixture, wherein MIBK and acetic acid is in the ratio of 11:4 to 12:4.5 to prepare Apremilast (Formula I) having less than 0.15% w/w by HPLC of Des-acetyl impurity.
- 3) (CURRENTLY AMENDED) The process as claimed in claim 1 wherein in step i, the reducing agent is 10% Palladium on carbon or Raney nickel, and the hydrogenation is carried out at temperature range of 5°C to 25°C.
- 4) (CURRENTLY AMENDED) The process as claimed in claim 1 wherein the Cyclization and acetylation of 3-aminobenzene-1, 2-dicarboxylic acid is carried out at temperature range of 90°C to 140°C.
- 5) (PREVIOUSLY CANCELLED)
- 6) (ORIGINAL) The process as claimed in claim 1, wherein suitable solvent for crystallization in step iv is selected from acetone, ethanol and mixture thereof.
- 7) (PREVIOUSLY CANCELLED)
- 8) (PREVIOUSLY CANCELLED)
- 9) (PREVIOUSLY CANCELLED)
- 10) (PREVIOUSLY CANCELLED)
- 11) (CURRENTLY AMENDED) A process of hydrogenation of 3-nitrobenzene-1, 2-dicarboxylic acid (Formula - II) to prepare 3-aminobenzene-1, 2-dicarboxylic acid (Formula -III) in the presence of catalyst using Acetone as a solvent.
- 12) (ORIGINAL) The process as claimed in claim 11, wherein the catalyst is selected from 10% Palladium on carbon and Raney Nickel.

13) (PREVIOUSLY CANCELLED)

14) (PREVIOUSLY CANCELLED)

15) (PREVIOUSLY CANCELLED)

16) (PREVIOUSLY CANCELLED)

17) (CURRENTLY AMENDED) The process as claimed in claim 2 wherein in step i, the catalyst is 10% Palladium on carbon or Raney nickel, and the hydrogenation is carried out at temperature range of 5°C to 25°C.

18) (CURRENTLY AMENDED) The process as claimed in claim 2 wherein the Cyclization and acetylation of 3-aminobenzene-1, 2-dicarboxylic acid is carried out at a temperature range of 90°C to 140°C.

REMARKS

I. Status of the Application

Claims 1-4, 6, 11-12 and 17-18 are pending in this application. Claims 1-4, 11, 17 and 18 are amended. Claims 1, 2 and 11 are amended to address minor typographical informalities. Claims 3 and 17 are amended to remove the preferred temperature range (i.e. preferred range being 15°C to 20°C) and to address minor grammatical errors. Claims 4 and 18 are amended to remove the preferred temperature range (i.e. preferred range being 130°C to 140°C).

Taken together, these changes add no new matter.

In view of the following discussion, the Examiner is respectfully requested to reconsider and withdraw the objections and rejections.

II. Response to Claim Objections

The Office Action objects to Claims 1 and 11 because of informalities.

As suggested by the Office, the misspelling of “dihydro” and “dicarboxylic” has been corrected in Claims 1 and 11 respectively. Withdrawal of these objections is therefore respectfully requested.

III. Response to 35 USC § 112 Rejections

The Office Action rejects Claims 3, 4, 17 and 18 as indefinite under 35 U.S.C. 112(b) or 35 U.S.C. 112(pre-AIA) second paragraph.

Claims 3, 4, 17 and 18 have been amended to remove the preferred feature. As such, the indefiniteness rejection is rendered moot and can be withdrawn.

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

The Office Action rejects Claims 11 and 12 under 35 U.S.C. 103 as allegedly being unpatentable over Muller et al. (USPN 8,093,283) hereinafter referred to as “**Muller**” in view

of Dyson et al. (*Catal. Sci. Technol*, 2016, 3302-3316) hereinafter referred to as “**Dyson**”. Applicants respectfully traverse the rejection for the following reasons.

Muller teaches (column 39, lines 23-40) a process for hydrogenating 3-nitrobenzene-1,2-dicarboxylic acid to prepare 3-aminobenzene-1,2-dicarboxylic acid in the presence of 10% Pd/C using ethanol as a solvent. As already admitted in the Office Action, Muller does not teach acetone as a solvent for hydrogenating 3-nitrobenzene-1,2-dicarboxylic acid to corresponding amine.

Dyson fails to cure the deficiencies of Muller. Applicant respectfully submits that present Claim 11 requires hydrogenating 3-nitrobenzene-1, 2-dicarboxylic acid (Formula II) in acetone to prepare 3-aminobenzene-1,2-dicarboxylic acid. Dyson does not teach catalytic hydrogenation of a nitro compound to an amine, let alone catalytic hydrogenation of a nitro compound to an amine in acetone as a solvent. Dyson gives only generic information about solvent effects in catalytic hydrogenation reactions, and the person of ordinary skill does not find any hint in this reference suggesting the use of acetone as a solvent for catalytic hydrogenation of 3-nitrobenzene-1,2-dicarboxylic acid to corresponding amine.

Further, Dyson teaches, in accordance with the catalytic hydrogenation reactions, that “**A solvent may** interact with or react with a **starting material** activating it towards reaction or **deactivating it**.....” (see, page 3306, right column, item (5)), and that “**A solvent may** interact with or coordinate to the catalyst and thereby activate or **deactivate the catalyst**, influence the selectivity of the catalyst and influence catalyst stability.....” (see, page 3307, right column, item (10)). This emphasizes the criticality of the choice of solvent for catalytic hydrogenation reactions. It is therefore respectfully submitted that a person of ordinary skill in the art would require inventive efforts in order to arrive at the process of claim 11 of the present applicaiton.

Dyson teaches (Table 1) that hydrogen is more soluble in acetone than ethanol. However, Dyson itself states (page 3304, right column, last paragraph) that “A solvent in which the solubility of reagents (solid, liquid or gas) is high could lead to an increased rate of reaction compared to a solvent in which reagent solubility is low. **This statement may seem obvious, but it may not always be true**”. For example, **for gaseous reagents, the thermodynamic ability of the solvent to dissolve the gas is not necessarily important**.....”. Dyson thus emphasizes that the higher solubility of hydrogen gas in acetone has no significance on

catalytic hydrogenation reactions. A person of ordinary skill in the art thus could not have singled out acetone as being more suitable than the others.

Furthermore, one of skill in the art would not have been motivated to use acetone as a solvent in catalytic hydrogenation reactions, particularly in view of the fact that acetone is susceptible to hydrogenation and that catalytic hydrogenations using acetone as solvent generate isopropanol as by-product which a skilled artisan would generally prefer to avoid as it often has an unpredictable effect on chemical processes. Because no motivation exists to use acetone in the catalytic hydrogenation reaction of Muller, there can be no prima facie case of obviousness.

Based on the above, Applicant respectfully submits that the process as recited in independent claim 11 is neither taught nor suggested by the combination of Muller and Dyson and hence is patentable over the proposed prior art combination.

Claims 12 refers to or depends from independent claim 11, and accordingly incorporates all of the features thereof and is patentable over the prior art combination for at least the same reasons as independent claim 11.

Additionally, Applicant would like to mention the advantages of the presently claimed process over the method disclosed in the Muller reference, which would not have been suggested to one of ordinary skill in the art.

In Muller, the hydrogenation of 3-nitrobenzene-1, 2-dicarboxylic acid (3-nitrophthalic acid) in ethanol to obtain 3-aminobenzene-1, 2-dicarboxylic acid (3-aminophthalic acid) is completed in a reaction time of **13 hours**. Normally, longer reaction times result in decreasing product yield because of competitive side reactions. Applicants use acetone as solvent which reduces the reaction time from **13 hours to 3 hours**. (see, Example 1 of the present application, and Column 39, lines 23-40 of Muller). Applicant's superior result, which is attributable to the use of acetone as solvent, clearly weights in favour of finding Applicant's process non-obvious.

In Muller, the hydrogenation of 3-nitrobenzene-1, 2-dicarboxylic acid (3-nitrophthalic acid) in ethanol to yield 3-aminobenzene-1, 2-dicarboxylic acid (3-aminophthalic acid) is carried out in a **84% yield**. Unexpectedly, when the reaction is performed in acetone, the yield is increased to **95% yield**. (see, Example 1 of the present application, and Column 39, lines 23-40 of Muller)

Thus, the process claimed in claim 11 of the present application is simpler, more industrially viable and efficient over Muller reference. In addition, the unexpected and much better results obtained by the presently claimed process are not predicted by Muller either alone or in view of other cited references.

Applicant respectfully requests that the obviousness rejection be withdrawn.

The Office Action rejects Claims 1-4, 6, 17 and 18 as allegedly being unpatentable over Muller in view of Dyson and Vakamudi et al. (WO 2016/199031) hereinafter referred to as "Vakamudi". Applicants respectfully disagree.

As discussed above, the process claimed in Claim 11 is patentable over Muller and Dyson. Vakamudi does not cure the defects of Muller or Dyson. Therefore, Claim 11 is patentable, in further view of Vakamudi. Claims 1-4, 6, 17 and 18 include every limitation of Claim 11. Accordingly, applicant respectfully submits that Claims 1-4, 6, 17 and 18 are unobvious over the combined teachings of Muller, Dyson and Vakamudi. Further, the excellent yield and reduced reaction time achieved by using acetone as solvent in the preparation of 3-aminobenzene-1, 2-dicarboxylic acid (Formula III) also strongly support the patentability of the claimed processes.

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

Respectfully submitted,

Date: XXXXXX

Attorney for Applicant