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16/641,985	02/25/2020	Steven C. Quay	109559-669805	7650
27148	7590	09/07/2021	EXAMINER	
POL SINELLI PC PO Box 140310 KANSAS CITY, MO 64114-0310			DAVIS, BRIAN J	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocketing@polsinelli.com  
rendsley@polsinelli.com



## **DETAILED ACTION**

### ***Notice of Pre-AIA or AIA Status***

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

### ***Information Disclosure Statement***

The information disclosure statement filed 5/29/2020 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the lined-through information referred to therein has not been considered.

The references which correspond to the NPL listings 002, 017, 027, 028 and 030 of the 5/29/2020 IDS, while having the physically reproduced form of journal articles, are either wholly or partially comprised of text which is simply a random assemblages of letters. In fact, it appears that some sort of scrambling or encryption has been inadvertently introduced into these digital documents (i.e. this does not appear to be a USPTO error). Since the documents are either partially or wholly illegible, their listings have been lined-through.

***Drawings***

Figure 1 should be designated by a legend such as --Prior Art-- because only that which is old is illustrated. See MPEP § 608.02(g). Figure 1 simply reproduces known metabolic pathways.

Corrected drawings in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action.

The objection to the drawings will not be held in abeyance.

***Claim Rejections - 35 USC § 112(b)***

The following is a quotation of 35 U.S.C. 112(b):

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 43 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

The identity of Form I of the compound of Formula (III) is unclear because it is undefined. It is only by reference to the specification that an explanation/definition may be found that Form I of the compound of Formula (III) is a polymorph with a characteristic powder X-ray diffraction pattern (for instance at specification page 3, [0011]). However, note that incorporation by reference to a specific figure or table (in this case a set of diffraction peaks) is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience (MPEP 2173.05(s)).

The examiner respectfully suggests that the limitations of claim 3 should be incorporated into independent claims 1 and 43 in order to properly define the Form I polymorph of the compound of Formula (III).

Furthermore, the last limitation of the claims ("...and the crystalline form of the compound of Formula (III) is Form I...") is ambiguous and therefore unclear. The limitation is ambiguous because the composition may contain up to 10% of, presumably, the corresponding (E)-isomer of the compound of Formula (III). That being the case, "the crystalline form of the compound of Formula (III)", i.e. the mixture, cannot simply be Form I, because Form I is taught in the specification as a polymorph of the (Z)-isomer.

The examiner respectfully suggests a slight rewording, something along the lines of: *...and the crystalline form of the (Z)-isomer of the compound of Formula (III) is Form I.*

Claims 35, 38, 39, 41 and 42 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

There is insufficient antecedent basis for the limitation “endoxifen” in the claims. Independent claim 1, the claim from which claim 35, for instance, ultimately depends, refers to the instant compound as a compound of formula (III), not endoxifen.

Analysis of the remaining claims is similar.

The examiner respectfully suggests, in order to avoid any ambiguity, that a consistent use of terminology be maintained throughout the claim set. (The examiner notes that instant diagramed Formula (III) is (E)/(Z)-endoxifen.)

Claims 38 and 43 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

It is unclear who might be “...a subject in need thereof...”. Candidates for inclusion in the set of “subjects in need thereof” is impossible to determine since there are no criteria as to how/why such subjects might be selected.

Claims 49 and 52 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and

distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

With respect to claim 49, there is insufficient antecedent basis for the limitation “(Z)-endoxifen” in the claim. With respect to claim 52, there is insufficient antecedent basis for the limitation “endoxifen” in the claim. Independent claim 43, the claim from which both claims 49 and 52 immediately depend, refers to the instant compound as a compound of formula (III), not (Z)-endoxifen or endoxifen.

The examiner respectfully suggests, or order to avoid any ambiguity, that a consistent use of terminology be maintained throughout the claim set. (The examiner notes that instant diagramed Formula (III) is (E)/(Z)-endoxifen.)

Claim 62 is rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

It is unclear, in the second step of the procedure, how recrystallization from a second solvent can be accurately described as concentrating the first mother liquor. It would appear that there is no second solvent in this case. It is the same solvent, but at a reduced volume. Note that while an applicant may be his own lexicographer, applicant may not distort art-recognized terms (i.e. second solvent). *Ex parte Klager*, 132 USPQ 203 (POBA 1959).

Clarification is in order.

Claims 4-9, 32-34, 40, 44, 46 and 47 are also rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as claims which depend from indefinite claims are also indefinite. *Ex parte Cordova*, 10 USPQ 2d 1949, 1952 (PTO Bd. App. 1989).

### ***Claim Rejections - 35 USC § 103***

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

**Claim 62 is rejected under 35 U.S.C. 103 as being unpatentable over WO 2017/070651 A1**, cited in the IDS.

Inventor teaches a method of manufacturing (Z)-endoxifen comprising subjecting an (E)/(Z) mixture of endoxifen isomers to fractional crystallization from a first solvent such that a first crystalline solid is formed and a first mother liquor having an (E)/(Z) ratio of at least 50% higher (Z)-endoxifen compared with the ratio in the starting mixture. This first mother liquor is then subjected to recrystallization from a second solvent by concentrating the first mother liquor, or by swapping out the first solvent from the first mother liquor with a second solvent one or more times, to form a second crystalline solid which is  $\geq 90\%$  (Z)-endoxifen and a second mother liquor. The second crystalline solid may then be optionally subjected to recrystallization from a third solvent, or chromatographic treatment, one or more times to form a third crystalline solid.

WO 2017/070651 A1 teaches recrystallization of an (Z)/(E)-endoxifen crystalline solid mixture from a first solvent such that a first crystalline solid is formed and a first mother liquor having a (Z)/(E) ratio at least 1.3 times greater compared to the starting crystalline solid. Then recrystallizing a solid produced by concentrating the first mother liquor, or by removal of the first solvent from the mother liquor, from a second solvent to give a second crystalline solid and a second mother liquor. The second crystalline solid may then be optionally recrystallized one to five additional times to give a third crystalline solid.

Inventor principally distinguishes over the prior art in the parameter of the ratio of desired isomer ((Z)-endoxifen) to the undesired isomer ((E)-endoxifen)). However, the actual procedures of the prior art method and that of the instant invention are same. That is, the instant method is intrinsic to the prior art method.

Furthermore, one of ordinary skill in the art, before the effective filing date of the instant invention, would have recognized that the ordinary parameters of recrystallizations such as solvent choice, temperature, etc., could be manipulated such that a desired (E)/(Z) isomer ratio could be achieved in a mother liquor - since both the prior art and instant methods are predicated on the differing solubilities of the two isomers. One of ordinary skill would have been motivated to do this by ordinary economic considerations (efficiency/ease/speed of separation; minimizing solvent volume/use; etc.).

***Allowable Subject Matter***

The subject matter of claims 1, 4-9, 32-35, 38-44, 46, 47, 49 and 52 would be allowable once the 112 rejections outlined above have been overcome. The following is a statement of reasons for the indication of allowable subject matter:

The key to instant claims 1, 4-9, 32-35, 38-44, 46, 47, 49 and 52 is the polymorph of Form I. The closest prior art appears to be WO 2014/141292 A2, cited in the IDS, which teaches an endoxifen citrate polymorph (abstract; page 4, 5<sup>th</sup> full paragraph). (Instant diagramed Formula (III) is (E)/(Z)-endoxifen.) The reference does not teach, show, suggest or make obvious the instant Form I polymorph.

***Conclusion***

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: WO 2017/080770 A1 (and its corresponding English language machine translation (Google)) is cited to show a related synthesis of (Z)-endoxifen hydrochloride.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRIAN J DAVIS whose telephone number is (571)272-0638. The examiner can normally be reached on M-F 8:30-5:00 PM EDT.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fred Krass, can be reached at 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <https://ppair-my.uspto.gov/pair/PrivatePair>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BRIAN J DAVIS/  
Primary Examiner, Art Unit 1612  
8/31/2021