

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2018/050272

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/138; A61P 35/00; C07C 217/18; C07C 217/54 (2018.01)

CPC - A61K 31/138; A61P 35/00; C07C 217/18; C07C 217/54 (2018.08)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC - 514/648 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/070651 A1 (THE UNITED STATES OF AMERICA, AS REPRESENTED BY THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES et al) 27 April 2017 (27.04.2017) entire document	1-7
Y	US 2012/0164075 A1 (AHMAD et al) 28 June 2012 (28.06.2012) entire document	135-137
Y	GOETZ et al., First-in-Human Phase I Study of the Tamoxifen Metabolite Z-Endoxifen in Women With Endocrine-Refractory Metastatic Breast Cancer, J. Clin. Oncol., Vol. 35, No. 30, August 2017 [retrieved on 11 December 2018]. Retrieved from the Internet: <URL: http://ascopubs.org/doi/pdf/10.1200/JCO.2017.73.3246 >, Pgs. 3391-3400 and Appendix	135-137
A	WO 2014/141292 A2 (INTAS PHARMACEUTICALS LIMITED) 18 September 2014 (18.09.2014) entire document	1-7, 135-137
A	HENDERSON et al., Profound reduction in tamoxifen active metabolite endoxifen in a breast cancer patient treated with rifampin prior to initiation of an anti-TNF α biologic for ulcerative colitis: a case report, BMC Cancer, Vol. 16, 11 May 2016, Pgs. 1-6	1-7, 135-137



Further documents are listed in the continuation of Box C.



See patent family annex.

*

Special categories of cited documents:

"A"

document defining the general state of the art which is not considered to be of particular relevance

"E"

earlier application or patent but published on or after the international filing date

"L"

document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O"

document referring to an oral disclosure, use, exhibition or other means

"P"

document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

11 December 2018

Date of mailing of the international search report

03 JAN 2019

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. 571-273-8300

Authorized officer

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PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2018/050272

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 8-11, 17, 19-22, 26, 28-61, 63-99, 101-120, 122-134, 138-150, 154-157
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Extra Sheet

Claims 1-7 and 135-137 have been analyzed subject to the restriction that the claims read on the Formula (III) as described in the Lack of Unity of Invention (See Extra Sheet). The claims are restricted to a composition comprising a crystalline form of a compound of Formula (III), wherein the compound is at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer; and oral compositions.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-7, 135-137

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-7, 12-16, 18, 23-25, 27, and 135-137 are drawn to compositions and oral compositions.

Group II: claims 62, 100, 121, and 151-153 are drawn to industrially scalable processes for manufacturing (Z)-endoxifen, an industrially scalable process of reequilibrating a mixture of (E)-endoxifen and (Z)-endoxifen, and methods of treating a subject having or at risk of having a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder or both.

The first invention of Group I+ is restricted to a composition comprising a crystalline form of a compound of Formula (III), wherein the compound is at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer; and oral compositions. It is believed that claims 1-7 and 135-137 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a composition comprising a crystalline form of a compound of Formula (III), wherein the composition comprises the (E)-isomer and the (Z)-isomer of the compound of Formula (III) in an E/Z ratio between 0.9 and 1.3; and oral compositions. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ and II do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I+, compositions and oral compositions, are not present in Group II; and the special technical features of Group II, industrially scalable processes for manufacturing (Z)-endoxifen, an industrially scalable process of reequilibrating a mixture of (E)-endoxifen and (Z)-endoxifen, and methods of treating a subject having or at risk of having a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder or both, are not present in Group I+.

The Groups I+ and II formulae do not share a significant structural element requiring the selection of alternatives for the compound double bond isomer and the crystalline form and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ and II were considered to share the technical features of a composition comprising a crystalline form of a compound of Formula (III); and an oral composition comprising 1 mg to 200 mg per unit dose of (Z)-endoxifen free base or a salt thereof, for administration to a subject in need thereof, wherein daily administration of the oral composition achieves in the subject: (a) a steady state plasma level of endoxifen within 7 to 21 days; (b) a steady state plasma level of endoxifen ranging from 25 nM to 300 nM; (c) a steady state plasma level of endoxifen greater than 30 nM; (d) maximal plasma levels of endoxifen within 2 to 10 hours after administering; or (e) any combination thereof, these shared technical features do not represent a contribution over the prior art as disclosed by US 2012/0164075 A1 to Ahmad et al. and "Profound reduction in tamoxifen active metabolite endoxifen in a breast cancer patient treated with rifampin prior to initiation of an anti-TNF α biologic for ulcerative colitis: a case report" to Henderson et al.

US 2012/0164075 A1 to Ahmad et al. teach a composition (Para. [0011],...a composition comprising a therapeutically active amount of endoxifen and administering the composition.; Abstract) comprising a crystalline form of a compound of Formula (III) (Para. [0011],...a composition comprising a therapeutically active amount of endoxifen and administering the composition.; Abstract,...see shown structure of endoxifen that shows the compound as the (Z)-isomer); and an oral composition (Para. [0011],...a composition comprising a therapeutically active amount of endoxifen and administering the composition.; Abstract; Para. [0155]. For the oral mode of administration, preferred forms of endoxifen or endoxifen lipid complex...) comprising 1 mg to 200 mg per unit dose of (Z)-endoxifen free base or a salt thereof (Para. [0210],...oral doses of endoxifen (1 mg-10 mg/day)...; Para. [0137],...more preferably between 1 mg/mL and 5 mg/mL.), for administration to a subject in need thereof (Para. [0011]).

"Profound reduction in tamoxifen active metabolite endoxifen in a breast cancer patient treated with rifampin prior to initiation of an anti-TNF α biologic for ulcerative colitis: a case report" to Henderson et al. teach (b) a steady state plasma level of endoxifen ranging from 25 nM to 300 nM (Pg. 2, Fig. 1A, See the plasma concentration from April 2013 until baseline shows the steady state plasma level of endoxifen is between 40 and 60 nM.).

The inventions listed in Groups I+ and II therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

Written Opinion

Application No.
11202002105W

Application filing date 10/09/2018	(Earliest) Priority Date 11/09/2017	Examiner's Reference Number IPOS/AAG
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1. This first Written Opinion is issued under Section 29(5) of the *Patents Act* with effect from 14/02/2014.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Unity of invention
- V ☒ Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Defects in the form or contents of the application
- VII ☒ Clarity, Clear and Complete Disclosure, and Support
- VIII ☐ Double patenting

3. The search report used was issued by the Intellectual Property Office of Singapore.

4. If no reply is filed, the Examination Report will be established on the basis of this opinion.

Intellectual Property Office of Singapore 1 Paya Lebar Link #11-03 PLQ 1, Paya Lebar Quarter Singapore 408533 E-mail address: operation@iposinternational.com	Date of Written Opinion: 21/04/2021
	Authorized Officer Amylia Abdul Ghani (Dr)

Written Opinion

Application No.
11202002105W

I. Basis of the opinion			
1. This opinion has been drawn on the basis of:			
<input checked="" type="checkbox"/>	the description , page(s) 1, 2, 13-112 page(s) 3-12, 12a-12c	as originally filed filed as amendment sheet(s) dated	11/09/2020
<input checked="" type="checkbox"/>	the claim(s) , no. 1-158	filed as amendment sheet(s) dated	11/09/2020
<input checked="" type="checkbox"/>	the drawing(s) , page(s) 1-13	as originally filed	
2.	<input type="checkbox"/> This opinion has been established based on the exclusion of additional matter beyond the earlier application, as indicated in the supplemental box.		
3.	<input type="checkbox"/> This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the supplemental box.		
4. Additional observations, if necessary:			

Written Opinion

Application No.
11202002105W

V. Reasoned statement with regard to novelty, inventive step or industrial applicability; Citation and explanation supporting such statement

Statement with regard to novelty, inventive step or industrial applicability

Novelty (N)	Claim(s)	3-11, 14-31, 38-40, 47-50, 57, 58, 63-123, 125-128, 130-151, 153 AND 157	YES
	Claim(s)	1, 2, 12, 13, 32-37, 41-46, 51-56, 59-62, 124, 129, 152, 154-156 AND 158	NO
Inventive Step (IS)	Claim(s)	3-11, 14-31 AND 125	YES
	Claim(s)	1, 2, 12, 13, 32-124 AND 126-158	NO
Industrial applicability (IA)	Claim(s)	1-158	YES
	Claim(s)	NONE	NO

1. Citations

The following citations are referred to in this opinion. Full bibliographic details are provided in the Search Report:

- D1 ~ WO 2017/070651 A1
D2 ~ WO 2012/050263 A1

Please note that claim 43 is a first medical use claim where the disease, dosage regimen and administration route are not limiting on the scope of the claim.

2. Novelty (Section 14 of the *Patents Act*)

D1 discloses a process of preparing Z-endoxifen by recrystallizing a solid comprising a mixture of E- and Z-endoxifen from a first solvent to form a first crystalline solid and first mother liquor wherein the first mother liquor has a Z/E ratio of at least 1.3 times greater than the ratio in the input crystalline solid, recrystallizing a solid produced by concentrating the first mother liquor or by removal of the first solvent from the first mother liquor, from a second solvent to give a second crystalline solid and a second mother liquor, recrystallizing the second crystalline solid from the second solvent 1-5 times to give a third crystalline solid. The third crystalline solid has a Z/E ratio of greater than 20:1 (see paragraph 0006). D1 also discloses that isopropyl acetate can equilibrate a mixture of Z and E endoxifen (see paragraph 0018). Z-Endoxifen is a known drug and is administered to patients who are not responsive to tamoxifen (see paragraph 0003). The drug shows tumour regressions and is used to treat breast cancer (see also paragraph 0002). Since the drug is known to be administered, all claims relating to a result to be achieved by administering said drug are considered to be inherently anticipated.

D1 is considered to anticipate claims 1, 2, 12, 13, 32-37, 41-46, 51-56, 59-62, 124, 129, 152, 154-156 and 158.

D2 discloses a fractional recrystallizing step giving an endoxifen mixture (see paragraph 61). D2 also anticipates claims 1, 32-37, 41-46, 51-56, 59-62, 124, 129, 152, 154-156 and 158.

Remaining claims 3-11, 14-31, 38-40, 47-50, 57, 58, 63-123, 125-128, 130-151, 153 and 157.

3. Inventive Step (Section 15 of the *Patents Act*)

Given the novelty objection, claims 1, 2, 12, 13, 32-37, 41-46, 51-56, 59-62, 124, 129, 152, 154-156 and 158 are also considered to lack an inventive step.

Written Opinion

Application No.

11202002105W

**V. Reasoned statement with regard to novelty, inventive step or industrial applicability;
Citation and explanation supporting such statement**

Claims 38-40, 47-50, 57, 58, 130-151, 153 and 157 are directed to further features of the composition that are considered to be well within the purview of the skilled person as part of routine experimentation and as such are not considered to involve an inventive step. A dose of 160 mg is also known in a clinical trial of Z-Endoxifen that was first posted in 2011 (URL: <https://clinicaltrials.gov/ct2/show/NCT01327781>).

Claims 63-123 and 126-128 are directed to an industrially scalable process of making the crystalline form of the claimed compound, and a process of reequilibrating a mixture of E-endoxifen and Z-endoxifen. These claims differ from D1 in that the claims define an E/Z ratio of at least 50% higher Z endoxifen in the first mother liquor as compared with the E/Z ratio of the mixture of E and Z-endoxifen. The claims also define reequilibrating a mixture of E and Z endoxifen having an E/Z ratio of 45:55 to 55:45. D1 does not explicitly disclose the E/Z ratio. However, these features are also considered to be well within the purview of the skilled person as part of routine experimentation and as such are not considered to involve an inventive step.

Claims 3-11, 14-31 and 125 are directed to compositions comprising crystalline forms I, II or III. Such crystalline forms that are characterised by specific XRD patterns are not known from any of the cited documents. As such, claims 3-11, 14-31 and 125 appear to be non-obvious in view of D1 or D2 and appear to involve an inventive step.

4. Industrial Applicability (Section 16 of the *Patents Act*)

Claims 1-158 are capable of industrial application.

Written Opinion

Application No.

11202002105W

VII. Clarity, Clear and Complete Disclosure, and Support

The following observations on the clarity of the claim(s), on the question whether the disclosure is clear and complete, or on the question whether the claim(s) is (are) supported by the description, are made:

1. Clarity (Section 25(5)(b) of the *Patents Act*)

Claim 37 is unclear if it is intended to define a composition that is merely suitable for the treatment of said disorders, or if it is intended to claim for a first medical use. The claim has been broadly construed as directed to a composition suitable for treating said disorders.

Claims 44 and 141 are second medical use claims. Second medical use claims are meant to protect specific diseases but no disease or medical condition has been defined in claims 44 and 141.

Claim 92 is unclear. In particular claim 3, in which claim 92 is dependent upon is directed to a composition and not to a process.

Claims 120, 124, 129 and 130 are product by process claims and are not allowable. Product by process claims may be allowable if the product cannot be satisfactorily characterized with reference to its structure, composition, properties or other means. However, it appears that the compound can be adequately defined by its structure (as in claim 1) and as such claims 120, 124, 129 and 130 are not allowed.

Claims 126-130 are unclear. Not all claims 63-126, in which these claims are dependent on are directed to processes.

Forms I, II and III as defined in the claims are unclear as they do not include any characterizing data.

The terms NMT and NLT should be defined at least once in the claims for clarity.

Thank you for choosing our services.

For clarification of the Patent Examiner's comments in this report, direct communication may be arranged with the Patent Examiner via email. For the procedure to initiate such communication, please refer to the Patents Formalities Manual (please click [here](#)), under the heading **"Direct Communication with the Patent Examiner"**.

The IPOS Search & Examination Unit would like to invite you to complete a short survey on the quality of our work (please click [here](#)). This survey will help the Unit to continue to improve, and also to ensure that high quality products and services are consistently delivered to our customers.

If the above hyperlink does not work, please copy and paste <http://goo.gl/1rRO7M> into your browser to access the survey.

Thank you.

Search Report

Application No.
11202002105W

Application filing date 10/09/2018	(Earliest) Priority Date 11/09/2017	Examiner's Reference Number IPOS/AAG
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This Search Report is issued under Section 29(5) of the *Patents Act* with effect from 14/02/2014.

☒ It is also accompanied by a copy of each prior art document cited in this report, except where otherwise indicated.

1. ☐ Certain claims where found **unsearchable** (see Box I)

2. ☐ **Unity of invention** is lacking (see Box II)

3. ☐ The application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the search was carried out on the basis of the sequence listing.

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Office to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Office as appears in Box III.

6. The figure of the **drawings** to be published with the abstract is Fig. no. 1,

☒ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ because there are no drawings in the application.

☐ none of the figures.

Search Report

Application No.
11202002105W

A. CLASSIFICATION OF SUBJECT-MATTER According to International Patent Classification (IPC) A61K 31/138, A61P 35/00, C07C 217/18, C07C 217/54		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic database consulted during the search (name of database and, where applicable, search terms used) CAPLUS: endoxifen, 112093-28-4, crystalline and related terms		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim no.
X A	WO 2017/070651 A1 (THE UNITED STATES OF AMERICA AS REPRESENTED BY THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES) 27 April 2017 Paragraphs 0002, 0003, 0006, 0018	1, 2, 12, 13, 32-124, 126-158 3-11, 14-31, 125
X	WO 2012/050263 A1 (CI CHEILJEDANG CORP) 19 April 2012 Paragraph 61	1, 2, 12, 13, 32-124, 126-158
<input type="checkbox"/> Further documents are listed in the continuation of box C. <input type="checkbox"/> See supplemental box for details of the scope of the search.		
Special categories of cited documents:		
A: document defining the general state of the art which is not considered to be of particular relevance E: earlier application or patent but published on or after the filing date L: document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) O: document referring to an oral disclosure, use, exhibition or other means P: document published prior to the filing date but later than the priority date claimed T: later document published after the filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention X: document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone Y: document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents; such combination being obvious to a person skilled in the art &: document member of the same patent family		
Intellectual Property Office of Singapore 1 Paya Lebar Link #11-03 PLQ 1, Paya Lebar Quarter Singapore 408533 Email: operation@iposinternational.com		Date of actual completion of the search: 15/04/2021 Authorized Officer Amylia Abdul Ghani (Dr)

Questions about this communication ?
Contact Customer Services at www.epo.org/contact



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ROYAUME UNI

Date	28.05.21
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Reference N418882EP	Application No./Patent No. 18853361.6 - 1109 / 3681491 PCT/US2018050272
Applicant/Proprietor Atossa Therapeutics, Inc.	

Communication

The extended European search report is enclosed.

The extended European search report includes, pursuant to Rule 62 EPC, the supplementary European search report (Art. 153(7) EPC) and the European search opinion.

Copies of documents cited in the European search report are attached.

☒ 0 additional set(s) of copies of such documents is (are) enclosed as well.

Refund of the search fee

If applicable under Article 9 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.

Should you wish to further prosecute this application in the examination phase, your attention is drawn to the provisions of Rule 70a EPC. An invitation to respond to the extended European search report will be issued shortly (R. 70(2) EPC).



**SUPPLEMENTARY
EUROPEAN SEARCH REPORT**

Application Number
EP 18 85 3361

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
	No further relevant documents disclosed -----		INV. C07C217/18 C07C217/54 A61K31/138 A61P35/00
			TECHNICAL FIELDS SEARCHED (IPC) C07C A61K A61P
The supplementary search report has been based on the last set of claims valid and available at the start of the search.			
Place of search		Date of completion of the search	Examiner
The Hague		11 May 2021	Diedereren, Jeroen
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

1

EPC FORM 1503 03.82 (P04C04)

Information on Search Strategy - Pilot phase (see OJ 2015, A86)

The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number

EP 18 85 3361

TITLE: METHODS FOR MAKING AND USING ENDOXIFEN

APPLICANT: Atossa Therapeutics, Inc.

IPC CLASSIFICATION: C07C217/18, C07C217/54, A61K31/138, A61P35/00

EXAMINER: Diederer, Jeroen

CONSULTED DATABASES: CAPLUS

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC:

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:

The examination is being carried out on the **following application documents**

Description, Pages

1-112 as published

Claims, Numbers

1-15 filed in electronic form on 26-10-2020

Drawings, Sheets

1/13-13/13 as published

1. Amendments (Article 123(2) EPC)

The amended set of claims is allowable under Article 123(2) EPC.

2. Novelty (Article 54 EPC)

The present application does not meet the requirements of Article 52(1) EPC because the subject-matter of claims 1-15 is not new within the meaning of Article 54(1) and (2) EPC.

The following document has been cited in the international search report; the numbering will be adhered to in the rest of the procedure.

D1 WO 2017/070651 A1 (THE UNITED STATES OF AMERICA, AS
REPRESENTED BY THE SECRETARY, DEPARTM) 27 April 2017
(2017-04-27)

Document D1 discloses the preparation of crystalline (Z)-endoxifen from acetone in example 7. The disclosed mixture falls within the scope of claims 1-15 of the present application.

3. Inventive Step (Article 56 EPC)

The present application does not meet the requirements of Article 52(1) EPC because the subject-matter of claims 1-15 does not involve an inventive step within the meaning of Article 56 EPC.

If the applicant can show by experimental evidence that the crystalline form of (Z)-endoxifen, characterised by an xray powder diffractogram according to claim 2 is novel over the crystalline form of D1, the examining division is of the opinion that the presently claimed form is not inventive over the crystalline form as disclosed in D1.

There are no apparent advantages of the claimed form and the disclosed form as disclosed in D1.

The problem underlying the present application may be formulated as the provision of an alternative crystalline form of (Z)-endoxifen.

Starting from D1, a skilled person would arrive at the subject matter of the present application as he would know how to prepare alternative crystalline forms of (Z)-endoxifen. He would then end up with the crystalline form of the present application without the need of an inventive skill.

The present form may only be considered inventive, if it has an unexpected effect over the disclosed form of D1.

4. Clarity (Article 84 EPC)

The application does not meet the requirements of Article 84 EPC, because claim 1 is not clear.

The term "Form I" in present claim 1 is not clear under Article 84 EPC. The applicant is requested to incorporate claim 2 into claim 1 to render claim 1 clear under Article 84 EPC.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/641,985	02/25/2020	Steven C. Quay	109559-669805	7650
27148	7590	09/07/2021	EXAMINER	
POL SINELLI PC			DAVIS, BRIAN J	
PO Box 140310				
KANSAS CITY, MO 64114-0310				
			ART UNIT	PAPER NUMBER
			1612	
			NOTIFICATION DATE	DELIVERY MODE
			09/07/2021	ELECTRONIC

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

Office Action Summary

Application No.

16/641,985

Applicant(s)

Quay et al.

Examiner

BRIAN J DAVIS

Art Unit

1612

AIA (FITF) Status

Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on _____.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 1,4-9,32-35,38-44,46-47,49,52 and 62 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

- 6) ☐ Claim(s) _____ is/are allowed.

- 7) ☒ Claim(s) 1,4-9,32-35,38-44,46-47,49,52 and 62 is/are rejected.

- 8) ☐ Claim(s) _____ is/are objected to.

- 9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☒ The drawing(s) filed on 25 February 2020 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some** c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date 5/29/2020; 6/29/2021.
- 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____.
- 4) ☐ Other: _____.

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 assemblage 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, 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.)

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, 5th 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

I hereby certify that this correspondence is being filed via
EFS-Web with the United States Patent and Trademark Office
on _____/Megan Thornton/

Attorney Docket No.: 109559-669805

POLSINELLI PC

By: _____ October 15, 2021

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Steven C. QUAY et al.

Application No.: 16/641,985

Filed: February 25, 2020

For: METHODS FOR MAKING AND
USING ENDOXIFEN

Customer No. 27148

Confirmation No. 7650

Examiner: Brian J. Davis

Art Unit: 1612

AMENDMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

In response to the Non-Final Office Action mailed September 7, 2021, please enter the following amendments and remarks.

Amendments to the Drawings are reflected in an attached replacement sheet and are discussed on page 2.

Amendments to the Claims are reflected in the listing of claims beginning on page 3.

Remarks begin on page 10.

Amendments to the Drawings:

The attached sheets of drawings include changes to Figure 1. The first sheet, which includes Figure 1, replaces the original sheet 1 including Figure 1.

Attachment: Replacement Sheets

REMARKS

Upon entry of this amendment, claims 1, 5-9, 32-35, 38-43, 46, 47, 49, 52, and 158 will be pending in the present application. Claims 4, 44, and 62 are canceled herein without prejudice or disclaimer. Applicant reserves the right to pursue any canceled subject matter in a related, future application. New claims 158 has been added. Claims 1, 5-9, 35, 38, 39, 41-43, 49, and 52 have been amended. Support for new claims and amendments can be found in the specification as originally filed (US 16/641,985, hereinafter “the Application”). For example, support for new claim 158 can be found at least at paragraph [0149] of the Application. Accordingly, no new matter has been added. Reconsideration is respectfully requested.

Objections to the Drawing

The Examiner has indicated that “Figure 1 should be designated by a legend such as – Prior Art,” (Office Action at p. 3).

A replacement drawing sheet accompanies this response in which Figure 1 is amended to including a legend which reads, “Prior Art.” Accordingly, withdrawal of the objection to the drawings is respectfully requested.

Information Disclosure Statement

The Information Disclosure Statement filed on May 29, 2020 allegedly fails to comply with 37 C.F.R. 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.

An Information Disclosure Statement which includes replacement copies of the indicated references accompanies this response. Accordingly, withdrawal of the objection to the Information Disclosure Statement is respectfully requested.

Claim Rejections – 35 USC § 112

Claims 1, 35, 38, 39, 41-43, 49, 52 and 62 stand rejected under 35 U.S.C. § 112(b) or 35 U.S.C. § 112 (pre-AIA), second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. Claims 4-9, 32-34, 40, 44, 46, and 47 also stand rejected under 35 U.S.C. § 112, second paragraph for their dependence from rejected claims 1 and 43.

Claims 1 and 43

The Examiner alleges that “the identity of Form I of the compound of Formula (III) [recited in claims 1 and 43] is unclear because it is undefined,” (Office Action at p. 4). The Examiner further alleges that “... and the crystalline form of the compound of Formula (III) is Form I” [recited in claims 1 and 43] is ambiguous . . . [because] the mixture, cannot simply be Form I, because Form I is taught in the specification as a polymorph of the (Z)-isomer.”

Claims 1 and 43 have been amended to recite, “wherein the crystalline form of the (Z)-isomer is Form I, characterized by an x-ray powder diffraction pattern comprising major peaks at $16.8 \pm 0.3^\circ$, $17.1 \pm 0.3^\circ$ and $21.8 \pm 0.3^\circ$ two theta.

Applicant thanks the Examiner for suggesting incorporating the limitations of claim 3, which Applicant has understood to mean claim 4 since claim 3 was previously canceled, in to claims 1 and 43. Additionally, Applicant thanks the Examiner for suggesting the slight rewording of “... and the crystalline form of the (Z)-isomer of the compound of Formula (III).” Amended claims 1 and 43 recite the limitations of prior claim 4, specifying an x-ray powder diffraction pattern of Form I, and clarify that the crystalline form of the (Z)-isomer is Form I. As such, Applicant submits that claims 1 and 43, as amended, are clear.

Claims 35, 38, 39, 41, and 42

The Examiner alleges that “there is insufficient antecedent basis for the limitation ‘endoxifen’ in [claims 35, 38, 39, 41, and 42],” (Office Action at p. 5).

Claims 35, 38, 39, 41, and 42 have been amended to recite “the compound of Formula (III)” in place of “endoxifen.”

Applicant thanks the Examiner for the suggestions to avoid ambiguity. Applicant submits that claims 35, 38, 39, 41, and 42, as amended, have sufficient antecedent basis, and clearly distinguish between the compound of Formula (III) and the (Z)-isomer. As such, Applicant submits that amended claims 35, 38, 39, 41, and 42.

Claims 38 and 43

The Examiner alleges that “it is unclear who might be ‘ . . . a subject in need thereof . . . ,’” (Office Action at p. 5), as recited in claims 38 and 43.

Claims 38 has been amended to recite, in part, “a subject treated with the composition,” and claim 43 has been amended to recite, in part, “a method of treating or preventing a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in subject.”

The parameters recited in amended claim 38 may be produced in a subject treated with the composition, independent of the “need” or condition of the subject. Therefore, Applicant submits that recitation of “a subject treated with the composition” in amended claim 38 is sufficiently clear. Additionally, amended claim 43 recites conditions, namely “a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder,” that may be treated in a subject using the claimed method. As such, Applicant submits that the recitation of “a method of treating or preventing a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in subject” in amended claim 43 is sufficiently clear.

Claims 49 and 52

The Examiner alleges that “there is insufficient antecedent basis for the limitation ‘(Z)-endoxifen’ in [claim 49],” and that “there is insufficient antecedent basis for the limitation ‘endoxifen’ in [claim 52],” (Office Action at p. 6).

Claim 49 has been amended to recite “the (Z)-isomer” in place of “(Z)-endoxifen,” and claim 53 has been amended to recite “the compound of Formula (III)” in place of “endoxifen.”

Applicant submits that claims 49 and 53, as amended, are clear at least because “the (Z)-isomer,” recited in amended claim 49, and “the compound of Formula (III),” recited in amended claim 53 have antecedent basis in claim 43 from which the depend.

For at least the reasons set forth above, Applicant submits that claims 1, 35, 38, 39, 41-43, 49, and 52 are clear. Claims 4-9, 32-34, 40, 44, 46, and 47 are clear at least for their

dependence from claims 1 and 43, and by their own merits. Accordingly, withdrawal of the rejection of claims 1, 4-9, 32-35, 38-44, 46, 47, 49, and 52 under 35 U.S.C. § 112 is respectfully requested.

Claim 62

The Examiner alleges that “it is unclear, in the second step of the procedure [of claim 62], how recrystallization from a second solvent can be accurately described as concentrating the first mother liquor,” (Office Action at p. 6).

Without conceding on the merits of the rejection, claim 62 is herein canceled, rendering the rejection moot. Accordingly, withdrawal of the rejection of claim 62 under 35 U.S.C. § 112 is respectfully requested.

Claim Rejections – 35 USC § 103

Claim 62 stands rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over WO 2017/070651 A1 (hereinafter, “Heinkele”). The Examiner alleges that “the actual procedures of the prior art method and that of the instant invention are the same,” (Office Action at p. 9).

Without conceding on the merits of the rejection, claim 62 is herein canceled, rendering the rejection moot. Accordingly, for the reasons set forth above, withdrawal of the rejection of claim 62 under 35 U.S.C. § 103(a) is respectfully requested.

Allowable Subject Matter

The Applicant thanks the Examiner for the indication of allowable subject matter. Although the undersigned agent agrees with the Examiner's conclusion that claims 1, 4-9, 32-35, 38-44, 46, 47, 49, and 52 contain allowable subject matter, the undersigned agent notes that the claims may be allowable for reasons other than those identified by the Examiner.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Further, the Commissioner is hereby authorized to charge any additional fees or credit any overpayment in connection with this paper to Deposit Account No. 50-1662.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-393-5449.

Respectfully submitted,

Dated: October 15, 2021

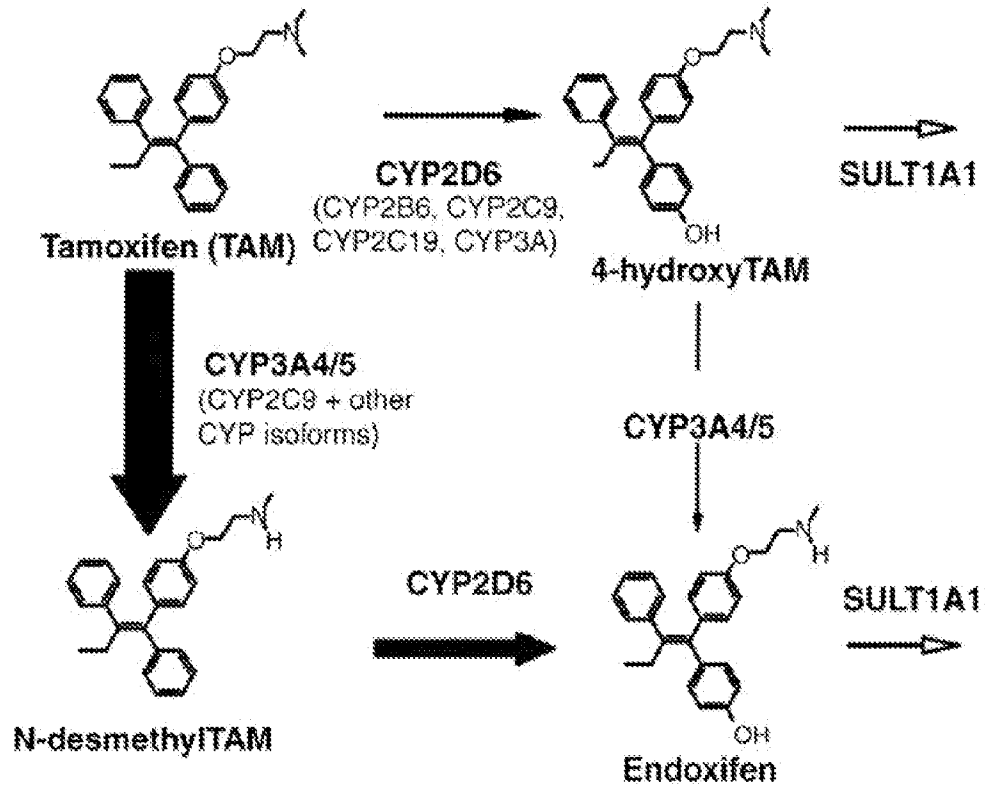
/Lisa G Lippert/

Lisa G. Lippert, Ph.D.
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REPLACEMENT SHEET

Fig. 1



PRIOR ART