PTO-1390 (01-18)
Approved for use through 8/31/2019. OMB 0651-0021
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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# TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371

| Attorney Docket No. | |
|---|---|
| 38602-758.831 | |
| U.S. Application No. (if known, see 37 CFR 1.5) | |

| International Application No. | International Filing Date | Priority Date Claimed |
|---|---|---|
| PCT/US2018/050272 | September 10, 2018 | September 11, 2017 |

Title of Invention
METHODS FOR MAKING AND USING ENDOXIFEN

First Named Inventor
Steven C. Quay

**Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.**

1. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). NOTE: The express request under 35 U.S.C. 371(f) will not be effective unless the requirements under 35 U.S.C. 371(c)(1), (2), and (4) for payment of the basic national fee, copy of the International Application and English translation thereof (if required), and the oath or declaration of the inventor(s) have been received.
2. ☐ A copy of the International Application (35 U.S.C. 371(c)(2)) is attached hereto (not required if the International Application was previously communicated by the International Bureau or was filed in the United States Receiving Office (RO/US)).
3. An English language translation of the International Application (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
4. An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4))
   a. ■ is attached.
   b. ☐ was previously filed in the international phase under PCT Rule 4.17(iv).

**Items 5 to 8 below concern amendments made in the international phase.**

PCT Article 19 and 34 amendments

5. ☐ Amendments to the claims under PCT Article 19 are attached (not required if communicated by the International Bureau) (35 U.S.C. 371(c)(3)).
6. ☐ English translation of the PCT Article 19 amendment is attached (35 U.S.C. 371(c)(3)).
7. ☐ English translation of annexes (Article 19 and/or 34 amendments only) of the International Preliminary Examination Report is attached (35 U.S.C. 371(c)(5)).

Cancellation of amendments made in the international phase

8a. ☐ Do not enter the amendment made in the international phase under PCT Article 19.

8b. ☐ Do not enter the amendment made in the international phase under PCT Article 34.

NOTE: A proper amendment made in English under Article 19 or 34 will be entered in the U.S. national phase application absent a clear instruction from applicant not to enter the amendment(s).

**The following items 9 to 17 concern a document(s) or information included.**

9. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
10. ■ A preliminary amendment.
11. ■ An Application Data Sheet under 37 CFR 1.76.
12. ☐ A substitute specification. NOTE: A substitute specification cannot include claims. See 37 CFR 1.125(b).
13. ☐ A power of attorney and/or change of address letter.
14. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.3 and 37 CFR 1.821-1.825 (not required if sequence listing in text format was indicated on the PCT Request as part of the International Application and the sequence listing was published as part of the international application).
15. ☐ Assignment papers *(cover sheet and document(s))*. Name of Assignee: _____
16. ☐ 37 CFR 3.73(c) Statement *(when there is an Assignee)*.

This collection of information is required by 37 CFR 1.414 and 1.491-1.492. The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 15 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

| U.S. APPLN. No. (if known – see 37 CFR 1.5) | INTERNATIONAL APPLICATION No. | ATTORNEY DOCKET No. |
|---|---|---|
| | PCT/US2018/050272 | 38602-758.831 |

17. ☐ Other items or information:

| **The following fees have been submitted.** | CALCULATIONS |
|---|---|
| 18. ■ Basic national fee (37 CFR 1.492(a)) ..... **$300** | $ 300.00 |
| 19. ■ Examination fee (37 CFR 1.492(c))<br>• If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4)..... **$0**<br>• All other situations ..... **$760** | $ 760.00 |
| 20. ■ Search fee (37 CFR 1.492(b))<br>• If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4)..... **$0**<br>• Search fee (37 CFR 1.445(a)(2)) has been paid on the international application to the USPTO as an International Searching Authority ..... **$140**<br>• International Search Report prepared by an ISA other than the US and provided to the Office or previously communicated to the US by the IB..... **$520**<br>• All other situations ..... **$660** | 140.00<br>$ |
| **TOTAL OF 18, 19, and 20 =** | $ 1,200.00 |
| ☐ Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing in compliance with 37 CFR 1.821(c) or (e) in an electronic medium or computer program listing in an electronic medium) (37 CFR 1.492(j)).<br>Fee for each additional 50 sheets of paper or fraction thereof ..... **$400** | 0.00 |

| Total Sheets | Extra Sheets | Number of each additional 50 or fraction thereof (round **up** to a whole number) | RATE |
|---|---|---|---|
| - 100 = | / 50 = | | x **$400** |

$

| | |
|---|---|
| Surcharge for furnishing any of the search fee, examination fee, or the oath or declaration after the date of commencement of the national stage (37 CFR 1.492(h)).....**$140** | $ 0.00 |

| CLAIMS | NUMBER FILED | NUMBER EXTRA | RATE | |
|---|---|---|---|---|
| Total claims | - 20 = | | x **$100** | $ 0.00 |
| Independent claims | - 3 = | | x **$460** | $ 0.00 |
| MULTIPLE DEPENDENT CLAIM(S) (if applicable) | | | **+ $820** | $ 0.00 |

| | |
|---|---|
| Fee for submission of Sequence Listing text file of 300 MB to 800 MB (37 CFR 1.21(o)(1))..... **$1,000** | $ 0.00 |
| Fee for submission of Sequence Listing text file of more than 800 MB (37 CFR 1.21(o)(2))..... **$10,000** | $ 0.00 |
| Processing fee for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(i))..... **$140 +** | $ 0.00 |
| **TOTAL OF ABOVE CALCULATIONS =** | $ 1,200.00 |
| ■ **Applicant asserts small entity status.** See 37 CFR 1.27. Fees above are reduced by ½. | |
| ☐ **Applicant certifies micro entity status.** See 37 CFR 1.29. Fees above are reduced by ¾. Applicant must attach form PTO/SB/15A or B or equivalent. | |
| **TOTAL NATIONAL FEE =** | $ 600.00 |
| Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31)..... **$50.00** per property **+** | $ 0.00 |
| **TOTAL FEES ENCLOSED =** | $ 600.00 |

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 23-2415 in the amount of $ 600.00 to cover the above fees.

c. ☐ The Director is hereby authorized to charge additional fees which may be required, or credit any overpayment, to Deposit Account No. _____ as follows:

i. ☐ any required fee.

ii. ☐ any required fee except for excess claims fees required under 37 CFR 1.492(d) and (e) and multiple dependent claim fee required under 37 CFR 1.492(f).

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038. The PTO-2038 should only be mailed or faxed to the USPTO. However, when paying the basic national fee, the PTO-2038 may NOT be faxed to the USPTO.

**ADVISORY:** If filing by EFS-Web, do **NOT** attach the PTO-2038 form as a PDF along with your EFS-Web submission. Please be advised that this is **not** recommended and by doing so your **credit card information may be displayed via PAIR**. To protect your information, it is recommended to pay fees online by using the electronic payment method.

**NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the International Application to pending status.**

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications**

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013, and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

**NOTE 1:** By providing this statement under 37 CFR 1.55 or 1.78, **this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA**.

**NOTE 2:** A U.S. national stage application may not claim priority to the international application of which it is the national phase. The filing date of a U.S. national stage application is the international filing date. See 35 U.S.C. 363.

**Correspondence Address**

☒ The address associated with Customer Number: 021971 **OR** ☐ Correspondence address below

| | | | | | |
|---|---|---|---|---|---|
| Name | | | | | |
| Address | | | | | |
| City | | State | | Zip Code | |
| Country | | Telephone | | | |
| Email | | | | | |

| | | | |
|---|---|---|---|
| Signature | /Lisa G Lippert/ | Date | February 25, 2020 |
| Name (Print/Type) | Lisa G. Lippert, Ph.D. | Registration No. (Attorney/Agent) | 78,332 |

# Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 38602-758.831 |
|---|---|---|
| | Application Number | |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

## Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

## Inventor Information:

**Inventor 1** Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | Steven | C. | Quay | |

**Residence Information (Select One)** ◉ US Residency ○ Non US Residency ○ Active US Military Service

| City | Seattle | State/Province | WA | Country of Residence | US |
|---|---|---|---|---|---|

**Mailing Address of Inventor:**

| Address 1 | 107 Spring Street | | |
|---|---|---|---|
| Address 2 | | | |
| City | Seattle | State/Province | WA |
| Postal Code | 98104 | Country | US |

**Inventor 2** Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | YaoLin | | Sun | |

**Residence Information (Select One)** ○ US Residency ◉ Non US Residency ○ Active US Military Service

| City | Kaohsiung City | Country of Residence | TW |
|---|---|---|---|

**Mailing Address of Inventor:**

| Address 1 | 13F., No. 339-12, Sec. 2, Guangfu Rd. | | |
|---|---|---|---|
| Address 2 | Fengshan Dist. | | |
| City | Kaohsiung City | State/Province | |
| Postal Code | 830 | Country | TW |

**Inventor 3** Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | LungHu | | Wang | |

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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 38602-758.831 |
|---|---|---|
| | Application Number | |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

**Residence Information (Select One)** ○ US Residency ◉ Non US Residency ○ Active US Military Service

| City | Kaohsiung City | Country of Residence [i] | TW |
|---|---|---|---|

**Mailing Address of Inventor:**

| Address 1 | No. 102-2, Beishan Ln. | | |
|---|---|---|---|
| Address 2 | Qijin Dist. | | |
| City | Kaohsiung City | State/Province | |
| Postal Code | 805 | Country [i] | TW |

**Inventor 4** Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | ChangJung | | Wu | |

**Residence Information (Select One)** ○ US Residency ◉ Non US Residency ○ Active US Military Service

| City | Kaohsiung City | Country of Residence [i] | TW |
|---|---|---|---|

**Mailing Address of Inventor:**

| Address 1 | No. 28, Ln. 150, Youchang St. | | |
|---|---|---|---|
| Address 2 | Nanzi Dist. | | |
| City | Kaohsiung City | State/Province | |
| Postal Code | 811 | Country [i] | TW |

**Inventor 5** Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | ChuanDer | | Huang | |

**Residence Information (Select One)** ○ US Residency ◉ Non US Residency ○ Active US Military Service

| City | Tainan City | Country of Residence [i] | TW |
|---|---|---|---|

**Mailing Address of Inventor:**

| Address 1 | No. 21, Aly. 11, Ln. 176, Sec. 1 Bei'an Rd. | | |
|---|---|---|---|
| Address 2 | North Dist. | | |
| City | Tainan City | State/Province | |
| Postal Code | 704 | Country [i] | TW |

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 38602-758.831 |
|---|---|---|
| | Application Number | |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

## Correspondence Information:

**Enter either Customer Number or complete the Correspondence Information section below.**
**For further information see 37 CFR 1.33(a).**

☐ **An Address is being provided for the correspondence Information of this application.**

| | | | |
|---|---|---|---|
| **Customer Number** | 021971 | | |
| **Email Address** | patentdocket@wsgr.com | Add Email | Remove Email |

## Application Information:

| | | | |
|---|---|---|---|
| **Title of the Invention** | METHODS FOR MAKING AND USING ENDOXIFEN | | |
| **Attorney Docket Number** | 38602-758.831 | **Small Entity Status Claimed** | ☒ |
| **Application Type** | Nonprovisional | | |
| **Subject Matter** | Utility | | |
| **Total Number of Drawing Sheets (if any)** | 13 | **Suggested Figure for Publication (if any)** | 1 |

## Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

| Application number of the previously filed application | Filing date (YYYY-MM-DD) | Intellectual Property Authority or Country |
|---|---|---|
| | | |

## Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

## Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

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| **Application Data Sheet 37 CFR 1.76** | Attorney Docket Number | 38602-758.831 |
|---|---|---|
| | Application Number | |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

| Please Select One: | ◉ Customer Number | ○ US Patent Practitioner | ○ Limited Recognition (37 CFR 11.9) |
|---|---|---|---|
| Customer Number | 021971 | | |

## Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

| Prior Application Status | Pending | | Remove |
|---|---|---|---|
| Application Number | Continuity Type | Prior Application Number | Filing or 371(c) Date (YYYY-MM-DD) |
| | a 371 of international | PCT/US2018/050272 | 2018-09-10 |
| Prior Application Status | Expired | | Remove |
| Application Number | Continuity Type | Prior Application Number | Filing or 371(c) Date (YYYY-MM-DD) |
| PCT/US2018/050272 | Claims benefit of provisional | 62/556799 | 2017-09-11 |
| Prior Application Status | Expired | | Remove |
| Application Number | Continuity Type | Prior Application Number | Filing or 371(c) Date (YYYY-MM-DD) |
| PCT/US2018/050272 | Claims benefit of provisional | 62/556884 | 2017-09-11 |
| Prior Application Status | Expired | | Remove |
| Application Number | Continuity Type | Prior Application Number | Filing or 371(c) Date (YYYY-MM-DD) |
| PCT/US2018/050272 | Claims benefit of provisional | 62/624787 | 2018-01-31 |
| Prior Application Status | Expired | | Remove |
| Application Number | Continuity Type | Prior Application Number | Filing or 371(c) Date (YYYY-MM-DD) |
| PCT/US2018/050272 | Claims benefit of provisional | 62/693885 | 2018-07-03 |

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

## Foreign Priority Information:

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| **Application Data Sheet 37 CFR 1.76** | Attorney Docket Number | 38602-758.831 |
|---|---|---|
| | Application Number | |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

| Application Number | Country[i] | Filing Date (YYYY-MM-DD) | Access Code[i] (if applicable) |
|---|---|---|---|
| | | | |

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

## Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 38602-758.831 |
|---|---|---|
| | Application Number | |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

## Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

**NOTE**: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

**1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)**

**A. Priority Document Exchange (PDX)** - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

**B. Search Results from U.S. Application to EPO** - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

**2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)**

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

**NOTE:** Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

PTO/AIA/14 (02-18)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 38602-758.831 |
|---|---|---|
| | Application Number | |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

## Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

**Applicant 1**

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

| | | |
|---|---|---|
| ◉ Assignee | ○ Legal Representative under 35 U.S.C. 117 | ○ Joint Inventor |
| ○ Person to whom the inventor is obligated to assign. | ○ Person who shows sufficient proprietary interest | |

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

| | |
|---|---|
| Name of the Deceased or Legally Incapacitated Inventor: | |

If the Applicant is an Organization check here. ☒

| | |
|---|---|
| Organization Name | ATOSSA THERAPEUTICS, INC. |

**Mailing Address Information For Applicant:**

| | | | |
|---|---|---|---|
| **Address 1** | 107 Spring Street | | |
| Address 2 | | | |
| **City** | Seattle | **State/Province** | WA |
| **Country** | US | Postal Code | 98104 |
| Phone Number | | Fax Number | |
| Email Address | | | |

Additional Applicant Data may be generated within this form by selecting the Add button.

## Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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| **Application Data Sheet 37 CFR 1.76** | Attorney Docket Number | 38602-758.831 |
|---|---|---|
| | Application Number | |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

**Assignee 1**

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

| Prefix | **Given Name** | Middle Name | **Family Name** | Suffix |
|---|---|---|---|---|
| | | | | |

**Mailing Address Information For Assignee including Non-Applicant Assignee:**

| | | | |
|---|---|---|---|
| **Address 1** | | | |
| Address 2 | | | |
| **City** | | **State/Province** | |
| **Country** i | | Postal Code | |
| Phone Number | | Fax Number | |
| Email Address | | | |

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

## Signature:

**NOTE:** This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

| **Signature** | /Lisa G Lippert/ | | | Date (YYYY-MM-DD) | 2020-02-25 |
|---|---|---|---|---|---|
| First Name | Lisa G. | Last Name | Lippert, Ph.D. | Registration Number | 78332 |

Additional Signature may be generated within this form by selecting the Add button.

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| **Application Data Sheet 37 CFR 1.76** | Attorney Docket Number | 38602-758.831 |
|---|---|---|
| | Application Number | |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

# Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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# DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

| **Title of Invention** | METHODS FOR MAKING AND USING ENDOXIFEN |
|---|---|

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number PCT/US2018/050272

filed on September 10, 2018

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

## WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Steven C. Quay Date (Optional): 09/27/2018

Signature:

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

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| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN |
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This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number PCT/US2018/050272 filed on September 10, 2018

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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LEGAL NAME OF INVENTOR

Inventor: YaoLin Sun Date (Optional): 2019/09/19

Signature: YaoLin Sun

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN |
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☒ United States application or PCT international application number PCT/US2018/050272 filed on September 10, 2018.

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LEGAL NAME OF INVENTOR

Inventor: LungHu Wang Date (Optional): 2018/09/19

Signature: LungHu Wang

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

Attorney Docket No.: 38602-758.831

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| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN |
|---|---|

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number PCT/US2018/050272 filed on September 10, 2018.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

## WARNING:

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LEGAL NAME OF INVENTOR

Inventor: ChangJung Wu Date (Optional): 2018/09/19.

Signature: ChangJung Wu.

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

Attorney Docket No.: 38602-758.831

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# DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

| **Title of Invention** | METHODS FOR MAKING AND USING ENDOXIFEN |
|---|---|

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I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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LEGAL NAME OF INVENTOR

Inventor: ChuanDer Huang Date (Optional): 2018/09/26

Signature: C.D.H

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on February 25, 2020.

WILSON SONSINI GOODRICH & ROSATI

By: /Danielle Hoffman/

Attorney Docket No.: 38602-758.831

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re Application of:<br>Steven C. Quay et al. | Confirmation No.: Not Yet Assigned |
| Application No.: Not Yet Assigned<br>International Appl. No.: PCT/US2018/050272 | Examiner: Not Yet Assigned |
| Filed: Herewith<br>International Appl. Filed: September 10, 2018 | Art Unit: Not Yet Assigned |
| For: METHODS FOR MAKING AND USING ENDOXIFEN | PRELIMINARY AMENDMENT |
| Customer No.: 021971 | |

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

Commissioner:

Prior to examination of the above-referenced application, please enter the following amendments and remarks:

**Amendments to the Specification** begin on page 2 of this paper.

**Remarks** begin on page 3 of this paper.



**Intas Exhibit 1002**
**Page 20 of 598**
**IPR2025-00799**

**Amendments to the Specification:**

Please replace paragraph [0001] with the following amended paragraph:

**[0001]** This application is a U.S. National Phase Application under 35 U.S.C. § 371 of International Application No. PCT/US2018/050272, filed September 10, 2018, which claims the benefit of U.S. Provisional Application No. 62/556,799, filed September 11, 2017; U.S. Provisional Application No. 62/556,884, filed September 11, 2017; U.S. Provisional Application No. 62/624,787, filed January 31, 2018; and U.S. Provisional Application No. 62/693,885, filed July 3, 2018, each incorporated herein by reference in its entirety.



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## REMARKS

The Specification has been amended to include the immediate priority information. No new matter has been added by way of this amendment.

## CONCLUSION

In view of the foregoing, Applicants believe 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.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-883-2574.

Respectfully submitted,

Dated: February 25, 2020

/Lisa G Lippert/
Lisa G. Lippert, Ph.D.
Reg. No. 78,332

WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304-1050
Phone 650-493-9300
Fax 650-493-6811
LLIP:dhof



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**IPR2025-00799**

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | |
| **Filing Date:** | |
| **Title of Invention:** | METHODS FOR MAKING AND USING ENDOXIFEN |
| **First Named Inventor/Applicant Name:** | Steven C. Quay |
| **Filer:** | Lisa Gail Lippert/Danielle Hoffman |
| **Attorney Docket Number:** | 38602-758.831 |

Filed as Small Entity

**Filing Fees for U.S. National Stage under 35 USC 371**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| BASIC NATIONAL STAGE FEE | 2631 | 1 | 150 | 150 |
| NATL STAGE SEARCH FEE - U.S. WAS THE ISA | 2641 | 1 | 70 | 70 |
| NATL STAGE EXAM FEE - ALL OTHER CASES | 2633 | 1 | 380 | 380 |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |
| **Miscellaneous:** | | | | |
| | | **Total in USD ($)** | | **600** |

# Electronic Acknowledgement Receipt

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| **Application Number:** | 16641985 |
| **International Application Number:** | PCT/US18/50272 |
| **Confirmation Number:** | 7650 |
| **Title of Invention:** | METHODS FOR MAKING AND USING ENDOXIFEN |
| **First Named Inventor/Applicant Name:** | Steven C. Quay |
| **Customer Number:** | 21971 |
| **Filer:** | Lisa Gail Lippert/Danielle Hoffman |
| **Filer Authorized By:** | Lisa Gail Lippert |
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| **Application Type:** | U.S. National Stage under 35 USC 371 |

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## File Listing:

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| 1 | Transmittal of New Application | 38602-758-831_Transmittal_filed_02-25-20.pdf | 264189<br>90bfb12b45ee181fa7c632906e45ab9bc362f8e6 | no | 4 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Application Data Sheet | 38602-758-831_ADS_filed_02-25-20.pdf | 3315828<br>4ad38bdc5fa7d87ecc7381da924db7fe3103ff2d | no | 10 |
| **Warnings:** | | | | | |
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| 3 | Oath or Declaration filed | 38602-758-831_Declarations_filed_02-25-20.pdf | 2541917<br>33f3ce1b6ef8555d193c468d4144bd7028d518bb | no | 5 |
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| 4 | | 38602-758-831_Preliminary_Amendment_filed_02-25-20.pdf | 114168<br>99d0f2820224cf2f0092fb158d0c57a32bacba9e | yes | 3 |

**Multipart Description/PDF files in .zip description**

| Document Description | Start | End |
|---|---|---|
| Preliminary Amendment | 1 | 1 |
| Specification | 2 | 2 |
| Applicant Arguments/Remarks Made in an Amendment | 3 | 3 |

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|---|---|
| **Warnings:** | |
| **Information:** | |

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| 5 | Fee Worksheet (SB06) | fee-info.pdf | 35208<br>6736a16e8b120aaf8e3d54a46a50080ce0aacb83 | no | 2 |
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**New Applications Under 35 U.S.C. 111**

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**New International Application Filed with the USPTO as a Receiving Office**

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(71) Applicant: **ATOSSA GENETICS INC.** [US/US]; 107 Spring Street, Seattle, Washington 98104 (US).

(72) Inventors: **QUAY, Steven C.**; 107 Spring Street, Seattle, Washington 98104 (US). **SUN, YaoLin**; 13F., No. 339-12, Sec. 2, Guangfu Rd., Fengshan Dist., Kaohsiung City, 830 (TW). **WANG, LungHu**; No. 102-2, Beishan Ln., Qijin Dist., Kaohsiung City, 805 (TW). **WU, ChangJung**; No. 28, Ln. 150, Youchang St., Nanzi Dist., Kaohsiung City, 811 (TW). **HUANG, ChuanDer**; No. 21, Aly. 11, Ln. 176, Sec. 1, Bei'an Rd., North Dist., Tainan City, 704 (TW).

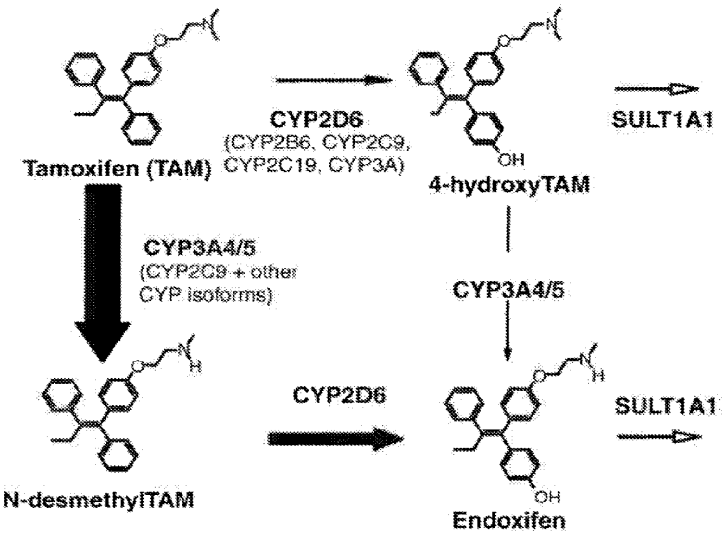
(74) Agent: **WELCH, Timothy R.** et al.; Wilson Sonsini Goodrich & Rosati, 650 Page Mill Road, Palo Alto, California 94304-1050 (US).

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(54) Title: METHODS FOR MAKING AND USING ENDOXIFEN

Fig. 1




(57) Abstract: The present disclosure provides industrially scalable methods of making (Z)-endoxifen or a salt thereof, crystalline forms of endoxifin, and compositions comprising them. The present disclosure also provides methods for treating hormone-dependent breast and hormone-dependent reproductive tract disorders.

*[Continued on next page]*

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TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

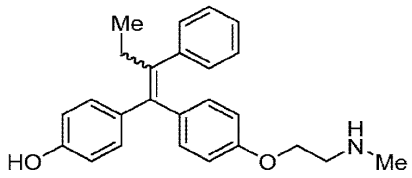
**Published:**

— *with international search report (Art. 21(3))*
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## CLAIMS

WHAT IS CLAIMED IS:

1. A composition comprising a crystalline form of a compound of Formula (III):




Formula (III).

2. The composition of claim 1, wherein at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer.

3. The composition of claim 2, wherein the crystalline form is Form I of the compound of Formula (III).

4. The composition of claim 3, wherein the crystalline form is characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta.

5. The composition of claim 4, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from 16.0 ± 0.3°, 18.8 ± 0.3° and 26.5 ± 0.3° two theta.

6. The composition of claim 4 or 5, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from 12.3 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta.

7. The composition of claim 4, wherein the x-ray powder diffraction pattern further comprises peaks at 12.3 ± 0.3°, 16.0 ± 0.3°, 18.8 ± 0.3°, 26.5 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta.

8. The composition of any one of claims 3 to 7, wherein the crystalline form is characterized by an x-ray powder diffraction pattern substantially as set forth in Fig. 9 or Fig. 10.

9. The composition of any one of claims 3 to 8, wherein greater than 90%, 95% or 99% by weight of the compound of Formula (III) in the composition is crystalline Form I.

10. The composition of any one of claims 3 to 9, wherein the composition comprises 0.01 mg to 200 mg of crystalline Form I.

11. The composition of claim 10, wherein the composition comprises about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of crystalline Form I.

12. The composition of claim 1, 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.

13. The composition of claim 12, wherein the E/Z ratio is about 1.1.

14. The composition of claim 12 or 13, wherein the crystalline form is Form II of the compound of Formula (III).



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15. The composition of claim 14, wherein the crystalline form is characterized by an x-ray powder diffraction pattern comprising major peaks at 7.0 ± 0.3°, 11.9 ± 0.3°, 14.0 ± 0.3° and 18.4 ± 0.3° two theta.

16. The composition of claim 15, wherein the x-ray powder diffraction pattern further comprises a peak at 22.0 ± 0.3° two theta.

17. The composition of claim 15 or 16, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from 6.6 ± 0.3°, 13.3 ± 0.3° and 20.0 ± 0.3° two theta.

18. The composition of claim 15, wherein the x-ray powder diffraction pattern further comprises peaks at 6.6 ± 0.3°, 13.3 ± 0.3°, 20.0 ± 0.3° and 22.0 ± 0.3° two theta.

19. The composition of any one of claims 14 to 18, wherein the crystalline form is characterized by an x-ray powder diffraction pattern substantially as set forth in Fig. 11 or Fig. 12.

20. The composition of any one of claims 14 to 19, wherein greater than 90%, 95% or 99% by weight of the compound of Formula (III) in the composition is crystalline Form II.

21. The composition of any one of claims 14 to 20, wherein the composition comprises 0.01 mg to 200 mg of crystalline Form II.

22. The composition of claim 21, wherein the composition comprises about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of crystalline Form II.

23. The composition of claim 12 or 13, wherein the crystalline form is Form III of the compound of Formula (III).

24. The composition of claim 23, wherein the crystalline form is characterized by an x-ray powder diffraction pattern comprising major peaks at 11.9 ± 0.3°, 13.9 ± 0.3°, 17.1 ± 0.3° and 17.7 ± 0.3° two theta.

25. The composition of claim 24, wherein the x-ray powder diffraction pattern further comprises a peak at 25.3 ± 0.3° two theta.

26. The composition of claim 24 or 25, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from 18.2 ± 0.3°, 22.5 ± 0.3° and 26.8 ± 0.3° two theta.

27. The composition of claim 24, wherein the x-ray powder diffraction pattern further comprises peaks at 18.2 ± 0.3°, 22.5 ± 0.3°, 25.3 ± 0.3° and 26.8 ± 0.3° two theta.

28. The composition of any one of claims 23 to 27, wherein the crystalline form is characterized by an x-ray powder diffraction pattern substantially as set forth in Fig. 13.

29. The composition of any one of claims 23 to 28, wherein greater than 90%, 95% or 99% by weight of the compound of Formula (III) in the composition is crystalline Form III.



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30. The composition of any one of claims 23 to 29, wherein the composition comprises 0.01 mg to 200 mg of crystalline Form III.

31. The composition of claim 30, wherein the composition comprises about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of crystalline Form III.

32. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the composition of any one of the preceding claims.

33. The composition of any one of the preceding claims, wherein the composition is formulated for oral, parenteral, topical, or intraductal delivery.

34. The composition of any one of the preceding claims, wherein the composition is formulated for oral delivery as a tablet, a caplet, a capsule, or a pill.

35. The composition of any one of the preceding claims, wherein a mean half-life of endoxifen in a subject treated with the composition is between 30 hours to 60 hours.

36. The composition of any one of the preceding claims, wherein the composition is formulated for oral delivery as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

37. The composition of any one of the preceding claims, wherein the composition is administered to a subject for the treatment or prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both in the subject.

38. An oral composition comprising 1 mg to 200 mg per unit dose of the composition of any one of the preceding claims for administration to a subject in need thereof, wherein daily administration of the oral composition achieves in the subject:

a steady state plasma level of endoxifen within 7 to 21 days;

a steady state plasma level of endoxifen ranging from 25 nM to 300 nM;

a steady state plasma level of endoxifen greater than 30 nM;

maximal plasma levels of endoxifen within 2 to 10 hours after administering; or

any combination thereof.

39. The oral composition of claim 38, wherein a mean half-life of endoxifen in a subject treated with the composition is between 40 hours to 55 hours.

40. The oral composition of claim 38 or 39, wherein the composition is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

41. The composition of any one of the preceding claims, wherein at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of endoxifen in the composition is released in the intestines.



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42. The composition of any one of the preceding claims, having a mean area under the curve extrapolated to time infinity ($AUC_{0\text{-}inf}$) of endoxifen of 200 hr*ng/mL to 10000 hr*ng/mL, of 300 hr*ng/mL to 8000 hr*ng/mL, of 400 hr*ng/mL to 6000 hr*ng/mL or of 700 hr*ng/mL to 6000 hr*ng/mL.

43. A method of treating a subject in need thereof, the method comprising administering to the subject the composition of any one of claims 1 to 42.

44. The method of claim 43, wherein the subject has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both.

45. The method of claim 44, wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer.

46. The method of any one of claims 43 to 45, wherein the subject has prostate cancer and wherein the subject further has or is at risk of having gynecomastia.

47. The method of any one of claims 43 to 46, wherein the subject has tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder.

48. The method of any one of claims 43 to 47, wherein the subject is or will be treated with an SSRI drug selected from the group consisting of citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and vilazodone.

49. The method of any one of claims 43 to 48, wherein the composition comprises 0.01 mg to 200 mg of (Z)-endoxifen.

50. The method of any one of claims 43 to 49, wherein the subject is administered about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of (Z)-endoxifen daily.

51. The method of any one of claims 43 to 50, wherein a steady state plasma level of endoxifen in the subject is greater than 30 nM.

52. The method of any one of claims 43 to 51, wherein the steady state plasma level of endoxifen is achieved within 7 to 21 days of the first administration of the composition.

53. The method of any one of claims 43 to 52, wherein time to maximum plasma levels of endoxifen ranges from 2 hours to 10 hours or from 4 hours to 8 hours after administering the composition.

54. A method of treating a subject having or at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, the method



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comprising administering the composition of any one of claims 1 to 42, wherein administration of the composition achieves:

a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;

a time to maximum plasma levels of endoxifen ranging from 4 hours to 8 hours after administration; and

a steady state plasma level of endoxifen greater than 30 nM.

55. The method of claim 54, wherein the hormone-dependent breast disorder and the hormone-dependent reproductive tract disorder are selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, and vulvar cancer.

56. The method of claim 54 or 55, wherein the composition comprises 0.01 mg to 200 mg of (Z)-endoxifen.

57. The method of claim 56, wherein the subject is administered about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of (Z)-endoxifen.

58. The method of any one of claims 43 to 57, wherein the mean area under the curve extrapolated to time infinity ($AUC_{0\text{-}inf}$) of endoxifen is 200 hr*ng/mL to 10000 hr*ng/mL, 300 hr*ng/mL to 8000 hr*ng/mL, 400 hr*ng/mL to 6000 hr*ng/mL or 700 hr*ng/mL to 6000 hr*ng/mL.

59. The method of any one of claims 43 to 58, wherein the composition is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

60. The method of any one of claims 43 to 59, wherein at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of endoxifen in the composition is released in the intestines.

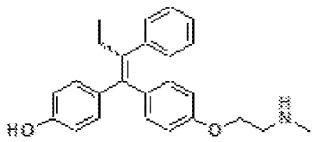
61. The method of any one of claims 43 to 60, wherein the composition is administered once a day, twice a day, thrice a day, four times a day, every other day, twice a week, weekly, fortnightly, twice a month, monthly, quarterly, once every six months, or annually.

62. An industrially scalable process for manufacturing (Z)-endoxifen, comprising the steps of:

(a) subjecting a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), represented by



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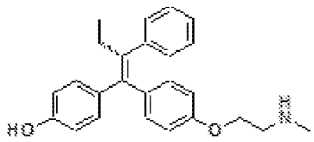
to fractional crystallization from a first solvent to form a first crystalline solid and first mother liquor, wherein the first mother liquor has an E/Z ratio of at least 50% higher (Z) endoxifen as compared with the E/Z ratio of the mixture of (E)-endoxifen and (Z)-endoxifen;

(b) subjecting the first mother liquor 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 the second solvent one or more times, to form a second crystalline solid and a second mother liquor, wherein the second crystalline solid is ≥ 90% (Z)-endoxifen; and

(c) optionally, subjecting the second crystalline solid to recrystallization from a third solvent or chromatographic treatment one or more times to form a third crystalline solid.

63. An industrially scalable process for manufacturing the crystalline form of any one of claims 1 to 11, comprising the steps of:

(a) subjecting a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), represented by



to fractional crystallization from a first solvent to form a first crystalline solid and first mother liquor, wherein the first mother liquor has an E/Z ratio of at least 50% higher (Z) endoxifen as compared with the E/Z ratio of the mixture of (E)-endoxifen and (Z)-endoxifen;

(b) subjecting the first mother liquor 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 the second solvent one or more times, to form a second crystalline solid and a second mother liquor, wherein the second crystalline solid is ≥ 90% (Z)-endoxifen; and

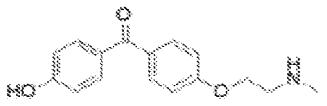
(c) subjecting the second crystalline solid to recrystallization from a third solvent or chromatographic treatment one or more times to form a third crystalline solid, wherein the third crystalline solid is the crystalline form of any one of claims 1 to 11.

64. The process of claim 62 or 63, wherein the mixture of (E)-endoxifen and (Z)-endoxifen is prepared by coupling a compound of Formula (II), (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl) methanone, to propiophenone mediated by a McMurry reaction

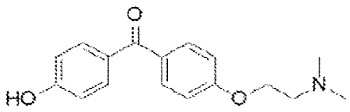


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via a titanium salt and a reducing agent in an inert organic solvent to form the mixture of (E)-endoxifen and (Z)-endoxifen; and wherein the compound of Formula (II) has a structure represented by



65. The process of claim 64, further comprising preparing the compound of Formula (II) by demethylating [4-[2-(dimethylamino)ethoxy]phenyl](4-hydroxyphenyl)methanone, a compound of Formula (I), wherein the compound of Formula (I) has the structure



with a demethylating agent and a proton acceptor in an inert organic solvent to form the compound of Formula (II).

66. The process of any one of claims 62 to 65, wherein the first solvent is ethyl acetate, IPA, IPA/PPW, ACN, ACN/PPW or acetone.

67. The process of any one of claims 62 to 66, wherein the second solvent is IPA, IPA/PPW, acetone, ethanol, ethyl acetate, or acetone/MTBE.

68. The process of any one of claims 62 to 67, wherein the third solvent is ethanol, methanol, ethyl acetate, IPA, IPA/PPW, n-heptane, or acetone.

69. The process of any one of claims 62 to 68, further comprising pre-heating any one or more of the first solvent, the second solvent and the third solvent to a temperature ranging from 40 °C to 80 °C.

70. The process of any one of claims 62 to 69, wherein each fractional crystallization and recrystallization step independently comprises a step of distillation at 50 °C to 80 °C; and cooling the solution to a temperature ranging from 0 °C to NMT 35 °C.

71. The process of any one of claims 64 to 70, further comprising the steps of:

(a) reacting the compound of Formula (II) with propiophenone in an inert organic solvent;

(b) preparing a titanium salt and a reducing agent in an inert organic solvent; and



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(c) reacting the compound of Formula (II) of step (a) with the titanium salt and a reducing agent in an inert organic solvent of step (b) to form the mixture of (E)-endoxifen and (Z)-endoxifen.

72. The process of any one of claims 64 to 71, further comprising the steps of:

(a) reacting the compound of Formula (II) with propiophenone (1:0.01 to 1:5 wt/wt) in an inert organic solvent (1:1 to 1: 20 wt/wt);

(b) preparing a titanium salt (1:0.1 to 1:12 wt/wt) and a reducing agent (1:0.01 to 1:10 wt/wt) in an inert organic solvent (1:1 to 1: 20 wt/wt); and

(c) reacting the compound of Formula (II) of step (a) with the titanium salt and a reducing agent in an inert organic solvent of step (b) to form the mixture of (E)-endoxifen and (Z)-endoxifen;

wherein wt/wt is with respect to compound of Formula (II).

73. The process of any one of claims 64 to 72, wherein the titanium salt is selected from the group consisting of titanium halides (such as titanium trichloride ($TiCl_3$), titanium tetrachloride ($TiCl_4$), titanium iodides, titanium bromides, and titanium fluorides), titanium(IV) trichloride isopropoxide, and titanium isopropoxide.

74. The process of any one of claims 64 to 73, wherein the reducing agent is selected from the group consisting of zinc, zirconium, vanadium, niobium, molybdenum, tungsten, aluminum, magnesium, potassium, zinc-copper couple, alkali and alkali earth metals, butylium, lithium, and lithium aluminum hydride.

75. The process of any one of claims 64 to 74, wherein the inert organic solvent is selected from the group consisting of dichloromethane, dichloroethane, chloroform, carbon tetrachloride, chlorobenzene, diethyl ether, 1,4-dioxane, tert-butyl methyl ether, tetrahydrofuran, N,N-dimethylformamide, N-methylpyrrolidone, diglyme, nitromethane, 1,2-dimethoxyethane, pyridine, acetone, acetonitrile, benzene, o-xylene, m-xylene, p-xylene, xylenes, hexanes, cyclohexane, heptane, octane, nonane, and decane, or a combination thereof.

76. The process of any one of claims 64 to 75, wherein the preparation of the titanium salt and the reducing agent in the inert organic solvent in step (b) further comprises maintaining the temperature of the reaction at a temperature of NMT 75 °C, NMT 65 °C, NMT 55 °C, NMT 50 °C, NMT 45 °C, NMT 40 °C, NMT 35 °C, NMT 30 °C, NMT 25 °C, NMT 20 °C, or NMT 15 °C when the titanium salt is added to the reducing agent and the inert organic solvent.

77. The process of any one of claims 64 to 76, wherein the preparation of the titanium salt and the reducing agent in the inert organic solvent further comprising maintaining the temperature of the reaction at a temperature NMT 75 °C, NMT 70 °C, NMT 65 °C, NMT 60 °C,



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NMT 55 °C, NMT 50 °C, or NMT 45 °C when the titanium salt is added to the reducing agent and the inert organic solvent.

78. The process of any one of claims 64 to 77, wherein the preparation of the titanium salt and the reducing agent in the inert organic solvent in step (b) further comprises heating the titanium salt and the reducing agent in the inert organic solvent to a temperature ranging from 20 °C to 250 °C, from 40 °C to 70 °C, from 50 °C to 230 °C, from 50 °C to 120 °C, or from 150 °C to 200 °C.

79. The process of any one of claims 64 to 78, wherein the preparation of the titanium salt and the reducing agent in the inert organic solvent in step (b) further comprises heating the titanium salt and the reducing agent in the inert organic solvent under reflux for NLT 30 min, NLT 1 hour, NLT 2 hours, NLT 4 hours, NLT 6 hours, or NLT 8 hours under $N_2$ or argon.

80. The process of any one of claims 64 to 79, wherein the compound of Formula (II) of step (a) is reacted with titanium salt and a reducing agent in an inert organic solvent of step (b) under reflux to form the mixture of (E)-endoxifen and (Z)-endoxifen.

81. The process of any one of claims 64 to 80, wherein the compound of Formula (II) of step (a) is reacted with titanium salt and a reducing agent in an inert organic solvent of step (b) at a temperature ranging from 40 °C to 80 °C to form the mixture of (E)-endoxifen and (Z)-endoxifen for NLT 4 hours, NLT 6 hours, NLT 8 hours, NLT 12 hours, NLT 24 hours, or NLT 48 hours.

82. The process of any one of claims 64 to 81, further comprising a step of cooling the mixture of (E)-endoxifen and (Z)-endoxifen to a temperature ranging from 0 °C to 30 °C.

83. The process of any one of claims 64 to 82, further comprising one or more steps of:

(a) extraction of the mixture of (E)-endoxifen and (Z)-endoxifen;

(b) washing the mixture of (E)-endoxifen and (Z)-endoxifen;

(c) distillation of the mixture of (E)-endoxifen and (Z)-endoxifen; and

(d) crystallization to afford a crystalline solid mixture of (E)-endoxifen and (Z)-endoxifen.

84. The process of claim 83, wherein the extraction is carried out one or more times in MeTHF or THF.

85. The process of any one of claims 65 to 84, further comprising generating the compound of Formula (II) by demethylating the compound of Formula (I) with a demethylating agent (1:0.5 to 1:10 wt/wt) and a proton acceptor (1:0.5 to 1:10 wt/wt) in an inert organic solvent (1:1 to 1: 20 wt/wt) to form the compound of Formula (II), wherein the wt/wt ratios are with respect to the compound of Formula (I).



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86. The process of any one of claims 65 to 85, wherein the proton acceptor is selected from the group consisting of carbonates, such as sodium carbonate and potassium carbonate, and bicarbonates, such as sodium bicarbonate and potassium bicarbonate, proton sponge, and DIPEA.

87. The process of any one of claims 65 to 86, wherein the demethylating agent is selected from the group consisting of N-iodosuccinamide, ethyl chloroformates (such as 1-chloroethyl chloroformate, dichloroethyl chloroformate, trichloroethyl chloroformate, α-chloroethyl chloroformate), vinyl chloroformate, cynogen bromide, diethyl azodicarboxylate, and pyridinium chloride.

88. The process of any one of claims 65 to 87, wherein the compound of Formula (I) is reacted with the demethylating agent and the proton acceptor at a temperature ranging from 20 °C to 250 °C, from 40 °C to 80 °C, from 50 °C to 230 °C, from 50 °C to 120 °C, and from 150 °C to 200 °C.

89. The process of any one of claims 65 to 88, wherein the compound of Formula (I) is reacted with the demethylating agent and the proton acceptor under reflux.

90. The process of any one of claims 65 to 89, wherein the compound of Formula (I) is reacted with the demethylating agent and the proton acceptor for NLT 5 hours, NLT 8 hours, NLT 12 hours, NLT 24 hours, NLT36 hours, NLT 48 hour or NLT 72 hours.

91. The process of any one of claims 3 or 85 to 90, further comprising one or more steps of:

(a) distillation;

(b) reaction with solvent/acid mixture;

(c) neutralization with a neutralizing agent; and

(d) drying under reduced pressure.

92. The process of claim 91, wherein the distillation step comprises one or more solvent swaps with an organic distillation solvent selected from the group consisting of ethyl acetate, alcohols, such as methanol, ethanol, n-propanol, and isopropanol, benzene, acetone, acetonitrile, toluene, dichloromethane, 1,2-dichloroethane, and chloroform.

93. The process of claim 91 or 92, wherein the solvent/acid mixture is selected from the group consisting of methanol/HCl, ethanol/HCl, propanol/HCl, isopropanol/HCl, methanol/sulfuric acid, methanol/phosphoric acid, ethanol/sulfuric acid, ethanol/phosphoric acid, propanol/sulfuric acid, propanol/phosphoric acid, isopropanol/sulfuric acid, isopropanol/phosphoric acid, methanol/acetic acid, ethanol/acetic acid, propanol/acetic acid, isopropanol/acetic acid, methanol/formic acid, ethanol/formic acid, propanol/formic acid, and isopropanol/formic acid.



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94. The process of any one of claims 91 to 93, wherein neutralizing agent is sodium hydroxide, ammonium hydroxide, potassium hydroxide, or aminomethylpropanol.

95. The process of any one of claims 62 to 94, further comprising converting (E)-endoxifen to (Z)-endoxifen by reacting a mixture of (E)-endoxifen and (Z)-endoxifen to an acid (1:1 to 1:5 wt/wt) in a solvent (1:1 to 1:20 wt/wt), wherein the wt/wt ratios are with respect to compounds of Formula (III).

96. The process of claim 95, wherein the acid is HCl, TCA, or TFA.

97. The process of claim 95 or 96, wherein the solvent is acetonitrile, acetonitrile/PPW, IPA, IPA/PPW, dichloromethane, or ethyl acetate.

98. The process of any one of claims 95 to 97, wherein the mixture of (E)-endoxifen and (Z)-endoxifen is heated with the acid in the solvent under reflux and stirred for NLT 4 hours, NLT 6 hours, NLT 12 hours, NLT 24 hours, or NLT 48 hours.

99. The process of any one of claims 95 to 98, further comprising one or more steps of:

(a) neutralization with a neutralizing agent;

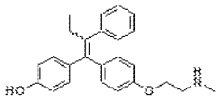
(b) extraction;

(c) one or more washes; and

(d) treatment with activated carbon.

100. An industrially scalable process for manufacturing (Z)-endoxifen, comprising the steps of:

(a) subjecting a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III) represented by



to fractional crystallization from ethyl acetate to form a first crystalline solid and first crystalline mother liquor, wherein the first mother liquor has an E/Z ratio of at least 50% higher (Z) endoxifen as compared with the E/Z ratio of the mixture of (E)-endoxifen and (Z)-endoxifen;

(b) subjecting the first mother liquor to recrystallization from the IPA or IPA/PPW (1:1 v/v) by concentrating the first mother liquor, or by swapping out the ethyl acetate from the first mother liquor with IPA or IPA/PPW one or more times, to form a second crystalline solid and a second mother liquor, wherein the second crystalline solid is $\geq$ 90% (Z)-endoxifen; and

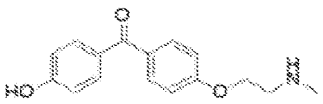
(c) optionally, subjecting the second crystalline solid to recrystallization from ethanol or column chromatographic treatment one or more times to form a third crystalline solid.



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101. The process of claim 99 or 100, wherein the mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), in step a is pretreated with 6N HCl and neutralized with 8N NaOH.

102. The process of any one of claims 99 to 101, wherein the mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), is prepared by coupling a compound of Formula (II), (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl) methanone, to propiophenone catalyzed in a McMurry reaction via $TiCl_4$ and Zn in THF to form the mixture of (E)-endoxifen and (Z)-endoxifen; and wherein the compound of Formula (II) has a structure represented by



103. The process of claim 102, further comprising the steps of:

(a) reacting the compound of Formula (II) with propiophenone in THF;

(b) preparing $TiCl_4$ and Zn in THF; and

(c) reacting the compound of Formula (II) of step (a) with the $TiCl_4$ and Zn in THF of step (b) to form the mixture of (E)-endoxifen and (Z)-endoxifen.

104. The process of claim 102 or 103, comprising the steps of:

(a) reacting the compound of Formula (II) with propiophenone in THF (1:1 to 1:20 wt/wt);

(b) preparing a $TiCl_4$ (0.1 to 12 wt/wt) and Zn (0.01 to 1:10 wt./wt) in THF (1:1 to 1:20 wt/wt); and

(c) reacting the compound of Formula (II) of step (a) with the $TiCl_4$ and Zn in THF of step (b) to form the mixture of (E)-endoxifen and (Z)-endoxifen,

wherein wt/wt is with respect to the compound of Formula (II).

105. The process of any one of claims 102 to 104, wherein preparation of $TiCl_4$ and Zn in THF further comprises heating under reflux for NLT 2 hours under $N_2$.

106. The process of any one of claims 102 to 105, further comprising the steps of extractive purification, distillation, and crystallization.

107. The process of any one of claims 102 to 106, wherein the mixture of (E)-endoxifen and (Z)-endoxifen is subjected to extractive purification comprising a step of:

(a) extraction one or more times with ammonium chloride, silicon dioxide, 40% $K_2CO_3$, and THF;

(b) extraction one or more times with $K_2CO_3$ and MeTHF;



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(c) extraction one or more times with NaOH, NaCl, and MeTHF;

(d) extraction one or more times with MeTHF or THF;

(e) extraction one or more times with 20% NaCl; or

(f) a combination thereof.

108. The process of any one of claims 102 to 107, wherein the mixture of (E)-endoxifen and (Z)-endoxifen is subjected to extractive purification comprising the steps of:

(a) extraction one or more times with 40% $K_2CO_3$ (1:1 to 1:10 wt/wt) and MeTHF (1:1 to 1:10 wt/wt);

(b) extraction one or more times with 1N NaOH (1:1 to 1:20 wt/wt), NaCl (1:0.01 to 1:0.5 wt/wt) and MeTHF (1:1 to 1:10 wt/wt);

(c) extraction one or more times with MeTHF (1:1 to 1:5 wt/wt); and

(d) extraction with 20% NaCl (1:1 to 1:10 wt/wt);

wherein the wt/wt is with respect to the compound of Formula (II).

109. The process of any one of claims 102 to 108, wherein the mixture of (E)-endoxifen and (Z)-endoxifen is subjected to extractive purification comprising the steps of:

(a) extraction with 25% ammonium chloride (1:10 to 1:30 wt/wt), silicon dioxide (1:0.01 to 1:5 wt/wt) and THF (1:1 to 1:5 wt/wt);

(b) one or more washes with THF (1:1 to 1:5 wt/wt); and

(c) one or more washes with 40% $K_2CO_3$ (1:1 to 1:10 wt/wt);

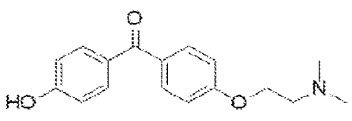
wherein the wt/wt is with respect to the compound of Formula (II).

110. The process of claim 108 or 109, wherein the step of distillation is performed 1 to 5 times with EtOAc (1:1 to 1:10 wt/wt) or IPA (1:1 to 1:10 wt/wt).

111. The process of any one of claims 106 to 110, wherein the step of distillation is performed at a temperature ranging from 30 °C to 90 °C.

112. The process of any one of claims 106 to 111, wherein the distillation is performed at NMT 75 °C.

113. The process of any one of claims 102 to 112, wherein the compound of Formula (II) is prepared by demethylating [4-[2-(dimethylamino)ethoxy]phenyl](4-hydroxyphenyl)methanone, a compound of Formula (I), wherein the compound of Formula (I) has the structure




with 1-chloroethyl chloroformate and DIPEA in THF to form the compound of Formula (II).



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114. The process of claim 113, comprising the steps of:

(a) reacting the compound of Formula (I) with DIPEA in tetrahydrofuran;

(b) adding 1-chloroethyl chloroformate;

(c) distilling with methanol;

(d) reacting with methanol/6N HCl; and

(e) neutralizing with 8N NaOH.

115. The process of claim 113 or 114, comprising the steps of:

(a) reacting the compound of Formula (I) with DIPEA (1:1 to 1:10 wt/wt) in THF (1:20 wt/wt);

(b) adding 1-chloroethyl chloroformate (1:1 to 1:10 wt./wt);

(c) distilling with methanol one or more times (1:1 to 1:10 wt./wt);

(d) reacting with methanol (1:1 to 1:5 wt/wt)/6N HCl (1:1 to 1:10 wt/wt); and

(e) neutralizing with 8N NaOH (1:1 to 1:10 wt/wt);

wherein wt/wt is with respect to the compound of Formula (I).

116. The process of any one of claims 113 to 115, further comprising one or more steps of:

(a) washing the compound of Formula (II) with purified water (1:1 to 1:5 vol/wt);

(b) washing the compound of formula (II) with ethyl acetate (1:1 to 1: 5 wt/wt); and

(c) drying the compound of Formula (II) under reduced pressure at NMT 50°C;

wherein wt/wt is with respect to the compound of Formula (I).

117. The process of any one of claims 62 to 116, further comprising converting (E)-endoxifen to (Z)-endoxifen by reacting a mixture of (E)-endoxifen and (Z)-endoxifen to 6N HCl (1:1 to 1:5 wt/wt) in EtOAc (1:1 to 1:20 wt/wt), wherein wt/wt is with respect to the mixture of (E)-endoxifen and (Z)-endoxifen.

118. The process of claim 117, further comprising the steps of:

(a) neutralizing with 8N NaOH (1:1 to 1:20 wt/wt);

(b) extraction with ethyl acetate (1:1 to 1:10 wt/wt);

(c) one or more washes with 20% NaCl (1:1 to 1:10 wt/wt); and

(d) treatment with activated carbon (1:0.01 to 1:0.1 wt/wt);

wherein wt/wt is with respect to the compound of Formula (III).

119. A crystalline form of a compound of Formula (III) produced according to the method of any one of claims 62 to 118.



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120. The crystalline form of claim 119, wherein the crystalline form is Form I of the compound of Formula (III).

121. An industrially scalable process of reequilibriating a mixture of (E)-endoxifen and (Z)-endoxifen having an E/Z ratio ranging from 45:55 to 55:45 comprising the steps of:

(a) reacting to 6N HCL (1:1 to 1:5 wt/wt) in ethyl acetate (1:1 to 1:20 wt/wt) a starting mixture of (E)-endoxifen and (Z)-endoxifen having an E/Z-ratio ranging from 99:1 to 60:40;

(b) neutralizing with 8N NaOH (1:1 to 1:20 wt/wt);

(c) washing one or more times with ethyl acetate; and

(d) washing one or more times with IPA;

wherein wt/wt is with respect the starting mixture of (E)-endoxifen and (Z)-endoxifen.

122. An industrially scalable process for manufacturing the crystalline form of any one of claims 12 to 31, comprising:

(a) reacting to 6N HCL (1:1 to 1:5 wt/wt) in ethyl acetate (1:1 to 1:20 wt/wt) a starting mixture of (E)-endoxifen and (Z)-endoxifen having an E/Z-ratio ranging from 99:1 to 40:60;

(b) neutralizing with 8N NaOH (1:1 to 1:20 wt/wt);

(c) washing one or more times with ethyl acetate;

(d) washing one or more times with a mixture of ethyl acetate and n-heptane; and

(e) recovering the crystalline form of any one of claims 12 to 31;

wherein wt/wt is with respect the starting mixture of (E)-endoxifen and (Z)-endoxifen.

123. A crystalline form of a compound of Formula (III) produced according to the method of claim 121 or 122.

124. The crystalline form of claim 123, wherein the crystalline form is Form II or Form III of the compound of Formula (III).

125. The process of any one of claims 62 to 122, wherein the (Z)-endoxifen is reacted with D-gluconate or L-Gluconate to form (Z)-endoxifen L-gluconate or (Z)-endoxifen D-gluconate.

126. The process of any one of claims 62 to 125, wherein the (Z)-endoxifen free base has < 1% impurity.

127. The process of any one of claims 62 to 126, wherein the (Z)-endoxifen free base is stable at ambient temperature for at least 9 months.



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128. (Z)-endoxifen, (E)-endoxifen, a compound of Formula (III), a compound of Formula (II), or a salt thereof, prepared by the process of any one of claims 62 to 127.

129. A composition comprising (Z)-endoxifen free base or a salt thereof prepared by the process of any one of claims 62 to 127.

130. The composition of claim 129, wherein the composition is formulated for oral, parenteral, topical, or intraductal delivery.

131. The composition of claim 129 or 130, wherein the composition is formulated for oral delivery as a tablet, a caplet, a capsule, or a pill.

132. The composition of claim 131, having a mean half-life of endoxifen in a subject ranging from 30 hours to 60 hours after administration.

133. The composition of any one of claims 129 to 132, wherein the composition is formulated for oral delivery as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

134. The composition of any one of claims 129 to 133, wherein the composition is administered to a subject for the treatment or prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both in the subject.

135. 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.

136. The oral composition of claim 135, having a mean half-life of endoxifen in a subject ranging from 40 hours to 55 hours after administration.

137. The oral composition of claim 135 or 136, wherein the composition is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

138. The oral composition of claim 133 or 137, wherein at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% endoxifen is released in the intestines.

139. The composition or oral composition of any one of claims 129 to 138, having a mean area under the curve extrapolated to time infinity ($AUC_{0\text{-}inf}$) of 200 hr*ng/mL to 10000



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hr*ng/mL, of 300 hr*ng/mL to 8000 hr*ng/mL, of 400 hr*ng/mL to 6000 hr*ng/mL or of 700 hr*ng/mL to 6000 hr*ng/mL.

140. A method of treating a subject in need thereof, the method comprising administering to the subject an oral composition of any one of claims 129 to 139.

141. The method of claim 140, wherein the subject has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both.

142. The method of claim 141, wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer.

143. The method of claim 141 or 142, wherein the subject has prostate cancer and wherein the subject further has or is at risk of having gynecomastia.

144. The method of any one of claims 141 to 143, wherein the subject has tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder.

145. The method of any one of claims 141 to 144, wherein the subject is or will be treated with an SSRI drug selected from the group consisting of citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and vilazodone.

146. The method of any one of claims 141 to 145, wherein the subject is administered 0.01 mg to 200 mg of (Z)-endoxifen.

147. The method of any one of claims 141 to 146, wherein the subject is administered 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of (Z)-endoxifen daily.

148. The method of any one of claims 141 to 147, wherein a steady state plasma level of endoxifen in the subject is greater than 30 nM.

149. The method of any one of claims 141 to 148, wherein the steady state plasma level of endoxifen is achieved within 7 to 21 days of the first administration of the composition.

150. The method of any one of claims 141 to 149, wherein time to maximum plasma levels of endoxifen ranges from 2 hours to 10 hours or from 4 hours to 8 hours after administering the composition.

151. A method 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 method comprising administering an oral composition comprising (Z)-endoxifen or a salt thereof, wherein administration of the composition achieves:



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(a) a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;

(b) a time to maximum plasma levels of endoxifen ranging from 4 hours to 8 hours after administration; and

(c) a steady state plasma level of endoxifen greater than 30 nM.

152. The method of claim 151, wherein the subject is administered 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of (Z)-endoxifen.

153. The method of claim 151 or 152, wherein the mean area under the curve extrapolated to time infinity ($AUC_{0\text{-}inf}$) is 200 hr*ng/mL to 10000 hr*ng/mL, of 300 hr*ng/mL to 8000 hr*ng/mL, of 400 hr*ng/mL to 6000 hr*ng/mL or of 700 hr*ng/mL to 6000 hr*ng/mL.

154. The method of any one of claims 151 to 153, wherein the composition is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

155. The method of any one of claims 151 to 154, wherein at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of the endoxifen is released in the intestines.

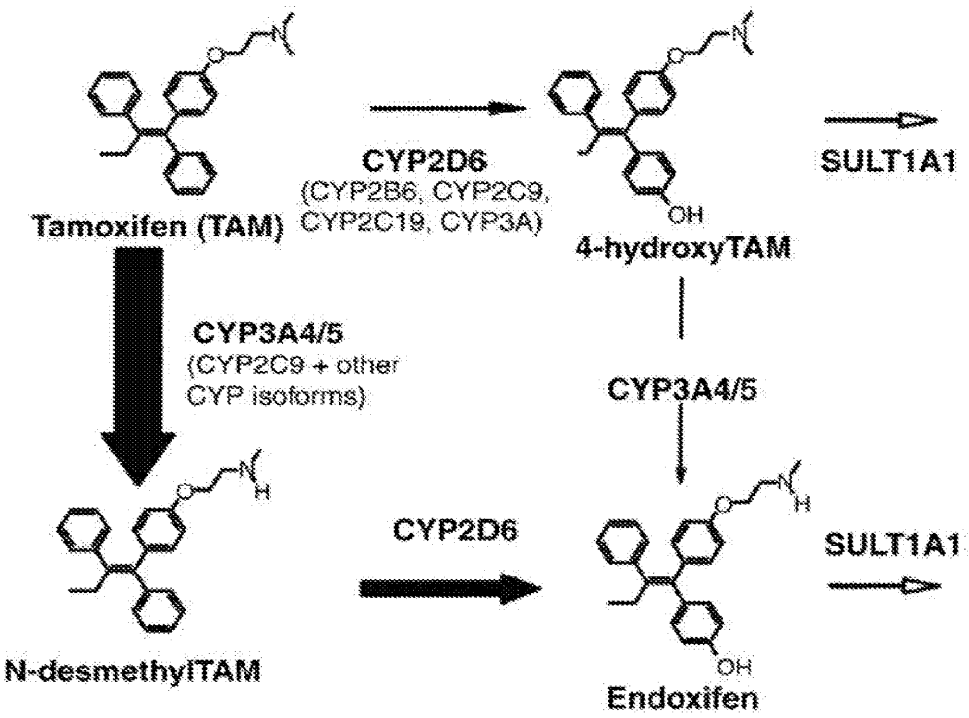
156. The method of claim 151 or 155, wherein the composition is administered once a day, twice a day, thrice a day, four times a day, every other day, twice a week, weekly, fortnightly, twice a month, monthly, quarterly, once every six months, or annually.

157. The method of any one of claims 151 to 156, wherein the hormone-dependent breast disorder and the hormone-dependent reproductive tract disorder are selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, and vulvar cancer.



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Fig. 1






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**Fig. 2**

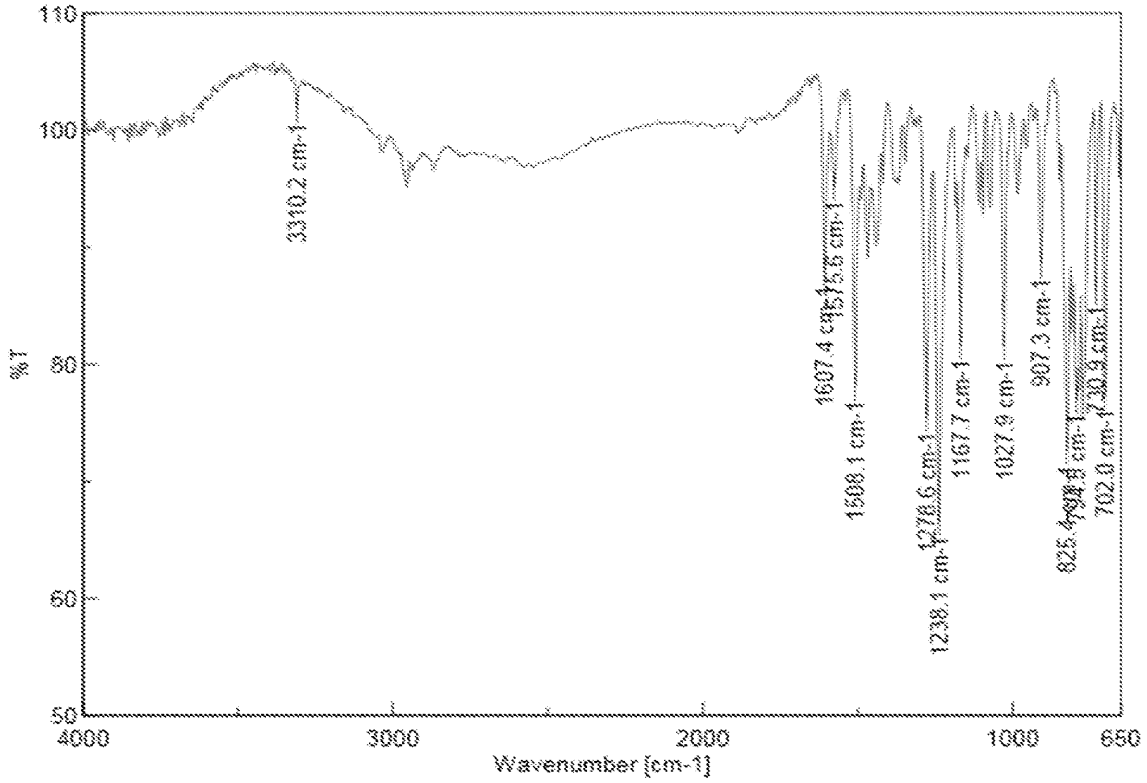
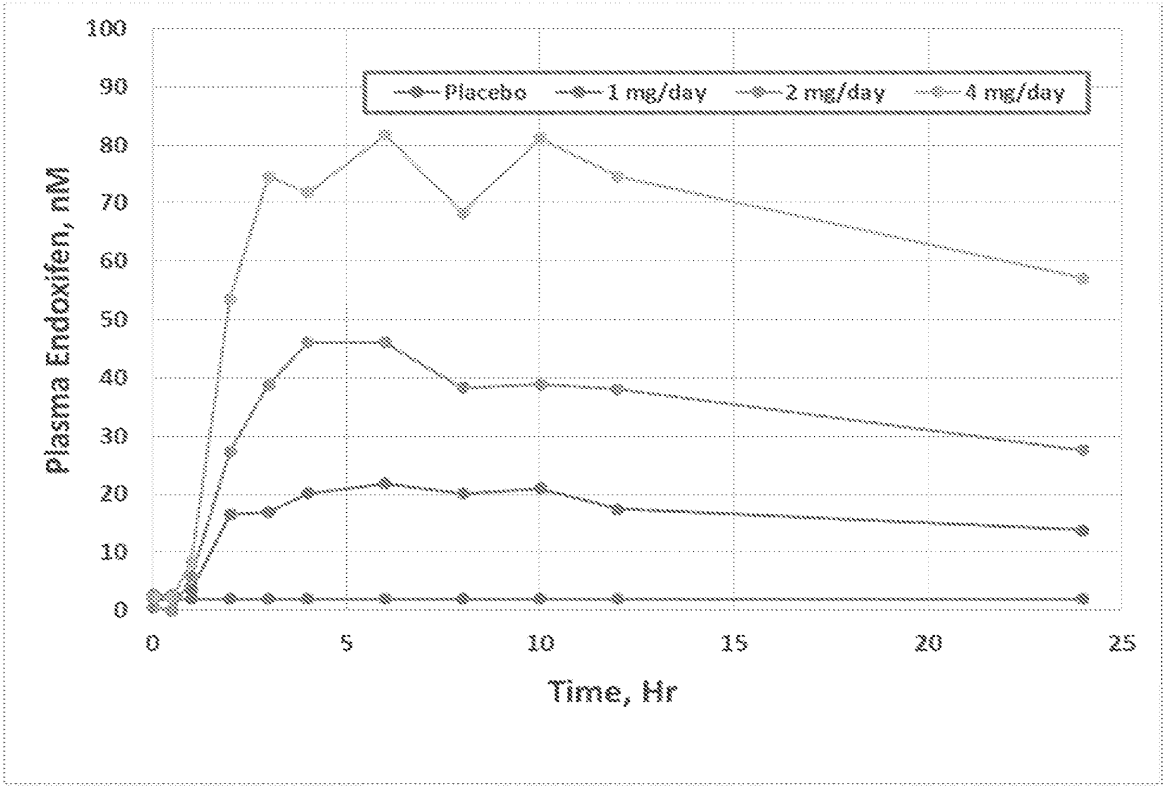

110
100
90
80
70
60
50
%T
3310.2 cm-1
1607.4 cm-1
1578.5 cm-1
1508.1 cm-1
1238.1 cm-1
1278.6 cm-1
1167.7 cm-1
1027.9 cm-1
907.3 cm-1
826.4 cm-1
730.5 cm-1
702.0 cm-1
4000
3000
2000
1000
650
Wavenumber [cm-1]

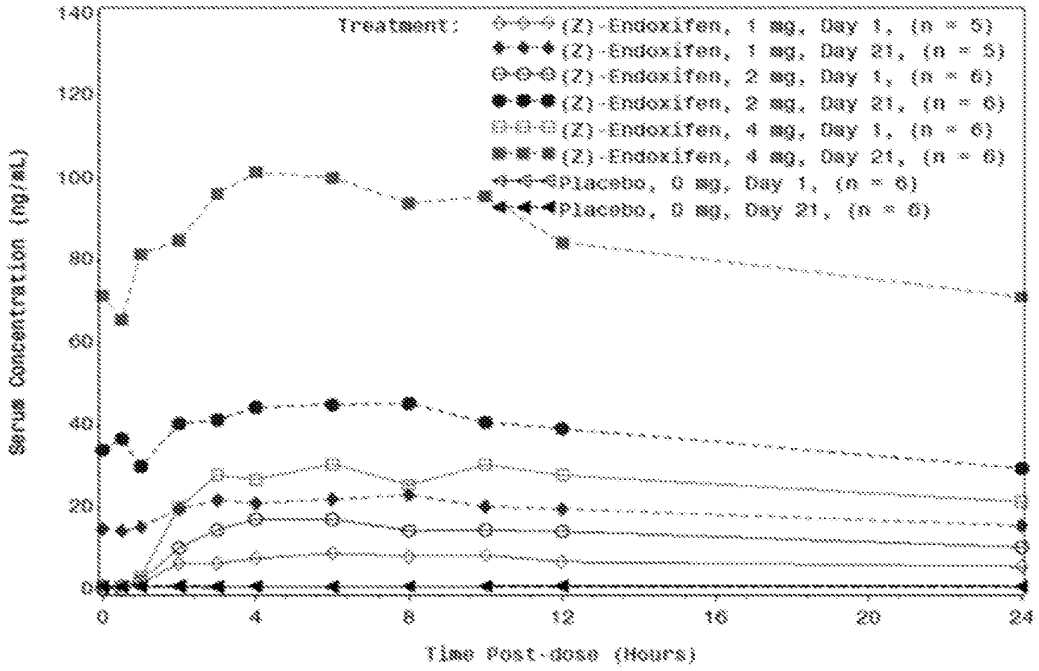
**Fig. 3**






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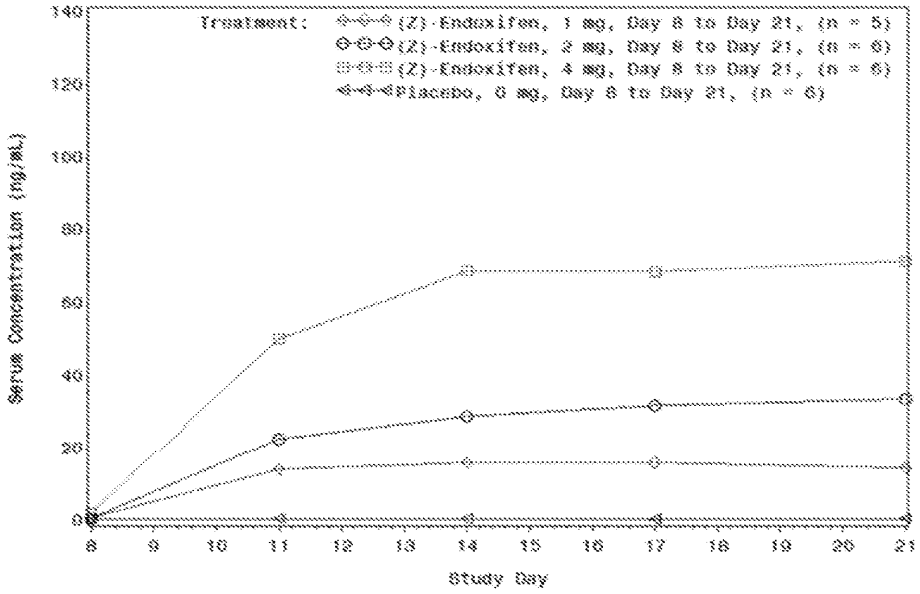
**Fig. 4**






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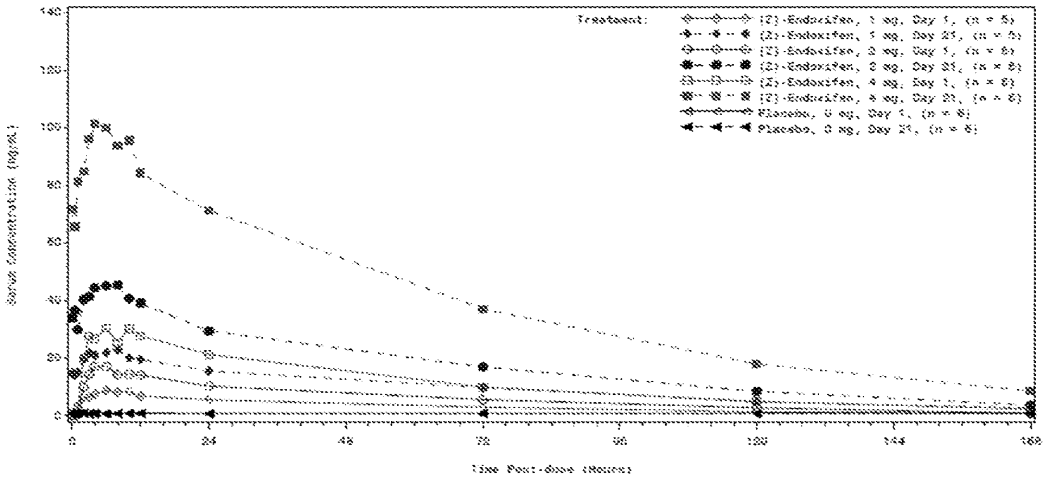
**Fig. 5**






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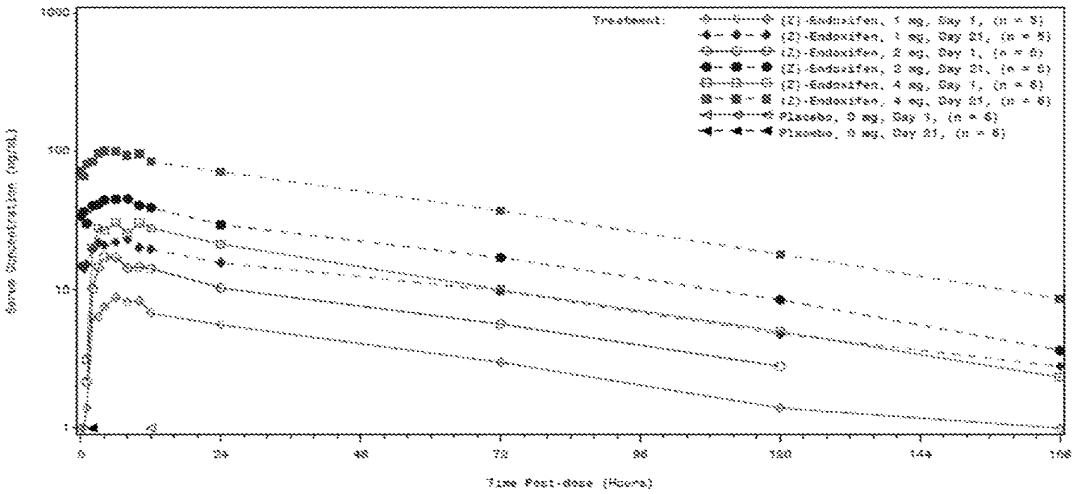
**Fig. 6**






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**Fig. 7**






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**Fig. 8**

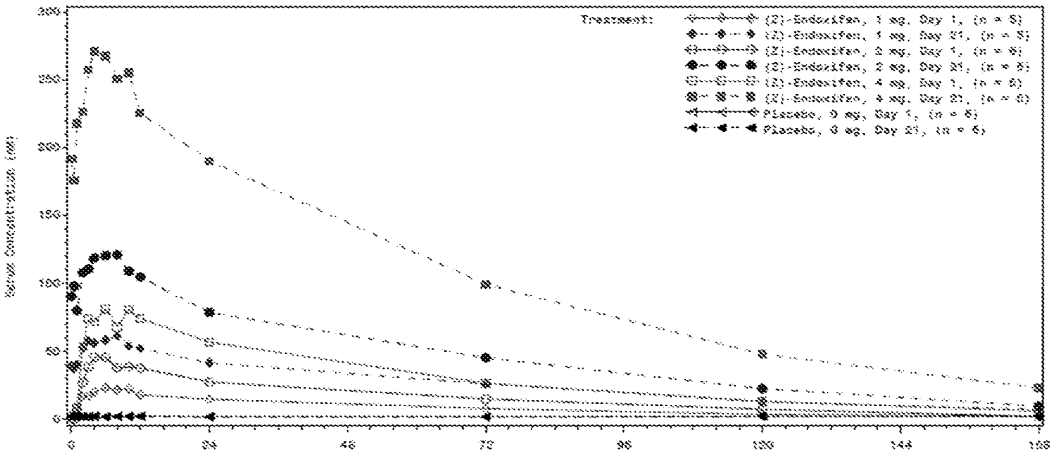
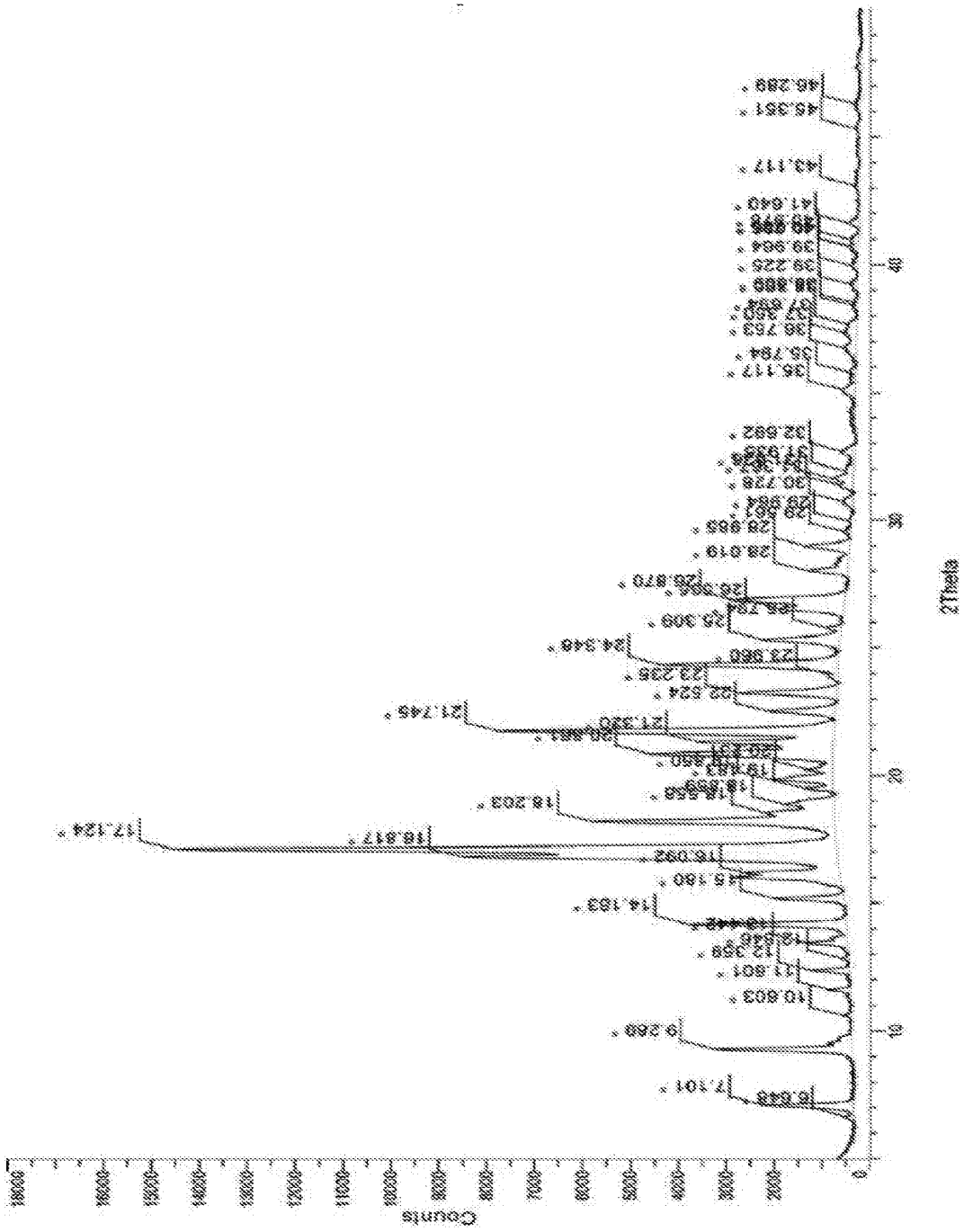

Treatment:
(Z)-Endoxifen, 1 mg, Day 1, (n = 5)
(Z)-Endoxifen, 1 mg, Day 21, (n = 5)
(Z)-Endoxifen, 2 mg, Day 1, (n = 6)
(Z)-Endoxifen, 2 mg, Day 21, (n = 6)
(Z)-Endoxifen, 4 mg, Day 1, (n = 6)
(Z)-Endoxifen, 4 mg, Day 21, (n = 6)
Placebo, 0 mg, Day 1, (n = 6)
Placebo, 0 mg, Day 21, (n = 6)
Serum Concentration (ng)
200
150
100
50
0
0
24
48
72
96
120
144
168

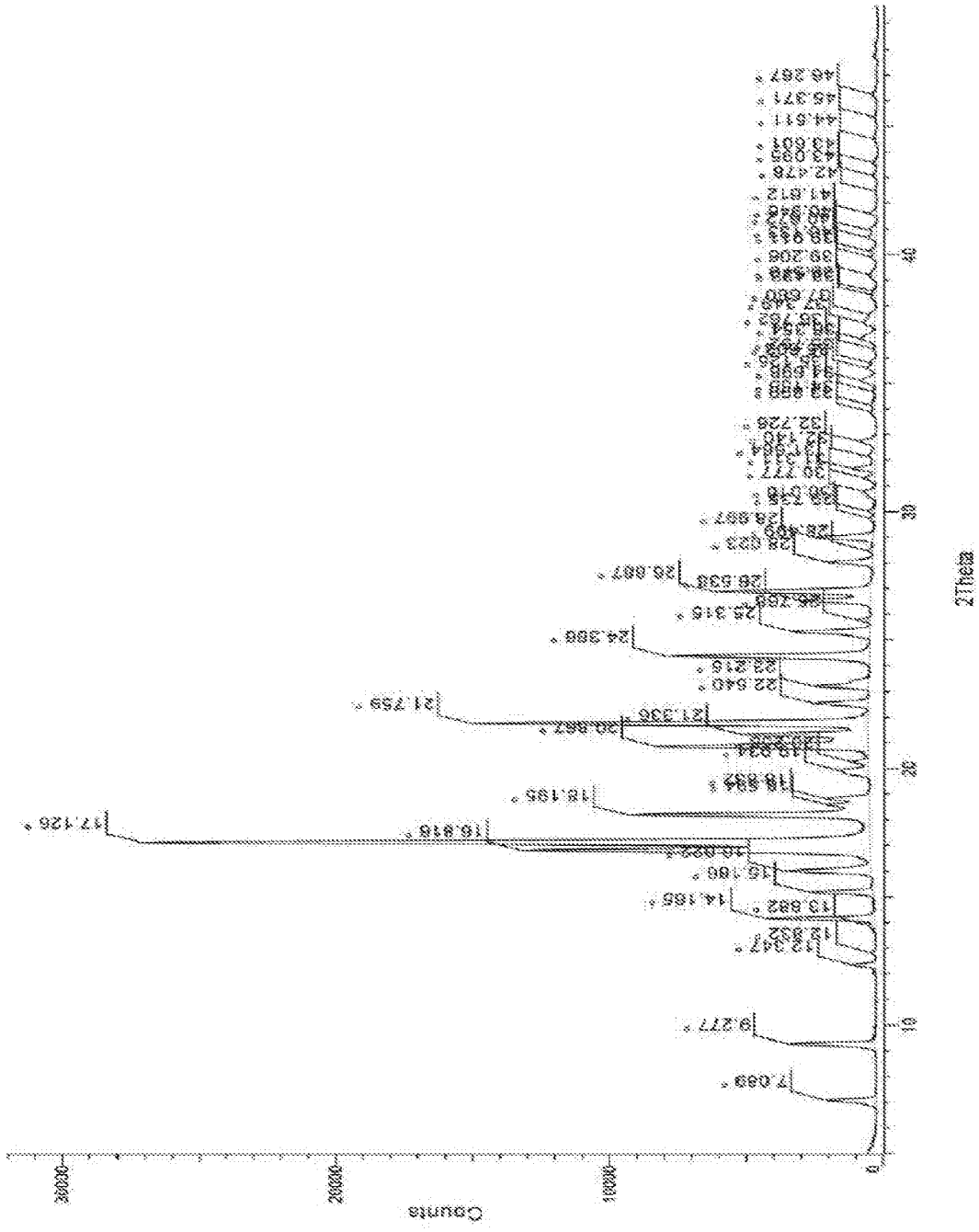
**Fig. 9**






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**Fig. 10**






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**Fig. 11**

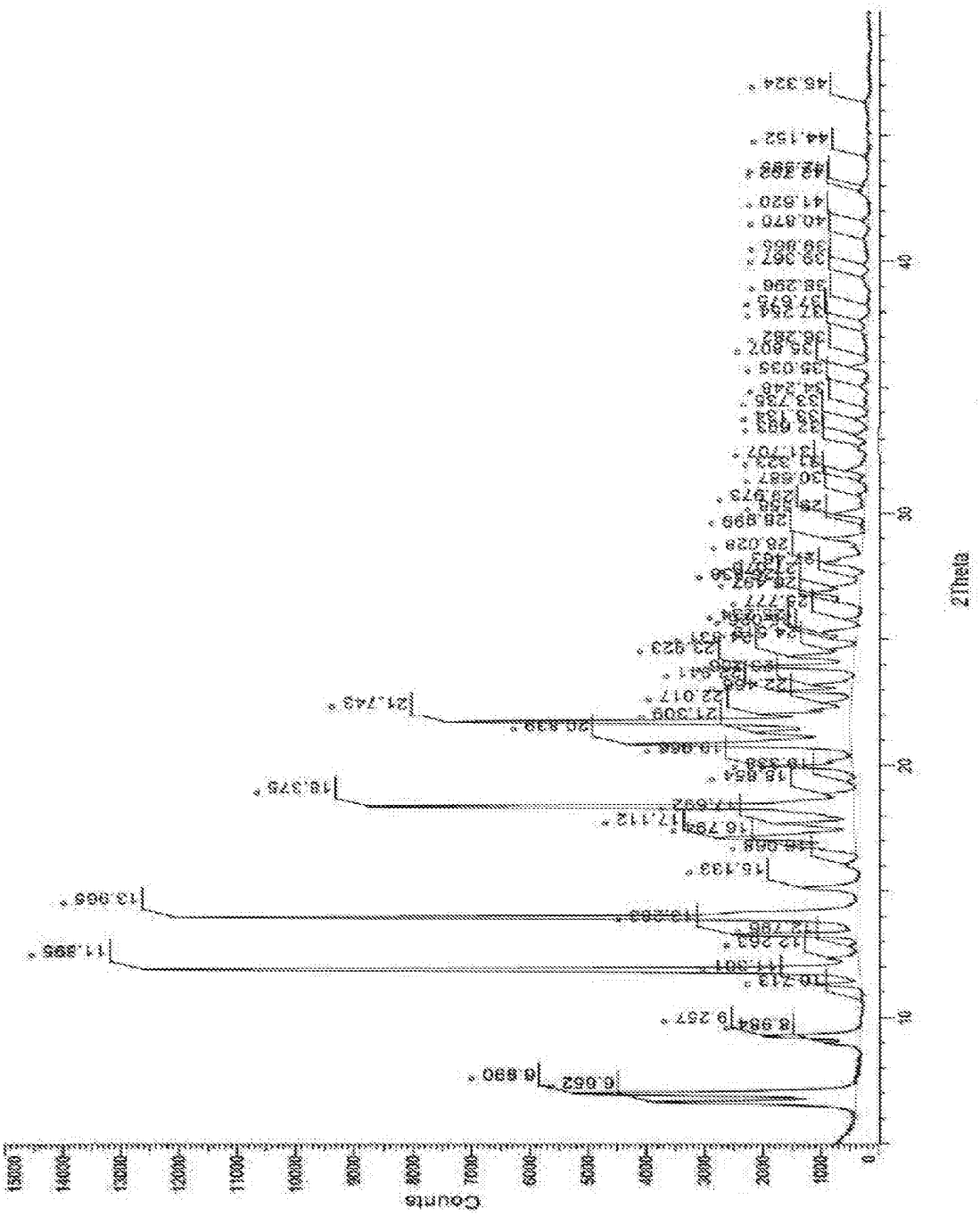


**Fig. 12**

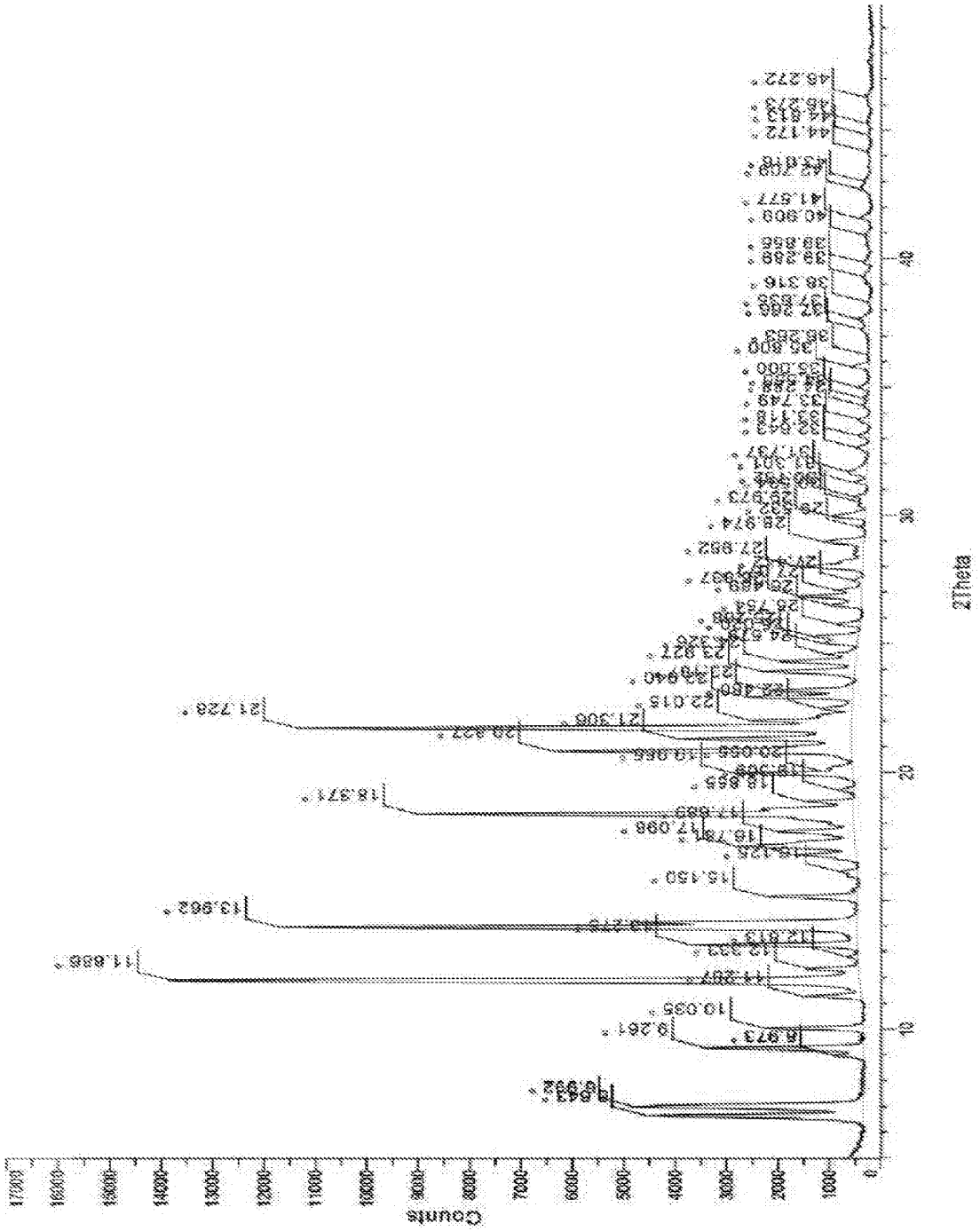
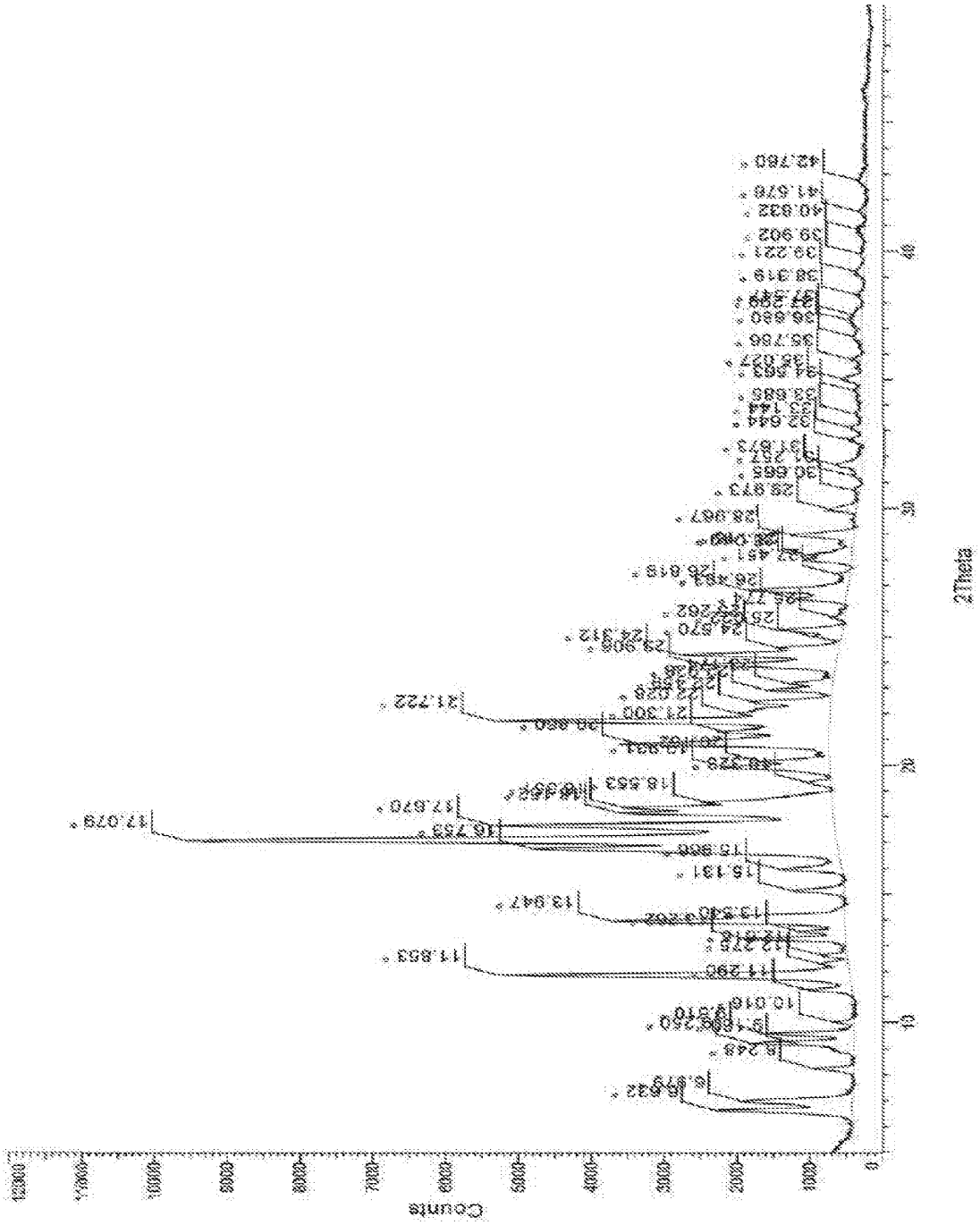


**Fig. 13**






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IPR2025-00799

From the INTERNATIONAL BUREAU

# PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

WELCH, Timothy R.
Wilson Sonsini Goodrich & Rosati
650 Page Mill Road
Palo Alto, California 94304-1050
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing *(day/month/year)*
13 February 2020 (13.02.2020)

Applicant's or agent's file reference
38602-758601

**IMPORTANT NOTIFICATION**

International application No.
PCT/US2018/050272

International filing date *(day/month/year)*
10 September 2018 (10.09.2018)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address
ATOSSA GENETICS INC.
107 Spring Street
Seattle, Washington 98104
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address
ATOSSA THERAPEUTICS, INC.
107 Spring Street
Seattle, Washington 98104
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer
Laskowski Marek
e-mail pct.team4@wipo.int
Telephone No. +41 22 338 74 04

Form PCT/IB/306 (January 2009) 1/EK9ZYEP3KYCJS0

**PCT REQUEST**

Paper Copy (NOT for submission)

| | | |
|---|---|---|
| **0** | **For receiving Office use only** | |
| **0-1** | International Application No. | PCT/US18/50272 |
| **0-2** | International Filing Date | 10 SEP 2018 (10.09.18) |
| **0-3** | Name of receiving Office and "PCT International Application" | PCT INTERNATIONAL APPLICATION<br>RO/US |

| | | |
|---|---|---|
| **0-4** | **Form PCT/RO/101 PCT Request** | |
| 0-4-1 | Prepared Using | PCT-SAFE [EFS-Web mode]<br>Version 3.51.083.259 MT/FOP<br>20180701/0.20.5.24 |
| **0-5** | **Petition**<br>The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty | |
| **0-6** | **Receiving Office (specified by the applicant)** | United States Patent and Trademark Office (USPTO) (RO/US) |
| **0-7** | **Applicant's or agent's file reference** | 38602-758601 |
| **I** | **Title of Invention** | METHODS FOR MAKING AND USING ENDOXIFEN |
| **II** | **Applicant** | |
| II-1 | This person is | Applicant only |
| II-2 | Applicant for | All designated States |
| II-4 | Name | ATOSSA GENETICS INC. |
| II-5 | Address | 107 Spring Street<br>Seattle, Washington 98104<br>United States of America |
| II-6 | State of nationality | US |
| II-7 | State of residence | US |
| **III-1** | **Applicant and/or inventor** | |
| III-1-1 | This person is | Inventor only |
| III-1-3 | Inventor for | All designated States |
| III-1-4 | Name (LAST, First) | QUAY, Steven C. |
| III-1-5 | Address | 107 Spring Street<br>Seattle, Washington 98104<br>United States of America |
| **III-2** | **Applicant and/or inventor** | |
| III-2-1 | This person is | Inventor only |
| III-2-3 | Inventor for | All designated States |
| III-2-4 | Name (LAST, First) | SUN, YaoLin |
| III-2-5 | Address | 13F., No. 339-12, Sec. 2, Guangfu Rd.,<br>Fengshan Dist.<br>830 Kaohsiung City<br>Taiwan Province of China |

| | | |
|---|---|---|
| III-3 | **Applicant and/or inventor** | |
| III-3-1 | This person is | Inventor only |
| III-3-3 | Inventor for | All designated States |
| III-3-4 | Name (LAST, First) | WANG, LungHu |
| III-3-5 | Address | No. 102-2, Beishan Ln., Qijin Dist.<br>805 Kaohsiung City<br>Taiwan Province of China |
| III-4 | **Applicant and/or inventor** | |
| III-4-1 | This person is | Inventor only |
| III-4-3 | Inventor for | All designated States |
| III-4-4 | Name (LAST, First) | WU, ChangJung |
| III-4-5 | Address | No. 28, Ln. 150, Youchang St., Nanzi Dist.<br>811 Kaohsiung City<br>Taiwan Province of China |
| III-5 | **Applicant and/or inventor** | |
| III-5-1 | This person is | Inventor only |
| III-5-3 | Inventor for | All designated States |
| III-5-4 | Name (LAST, First) | HUANG, ChuanDer |
| III-5-5 | Address | No. 21, Aly. 11, Ln. 176, Sec. 1, Bei'an Rd., North Dist.<br>704 Tainan City<br>Taiwan Province of China |
| IV-1 | **Agent or common representative; or address for correspondence**<br>The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: | Agent |
| IV-1-1 | Name (LAST, First) | WELCH, Timothy R. |
| IV-1-2 | Address | WILSON SONSINI GOODRICH & ROSATI<br>650 Page Mill Road<br>Palo Alto, California 94304-1050<br>United States of America |
| IV-1-3 | Telephone No. | 650.493.9300 |
| IV-1-4 | Facsimile No. | 650.493.6811 |
| IV-1-5 | e-mail | patentdocket@wsgr.com |
| IV-1-5(a) | E-mail authorization<br>The receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority are authorized to use this e-mail address, if the Office or Authority so wishes, to send notifications issued in respect of this international application: | exclusively in electronic form (no paper notifications will be sent) |
| IV-1-6 | Agent's registration No. | 74,838 |

| | | |
|---|---|---|
| IV-2 | Additional agent(s) | additional agent(s) with same address as first named agent |
| IV-2-1 | Name(s) | HARWOOD, Melissa M.(60,229); YIN, Eva F.(74,922) |
| V | DESIGNATIONS | |
| V-1 | The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents. | |
| VI-1 | Priority claim of earlier national application | |
| VI-1-1 | Filing date | 11 September 2017 (11.09.2017) |
| VI-1-2 | Number | 62/556,799 |
| VI-1-3 | Country or Member of WTO | US |
| VI-2 | Priority claim of earlier national application | |
| VI-2-1 | Filing date | 11 September 2017 (11.09.2017) |
| VI-2-2 | Number | 62/556,884 |
| VI-2-3 | Country or Member of WTO | US |
| VI-3 | Priority claim of earlier national application | |
| VI-3-1 | Filing date | 31 January 2018 (31.01.2018) |
| VI-3-2 | Number | 62/624,787 |
| VI-3-3 | Country or Member of WTO | US |
| VI-4 | Priority claim of earlier national application | |
| VI-4-1 | Filing date | 03 July 2018 (03.07.2018) |
| VI-4-2 | Number | 62/693,885 |
| VI-4-3 | Country or Member of WTO | US |
| VI-5 | Priority document request | |
| | The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): | VI-1<br>VI-2<br>VI-3<br>VI-4 |

**PCT REQUEST**

Paper Copy (NOT for submission)

| | | | |
|---|---|---|---|
| **VI-6** | **Incorporation by reference :**<br>where an element of the international application referred to in Article 11(1)(iii)(d) or (e) or a part of the description, claims or drawings referred to in Rule 20.5(a) is not otherwise contained in this international application but is completely contained in an earlier application whose priority is claimed on the date on which one or more elements referred to in Article 11(1)(iii) were first received by the receiving Office, that element or part is, subject to confirmation under Rule 20.6, incorporated by reference in this international application for the purposes of Rule 20.6. | | |
| **VII-1** | **International Searching Authority Chosen** | United States Patent and Trademark Office (USPTO) (ISA/US) | |
| **VIII** | **Declarations** | Number of declarations | |
| VIII-1 | Declaration as to the identity of the inventor | - | |
| VIII-2 | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | - | |
| VIII-3 | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | - | |
| VIII-4 | Declaration of inventorship (only for the purposes of the designation of the United States of America) | - | |
| VIII-5 | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty | - | |
| **IX** | **Check list** | Number of sheets | Electronic file(s) attached |
| IX-1 | Request (including declaration sheets) | 5 | ✓ |
| IX-2 | Description | 112 | - |
| IX-3 | Claims | 18 | - |
| IX-4 | Abstract | 1 | ✓ |
| IX-5 | Drawings | 13 | - |
| IX-7 | TOTAL | 149 | |
| | **Accompanying Items** | Paper document(s) attached | Electronic file(s) attached |
| IX-8 | Fee calculation sheet | ✓ | - |
| **IX-20** | **Figure of the drawings which should accompany the abstract** | 1 | |
| **IX-21** | **Language of filing of the international application** | English | |
| **X-1** | **Signature of applicant, agent or common representative** | /Timothy R. Welch/ | |
| **X-1-1** | Name (LAST, First) | WELCH, Timothy R. | |
| **X-1-3** | Capacity (if such capacity is not obvious from reading the request) | Reg. No. 74,838, Agent of Record | |

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|---|---|---|
| 10-1 | Date of actual receipt of the purported international application | 10 SEP 2018 (10.09.18) |
| 10-2 | Drawings: | |
| 10-2-1 | Received | |
| 10-2-2 | Not received | |
| 10-3 | Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application | |
| 10-4 | Date of timely receipt of the required corrections under PCT Article 11(2) | |
| 10-5 | International Searching Authority | ISA/US |
| 10-6 | Transmittal of search copy delayed until search fee is paid | |

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# METHODS FOR MAKING AND USING ENDOXIFEN

## CROSS-REFERENCE

**[0001]** This application claims the benefit of U.S. Provisional Application No. 62/556,799, filed September 11, 2017; U.S. Provisional Application No. 62/556,884, filed September 11, 2017; U.S. Provisional Application No. 62/624,787, filed January 31, 2018; and U.S. Provisional Application No. 62/693,885, filed July 3, 2018, each incorporated herein by reference in its entirety.

## BACKGROUND OF THE INVENTION

**[0002]** Breast cancer is by far the most common form of cancer in women, and it is the second leading cause of cancer death in humans. Despite advances in diagnosing and treating breast cancer, the prevalence of this disease has been steadily rising at a rate of about 1% per year since 1940. Today, the likelihood that a woman living in North America will develop breast cancer during her lifetime is one in eight. In addition to breast cancers, other breast disorders affecting a large number of women include benign but often precancerous lesions, such as ductal hyperplasia, lobular hyperplasia, atypical ductal hyperplasia, and atypical lobular hyperplasia.

**[0003]** Current best practice for the treatment of breast cancer is to diagnose breast cancer with mammography and then treat the patient with surgery, radiation therapy, and chemotherapy. The current widespread use of mammography has resulted in improved detection of breast cancer. Although breast cancer is about 100 times less common among men than among women, the lifetime risk of men getting breast cancer is about 1 in 1,000. About 2,470 new cases of invasive breast cancer will be diagnosed in men and about 460 men will die from breast cancer. American Cancer Society estimates that in 2017, 255,180 new cases of breast cancer will be diagnosed in both men and women combined and 41,070 subjects will die of breast cancer. Nonetheless, the death rate due to breast cancer has remained relatively unchanged at about 21 deaths per 100,000 women and 0.4 deaths per 100,000 men. All too often, breast cancer is discovered at a stage that is too far advanced, when therapeutic options and survival rates are severely limited.

**[0004]** Breast cancers include any malignant tumor of breast cells. There are several types of breast cancer. Exemplary breast cancers include, but are not limited to, ductal carcinoma in situ, lobular carcinoma in situ, invasive (or infiltrating) ductal carcinoma, invasive (or infiltrating) lobular carcinoma, inflammatory breast cancer, triple-negative breast cancer, ER+ breast cancer, HER2+ breast cancer, adenoid cystic (or adenocystic) carcinoma, low-grade adenosquamous carcinoma, medullary carcinoma, mucinous (or colloid) carcinoma, papillary carcinoma, tubular carcinoma, metaplastic carcinoma, and micropapillary carcinoma. A single breast tumor can be a combination of these types or be a mixture of invasive and in situ cancer.



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**[0005]** Tamoxifen is a selective estrogen receptor modulator that is used for the treatment of women with endocrine responsive breast cancer, i.e., hormone-dependent or hormone-sensitive breast cancer. Adjuvant therapy primarily via oral delivery of tamoxifen is known to have severe side effects such as vasomotor symptoms, for example hot flashes, and reproductive tract (gynecologic) cancers. Patient compliance remains a problem with tamoxifen therapy. Further, the majority of the individuals on adjuvant tamoxifen therapy do not respond to the drug and 30 – 50% of the patients subsequently die of their disease.

**[0006]** Several cytochrome P450 (CYP) mutations have been proposed to cause reduced conversion of tamoxifen to its active metabolite, endoxifen, and reduce tamoxifen efficacy and increase resistance to the drug (Dickschen et al. Front Pharmacol. 2012; 3: 92. PMCID: PMC3357105). So far, over 140 allelic variants of CYP2D6 have been described and a substantial part of these are associated with reduced or absent activity of the encoded enzyme. Based on the combination of the carried alleles, each individual subject can be classified into one of four phenotypic groups: poor metabolizer (PM) with plasma endoxifen levels less than 30 nM, intermediate metabolizer (IM), extensive metabolizer (EM) and ultra-rapid metabolizer (UM), reflecting variations in levels of serum endoxifen. However, changes in the CYP genotype do not fully explain the tamoxifen resistance and the reduced endoxifen levels observed in some subjects.

**[0007]** Therefore, several alternatives to tamoxifen are being developed for the treatment of breast cancer, which include low dose-tamoxifen (Lazzeroni M et al. Breast Cancer Res. 2012 Oct 29;14(5):214) and tamoxifen's active metabolites, afimoxifene (*see*, U.S. Patent Nos. 7,485,623; 7,507,769; 7,704,516; 7,786,172; 7,968,532; and 8,048,927; Mansel R et al. Breast Cancer Res Treat. 2007 Dec;106(3):389-97. PubMed PMID: 17351746; Rouanet P et al. J ClinOncol. 2005 May 1;23(13):2980-7. PubMed PMID: 15860853), endoxifen (*see*, US9333190; U.S. Patent Nos. 9,220,680; 9,090,640; and 9,200,045; U.S. Publication Nos. 2009/0291134 and US20100112041), and their derivatives (*see*, U.S. Patent Nos. 8,063,249; U.S. Publication Nos. 2015/0080339 and 2014/0193334). It is widely accepted that (Z)-endoxifen is the main active metabolite responsible for the clinical efficacy of tamoxifen.

**[0008]** While hydrochloride and citrate salts of endoxifen (*See*, *e.g.*, Fauq *et al.*, Bioorganic & Medicinal Chemistry Letters. 20 (2010) 3036 – 3038; Stearns *et al.*, J. Natl. Cancer Inst. Vol 95, No. 23, 2003; US Publication Nos. 2009/0291134 and 2010/0112041; Clinical Trials Gov. Identifier Nos. NCT01273168 and NCT02311933; Goetz et al., 2015, San Antonio Cancer Symposium; Ahmad *et al.*, Clinical Pharmacology & Therapeutics. 88(6) 814-817, 2010; and J Clin. Oncol. 30, 2012 (suppl; abstr 3089); Ahmad et al. Breast Cancer Research and Treatment 2010, 122, 579-584) are known in the art and currently under evaluation for metastatic cancer,



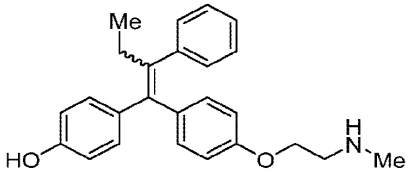
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there remains unmet medical need for new compositions and methods for the treatment and/or prevention of hormone-dependent breast and reproductive tract (gynecologic) disorders.

## SUMMARY OF THE INVENTION

**[0009]** The present disclosure addresses this need by providing compositions and methods for the treatment and/or prevention of hormone-dependent breast and reproductive tract (gynecologic) disorders. In certain aspects, the present disclosure provides novel industrially scalable methods of making Z-endoxifen or salts thereof, crystalline forms of endoxifen, and compositions comprising them. In certain aspects, the present disclosure provides novel crystalline forms of endoxifen wich may provide advantages including improved bioavailability and stability relative to other crystalline or amorphous forms.

**[0010]** In certain aspects, the present disclosure provides a composition comprising a crystalline form of a compound of Formula (III):




Formula (III).

**[0011]** In some embodiments, at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer. In some embodiments, the crystalline form is Form I of the compound of Formula (III). Crystalline Form I may be characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta, and optionally further comprising at least one peak selected from 16.0 ± 0.3°, 18.8 ± 0.3° and 26.5 ± 0.3° two theta. In some embodiments, the x-ray powder diffraction pattern further comprises at least one peak selected from 12.3 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta. The x-ray powder diffraction pattern may further comprise peaks at 12.3 ± 0.3°, 16.0 ± 0.3°, 18.8 ± 0.3°, 26.5 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta. In some embodiments, crystalline Form I is characterized by an x-ray powder diffraction pattern substantially as set forth in **Fig. 9** or **Fig. 10**. Greater than 90%, 95% or 99% by weight of the compound of Formula (III) in the composition may be crystalline Form I. In some embodiments, the composition comprises 0.01 mg to 200 mg of crystalline Form I, such as about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of crystalline Form I.

**[0012]** In some embodiments, 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, such as about 1.1. In some embodiments, the crystalline form is Form II of the compound of Formula (III). Crystalline Form II may be characterized by an x-ray powder diffraction pattern comprising major peaks at 7.0 ±



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0.3°, 11.9 ± 0.3°, 14.0 ± 0.3° and 18.4 ± 0.3° two theta, and optionally further comprising a peak at 22.0 ± 0.3° two theta. In some embodiments, the x-ray powder diffraction pattern further comprises at least one peak selected from 6.6 ± 0.3°, 13.3 ± 0.3° and 20.0 ± 0.3° two theta. The x-ray powder diffraction pattern may further comprise peaks at 6.6 ± 0.3°, 13.3 ± 0.3°, 20.0 ± 0.3° and 22.0 ± 0.3° two theta. In some embodiments, crystalline Form II is characterized by an x-ray powder diffraction pattern substantially as set forth in **Fig. 11** or **Fig. 12**. Greater than 90%, 95% or 99% by weight of the compound of Formula (III) in the composition may be crystalline Form II. In some embodiments, the composition comprises 0.01 mg to 200 mg of crystalline Form II, such as about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of crystalline Form II.

**[0013]** In some embodiments, 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, such as about 1.1. In some embodiments, the crystalline form is Form III of the compound of Formula (III). Crystalline Form III may be characterized by an x-ray powder diffraction pattern comprising major peaks at 11.9 ± 0.3°, 13.9 ± 0.3°, 17.1 ± 0.3° and 17.7 ± 0.3° two theta, and optionally further comprising a peak at 25.3 ± 0.3° two theta. In some embodiments, the x-ray powder diffraction pattern further comprises at least one peak selected from 18.2 ± 0.3°, 22.5 ± 0.3° and 26.8 ± 0.3° two theta. The x-ray powder diffraction pattern may further comprise peaks at 18.2 ± 0.3°, 22.5 ± 0.3°, 25.3 ± 0.3° and 26.8 ± 0.3° two theta. In some embodiments, crystalline Form III is characterized by an x-ray powder diffraction pattern substantially as set forth in **Fig. 13**. Greater than 90%, 95% or 99% by weight of the compound of Formula (III) in the composition may be crystalline Form III. In some embodiments, the composition comprises 0.01 mg to 200 mg of crystalline Form III, such as about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of crystalline Form III.

**[0014]** In certain aspects, the present disclosure provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the composition comprising a crystalline form of a compound of Formula (III). A composition of the present disclosure may be formulated for oral, parenteral, topical, or intraductal delivery. In some embodiments, the composition is formulated for oral delivery as a tablet, a caplet, a capsule, or a pill. In some embodiments, a mean half-life of endoxifen in a subject treated with the composition is between 30 hours to 60 hours. A composition comprising a crystalline form of a compound of Formula (III) may be formulated for oral delivery as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule. In some embodiments, the composition is administered to a subject for the treatment or prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both in the subject.



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**[0015]** In certain aspects, the present disclosure provides an oral composition comprising 1 mg to 200 mg per unit dose of the composition comprising a crystalline form of a compound of Formula (III) for administration to a subject in need thereof, wherein daily administration of the oral composition achieves in the subject:

a steady state plasma level of endoxifen within 7 to 21 days;

a steady state plasma level of endoxifen ranging from 25 nM to 300 nM;

a steady state plasma level of endoxifen greater than 30 nM;

maximal plasma levels of endoxifen within 2 to 10 hours after administering; or

any combination thereof.

**[0016]** In some embodiments, a mean half-life of endoxifen in a subject treated with the composition comprising a crystalline form of a compound of Formula (III) is between 40 hours to 55 hours. In some embodiments, the composition is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule. In some embodiments, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of endoxifen in the composition is released in the intestines. In some embodiments, the composition comprising a crystalline form of a compound of Formula (III) exhibits a mean area under the curve extrapolated to time infinity ($AUC_{0\text{-}inf}$) of endoxifen of 200 hr*ng/mL to 10000 hr*ng/mL, of 300 hr*ng/mL to 8000 hr*ng/mL, of 400 hr*ng/mL to 6000 hr*ng/mL or of 700 hr*ng/mL to 6000 hr*ng/mL.

**[0017]** In certain aspects, the present disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject the composition comprising a crystalline form of a compound of Formula (III). In some embodiments, the subject has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both. The hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder may be a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer. In some embodiments, the subject has prostate cancer and has or is at risk of having gynecomastia. The subject may have tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder. In some embodiments, the subject is or will be treated with an SSRI drug selected from the group consisting of citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and vilazodone.

**[0018]** In practicing any of the subject methods, the composition may comprise 0.01 mg to 200 mg of (Z)-endoxifen. In some embodiments, the subject is administered about 1 mg, 2 mg, 4 mg,



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6 mg, 10 mg or 20 mg of (Z)-endoxifen daily. In some embodiments, a steady state plasma level of endoxifen in the subject is greater than 30 nM. The steady state plasma level of endoxifen may be achieved within 7 to 21 days of the first administration of the composition. In some embodiments, time to maximum plasma levels of endoxifen ranges from 2 hours to 10 hours or from 4 hours to 8 hours after administering the composition.

**[0019]** In certain aspects, the present disclosure provides a method of treating a subject having or at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, the method comprising administering the composition comprising a crystalline form of a compound of Formula (III), wherein administration of the composition achieves:

a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;

a time to maximum plasma levels of endoxifen ranging from 4 hours to 8 hours after administration; and

a steady state plasma level of endoxifen greater than 30 nM.

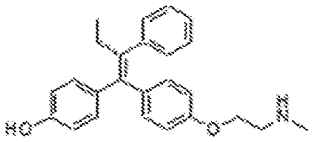
**[0020]** In some embodiments, the hormone-dependent breast disorder and the hormone-dependent reproductive tract disorder are selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, and vulvar cancer.

**[0021]** In practicing any of the subject methods, the composition may comprise 0.01 mg to 200 mg of (Z)-endoxifen. In some embodiments, the subject is administered about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of (Z)-endoxifen. The mean area under the curve extrapolated to time infinity ($AUC_{0\text{-}inf}$) of endoxifen may be 200 hr*ng/mL to 10000 hr*ng/mL, 300 hr*ng/mL to 8000 hr*ng/mL, 400 hr*ng/mL to 6000 hr*ng/mL or 700 hr*ng/mL to 6000 hr*ng/mL. In some embodiments, the composition is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule. In some embodiments, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of endoxifen in the composition is released in the intestines. The composition may be administered once a day, twice a day, thrice a day, four times a day, every other day, twice a week, weekly, fortnightly, twice a month, monthly, quarterly, once every six months, or annually.

**[0022]** In one aspect, the present disclosure provides an industrially scalable process for manufacturing (Z)-endoxifen or salts thereof, comprising the steps of: (a) subjecting a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), represented by

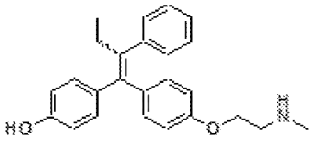


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to fractional crystallization from a first solvent to form a first crystalline solid and first crystalline mother liquor, wherein the first mother liquor has an E/Z ratio of at least 50% higher (Z) endoxifen as compared with the E/Z ratio of the mixture of (E)-endoxifen and (Z)-endoxifen; (b) subjecting the first mother liquor to recrystallization from a second solvent by concentrating the first mother liquor or by swapping out the first solvent from the first mother liquor one or more times with the second solvent, to form a second crystalline solid and a second mother liquor, wherein the second crystalline solid is ≥90% (Z)-endoxifen; and (c) optionally, subjecting the second crystalline solid to recrystallization from a third solvent or chromatographic treatment one or more times to form a third crystalline solid. In some embodiments, any one or more of the first solvent, the second solvent, and the third solvent are preheated to a temperature ranging from 40 °C to 80 °C.

**[0023]** In some aspects, the present disclosure provides an industrially scalable process for manufacturing crystalline Form I of the compound of Formula (III), comprising the steps of (a) subjecting a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), represented by



to fractional crystallization from a first solvent to form a first crystalline solid and first mother liquor, wherein the first mother liquor has an E/Z ratio of at least 50% higher (Z) endoxifen as compared with the E/Z ratio of the mixture of (E)-endoxifen and (Z)-endoxifen; (b) subjecting the first mother liquor 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 the second solvent one or more times, to form a second crystalline solid and a second mother liquor, wherein the second crystalline solid is ≥ 90% (Z)-endoxifen; and (c) subjecting the second crystalline solid to recrystallization from a third solvent or chromatographic treatment one or more times to form a third crystalline solid, wherein the third crystalline solid is crystalline Form I of the compound of Formula (III).

**[0024]** In certain aspects, the present dislcosure provides a crystalline form of a compound of Formula (III) produced according to a method described herein. In some embodiments, the crystalline form is Form I of the compound of Formula (III). In some embodiments, the

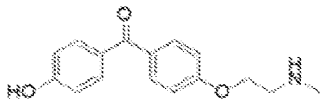


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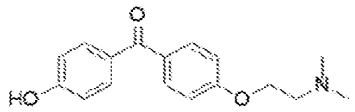
crystalline form is Form II of the compound of Formula (III). In some embodiments, the crystalline form is Form III of the compound of Formula (III).

**[0025]** In another aspect, the present disclosure provides that the mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), in step a is pretreated with 6N HCl and neutralized with 8N NaOH.

**[0026]** In another aspect, the industrially scalable process further comprises preparing the mixture of (E)-endoxifen and (Z)-endoxifen by coupling the compound of Formula (II), (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl) methanone, to propiophenone mediated by a McMurry reaction via a titanium salt and a reducing agent in an inert organic solvent to form the mixture of (E)-endoxifen and (Z)-endoxifen; and wherein the compound of Formula (II) has a structure represented by

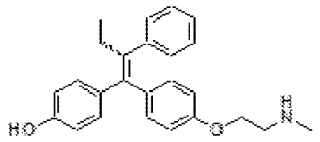


**[0027]** In yet another aspect, the industrially scalable process further comprises preparing the compound of Formula (II) by demethylating [4-[2-(dimethylamino)ethoxy]phenyl](4-hydroxyphenyl)methanone, the compound of Formula (I), wherein the compound of Formula (I) has the structure



with a demethylating agent and a proton acceptor in an inert organic solvent to form the compound of Formula (II).

**[0028]** The present disclosure also provides an industrially scalable process for manufacturing (Z)-endoxifen and salts thereof, comprising the steps of: (a) subjecting a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III) represented by



to fractional crystallization from ethyl acetate to form a first crystalline solid and first crystalline mother liquor, wherein the first mother liquor has an E/Z ratio of at least 30% higher (Z) endoxifen as compared with the E/Z ratio of the mixture of (E)-endoxifen and (Z)-endoxifen; (b)



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subjecting the first mother liquor to recrystallization from IPA or IPA/PPW (1:1 v/v) by concentrating the first mother liquor, or by swapping out ethyl acetate from the first mother liquor one or more times with IPA or IPA/PPW, to form a second crystalline solid and a second mother liquor, wherein the second crystalline solid is ≥90% (Z)-endoxifen; and (b) optionally, subjecting the second crystalline solid to recrystallization from ethanol or column chromatographic treatment one or more times to form a third crystalline solid.

**[0029]** In some embodiments, the mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), is prepared by coupling the compound of Formula (II), (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl) methanone, to propiophenone mediated by a McMurry reaction comprising the steps of: (a) reacting the compound of Formula (II) with propiophenone (1:0.01 to 1.5 wt/wt) in an inert organic solvent (1:1 to 1: 20 wt/wt); (b) preparing a titanium salt (1:0.1 to 1:12 wt/wt) and a reducing agent (1:0.01 to 1:10 wt/wt) in an inert organic solvent (1:1 to 1: 20 wt/wt); and (c) reacting the compound of Formula (II) of step (a) with the titanium salt and a reducing agent in an inert organic solvent of step (b) to form the mixture of (E)-endoxifen and (Z)-endoxifen; and wherein wt/wt is with respect to the compound of Formula (II).

**[0030]** In other embodiments, the mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), is prepared by coupling the compound of Formula (II), (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl) methanone, to propiophenone mediated by a McMurry reaction comprising the steps of: (a) reacting the compound of Formula (II) with propiophenone (1:0.01 to 1:5 wt/wt) in THF (1:1 to 1:20 wt/wt); (b) preparing a $TiCl_4$ (0.1 to 4 wt/wt) and Zn (0.01 to 1:2 wt./wt) in THF (1:1 to 1:20 wt/wt; and (c) reacting the compound of Formula (II) of step (a) with the $TiCl_4$ and Zn in THF of step (b) to form the mixture of (E)-endoxifen and (Z)-endoxifen; and wherein wt/wt is with respect to the compound of Formula (II).

**[0031]** In some embodiments, the compound of Formula (II) is generated by demethylating the compound of Formula (I) with a demethylating agent (1:0.5 to 1:10 wt/wt) and a proton acceptor (1:0.5 to 1:10 wt/wt) in an inert organic solvent (1:1 to 1: 20 wt/wt) to form a compound of Formula (II), wherein the wt/wt is with respect to the compound of Formula (I).

**[0032]** In some embodiments, the compound of Formula (II) is prepared by demethylating the compound of Formula (I) with 1-chloroethyl chloroformate and DIPEA in THF to form the compound of Formula (II) comprising the steps of: (a) reacting the compound of Formula (I) with DIPEA (1:0.5 to 1:10 wt/wt) in THF (1:20 wt/wt); (b) adding 1-chloroethyl chloroformate (1:0.5 to 1:10 wt./wt); (c) distilling with methanol one or more times (1:1 to 1:10 wt./wt); (e) reacting with methanol (1:1 to 1:5 wt/wt)/HCl (1:1 to 1:10 wt/wt); and (e) neutralizing with NaOH (1:1 to 1:10 wt/wt); and wherein wt/wt is with respect to the compound of Formula (I).



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**[0033]** In another aspect, the present disclosure provides process for making (Z)-endoxifen gluconate salts by reacting (Z)-endoxifen with D-gluconate or L-Gluconate to form (Z)-endoxifen L-gluconate or (Z)-endoxifen D-gluconate.

**[0034]** In still another aspect, the present disclosure provides that (Z)-endoxifen, (E)-endoxifen, compounds of Formula (III), the compound of Formula (II), and salts thereof prepared by any of the processes as described herein are stable. In a particular aspect, the (Z)-endoxifen free base is stable at ambient temperature for at least 9 months.

**[0035]** In certain aspects, the present disclosure provides an industrially scalable process for manufacturing crystalline Form II or III of the compound of Formula (III), comprising (a) reacting to 6N HCL (1:1 to 1:5 wt/wt) in ethyl acetate (1:1 to 1:20 wt/wt) a starting mixture of (E)-endoxifen and (Z)-endoxifen having an E/Z-ratio ranging from 99:1 to 40:60; (b) neutralizing with 8N NaOH (1:1 to 1:20 wt/wt); (c) washing one or more times with ethyl acetate; (d) washing one or more times with a mixture of ethyl acetate and n-heptane; and (e) recovering crystalline Form II or III of the compound of Formula (III); wherein wt/wt is with respect the starting mixture of (E)-endoxifen and (Z)-endoxifen.

**[0036]** In yet another aspect, the present disclosure provides a composition comprising (Z)-endoxifen free base or a salt thereof prepared according to any of the processes described herein. The compositions are formulated for oral, parenteral, topical, and intraductal delivery. The compositions are formulated for oral delivery as tablets, caplets, capsules, or pills. In some embodiments, the compositions are formulated for oral delivery tablet as enteric tablets, enteric caplets, enteric capsules, delayed-release tablets, delayed-release caplets, and delayed-release capsules.

**[0037]** In certain aspects, the present disclosure provides compositions having certain pharmacokinetic profiles. In one aspect, the present disclosure provides that at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% of the endoxifen in the compositions is released in intestines. In another aspect, the present disclosure provides that the endoxifen in the compositions has a mean half-life of in a subject ranging from 30 hours to 60 hours after administration. In some embodiments, the mean half-life of endoxifen in a subject ranges from 40 hours to 55 hours after administration. In another aspect, the present disclosure provides that the mean area under the curve extrapolated to time infinity ($AUC_{0\text{-}inf}$) of 200 hr*ng/mL to 10000 hr*ng/mL, of 300 hr*ng/mL to 8000 hr*ng/mL, of 400 hr*ng/mL to 6000 hr*ng/mL or of 700 hr*ng/mL to 6000 hr*ng/mL.

**[0038]** In another aspect, the present disclosure provides oral compositions 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: (i) a



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steady state plasma level of endoxifen within 7 to 21 days; or (ii) a steady state plasma level of endoxifen ranging from 25 nM to 300 nM; or (iii) a steady state plasma level of endoxifen greater than 30 nM; or (iv) maximal plasma levels of endoxifen within 2 to 10 hours after administering; or (v) any combination thereof. The present disclosure also provides that the compositions are administered to a subject in need thereof for the treatment and prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both in a subject.

**[0039]** In certain aspect, the present disclosure provides methods of treating a subject in need thereof, the method comprising administering to the subject an oral composition as disclosed herein. In some embodiments, the subject has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both. In various embodiments, the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer.

**[0040]** In some embodiments, the subject has prostate cancer and wherein the subject further has or is at risk of having gynecomastia.

**[0041]** In certain aspects, the present disclosure provides certain patient populations that would benefit from such methods of treatment. In some embodiments, the patient population is a tamoxifen-refractory or tamoxifen resistant population. In certain embodiments, the subject has tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder. In other embodiments, the patient population comprises subjects that are or will be treated with an SSRI drug selected from the group consisting of citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and vilazodone.

**[0042]** In an aspect, the present disclosure provides certain doses of (Z)-endoxifen to be administered to subjects in need thereof. In various embodiments, the subjects are administered 0.01 mg to 200 mg of (Z)-endoxifen. In certain embodiments, the subject is administered 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of (Z)-endoxifen daily.

**[0043]** In another aspect, the present disclosure provides methods of treatment of subjects, wherein a steady state plasma level of endoxifen in of the subject is greater than 30 nM upon administration of the compositions. In some embodiments, such a steady state plasma level of endoxifen is achieved within 7 to 21 days of the first administration of the composition. In some embodiments, the time to maximum plasma levels of endoxifen ranges from 2 hours to 10 hours or from 4 hours to 8 hours after administering the composition.



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**[0044]** In another aspect, the present disclosure provides methods of treating a subject having or at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, the method comprising administering an oral composition comprising (Z)-endoxifen or a salt thereof, wherein administration of the composition achieves: (i) a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration; (ii) a time to maximum plasma levels of endoxifen ranging from 4 hours to 8 hours after administration; and (iii) a steady state plasma level of endoxifen greater than 30 nM. In certain embodiments, the subject is administered 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of (Z)-endoxifen. In other embodiments, the mean area under the curve extrapolated to time infinity ($AUC_{0\text{-}inf}$) of 200 hr*ng/mL to 10000 hr*ng/mL, of 300 hr*ng/mL to 8000 hr*ng/mL, of 400 hr*ng/mL to 6000 hr*ng/mL or of 700 hr*ng/mL to 6000 hr*ng/mL. In some embodiments, the composition is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule. In some embodiments, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% of the endoxifen is released in intestines. In some embodiments, the composition is administered once a day, twice a day, thrice a day, four times a day, every other day, twice a week, weekly, fortnightly, twice a month, monthly, quarterly, once every six months, or annually. In some embodiments, the hormone-dependent breast disorder and the hormone-dependent reproductive tract disorder are selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, and vulvar cancer.

## INCORPORATION BY REFERENCE

**[0045]** All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0046]** The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

**[0047]** **Fig. 1** is a scheme depicting the metabolic route of tamoxifen to endoxifen and other metabolites. The plasma concentrations of 4-hydroxytamoxifen are low relative to those of N-desmethyl tamoxifen, indicating that the primary route for metabolism of the parent drug is via



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N-demethylation by cytochrome P450 3A4 (CYP3A4) to N-desmethyl tamoxifen, followed by hydroxylation by cytochrome P450 2D6 (CYP2D6) to endoxifen.

**[0048] Fig. 2** is a representative infrared spectrum of (Z)-endoxifen free base prepared using methods disclosed herein.

**[0049] Fig. 3** shows the time to maximum serum levels (nM) of endoxifen following treatment with placebo or 1 mg, 2 mg or 4 mg endoxifen capsules.

**[0050] Fig. 4** shows the time to maximum serum levels of endoxifen following treatment with placebo or 1 mg, 2 mg or 4 mg endoxifen capsules at day 1 and day 21. The time post-dose (hours) is plotted on the X-axis and mean serum concentration (ng/mL) is plotted on the Y-axis.

**[0051] Fig. 5** shows the time to achieve steady state serum levels of endoxifen following treatment with placebo or 1 mg, 2 mg or 4 mg endoxifen capsules from day 0 (day 0 refers to day 8 on the X-axis) to day 21. The X-axis is time in days (Day 8 to Day 21) and the Y-axis is mean serum concentration in ng/mL. Blood was drawn on each day from day 0 to the end of the clinical trial period. Subjects were dosed on day 1 and plasma endoxifen levels were measured as shown in **Table 17**. Subjects were subsequently dosed daily starting on day 8 (labeled day 8 in **Fig. 5**) until the end of study period.

**[0052] Fig. 6** shows mean serum concentrations (ng/mL) over time following treatment with placebo or 1 mg, 2 mg or 4 mg endoxifen capsules at day 1 and day 21 (Linear).

**[0053] Fig. 7** shows mean serum concentrations (ng/mL) over time following treatment with placebo or 1 mg, 2 mg or 4 mg endoxifen capsules at day 1 and day 21 (Semi-log).

**[0054] Fig. 8** shows mean serum concentrations (nM) over time following treatment with placebo or 1 mg, 2 mg or 4 mg endoxifen capsules at day 1 and day 21 (Linear).

**[0055] Fig. 9** is an XRPD pattern obtained from a sample of Form I of the compound of Formula (III).

**[0056] Fig. 10** is an XRPD pattern obtained from a sample of Form I of the compound of Formula (III).

**[0057] Fig. 11** is an XRPD pattern obtained from a sample of Form II of the compound of Formula (III).

**[0058] Fig. 12** is an XRPD pattern obtained from a sample of Form II of the compound of Formula (III).

**[0059] Fig. 13** is an XRPD pattern obtained from a sample of Form III of the compound of Formula (III).



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## DETAILED DESCRIPTION OF THE INVENTION

**[0060]** Compounds are described using standard nomenclature. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

**[0061]** As used herein, the terms "a," "an," and "the" include plural reference unless the context dictates otherwise.

**[0062]** As used herein, the terms "active pharmaceutical ingredient", "active ingredient", "API," "drug," "active," "actives" or "therapeutic agent" may be used interchangeably to refer to the pharmaceutically active compound(s) in a pharmaceutical composition. This is in contrast to other ingredients in the compositions, such as excipients, which are substantially or completely pharmaceutically inert. A suitable API in accordance with the present disclosure is one where there is or likely may be patient compliance issues for treating a certain disease, condition, or disorder. The therapeutic agent as used herein includes the active compound and its salts, prodrugs, and metabolites. As used herein the term "drug" means a compound intended for use in diagnosis, cure, mitigation, treatment, and/or prevention of disease in man or other animals.

**[0063]** As used herein, "adjuvant therapy" refers to a therapy that follows a primary therapy and that is administered to subjects at risk of relapsing. Adjuvant systemic therapy in case of breast cancer or reproductive tract cancer, for example with tamoxifen, usually begins soon after primary therapy to delay recurrence, prolong survival or cure a subject.

**[0064]** As used herein, the term "tamoxifen" refers to (Z)-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanamine. Tamoxifen can also refer to the E-isomer or a combination of the E-isomer and the Z-isomer.

**[0065]** As used herein, the terms "4-hydroxytamoxifen," "afimoxifene," and "4-OHT" used interchangeably refer to 4-1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-phenylbut-1-enyl]phenol, and constitutes an active metabolite of tamoxifen. 4-OHT can refer to the Z-isomer, E-isomer or a combination thereof.

**[0066]** As used herein, the term "endoxifen" refers to 4-hydroxy-N-desmethyl-tamoxifen. It is a secondary active metabolite of tamoxifen.

**[0067]** Embodiments that reference throughout this specification to "a compound", such as compounds of Formula (I), Formula (II), Formula (III) and Formula (IV), include the polymorphic, salt, free base, co-crystal, and solvate forms of the formulas and/or compounds disclosed herein. Thus, the appearances of the phrases "a compound", "compound of Formula (I)", "compound of Formula (II)", "compounds of Formula (III)" and "compound of Formula (IV)" include Form I of the compound of Formula (IV), Forms II-III of the compounds of



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Formula (III), the free base of the compound of Formula (IV), the free base of the compounds of Formula (III), and/or the gluconate salts as described herein.

**[0068]** The terms "crystalline form", "polymorph" and "Form" may be used interchangeably herein, and are meant to include all crystalline and amorphous forms of the compound, including, for example, polymorphs, pseudopolymorphs, salts, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms, as well as mixtures thereof, unless a particular crystalline or amorphous form is referred to. Compound of the present disclosure include crystalline and amorphous forms of those compounds, including, for example, polymorphs, pseudopolymorphs, salts, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof.

**[0069]** All compounds disclosed herein are further understood to include all possible isotopes of atoms occurring in the compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of example, and without limitation, isotopes of hydrogen include tritium and deuterium and isotopes of carbon include $^{11}C$, $^{13}C$ and $^{14}C$.

**[0070]** As used herein and in the claims, the terms "comprising," "containing," and "including" are inclusive, open-ended and do not exclude additional unrecited elements, compositional components or method steps. Accordingly, the terms "comprising" and "including" encompass the more restrictive terms "consisting of" and "consisting essentially of."

**[0071]** As used herein, the term "combination therapy" refers to the use of a composition described herein in combination with one or more additional treatment. Treatment in combination therapy can be any treatment such as any prophylactic agent, therapeutic agent (such as chemotherapy), radiotherapy, surgery and the like. The combination can refer to inclusion of a therapeutic or prophylactic agent in a same composition as a composition disclosed herein (for example, in the same capsule, tablet, ointment, etc.) or in separate compositions (for example, in 2 separate capsules). The separate compositions may be in a different dosage form. The use of the terms "combination therapy" and "in combination with" does not restrict the order in which a composition described herein and prophylactic and/or therapeutic agent and/or treatment are administered to a subject in need thereof. Compositions of the present disclosure can be administered prior to (e.g., 1 minute (min), 5 min, 15 min, 30 min, 45 min, 1 hour (h), 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, 24 h, 36 h, 48 h, 72 h, 96 h, 1 week (wk), 2 wk, 3 wk, 4 wk, 5 wk, 6 wk, 8 wk, 12 wk, 6 months (m), 9 m, or 1 year before), concomitant with, or subsequent to (e.g., 1 minute (min), 5 min, 15 min, 30 min, 45 min, 1 hour (h), 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, 24 h, 36 h, 48 h, 72 h, 96 h, 1 week (wk), 2 wk, 3 wk, 4 wk, 5 wk, 6 wk, 8 wk, 12 wk, 6 months (m), 9 m, or 1 year after) administration of one or more prophylactic and/or therapeutic



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agent and/or treatment to a subject in thereof. Combination therapy as used herein can also refer to treatment of a subject having a single disease or multiple diseases, for example, prostate cancer in men and gynecomastia.

**[0072]** As used herein, the term "test sample" means sample of blood obtained from a subject. It is to be understood that when blood sample is obtained from a subject, subject's blood is used for determining the subject's endoxifen levels and/or other biomarkers that may be measured or tested. As used herein "plasma endoxifen" is used to refer to endoxifen levels in the subject's test sample, whether the test is conducted on whole blood, plasma or serum.

**[0073]** As used herein, the term "dosage form" means the form in which the compounds or compositions of the present disclosure are delivered to a patient.

**[0074]** As used herein, the term "pharmaceutically acceptable" or "pharmacologically acceptable" means materials, compositions, or vehicles that are compatible with other ingredients of the formulation and that they do not substantially produce adverse reactions, e.g., toxic, allergic, or immunological reactions, when administered to a subject. They may be approved by a regulatory agency, e.g., of the U.S. Federal or state government or listed in the U.S. pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

**[0075]** As used herein, the term "pharmaceutically acceptable carrier" or "carrier" means a pharmaceutically acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, solvent, or encapsulating material, involved in carrying or transporting one or more of the compounds of the present disclosure from one tissue, organ, or portion of the body or across the skin.

**[0076]** As used herein, the term "pharmaceutically acceptable salt" refers to any salt (e.g., obtained by reaction with an acid or a base) of a compound of the present disclosure that is physiologically tolerated in a subject (e.g., a mammal, and/or in vivo, ex-vivo, in vitro cells, tissues, or organs). A "salt" of a compound of the present disclosure may be derived from inorganic or organic acids and bases. Suitable anion salts include, arecoline, besylate, bicarbonate, bitartarate, butylbromide, citrate, camysylate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthanoate, isethionate, malate, mandelate, mesylate, methylbromide, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamaoate (Embonate), pantothenate, phosphate/diphosphate, polygalacuronate, salicylate, stearate, sulfate, tannate, teoclate, fatty acid anions, and triethiodide.



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**[0077]** Suitable cations include benzathine, clemizole, chloroprocaine, choline, diethylamine, diethanolamine, ethylenediamine, meglumine, piperazine, procaine, aluminum, barium, bismuth, lithium, magnesium, potassium, and zinc.

**[0078]** For the purposes of this application, the salts of the compounds of the present disclosure are contemplated to be pharmaceutically acceptable for therapeutic uses. However, salts of acids and bases that are non-pharmaceutically acceptable may also be useful, for example, in the preparation or purification of a pharmaceutically acceptable compound.

**[0079]** As used herein, the term "pharmaceutical composition" means a combination of the active agent (e.g., an active pharmaceutical compound or ingredient, API) with a carrier, inert or active (e.g., a phospholipid), making the compositions specially suitable for diagnostic or therapeutic uses *in vitro*, *in vivo*, or *ex vivo*.

**[0080]** As used herein "primary therapy" refers to a first line of treatment upon initial diagnosis of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both in a subject. Exemplary primary therapies may involve surgery, a wide range of chemotherapies, and radiotherapy.

**[0081]** As used herein, the terms "subject," "patient," "participant," and "individual," may be used interchangeably herein and refer to a mammal such as a human. Mammals also include pet animals such as dogs, cats, laboratory animals, such as rats, mice, and farm animals such as cows and horses. Unless otherwise specified, a mammal may be of any gender or sex.

**[0082]** As used herein, the term "tamoxifen refractory" refers to a subject that has been dosed daily with tamoxifen for at least 2 days and has a level of plasma endoxifen of less than 30 nM (e.g., less than 20 nM, less than 25 nM, or less than 30 nM). As used herein, the term "tamoxifen resistance" refers to two classes of resistance: (a) de novo resistance, i.e., non-responsiveness to tamoxifen therapy from the beginning of the treatment, or (b) acquired resistance, i.e., non-responsiveness to tamoxifen therapy after initial responsiveness or tamoxifen-dependent growth /stimulated growth while continuing to express estrogen receptors (Minsun Chang. Biomol. Ther. 20(3), 256-267 (2012)). The acquired resistance to tamoxifen may develop as early as 3 m to 1 year to as late as 5 to 10 years. As used herein, the term "reference plasma endoxifen level" refers to a value of 30 nM.

**[0083]** As used herein, the term "unit dosage form" refers to physically discrete units suitable for unitary dosages for subjects, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

**[0084]** It is specifically understood that any numerical value cited herein includes all values from the lower value to the upper value, i.e., all possible combination of numerical values between the



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lowest value and the highest value enumerated are to be considered to be expressly stated in this application and the endpoint of all ranges are included within the range and independently combinable. For example, if a concentration range or beneficial range is stated as 1% to 50%, it is intended that values such as 2% to 40%, 10% to 30%, or 1% to 3% etc., are expressly enumerated in this specification. It is also to be understood that if a concentration or dose is stated as a specific value such as 1 mg or 10 mg, it is intended that it is intended to include 10% variation. As another example, a stated concentration of 20% is intended to include values ±10%. Yet another example, if a ratio of 1:10 to 10:1 is stated, then it is intended that ratios such as 1:9 to 9:1, from 1:8 to 8:1, from 1:7 to 7:1, from 1:6 to 6:1, from 1:5 to 5:1, from 1:4 to 4:1, from 1:3 to 3:1, from 1:2 to 2:1, from 1:1 to 2:1 or from 2:5 to 3:5 etc. are specifically intended. There are only some examples of what is specifically intended. Unless specified otherwise, the values of the constituents or components of the compositions are expressed in weight percent of each ingredient in the component.

**[0085]** All methods described herein can be performed in a suitable order unless otherwise indicated or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as" and "the like") is intended merely to illustrate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as any indicating any non-claimed element as essential to practice of the invention as used herein.

**[0086]** As used herein, the terms "hormone-dependent breast disorder," "hormone-dependent reproductive tract disorder," "hormone-dependent breast and reproductive tract disorder" each and collectively include, without limitation, any breast or reproductive tract (gynecologic) disorder that is related to or is sensitive to high estrogen or normal estrogen levels that need to be reduced, disorders with estrogen-receptor positive (ER+) and/or progesterone-receptor positive (PR+) disorders, for example, breast disorders, endometriosis, uterine fibroids (also called leiomyomas) etc. Reproductive tract disorders include endometrial, ovarian, cervical, uterus, vaginal, and vulvar cancers. The terms "estrogen-related disorder" and "estrogen-receptor related disorder" may be used interchangeably to refer to the foregoing hormone dependent disorders. The disorders may be presented primarily or secondarily to an underlying disease, for example, prostate cancer or other disorders such as liver diseases. Hormone-dependent breast and reproductive tract disorder include, for example, McCune-Albright syndrome, which is a disorder caused by a mutation in the GNAS gene affecting bones, skin, and several hormone-producing (endocrine) tissues, often resulting in abnormal scar-like (fibrous) tissue in their bones, a condition called polyostotic fibrous dysplasia, hyperthyroidism in individuals carrying such mutations, and in girls often resulting in precocious puberty.



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**[0087]** As used herein, "breast disorder" means any aberration or a constellation of aberrations in the breast. Such aberration may be proliferative, non-proliferative, benign or malignant. Breast disorders include benign lesions of the breast (e.g., hyperplasia), increased breast density, gynecomastia, mastalgia, and breast cancer. Benign breast lesions include, but are not limited to, hyperplasia, atypia, ductal hyperplasia, lobular hyperplasia, atypical ductal hyperplasia (ADH), and atypical lobular hyperplasia (ALH). While not cancerous, ADH and ALH may be indicative of a predisposition for breast cancer.

**[0088]** Breast density is a breast disorder identified by visual techniques such as mammography and reflects increased fibroglandular tissue within the breast, i.e., overgrowth of stromal and epithelial cells in the breast. Breast density is classified in 4 classes—Class A, B, C and D—based on the degree of severity of the density. It is an independent risk factor for breast cancer. At least 23 states in the USA require physicians to inform subjects if they have dense breast(s). There is currently no treatment for dense breasts, although subjects are reminded to make healthy lifestyle choices and undergo regular mammograms to monitor changes in breast.

**[0089]** Gynecomastia is a common male breast condition reflecting increased hyperplasia of the breast tissue, including epithelial hyperplasia, with prevalence of asymptomatic gynecomastia of 60% to 90% in neonates, 50% to 60% in adolescents, and up to 70% in men aged 50 to 69 years (Therapeutics and Clinical Risk Management 2011:7, 145 – 148). Newborn gynecomastia usually resolves itself within 4 weeks of birth and at least half of adolescent males experience gynecomastia with typical onset of 13 to 14 years of age (Tanner stage 3 or 4). Gynecomastia has been proposed to be a risk factor for male breast cancer.

**[0090]** Further, gynecomastia often presents itself secondarily to an underlying disorder such as prostate cancer, cirrhosis and liver disease, male hypogonadism, hyperthyroidism, renal failure and in patients undergoing hemodialysis, Type I diabetes mellitis, etc. Further, medications, such as anti-androgen medications or certain anti-psychotics, themselves have been reported to cause up to 25% of cases of gynecomastia and can be categorized by their hormone-like action. For example, the most common side effects attributed to bicalutamide, a nonsteroidal antiandrogen used for treatment of prostate cancer, are gynecomastia and breast pain.

**[0091]** As used herein, "breast cancer" means any malignant tumor of breast cells. Breast cancer may be at any stage of breast cancer, including stages of a pre-cancer, an early stage cancer, a non-metastatic cancer, a pre-metastatic cancer, a locally advanced cancer, and a metastatic cancer. There are several types of breast cancer. Exemplary breast cancers include, but are not limited to, ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), invasive (or infiltrating) lobular carcinoma (ILC), invasive (or infiltrating) ductal carcinoma (IDC), microinvasive breast carcinoma (MIC), inflammatory breast cancer, ER-positive (ER+) breast



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cancer, ER-negative (ER-) breast cancer, HER2+ breast cancer, triple negative breast cancer (TNBC), adenoid cystic (adenocystic) carcinoma, low-grade adenosquamatous carcinoma, medullary carcinoma, mucinous (or colloid) carcinoma, papillary carcinoma, tubular carcinoma, metaplastic carcinoma, or micropapillary carcinoma. A single breast cancer tumor can be a combination of these types or be a mixture of invasive and in situ cancer.

**[0092]** DCIS is the most common non-invasive breast cancer. It involves the cell lining of the breast ducts. In DCIS, the cells have not spread beyond the walls of the duct into the surrounding breast tissue. About 1 in 5 new breast cancer cases will be DCIS. LCIS is a pre-cancerous neoplasia. It may be indicative of a predisposition for invasive cancer. LCIS only accounts for about 15% of the in situ (ductal or lobular) breast cancers.

**[0093]** IDC is the most invasive breast cancer. As the name applies, it is a carcinoma that begins in the breast ducts and then invades the surrounding fatty tissue. About 8 to 10 invasive breast cancers are infiltrating ductal carcinomas. IDC is often treated by surgery to excise the cancerous tissue, and radiation therapy. In addition, chemotherapy combined with immunotherapy (e.g., tamoxifen and tratuzumab) is often used to treat IDC. If the tumor is larger than 4 cm, then a radical mastectomy may be performed.

**[0094]** ILC is a cancer that develops in the lobules of the breast and has invaded the surrounding tissue. About 1 in 10 invasive breast cancer is an ILC. ILC is treated by surgery to excise the cancerous tissue, and radiation therapy. In addition, chemotherapy and immunotherapy combination (e.g., tamoxifen and tratuzumab) is often used as an adjuvant therapy to treat ILC.

**[0095]** Inflammatory breast cancer accounts for about 1% to 3% of all breast cancers. In inflammatory breast cancer, cancer cells block lymph vessels in the skin, resulting in the beast turning red and feeling warm. The affected breast may become larger or firmer, tender, or itchy. Inflammatory breast cancer is treated with chemotherapy, immunotherapy, radiation therapy and in some cases, surgery.

**[0096]** Estrogen Receptor positive (ER+) breast cancer is characterized by the presence of estrogen receptors on the surface of the cancerous cells. Growth of ER+ cancer cells is associated with the availability of estrogen (hormone-dependent or hormone sensitive breast cancer). Approximately, 80% of all breast cancers are ER+ breast cancers. Treatment options for ER+ breast cancer include chemotherapeutic agents that block estrogen (e.g., tamoxifen).

**[0097]** The present disclosure relates to methods of manufacturing stable preparations of (Z)-endoxifen free base, mixtures of (E)-endoxifen and (Z)-endoxifen (E/Z-mix), and salts thereof, and uses thereof. The present disclosure further relates to oral compositions comprising (Z)-endoxifen or salts thereof and methods of treating a subject in need thereof. The present disclosure also provides methods of treating a subject having or at risk of having a hormone-



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dependent breast disorder, a hormone-dependent reproductive tract (gynecologic) disorder, or both by administering to the subject an oral composition comprising (Z)-endoxifen, E/Z-mix, or a salt thereof.

**[0098]** In an aspect, the present disclosure relates to oral compositions comprising endoxifen or salts thereof. Endoxifen comprised in compositions of the present disclosure may be (Z)-endoxifen, (E)-endoxifen or a combination thereof. In one aspect, the present disclosure relates to compositions comprising stable (Z)-endoxifen free base.

**[0099]** In one aspect, the present disclosure provides industrially scalable methods of making (Z)-endoxifen free base, mixtures of (E)-endoxifen and (Z)-endoxifen (E/Z-mix), and salts thereof. In an aspect, the industrially scalable methods are synthetic methods of making stable (Z)-endoxifen free base, E/Z-mix, and salts thereof. In another aspect, the present disclosure provides methods of making compositions comprising stable (Z)-endoxifen free base, E/Z-mix, and salts thereof.

**[0100]** In certain aspects, the present disclosure provides crystalline forms of (Z)-endoxifen free base and crystalline forms of mixtures of (E)-endoxifen and (Z)-endoxifen, as well as pharmaceutical compositions of endoxifen comprising the crystalline forms described herein.

***Synthesis of (Z)-endoxifen Free Base***

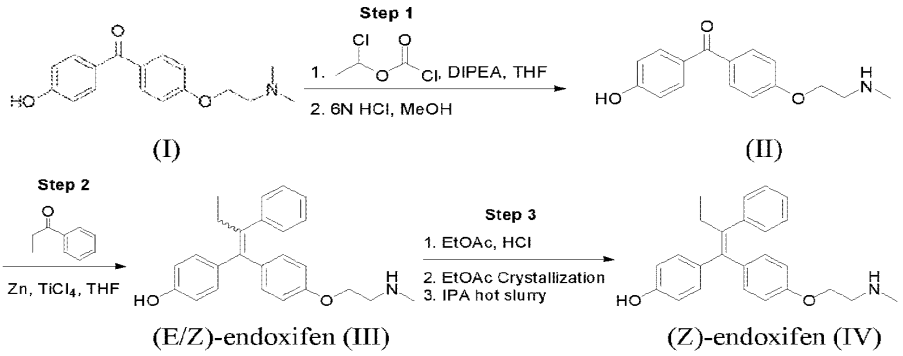
**[0101]** Several methods for the synthetic preparation of endoxifen are known in the art. For e.g., methods of synthetic preparations of endoxifen and their prodrugs and salts are described in U.S. Patent No. 9,333,190 (Ahmad, Jina Pharmaceuticals); WO 2008/070463 (Ahmad, Jina Pharmaceuticals), U.S. Pub. No. 2010/0112041 (Ahmad, Jina Pharmaceuticals), WO 2012/050263 (Ahmad, Jina Pharmaceuticals), WO 2014/141292 (Desai, Intas Pharmaceuticals), WO 2017/070651 (USA/Alchem Lab. Corp.); WO 2009/120999A2 (Kushner), U.S. Patent No. 8,063,249 (Kushner, Olema Pharmaceuticals), U.S. Patent Nos. 7,531,578 and 8,119,695 (Forman and Yu), and WO 2012/050263 (Song, CJ Cheiljedang Corp).

**[0102]** Methods of synthetic preparation of endoxifen have also been published in research literature. (Gauthier *et al.*, J. Org. Chem, 61, 3890 – 3893 (1996), Fauq *et al.*, Bioorg Med Chem Lett. 2010 May 15;20(10):3036-3038); Stearns *et al.*, J. Natl. Cancer Inst. Vol 95, No. 23, 2003; Johnson *et al.*, Breast Cancer Research and Treatment. 85:151-159, 2004; Ogawa, et al. Chem. Pharm. Bull. 39, 911 – 916, 1991). However, there remains an unmet need for large scale industrial scalable manufacturing. Stable (Z)-endoxifen free base may be prepared accordance to **Schema 1** as further described below and in **Examples 1** to **9**.



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**Schema 1.** ***Synthesis of (Z)-endoxifen Free Base***




***Demethylation***

**[0103]** In one aspect, the present disclosure relates to an industrially scalable process of making substantially purified (Z)-endoxifen free base, E/Z-mix, or salts thereof comprising demethylating the compound of Formula (I), [4-[2-(dimethylamino)ethoxy]phenyl](4-hydroxyphenyl)methanone), (available from AstaTech Pharmaceuticals, Inc., China ) to form the compound of Formula (II). Accordingly, in some embodiments, the industrial process comprises preparing the compound of Formula (II) by demethylating [4-[2-(dimethylamino)ethoxy]phenyl](4-hydroxyphenyl)methanone) with a demethylating agent and a proton acceptor in an inert organic solvent to form the compound of Formula (II). The industrially scalable process for making the compound of Formula (II), (Z)-endoxifen free base, E/Z-mix, or salts thereof comprises demethylating the compound of Formula (I) in amounts ranging from 1 mg to 1000 kg per reaction.

**[0104]** In some embodiments, the compound of Formula (I) can be demethylated by reacting the compound of Formula (I) with a demethylating agent. The demethylating agent is any agent suitable for the purpose. Examples of suitable demethylating agents include N-iodosuccinamide (NIS), ethyl chloroformates (such as 1-chloroethyl chloroformate, dichloroethyl chloroformate, trichloroethyl chloroformate, α-Chloroethylchloroformate (ACE-Cl)), vinyl chloroformate (VO-Cl), cynogen bromide (BrCN: von Braun's reaction), diethyl azodicarboxylate, pyridinium chloride, and the like.

**[0105]** In some embodiments, the demethylating agent is a chloroformate selected from the group consisting of 1-chloroethyl chloroformate, dichloroethyl chloroformate, trichloroethyl chloroformate, α-Chloroethylchloroformate (ACE-Cl), and vinyl chloroformate (VO-Cl). In other embodiments, the demethylating agent is an ethyl chloroformate selected from the group consisting of selected from the group consisting of ethyl chloroformates, such as 1-chloroethyl chloroformate, dichloroethyl chloroformate, trichloroethyl chloroformate, and α-



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Chloroethylchloroformate (ACE-Cl). In at least one embodiment, the demethylating agent is 1-chloroethyl chloroformate.

**[0106]** In some embodiments, a demethylating agent is added to the reaction mixture at a wt/wt ratio of the compound of Formula (I) to demethylating agent ranging from 1:0.5 to 1:10. In other embodiments, the demethylating agent is present at ratios (wt/wt) of the compound of Formula (I) to demethylating agent ranging from 1:2: to 1:5. In at least one embodiment, the demethylating agent is present at a ratio (wt/wt) of the compound of Formula (I) to demethylating agent of 1:2. In at least one embodiment, demethylating agent is present at a ratio (wt/wt) of the compound of Formula (I) to demethylating agent of 1:3.3. In other embodiments, the demethylating agent 1-chloroethyl chloroformate is present at a ratio (wt/wt) of the compound of Formula (I) to demethylating agent ranging from 1:0.5 to 1:10.

**[0107]** The demethylation reaction can be carried out in an inert organic solvent suitable for the demethylation reaction in the presence of a proton acceptor. Such inorganic solvents include dichloromethane, dichloroethane, chloroform, carbon tetrachloride, chlorobenzene, diethyl ether, 1,4-dioxane, tert-butyl methyl ether (TBME), tetrahydrofuran (THF), N,N-dimethylformamide (DMF), N-methylpyrrolidone (NMP), diglyme, nitromethane, 1,2-dimethoxyethane (DME), pyridine, acetone, acetonitrile, benzene, o-xylene, m-xylene, p-xylene, xylenes, hexanes, cyclohexane, heptane, octane, nonane, and decane, or a combination thereof. In an aspect, the industrially scalable process comprises one or more inert organic solvents for demethylation at a (wt/wt) ratio of the compound of Formula (I) to inert organic solvent ranging from 1:1 to 1:50. In some embodiments, the demethylation solvent is THF at a ratio of the compound of Formula (I) to THF (wt/wt) ranging from 1:1 to 1:50. In other embodiments, the THF is present in ratios (wt/wt) of the compound of Formula (I) to THF ranging from 1:1 to 1:20.

**[0108]** Proton acceptors suitable for the purpose of the present disclosure include, but are not limited to carbonates, such as sodium carbonate and potassium carbonate, and bicarbonates, such as sodium bicarbonate and potassium bicarbonate, proton sponge, and ethyldiisopropylamine, (N',N-diisopropyleamine, "DIPEA"). In an aspect, the industrially scalable process comprises a proton acceptor added to the reaction mixture at a wt/wt ratio of the compound of Formula (I) to proton acceptor ranging from 1:0.5 to 1:10. In some embodiments, the proton acceptor is present in a ratio (wt/wt) of the compound of Formula (I) to proton acceptor of 1:1:8.

**[0109]** One of skill in the art will be readily able to determine other solvents and proton acceptors known in the art suitable for demethylation reaction of the present disclosure.

**[0110]** Demethylating agents, solvents for demethylation reaction, and the compound of Formula (I) may be added in any order. Each reagent may be added to a suitable reactor in a single bolus or in multiple boluses and stirred.



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**[0111]** In some embodiments, the compound of Formula (I) is charged to a suitable reactor to which inert organic solvent THF and proton acceptor DIPEA are added for demethylation reaction, and cooled to 0 °C to 20 °C, followed by addition of one or more demethylating agents. THF is added at a wt/wt ratio of 1:1 to 1:20, and proton acceptor DIPEA is added at a wt/wt ratio of 1:0.5 to 1:10 to the demethylation reaction mixture, where wt/wt is with respect to the compound of Formula (I). In some embodiments, the reaction mixture is cooled to not more than (NMT) 15 °C followed by slow addition of one or more demethylating agents. The reaction may be carried out under inert conditions, such as under nitrogen or argon.

**[0112]** The reaction mixture comprising the compound of Formula (I), one or more demethylating agents (for example, 1-chloroethyl chloroformate) in one or more inert organic solvents can be heated at temperature ranging from 20 °C to 250 °C, such as from 40 °C to 80 °C, from 50 °C to 230 °C, from 50 °C to 120 °C, and from 150 °C to 200 °C. In some embodiments, the reaction mixture is heated under reflux. In other embodiments, the compound of Formula (I) is reacted with demethylating agent and proton acceptor for not less than (NLT) 5 hours, NLT 8 hours, NLT 12 hours, NLT 24 hours, NLT 36 hours, NLT 48 hour and NLT 72 hours. In at least one embodiment, the reaction is heated under reflux NLT 12 hours. The reaction may be held and stored until further use. In some embodiments, the reaction mixture is held not more than (NMT) 24 hours under reflux conditions while stirring.

**[0113]** The mixture can be subjected to one or more rounds of distillation under reduced pressure. Distillation may be carried out at NMT 100 °C, at NMT 95 °C, at NMT 90 °C, at NMT 85 °C, at NMT 80 °C, or at NMT 70 °C with solvents suitable for distillation such as ethyl acetate, lower alcohols (non-limiting examples include methanol, ethanol, n-propanol, and isopropanol), benzene, acetone, acetonitrile, toluene, dichloromethane, 1,2-dichloroethane, and chloroform. One of skill in the art will be able to readily determine additional suitable solvents useful for the purpose.

**[0114]** In at least one embodiment, the solvent used for distillation is methanol. As a non-limiting example, methanol may be used for solvent swap for 2 to 5 rounds of distillation under reduced pressure.

**[0115]** Solvents, such as methanol, may be used for distillation at a (wt/wt) ratio of the compound of Formula (I) to solvent ranging from 1:1 to 1:10 per round of distillation.

**[0116]** Then, the mixture can be reacted with a solvent/acid mixture by addition of an acid (wt/wt ratio of the compound of Formula (I) to acid ranging from 1:1 to 1:10) to the solvent while stirring and heating under reflux. The acid can be any suitable acid. HCl is an example of acid suitable for the purpose of the present disclosure. Non-limiting examples of suitable solvent/acid mixtures include methanol/HCl, ethanol/HCl, propanol/HCl, isopropanol/HCl,



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methanol/sulfuric acid, methanol/phosphoric acid, ethanol/sulfuric acid, ethanol/phosphoric acid, propanol/sulfuric acid, propanol/phosphoric acid, isopropanol/sulfuric acid, isopropanol/phosphoric acid, methanol/acetic acid, ethanol/acetic acid, propanol/acetic acid, isopropanol/acetic acid, methanol/formic acid, ethanol/formic acid, propanol/formic acid, and isopropanol/formic acid. In at least one embodiment, the solvent/acid mixture is methanol/6N HCl. As a non-limiting example, methanol in methanol/HCl mixture may be added at a wt/wt ratio of the compound of Formula (I) to methanol in solvent/acid mixture at 1:3.2 while HCl in the methanol/HCl mixture may be at a wt/wt ratio of the compound of Formula (I) to HCl in the solvent/acid mixture at 1:4. In at least one embodiment, the methanol/6N HCl mixture is added at a wt/wt ratio of the compound of Formula (I) to methanol/6N HCl ranging from 1:1 to 1:10, such as 1:1 to 1:5.

**[0117]** Distillation may be carried out for NLT 5 hours, NLT 8 hours, NLT 10 hours, NLT 12 hours, NLT 14 hours under reduced pressure. Distillation may be carried out at a temperature NMT 70 °C, NMT 75 °C, NMT 80 °C, NMT 85 °C, NMT 90 °C and NMT 90 °C.

**[0118]** The reaction mixture may be held and stored until further use. In some embodiments, the reaction mixture may be held for NMT 24 hours under reflux conditions while stirring.

**[0119]** The reaction mixture can be neutralized with a neutralizing agent such as sodium hydroxide (NaOH), ammonium hydroxide, aminomethylpropanol and the like, and filtered. The resulting wet cake can be washed with water and an organic solvent such as ethyl acetate (EtOAc) to obtain (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl)methanone, the compound of Formula (II).

**[0120]** The neutralizing agent may be at a wt/wt ratio of the compound of Formula (I) to the neutralizing agent ranging from 1:1 to 1:10. In some embodiments, the neutralizing agent is 8N sodium hydroxide at a ratio ranging from 1:1 to 1:10. In other embodiments, the neutralizing agent is 8N sodium hydroxide at a ratio ranging from 1:2 to 1:8.

**[0121]** In another aspect, the industrially scalable process for making (Z)-endoxifen free base, E/Z-mix or salts thereof comprises one or more steps of washing filtered product (the compound of Formula (II)) with purified water (1:1 to 1:5 wt/wt) and organic solvents such as ethyl acetate (EtOAc) (1:0.5 to 1:10 wt/wt) wherein the wt/wt is with respect to the compound of Formula (I). The wet cake is dried under reduced pressure/vacuum. The temperature for can range from 25 °C to 60 °C. In some embodiments, the drying is carried out at a temperature NMT 50 °C.

***McMurry Reaction***

**[0122]** In another aspect, the present disclosure relates to an industrially scalable process of making (Z)-endoxifen free base, E/Z-mix, and salts thereof comprising subjecting the compound



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of Formula (II) to a McMurry reaction to afford an E/Z-mix (i.e., a mixture of (E)-endoxifen and (Z)-endoxifen free bases), compounds of Formula (III).

**[0123]** The McMurry reaction has been used to prepare tamoxifen (European Patent Application No. 168175). The present disclosure relates to an industrially scalable process wherein the compound of Formula (II), (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl) methanone, is coupled to propiophenone mediated by a McMurry reaction via titanium salts such as chloride salts of titanium (for example, titanium trichloride and titanium tetrachloride ($TiCl_4$)) and reducing agents in inert organic solvents to form an E/Z mix of compounds of Formula (III).

**[0124]** Salts of titanium that are useful for the present disclosure include titanium halides (such as titanium trichloride ($TiCl_3$), Titanium tetrachloride ($TiCl_4$), titanium iodides, titanium bromides, and titanium fluorides), titanium (IV) trichloride isopropoxide, and titanium isopropoxide. In some embodiments, the titanium salt is $TiCl_4$. Titanium salts, such as $TiCl_4$, are added at a wt/wt ratio of the compound of Formula (II) to titanium salt ranging from 1:0.1 to 1:12.

**[0125]** Reducing agents include zinc, zirconium, vanadium, niobium, molybdenum, tungsten, aluminum, magnesium, potassium, zinc-copper couple, alkali and alkali earth metals, butylium, lithium, and lithium aluminum hydride. In at least one embodiment, the reducing agent is zinc. The McMurry synthesis is conveniently carried out using a reducing agent such as zinc at a wt/wt ratio of the compound of Formula (II) to reducing agent ranging from 1:0.1 to 1:10. In some embodiments, the ratio of reducing agent is in excess compared to titanium salts.

**[0126]** The McMurry synthesis can be carried out in one or more inert organic solvents. Inert organic solvents useful for the McMurry reaction include dichloromethane, dichloroethane, chloroform, carbon tetrachloride, chlorobenzene, diethyl ether, 1,4-dioxane, tert-butyl methyl ether (TBME), tetrahydrofuran (THF), N,N-dimethylformamide (DMF), N-methylpyrrolidone (NMP), diglyme, nitromethane, 1,2-dimethoxyethane (DME), pyridine, acetone, acetonitrile, benzene, o-xylene, m-xylene, p-xylene, xylenes, hexanes, cyclohexane, heptane, octane, nonane, and decane, or a combination thereof. In some embodiments, the inert organic solvent is at wt/wt ratio of the compound of Formula (II) to solvent ranging from 1:1 to 1:50. In other embodiments, the inert organic solvent is at wt/wt ratios of the compound of Formula (II) to solvent ranging from 1:1 to 1:20. In some embodiments, the inert organic solvent used for the McMurry reaction is THF. THF, in some embodiments, is at wt/wt ratio of the compound of Formula (II) to THF ranging from 1:1 to 1:20.

**[0127]** It is advantageous to combine titanium salts and reducing agent in the inert organic solvents to create a pre-mix. Titanium salts are added to the reducing agent and inert organic solvents at such a rate so as to keep the internal temperature at NMT 75 °C, such as NMT 65 °C,



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NMT 55 °C, NMT 45 °C, NMT 40 °C, NMT 35 °C, NMT 30 °C, NMT 25 °C, NMT 20 °C, and NMT 15 °C. Accordingly, titanium salts and reducing agent in the inert organic solvents are combined to create a pre-mix. In some embodiments, Zn, $TiCl_4$ and THF are combined to create Zn/$TiCl_4$/THF mixture. In at least one embodiment, $TiCl_4$ is added to Zn and THF and mixed keeping the internal temperature NMT 20 °C for NLT 10 min.

**[0128]** Preparation of titanium salt and a reducing agent in an inert organic solvent may further comprise heating titanium salt and reducing agent in an inert organic solvent to a temperature ranging from 20 °C to 250 °C, such as from 40 °C to 80 °C, from 50 °C to 230 °C, from 50 °C to 120 °C, and from 150 °C to 200 °C. In some embodiments, titanium salt and reducing agent present in an inert organic solvent are heated at NLT 60 °C. In some embodiments, preparation of titanium salt and a reducing agent in an inert organic solvent further comprises heating titanium salt and reducing agent in an inert organic solvent under reflux. Titanium salt and reducing agent in inert organic solvent are heated under reflux for NLT 30 min, such as NLT 1 hour, NLT 2 hours, NLT 4 hours, NLT 6 hours and NLT 8 hours, under inert conditions such as under $N_2$ or argon.

**[0129]** It is also advantageous to pre-mix the compound of Formula (II) with inert organic solvent such as THF and propiophenone and then reacting the compound of Formula (II) to pre-mixed reducing agent/titanium salt/solvent mixture such as a Zn/$TiCl_4$/THF mixture to form a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III). Propiophenone can be added at a wt/wt ratio of the compound of Formula (II) to propiophenone ranging from 1:0.01 to 1:5. Inert organic solvent can be at a wt/wt ratio of the compound of Formula (II) to solvent ranging from 1:1 to 1:20. The compound of Formula (II) of step (a) is reacted with titanium salt and a reducing agent in an organic solvent under reflux for NLT 0.5 hours, NLT 1 hour, NLT 2 hours, NLT 4 hours, NLT 6 hours, NLT 8 hours, NLT 12 hours, NLT 24 hours, and NLT 48 hours. In at least one embodiment, the compound of Formula (II) is mixed with THF and propiophenone and reacted to a pre-mixture of Zn, $TiCl_4$, THF and heat under reflux for NLT 2 hours. In another embodiment, the compound of Formula (II) is mixed with THF and propiophenone and reacted to the Zn/THF/$TiCL_4$ mixture as described above and heated under reflux for NLT 8 hours. The reaction mixture may then be allowed to cool to 0 °C to 35 °C.

**[0130]** The mixture of (E)-endoxifen and (Z)-endoxifen in the reaction mixture can be then subjected to extractive purification, distillation and crystallization to afford a purified mixture of (E)-endoxifen and (Z)-endoxifen. The mixture of (E)-endoxifen and (Z)-endoxifen in the reaction mixture can be subject to extractive purification by extracting with inert organic solvents, such as THF and MeTHF, or by addition of salts, such as potassium carbonate,



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ammonium chloride, sodium chloride, sodium hydroxide, to the reaction mixture and extraction with an inert organic solvent, such as THF and MeTHF.

**[0131]** In some embodiments, the reaction mixture is extracted one or more times with ammonium chloride, such as 25% ammonium chloride (1:1 to 1:30 wt/wt); silica (Celite®) bed (1:0.01 to 1:5 wt/wt); and/or solvent, such as THF (1:1 to 1:10 wt/wt). In other embodiments, the reaction mixture is extracted one or more times with potassium carbonate ($K_2CO_3$), such as 40% $K_2CO_3$ (1:1 to 1:10 wt/wt) and MeTHF (1:1 to 1:10 wt/wt). In some embodiments, the E/Z mixture may be further extracted with NaOH, such as 1N NaOH (1:1 to 1:20 wt/wt). In at least one embodiment, NaCl (1:0.1 to 1:0.5 wt/wt) may be added to 1N NaOH for the extraction step.

**[0132]** In some embodiments, the reaction mixture may be further extracted one or more times with THF or MeTHF. In at least one embodiment, the reaction mixture is extracted 3 or more times with MeTHF. The applicants have found MeTHF to be surprisingly suitable for the step of extraction of a mixture of (E)-endoxifen and (Z)-endoxifen, affording higher yields of purified mixtures of (Z)-endoxifen and (E)-endoxifen. In at least one embodiment, the mixture may be still further extracted with 20% sodium chloride (1:1 to 1:10 wt/wt).

**[0133]** The reaction mixture can be next subjected to 2 to 5 rounds of solvent swap and distillation with a suitable solvent, such as ethyl acetate, IPA, and IPA/PPW (1:1 to 1:10 wt/wt with respect to the compound of Formula (III)). Distillation may be carried out under reduced pressure/vacuum at temperatures ranging from 30 °C to 90 °C. In some embodiments, the distillation may be performed at temperature NMT 30 °C, NMT 35 °C, NMT 40 °C, NMT 45 °C, NMT 50 °C, NMT 55 °C, NMT 60 °C, NMT 65 °C, NMT 70 °C, NMT 75 °C, NMT 80 °C and NMT 90 °C, and filtered. The filtered product may be washed with solvents such as EtOAc, IPA, IPA/PPW or n-heptane and then crystallized with crystallization systems such as EtOAc/n-heptane (1:2 v/v) or IPA/n-heptane (1:2.7 v/v) at a wt/wt ratio of a compound of Formula (III) to EtOAc/n-heptane or IPA/n-heptane ranging from 1:1 to 1:20 and dried, for example, at NMT 60 °C, to afford a crystalline solid mixture of (E)-endoxifen and (Z)-endoxifen free bases, compounds of Formula (III).

**[0134]** In yet another aspect, the present disclosure relates to an industrially scalable method of manufacturing or reequilibriating an E/Z-mix having an E/Z ratio of approximately 1:1 (45:55 to 55:45). A suitable reactor may be charged with the compounds of Formula (III) dissolved in an inert organic solvent, such as ethyl acetate, prepared in a McMurry reaction as described above. The compounds of Formula (III) can have an E/Z ratio of 99:1 to 60:40. The mixture can be concentrated at temperatures ranging from 40 °C to 85 °C. In some embodiments, the mixture is concentrated at temperature NMT 75 °C until the volume reaches 5 vol. The mixture is heated to reflux and then cooled to temperatures ranging from 40 °C to 60 °C. In some embodiments, the



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temperature of the mixture is cooled to 50±5 °C. n-heptane, at a ratio of the compounds of Formula (III) to n-heptane ranging from 1:1 to 1:20, may be added slowly to the mixture and the mixture may be then cooled to 0±5 °C. The mixture may be stirred at 0±5 °C for NLT 0.5 hours, such as NLT 1 hour, NLT 2 hours, NLT 4 hours, NLT 8 hours, NLT 12 hours or NLT 24 hours. The mixture may be filtered and washed with ethyl acetate /n-Heptane (1:2 v/v) at a wt/wt ratio of the compounds of Formula (III) to ethyl acetate/n-heptane ranging from 1:1 to 1:10. The wet cake may be dried under reduced pressure to afford E/Z-endoxifen mixture having an E/Z-ratio of approximately 1:1. Drying may be carried out at temperatures ranging from 30 °C to 70 °C. In at some embodiments, the wet cake is dried under reduced pressure or vacuum at NMT 60 °C to afford E/Z-endoxifen mixture having an E/Z-ratio of approximately 1:1 (45:55 to 55:45).

**[0135]** In still another aspect, the compounds of Formula (III) may be further purified or enriched or reequilibrated to obtain substantially pure (Z)-endoxifen as described below.

***Enrichment Purification of (Z)-endoxifen Free Base***

**[0136]** In still another aspect, the present disclosure relates to industrially scalable methods of manufacturing by enrichment and purification (Z)-endoxifen free base. Industrially scalable enrichment and purification of (Z)-endoxifen may be carried out as described herein using the method of Step 3 of exemplary **Schema 1**, and as further described in **Examples 1, 2, 4,** and **9**. The starting mixture of (E)-endoxifen and (Z)-endoxifen used for fractional crystallization can have any E/Z ratio, for example, E/Z ratio ranging from 99:1 to 1:10. In some embodiments, the E/Z-ratio of the starting (E)/(Z)-endoxifen mixtures ranges from 30:70 to 70:30. In some embodiments, the E/Z-ratio of the starting (E)/(Z)-endoxifen mixtures ranges from 99:1 to 1:99. In some embodiments, the E/Z-ratio of the starting (E)/(Z)-endoxifen mixtures is 51:1, 1:1.8 or 1:5.6.

**[0137]** The E/Z-mix can be the compounds of Formula (III) obtained as described above or it can be commercially sourced (for example, from Sigma-Aldrich). A mixture of (E)-endoxifen and (Z)-endoxifen (E/Z-mix) is subjected to fractional crystallization to obtain a first crystalline solid and a first mother liquor enriched with (Z)-endoxifen free base (Example 1). Fractional crystallization is carried using a first solvent which is capable of triturating endoxifen and its derivatives such that (Z)-endoxifen tends to remain in filtrate. Suitable first solvents are those that differentially solubilize the endoxifen isomers, and include, without limitation, ethyl acetate, isopropanol, isopropanol/PPW, acetonitrile, acetonitrile/PPW, and dichloromethane. In some embodiments, the first solvent is ethyl acetate. The first solvent, for example, ethyl acetate, is added at a wt/wt ratio of the compounds of Formula (III) to first solvent ranging from 1:1 to 1:20. In some embodiments, the the compounds of Formula (III) are dissolved in first solvent, and heated to a temperature ranging from 50 °C to 80 °C and cooled to NMT 35 °C.



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**[0138]** It has been a surprising discovery that acidification of the mixture enhances the conversion of (E)-endoxifen to (Z)-endoxifen. Accordingly, in some embodiments, the compounds of formula (III) are pretreated with an acid and then neutralized with a base.

**[0139]** As a non-limiting example, a suitable reactor is charged with the compounds of Formula (III) to which first solvent is added and cooled to 0 °C – 5 °C. Next, an acid such as HCl or TFA may be added slowly. In some embodiments, the acid is added to the E/Z-endoxifen mixture at a wt/wt ratio of the compounds of Formula (III) to acid ranging from 1:1 to 1:5. The reaction mixture may then be heated at temperatures ranging from 50 °C to 70 °C while stirring. In some embodiments, the reaction is carried out under reflux. The reaction may be carried out for NLT 4 hours, such as NLT 6 hours, NLT 12 hours, NLT 24 hours, and NLT 48 hours. The reaction mixture is cooled to 0 °C – 5 °C and neutralized with a neutralizing agent.

**[0140]** In some embodiments, the neutralizing agent is added to the reaction mixture at a wt/wt ratio of the compounds of Formula (III) to neutralizing agent ranging from 1:1 to 1:5. Suitable neutralizing agents include sodium hydroxide, potassium hydroxide, ammonium hydroxide, aminomethylpropanol, and the like. In some embodiments, the neutralizing agent is 8N sodium hydroxide. The pH of the reaction mixture is preferably alkaline. In some embodiments, the pH is $\geq$ 10, such as $\geq$ 11 or $\geq$ 12.

**[0141]** In some embodiments, (Z)-endoxifen is extracted into the organic layer and collected, and the aqueous phase is washed one or more times with the first solvent such as ethyl acetate (added at a wt/wt ratio of the compounds of Formula (III) to first solvent ranging from 1:1 to 1:10). The organic layers are pooled, and washed one or more times with brine (20% NaCl; added at a wt/wt ratio of the compounds of Formula (III) to NaCl ranging from 1:1 to 1:10). The organic layer is treated with activated carbon and filtered over silicon dioxide (Celite®) bed (added at a wt/wt ratio of the compounds of Formula (III) to silica ranging from 1.01 to 1:0.1). The product is washed again one or more times with first solvent (added at a wt/wt ratio of the compounds of Formula (III) to first solvent ranging from 1:1 to 1:10), and distilled. Distillation may be carried out at temperatures ranging from 50 °C to 80 °C. In some embodiments, the temperature may be NMT 75 °C.

**[0142]** The first mother liquor is enriched in (Z)-endoxifen as seen in **Example 1** and **Tables 2** and **3**. In some embodiments, the first mother liquor is enriched by at least 50% as compared to with the E/Z-ratio of the mixture of E-endoxifen and Z-endoxifen. In other embodiments, the first mother liquor is enriched in (Z)-endoxifen by at least 70% as compared to the E/Z-ratio of the mixture of E-endoxifen and Z-endoxifen.

**[0143]** The first mother liquor may be subjected to recrystallization by concentrating the first mother liquor, or swapping out the first solvent from the first mother liquor one or more times to



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obtain second crystalline solid and a second mother liquor (**Table 5**). Recrystallization is carried out using a second solvent for swapping. The second solvent is added at a wt/wt ratio of the compounds of Formula (III) to second solvent ranging from 1:1 to 1:10 to create a slurry. Suitable second solvents include IPA, IPA/PPW, acetone, acetone/MTBE, ethanol, EtOAc, EtOAc/n-heptane. In some embodiments, the second solvent is IPA. Surprisingly, IPA has been found to triturate (Z)-endoxifen into solid fraction at levels higher than EtOAc. Accordingly, in some embodiments, when the first solvent is EtOAc, the second solvent is IPA or IPA/PPW. This is useful in directing (Z)-endoxifen first into the filtrate (first mother liquor) from EtOAc, and then into the solid fraction from IPA or IPA/PPW. In at least one embodiment, the second solvent is IPA/PPW (**Table 7**). In yet another embodiment, the second solvent is acetone/MTBE. The second crystalline solid is (Z)-endoxifen, (Z)-4-(1-(4-(2-(methylamino)ethoxy)phenyl)-2-phenylbut-1-enyl)phenol, the compound of Formula (IV). (Molecular weight 373.49; Molecular formula: $C_{25}H_{27}NO_2$; Melting point 139 °C – 143 °C. The second crystalline solid is ≥70% (Z)-endoxifen, such as ≥75% (Z)-endoxifen, ≥80% (Z)-endoxifen or ≥90% (Z)-endoxifen. In some embodiments, the second crystalline solid is ≥90% (Z)-endoxifen.

**[0144]** The second crystalline solid may optionally be subjected to recrystallization to obtain a third crystalline solid, (Z)-endoxifen (**Table 5**). The third crystalline solid may be ≥90% (Z)-endoxifen, such as ≥91% (Z)-endoxifen, ≥92% (Z)-endoxifen, ≥93% (Z)-endoxifen, ≥94% (Z)-endoxifen, ≥95% (Z)-endoxifen, ≥96% (Z)-endoxifen, ≥97% (Z)-endoxifen, ≥98% (Z)-endoxifen, or ≥99% (Z)-endoxifen. In some embodiments, the third crystalline solid is ≥90% (Z)-endoxifen. In some embodiments, the third crystalline solid is ≥95% (Z)-endoxifen. This optional recrystallization is carried out using a third solvent. The third solvent is selected from the group consisting of ethanol, methanol, ethyl acetate, IPA, IPA/PPW, acetone, acetone/MTBE and EtOAc/n-heptane.

**[0145]** In an aspect, the present disclosure relates to pre-heating first solvent, second solvent, and third solvent prior to use (**Table 2**). In some embodiments, one or more of the first solvent, second solvent, and third solvent can each be independently preheated to a temperature ranging from 40 °C to 80 °C. Fractional crystallization and recrystallization steps may also include steps of distilling at 60 °C to 80 °C and/or cooling the resulting solution to a temperature ranging from 0 °C to 35 °C.

**[0146]** It is to be understood that in some embodiments, first, second, and third crystalline solids as well as the second mother liquor obtained as described above may be further subjected to fractional crystallization and recrystallization as described above one or more time to obtain purified (Z)-endoxifen. It is also to be understood that first, second, and/or third crystalline solids



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obtained may be optionally reprocessed using column chromatography techniques to obtain more (Z)-endoxifen.

**[0147]** In certain embodiments, the industrially scalable methods described herein independently comprises additional steps or procedures (e.g., to remove reaction by-products, or to workup, isolate or purify reaction products) as detailed in examples herein. In some embodiments, the (Z)-endoxifen free base has <2%, <1%, and <0.5% impurity. In other embodiments, the compounds of Formula (III) have <2%, <1%, and <0.5% impurity.

**[0148]** A person of skill in the art will recognize several parameters of the foregoing process that may be varied in order to obtain a desirable outcome. These parameters include for example, the methods and means of purification of reaction components and solvents; the order of addition of said reaction components and solvents to the reaction mixture, duration of reaction of said reaction components and solvents; and temperature and rate of stirring, mixing or agitation of the reaction components and solvents during the reactions.

**[0149]** It was found that the process embodied by the methods herein (also including the particular process steps) fulfills one or more of the following criteria: better stability, safer, simpler, higher yielding and more economical when compared with the known processes for manufacturing compounds of Formula (II), (III) and (IV). (Z)-Endoxifen prepared by the processes disclosed below is stable for at least 9 months at 5 °C and 25 °C at 60% relative humidity (25 °C/60% RH) and for at least 3 moths at 40 °C/75% RH (**Example 9**). Stability at elevated temperatures is indicative of long term stability. Accordingly, (Z)-endoxifen free base prepared by the processes of the present disclosure are stable for at least 6 months, such as for at least 9 months, at least 12 months, or at least 18 months. Further, the process described herein is considered scalable in multi-kilogram operations, making it suitable for commercial production.

***Endoxifen Salts***

**[0150]** In still another aspect, the present application provides endoxifen salts and methods of making endoxifen salts. Endoxifen salts known in the art include hydrochloride (Fauq *et al.*, Bioorg Med Chem Lett. 2010 May 15;20(10):3036-3038) and citrate salts of endoxifen (U.S. Patent No. 9333190; U.S. Publication No. 2010/0112041) and are being evaluated for oral administration to subjects.

**[0151]** In certain embodiments, the present disclosure provides anion salts of endoxifen selected from the group consisting of arecoline, besylate, bicarbonate, bitartarate, butylbromide, citrate, camysylate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthanoate, isethionate, malate, mandelate, mesylate, methylbromide, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate,



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pamaoate (Embonate), pantothenate, phosphate/diphosphate, polygalacuronate, salicylate, stearate, sulfate, tannate, Teoclate, and triethiodide.

**[0152]** In other embodiments, the present disclosure provides cation salts of endoxifen selected from the group consisting of benzathine, clemizole, chloroprocaine, choline, diethylamine, diethanolamine, ethylenediamine, meglumine, piperazine, procaine, aluminum, barium, bismuth, lithium, magnesium, potassium, and zinc.

**[0153]** The endoxifen salts of the present disclosure may be made using any of the compounds of Formulae (I), (II), (III) and (IV), prepared as described above.

***Endoxifen Gluconate***

**[0154]** In some embodiments, the present disclosure provides a gluconate salt of endoxifen, or a chemical equivalent thereof. Accordingly, in at least one embodiment, the endoxifen comprised in a composition of the present disclosure is an endoxifen gluconate or a chemical equivalent thereof. Unless specified otherwise, it will be understood that when referring to endoxifen gluconate herein, its chemical equivalents will also be encompassed.

**[0155]** For the purposes of the present disclosure, chemical equivalents of endoxifen gluconate include all anionic, cationic, and non-ionic reaction complexes between the endoxifen molecule and the gluconate moiety. Such complexes typically react with the hydroxyl group of the endoxifen molecule. The gluconate moiety includes D-gluconic acid, gluconic acid, glycogenic acid, glycan-Δ-lactone, and the like. In some embodiments, the gluconate moiety is a pharmaceutically acceptable gluconate salt. Such salts include calcium gluconate, sodium gluconate, and salts of alkali metals and alkaline earth metals such as potassium gluconate, magnesium gluconate, lithium gluconate, and the like.

**[0156]** Both stereoisomers of gluconate, the D-form and the L-form, are embraced in the present disclosure. In some embodiments, endoxifen gluconate comprised in the compositions of the present disclosure is selected from the group consisting of (Z)-endoxifen D-gluconate, (Z)-endoxifen L-gluconate, (E)-endoxifen D-gluconate, (E)-endoxifen L-gluconate and combinations thereof. In some embodiments, the pharmaceutical composition comprises (Z)-endoxifen L-gluconate. In certain embodiments, the pharmaceutical composition comprises (Z)-endoxifen D-gluconate. The compositions may be present as racemic mixtures, pure stereoisomers (e.g., enantiomers and diastereoisomers), stereo-enriched mixtures and the like unless otherwise indicated. When a particular stereoisomer is shown or named herein, it will be understood by those skilled in the art that minor amounts of other stereoisomers may be present in the compositions of the present disclosure unless otherwise indicated, provided that the utility of the composition as a whole is not eliminated by the presence of such other isomers. Individual isomers may be obtained by numerous methods that are well known in the art, including chiral



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chromatography using a suitable chiral stationary phase or support, or by chemically converting them into diastereoisomers, separating the diastereoisomers by conventional means such as chromatography or recrystallization, then regenerating the original stereoisomer.

**[0157]** The present disclosure also includes methods of making endoxifen gluconate or a chemical equivalent thereof, which includes mixing endoxifen with a gluconate moiety to yield endoxifen gluconate. Methods of making gluconate salts of therapeutic agents are known in the art (for example, U.S. Publication No. 2002/0127665).

**[0158]** In some embodiments, an endoxifen D-gluconate (such as (Z)-endoxifen D-gluconate) salt may be obtained by mixing an ethanolic slurry of the endoxifen (such as (Z)-endoxifen prepared by the methods described above) as the free base with an aqueous solution of D-gluconic acid, obtained by hydrolyzing a 20% w/v solution of D-gluconolactone in water by heating at 70 °C for 15 to 30 min. In some embodiments, a minimum volume of ethanol is used and 5 ml of the aqueous D-gluconic acid solution is added per 1 g of endoxifen free base. Stirring is then continued until a clear solution is obtained. The required volume of this solution is then added to one or more of other excipients to produce formulations in which the "active ingredient" is (Z)-endoxifen D-gluconate or (Z)-endoxifen L-gluconate salt. The salt may be purified by any of the methods known in the art and disclosed herein.

**[0159]** Purified (Z)-endoxifen free base or a mixture of (E)/(Z)-endoxifen is both useful for the purpose of preparation of the endoxifen gluconate salt. A solution of (Z)-endoxifen D-gluconate or (Z)-endoxifen L-gluconate may also be purified from a mixture of (E)/(Z)-endoxifen gluconate salt as described herein by fractional crystallization or recrystallization (**Examples 1-3**) to obtain a solid purified (Z)-endoxifen salt. The solid salt may be stored at -5 °C under $N_2$ until further use.

**[0160]** It will be understood by those skilled in the art that other endoxifen salts can also be used as starting material with gluconate moiety or gluconate salts to yield endoxifen gluconate or chemical equivalents thereof.

**[0161]** Endoxifen gluconate or chemical equivalent thereof may be prepared using (Z)-endoxifen prepared as described above or with starting reactants that are readily available. For example, crude endoxifen HCl (≥98%) and sodium gluconate are readily available from Sigma-Aldrich, USA.

**[0162]** In some embodiments, endoxifen HCl and sodium gluconate are dissolved in a suitable solvent to yield endoxifen gluconate or a chemical equivalent thereof. In at least one embodiment, the composition comprising endoxifen gluconate also comprises endoxifen HCl. In other embodiments, an (E)/(Z)-endoxifen mixture (compounds of Formula (III)) and sodium



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gluconate are dissolved in a suitable solvent to afford endoxifen gluconate or a chemical equivalent thereof.

**[0163]** Suitable solvents for making endoxifen gluconate or chemical equivalents thereof include, but are not limited to, organic solvents such as alcohols, acetones, DMSO, polyethylene glycol, fatty acids and fatty alcohols and their derivatives, hydroxyl acids, pyrrolidones, urea, vegetable oils, animal oils such as fish oils, essential oils, and the like or mixtures thereof, and water-miscible solvents such as water miscible alcohols, dimethylsulfoxide, dimethylformamide, water-miscible ether, for example, tetrahydrofuran, water-miscible nitrile, for example acrylonitrile, a water miscible ketone such as acetone or methyl ethyl ketone, an amide such as dimethylacetamide, propylene glycol, glycerin, polyethylene glycol 400, glycofurol, tetraglycol, and the like, or mixtures thereof.

**[0164]** Water-miscible solvents useful for the preparation of endoxifen gluconate are glycerin, ethanol, propanol, isopropanol, propylene glycol, polyethylene glycols, or mixtures thereof. Additional solvents that are useful include diglycol monoethyl ether (transcutol); alkelene glycols, such as dipropylene glycol, propylene glycol, polyethylene glycols such as PEG 300, 400, 3395, 4450 and the like; dimethyl isosorbide; and dehydrated alcohol. In some embodiments, the solvent is a dehydrated alcohol, such as absolute alcohol. In certain embodiments, the amount of solvent is sufficient to dissolve the endoxifen (free base, salts) and gluconate salts. The concentration of the solvent can also be adjusted as needed. The reaction can be carried out at room temperature and at atmosphere of pressure.

**[0165]** The amount of endoxifen free base or endoxifen salt (such as endoxifen HCl and the like) and gluconate salt (such as and sodium gluconate and the like) that can be used to make endoxifen gluconate or chemical equivalent thereof can vary depending on the amount of reactants used. The resulting endoxifen gluconate will have endoxifen:gluconate moiety at 1:1 ratio.

**[0166]** In some embodiments, the amount of endoxifen or endoxifen salt used for making endoxifen gluconate is from 0.01% to 40% (e.g., from 1% to 10%, or from 3% to 5%) by weight of the total composition (wt/wt). In some embodiments, the gluconate salt used for making endoxifen gluconate is from 0.01% to 40% (wt/wt) (e.g., from 1% to 10% (wt/wt), or from 3% to 5% (wt/wt)). One of skill in the art will be guided by skill and knowledge in the field and the present disclosure, including without limitation, amounts of reactants which are effective to achieve the desired yields.

***Crystalline Forms***

**[0167]** In certain aspects, the present disclosure provides crystalline forms of endoxifen, including crystalline forms of (Z)-endoxifen free base and crystalline forms of mixtures of (E)-



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endoxifen and (Z)-endoxifen. The present disclosure further provides pharmaceutical compositions of endoxifen comprising the crystalline forms described herein. A crystalline form of endoxifen may provide the advantage of bioavailability and stability, suitable for use as an active ingredient in a pharmaceutical composition. Variations in the crystal structure of a pharmaceutical drug substance or active ingredient may affect the dissolution rate (which may affect bioavailability, etc.), manufacturability (e.g., ease of handling, ability to consistently prepare doses of known strength) and stability (e.g., thermal stability, shelf life, etc.) of a pharmaceutical drug product or active ingredient. Such variations may affect the preparation or formulation of pharmaceutical compositions in different dosage or delivery forms, such as solid oral dosage forms including tablets and capsules. Compared to other forms such as non-crystalline or amorphous forms, crystalline forms may provide desired or suitable hygroscopicity, particle size controls, dissolution rate, solubility, purity, physical and chemical stability, manufacturability, yield, and/or process control. Thus, crystalline forms of endoxifen may provide advantages such as: improving the manufacturing process of an active agent or the stability or storability of a drug product form of the compound or an active ingredient, and/or having suitable bioavailability and/or stability as an active agent.

**[0168]** The use of certain solvents and fractional crystallization methods has been found to produce different polymorphic forms of endoxifen, including any one or more of polymorphic Forms I, II and II, which may exhibit one or more favorable characteristics described above. The processes for the preparation of the polymorphs described herein, and characterization of these polymorphs are described in greater detail below.

***Formula III, Form I***

**[0169]** In certain aspects, the present disclosure provides polymorphic Form I of a compound of Formula (III), wherein at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer (i.e., (Z)-endoxifen). In some embodiments, polymorphic Form I exhibits an x-ray powder diffraction (XRPD) pattern substantially as shown in **Fig. 9** or **Fig. 10**. In some embodiments, polymorphic Form I has an XRPD pattern comprising at least two, at least three, at least four, at least five, or at least six of the major peaks as the XRPD pattern substantially as shown in **Fig. 9** or **Fig. 10**.

**[0170]** The term "substantially as shown in" when referring, for example, to an XRPD pattern, includes a pattern that is not necessarily identical to those depicted herein, but that falls within the limits of experimental error or deviations when considered by one of ordinary skill in the art. The relative intensities of XRPD peaks can vary, depending upon the particle size, the sample preparation technique, the sample mounting procedure and the particular instrument employed. Moreover, instrument variation and other factors can affect the two theta ($2\theta$) values.



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Accordingly, when a specified two theta angle is provided, it is to be understood that the specified two theta angle can vary by the specified value ± 0.5°, such as ± 0.4°, ± 0.3°, ± 0.2°, or ± 0.1°. As used herein, "major peak" refers to an XRPD peak with a relative intensity greater than 30%, such as greater than 35%. Relative intensity is calculated as a ratio of the peak intensity of the peak of interest versus the peak intensity of the largest peak in the XRPD pattern.

**[0171]** In certain embodiments, polymorphic Form I is characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta. In some embodiments, polymorphic Form I is characterized by an x-ray powder diffraction pattern comprising peaks at 16.0 ± 0.3°, 18.8 ± 0.3° and 26.5 ± 0.3° two theta. In some embodiments, polymorphic Form I is characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta, and at least one peak selected from 16.0 ± 0.3°, 18.8 ± 0.3° and 26.5 ± 0.3° two theta. In some embodiments, polymorphic Form I is characterized by an x-ray powder diffraction pattern comprising peaks at 12.3 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta. In some embodiments, polymorphic Form I is characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta, and at least one peak selected from 12.3 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta. In some embodiments, polymorphic Form I is characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta, and at least one peak selected from 12.3 ± 0.3°, 16.0 ± 0.3°, 18.8 ± 0.3°, 26.5 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta. In some embodiments, polymorphic Form I is characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta, and peaks at 12.3 ± 0.3°, 16.0 ± 0.3°, 18.8 ± 0.3°, 26.5 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta.

**[0172]** In certain embodiments, the present disclosure provides a composition comprising polymorphic Form I. Greater than 90%, 95% or 99% by weight of the compound of Formula (III) in the composition may be polymorphic Form I. In some embodiments, the composition comprises 0.01 mg to 200 mg of polymorphic Form I. In some embodiments, the composition comprises about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of polymorphic Form I.

***Formula III, Form II***

**[0173]** In certain aspects, the present disclosure provides polymorphic Form II of a compound of Formula (III), wherein the composition comprises the (E)-isomer and the (Z)-isomer of the compound of Formula (III) (i.e., (E)-endoxifen and (Z)-endoxifen) in an E/Z ratio between 0.9 and 1.3, such as about 1.1. In some embodiments, polymorphic Form II exhibits an x-ray powder diffraction (XRPD) pattern substantially as shown in **Fig. 11** or **Fig. 12**. In some embodiments, polymorphic Form II has an XRPD pattern comprising at least two, at least three, at least four, at



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least five, or at least six of the major peaks as the XRPD pattern substantially as shown in **Fig. 11** or **Fig. 12**.

**[0174]** In certain embodiments, polymorphic Form II is characterized by an x-ray powder diffraction pattern comprising major peaks at 7.0 ± 0.3°, 11.9 ± 0.3°, 14.0 ± 0.3° and 18.4 ± 0.3° two theta. In some embodiments, polymorphic Form II is characterized by an x-ray powder diffraction pattern comprising a peak at 22.0 ± 0.3° two theta. In some embodiments, polymorphic Form II is characterized by an x-ray powder diffraction pattern comprising major peaks at 7.0 ± 0.3°, 11.9 ± 0.3°, 14.0 ± 0.3° and 18.4 ± 0.3° two theta and a peak at 22.0 ± 0.3° two theta. In some embodiments, polymorphic Form II is characterized by an x-ray powder diffraction pattern comprising at least one peak selected from 6.6 ± 0.3°, 13.3 ± 0.3° and 20.0 ± 0.3° two theta. In some embodiments, polymorphic Form II is characterized by an x-ray powder diffraction pattern comprising major peaks at 7.0 ± 0.3°, 11.9 ± 0.3°, 14.0 ± 0.3° and 18.4 ± 0.3° two theta, and at least one peak selected from 6.6 ± 0.3°, 13.3 ± 0.3° and 20.0 ± 0.3° two theta. In some embodiments, polymorphic Form II is characterized by an x-ray powder diffraction pattern comprising major peaks at 7.0 ± 0.3°, 11.9 ± 0.3°, 14.0 ± 0.3° and 18.4 ± 0.3° two theta, and at least one peak selected from 6.6 ± 0.3°, 13.3 ± 0.3°, 20.0 ± 0.3° and 22.0 ± 0.3° two theta. In some embodiments, polymorphic Form II is characterized by an x-ray powder diffraction pattern comprising major peaks at 7.0 ± 0.3°, 11.9 ± 0.3°, 14.0 ± 0.3° and 18.4 ± 0.3° two theta, and peaks at 6.6 ± 0.3°, 13.3 ± 0.3°, 20.0 ± 0.3° and 22.0 ± 0.3° two theta.

**[0175]** In certain embodiments, the present disclosure provides a composition comprising polymorphic Form II. Greater than 90%, 95% or 99% by weight of the compound of Formula (III) in the composition may be polymorphic Form II. In some embodiments, the composition comprises 0.01 mg to 200 mg of polymorphic Form II. In some embodiments, the composition comprises about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of polymorphic Form II.

***Formula III, Form III***

**[0176]** In certain aspects, the present disclosure provides polymorphic Form III of a compound of Formula (III), wherein the composition comprises the (E)-isomer and the (Z)-isomer of the compound of Formula (III) (i.e., (E)-endoxifen and (Z)-endoxifen) in an E/Z ratio between 0.9 and 1.3, such as about 1.1. In some embodiments, polymorphic Form III exhibits an x-ray powder diffraction (XRPD) pattern substantially as shown in **Fig. 13**. In some embodiments, polymorphic Form III has an XRPD pattern comprising at least two, at least three, at least four, at least five, or at least six of the major peaks as the XRPD pattern substantially as shown in **Fig. 13**.

**[0177]** In certain embodiments, polymorphic Form III is characterized by an x-ray powder diffraction pattern comprising major peaks at 11.9 ± 0.3°, 13.9 ± 0.3°, 17.1 ± 0.3° and 17.7 ±



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0.3° two theta. In some embodiments, polymorphic Form III is characterized by an x-ray powder diffraction pattern comprising a peak at 25.3 ± 0.3° two theta. In some embodiments, polymorphic Form III is characterized by an x-ray powder diffraction pattern comprising major peaks at 11.9 ± 0.3°, 13.9 ± 0.3°, 17.1 ± 0.3° and 17.7 ± 0.3° two theta and a peak at 25.3 ± 0.3° two theta. In some embodiments, polymorphic Form III is characterized by an x-ray powder diffraction pattern comprising at least one peak selected from 18.2 ± 0.3°, 22.5 ± 0.3° and 26.8 ± 0.3° two theta. In some embodiments, polymorphic Form III is characterized by an x-ray powder diffraction pattern comprising major peaks at 11.9 ± 0.3°, 13.9 ± 0.3°, 17.1 ± 0.3° and 17.7 ± 0.3° two theta, and at least one peak selected from 18.2 ± 0.3°, 22.5 ± 0.3° and 26.8 ± 0.3° two theta. In some embodiments, polymorphic Form III is characterized by an x-ray powder diffraction pattern comprising major peaks at 11.9 ± 0.3°, 13.9 ± 0.3°, 17.1 ± 0.3° and 17.7 ± 0.3° two theta, and at least one peak selected from 18.2 ± 0.3°, 22.5 ± 0.3°, 25.3 ± 0.3° and 26.8 ± 0.3° two theta. In some embodiments, polymorphic Form III is characterized by an x-ray powder diffraction pattern comprising major peaks at 11.9 ± 0.3°, 13.9 ± 0.3°, 17.1 ± 0.3° and 17.7 ± 0.3° two theta, and peaks at 18.2 ± 0.3°, 22.5 ± 0.3°, 25.3 ± 0.3° and 26.8 ± 0.3° two theta.

**[0178]** In certain embodiments, the present disclosure provides a composition comprising polymorphic Form III. Greater than 90%, 95% or 99% by weight of the compound of Formula (III) in the composition may be polymorphic Form III. In some embodiments, the composition comprises 0.01 mg to 200 mg of polymorphic Form III. In some embodiments, the composition comprises about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of polymorphic Form III.

***Endoxifen Free Base Compositions***

**[0179]** In one aspect, the present disclosure provides stable (Z)-endoxifen free base or salts thereof, and compositions comprising (Z)-endoxifen free base or salts thereof. In some embodiments, the pharmaceutical composition comprises endoxifen predominantly as (Z)-endoxifen free base.

**[0180]** In certain embodiments, compositions may comprise endoxifen as at least 0.1%, at least 0.2%, at least 0.3%, at least 0.4%, at least 0.5%, at least 1%, at least 5%, at least 10%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, at least 99.99%, or 100% of (Z)-endoxifen free base wt/wt of total endoxifen in the composition. In at least one composition, the composition comprises ≥90% of (Z)-endoxifen free base wt/wt of the total endoxifen in the composition. In another embodiment, the composition comprises ≥95% of (Z)-endoxifen free base wt/wt of the total endoxifen in the composition. In yet another embodiment, the



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compositions comprise ≥96%, ≥97%, ≥98%, ≥99%, or ≥99.5% of (Z)-endoxifen free base wt/wt of the total endoxifen in the composition.

**[0181]** In other embodiments, compositions comprising endoxifen comprise 0.01% to 20%, 0.05% to 15%, or 0.1% to 10% of (Z)-endoxifen wt/wt or w/v of the composition. In at least one embodiment, the compositions comprising endoxifen comprise 0.01% to 20% of (Z)-endoxifen wt/wt or w/v of the composition. In various other embodiments, the compositions comprising endoxifen comprise 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0,09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 2%, 3%, 4%, 5%, 10%, or 20% of (Z)-endoxifen wt/wt of the composition.

**[0182]** In an aspect, the compositions comprising (Z)-endoxifen further comprise (E)-endoxifen. In some embodiments, the endoxifen in the composition has a ratio of (E)-endoxifen to (Z)-endoxifen (E/Z-ratio) of 1:99; 5:95; 10:90, 15:85; 20:80, 25:75; 30:70; 40:70, 45:55; 50:50; 55:45; 60:40; 65:45; and 70:30. In other embodiments, compositions comprise endoxifen having E/Z-ratio ranging from 10:90 to 70:30. In still other embodiments, compositions comprise endoxifen having E/Z-ratio ranging from 45:55 to 55:45.

**[0183]** Unless specifically referred to by the prefix (Z), (E) or (E/Z), endoxifen used generally without a prefix is used herein to include to any or all endoxifen isoforms.

***Endoxifen Salt Compositions***

**[0184]** In some embodiments, the present disclosure provides compositions comprising salts of endoxifen. In some embodiments, the present disclosure provides compositions comprising pharmaceutically acceptable salts of endoxifen. Provided herein in certain embodiments are compositions comprising 1%, 5%, 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.99% or 100% of endoxifen salt.

**[0185]** In some embodiments, the salt is selected from the group consisting of arecoline, besylate, bicarbonate, bitartarate, butylbromide, citrate, camysylate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthanoate, isethionate, malate, mandelate, mesylate, methylbromide, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamaoate (Embonate), pantothenate, phosphate/diphosphate, polygalacuronate, salicylate, stearate, sulfate, tannate, Teoclate, triethiodide, benzathine, clemizole, chloroprocaine, choline, diethylamine, diethanolamine, ethylenediamine, meglumine, piperazine, procaine, aluminum, barium, bismuth, lithium, magnesium, potassium, and zinc. In some embodiments, the salt is endoxifen gluconate. Endoxifen gluconate can be selected from the group consisting of (Z)-endoxifen D-gluconate, (E)-endoxifen D-gluconate, (Z)-endoxifen L-gluconate, (E)-endoxifen L-gluconate or a combination thereof.



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**[0186]** In some embodiments, a composition comprising endoxifen gluconate is comprised of 10% to 100% of (Z)-endoxifen D-gluconate on a wt/wt basis of total endoxifen gluconate in the composition. In some embodiments, a composition comprising endoxifen gluconate is comprised of 10% to 100% of (Z)-endoxifen L-gluconate on a wt/wt basis of total endoxifen in the composition.

**[0187]** In other embodiments, a composition comprising endoxifen gluconate is comprised of 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.75%, 99.99%, or 100% of (Z)-endoxifen D-gluconate or (Z)-endoxifen L-gluconate with respect to total endoxifen gluconate. In some embodiments, the compositions comprise at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, or at least 99.99% of (Z)-endoxifen D-gluconate, (Z)-endoxifen L-gluconate or a combination thereof.

**[0188]** Provided herein in some embodiments are compositions comprising (Z)-endoxifen D-gluconate and (E)-endoxifen D-gluconate. (Z)-endoxifen D-gluconate and (E)-endoxifen D-gluconate may be present in the compositions at ratios ranging from 10:90 to 99:1 wt/wt or v/v respectively. In some embodiments, the ratio of (Z)-endoxifen D-gluconate to (E)-endoxifen D-gluconate is (wt/wt or v/v) 10:90 to 99:1 (e.g., 45:55, 50:50, 60:40, 70:30, 80: 20, 90:10; 91:9; 92:8; 93:7; 94:8; 95:5, 96:4, 97:3, 98:2, 99:1, 99.5:0.5, or 99.99:0.01) respectively. In certain embodiments, the ratio of (Z)-endoxifen D-gluconate to (E)-endoxifen D-gluconate (wt/wt or v/v) is 90:10; 91:9; 92:8; 93:7; 94:8; 95:5, 96:4, 97:3, 98:2, 99:1, 99.5:0.5, or 99.99:0.01. One of skill in the art will recognize that other combinations of endoxifen gluconate isomers are encompassed in the present disclosure.

**[0189]** In some embodiments, a composition comprising endoxifen gluconate comprises 0.01%, 0.05%, 0.01%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19% or 20% endoxifen gluconate (wt/wt) or (w/v) of the composition. In some embodiments, a composition comprising endoxifen gluconate comprises 0.01%, 0.05%, 0.01%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19% or 20% (Z)-endoxifen gluconate (wt/wt) or (w/v) of the composition.

**[0190]** The compounds and compositions of the present disclosure can be administered to a subject in need thereof by any route known in the art, including without limitation, oral, parenteral, topical, and intraductal delivery. Accordingly, compositions disclosed herein are formulated to be compatible with the intended route of administration.



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**[0191]** In some embodiments, the compositions comprising endoxifen further comprise an excipient. Such an excipient can be compatible with the intended route of administration.

***Endoxifen Polymorph Compositions***

**[0192]** In one aspect, the present disclosure provides compositions comprising one or more polymorphic forms, such as Form I, Form II, or Form II described herein, of endoxifen. In some embodiments, the pharmaceutical composition comprises endoxifen predominantly as polymorph Form I. In some embodiments, the pharmaceutical composition comprises endoxifen predominantly as polymorph Form II. In some embodiments, the pharmaceutical composition comprises endoxifen predominantly as polymorph Form III.

**[0193]** In certain embodiments, a composition comprises endoxifen as at least 0.1%, at least 0.2%, at least 0.3%, at least 0.4%, at least 0.5%, at least 1%, at least 5%, at least 10%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, at least 99.99%, or 100% of a single polymorphic Form of endoxifen, such as Form I, Form II, or Form III, wt/wt of total endoxifen in the composition. In at least one composition, the composition comprises ≥90% of a single polymorphic Form of endoxifen, such as Form I, Form II, or Form III, wt/wt of the total endoxifen in the composition. In another embodiment, the composition comprises ≥95% of a single polymorphic Form of endoxifen, such as Form I, Form II, or Form III, wt/wt of the total endoxifen in the composition. In yet another embodiment, the composition comprises ≥96%, ≥97%, ≥98%, ≥99%, or ≥99.5% of a single polymorphic Form of endoxifen, such as Form I, Form II, or Form III, wt/wt of the total endoxifen in the composition. When a particular percentage by weight of endoxifen is a single polymorphic form, the remainder of endoxifen in the composition is some combination of amorphous endoxifen and/or one or more polymorphic forms of endoxifen excluding the single polymorphic form. When the polymorphic endoxifen is defined as one particular form of endoxifen, the remainder is made up of amorphous endoxifen and/or one or more polymorphic forms other than the particular form specified. Examples of single polymorphic forms include Forms I, II and III of endoxifen, as well as descriptions of a single polymorphic form characterized by one or more properties as described herein.

**[0194]** In other embodiments, a composition comprising endoxifen comprises 0.01% to 20%, 0.05% to 15%, or 0.1% to 10% of a single polymorphic Form of endoxifen, such as Form I, Form II, or Form III, wt/wt or w/v of the composition. In at least one embodiment, the composition comprising endoxifen comprises 0.01% to 20% of a single polymorphic Form of endoxifen, such as Form I, Form II, or Form III, wt/wt or w/v of the composition. In various other embodiments, the composition comprising endoxifen comprises 0.01%, 0.02%, 0.03%,



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0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0,09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 2%, 3%, 4%, 5%, 10%, or 20% of a single polymorphic Form of endoxifen, such as Form I, Form II, or Form III, wt/wt of the composition. In an aspect, a composition comprising a single polymorphic Form of endoxifen, such as Form I, Form II, or Form III, further comprises a second polymorphic Form of endoxifen.

***Oral Formulations***

**[0195]** In some embodiments, a pharmaceutical composition of the present disclosure is formulated for oral delivery. Compositions intended for oral use may be prepared in solid or fluid unit dosage forms. In at least some embodiments, the compositions are formulated for oral delivery as tablets, caplets, capsules, pills, powders, troches, elixirs, suspensions, syrups, wafers, chewing gums, dragees, lozenges, and the like.

**[0196]** In some embodiments, the oral dosage forms are solid oral dosage forms such as tablets, caplets, and capsules. In some embodiments, the capsule is a hard capsule or a soft capsule. In other embodiments, the capsule is a gelatin capsule, gelatin-free capsule, a "cap-in-cap" capsule, alginate capsule, hydroxypropylmethyl cellulose (HPMC) capsule, a polyvinyl alcohol (PVA) capsule, a hypromellose capsule, or a starch capsule.

***Excipients***

**[0197]** In some embodiments, an oral composition comprising (Z)-endoxifen or a salt thereof further comprises one or more excipients. In some embodiments, an oral composition comprising endoxifen or a polymorph thereof further comprises one or more excipients. Accordingly, compositions designed for oral administration can be made with an inert or active excipient or with an edible carrier as disclosed herein.

**[0198]** In various embodiments, the composition provided herein comprises from about 1% to about 99.99%, about 5% to about 95%, about 5% to about 90%, about 10% to about 80%, about 15% to about 70%, about 20% to about 60%, from about 30% to about 95%, from about 50% to about 90%, from about 60% to about 90%, from about 60% to about 80%, or from about 70% to about 80% by weight of one or more excipients. In certain embodiments, the composition provided herein comprises about 99.99%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, or about 50% by weight of one or more excipients. In certain embodiments, the composition provided herein comprises about 99.99%, about 99%, about 98%, about 97%, about 96%, about 95%, about 94%, about 93%, about 92%, about 91%, about 90%, about 89%, about 88%, about 87%, about 86%, or about 85% by weight of one or more excipients. In certain embodiments, the composition provided herein comprises about 85%, about 84%, about 83%, about 82%, about 80%, about 79%, about 78%, about 77%,

about 76%, about 75%, about 74%, about 73%, about 72%, about 71%, about 70%, about 69%, about 68%, about 67%, about 66%, or about 65% by weight of one or more excipients. In certain embodiments, the composition provided herein comprises about 55%, about 54%, about 53%, about 52%, about 51%, about 50%, about 49%, about 48%, about 47%, about 46%, or about 45% by weight of one or more excipients. In certain embodiments, the composition provided herein comprises about 30%, about 29%, about 28%, about 27%, about 26%, about 25%, about 24%, about 23%, about 22%, about 21%, or about 20% by weight of one or more excipients.

**[0199]** Examples of excipients that can be used in the compositions formulated for oral administration are provided herein and can include, but are not limited to, one or more of bulking agents, binders, fillers, disintegrating agents, lubricants, glidants, control release agents, enteric coatings, film-forming agents, plasticizers, colorants, sweetners, flavoring agents and the like, or any combination thereof.

**[0200]** Binders suitable for use in the pharmaceutical compositions provided herein include, but are not limited to, sucrose, starches such as corn starch, potato starch, or starches such as starch paste, pregelatinized starch, and starch 1500, PEG 6000, methocel, walocel HM, Luvitec, Luvicaparolactam, Avicel, SMCC, UNIPURE, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, polyvinyl pyrrolidone, hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof. Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL PH 101, AVICEL PH 103 AVICEL RC 581, AVICEL PH 105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, Pa.), and mixtures thereof. In some embodiments, the binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose. Suitable anhydrous or low moisture excipients or additives include AVICEL PH 103 and Starch 1500 LM.

**[0201]** Examples of fillers suitable for use in the pharmaceutical compositions provided herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), sugars such as dextrose, sucrose, lactose, a salt such as calcium carbonate, calcium phosphate, sodium carbonate, sodium phosphate, starches, microcrystalline cellulose, powdered cellulose, cellulosic bases such as methyl cellulose, carboxymethyl cellulose dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pregelatinized starch, and mixtures thereof.

**[0202]** One or more binder or filler in compositions is typically present in from about 10% to about 99% (wt/wt) of the composition or the dosage form. In some embodiments, binders and/or



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fillers in a composition comprise about 15% to 99%, about 20% to 60%, about 25% to 55%, about 30% to 50%, about 35% to 60%, about 50% to 99% (wt/wt) of the composition.

**[0203]** Disintegrants can be used in the compositions to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms. In some embodiments, the disintegrant is deep in the oral solid dosage form to delay disintegration. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

**[0204]** Typical compositions comprise from 0.5% to 15% (wt/wt) of disintegrant. In some embodiments, compositions comprise from 1% to 5% (wt/wt) of disintegrant in the composition. In another embodiment, the disintegrant is 1% to 25%, 2% to 20%, 5% to 15%, 8% to 12%, or about 10% (wt/wt) of the composition.

**[0205]** Disintegrants that can be used in the pharmaceutical compositions provided herein include, but are not limited to, agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

**[0206]** Lubricants that can be used in the pharmaceutical compositions provided herein include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, magnesium stearate or potassium stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, Md.), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, Tex.), CAB O SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, Mass.), Q7-9120 (Dow Corning), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than 1% (wt/wt) of the compositions or dosage forms into which they are incorporated. In yet another embodiment, the lubricant is 0.1% to 3%, such as 0.5% to 1% (wt/wt), of the composition.

**[0207]** Plasticizers may be added to control the softness or pliability of oral dosage forms such as shell of a capsule, caplet or a tablet and thus, may improve the mechanical properties of the pH-sensitive materials of the coatings on the oral dosage forms. Suitable plasticizers, include,



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without limitation, petroleum oils (for e.g., a paraffinic process oil, a naphthenic process oil, and an aromatic process oil), squalene, squalane, plant oils, (e.g., olive oil, camelia oil, castor oil, tall oil, and a peanut oil), silicon oils, dibasic acid esters, (e.g., dibutyl phthalate, and dioctyl phthalate), liquid rubbers (e.g., polybutene and a liquid isoprene rubber), liquid fatty acid esters (e.g., isopropyl myristate ISM), hexyl laurate, diethyl sebacate, and diisopropyl sebacate, triethyl citrate, triacetin, diethylene glycol, polyethylene glycols, polypropylene glycol, phthalates, sorbitol, glycol salicylate, crotaminton, and glycerin or mixtures thereof. The amount of plasticizer may vary depending upon the chemical composition of the pharmaceutical preparation. In one embodiment, the at least one plasticizer is sorbitol, dimethyl isosorbide, or a glycerol. In another embodiment, the plasticizer is 1% to 10%, such as 3% to 5% (wt/wt), of the composition.

**[0208]** Examples of glidants include, but are not limited to, colloidal silicone dioxide, cellulose, calcium phosphate, di or tri-basic and the like.

**[0209]** As an example of sweetners or sweetening agents include sucrose, saccharin, dextrose, maltose, sugar substitutes, aspartame, xylitol, mannitol, cyclamate, sucralose, maltitol, sorbitol, acesulfame K and the like.

**[0210]** Examples of flavoring agents include peppermint, methyl salicylate, peppermint, spearment, methyl salicylate, raspberry, red berry, strawberry, pineapple, orange, cherry and the like.

**[0211]** Compositions formulated for oral delivery as disclosed herein, for example, tablets, caplets, and capsules, may be coated with one or more enteric coating agent, control release agent or film forming agent to control or delay disintegration and absorption of the compositions comprising endoxifen or salts thereof in the gastrointestinal tract and thereby provide a sustained action over a longer period of time. Accordingly, in some embodiments, the tablet can be an enteric tablet, the caplet can be an enteric caplet, or the capsule can be an enteric capsule. The enteric tablets, enteric caplets, or enteric capsules of the present disclosure may be prepared by techniques known in the art.

**[0212]** Pharmaceutical preparations disclosed herein may comprise a control release agent. Examples of control release agent suitable for use include, without limitation, pH-dependent polymers, acid-insoluble polymers, methyl acrylate-methacrylic acid copolymers, cellulose acetate phthalate (CAP), cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate (hypromellose acetate succinate), polyvinyl acetate phthalate (PVAP), methyl methacrylate-methacrylic acid copolymers, shellac, cellulose acetate trimellitate, sodium alginate, zein, waxes, including synthetic waxes, microcrystalline waxes, paraffin wax, carnauba wax, and beeswax; polyethoxylated castor oil derivatives,



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hydrogenated oils, glyceryl mono-, di- tribenates, glyceryl monostearate, glyceryl distearate, long chain alcohols, such as stearyl alcohol, cetyl alcohol, and polyethylene glycol; and mixtures thereof. In some embodiments, a time delay material such as glyceryl monostearate or glyceryl distearate may be used. In other embodiments, the controlled release reagent is a digestible waxy substance such as hard paraffin wax.

**[0213]** In some embodiments, compositions may comprise one or more of pH-dependent polymers such as acid insoluble polymers. The pH-dependent polymers become increasingly permeable above pH 5.0 but are impermeable at pH below 5.0 whereas acid insoluble polymers become soluble in neutral to weakly alkaline conditions. Such control release polymers target upper small intestines and colon. Non-limiting examples of acid-insoluble polymers include cellulose acetate phthalate, cellulose acetate butyrate, hydroxypropyl methyl cellulose phthalate, algenic acid salts such as sodium or potassium alginate, shellac, pectin, acrylic acid-methylacrylic acid copolymers (commercially available under the tradename EUDRAGIT® L and EUDRAGIT® S from Rohm America Inc., Piscataway, NJ as a powder or a 30% aqueous dispersion; or under the tradename EASTACRYL®, from Eastman Chemical Co., Kingsport, TN, as a 30% dispersion). Additional examples include EUDRAGIT® L100-55, EUDRAGIT® L30D-55, EUDRAGIT® L100, EUDRAGIT® L100 12,5, EUDRAGIT® S100, EUDRAGIT® S12,5, EUDRAGIT® FS 30D, EUDRAGIT® E100, EUDRAGIT® E 12,5, and EUDRAGIT® PO. In at least one embodiment, the composition comprises EUDRAGIT® L100-55. EUDRAGIT® RS and RL and EUDRAGIT®NE and NM are also useful polymers for the purpose of this disclosure. In some embodiments, the composition comprises EUDRAGIT ® L30D 55. In another embodiment, the preparation comprises EUDRAGIT® FS 30D. One of skill in the art will recognize that at least some acid insoluble polymers listed herein will also be biodegradable.

**[0214]** For time delay or delayed-release pharmaceutical preparations of oral dosage forms, glyceryl monostearate, glyceryl distearate, and acid-insoluble polymers, for example polymethacrylate pH-sensitive polymer-based coatings can be used, (e.g., as coating material, i.e., enteric coating agents, for enteric coating of capsules, caplets, and tablets). Commercial sources for delayed-release oral dosage forms are available, for example DRCaps made of hypromellose (HPMC) from Capsugel, USA. Such delayed-release oral dosage forms forms are acid-resistant and can resist acidity as seen in stomach for at least 30 min, such as for at least 1 hour, for at least 1.5 hour, or for at least 2 hours. Such delayed release oral dosage forms can release at least 40%, at least 50%, at least 60%, at least 70%, at least 80% or at least 90% of the endoxifen or salts thereof in the intestines (small intestines, large intestine/colon etc).



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**[0215]** In an aspect of the present disclosure, the enteric tablets, enteric caplets, and enteric capsules may be uncoated. Hard uncoated capsules with enteric capability using intrinsically enteric capsule technology (for example, EnTrinsic Drug Delivery available from Capsugel) are suitable for the purpose of the present disclosure.

**[0216]** In various embodiments, the enteric tablet is a hard tablet made with free-flowing powder of (Z)-endoxifen or a salt thereof. In various embodiments, the enteric capsule is a capsule made with free-flowing powder of (Z)-endoxifen or a salt thereof. In various embodiments, the enteric tablet is a hard tablet made with free-flowing powder of endoxifen or a polymorph thereof. In various embodiments, the enteric capsule is a capsule made with free-flowing powder of endoxifen or a polymorph thereof.

**[0217]** In some embodiments, the enteric capsule is a non-animal based capsule, such as a hypromellose capsule (for example, commercially available self-gelling Vcaps, VCaps Plus, VCaps enteric, other enteric capsules made using Xcellodose, ENCODE colonic delivery technology, and EnTrinsic™ drug delivery technology from Capsugel). Other technologies known in the art and available commercially (for example, Qualicaps, USA, Nutrascience, USA, etc.) for the formulating enteric forms of oral solid dosage forms can also be utilized. In at least one embodiment, the capsule is an API-in-capsule, meaning that the (Z)-endoxifen free base or salts thereof is filled neat into the capsule. In such API-in-capsule oral dosage forms, the active ingredient, (Z)-endoxifen or salts thereof can be free flowing powders or micronized powders. When the dosage form is a capsule, in at least one embodiment, the capsule can be a seamless capsule or a banded capsule.

**[0218]** Rapid absorption and bioavailability of the anti-cancer therapeutics such as endoxifen that can further reduce the cancer growth rate are highly desirable. In an aspect, the present disclosure provides that the compositions are formulated for certain pharmacokinetic (PK) properties.

**[0219]** In one aspect, rapid achievement of maximal and steady state plasma levels of endoxifen is a particular aspect of the present disclosure. The present disclosure provides compositions that achieve a maximal plasma level of endoxifen ranging within 2 to 30 hours, within 3 to 20 hours, within 2 to 10 hours or within 4 to 8 hours after administration of the compositions. Accordingly, in some embodiments, time to maximal (peak) plasma level of endoxifen ranges from 2 to 10 hours after administration of the composition. In some embodiments, the time to maximal plasma level of endoxifen ranges from 4 to 8 hours after administration of a composition disclosed herein.

**[0220]** Rapid achievement of steady-state plasma levels of endoxifen is also highly desirable, and a composition of the present disclosure may provide a plasma level of endoxifen in a subject



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administered the composition comprising a polymorphic form of endoxifen, (Z)-endoxifen or a salt thereof that rapidly achieves steady state. Steady state plasma levels can be achieved from day 7 to day 21. In some embodiments, the steady state plasma levels can be achieved by day 7 (Figure 5) upon daily administration of a composition disclosed herein.

**[0221]** In an aspect, the present disclosure provides that circulating endoxifen released from a composition disclosed herein can be cleared faster than tamoxifen. Terminal elimination half life of tamoxifen is said to be 5-7 days (Jordan C. Steroids. 2007 Nov; 72(13): 829–842) and peak concentration time of tamoxifen is approximately 5 hours post-dose. Endoxifen released from a composition disclosed herein can have a terminal elimination half-life ranging from 30 to 60 hours, significantly lower than tamoxifen. In some embodiments, the mean half -life ranges from 40 to 53 hours. The mean ratio of $AUC_{24hr}$ (Day 21)/$AUC_{0\text{-}inf}$ (Day1) typically ranges from 0.7 to 1.2 for compositions comprising 1 mg to 4 mg (Z)-endoxifen, or a salt thereof. Thus, accumulation of endoxifen released from a compositions disclosed herein does not significantly vary over continued treatment.

**[0222]** In another aspect, a composition described herein achieves absorption of endoxifen that is therapeutically effective.

**[0223]** Area under Curve $AUC_{(0\text{-}24hr)}$ ("$AUC_{24hr}$") describes the total exposure of the subject to a drug from time of dosing (0 hr) over a 24 hour period. Compositions comprising (Z)-endoxifen or a salt thereof typically achieve mean ($AUC_{24hr}$) of 150 hr*ng/mL to 600 hr*ng/mL on Day 1 of initial (first) dose of a composition comprising 1 mg to 4 mg of (Z)-endoxifen. Compositions comprising (Z)-endoxifen or a salt thereof typically achieve mean $AUC_{24hr}$ of 400 hr*ng/mL to 2500 hr*ng/mL on Day 21 of initial (first) dose of compositions comprising 1 mg to 4 mg of (Z)-endoxifen.

**[0224]** $AUC_{0\text{-}inf}$ ("$AUC_{0\text{-}inf}$"), a time-averaged concentration of drug circulating in the body fluid analyzed (normally plasma, blood or serum), describes the total exposure of the subject to a drug. The present disclosure provides that the exposure of a subject to endoxifen ($AUC_{0\text{-}inf}$) can be dose proportional. In some embodiments, $AUC_{0\text{-}inf}$ ranges from 200 hr*ng/mL to 10000 hr*ng/mL. In other embodiments, the $AUC_{0\text{-}inf}$ ranges from 300 hr*ng/mL to 8000 hr*ng/mL. In certain embodiments, the $AUC_{0\text{-}inf}$ ranges from 400 hr*ng/mL to 6000 hr*ng/mL over the dosing range of 1 mg to 4 mg of (Z)-endoxifen (for example, see **Table 17**).

**[0225]** Dissolution of the oral dosage forms disclosed herein is tested by the dissolution tests according to the current methods of USP 711. In some embodiments, the oral dosage forms disclosed herein are protected from the acidic environment of the stomach and do not dissolve for at least 2 hours, at least 3 hours, at least 4 hours, at least 5 hours, 6 hours, at least 7 hours or at least 8 hours. In at least one embodiment, the oral dosage forms do not release endoxifen for at



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least 6 hours. In another embodiment, the oral dosage forms do not release endoxifen or a salt thereof for at least 2 hours.

**[0226]** In other embodiments, less than 10% of (Z)-endoxifen in a composition comprising endoxifen or a salt thereof disclosed herein is released in the stomach ater 2 hours after administration; or wherein less than 40% of (Z)-endoxifen is released in the stomach after 4 hours of administration; or less than 50% of (Z)-endoxifen is released in the stomach after 6 hours of administration, as tested by a method of USP 711.

**[0227]** In another embodiment, a composition disclosed herein releases in the stomach less than 10% of (Z)-endoxifen in 2 hours after administration, less than 40% of (Z)-endoxifen in 4 hours after administration; and less than 50% of (Z)-endoxifen in 6 hours after administration, as tested by a method of USP 711.

**[0228]** In yet another embodiment, the composition is formulated to release in the small intestine, such that at least 10% of endoxifen is released after 4 hours after administration; or at least 30% of endoxifen is released after 6 hours after administration; or at least 40% of endoxifen is released after 7 hours after administration; or at least 50% of endoxifen is released after 8 hours after administration, as tested by a method of USP 711.

**[0229]** In a further embodiment, as determined by a method of USP 711, the composition is formulated to release in the colon at least 50% of endoxifen after 8 hours after administration.

**[0230]** In still further embodiments, the composition is formulated to release in the colon at least 20% of endoxifen after 4 hours after administration; at least 40% of endoxifen after 6 hours after administration; at least 60% of endoxifen after 7 hours after administration; or at least 80% of endoxifen after 8 hours after administration.

**[0231]** An oral dosage form can be of any shape suitable for oral administration, such as spherical (0.05 - 5 mL), oval (0.05 - 7 mL), ellipsoidal, pear (0.3 - 5 mL), cylindrical, cubic, regular and/or irregular shaped. An oral dosage form may be of any size suitable for oral administration, for example, size 0, size 2, and the like.

**[0232]** One of skill in the art will further recognize that compositions disclosed herein may comprise one or more of the excipients known in the art and disclosed herein in any combination appropriate for a desired formulation or preparation. Additional excipients may generally be found in Remington's The Science and Practice of Pharmacy, Meade Publishing Co., United States Pharmacopeia/National Formulary. One of skill in the art will be able to select suitable excipients necessary for the preparation of the formulations and appropriate dosage forms compatible with the route of administration based on his or her skill and knowledge in the art and the disclosures made herein. In all cases, the ultimate dosage form should be sterile and stable under the conditions of manufacture and storage.



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**[0233]** For formulations of the solid dosage compositions disclosed herein, as the water activity ($A_w$) is less than 0.75, testing Total Aerobic Plate Count (TAC) and USP indicator organism is typically not necessary. The publication, "Microbial Bioburden on Oral Solid Dosage Form," by Jose E. Martinez, Pharmaceutical Technology, February 2002, pages 58 to 70, is hereby incorporated by reference in its entirety.

**[0234]** Furthermore, since formulations of the compositions disclosed herein also have water activity of less than 0.75, then detailed microbial testing is typically not necessary. TAC is an estimation of the total viable aerobic microbes present in a sample of raw material, in-process material, or finished product. Samples are analyzed in accordance with the most current USP 39 <61>, "Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests."

**[0235]** Acceptable TAC for oral solid dosage forms (OSDFs) are established for the formulation of the inventive compositions in terms of alert and action levels, which could be 1000 cfu g/mL, and 10,000 cfu g/mL, respectively. A TAC that is 20,000 cfu g/mL may be considered unacceptable.

**[0236]** For other formulations, such as liquid or fluid formulations with water activity of less than 0.75, Tests for Specified Microorganisms (*S. aureus*, *Ps. aeruginosa*, Salmonella, *C. albicans*, Clostridia, *E. coli* and Bile Tolerant Gram negative bacteria) in compliance with USP Guidelines Chapter 62 may not need to be performed.

***Methods of Use***

**[0237]** Compounds of Formulae (I), (II), (III), and (IV), endoxifen salts disclosed herein, polymorphic forms of endoxifen disclosed herein, and compositions comprising them may be used in the manufacture of medicaments for use in the treatment of a subject in need thereof, for example, subjects having or at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both.

**[0238]** The compositions of the present disclosure may be used as a primary therapy, as a part of a neo-adjuvant therapy (to primary therapy), or as part of adjuvant therapy regimen, where the intention is to ameliorate or cure a subject having or at risk of having a hormone-dependent breast disorder, hormone-dependent reproductive tract disorder, or both.

**[0239]** In certain embodiments, the disorder is a hormone-dependent breast disorder. In other embodiments, the disorder is hormone-dependent reproductive tract disorder. In still other embodiments, the subject has both a hormone-dependent breast disorder and a hormone-dependent reproductive tract disorder. In some embodiments, the hormone dependent disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer or vulvar cancer.



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**[0240]** In some embodiments, the breast disorder is increased breast density. For example, the breast disorder is a class B (formerly Class II), class C (formerly class III) or class D (formerly class IV) breast density.

**[0241]** In some embodiments, the hormone-dependent breast disorder or hormone-dependent reproductive tract disorder is precocious puberty. In other embodiments, the hormone-dependent breast disorder or hormone-dependent reproductive tract disorder is McCune-Albright Syndrome.

**[0242]** In some embodiments, the breast disorder is gynecomastia. In some embodiments, gynecomastia is presented secondarily to an underlying disease. Accordingly in some embodiments, the subject also has underlying disease selected from the group consisting of prostate cancer, cirrhosis and liver disease, male hypogonadism, hyperthyroidism, renal failure and in patients undergoing hemodialysis, or type I diabetes mellitis. In certain embodiments, the subject has prostate cancer as the underlying disease, wherein the subject has or is at risk of having gynecomastia.

**[0243]** In certain embodiments, the breast cancer is DCIS, LCIS, ILC, IDC, MIC, inflammatory breast cancer, ER-positive (ER+) breast cancer, HER2+ breast cancer, adenoid cystic (adenocystic) carcinoma, low-grade adenosquamatous carcinoma, medullary carcinoma, mucinous (or colloid) carcinoma, papillary carcinoma, tubular carcinoma, metaplastic carcinoma, or micropapillary carcinoma. In at least one embodiment, a single breast cancer tumor may be a combination of the foregoing or be a mixture of invasive and in situ cancer.

**[0244]** The present disclosure contemplates the use of the compounds and compositions disclosed herein at various stages in tumor development and progression, including the treatment of advanced and/or aggressive neoplasms, i.e., overt disease in a subject that is not amenable to cure by local modalities of treatment such as surgery or radiotherapy, metastatic disease, or locally advanced disease. Accordingly in some embodiments, the breast cancer is a pre-cancer, an early stage cancer, a non-metastatic cancer, a pre-metastatic cancer, or a locally advanced cancer. In at least one embodiment, the breast disorder is metastatic cancer. In some embodiments, the subject further has prostate cancer.

**[0245]** Current choice for therapeutics for such disorders remains tamoxifen, despite serious adverse effects, poor patient compliance and resistance to the drug due to low plasma endoxifen levels seen subjects. Such subjects may have low endoxifen levels upon dosing with tamoxifen for any number of reasons, such as having CYP gene mutations, for example, in CYP2D6, CYP3A4, or CYP2C9, making them unable to metabolize tamoxifen to its active metabolite, endoxifen, or low or dysfunctional estrogen receptor preventing (or decreasing) sufficient tamoxifen uptake, for other reasons yet to be identified. Reported therapeutic levels of plasma



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tamoxifen in subjects dosed with 20 mg of oral tamoxifen is ≥ 30 nM ((Lyon et al. Genet Med. 2012 Dec;14(12):990-1000). Notwithstanding the mechanism underlying the low plasma endoxifen in a subject, the compositions of the present disclosure are useful for any condition wherein a subject has low endoxifen or the subject has or is at a risk of having hormone-dependent breast disorder or hormone-dependent reproductive tract disorder. Therefore, the compositions of the present disclosure can be particularly important in the treatment of tamoxifen-resistant, hormone-dependent breast disorders or hormone-dependent reproductive tract disorders.

**[0246]** Provided herein in certain embodiments are patient populations for whom the pharmaceutical compositions are particularly useful. The compositions of the present disclosure are also particularly important in the treatment of tamoxifen-refractory subjects with hormone-dependent breast disorders or hormone-dependent reproductive tract disorders. Accordingly, in some embodiments, the compositions disclosed herein are useful for the treatment of tamoxifen refractory or tamoxifen resistant subjects having or at risk of having hormone-dependent breast disorders, hormone-dependent reproductive tract disorders, or both. In some embodiments, compositions comprising an endoxifen salt, such as endoxifen gluconate, administered to such subject at the doses disclosed herein, will be advantageous.

**[0247]** Further, Donneyong et al. have shown that drug interactions between tamoxifen and selective serotonin reuptake inhibitors (SSRI) drugs like Prozac and Paxil (paroxetine) exist and are detrimental to breast cancer subjects (Donneyong et al. BMJ 2016;354:i5014). The SSRI drugs reduce or stop liver metabolism of tamoxifen to endoxifen in subjects on SSRI drugs. Thus, provided herein in certain embodiments are patient populations being treated or to be treated with SSRI drugs that would be benefitted by treatment with compositions of the present disclosure.

**[0248]** Compositions disclosed herein administered orally maintain the subject's plasma endoxifen at steady state levels greater than 30 nM, for example, at levels ranging from 30 nM to 80 nM or at levels ranging from 30 nM to 300 nM. In some embodiments, the plasma steady state endoxifen levels are maintained at >40 nM. Maintenance of such a plasma endoxifen at steady state levels greater than 30 nM is advantageous in that the likelihood of recurrence (relapse) of hormone-dependent breast disorders or hormone-dependent reproductive tract disorders, particularly breast cancer, at plasma endoxifen levels lower than 30 nM is reduced. It is particularly advantageous for subjects that are poor-metabolizers of tamoxifen (with plasma endoxifen levels lower than 16 nM), intermediate metabolizers of tamoxifen (with plasma endoxifen levels lower than 27 nM) to be dosed with a composition disclosed herein. It also advantageous for subjects being treated or to be treated with antidepressant drugs such as SSRI



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drugs such as citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), paroxetine (Paxil, Pexeva), sertraline (Zoloft), vilazodone (Viibryd) and the like, for example, a subject having or likely to have depression.

**[0249]** Whether a subject is tamoxifen-refractory may be determined by dosing a subject with an initial dosage of tamoxifen and determining the subject's plasma endoxifen steady state level. Plasma endoxifen steady state levels in a subject dosed with tamoxifen serves as a biomarker for the tamoxifen-refractory subjects. The plasma endoxifen levels (acute and/or steady state) may be determined by obtaining from the subject a test sample, which may be blood sample, collected from the subject after dosing the subject with tamoxifen. Plasma or serum may be obtained from blood samples for testing the biomarker endoxifen levels. The initial dosage may comprise administering tamoxifen daily for at least 1 day, 2 days, 3 days, 15 days, 1 week, 2 weeks, 4 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months. The subject may also be administered with a first composition comprising tamoxifen daily for at least 1 day, 2 days, 3 days, 15 days, 1 week, 2 weeks, 4 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years or 10 years.

**[0250]** A subject's plasma endoxifen steady state level may be determined by measuring endoxifen in a test sample. The subject's plasma endoxifen steady state levels are compared to a reference plasma endoxifen level. For the purposes of the present disclosure, the reference plasma level is 30 nM. If the subject's plasma endoxifen level is determined to be lower than 30 nM, then the subject is defined as tamoxifen-refractory. Such a tamoxifen-refractory subject who has or who may be at risk of having a hormone-dependent breast disorder or hormone-dependent reproductive tract disorder is treated by administering to the subject an oral composition comprising (Z)-endoxifen or a salt thereof disclosed herein, or a polymorphic form of endoxifen disclosed herein. In some embodiments, the composition administered to such a subject comprises (Z)-endoxifen free base. In some embodiments, the composition administered to such a subject comprises a polymorphic form, such as Form I, Form II or Form III, of endoxifen. In other embodiments, the composition administered to such a subject comprises endoxifen gluconate selected from the group consisting of (Z)-endoxifen D-gluconate, (Z)-endoxifen L-gluconate, (E)-endoxifen D-gluconate, (E)-endoxifen L-gluconate, or a combination thereof. In other embodiments, the composition comprising endoxifen is endoxifen HCl or endoxifen citrate. The present disclosure also contemplates that a subject's plasma endoxifen levels are tracked or monitored periodically or as necessary. If required, a subject who has been administered an initial dosage of tamoxifen may have his or her plasma endoxifen steady state levels adjusted by administering a composition comprising endoxifen on an ongoing basis based on the test results.



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**[0251]** In some embodiments, the subject's tamoxifen-refractory status may be determined by determining the subject's tamoxifen-metabolites profile which is compared with a reference tamoxifen-metabolite profile as seen in control or normal subjects. Subjects with low plasma endoxifen levels in subject's tamoxifen-metabolite profile as compared to the reference tamoxifen-metabolite profile are administered an oral composition comprising endoxifen or a salt thereof. Such compositions may comprise synthetically prepared endoxifen.

**[0252]** The plasma endoxifen may be measured by any of method known in the art. The levels of plasma endoxifen in test sample may be determined based on subject's genes, DNA, RNA, protein, tamoxifen-metabolite profile or a combination thereof. The tamoxifen-metabolites profile can include at least tamoxifen, 4-OHT, N-desmethyltamoxifen, and/or endoxifen. In some embodiments, the level of plasma endoxifen and/or tamoxifen-metabolite profile in the test sample is measured by High Performance Liquid Chromatography (HPLC), Gas Chromatography Mass Spectrometry (GC-MS), Liquid Chromatography Mass spectrometry (LC-MS), Liquid Chromatography Tandem Mass spectrometry (LC-MS/MS), immunohistochemistry (IHC), polymerase chain reaction (PCR), quantitative PCR (qPCR), and the like. In some embodiments, the tamoxifen-metabolites profile is predicted based on the subject's genetic composition. In some embodiments, the subject's CYP genotype includes, without limitation, analysis of CYP2D6, CYP3A4, CYP2C9 genes. In some embodiments, subject's estrogen receptor levels may be analyzed. In other embodiments, the determination of plasma endoxifen may be done by a third party laboratory.

**[0253]** Accordingly, provided herein are methods of maintaining in a subject in need thereof a plasma endoxifen a level greater than 30 nM by administering to the subject a composition comprising endoxifen or a salt thereof. In some embodiments, the subject's plasma endoxifen level is maintained at a steady state level greater than 30 nM. In some embodiments, the subject's plasma endoxifen levels are maintained at a steady state level ranging from 30 nM to 300 nM (for example, from 30 nM to 200 nM, or from 30 nm to 80 nM). In some embodiments, the subject's plasma endoxifen levels are maintained at a steady state level >40 nM.

**[0254]** In another aspect, the subjects may have their test samples tested for their biomarker profile that may be indicative or monitoring a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both. Such biomarkers are known in the art and include, by way of non-limiting examples, biomarkers such as CYP2D6, BRCA-1, BRCA-2, ER, PR, Her2, uPA, PAI, Tf, p53, Ki67, cytokeratins, cancer tumor antigens, and other biomarkers measured by Mammaprint, OncotypeDx, PAM50, EndoxPredict, MammoStrat, and other diagnostic and predictive tests. A subject with biomarker profile indicating that the subject has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive



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tract disorder, or both can be administered a composition disclosed herein. In one aspect, the present disclosure provides a method of treating a subject having or at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, comprising determining a subject's tamoxifen-refractory or tamoxifen-resistant status and administering to the subject a composition described herein.

**[0255]** In some aspects, provided herein are methods of treating a tamoxifen-refractory or tamoxifen-resistant subject, the method comprising administration to the subject a composition comprising endoxifen, or a salt or polymorph thereof.

**[0256]** In some embodiments disclosed herein are methods of treating a tamoxifen-refractory subject having or at risk for having a hormone-sensitive breast disorder, a hormone-sensitive reproductive tract disorder, or both, the method comprising administration to the subject an oral composition comprising endoxifen, or a salt thereof, wherein the subject has plasma endoxifen level of less than 30 nM, less than 25 nM, less than 20 nM, less than 15 nM, less than 10 nM, less than 5 nM or less than 1 nM. In certain embodiments, the composition comprising endoxifen salt is endoxifen gluconate, endoxifen HCl, or endoxifen citrate. In other embodiments, an oral solid dosage form comprising at least 90% (Z)-endoxifen or a salt thereof is administered. In other embodiments, an oral solid dosage form comprising at least 90% of polymorph Form I, Form II, or Form III of endoxifen is administered.

**[0257]** Also provided herein are methods of treating a tamoxifen-refractory subject, the method comprising: (a) determining or having determined plasma endoxifen level in a test sample obtained from the subject; (b) comparing or having compared or having determined the level of plasma endoxifen in the test sample with a reference plasma endoxifen level; (c) determining or having determined a reduced level of plasma endoxifen in the test sample as compared to the reference plasma endoxifen level; and (d) administering a composition comprising endoxifen or a salt or polymorph thereof to the subject. The administration of a composition comprising endoxifen or a salt or polymorph thereof maintains the levels of plasma endoxifen in the subject at steady state levels greater than 30 nM. In some embodiments, the levels of plasma endoxifen in the subject are maintained at steady state levels ranging from 30 nM to 80 nM.

**[0258]** Provided herein are methods of treating a subject having or at risk of having a hormonal dependent breast disorder or a hormonal dependent reproductive tract disorder, the method comprising: (a) administering to the subject a first composition comprising tamoxifen; (b) determining or having determined the level of plasma endoxifen in a test sample obtained from the subject; (c) determining or having determined reduced level of plasma endoxifen in test sample as compared to a reference level of plasma endoxifen; and (d) administering an oral composition disclosed herein to the subject. The subject may be administered with the first



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composition comprising tamoxifen daily for at least 1 day, 2 days, 3 days, 15 days, 1 week, 2 weeks, 4 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years or 10 years. In some embodiments, administration of the oral composition comprising endoxifen or a salt or polymorph thereof maintains the subject's plasma endoxifen at levels greater than 30 nM. In other embodiments, administration of the oral composition comprising endoxifen or a salt or polymorph thereof maintains the subject's plasma endoxifen at levels ranging from 30 nM to 300 nM (e.g., from 30 nM to 200 nM, or from 30 nM to 80 nM). In some embodiments, the subject is administered an oral composition comprising (Z)-endoxifen D-gluconate, (Z)-endoxifen L-gluconate, (E)-endoxifen D-gluconate, (E)-endoxifen L-gluconate, or a combination thereof. In other embodiments, the oral composition comprising endoxifen salt is endoxifen HCl or endoxifen citrate. In some embodiments, the subject is administered an oral composition comprising polymorph Form I, Form II or Form III of endoxifen disclosed herein.

**[0259]** Provided herein are methods of treating a subject with a hormone-dependent breast disorder or hormone-dependent reproductive tract disorder, the method comprising: (a) dosing the subject with a first composition comprising tamoxifen; (b) determining or having determined the subject's tamoxifen-metabolites profile in a test sample obtained from the subject; (c) determining a reduced level of subject's plasma endoxifen based on the subject's tamoxifen-metabolites profile to compared to a level of reference plasma endoxifen in a reference tamoxifen-metabolites profile; and (d) administering an oral composition comprising endoxifen or a salt or polymorph thereof to the subject. In certain embodiments, the composition comprising endoxifen is endoxifen gluconate, endoxifen HCl, or endoxifen citrate. In some embodiments, the composition comprises polymorph Form I, Form II, or Form III of endoxifen.

**[0260]** Provided herein are methods for adjusting plasma endoxifen levels in a subject being treated for hormone-dependent breast disorder or hormone-dependent reproductive tract disorder who has one or more CYP2D6 or CYP3A4 mutations or has previously administered with initial dosage of tamoxifen, and who has a plasma endoxifen level less than reference plasma endoxifen level, the method comprising: (a) measuring the subject's plasma endoxifen level after initial dosage of tamoxifen; (b) comparing the subject's plasma endoxifen levels to the reference plasma endoxifen level; (c) administering an oral composition comprising endoxifen or a salt or polymorph thereof to the subject to maintain the subject's plasma endoxifen level at levels greater than 30 nM. In some embodiments, administration of the oral composition comprising endoxifen or a salt or polymorph thereof maintains the subject's plasma endoxifen at levels ranging from 30 nM to 300 nM (e.g., from 30 nM to 200 nM, or from 30 nM to 80 nM). In some embodiments, the subject's plasma endoxifen level is maintained at a steady state level. The subject may be administered with initial dosage of tamoxifen daily for at least 1 day, 2 days, 3



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days, 15 days, 1 week, 2 weeks, 4 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months.

**[0261]** Provided herein are methods for adjusting the level of plasma endoxifen in a subject being treated for hormone-dependent breast disorder or hormone-dependent reproductive tract disorder who has been previously administered an initial dosage of tamoxifen and who has a level of plasma endoxifen less than 30 nM, the method comprising: (a) measuring the level of plasma tamoxifen-metabolite endoxifen of the subject after the initial dosage of tamoxifen; (b) comparing the plasma level of tamoxifen-metabolite endoxifen to the reference level for normal tamoxifen-metabolite endoxifen level; (c) administering an adjusting dosage of a composition comprising synthetically prepared endoxifen, wherein the dosage of synthetically prepared endoxifen is sufficient to maintain the subject's plasma endoxifen at a level greater than 30 nM. In some embodiments, administration of the second composition comprising a synthetically prepared endoxifen maintains the subject's plasma endoxifen at levels ranging from 30 nM to 300 nM (e.g., from 30 nM to 200 nM, from 30 nM to 80 nM). In some embodiments, the steps (a) to (c) may be repeated until the subject exhibits a desired plasma level of endoxifen.

**[0262]** In an aspect, the present disclosure contemplates a method of treating a subject having or at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, the method comprising resection of breast tissue of the subject or administering radiotherapy to the subject and administering an oral composition comprising endoxifen or a salt or polymorph thereof disclosed herein. In another aspect, the present disclosure contemplates a method of treating a subject having or at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, the method comprising administering an oral composition disclosed herein prior to resection of breast tissue of the subject or administering radiotherapy to the subject.

**[0263]** Dosage to be administered to a subject will be usually in a unit dosage form. Examples of ranges for endoxifen in each dosage unit form are from 0.01 mg to 200 mg. Dosage shall generally be an effective amount and equivalent, on a molar basis, of the pharmacologically active (Z)-free form produced by a dosage formulation upon metabolic release of the active free drug to achieve its desired pharmacological and physiological effects. In some embodiments, the compositions comprising endoxifen or an endoxifen salt or polymorph are administered to the subject at a dose of 0.01 mg to 200.0 mg. In other embodiments, the oral compositions comprising endoxifen or an endoxifen salt or polymorph are administered to the subject at a dose of 1 mg to 200.0 mg. In some embodiments, the oral compositions comprising endoxifen or an endoxifen salt or polymorph are administered to the subject at a dose of 0.01 mg, 0.05 mg, 0.1 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.5 mg, 2.0 mg, 4.0 mg, 6 mg, 8 mg, 10 mg, 20 mg, 40



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mg, 50 mg, 100 mg or 200 mg per unit dose. In certain embodiments, the oral compositions comprising at least 90% (Z)-endoxifen (wt/wt) of endoxifen are administered at a dose of 1 mg, 2.0 mg, 4.0 mg 6 mg, 8 mg, 10 mg, 20 mg, 40 mg, 50, 100 mg or 200 mg per unit dose. In some embodiments, the compositions comprising endoxifen gluconate are administered at a dose ranging from 0.01 to 20 mg. In some embodiments, a composition comprising (Z)-endoxifen D-gluconate is administered at 0.5 mg, 1 mg, 2 mg 4.0 mg, 6 mg, 8 mg, 10 mg, 20 mg, 40 mg, 50 mg, 100 mg, and 200 mg per unit dose. In some embodiments, a composition comprising 1 mg of (Z)-endoxifen D-gluconate is administered. In other embodiments, a composition comprising 1 mg of (Z)-endoxifen L-gluconate is administered. In yet other embodiments, a composition comprising 2 mg of (Z)-endoxifen D-gluconate and (E)-endoxifen D-gluconate is administered. In certain embodiments, an oral composition comprising at least 90% of a polymorph, such as polymorph Form I, Form II or Form III, of endoxifen (wt/wt) is administered at a dose of 1 mg, 2.0 mg, 4.0 mg 6 mg, 8 mg, 10 mg, 20 mg, 40 mg, 50, 100 mg or 200 mg per unit dose. In some embodiments, a composition comprising a polymorphic form, such as Form I, Form II or Form III, of endoxifen is administered at a dose ranging from 0.01 to 20 mg.

**[0264]** Breast cancer growth rate studies have shown, using mammographic screening of subjects with breast cancer, that the breast cancer growth rate in the 25$^{th}$ percentiles of women ages 50 to 59 indicate an unmet need for fast exposure of the subject to therapeutics (Weeden-Fekjaer et al. Breast Cancer Research200810:R41). Rapid absorption and bioavailability of the anti-cancer therapeutics such as endoxifen that can further reduce the cancer growth rate is highly desirable.

**[0265]** In one aspect, rapid achievement of maximal and steady state plasma levels of endoxifen is a particular aspect of the present disclosure. The present disclosure provides that administration of compositions disclosed herein to a subject achieves a maximal plasma level of endoxifen ranging within 2 to 30 hours, within 3 to 20 hours, within 2 to 10 hours or within 4 to 8 hours after administration of the compositions. Accordingly, in some embodiments, time to maximal (peak) plasma level of endoxifen ranges from 2 to 10 hours after administration of the compositions. In some embodiments, the time to maximal plasma level of endoxifen ranges from 4 to 8 hours after administration of composition disclosed herein.

**[0266]** Rapid achievement of steady-state plasma levels of endoxifen is also highly desirable. Plasma levels of endoxifen in a subject administered with a composition disclosed herein comprising (Z)-endoxifen or a salt or polymorph thereof rapidly achieves steady state. Steady state plasma levels can be achieved from day 7 to day 21. In some embodiments, the steady state plasma levels can be achieved by day 7 (Figure 5) following daily administration of a composition disclosed herein.



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**[0267]** In an aspect, the present provides that circulating endoxifen released from compositions disclosed herein can be cleared faster than tamoxifen. Terminal elimination half life of tamoxifen is said to be 5-7 days (Jordan C. Steroids. 2007 Nov; 72(13): 829–842) and peak concentration time of tamoxifen is approximately 5 hours post-dose. Endoxifen released from a composition disclosed herein can have a terminal elimination half-life ranging from 30 to 60 hours, significantly lower than tamoxifen. In some embodiments, the mean half -life ranges from 40 to 53 hours. Mean Ratio of $AUC_{24hr}$ (Day 21)/$AUC_{0\text{-}inf}$ (Day1) typically ranges from 0.7 to 1.2 for compositions comprising 1 mg to 4 mg (Z)-endoxifen or a salt or polymorph thereof. Thus, accumulation of endoxifen released from the compositions disclosed herein do not significantly vary over continued treatment.

**[0268]** In another aspect, the present disclosure provides that administration of compositions disclosed herein achieve absorption of endoxifen that is therapeutically effective.

**[0269]** Area under Curve $AUC_{(0\text{-}24hr)}$ ("$AUC_{24hr}$") describes the total exposure of the subject to a drug from time of dosing (0 hr) over a 24 hour period. Compositions comprising (Z)-endoxifen or a salt thereof typically achieve mean ($AUC_{24hr}$) of 150 hr*ng/mL to 600 hr*ng/mL on Day 1 of initial (first) dose of compositions comprising 1 mg to 4 mg of (Z)-endoxifen. Compositions comprising (Z)-endoxifen or salts thereof typically achieve mean $AUC_{24hr}$ of 400 hr*ng/mL to 2500 hr*ng/mL on Day 21 of initial (first) dose of compositions comprising 1 mg to 4 mg of (Z)-endoxifen.

**[0270]** $AUC_{(0\text{-}inf)}$ ("$AUC_{0\text{-}inf}$"), a time-averaged concentration of drug circulating in the body fluid analyzed (normally plasma, blood or serum), describes the total exposure of the subject to a drug. The present provides that the exposure of subjects to endoxifen ($AUC_{0\text{-}inf}$) can be dose proportional. In some embodiments, $AUC_{0\text{-}inf}$ ranges from 200 hr*ng/mL to 10000 hr*ng/mL. In other embodiments, the $AUC_{0\text{-}inf}$ ranges from 300 hr*ng/mL to 8000 hr*ng/mL. In certain embodiments, the $AUC_{0\text{-}inf}$ ranges from 400 hr*ng/mL to 6000 hr*ng/mL over the dosing range of 1 mg to 4 mg of (Z)-endoxifen (for example, see **Table 17**).

**[0271]** A healthcare professional, such as an attending physician, may adjust the dosing regimen based on the pharmacokinetic profile of the composition in the subject.

**[0272]** In one aspect, the compositions of the disclosure can be used alone or in a combination therapy. For example, compositions disclosed herein may be used in combination with one or more therapeutic agents as part of primary therapy, neoadjuvant therapy, or an adjuvant therapy. It is an aspect of the present disclosure that the compositions of the disclosure can be used in combination with other therapies such as surgery and radiation as neo-adjuvant or adjuvant therapy. Combinations of the compositions may act to improve the efficacy of the therapeutic agents, and therefore can be used to improve standard cancer therapies. For example, when a



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subject has prostate cancer and is on bicalutamide or enzalutamide therapy for the treatment of prostate cancer, the subject is likely to develop gynecomastia a result of the therapy. The compositions disclosed herein can be administered as a combination therapy to the subject having prostate cancer in order to prevent and/or treat gynecomastia. As another example, a subject with ER+/Her2+ positive breast cancer would be on a combination therapy with trastuzumab or other oncology drugs such as anti-neoplastics or immunotherapy, and a composition disclosed herein can be used to treat such a subject with ER+/Her2+ positive breast cancer. Accordingly, in some embodiments, the compositions further comprise bicalutamide, enzalutamide or anticancer drugs such as trastuzumab, antineoplastics such as capecitabine (Xeloda), carboplatin (Paraplatin), cisplatin (Platinol), cyclophosphamide (Neosar), docetaxel (Docefrez, Taxotere), doxorubicin (Adriamycin), pegylated liposomal doxorubicin (Doxil), epirubicin (Ellence), fluorouracil (5-FU, Adrucil), gemcitabine (Gemzar), methotrexate (multiple brand names), paclitaxel (Taxol), protein-bound paclitaxel (Abraxane), vinorelbine (Navelbine), eribulin (Halaven), ixabepilone (Ixempra), and ATP-cassette binding protein inhibitors.

**[0273]** In another aspect, a composition disclosed herein may comprise therapeutic agents that increase bioavailability of endoxifen in a subject. P-glycoprotein (P-gp, ABCB1) is a highly efficient drug efflux pump expressed in brain, liver, and small intestine, but also in cancer cells, that affects pharmacokinetics and confers therapy resistance for many anticancer drugs. Accordingly, in some embodiments, the compositions further comprise inhibitors of ATP-binding cassette (ABC family) transporters, such as inhibitors of breast cancer resistance protein (BCRP protein) and P-gp. Several inhibitors of BCRP protein and P-Gp are known in the art. For example, inhibitors of BCRP protein include cyclosporine, omeprazole, pantoprazole, saquinavir, and tacrolimus.

**[0274]** Non-limiting examples of P-gp inhibitors include first generation inhibitors such as Verapamil, cyclosporin A, reserpine, quinidine, yohimbine, tamoxifen and toremifene, second generation inhibitors such as Dexverapamil, dexniguldipine, valspodar (PSC 833), and Dofequidar fumarate (MS-209), third generation P-gp inhibitors such as Cyclopropyldibenzosuberane zosuquidar (LY335979), laniquidar (R101933), mitotane (NSC-38721), biricodar (VX-710), elacridar (GF120918/GG918), ONT-093, tariquidar (XR9576), and HM30181 and anti-P-gp monoclonal antibodies such as MRK-16).

**[0275]** The present disclosure additionally provides for therapeutic kits containing one or more of the compositions for use in the treatment of a subject having or at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both. The kits of the present disclosure may include an oral composition disclosed herein, a sealed container for housing the composition, and instructions for use of the orally administered composition. In an



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aspect, the kits of the present disclosure can include a second therapeutic agent. Such a second therapeutic agent may be bicalutamide, enzalutamide or an anticancer drug such as trastuzumab, antineoplasitcs such as capecitabine (Xeloda), carboplatin (Paraplatin), cisplatin (Platinol), cyclophosphamide (Neosar), docetaxel (Docefrez, Taxotere), doxorubicin (Adriamycin), pegylated liposomal doxorubicin (Doxil), epirubicin (Ellence), fluorouracil (5-FU, Adrucil), gemcitabine (Gemzar), methotrexate (multiple brand names), paclitaxel (Taxol), protein-bound paclitaxel (Abraxane), vinorelbine (Navelbine), eribulin (Halaven), ixabepilone (Ixempra), and ATP-binding cassette (ABC transporter) inhibitors such as P-gp inhibitors.

***Exemplary Compositions***

**[0276]** Exemplary, non-limiting compositions are provided below. As mentioned above, percentages (%) refer to amounts by weight based upon the total weight of the composition (wt/wt). The sum of the different components of the composition adds up to 100% (wt/wt) of the total composition. The at least 90% (≥90%) (Z)-endoxifen free base refers to the percent weight of (Z)-endoxifen isomer as compared to the total weight of endoxifen in any composition.

**[0277]** In an aspect, the present disclosure relates to industrially scalable processes for manufacturing (Z)-endoxifen, compounds of Formula (III), the compound of Formula (II), and salts and polymorphs thereof.

**[0278]** In an aspect, the present disclosure relates to an industrially scalable process for manufacturing (Z)-endoxifen, comprising the steps of: (a) reacting a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), to 6N HCL (1:1 to 1:5 wt/wt) in EtOAc (1:1 to 1:20 wt/wt), (b) neutralizing with 8N NaOH (1:1 to 1:20 wt/wt); (c) washing one or more times with EtOAc (1:1 to 1:10 wt/wt); (d) extracting with 20% NaCl (1:1 to 1:5 wt/wt); (e) reacting with activated carbon (1:0.01 to 1:1); (f) washing one or more times with IPA (1:1 to 1:10 wt/wt) and extracting with MeOH/PPW (1:1 to 1:10 wt/wt); wherein the wt/wt is with respect to the mixture of (E)-endoxifen and (Z)-endoxifen, e.g., compounds of Formula (III).

**[0279]** In an aspect, the present disclosure relates to an industrially scalable process for manufacturing a mixture of (E)-endoxifen and (Z)-endoxifen (compounds of Formula (III)), comprising: (a) reacting the compound of Formula (II) with propiophenone in THF (4.4 wt/wt); (b) preparing a solution of $TiCl_4$ (1.4 wt/wt) and Zn (0.9 wt/wt) in THF (8.9 wt/wt); and (c) reacting the compound of Formula (II) of step (a) with $TiCl_4$ and Zn in THF from step (b) to form a mixture of (E)-endoxifen and (Z)-endoxifen; wherein wt/wt is with respect to the compound of Formula (II).

**[0280]** In an aspect, the present disclosure relates to an industrially scalable process for manufacturing a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), comprising one or more steps of : (a) extraction with 25% ammonium chloride (1:20 wt/wt) and



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silica (Celite) (1:1 wt/wt); (b) one or more washes with THF (1:1 to 1:5 wt/wt); (c) one or more washes with 20% sodium chloride (1:3 wt/wt); (c) distillation with EtOAc (1:4.5 wt/wt); and (d) crystallization with (1:2 v/v) EtOAc/n-heptane (1:3.8 wt/wt); wherein the wt/wt is with respect to the compound of Formula (II).

**[0281]** In an aspect, the present disclosure relates to an industrially scalable process for manufacturing a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), further comprising one or more steps of: (a) extraction one or more times with 40% $K_2CO_3$ (1:2 wt/wt); (b) extraction with 1N NaOH (1:10 wt/wt) and MeTHF (1:1 to 1:10 wt/wt); (c) two more extractions with MeTHF (1:1 to 1:20 wt/wt); (d) extraction with 20% sodium chloride (1:5 wt/wt); (e) distillation with IPA (1:4.5 wt/wt); and (f) crystallization with (1:2.7 v/v) IPA/n-heptane (1:3.4 wt/wt); wherein the wt/wt is with respect to the compound of Formula (II).

**[0282]** In an aspect, the present disclosure relates to an industrially scalable process for manufacturing the compound of Formula (II), comprising the steps of: (a) reacting the compound of Formula (I) (1 equiv.) with DIPEA (3 wt/wt) in THF (4.9 wt/wt); (b) adding 1-chloroethyl chloroformate (3.3 wt/wt); (c) distilling one to five times with methanol (4.0 wt/wt); (d) distilling with methanol (3.2 wt/wt); (e) reacting with methanol (3.2 wt/wt)/6N HCl (4 wt/wt); and (f) neutralizing with 8N NaOH (5 wt/wt); and wherein wt/wt is with respect to the compound of Formula (I).

**[0283]** In an aspect, the present disclosure relates to (Z)-endoxifen, (E)-endoxifen, compounds of Formula (III), and the compound of Formula (II), and salts thereof, prepared according to processes described herein. In an aspect, the present disclosure relates to (Z)-endoxifen prepared according to a process disclosed herein, wherein the (Z)-endoxifen is stable at ambient temperature for at least 6 months, at least 9 months, at least 12 months, or at least 18 months.

**[0284]** In another aspect, the (Z)-endoxifen free based prepared in accordance with the processes disclosed herein have <1% impurity. In still another aspect, the (E)/(Z)-endoxifen free base prepared in accordance with the processes disclosed herein has <1% impurity.

**[0285]** In an aspect, the present disclosure relates to compositions comprising (Z)-endoxifen free base or a salt thereof prepared according to any of the methods disclosed herein.

**[0286]** In another aspect, the present disclosure relates to compositions comprising (Z)-endoxifen free base or a salt thereof prepared according to any of the methods disclosed herein, wherein the (Z)-endoxifen is at least 90% (Z)-endoxifen free base wt/wt of total endoxifen in the composition.

**[0287]** In still another aspect, the compositions further comprise (E)-endoxifen, wherein the ratio of (E)-endoxifen to (Z)-endoxifen (E/Z-ratio) is 1:99; 5:95; 10:90, 15:85; 20:80, 25:75; 30:70; 40:70, 45:55; 50:50; 55:45; 60:40; 65:45; or 70:30.



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**[0288]** In a further aspect, the compositions further comprise (E)-endoxifen, wherein the E/Z-ratio ranges from 45:55 to 55:45 or is approximately 1:1.

**[0289]** In an aspect, the compositions comprise (Z)-endoxifen or a salt or polymorph thereof prepared according to any of the methods disclosed herein, wherein the (Z)-endoxifen is stable at ambient temperature for at least 6 months, at least 9 months, at least 12 months or at least 18 months;

**[0290]** In another aspect, the compositions comprise (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein,

a. wherein the compositions have aerobic bacterial plate count of not more than 20,000 g/mL;
b. wherein water content of the compositions is not more than 1.0% as tested by Method Ic of the USP 921;
c. wherein the water activity (Aw) of the compositions is less than 0.9,
d. wherein the residue on ignition is not more than 0.1% as tested by a method of USP 281;
e. wherein a heavy metal is not more than 20 ppm as tested by Method II of USP 231; or
f. wherein methanol is NMT 3000 ppm, tetrahydrofuran is NMT 720 ppm, isopropanol is NMT 5000 ppm, ethyl acetate is NMT 5000 ppm; n-Heptane is NMT 5000 ppm, and ethanol is NMT 5000 ppm as tested by a validated HPLC method

**[0291]** In still another aspect, the compositions comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein comprise 0.01 mg to 200 mg (Z)-endoxifen or a salt or polymorph thereof per unit dose.

**[0292]** In yet another aspect, the compositions comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein comprise 1 mg to 20 mg of (Z)-endoxifen or a salt or polymorph thereof per unit dose.

**[0293]** In a further aspect, the compositions comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein comprise 0.01% to 20% (wt/wt) of endoxifen or a salt or polymorph thereof.

**[0294]** In a still further aspect, the present disclosure relates to compositions comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition comprises 0.1% to 10% (wt/wt) of (Z)-endoxifen or a salt or polymorph thereof.



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**[0295]** In another aspect, the present disclosure relates to compositions comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein further comprising one or more excipient.

**[0296]** In yet another aspect, the present disclosure relates to compositions comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, further comprising one or more excipient, wherein the excipient is a binder, a filler, a disintegrating agent, a lubricant, a glidant, a control release agent, an enteric coating agent, a film forming agent, a plasticizer, a sweetening agent, a flavoring agent, or a combination thereof.

**[0297]** In still another aspect, the present disclosure relates to compositions comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, further comprising one or more excipient, wherein the excipients are about 0.1% to about 99% wt/wt of the composition.

**[0298]** In a further aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition comprises one or more control release agents selected from the group consisting of acid-insoluble polymers, methyl acrylate-methacrylic acid copolymers, cellulose acetate phthalate (CAP), cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate (hypromellose acetate succinate), polyvinyl acetate phthalate (PVAP), methyl methacrylate-methacrylic acid copolymers, shellac, cellulose acetate trimellitate, sodium alginate, zein, waxes, including synthetic waxes, microcrystalline waxes, paraffin wax, carnauba wax, and beeswax, polyethoxylated castor oil derivatives, hydrogenated oils, glyceryl mono-, di- tribenates, glyceryl monostearate, glyceryl distearate, long chain alcohols, such as stearyl alcohol, cetyl alcohol, polyethylene glycol, and mixtures thereof.

**[0299]** In one aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition is formulated for oral, parenteral, topical, and intraductal delivery.

**[0300]** In another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition formulated for oral delivery is a tablet, a caplet, a capsule, a pill, a powder, a troche, an elixir, a suspension, a syrup, a wafer, a chewing gum, a dragee, and a lozenge.

**[0301]** In yet another aspect, the present disclosure relates to compositions comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the compositions formulated for oral delivery are tablets formulated as enteric tablets, caplets formulated as enteric caplets, and capsule formulated as enteric capsules.



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**[0302]** In yet another aspect, the present disclosure relates to compositions comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the compositions formulated for oral delivery are tablets formulated as delayed-release tablets, caplets formulated as delayed-release caplets, or capsules formulated as delayed-release capsules.

**[0303]** In yet another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition is formulated for oral delivery, and wherein as tested by a method of USP 711 or 701, the composition releases in stomach:

a. less than 10% of endoxifen in 2 hours after administration;
b. less than 20% of endoxifen in 2 hours after administration;
c. less than 30% of endoxifen in 2 hours after administration;
d. less than 40% of endoxifen in 4 hours after administration; or
e. less than 50% of endoxifen in 6 hours after administration.

**[0304]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition is formulated for oral delivery, and wherein as tested by a method of USP 711 or 701, the composition releases in stomach:

a. less than 10% of (Z) endoxifen in 2 hours after administration;
b. less than 20% of (Z) endoxifen in 2 hours after administration;
c. less than 40% of (Z) endoxifen in 4 hours after administration; or
d. less than 50% of (Z) endoxifen in 6 hours after administration.

**[0305]** In another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition is formulated for oral delivery, and wherein as tested by a method of USP 711 or 701, the composition releases at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% endoxifen in the intestines.

**[0306]** In another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition is formulated for oral delivery, and wherein as tested by a method of USP 711 or 701, the composition releases in the intestines at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% endoxifen in 2 hours after administration.

**[0307]** In another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition is formulated for oral delivery, and wherein as tested by a method of USP 711 or



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701, the composition releases in the intestines at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% endoxifen in 3 hours after administration.

**[0308]** In another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition is formulated for oral delivery, and wherein as tested by a method of USP 711 or 701, the composition releases in the intestines at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% endoxifen in 4 hours after administration.

**[0309]** In another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition is formulated for oral delivery, and wherein as tested by a method of USP 711 or 701, the composition releases in small intestine:

a. at least 10% of endoxifen after 4 hours after administration;
b. at least 30% of endoxifen after 6 hours after administration;
c. at least 40% of endoxifen after 7 hours after administration;
d. at least 50% of endoxifen after 8 hours after administration;
e. at least 50% of endoxifen after 2 hours after administration;
f. at least 60% of endoxifen after 2 hours after administration;
g. at least 70% of endoxifen after 2 hours after administration;
h. at least 80% of endoxifen after 2 hours after administration; or
i. at least 90% of endoxifen after 2 hours after administration.

**[0310]** In another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition is formulated for oral delivery, and wherein as tested by a method of USP 711, the composition is formulated to release at least 50% of endoxifen after 8 hours after administration in the colon.

**[0311]** In another aspect, the present disclosure relates to a composition formulated for oral administration comprising: 1 mg to 200 mg of endoxifen per unit dose; and wherein the composition is stable for at least 6 months.

**[0312]** In another aspect, the present disclosure relates to a composition formulated for oral administration comprising: 1 mg to 200 mg of endoxifen per unit dose;

wherein the endoxifen is at least 90% (Z)-endoxifen free base; and

wherein:

the composition has an aerobic bacterial plate count of not more than 20,000 g/ml;

water content of the (Z)-endoxifen is not more than 1% as determined by Method Ic of the USP 921;



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residue on ignition of the (Z)-endoxifen is not more than 0.10% as tested by a method of USP 281; or

a heavy metal is not more than 20 ppm as tested by Method II of USP 231.

**[0313]** In another aspect, the present disclosure relates to a composition formulated for oral administration comprising: 1 mg to 200 mg of endoxifen per unit dose,

wherein the composition is formulated as an enteric tablet, an enteric caplet, and an enteric capsule;

wherein as determined by a method of USP 711, the composition is formulated to release in small intestine:

at least 25% of endoxifen after 4 hours after administration;

at least 30% of endoxifen after 6 hours after administration;

at least 40% of endoxifen after 7 hours after administration; or

at least 50% of endoxifen after 8 hours after administration; or

wherein as determined by a method of USP 711, the composition is formulated to release at least 50% of endoxifen in the colon.

**[0314]** In another aspect, the present disclosure relates to an oral solid dosage form composition comprising: 1 mg to 200 mg of endoxifen per unit dose;

wherein the endoxifen is at least 90% (Z)-endoxifen free base; and

wherein

the composition has an aerobic bacterial plate count of not more than 20,000 g/ml;

water content of the (Z)-endoxifen is not more than 1% as determined by Method Ic of the USP 921;

residue on ignition of the (Z)-endoxifen is not more than 0.10% as tested by a method of USP 281; or

a heavy metal is not more than 20 ppm as tested by Method II of USP 231; and

wherein the composition is formulated as an enteric tablet, an enteric caplet and an enteric capsule; and

wherein the endoxifen is neat; or

wherein the composition further comprises an excipient selected from the group consisting of a binder, a filler, a disintegrating agent, a lubricant, a glidant, a control release agent, an enteric coating agent, a film forming agent, a plasticizer, a colorant, a sweetening agent, and a flavoring agent, or a combination thereof.

**[0315]** In another aspect, the present disclosure relates to an enteric capsule, comprising (Z)-endoxifen free base prepared by a process described herein.



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**[0316]** In another aspect, the present disclosure relates to an enteric capsule comprising 1 mg to 200 mg of neat endoxifen per unit dose:

wherein the endoxifen is at least 90% (Z)-endoxifen free base; and

wherein

the composition has an aerobic bacterial plate count of not more than 20,000 g/ml;

water content of the (Z)-endoxifen is not more than 1% as determined by Method Ic of the USP 921;

residue on ignition of the (Z)-endoxifen is not more than 0.10% as tested by a method of USP 281; and

a heavy metal is not more than 20 ppm as tested by Method II of USP 231.

**[0317]** In another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the endoxifen salt is selected from the group consisting of arecoline, besylate, bicarbonate, bitartarate, butylbromide, citrate, camysylate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthanoate, isethionate, malate, mandelate, mesylate, methylbromide, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamaoate (Embonate), pantothenate, phosphate/diphosphate, polygalacuronate, salicylate, stearate, sulfate, tannate, Teoclate, triethiodide, benzathine, clemizole, chloroprocaine, choline, diethylamine, diethanolamine, ethylenediamine, meglumine, piperazine, procaine, aluminum, barium, bismuth, lithium, magnesium, potassium, and zinc.

**[0318]** In yet another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the endoxifen salt is endoxifen gluconate.

**[0319]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the endoxifen salt is endoxifen gluconate selected from the group consisting of (Z)-endoxifen D-gluconate, (E)-endoxifen D-gluconate, (Z)-endoxifen L-gluconate, and (E)-endoxifen L-gluconate, or a combination thereof.

**[0320]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the endoxifen salt is endoxifen gluconate, and wherein the endoxifen gluconate comprises 1%, 5%, 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.99% or 100% (wt/wt) of (Z)-endoxifen D-gluconate or (Z)-endoxifen L-gluconate.



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**[0321]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the endoxifen salt is endoxifen gluconate, and wherein the endoxifen gluconate comprises (Z)-endoxifen D-gluconate and (E)-endoxifen D-gluconate (wt/wt) at Z/E-ratio of 10:90, 20:80, 30:70; 40:60; 50:50, 60:40, 70:30, 80:20, 90:10; 91:9; 92:8; 93:7; 94:8; 95:5, 96:4, 97:3, 98:2, 99:1; 99.5:0.5; or 99.99:0.01.

**[0322]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein for the treatment and prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both.

**[0323]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein for the treatment and prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer.

**[0324]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein for the treatment and prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, wherein the hormone-dependent breast disorder is breast cancer.

**[0325]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein for the treatment and prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, wherein the hormone-dependent breast disorder is breast cancer and wherein the breast cancer is a pre-cancer, an early stage cancer, a non-metastatic cancer, a pre-metastatic cancer, a locally advanced cancer, or a metastatic cancer.

**[0326]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein for the treatment and prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is tamoxifen-refractory or tamoxifen resistant.



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**[0327]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to a subject in need thereof.

**[0328]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to a subject in need thereof and wherein the subject has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both.

**[0329]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to a subject in need thereof, wherein the subject's hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer.

**[0330]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to a subject in need thereof, wherein the subject has breast cancer and wherein breast cancer is a pre-cancer, an early stage cancer, a non-metastatic cancer, a pre-metastatic cancer, a locally advanced cancer, or a metastatic cancer.

**[0331]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to a subject in need thereof, wherein the subject has prostate cancer and wherein the subject has or is about to initiate prostate cancer therapy.

**[0332]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to a subject in need thereof, wherein the subject has prostate cancer, and wherein the subject has or is at risk of having gynecomastia.

**[0333]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to a subject that has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, and wherein the subject's hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is tamoxifen-refractory or tamoxifen resistant.



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**[0334]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to the subject at a unit dose of 0.01 mg, 0.05 mg, 0.1 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.5 mg, 2.0 mg, 4 mg, 5 mg, 10 mg, 20 mg, 25 mg, 50 mg or 200 mg of (Z)-endoxifen.

**[0335]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to the subject at a dose of 0.01 mg, 0.05 mg, 0.1 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.5 mg, 2.0 mg, 4 mg, 5 mg, 10 mg, 20 mg, 25 mg, 50 mg or 200 mg of (Z)-endoxifen.

**[0336]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to the subject once a day, twice a day, thrice a day, four times a day, every other day, twice a week, weekly, fortnightly, twice a month, monthly, quarterly, once every six months, or annually.

**[0337]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein administration of the composition orally maintains the subject's plasma endoxifen at a level greater than 30 nM.

**[0338]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to a subject as combination therapy.

**[0339]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered as a primary therapy, a neo-adjuvant therapy, or an adjuvant therapy.

**[0340]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to a subject either alone in combination with a second therapeutic agent.

**[0341]** In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to a subject either alone in combination with a second therapeutic agent, and wherein the second therapeutic agent is bicalutamide, enzalutamide, or an anticancer drug such as trastuzumab, antineoplastic such as capecitabine (Xeloda), carboplatin

(Paraplatin), cisplatin (Platinol), cyclophosphamide (Neosar), docetaxel (Docefrez, Taxotere), doxorubicin (Adriamycin), PEGylated liposomal doxorubicin (Doxil), epirubicin (Ellence), fluorouracil (5-FU, Adrucil), gemcitabine (Gemzar), methotrexate (multiple brand names), paclitaxel (Taxol), protein-bound paclitaxel (Abraxane), vinorelbine (Navelbine), eribulin (Halaven), ixabepilone (Ixempra), or inhibitors of ATP-binding cassette transporters.

**[0342]** In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition prepared according to any one of the processes disclosed herein.

**[0343]** In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein.

**[0344]** In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein the subject has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both.

**[0345]** In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein the subject has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer.

**[0346]** In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein the subject has breast cancer.

**[0347]** In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein the subject has breast cancer, and wherein the breast cancer is a pre-cancer, an early stage cancer, a non-metastatic cancer, a pre-metastatic cancer, a locally advanced cancer, or a metastatic cancer.



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**[0348]** In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein the subject has prostate cancer and wherein the subject further has or is at risk of having gynecomastia.

**[0349]** In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein the subject has tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder.

**[0350]** In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein the composition is administered to the subject at a unit dose of 0.01 mg, 0.05 mg, 0.1 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.5 mg, 2.0 mg, 4 mg, 5 mg, 6 mg, 8 mg, 10 mg, 20 mg, 25 mg, 50 mg, 100 mg or 200 mg.

**[0351]** In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein the composition is administered once a day, twice, a day, thrice a day, four times a day, every other day, twice a week, weekly, fortnightly, twice a month, monthly, quarterly, once every six months, or annually.

**[0352]** In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein administration of the composition orally maintains the subject's plasma endoxifen at a steady state level greater than 30 nM.

**[0353]** In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein administration of the composition orally achieves the subject's plasma endoxifen at a steady state level greater than 30 nM by day 14 after the administration of the first dose (on day 1).

**[0354]** In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof, wherein administration of the composition orally achieves the subject's



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plasma endoxifen at a steady state level greater than 30 nM by day 14 after the administration of the first dose (on day 1).

**[0355]** In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein administration of the composition orally achieves a time to maximal plasma levels of endoxifen in the subject from 2 to 10 hours after administration (post-dose).

**[0356]** In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof, wherein administration of the composition orally achieves a time to maximal plasma levels of endoxifen in the subject from 2 to 10 hours after administration (post-dose).

**[0357]** In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof, wherein the mean terminal elimination half-life of endoxifen in the subject ranges from 30 to 60 hours post dose.

**[0358]** In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof, wherein the mean terminal elimination half-life of endoxifen in the subject ranges from 40 to 55 hours post dose.

**[0359]** In another aspect, the present disclosure relates to a method of treating a subject having or at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, the method comprising administering an oral composition comprising (Z)-endoxifen or a salt or polymorph thereof, wherein administration of the composition achieves:

a. a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;
b. a time to maximum plasma levels of endoxifen ranging from 2 hours to 10 hours after administration; and
c. a steady state plasma level of endoxifen greater than 30 nM.

**[0360]** In another aspect, the present disclosure relates to a method of treating a subject having or at risk of having a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, and vulvar cancer, the



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method comprising administering an oral composition comprising (Z)-endoxifen or a salt or polymorph thereof, wherein administration of the composition achieves:

a. a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;
b. a time to maximum plasma levels of endoxifen ranging from 2 hours to 10 hours after administration; and
c. a steady state plasma level of endoxifen greater than 30 nM.

**[0361]** In another aspect, the present disclosure relates to a method of treating a subject having or at risk of having a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancera and vulvar cancer, the method comprising administering an oral composition comprising (Z)-endoxifen or a salt or polymorph thereof formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet, or a delayed-release capsule, wherein administration of the composition achieves:

a. a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;
b. a time to maximum plasma levels of endoxifen ranging from 2 hours to 10 hours after administration; and
c. a steady state plasma level of endoxifen greater than 30 nM.

**[0362]** In another aspect, the present disclosure relates to a method of treating a subject having or at risk of having a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, and vulvar cancer, the method comprising administering an oral composition comprising (Z)-endoxifen or a salt or polymorph thereof formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet, or a delayed-release capsule, wherein administration of the composition achieves:

a. a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;



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b. a time to maximum plasma levels of endoxifen ranging from 2 hours to 10 hours after administration; and

c. a steady state plasma level of endoxifen greater than 30 nM; and

wherein at least 50%, at least 60%, at least 70%, at least 80% or at least 90% of the endoxifen is released in the intestines.

**[0363]** In another aspect, the present disclosure relates to a method of treating a subject having or at risk of having a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, and vulvar cancer, the method comprising administering an oral composition comprising 0.01 mg to 200 mg of (Z)-endoxifen or a salt or polymorph thereof formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet, or a delayed-release capsule, wherein administration of the composition achieves:

a. a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;

b. a time to maximum plasma levels of endoxifen ranging from 2 hours to 10 hours after administration; and

c. a steady state plasma level of endoxifen greater than 30 nM; and

wherein at least 50%, at least 60%, at least 70%, at least 80% or at least 90% of the endoxifen is released in the intestines.

**[0364]** In another aspect, the present disclosure relates to a method of treating a subject having or at risk of having a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, and vulvar cancer, the method comprising administering daily an oral composition comprising 0.01 mg to 200 mg of (Z)-endoxifen or a salt or polymorph thereof formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet, or a delayed-release capsule, wherein administration of the composition achieves:

a. a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;



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b. a time to maximum plasma levels of endoxifen ranging from 2 hours to 10 hours after administration; and

c. a steady state plasma level of endoxifen greater than 30 nM.

**[0365]** In another aspect, the present disclosure relates to a method of treating a subject having or at risk of having a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, and vulvar cancer, the method comprising administering daily an oral composition comprising 0.01 mg to 200 mg of (Z)-endoxifen or a salt or polymorph thereof formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet, or a delayed-release capsule, wherein administration of the composition achieves:

a. a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;

b. a time to maximum plasma levels of endoxifen ranging from 2 hours to 10 hours after administration; and

c. a steady state plasma level of endoxifen greater than 30 nM; and

wherein at least 50%, at least 60%, at least 70%, at least 80% or at least 90% of the endoxifen is released in the intestines.

**[0366]** In another aspect, the present disclosure relates to a method of treating a subject having or at risk of having a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, and vulvar cancer, the method comprising administering daily an oral composition comprising 0.01 mg to 200 mg of (Z)-endoxifen or a salt or polymorph thereof formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet, or a delayed-release capsule, wherein administration of the composition achieves:

a. a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;

b. a time to maximum plasma levels of endoxifen ranging from 2 hours to 10 hours after administration; and

c. a steady state plasma level of endoxifen greater than 30 nM;



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wherein the mean area under the curve extrapolated to time infinity ($AUC_{0-inf}$) is 200 hr*ng/mL to 10000 hr*ng/mL, 300 hr*ng/mL to 8000 hr*ng/mL, 400 hr*ng/mL to 6000 hr*ng/mL or 700 hr*ng/mL to 6000 hr*ng/mL; and

wherein at least 50%, at least 60%, at least 70%, at least 80% or at least 90% of the endoxifen is released in the intestines.

**[0367]** In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein the method is a primary therapy, a neo-adjuvant therapy, or an adjuvant therapy.

**[0368]** In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein a composition is administered to a subject as combination therapy.

**[0369]** In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein a composition is administered to a subject either alone in combination with a second therapeutic agent.

**[0370]** In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein a composition is administered to a subject with a second therapeutic agent selected from the group consisting of bicalutamide, enzalutamide, or an anticancer drug such as trastuzumab, antineoplastics such as capecitabine (Xeloda), carboplatin (Paraplatin), cisplatin (Platinol), cyclophosphamide (Neosar), docetaxel (Docefrez, Taxotere), doxorubicin (Adriamycin), PEGylated liposomal doxorubicin (Doxil), epirubicin (Ellence), fluorouracil (5-FU, Adrucil), gemcitabine (Gemzar), methotrexate (multiple brand names), paclitaxel (Taxol), protein-bound paclitaxel (Abraxane), vinorelbine (Navelbine), eribulin (Halaven), ixabepilone (Ixempra), and ATP-cassette binding protein transport inhibitors.

**[0371]** In still another aspect, the present disclosure relates to a use for the treatment and prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, in a subject, the use comprising:

dosing the subject with a first composition comprising tamoxifen;

determining the subject's tamoxifen-metabolites profile in a test sample obtained from the subject;



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determining a reduced level of subject's plasma endoxifen based on subject's tamoxifen-metabolites profile as to compared to a level of plasma endoxifen in a reference tamoxifen-metabolites profile; and

administering to the subject a composition of the present disclosure.

**[0372]** In still another aspect, the present disclosure relates to a use for the treatment and prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, in a subject, the use comprising:

dosing the subject with a first composition comprising tamoxifen;

determining the subject's tamoxifen-metabolites profile in a test sample obtained from the subject;

determining a reduced level of subject's plasma endoxifen based on subject's tamoxifen-metabolites profile as to compared to a level of plasma endoxifen in a reference tamoxifen-metabolites profile; and

administering to the subject a composition of the present disclosure;

wherein the composition is administered orally in a dose sufficient to maintain the subject's plasma endoxifen at a steady state level greater than 30 nM;

wherein the tamoxifen-metabolites profile comprises a panel of at least tamoxifen, 4-hydroxytamoxifen, n-desmethyltamoxifen, or endoxifen;

wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer;

wherein the hormone-dependent breast disorder is a pre-cancer, an early stage cancer, a non-metastatic cancer, a pre-metastatic cancer, a locally advanced cancer, or metastatic cancer;

wherein the hormone-dependent breast disorder is a non-metastatic cancer;

wherein the subject has prostate cancer, and wherein the subject further has or is at risk of having gynecomastia; or

wherein the hormone-dependent breast disorder or hormone-dependent reproductive tract disorder is tamoxifen-refractory or tamoxifen resistant.

**[0373]** In still another aspect, the present disclosure relates to a kit for treating a subject having or at risk of having a hormone-dependent breast disorder or hormone dependent reproductive tract disorder, in a subject in need thereof comprising: (a) a composition of the present disclosure; and (b) a sealed container for housing the composition; and c) instructions for use of the orally administered composition.



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**[0374]** In still another aspect, the present disclosure relates to a kit for treating a subject having or at risk of having a hormone-dependent breast disorder or hormone dependent reproductive tract disorder, in a subject in need thereof comprising: (a) a composition of the present disclosure; and (b) a sealed container for housing the composition; and c) instructions for use of the orally administered composition, wherein the kit comprises a second therapeutic agent selected from the group consisting of bicalutamide, enzalutamide and anticancer drugs such as trastuzumab, antineoplastics such as capecitabine (Xeloda), carboplatin (Paraplatin), cisplatin (Platinol), cyclophosphamide (Neosar), docetaxel (Docefrez, Taxotere), doxorubicin (Adriamycin), PEGylated liposomal doxorubicin (Doxil), epirubicin (Ellence), fluorouracil (5-FU, Adrucil), gemcitabine (Gemzar), methotrexate (multiple brand names), paclitaxel (Taxol), protein-bound paclitaxel (Abraxane), vinorelbine (Navelbine), eribulin (Halaven), ixabepilone (Ixempra), and ATP-cassette binding protein transport inhibitors.

**[0375]** In still another aspect, the present disclosure relates to a method of administering a composition prepared in accordance with any of the processes described herein to a subject in need thereof in accordance with instructions for use comprised in a kit comprising the composition.

## EXAMPLES

**[0376] Abbreviations used herein**

ACN/PPW = Acetonitrile/Process Purified Water

$NaHCO_3$ = Sodium hydrocarbonate

HCl = hydrochloric acid

THF = Tetrahydrofuran

MeTHF = 2-Methyltetrahydrofuran

$CH_2Cl_2$ = Dicholoromethane

EtOH = Ethanol

MeOH = Methanol

EtOAc = Ethyl acetate

IPA = Isopropyl alcohol; isopropanol

TFA = Trifluoroacetic acid

TCA = Trichloroacetic acid

PPW = Process Purified Water

IPA/PPW = Isopropyl alcohol/Process Purified Water



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**Example 1:** ***Enrichment and Preparation of (Z)-Endoxifen Free Base***

**A. Fractional Crystallization**

**[0377]** (Z)-Endoxifen free base (drug substance) can be prepared from a mixture of (E)-endoxifen and (Z)-endoxifen by fractional crystallization described herein. Briefly, commercially available crude endoxifen mixture of (E)-endoxifen and (Z)-endoxifen isoforms (Astatech Ltd. China) were used as starting material to prepare (Z)-endoxifen as free base.

**[0378]** i. An E/Z-endoxifen solution was prepared by suspending 1 g of endoxifen having (E)-endoxifen and (Z)-endoxifen at ratios (E/Z ratio) of 51/1, 1/1.8, and 1/5.8, each in a 10x volume of the solvent, isopropanol (IPA). A second set of solutions was prepared by suspending 1 g each of endoxifen at E/Z ratios of 51/1, 1/1.8, and 1/5.8 in 10x volume of the solvent EtOAc. The solutions were heated to a first temperature of 50 °C creating a hot slurry and stirred overnight at 50 °C. The hot slurry samples were filtered using a cellulose filter pore size 0.5 μm. The mixtures were then cooled to a second temperature, room temperature 23 °C while stirring for 12 hours to effect crystallization. The aliquots of cooled samples were filtered using a cellulose filter pore size 0.5 μm. Aliquots of the solid and filtrates at each of temperatures 50 °C and 23 °C were taken and monitored by HPLC-UV to determine their E/Z-endoxifen ratio. The (Z)-endoxifen enriched filtrates and the E-endoxifen enriched filtrates were added back to their respective mother liquors.

**[0379]** HPLC-UV analyses of the samples was carried out using a Luna phenyl-hexyl column (4.6 mm x 150 mm x 3 μm of particle size). The column temperature was 40 °C and sample compartment temperature was maintained at ambient temperature. Samples were prepared by dissolving solids and filtrates at 0.2 mg/ml of sample in methanol as sample buffer. Samples were then injected into the column in an injection volume of 20 μl. Likewise, mildly acidic (pH 4.3) ammonium formate buffer/methanol in the mobile phase with gradient elution was used. Mobile phase system consisting of: Mobile Phase A (MPA) buffer was 10 mM $HCOONH_4$ with 0.03% HCOOH buffer in water, and Mobile Phase B (MBP) buffer was 10 mM $HCOONH_4$ in methanol with a gradient program used.

**[0380]** **Table 1**: Gradient Program

| Time (m) | MPA (%) | MPB (%) |
|---|---|---|
| 0 | 50 | 50 |
| 15 | 30 | 70 |
| 25 | 5 | 95 |
| 30 | 50 | 50 |

**[0381]** The run time was 30 m, the flow rate was 1.0 mL/m, and the delay time was 5 m. Samples were detected by UV detection at 243 nm. Retention times were typically from 12.95 to



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13.20 m for (E)-endoxifen and from 14.0 to 14.33 m for (Z)-endoxifen. Relative Retention Time (RRT) for (E)-endoxifen was 0.4 to 0.9 and 1.0 for (Z)-endoxifen.

**[0382]** **Table 2**: Enrichment of Endoxifen (Z)- and (E)- isomers from hot slurry of E/Z-endoxifen mixture in IPA and EtOAc.

| | | **Sample** | | | | | |
|---|---|---|---|---|---|---|---|
| | | **1** | **2** | **3** | **4** | **5** | **6** |
| E/Z-endoxifen ratio | | 51/1 | 1/1.8 | 1/5.8 | 51/1 | 1/1.8 | 1/5.8 |
| E/Z-endoxifen | | 1 g | 1 g | 1 g | 1 g | 1 g | 1 g |
| Solvent | | **IPA** (10 X) | | | **EtOAc** (10 X) | | |
| 50 °C | Solid | 85/1 (97.0%/1.1%) | N/A (dissolved) | 1/4.2 (18.9%/**79.6**%) | ≥100/1 (97.9%/0.7%) | 1.9/1 (65.4%/34.2%) | 1/24 (3.9%/**94.8**%) |
| | Filtrate | 12/1 (87.0%/7.0%) | N/A (dissolved) | 1/**47** (2.1%/**97.4**%) | 5.4/1 (66.2%/12.3%) | 1/2.4 (29.2%/**68.7**%) | 1/2.5 (28.0%/**70.1**%) |
| 23 °C | Solid | ≥100/1 (98.2%/0.3%) | 1/2.1 (31.8%/**67.2**%) | 1/**90** (1.1%/**98.1**%) | ≥100/1 (99.0%/0.4%) | 1.3/1 (55.9%/43.1%) | 1/6.9 (12.6%/**86.9**%) |
| | Filtrate | 3.6/1 (70.1%/19.6%) | 1/1.7 (36.5%/**60.6**%) | 1/1.3 (43.4%/54.9%) | 1.6/1 (37.7%/23.0%) | 1/6.7 (12.6%/**84.3**%) | 1/2.6 (26.2%/**84.3**%) |

**[0383]** Results **(Table 2)** show that Z-endoxifen can be enriched using a commercial crude E/Z-endoxifen starting material from a hot slurry of the endoxifen mixtures made with IPA and EtOAc. Z-endoxifen can be purified from E/Z-endoxifen mixtures having E/Z at 1:1 and with higher Z-endoxifen levels in the mixture, for example, 1:8, and 1:5.8. Substantial Z-endoxifen enrichment was achieved in a single step using fractional crystallization method, for example with an E/Z ratio of 1:90 described herein Example 1A. (Z)-endoxifen was seen to be more soluble than (E)-endoxifen in EtOAc. (Z)-endoxifen also tended to remain in the filtrate in greater amounts in EtOAc as compared with IPA. Both solids and filtrates are useful for the preparation of (Z)-endoxifen free base. Serial enrichment of Z-endoxifen by adding filtrates back to the first filtrate (first mother liquor) can also be performed.

**[0384]** Similarly, E-endoxifen can be purified from E/Z-endoxifen mixture having higher E-endoxifen levels in the E/Z mixture.

**[0385]** ii. Similar results were obtained in experiments where an E/Z-endoxifen mixture was suspended in a hot slurry prepared with a mixture of IPA/PPW (1:1 v/v) and extracted and washed with precooled IPA/PPW (1:1) to form crystalline solids and filtrates with enriched (Z)-endoxifen.

**B. Recrystallization from Solid Fraction**

**[0386]** Serial enrichment of (Z)-endoxifen can be performed by subjecting the endoxifen mixture with E/Z-endoxifen ratio of 51:1, 1:1.8 and 1:5.6, and the solids and mother liquors obtained from the fractional crystallization to one or more rounds of recrystallization.



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**[0387]** The (Z)-endoxifen can be enriched in substantially purified form from crude E/Z-endoxifen mixtures, (Z)-enriched crystalline solids and (Z)-enriched mother liquors by recrystallization with solvents such as ethanol, ethyl acetate/n-heptane, Acetone/MTBE, IPA, IPA/PPW, and the like under the conditions as described herein.

**[0388]** *Ethanol*. Crystalline solids obtained from E/Z-endoxifen hot IPA slurry mixture above were used to obtain further purified Z-endoxifen. After cooling to 23 °C, the solid fractions of sample 2 (80 g) and sample 3 (79 g) of **Table 2** above were combined and recrystallized using 1000 mL (1L) EtOH. The ethanol mixture was heated to reflux. The dissolution point was at 75 °C. The heated solution was filtered using a cellulose filter (pore size 0.5 μm) to remove foreign impurities such as cotton fibers by polish filtration. The filtrate solution was then stirred initially at 70 °C for 30 minutes. The solution was then cooled to 0 °C – 5 °C and stirred continually for 5 h at 0 °C – 5 °C. The solution was filtered again. The crystals on the filter were washed with 200 mL of EtOH.

**[0389]** Results show that solid crystals of endoxifen had E/Z ratio of ≥1/100 (0.22%/**99.48**%) and endoxifen in the filtrate had E/Z ratio of 1/5.9 (13.93%/**82.48**%) when recrystallized with EtOH. HPLC analysis of at least 3 different experiments conducted by this method showed that (Z) endoxifen retention time was 14.00 m, E-endoxifen retention time was 13.14 m. (Z)-endoxifen levels ranged from 97% to 99.48% while (E)-endoxifen levels ranged from 0.22% to 2.14%. Other impurities were <1%.

**[0390]** *Ethyl Acetate/n-heptane*. Feasibility of recrystallization with EtOAc/n-heptane was studied as described below.

**[0391]** 5 g Endoxifen (E/Z ratio 1/5.8) was added to EtOAc/n-heptane (140 mL, 1/1 v/v) and heated to reflux (~82 °C) while stirring overnight to obtain a clear solution. The cloud point of the mixture was 30 °C. The mixture was then cooled to room temperature to precipitate the product and filtered. After isolation as described above, endoxifen of the solid product was determined by HPLC to have an E/Z ratio of 1/8.1 (10.9%:**88.60**%) with a product yield of 66% (3.3 g). (Z)-Endoxifen in the filtrate was enriched with E/Z ratio of 1:3 (23.94%:**74.47**%). The recrystallization using EtOAc/n-heptane can also provide purified Z-endoxifen in ratios similar to the hot IPA slurry as shown in **Table 3**.

**[0392]** **Table 3**: Recrystallization of (Z)-endoxifen from E/Z-endoxifen mixture using EtOAc/n-heptane solvent.

| **Parameter** | **Result** |
|---|---|
| E/Z endoxifen – E/Z ratio **1/5.8** | 5 g |
| **EtOAc/n-heptane** solvent (1:1) | 140 mL |
| Heat to dissolution | ~82 °C (reflux) |
| Cloud point | ~30 °C |



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| Parameter | | Result |
|---|---|---|
| Cool to RT and filtration | | 23 °C, 1 hr |
| E/**Z** ratio of the product | Solid | 3.3 g, 1/8.1 (10.90%/**88.60%**) |
| | Filtrate | 1/3.0 (23.94%/**72.47%**) |

**[0393]** *Acetone/MTBE.* 0.5 g Endoxifen (E/Z ratio 1/1.8) was added to Acetone (10 v; 5 mL) solvent, and antisolvent MTBE (9 mL) was added to the solution and heated to reflux (~82 °C) while stirring overnight to obtain a clear solution. The cloud point of the mixture was ~22 °C. The mixture was then cooled to room temperature to precipitate the product and filtered. Endoxifen in the solid product was determined by HPLC to have an E/Z ratio of 39/1 while the filtrate was enriched with (Z)-endoxifen with E/Z ratio of 1:2.6. Acetone/MTBE solvent system is useful to separate E-endoxifen to solid from the (Z)-endoxifen in the filtrate.

**C. Recrystallization from Mother Liquor**

**[0394]** Purified (Z)-endoxifen can be recovered from mother liquor enriched with (Z)-endoxifen as shown in the following **Tables 4** and **5**.

**[0395]** i. Starting material of crude E/Z-endoxifen mixture can be dissolved in a first solvent, ethyl acetate, to form a first mother liquor from which (Z)-endoxifen can be recovered by a second step of addition of a second solvent such as n-heptane or ethanol as shown in **Table 4**.

**[0396] Table 4**. Recrystallization of Z-endoxifen

| **Parameter** | | **Results** | |
|---|---|---|---|
| | | **Lot Number** | |
| | | **1** | **2** |
| E/Z-endoxifen (**E/Z = 1/1.8**) | | 5 g | 10 g |
| **EtOAc** (First solvent) | | 50 mL | 50 mL |
| Heat to dissolution | | ~68 °C | ~78 °C (reflux) |
| Cloud Point° | | ~33 °C | ~38 °C |
| Cool to RT and filtration | | 23 °C, 1 h | 23 °C, 1 h |
| E/Z ratio of product | Solid | 0.87g, 8.5/1 (**89.37**%/10.49%) | 1.53 g, 1/1 (49.32%/49.80%) |
| | Filtrate | 1/**3.8** (20.13%/**76.86**%) | 1/ **2.6** (27.29%/**70.09**%) |
| Filtrate concentration<br>Heat to dissolution | | To 5 mL, 25 mL<br>~68 °C | To dryness<br>~68C |
| Add solvent/anti-solvent (second solvent) | | **n-heptane**, 40 mL, no precipitation observed | **EtOH**, 50 mL, heat to dissolution |
| Cool to RT and filtration | | 23 °C, overnight | 23 °C (cloud point ~28C) |
| E/Z ratio of product | Solid | 3.0g, 1/4.2 (18.70%/**78.95**%) | 3.2 g, 1/12 (7.52%/**90.24**%) |
| | Filtrate | 1/3.2 (21.65%/**70.35**%) | 1/1.5 (39.35%/**57.76**%) |



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**[0397]** ii. (Z)-endoxifen was prepared by a process involving: a first step of dissolving crude E/Z-endoxifen mixture in a first solvent, ethyl acetate, enriching (Z)-endoxifen to first mother liquor; a second step of addition of a second solvent, IPA to form crystalline (Z)-endoxifen and a second mother liquor; and a step of addition of a third solvent ethanol to recrystallize and recover (Z)-endoxifen from the second mother liquor.

**[0398]** Briefly, endoxifen (E/Z = 1/1.8, 30 g) and (E/Z = 1.2/1, 50 g non-GMP) was dissolved in EtOAc 300 mL and 500 mL respectively, heated to dissolution (~70 °C). The mixture was then cooled to 25 °C while stirring overnight for precipitation. The suspension was filtered and E/Z ratio of solid and the filtrate was determined by HPLC.

**[0399]** Next, the filtrates were concentrated to dryness and IPA 230 mL and 900 mL respectively were added to form hot slurries (50 °C) while stirring. The hot slurries were continuously stirred at 50 °C overnight. The slurries were then cooled to 25 °C for 0.5 h and 1 h respectively, and filtered. Z-endoxifen in the solid and the filtrates were determined again.

**[0400]** The solids of each sample (14.8 g and 21.6 g) were further recrystallized from 148 mL and 220 mL EtOH by heating to dissolution at NMT 70 °C and cooling to 25 °C for 0.5 h and 1 h respectively. The samples were further cooled to 0 °C – 5 °C for 1 h and filtered. The E/Z ratio of the solid and the filtrates were again determined by HPLC. E/Z ratios of each sample and purity are provided below in **Table 5**.

**[0401]** **Table 5**: Recovery of (Z)-endoxifen from (Z)-endoxifen enriched mother liquor

| **Parameter** | | **Results** | |
|---|---|---|---|
| | | **Lot Number** | |
| | | **1** | **2** |
| E/Z-endoxifen ratio | | 1/1.8 | 1.2/1 |
| E/Z-endoxifen amount | | 30 g | 50 g |
| **EtOAc** | | 300 mL | 500 mL |
| Heat to Dissolution | | ~70 °C | ~70 °C |
| Cloud Point | | ~33 °C | ~33 °C |
| Cool to RT | | 25 °C, 3 h | 25 °C, overnight |
| E/Z ratio of product | Solid | 4.5/1 (80.52%/17.73%) | 13.5/1 (92.44/6.83%) |
| | Filtrate | 1/5.0 (16.02%/**80.71%**) | 1/6.8 (12.34%/**84.45%**) |
| Filtrate concentration | | To remove EtOAc | Swap with IP (400 ml X 2) |
| Add **IPA** | | 230 mL | 900 mL |
| Final Volume | | | 250 mL |
| Hot Slurry | | 50 °C overnight | 50 °C, overnight |
| Cool to RT and filtration | | 25 °C, 4 h | 25 °C, 4 h |
| E/Z ratio of product | Solid | 1/31.7 (3.0%/**95.15%**) | 1.31.9 (2.94%/**93.74%**) |
| | Filtrate | 1/1.6 (36.16%/58.78%) | 1/1.7 (32.17%/55.92%) |
| E/Z-endoxifen for recrystallization | | 14.8 g | 21.6 g |
| **EtOH** | | 148 mL | 220 mL |
| Heat to Dissolution | | ~70 °C | ~70 °C |



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| | | | |
|---|---|---|---|
| Cool to RT | | 25 °C, 0.5 h | 25 °C, 1 h |
| E/Z ratio of Product | Solid | - | 1/76.9 (1.26%/**91.91%**) |
| | Filtrate | - | 1/20.1 (4.57%/**91.91%**) |
| Cool to 0 °C-5 °C and filtration | | 0 °C-5 °C, 1 h | 0 °C-5 °C, 1 h |
| E/Z ratio of product | Solid (?) | 1/51.8 (1.86%/**96.31%**) | 1/118.7 (0.82%/**97.30%**) |
| | Filtrate (?) | 1/6.8 (12.72%/**86.23%**) | 1/8 (10.54%/**84.66%**) |
| **Total Yield** | | **31%** | **29%** |

**[0402]** Results show that purified crystalline (Z)-endoxifen of greater than 90% can be obtained by subjecting an E/Z-endoxifen mixture to fractional crystallization with a first solvent, ethyl acetate, to form crystalline solid and a first mother liquor, subjecting the first mother liquor to crystallization with a second solvent such as hot IPA to form a second crystalline solid and second mother liquor, and then recrystallization of the solids from a third solvent such as ethanol. A yield of (Z)-endoxifen of greater than 95% is also feasible. The ratio of (E)/(Z)-endoxifen can be improved from ~1.2:1 and 1:1.8 to 1:51 to over 1:118. The impurity profile of (Z)-endoxifen was analyzed by an HPLC method as described above and was found to be less than <2%. Retention time of (Z)-endoxifen and (E)-endoxifen were 14.19 m and 13.2 m respectively.

**Example 2:** ***Reequilibriation of (E)-endoxifen-rich E/Z-mixture***

**[0403]** (E)-endoxifen-rich E/Z-endoxifen mixture is also useful for the preparation Z-endoxifen free base (in addition to being useful for the preparation of purified (E)-endoxifen). (E)-endoxifen-rich E/Z-endoxifen mixture is reequilibriated from a E/Z ratio of ≥1.5:1 (for example, E/Z ratio of 51:1) to about ~1:1 mixture. The present disclosure embraces the idea that reequilibration may be performed with a starting E/Z-endoxifen mixture having any E/Z ratio, such as 99:1 to 1:99. Such reequilibration is useful for preparation of stable (E)/(Z)-endoxifen ~1:1 mixture as well as further enrichment and purification of Z-endoxifen free base as described in Example 1 above.

**[0404]** Briefly, (E)-endoxifen is converted to (Z)-endoxifen by dissolving crude E/Z-endoxifen in an inert solvent such as acetonitrile/water (8:1) or dichloromethane in the presence of an acid such as hydrochloric acid, trichloroacetic acid or trifluoroacetic acid. The reaction mixture with ACN/PPW was stirred at 60 °C for 1 hour while the reaction mixture with dichloromethane and TFA was stirred at RT for 1 hour. After work up was performed as described in **Table 6**, the E/Z ratio of the product was determined to be E/Z-endoxifen (ratio about 1:1) with a purity greater than 90%.



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**[0405] Table 6**: Reequilibrium of E/Z-endoxifen (E/Z ratio 51/1) to E/Z ratio of about 1:1

| **Parameter** | **Results** | |
|---|---|---|
| | **Sample** | |
| | **1** | **2** |
| E/Z-endoxifen **(E/Z ratio = 51/1)** | 0.5 g (off-white powder | 0.5 g (off-white powder) |
| Solvent | **ACN/PPW** = 8/1, 5 mL (white slurry) | **$CH_2Cl_2$**, 5 mL (White slurry) |
| Acid | 6N HCl, 5 mL | TFA, 5 mL |
| Stir | ~60 °C, 6 h (Pink solution to clear solution) | ~23 °C, 1 h (orange clear solution) |
| Work up | Quench with saturated solution of $NaHCO_3$, wash the organic layer with brine and organic layer is evaporated to dryness | Quench with saturated solution of $NaHCO_3$, wash the organic layer with brine and organic layer is evaporated to dryness |
| Product | Beige solid | Off-white solid |
| E/Z ratio | ~1/1 (49.28%/47.70%) | ~1.3/1 (54.51%/41.9%) |
| Purity | 96.98% | 96.20% |

**Example 3:** ***Purification of (E)-endoxifen***

**[0406]** (E)-endoxifen was similarly purified by recrystallization in EtOH (500 mL) by heating the reaction mixture to NMT 70 °C to get a clear solution, cooled to 0 °C – 5 °C to precipitate the product. After purification by methods described herein, 38.1 g of (E)-endoxifen was obtained in 76% yield with 97.6% purity.

**Example 4:** ***Scale up***

**[0407]** Synthetic and purification methods disclosed herein also are useful in scaling up the preparation of (Z)-endoxifen for making industrial drug product dosage forms, for example, oral, transdermal/topical, nasal, intraductal parenteral dosage forms, for use clinical use in subjects. Feasibility studies of crystallization using 5 g, 100 g, and 110 g of E/Z-endoxifen mixture, compounds of Formula (III) at an E/Z ratio of 1/5.8 were performed by suspending the E/Z-endoxifen mixtures in 10x volume of IPA and heated to 50 °C and stirred for 4 h at 50 °C. The samples were filtered using a cellulose filter pore size 0.5 μm and the E/Z ratio was determined in the solids. Following filtration, the samples were cooled to 23 °C and stirred continuously for 4 h at 23 °C. The samples were filtered again. Solids and the filtrates were monitored for (E)-endoxifen and (Z)-endoxifen levels by HPLC as described above and the results are provided below in **Table 7**.



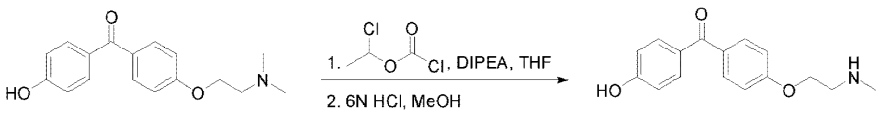
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**[0408]** **Table** 7. Scale up Preparation of (Z)-endoxifen

| **Parameter** | | **Results** | | |
|---|---|---|---|---|
| | | **Sample** | | |
| | | **1** | **2** | **3** |
| E/Z-endoxifen ratio 1/5.8 | | 5 g | 100 g | 110 g |
| **IPA** (10 X) | | 50 mL | 1000 mL | 1100 mL |
| 50 °C | Solid | 1/20 (4.71%/**94.50**%) | 1/22 (4.25%/**94.88**%) | 1/16 (5.85%/**93.24**%) |
| | Filtrate | 1/3.1 (26.54%/72.23%) | 1 /2.2 (30.62%/67.52%) | 1/2.3 (29.94%/68.04%) |
| Cooling to 23 °C stirring for 4 h | Solid | 1/78 (1.26%/**97.69**%) | 1/78 (2.14%/**97.24**%) | 1/74 (1.32%/**98.12**%) |
| | Filtrate | 1/1.1 (50/0.75%/47.1%) | 1.1/1 (51.47%/45.88%) | 1.2/1 (53.03%/43.81%) |

**[0409]** Results show that Z-endoxifen can be obtained from an E/Z-endoxifen mixture from IPA solvent at concentrations higher than ≥ 90% as crystalline solid as well as ≥ 65% (Z)-endoxifen free base in the filtrate. IPA is thus useful as a first solvent, or second solvent or both.

**Example 5:** ***Industrially Scalable Preparation of [4-[2-(methylamino)ethoxy]phenyl](4-hydroxyphenyl)methanone)***




(I) (II)

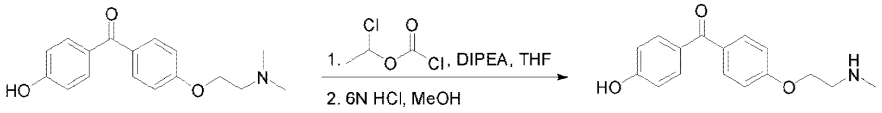
**[0410]** A suitable 10L reactor was charged with starting material [4-[2-(dimethylamino)ethoxy]phenyl](4-hydroxyphenyl)methanone, the compound of Formula (I) (0.5 kg, 1.0 equiv.), DIPEA (1.5 kg, 6.65 equiv., 3.0 wt./wt.) and tetrahydrofuran (5 L, 10 vol./wt., 8.9 wt./wt.) under $N_2$ atmosphere. 1-Chloroethyl chloroformate (1.7 kg, 6.65 equiv., 3.3 wt./wt.) was added slowly while maintaining the internal temperature at NMT 20 °C. The mixture was heated to reflux and stirred at reflux for NLT 12 hr. The mixture was evaporated under reduced pressure at NMT 75 °C until the volume reached the lowest agitateable volume. Methanol (2.5 L, 5 vol./wt., 4.0 wt./wt.) was added slowly and the mixture was distilled under reduced pressure at NMT 75 °C until the volume reached the lowest agitateable volume. Methanol (2.5 L, 5 vol./wt., 4.0 wt./wt.) was added and the mixture was distilled under reduced pressure at NMT 75 °C until the volume reached the lowest agitateable volume. Methanol (2.5 L, 5 vol./wt., 4.0 wt./wt.) was once again added and the mixture was further distilled under reduced pressure at NMT 75 °C until the volume once again reached the lowest agitateable volume. Methanol (2 L, 4 vol./wt., 3.2 wt./wt.) and 6N HCl (2 L, 4 vol./wt., 4.0 wt./wt.) were added to the mixture and the mixture was heated to reflux. The mixture was stirred at reflux for NLT 12 hr. After reaction completion, the



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mixture was evaporated under reduced pressure at NMT 75 °C until most of MeOH was removed. The mixture was cooled to 25±5 °C and 8N NaOH (2.5 L, 5 vol./wt., 5.0 wt./wt.) was added slowly until the pH of the mixture was 11-12. The mixture was stirred at 0–5 °C for NLT 2 hr. The mixture was filtered and washed with $H_2O$ (1 L, 2 vol./wt.) and ethyl acetate (1 L, 2 vol./wt., 1.8 wt./wt.). The wet cake was dried at NMT 50 °C under reduced pressure to afford (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl)methanone, the compound of Formula (II). **Yield: 297 gm, 63%; Purity: 100%** ***(Expected Yield – 60 – 90%)***

**Example 6:** ***Industrially Scalable Preparation of [4-[2-(methylamino)ethoxy]phenyl](4-hydroxyphenyl)methanone)***

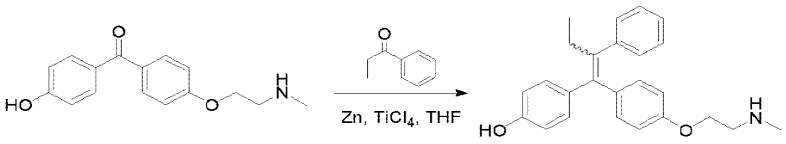



**[0411]** A suitable 2 L reactor was charged with starting material [4-[2-(dimethylamino)ethoxy]phenyl](4-hydroxyphenyl)methanone, the compound of Formula (I) (70 gm, 1.0 equiv.), N-Ethyldiisopropylamine (126 gm, 4.0 equiv., 1.8 wt.) and tetrahydrofuran (700 mL, 10.0 vol., 8.9 wt.) under $N_2$ atmosphere. The mixture was heated to NLT 60 °C and 1-chloroethyl chloroformate (140 gm, 4.0 equiv., 2.0 wt.) added. The mixture was heated to reflux and stirred for NLT 12 hr. The mixture was concentrated until the volume reached 3 vol. Methanol (350 mL, 5.0 vol., 4.0 wt.) was added slowly and the mixture was concentrated until the volume reached 3 vol. (210 mL). Next, methanol (350 mL, 5.0 vol., 4.0 wt.) was added and the mixture was concentrated until the volume reaches 4 vol. (280 mL). 6N HCl (280 mL, 4.0 vol., 4.0 wt.) was added and the mixture was heated to reflux. The mixture was stirred at reflux for NLT 12 hr. After reaction completion, the mixture was concentrated until the volume reaches ~4 vol. (280 mL). The mixture was cooled to ambient temperature, and 8N NaOH (NLT 350 mL, 5.0 vol., 5.0 wt.) was added slowly until the pH of the mixture is NLT 13. Ethyl acetate (280 mL, 4.0 vol., 3.6 wt.) was added to the mixture for extraction. After phase separation, to the aqueous layer was added 6N HCl (NLT 42 mL, 0.6 vol., 0.6 wt.) until the pH was 8-10. The mixture was cooled to 0±5 °C and stirred for NLT 2 hr. The mixture was filtered and washed with purified water (NLT 140 mL, 2.0 vol., 2.0 wt.) and ethyl acetate (NLT 140 mL, 2 vol., 1.8 wt.). The wet cake was dried at NMT 60 °C under reduced pressure to afford (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl)methanone, the compound of Formula (II). **Yield: 55.2 gm, 83%; Purity: 100%** ***(Expected Yield – NLT 70%)***.



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**Example 7:** ***Industrially Scalable Preparation of E/Z-endoxifen mixture in a McMurry Reaction***




(II) (III)

**[0412]** A suitable 10 L reactor was charged with Zn powder (0.27 kg, 4.0 equiv., 0.9 wt./wt.) and tetrahydrofuran (1.5 L, 5 vol./wt., 4.4 wt./wt.) under $N_2$ atmosphere. $TiCl_4$ (0.42 kg, 2.0 equiv., 1.4 wt./wt.) was added slowly while maintaining the internal temperature at NMT 15 °C. The reaction was heated to reflux and stirred at reflux for NLT 2 hr. A suspension of (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl)methanone, the compound of Formula (II) obtained from Step 1, (0.297 kg, 1.0 equiv.) and propiophenone (0.21 kg, 1.5 equiv., 0.7 wt./wt.) in tetrahydrofuran (3.0 L, 10 vol./wt., 8.9 wt./wt.) was added and the reflux was continued for NLT 8 hr. The mixture was cooled to 20-30 °C and added into 25% ammonium chloride (5.9 L, 20 vol./wt., 20 wt./wt.)/silica (diatomaceous earth/silicon dioxide; tradename Celite® S) available from Sigma Aldrich (0.3 kg, 1.0 wt./wt.) mixture. The mixture was filtered and washed with tetrahydrofuran (0.9 L, 3 vol./wt., 2.7 wt./wt.).

**[0413]** The mixture was settled for phase separation. The organic layer was collected and the aqueous layer was washed with tetrahydrofuran (0.9 L, 3 vol./wt., 2.7 wt./wt.). The organic layer was again collected and combined with the first organic layer. The combined organic layer was washed with 40% $K_2CO_3$ (1.2 L, 4 vol./wt., 5.6 wt./wt.). The organic layer was concentrated at NMT 75 °C under reduced pressure until the volume reached the lowest agitateable volume. Ethyl acetate (1.5 L, 5 vol./wt., 4.5 wt./wt.) was added and the mixture was distilled under reduced pressure at NMT 75 °C until the volume reached the lowest agitateable volume. Ethyl acetate (1.5 L, 5 vol./wt., 4.5 wt./wt.) was added and the mixture was distilled under reduced pressure at NMT 75 °C until the volume reached 5 vol. (1.5 L). The mixture was heated to dissolution and n-heptane (3.0 L, 10 vol./wt., 6.8 wt./wt.) was added. The mixture was cooled to 0±5 °C and stirred at 0±5 °C for NLT 2 hr. The mixture was filtered and the residue was washed with ethyl acetate /n-heptane=1/2 (v/v, 1.5 L, 5 vol./wt., 3.7 wt./wt.). The residue wet cake was dried under reduced pressure at NMT 60 °C to afford a mixture of (Z)-endoxifen and (E)-endoxifen, (E/Z)-4-[1-[4-[2-(Methylamino)ethoxy]phenyl]-2-phenyl-1-buten-1-yl]-phenol, compounds of Formula (III). Yield: 176 g, 42%; Purity: 81.96%. E/Z ratio: **3.1:1** (Expected yield – 40 – 60%).

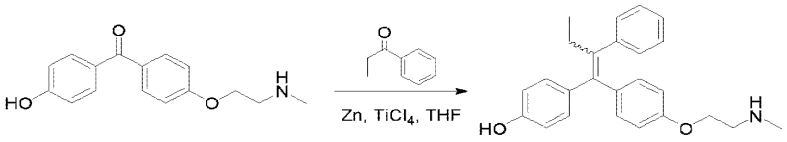
**[0414]** A suitable 10 L reactor was charged with the above (E/Z)-endoxifen (0.250 kg, 1.0 wt.), isopropanol (1.25 L, 5 vol./wt., 3.9 wt./wt.) and purified water (1.25 L, 5 vol./wt., 5.0 wt./wt.).



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The mixture was heated to 70±5 °C and stirred at 70±5 °C for NLT 2 hr. The mixture was cooled to 0±5 °C and stirred at 0-5 °C for NLT 2 hr. The mixture was filtered and washed with pre-cooled isopropanol/ purified water=1/1 (0.5 L, 2 vol./wt., 3.6 wt./wt.). The residue wet cake was dried at NMT 60 °C to afford a mixture of (Z)-endoxifen and (E)-endoxifen, (E/Z)-4-[1-[4-[2-(Methylamino)ethoxy]phenyl]-2-phenyl-1-buten-1-yl]-phenol, compounds of Formula (III). Yield: 105 g, 41%; Purity: 96.79%. E/Z ratio: **48.6:1** (Expected yield – 40 – 60%).

**Example 8:** ***Industrially Scalable Preparation of E/Z-endoxifen mixture in a McMurry Reaction***



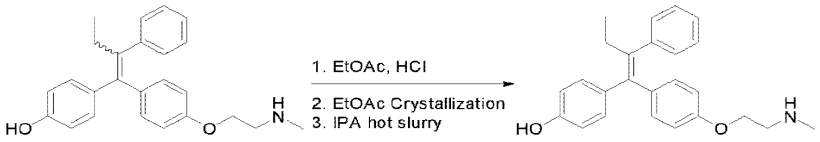

**[0415]** To a suitable reactor was charged zinc powder (10 gm, 4.0 equiv., 1.0 wt.) and tetrahydrofuran (50 mL, 5.0 vol., 4.3 wt.) under $N_2$ atmosphere. Titanium(IV) chloride (14 gm, 2.0 equiv., 1.4 wt.) was added slowly while maintaining the internal temperature at NMT 45 °C. The reaction was heated to 65±5 °C and stirred for NLT 2 hr. A suspension of (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl)methanone, the compound of Formula (II) obtained from Example 5, (10 gm, 1.0 equiv.) and propiophenone (5 gm, 1.0 equiv., 0.5 wt.) in Tetrahydrofuran (100 mL, 10.0 vol., 8.5 wt.) was added to the above mixture and stirred at 65±5 °C for NLT 8 hr. The mixture is cooled to NMT 30 °C and 40% $K_2CO_3$ (20 mL, 2.0 vol., 2.0 wt.) is added. The mixture was stirred for NLT 1 hr. The mixture was filtered and washed with Me-THF (40 mL, 4.0 vol., 3.5 wt.). The filtrate was added to 40% $K_2CO_3$ (30 mL, 3.0 vol., 3.0 wt.) and stirred for NLT 30 min. The mixture was filtered and washed with Me-THF (20 mL, 2.0 vol., 1.7 wt.). The filtrate was settled for phase separation and the organic layer is concentrated until the volume reached 3 vol. (30 mL). The mixture was extracted with 1N NaOH (100 mL, 10.0 vol., 10.0 wt.) and the organic layer was discarded. The aqueous layer was added sodium chloride (1 gm, 0.10 wt.) and then extracted 4 times with Me-THF (50 mL, 5.0 vol., 4.3 wt.). The 4 organic layers are combined and concentrated until the volume reached 5 vol. The mixture is extracted with 20% NaCl (50 mL, 5.0 vol., 5.0 wt.). The organic layer was added isopropanol (50 mL, 5.0 vol., 3.9 wt.) and the mixture was concentrated until the volume reached 3 vol. isopropanol (50 mL, 5.0 vol., 4.5 wt.) was added and the mixture is concentrated until the volume reached 3 vol. (30 mL). The mixture was heated to 65±5 °C and n-Heptane (120 mL, 12.0 vol., 8.2 wt.) was added. The mixture was cooled to NMT 5 °C and stirred at NMT 5 °C for NLT 2 hr. The mixture was filtered and washed with n-Heptane (50 mL, 5 vol., 3.4 wt.). The wet cake was dried at NMT 70 °C under reduced pressure to afford a mixture of (Z)-endoxifen and



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(E)-endoxifen, (E/Z)-4-[1-[4-[2-(Methylamino)ethoxy]phenyl]-2-phenyl-1-buten-1-yl]-phenol, compounds of Formula (III). Yield: 6.7 g, 45%; Purity: **96.79%**. E/Z ratio: **48.6:1** (Expected yield – NLT 30%).

**Example 9:** ***Industrially Scalable Enrichment of Z-Endoxifen***




(III) (IV)

**[0416]** A suitable reactor was charged with the mixture of (Z)-endoxifen and (E)-endoxifen, compounds of Formula III, (0.105 kg, 1.0 wt.) and first solvent, ethyl acetate, (1.1 L, 10 vol./wt., 9.0 wt./wt.). The mixture was cooled to 0-5 °C and 6N HCl (0.3 L, 3 vol./wt., 3.0 wt./wt.) was added slowly to the mixture. The mixture was heated to 60±5 °C and stirred at 60±5 °C for NLT 6 hr. The mixture was cooled to 0±5 °C and 8N NaOH (0.3 L, 3.0 vol./wt., 3.0 wt./wt.) was added slowly until the pH of the mixture was ≥ 12.

**[0417]** The mixture was settled for phase separation, the organic layer was collected and the aqueous layer was washed with the first solvent, ethyl acetate (0.5 L, 5 vol./wt., 4.5 wt./wt.). The organic layer was collected. The combined organic layers were washed with 20% NaCl (0.3 L, 3 vol./wt., 3.0 wt./wt.). The organic layer was treated with activated carbon (charcoal) (0.005 kg, 0.05 wt.) and stirred at 50±5 °C for NLT 1 hr. The mixture was filtered through a bed of diatomaceous earth/silica (Celite® S) and washed with ethyl acetate (0.5 L, 5 vol./wt., 4.5 wt./wt.). The filtrate was concentrated at NMT 75 °C until the volume reached 10 vol. (1.1 L). The mixture was cooled to 0-5 °C and stirred at 0-5 °C for NLT 2 hr. The mixture was filtered and the filtrate was collected. The filtrate was concentrated at NMT 75 °C until the volume reached the lowest agitateable volume.

**[0418]** A second solvent, isopropanol, (1.1 L, 10 vol./wt., 7.9 wt./wt.) was added and the mixture was concentrated at NMT 75 °C until the volume reached the lowest agitateable volume. Isopropanol (1.1 L, 10 vol./wt., 7.9 wt./wt.) was again added and the mixture was concentrated at NMT 75 °C until the volume reached the lowest agitateable volume. Isopropanol (1.1 L, 10 vol./wt., 7.9 wt./wt.) was added and the mixture was concentrated at NMT 75 °C until the volume reached 5 vol. (0.5 L). The suspension was stirred at 50±5 °C for NLT 6 hr. The mixture was cooled to 20±5 °C and stirred at 20±5 °C for NLT 4 hr. The mixture was filtered and washed with isopropanol (0.2 L, 2 vol./wt., 1.6 wt./wt.). The wet cake was dried at NMT 60 °C to afford purified (Z-endoxifen) solid compound of Formula (IV) as an off-white solid. Yield: 39.5 g, 36%, (E)/(Z) ratio: **1/12.2**; Purity (Z): **89.59%** by HPLC, Expected Yield (20-40%).



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**[0419]** A suitable 1 L reactor was charged with the above Z-endoxifen (39 g) solid compound of Formula (IV) and a third solvent, isopropanol (390 mL, 10 vol./wt.). The suspension was stirred at 50±5 °C for NLT 6 hr. The mixture was cooled to 20±5 °C and stirred at 20±5 °C for NLT 4 hr. The mixture was filtered and washed with isopropanol (78 mL, 2 vol./wt.). The wet cake was dried at NMT 60 °C to afford purified (Z-endoxifen) solid compound of Formula (IV) as an off-white solid. Yield: 25 g, 61%, (E)/(Z) ratio: 1/55.1; Purity (Z): **95.81%**, Expected Yield (50-70%).

**[0420]** In this manner, polymorph Form I of endoxifen was prepared. XRPD patterns for two batches of the resultant polymorph are provided in **Figs. 9** and **10**. The XRPD peaks from **Figs. 9** and **10** are provided in **Table 8**.

**[0421]** **Table 8**: XRPD peaks from **Figs. 9** and **10**.

| **Fig. 9** | |
|---|---|
| **Peak Position (°2θ)** | **Relative Intensity (%)** |
| 7.1 | 15 |
| 9.3 | 22 |
| 12.4 | 8 |
| 14.2 | 26 |
| 15.2 | 14 |
| 16.0 | 20 |
| 16.8 | 58 |
| 17.1 | 100 |
| 18.2 | 40 |
| 18.6 | 15 |
| 18.9 | 12 |
| 19.8 | 14 |
| 20.9 | 32 |
| 21.3 | 24 |
| 21.7 | 53 |
| 22.5 | 15 |
| 23.2 | 19 |
| 24.3 | 30 |
| 25.3 | 15 |
| 26.5 | 13 |
| 26.8 | 20 |
| 28.0 | 9 |
| 29.0 | 9 |

| **Fig. 10** | |
|---|---|
| **Peak Position (°2θ)** | **Relative Intensity (%)** |
| 7.1 | 8 |
| 9.3 | 13 |
| 12.3 | 4 |
| 14.2 | 16 |
| 15.2 | 10 |
| 16.0 | 14 |
| 16.8 | 49 |
| 17.1 | 100 |
| 18.2 | 35 |
| 18.6 | 8 |
| 18.8 | 8 |
| 19.9 | 6 |
| 20.9 | 31 |
| 21.3 | 19 |
| 21.8 | 55 |
| 22.5 | 9 |
| 23.2 | 9 |
| 24.4 | 29 |
| 25.3 | 12 |
| 26.5 | 11 |
| 26.9 | 23 |
| 28.0 | 7 |
| 29.0 | 9 |

**Example 10:** ***Industrially Scalable Enrichment of ~1:1 E/endoxifen/Z-Endoxifen Mixture***

**[0422]** A suitable reactor was charged with the mixture of (Z)-endoxifen and (E)-endoxifen, compounds of Formula III, (0.420 kg, 1.0 wt.) and ethyl acetate (4.2 L, 10 vol./wt., 9.0 wt./wt.). The mixture was cooled to 0-5 °C and 6N HCl (1.3 L, 3 vol./wt., 3.0 wt./wt.) was added slowly.



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The mixture was heated to 60±5 °C and stirred at 60±5 °C for NLT 6 hr. The mixture was cooled to 0±5 °C and 8N NaOH (1.3 L, 3.0 vol./wt., 3.0 wt./wt.) was added slowly until the pH of the mixture was ≥ 12.

**[0423]** The mixture was settled for phase separation, the organic layer was collected and the aqueous layer was washed with ethyl acetate (2.0 L, 5 vol./wt., 4.5 wt./wt.). The organic layer was collected. The combined organic layers were washed with 20% NaCl (1.3 L, 3 vol./wt., 3.0 wt./wt.). The organic layer was treated with activated carbon (charcoal) (0.02 kg, 0.05 wt.) and stirred at 50±5 °C for NLT 1 hr. The mixture was filtered through diatomaceous earth/silica (Celite® S) bed and washed with ethyl acetate (2.0 L, 5 vol./wt., 4.5 wt./wt.). The filtrate was concentrated at NMT 75 °C until the volume reached 5 vol. (2.0 L). The mixture was heated to reflux and then cooled to 50±5 °C. n-Heptane was added slowly at 50±5 °C. The mixture was cooled to 0±5 °C and stirred at 0±5 °C for NLT 2 hr. The mixture was filtered and washed with EtOAc/n-Heptane=1/2 (v/v). The wet cake was dried under reduced pressure at NMT 60 °C to afford substantially pure ~1:1 E/Z-endoxifen. [Yield: 106 g, 25%; (E)/(Z) ratio: 1.1/1; Purity (E/Z): 97.94%, Expected Yield (20-40%)].

**[0424]** In this manner, polymorph Forms II and III of endoxifen were prepared. Detailed parameters for the preparation of polymorph Forms II and III are provided in **Table 9**, and XRPD patterns are provided in **Figs. 11-13**. The XRPD peaks from **Figs. 11-13** are provided in **Table 10**

**[0425]** **Table 9**: Parameters for isolation of polymorph Form II and Form III

| Entry | 1 | 2 | 3 |
|---|---|---|---|
| Reactor capacity | 10 L | 10 L | 50 L |
| E/Z-endoxifen input | 0.37 kg | 0.17 kg | 0.83 kg |
| 6N HCl | 1.1 kg (3 vol.) | 0.68 kg (4 vol.) | 3.32 kg (4 vol.) |
| Reaction time | 60 °C, 6 hr | 60 °C, 6 hr | 60 °C, 6 hr |
| E/Z ratio in IPC | 1.1 | 1.1 | 1.1 |
| pH after 8N NaOH neutralization | 14 | 13 | 14 |
| NaCl extraction | 20% NaCl, 1.1 kg | 20% NaCl, 1.0 kg | 5% NaCl, 2.5 kg |
| Org. layer concentrate to 5 vol. | to 1.9 L (5.1 vol.) | to 1 L (5.8 vol.) | to 4 L (4.8 vol.) |
| n-Heptane (10 vol.) addition at 50 °C | 2.5 kg, 40 min | 1.2 kg, 30 min | 5.6 kg, 36 min |
| Agitation at 50 °C | 150 rpm, 40 min | 130 rpm, 1 hr | 150 rpm, 2 hr |
| Cool to 0 °C | 2 hr | 4 hr | 5 hr |
| Agitation at 0 °C | 150 rpm, 2 hr | 140 rpm, 6 hr | 150 rpm, 6 hr |
| Filtration time | 10 min | 10 min | 20 min |
| Drying | 50 °C, 4 hr | 68 °C, 18 hr | 69 °C, 26 hr |
| E/Z ratio of API | 1.1 | 0.92 | 1.1 |



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| Entry | 1 | 2 | 3 |
|---|---|---|---|
| XRPD pattern | Form II (**Fig. 11**) | Form III (**Fig. 13**) | Form II (**Fig. 12**) |

**[0426] Table 10**: XRPD peaks from **Figs. 11, 12** and **13**.

| Fig. 11 | |
|---|---|
| **Peak Position (°2θ)** | **Relative Intensity (%)** |
| 6.6 | 31 |
| 7.0 | 42 |
| 9.3 | 16 |
| 11.9 | 100 |
| 13.3 | 20 |
| 14.0 | 96 |
| 14.1 | 22 |
| 15.1 | 11 |
| 16.8 | 13 |
| 17.1 | 22 |
| 17.7 | 14 |
| 18.4 | 69 |
| 18.6 | 13 |
| 20.0 | 16 |
| 20.8 | 35 |
| 21.3 | 17 |
| 21.7 | 59 |
| 22.0 | 16 |
| 22.9 | 14 |
| 23.2 | 9 |
| 23.9 | 17 |
| 24.3 | 12 |
| | |

| Fig. 12 | |
|---|---|
| **Peak Position (°2θ)** | **Relative Intensity (%)** |
| 6.6 | 33 |
| 7.0 | 35 |
| 9.3 | 24 |
| 11.9 | 100 |
| 13.3 | 27 |
| 14.0 | 85 |
| 14.2 | 34 |
| 15.1 | 16 |
| 16.8 | 12 |
| 17.1 | 20 |
| 17.7 | 15 |
| 18.4 | 65 |
| 18.5 | 17 |
| 20.0 | 20 |
| 20.8 | 46 |
| 21.3 | 29 |
| 21.7 | 82 |
| 22.0 | 18 |
| 22.9 | 19 |
| 23.2 | 16 |
| 23.9 | 17 |
| 24.3 | 14 |
| | |

| Fig. 13 | |
|---|---|
| **Peak Position (°2θ)** | **Relative Intensity (%)** |
| 6.6 | 24 |
| 7.0 | 21 |
| 9.2 | 19 |
| 9.6 | 17 |
| 11.9 | 55 |
| 13.3 | 20 |
| 13.9 | 39 |
| 16.8 | 50 |
| 17.1 | 100 |
| 17.7 | 56 |
| 18.2 | 38 |
| 18.3 | 37 |
| 19.9 | 22 |
| 20.2 | 18 |
| 20.8 | 38 |
| 21.3 | 24 |
| 21.7 | 56 |
| 22.5 | 19 |
| 22.9 | 17 |
| 23.9 | 26 |
| 24.3 | 29 |
| 25.3 | 15 |
| 26.8 | 20 |

**Example 11:** ***Stability of Z-endoxifen Free Base***

**[0427]** Commercially, endoxifen is available as an E/Z isomer free base mixture, as well as ≥98% (Z)-endoxifen HCl and (Z)-endoxifen citrate salts. Stability of Z-endoxifen HCl salt in aqueous and solid forms has been previously published (Elkins et al. J Pharm Biomed Anal. 2014 January; 88: 174–179). Elkins et al. provide predicted t90 values for 10% conversion of (Z)-endoxifen HCl to (E)-endoxifen in the solid state of 53 months at 25 °C/60% RH and 4.3 months at 40 °C /75% RH. Conversion is expected to be more rapid in a solution environment. In an aqueous medium, Elkins et al. provide (Z)-endoxifen HCl t90 values of 149 days at room temperature and 9 days at 45 °C. There remains a need for (Z)-endoxifen free base preparations that are sufficiently stable for preparation of pharmaceutical compositions that are suitable for



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administering to subjects, for example, at ambient temperatures as well as at higher temperature and humidity.

**[0428]** Provided herein in the present disclosure are preparations of endoxifen free base that are substantially pure, at least 90% (Z)-endoxifen free base, and stable for at least 9 months under conditions of ambient and high temperature and humidity. Stability, for the purpose of this disclosure, is defined as the continued presence of at least 90% (Z)-endoxifen in a composition for at least 6 months, and is measurable by (Z)-endoxifen conversion to (E)-endoxifen starting from the date of synthesis.

**A. Accelerated 10-day Stability Study of (Z)-Endoxifen Free Base**

**[0429]** The stability of (Z)-endoxifen free base Sample 1 of **Table 11** was studied when stored at various temperatures in solid form and in ethanol (EtOH) solution. The (E)-endoxifen and (Z)-endoxifen levels were measured on days 2, 7 and 10 following placement of 1 g aliquots of purified (Z)-endoxifen free base in 180 mL HDPE bottles under dry $N_2$, which were then placed in double LDPE bags. The double bagged HDPE bottles containing each sample were individually packed in aluminum foil bags and thermally sealed until they were opened for testing the stability of the samples. The (E)- and (Z)-isomers of endoxifen were monitored by HPLC as disclosed above. The purity of (Z)-endoxifen in solid form remained at about 97% at 40 °C, 60 °C, and 80 °C up to 10 days. The results of the accelerated 10 days study indicate that (Z)-endoxifen in solid form does not interconvert to (E)-endoxifen at the tested temperatures up to 10 days.

**[0430] Table 11**: Accelerated Stability Test of Solid (Z)-endoxifen Free Base

| **No.** | | **1** | **2** | **3** |
|---|---|---|---|---|
| **Z-endoxifen** | | **1 g** | **1 g** | **1 g** |
| **Temperature** | | **40 °C** | **60 °C** | **80 °C** |
| 2 days | E/Z ratio | 1/76 (1.27%/**97.45%**) | 1/75 (1.30%/**97.43%**) | 1/76 (1.28%/**97.42%**) |
| | Total Impurity | 1.28% | 1.27% | 1.30% |
| 7 days | E/Z ratio | 1/81 (1.2%/**97.11%**) | 1/83 (1.17%/**87.11%**) | 1/72 (1.34%/**96.92%**) |
| | Total Impurity | 1.69% | 1.72% | 1.74% |
| 10 days | E/Z ratio | 1/75 (1.29%/**97.31%**) | 1/82 (1.27%/**97.48%**) | 1/77 (1.27%/**97.33%**) |
| | Total Impurity | 1.40% | 1.33% | 1.40% |



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**[0431] Table 12**: Accelerated Stability Study of (Z)-endoxifen Free Base Solution in Ethanol

| **No.** | | **1** | **2** | **3** | **4** |
|---|---|---|---|---|---|
| (Z)-endoxifen | | 0.1 g | 0.1 g | 0.05 | 0.05 g |
| Solvent | | 10 mL 99.5% EtOH | 10 mL 99.5% EtOH | 18 mL 70% EtOH | 18 mL 70% EtOH |
| Concentration | | 10 mg/mL | 10 mg/mL | 2.8 mg/mL | 2.8 mg/mL |
| Temperature | | **25 °C** | **40 °C** | **25 °C** | **40 °C** |
| 2 days | E/Z Ratio | 1/71 (1.37%/97.33%) | 1/57 (1.70%/96.98%) | 1/46 (2.09%/96.59%) | 1/21 (4.43%/94.23%) |
| | Total Impurity | 1.3% | 1.32% | 1.33% | 1.34% |
| 7 days | E/Z Ratio | 1/50 (1.91%/**96.37**%) | 1/34 (2.82%/**95.45**%) | 1/17 (5.62%**92.67**%) | 1/5.5 (15.23%/**83.04**%) |
| | Total Impurity | 1.72% | 1/73% | 1.71% | 1.73% |
| 10 days | E/Z Ratio | 1/37 (2.58%/**96.03**%) | 1/27 (3.56%/**95.10**%) | 1/8.4 (10.46%/**88.20**%) | 1/3.4 (22.59%/**76.09**%) |
| | Total Impurity | 1.39% | 1.34% | 1.34% | 1.32% |

**[0432]** Results show that (Z)-endoxifen free base is surprisingly stable in alcoholic (for example ethanol and isopropanol (data not shown)) solutions even at elevated temperatures (40 °C) at higher concentrations over 10 days. Accelerated stability at higher temperatures are generally considered predictive of long term (at least 18 m) stability at ambient temperatures.

**B. Bulk Drug Stability Study**

**[0433]** (Z)-endoxifen free base of the instant disclosure prepared by methods disclosed herein is surprisingly stable in bulk form. For bulk stability studies, ~1 g aliquots of (Z)-endoxifen free base were placed inside individually in double LDPE bags tied with a nylon cable tie. The LDPE bags were then placed in aluminum foil bags and thermally sealed. The samples for stability were placed in tightly capped, 180 mL HDPE bottles under inert conditions (dry nitrogen) at 5 °C and 25 °C/60% RH for 12 months, and at 40 °C/75% RH for 3 months. The samples were tested for (E)-endoxifen and (Z)-endoxifen concentrations and impurities, moisture or water content by Karl Fischer titration, aerobic bacterial colony forming units and appearance at time points day 0, 10 days, 1 m and 3 m. **Table 13** below provides bulk drug stability data at 9 m on endoxifen free base at varying storage conditions.



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**[0434]** **Table 13**: Bulk Drug Stability of (Z)-endoxifen Free Base

| **Endoxifen (Free Base)** | **%Purity Storage (5 °C)** | | | | **%Purity Storage 25 °C/60%RH** | | | | **%Purity Storage 40 °C/75%RH** | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **0 m** | **3 m** | **6 m** | **9 m** | **0 m** | **3 m** | **6 m** | **9 m** | **0 m** | **3 m** |
| (Z)-endoxifen | 99.5 | 99.6 | 99.5 | 99.5 | 99.5 | 99.6 | 99.5 | 99.5 | 99.5 | 99.5 |
| (E)-endoxifen | 0.19 | 0.17 | 0.18 | 0.19 | 0.19 | 0.17 | 0.18 | 0.19 | 0.19 | 0.17 |
| Water content (Karl Fischer) | 0.06 | 0.05 | 0.05 | 0.05 | 0.06 | 0.05 | 0.06 | 0.07 | 0.06 | 0.07 |
| Max Indiv. Impurity | 0.11 | 0.10 | 0.11 | 0.11 | 0.11 | 0.11 | 0.11 | 0.11 | 0.11 | 0.11 |
| (Z)-endoxifen USP <921≥ Plate Count (cfu g/mL) | 13990 | | | | 14030 | | | | 13776 | |

**[0435]** Results show that solid Z-endoxifen free base is stable for at least 9 months at 5 °C and 25 °C/60% RH. Accelerated stability at high temperatures is considered to be predictive of long term (at least 18 m) stability at ambient temperatures. (Z)-to-(E) endoxifen interconversion is minimal at the storage conditions studied, water content was not more than 1% and aerobic bacterial plate count TAC (cfu) is less than 20,000 cfu g/mL. Maximum individual impurities were determined at each time point and ranged from 0.10% to 0.11%.

**Example 12:** ***Characteristics of Purified Solid Z-endoxifen Free Base***

**[0436]** (Z)-endoxifen free base, produced by methods disclosed herein, was a white to off-white powder. The water content of such a powder was not more than 1% as determined using Method 1c (Karl Fischer titration) of USP 921. The residual solvents were measured. Methanol was not more than (NMT) 3000 ppm, tetrahydrofuran NMT 720 ppm, isopropanol, ethyl acetate, n-heptane, and ethanol were each NMT 5000 ppm.

**[0437]** Residue on ignition of (Z)-endoxifen was not more than 0.1% as determined by Method II of USP 281. Residue on ignition of (Z)-endoxifen ranged from 0.02% to 0.099%. In some embodiments, the residue upon ignition is not more than 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, and 0.1%. In another aspect, the heavy metals were NMT 20 ppm as tested by Method II of USP 231.

**[0438]** Elemental levels in solid (Z)-endoxifen free base is tested using test methods of USP 232 and USP 40.

**[0439]** Thus, the processes described herein and endoxifen prepared using these processes are suitable for manufacture of clinical and commercial grade (Z)-endoxifen.



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**[0440]** *FTIR spectrum of Z-endoxifen*

**[0441]** (Z)-endoxifen was analyzed using Fourier Transform Infra-Red Spectroscopy (Instrument type: FT/IR4600Type A; Jasco: S/N ratio 25,000:1, Max resolution 0.7 $cm^{-1}$) with standard light source and a TGS detector. Infrared spectra were recorded on a FTIR spectrometer (Model FT/IR 4600 Type A; manufacturer Jasco), equipped with triglycine sulfate (TGS) detector and KBr beam splitter, using AgBr windows. About 10 mg of (Z)-Endoxifen free base was placed onto the ATR crystal, pressure was applied with the tip, and the sample spectrum was collected. Spectra were collected with a scan speed to 2 mm/sec using hydrated films. Interferograms were accumulated over the spectral range 4000–650 $cm^{-1}$ with a nominal resolution of 0.4 $cm^{-1}$ and 32 scans. Fig 2 shows a representative IR Spectrum of (Z)-endoxifen free base.

**[0442]** Figure 2 shows that purified (Z)-endoxifen has peaks at 702.0, 730.9, 794.5, 825.4, 907.3, 1027.9, 1167.7, 1238.1, 1278.6, 1508.1, 1575.6, 1607.4, 3310.2 wavelengths $cm^{-1}$ +/- 0.4 $cm^{-1}$. A previously published FT/IR spectrum of free endoxifen showed peaks are at 706, 831, 1053, 1171, 1240, 1465, 1507 and 1604 wavelength $cm^{-1}$ (Agudelo et al. PLoS ONE 8(3): e60250. doi:10.1371/journal.pone.0060250).

**[0443]** **Table 14**: Spectral Assignments for IR spectrum of (Z)-endoxifen free base

| Assignment | Frequency | Strength |
|---|---|---|
| N-H stretching<br>O-H stretching | 3200 – 3500 | weak |
| C=C stretching | 1500 – 1680 | Medium |
| CH2 & CH3 bending | 1200 - 1500 | Medium |
| C-N stretching<br>C-O stretching | 1000 - 1200 | Medium |
| =C-H bending<br>=CH2 bending | 690 - 1000 | Medium |

**Example 13:** ***Oral Compositions of Z-endoxifen***

**[0444]** *API-in-Capsule*. ≥90% Z-endoxifen free base was prepared as disclosed above. Dry white-to-off-white powder is formulated as stable free-flowing powder and filled neat into a capsule as a Drug-in-Capsule (DIC, also called API-in-capsule, AIC) oral solid dosage form. 1 mg, 2 mg, and 4 mg of endoxifen which was at least 90% (Z)-endoxifen was filled neat in a VCaps® Plus enteric capsule using Xcellodose technology (Capsugel). AIC were of size 0, Swedish orange in color.

**[0445]** The VCaps® Plus enteric capsules (Capsugel) are made with gluten free, non-animal self-gelling product hypromellose (methyl and hydroxypropyl mixed ether of cellulose), with low-moisture content that is suitable for moisture-sensitive ingredients such as (Z)-endoxifen. The capsules are coated with an enteric coating designed to achieve intestinal targeting (upper GI and colon), by the method of Cole et al. (Cole et al., Int. Journal of Pharmaceutics Vol. 231 83–95,



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2002). Eudragit FS D30 is used as enteric coating for colonic targeted release and Eudragit L30 D55 is used as enteric coating for upper gastrointestinal targeted release.

**[0446]** (Z)-endoxifen free base in the AIC is released in predominantly in the intestines (upper GI and colon) and is protected from the acidic environment in the stomach for at least 6 hours. Enteric coating of the capsule prevents the release of (Z)-endoxifen in the stomach for at least 6 hours as tested by a method of USP 711.

**[0447]** Enteric AIC disclosed herein is stable for at least 6 months.

**[0448]** *Standards and testing for microbial contamination of the oral solid dosage forms of the instant disclosure*. For formulations of the solid dosage compositions disclosed herein, as the water content is NMT 1% and water activity (Aw) is less than 0.75, testing TAC and USP indicator organism is not necessary. The publication, "Microbial Bioburden on Oral Solid Dosage Form," by Jose E. Martinez, Pharmaceutical Technology, February 2002, pages 58 to 70, is hereby incorporated by reference in its entirety.

**[0449]** Furthermore, since formulations of the compositions disclosed herein also have water activity of less than 0.75, then no detailed microbial testing of that need be done. Total Aerobic Plate Count (TAC) is an estimation of the total viable aerobic bacteria present in a sample of raw material, in-process material, or finished product. Samples are analyzed in accordance with the most current USP Guidelines Chapter 61 (Microbial Limits Tests).

**[0450]** Acceptable TAC for oral solid dosage forms (OSDFs) are established for the formulation of the inventive compositions in terms of alert and action levels, which could be 1000 cfu g/ml, and 10,000 cfu g/mL respectively. A TAC that is 20,000 cfu g/mL is considered unacceptable.

**Example 14:** ***Preparation of (Z)-endoxifen Salt***

**[0451]** (Z)-Endoxifen D-gluconate salt is prepared by mixing an ethanolic slurry of (Z)-endoxifen as the free base with an aqueous solution of D-gluconic acid, followed by hydrolyzing a 20% w/v solution of D-gluconolactone in water and heating at 70 °C for 15 to 30 min. Minimum volume of ethanol is used and 5 ml of the aqueous D-gluconic acid solution is adder per 1 g of endoxifen free base. Stirring is then continued until a clear solution is obtained. (Z)-Endoxifen D-gluconate is crystallized using the methods disclosed above in Examples 1 to 4 to provide (Z)-endoxifen D-gluconate salt.

**[0452]** 1 mg, 2 mg, 5 mg, 10 mg, 20 mg and 40 mg AIC enteric capsules will be prepared as described above. Similarly, 1 mg to 50 mg tablets will be prepared using (Z)-endoxifen D-gluconate salt with enteric coatings EUDRAGIT ® FS D30 and EUDRAGIT ® L30D 55 to target small intestine and colon.



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**[0453] Table 15**: Exemplary Tablet

| Ingredient | wt/wt of composition |
|---|---|
| (Z)-endoxifen D-gluconate | 0.1% to 20% |
| croscarmellose sodium | 0.5% to 15% |
| microscrystalline cellulose | 15% to 90% |
| mannitol | 5% to 30% |
| Enteric coating EUDRAGIT ® L30D 55 | 0.01% to 3% |

**Example 15:** ***Placebo Controlled, Dose Escalation Safety and Pharmacokinetic Study of Oral (Z)-Endoxifen***

**[0454]** An objective of the study was to assess the safety and tolerability of oral (Z)-Endoxifen when administered as a topical application to the breast or orally as a capsule to healthy female volunteers. A secondary objective was to assess the pharmacokinetics of multiple doses of oral (Z)-Endoxifen in the subjects.

**[0455]** Generally, healthy female volunteers aged ≥ 18 years and ≤ 65 years were enrolled. 24 participants were enrolled in 3 cohorts and will be administered study drug orally. Three dose levels of orally administered (Z)-Endoxifen were investigated in 3 cohorts. In each cohort participants were randomized to receive an oral (Z)-Endoxifen or placebo in a blinded fashion. Enteric-resistant capsules used in the study were designed as delayed release capsules to resist rupture for at least 30 minutes, but typically, for about 2 hours, under gastric conditions and then open fully in intestinal fluid (DRCaps; Capsugel, a Lonza Company, USA). Enteric-resistant (Swedish Orange size Zero (0); Capsugel, USA) DRCaps capsules manually filled with 1, 2 or 4 mg of (Z)-endoxifen neat in compliance with GMP requirements were used. Placebo capsules contained microcrystalline cellulose an inert common capsule and tablet excipient.

**[0456]** Each cohort enrolled 8 participants, with 6 participants receiving (Z)-Endoxifen 1 mg capsules orally at 1 mg (Cohort 1), 2 mg (Cohort 2) or 4 mg (Cohort 3) doses and 2 participants receiving matching placebo capsules. In Cohort 1 (Dose Level = 1 mg) two participants (sentinels) were dosed 24 hours prior to the remaining participants. One sentinel was dosed with (Z)-Endoxifen and the other with placebo. The remaining six participants in Cohort 1 were dosed as no safety concerns were identified in the sentinel participants. The non-sentinel participants in Cohort 1 were admitted to the clinical research facility at least one day later than the sentinels. There were no sentinels in Cohorts 2 and 3.

**[0457]** Participant engagement in this study was for a period of 56 days. These included a 28 day screening period, and a 7 day post treatment period for Pharmacokinetic (PK) sampling. There were two confinement periods, one at the beginning and one at the end of the dosing periods. Participants were confined to the clinical facility on Days -1 through to Day 2 and Days 21 and



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22. If participants were to experience any clinically significant adverse events during the study, they would have been required to remain in the clinical facility for further observation at the discretion of the Principal Investigator (PI).

**[0458]** Healthy female volunteers were screened within 28 days prior to commencement of dosing. Participants were admitted to the clinical facility on Day -1 for up to 3 days. The first dose of (Z)-Endoxifen or placebo capsules was administered on Day 1. Following completion of all safety assessments and sampling for PK analyses, participants were discharged from the clinical facility on Day 2. The first dose on Day 1 was followed by a 6-day treatment free period (Days 2-7). Each participant returned to the clinical facility for PK blood draws and safety assessments during the treatment free period on study Days 4 and 6. On Day 8 participants commenced daily administration of (Z)-Endoxifen capsules or placebo capsules for 14 consecutive days (Days 8-21). Participants were supplied with study drug capsules and asked to self administer daily. Participants visited the clinical facility on Days 11, 14 and 17, prior to dose administration, for PK blood draws and safety assessments. On the morning of Day 21 each participant returned to the clinical facility prior to dose administration and were confined to the facility until Day 22 to allow for the collection of PK blood draws and safety assessments. The Day 21 dose was the last administration of study drug. Participants were discharged from the clinical facility on Day 22 and returned for PK blood draws and safety assessments on study Days 24, 26, and 28.

**[0459]** Study assessments included taking the subjects medical history, including evaluation of any on-study adverse events and concomitant medication use; height and weight; physical examination; periodic vital signs (body temperature, heart rate, respiratory rate, blood pressure); periodic 12-lead ECGs. Laboratory tests included hematology, coagulation, urinalysis, serum chemistry and biomarker analysis (e.g., CYP2D6, BRCA1/2, Ki67, tamoxifen metabolites, etc.). Specific assessments to evaluate treatment safety included the following: the frequency and type of adverse events, clinical laboratory testing, 12-lead ECGs and vital signs. A modified FACT-ES® scoring questionnaire was used to assess symptomatology.

**[0460]** Blood draws for PK analysis were collected pre-dose (within 10 min) and 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours following study drug administration on Days 1 and 21. PK samples for all other study days were collected within 10 min prior to dose administration. PK samples were obtained during the treatment free period on Days 4 and 6. Additional, PK samples were collected during the daily dosing period on Days 8, 11, 14 and 17 (within 10 min pre-dose). PK samples following completion of treatment will be collected on Days 24, 26 and 28. AUC(inf) was measured on Day 1 blood draw samples. Steady state plasma levels were determined starting from Day 8 onwards (which served as Day 0) for this determination.



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***Safety and Tolerability***

**[0461]** Safety endpoints were summarized by dose cohort, with placebos pooled across cohorts. Treatment-emergent AEs were coded using the latest version of MedDRA by System Organ Class (SOC) and Preferred Term, classified from verbatim terms. The incidence and frequency of AEs, and SAEs, were summarized by cohort according to SOC and Preferred Terms, and by severity and relationship. The duration of AEs was determined and included in listings, along with the action taken and outcome. Vital signs, ECG and safety laboratory parameters were summarized at each scheduled time point using descriptive statistics. Post-dose assessments were compared with baseline measurements. The incidence of laboratory abnormalities was summarized. Physical examination findings were presented in listings.

**[0462]** Treatment-emergent AEs deemed to be related to study drug (probably or possibly) were reported in 15 of 18 subjects (83%, 41 AEs) who received (Z)-Endoxifen and in 4 of 6 subjects (67%, 20 AEs) who received placebo. Most treatment-related AEs were mild in severity, with treatment related AEs of moderate severity reported in 5 of 18 subjects (28%, 6 AEs) who received (Z)-Endoxifen and in 2 of 6 subjects (33%, 2 AEs) who received placebo.

**[0463]** All AEs were classified as mild (75 of 84 AEs) or moderate (9 of 84 AEs) in severity, with no AEs classified as severe. Common adverse events of tension headache, headache, abdominal pain, nausea, dysmenorrhea and fatigue were reported both in subjects who received oral (Z)-Endoxifen and subjects who received placebo. Upper respiratory infection, hot flush, abdominal distension, dry mouth, and menstruation delayed were reported only in subjects who received (Z)-Endoxifen.

**[0464]** There were no clear differences in safety as assessed by clinical laboratory tests, vital signs, ECG assessments, FACT-ES responses in subjects who had received either topical or oral (Z)-Endoxifen compared with those who received placebo, and no dose-related trends in these safety assessments in those subjects who received (Z)-Endoxifen.

***Pharmacokinetics***

**[0465]** Mean and individual (Z)-Endoxifen serum concentration-time curves were tabulated for each dose cohort, and presented graphically with concentration displayed on a linear and logarithmic scale. Pharmacokinetic parameters were determined for each participant and summarized by cohort using descriptive statistics (arithmetic means, standard deviations, coefficients of variation, sample size, minimum, maximum and median). In addition, geometric means was calculated for AUC and Cmax. Analyses using linear models was performed to assess dose proportionality (both after a single dose and multiple dose), time dependence and accumulation (oral multiple dose), and attainment of steady state (multiple dose).



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**[0466]** Parameters determined for the first and last dose (Days 1 and 21) included time to maximum concentration (Tmax), maximum concentration (Cmax), area under the concentration-time curve from time 0 to 24 hours following drug administration ($AUC_{0-24h}$), terminal elimination rate constant (kel), terminal half-life ($t_{1/2}$), terminal clearance (CL/F) and volume of distribution (Vd/F). Area under the concentration-time curve from time 0 to infinity ($AUC_{0-inf}$) was also determined for the first dose, on Day 1.

**[0467]** The pharmacokinetic parameters were determined using non-compartmental method(s). Descriptive statistics of pharmacokinetic parameters included mean, standard deviation (SD), and coefficient of variation (CV), minimum (min) and maximum (max). Dose related trends in pharmacokinetic parameters were assessed.

**[0468]** Mean and individual endoxifen serum concentration-time curves were tabulated for each dose cohort. Pharmacokinetic parameters, were determined for each participant and summarized by cohort using descriptive statistics (arithmetic means, SD, CV, sample size [N], min, max and median). In addition, geometric means were calculated for AUC and Cmax. Analyses using linear models were performed to assess dose proportionality (both after a single dose (oral) and multiple dose (topical and oral)). Statistical analysis was performed on the pharmacokinetic parameters using SAS v9.3 and Phoenix WinNonLin version 7.0 or higher.

**[0469]** ***Abbreviations used:***

| | |
|---|---|
| CV | Coefficient of Variance |
| Tmax | time to maximum concentration |
| Cmax | maximum concentration, |
| $AUC_{0-24h}$ | ("AUC24hr") area under the concentration-time curve from time 0 to 24 hours following drug administration |
| kel | terminal elimination rate constant, and volume of |
| t1/2 | terminal half-life |
| CL/F | terminal clearance |
| Vd/F | distribution. |
| $AUC_{0-inf}$ | ("$AUC_{0-inf}$") Area under the concentration-time curve from time 0 to infinity was also determined for the first dose, on Day 1. |

**[0470]** A summary of serum pharmacokinetic parameters with terminal half-life of (Z)-endoxifen, terminal elimination half-life, Tmax, Cmax, and AUC are provided below in **Table 16**.



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**[0471] Table 16**: Model Serum Pharmacokinetic Parameters

| **Day** | **(Z)-Endoxifen Dose/Day (mg)** | **Median (Range)** | **Arithmetic Mean (CV%)** | | |
|---|---|---|---|---|---|
| | | **$T_{max}$ (hr)** | **$C_{max}$ (ng/mL)** | **$AUC_{24hr}$ (hr*ng/mL)** | **$t_{1/2}$ (hr)** |
| Day 1 | 1 mg (n = 5) | 6.0 (2.0 – 8.08) | 9.6 (18.9%) | 158 (20.3%) | 41.1 (15.8%) |
| | 2 mg (n = 6) | 4.17 (3.0 – 6.0) | 17.7 (23.4%) | 305 (17.9%) | 49.0 (26.0%) |
| | 4 mg (n = 6) | 5.08 (3.0 – 6.0) | 32.5 (52.3%) | 587 (53.3%) | 41.6 (22.9%) |
| Day 21 | 1 mg (n = 5) | 8.0 (4.0 – 6.05) | 24.6 (35.0%) | 458 (36.3%) | 52.6 (20.8%) |
| | 2 mg (n = 6) | 4.0 (2.0 – 6.05) | 50.0 (23.7%) | 911 (19.7%) | 43.4 (17.1%) |
| | 4 mg (n = 6) | 5.0 (2.0 – 10.0) | 115.0 (49.0%) | 2041 (50.4%) | 45.1 (15.2%) |

**[0472]** For once daily oral administration of the delayed-release (acid-resistant) (Z)-endoxifen capsules, there was dose-proportionality (linear dose response) in Cmax and $AUC_{24hr}$ of endoxifen across the three dose levels used in the study. Cmax increased from 9.6 ng/mL to 32.5 ng/mL for the 1 mg to 4 mg doses on day 1 and from 24.6 ng/mL to 115.0 ng/mL on Day 21. Median Tmax by dose level on Days 1 and 21 ranged from 4 to 8 hours. The apparent terminal half life ($t_{1/2}$) by dose level ranged between 42 and 53 hours, and steady state appeared to be attained after approximately 7 days (Figure 5 – dosing at Day 8 and Css at Day 14). Time to reach maximum blood levels ranged from 4 to 8 hours (Figure 4).

**[0473] Table 17**: Model $AUC_{(0\text{-}inf)}$: 1 mg. 2 mg, and 4 mg (Z)-endoxifen

| $AUC_{(0\text{-}inf)}$ hr* ng/mL | | |
|---|---|---|
| Dose: 1 mg | Dose: 2 mg | Dose: 4 mg |
| 441 | 755 | 736 |
| 534 | 954 | 1883 |
| 739 | 1242 | 2116 |
| 527 | 1489 | 4624 |
| 593 | 1009 | 1098 |
| | 1188 | 1642 |



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**[0474] Table 18A**: Model Serum Concentrations (nM) Over Time by Treatment, Dose: 1 mg (Z)-Endoxifen

| Statistic | Pre-dose | Day 1 | | | | | | | | | | Day 4 Hr 72 | Day 6 Hr 120 | Day 8 Pre-dose | Day 11 Pre-Dose | Day 14 Pre-dose | Day 17 Pre-Dose |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | hr 0.5 | hr 1 | hr 2 | hr 3 | hr 4 | hr 5 | hr 8 | hr 10 | hr 12 | hr 24 | | | | | | |
| Mean | 2.68 | 2.68 | 3.75 | 17.1 | 17.1 | 20.3 | 23.6 | 22.0 | 22.5 | 18.2 | 15.0 | 8.03 | 3.75 | 2.68 | 38.5 | 43.4 | 43.4 |
| Std Dev | 0.0 | 1.89 | 2.39 | 2.4 | 1.5 | 3.6 | 4.4 | 6.9 | 6.7 | 5.8 | 3.1 | 1.89 | 1.47 | 0.00 | 8.6 | 22.8 | 19.1 |
| CV (%) | 0 | 71 | 64 | 14 | 9 | 18 | 19 | 32 | 30 | 32 | 20 | 24 | 39 | 0 | 22 | 53 | 44 |
| Median | 2.68 | 2.68 | 2.68 | 18.7 | 16.1 | 18.7 | 24.1 | 21.4 | 21.4 | 21.4 | 16.1 | 8.03 | 2.68 | 2.68 | 42.8 | 40.2 | 45.5 |
| Min | 2.68 | 0.00 | 2.68 | 13.4 | 16.1 | 18.7 | 16.1 | 13.4 | 13.4 | 8.03 | 10.7 | 5.35 | 2.68 | 2.68 | 26.8 | 13.4 | 13.4 |
| Max | 2.68 | 5.35 | 8.03 | 18.7 | 18.7 | 26.8 | 26.8 | 32.1 | 32.1 | 21.4 | 18.7 | 10.7 | 5.35 | 2.68 | 45.5 | 75.0 | 64.2 |
| GeoMean | 2.68 | 3.18 | 3.33 | 17.0 | 17.1 | 20.1 | 23.2 | 21.1 | 21.6 | 17.1 | 14.7 | 7.84 | 3.53 | 2.68 | 37.7 | 37.6 | 38.5 |

**[0475] Table 18B**: Model Pharmacokinetic Parameters by Treatment; Dose 2 mg (Z)-Endoxifen (n=6).

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mean | 0.17 | 0.00 | 2.17 | 10.2 | 14.5 | 17.2 | 17.2 | 14.3 | 14.5 | 14.2 | 10.3 | 5.67 | 2.80 | 0.83 | 28.8 | 29.2 | 32.2 |
| Std Dev | 0.41 | 0.00 | 1.47 | 3.8 | 2.3 | 4.8 | 3.7 | 3.8 | 3.4 | 2.0 | 2.3 | 1.53 | 1.10 | 0.41 | 3.3 | 4.7 | 7.7 |
| CV (%) | 245% | 0% | 68% | 37% | 16% | 28% | 21% | 26% | 23% | 14% | 22% | 28% | 39% | 49% | 11% | 16% | 24% |
| Median | 0.00 | 0.00 | 2.50 | 10.0 | 14.5 | 17.5 | 17.0 | 14.5 | 14.5 | 14.0 | 10.5 | 5.50 | 3.00 | 1.00 | 22.5 | 28.5 | 28.5 |
| Minimum | 0.00 | 0.00 | 0.00 | 5.00 | 11.5 | 11.5 | 13.5 | 8.50 | 10.0 | 12.0 | 8.00 | 4.00 | 1.00 | 0.00 | 19.5 | 23.5 | 27.0 |
| Maximum | 1.00 | 0.00 | 4.00 | 16.0 | 17.0 | 22.5 | 22.0 | 19.0 | 19.0 | 18.0 | 13.0 | 8.00 | 4.00 | 1.00 | 28.0 | 37.0 | 47.0 |
| GeoMean | 1.00 | | 2.35 | 9.55 | 14.3 | 16.6 | 16.8 | 13.8 | 14.2 | 14.1 | 10.1 | 5.47 | 2.55 | 1.00 | 22.6 | 28.9 | 31.5 |

**[0476] Table 18C**: Model Pharmacokinetic Parameters by Treatment; Dose 4 mg (Z)-Endoxifen (n=6)

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| N | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 5 | 6 | 5 | 6 | 6 |
| Mean | 0.83 | 0.83 | 3.17 | 20.0 | 27.8 | 36.8 | 30.5 | 25.5 | 30.3 | 27.8 | 21.3 | 10.5 | 5.50 | 2.33 | 50.4 | 69.0 | 68.8 |
| Std Dev | 0.41 | 0.41 | 1.72 | 5.0 | 13.7 | 12.3 | 18.0 | 11.0 | 17.8 | 14.9 | 13.2 | 6.8 | 4.64 | 1.97 | 25.3 | 45.8 | 43.6 |
| CV (%) | 49% | 49% | 54% | 25% | 49% | 34% | 59% | 43% | 59% | 53% | 62% | 65% | 83% | 84% | 50% | 66% | 63% |
| Median | 1.00 | 1.00 | 4.00 | 19.0 | 24.5 | 34.0 | 28.5 | 25.0 | 25.0 | 25.5 | 19.5 | 8.00 | 4.00 | 1.50 | 45.0 | 64.0 | 73.0 |
| Minimum | 0.00 | 0.00 | 1.00 | 11.0 | 14.0 | 14.0 | 14.0 | 13.0 | 13.0 | 11.0 | 8.00 | 4.00 | 1.00 | 1.00 | 23.0 | 3.00 | 1.00 |
| Maximum | 1.00 | 1.00 | 5.00 | 35.0 | 52.0 | 49.0 | 62.0 | 42.0 | 62.0 | 52.0 | 43.0 | 23.0 | 13.0 | 6.00 | 77.0 | 145 | 115 |
| GeoMean | 1.00 | 1.00 | 2.82 | 18.9 | 25.3 | 34.8 | 26.7 | 23.5 | 25.4 | 24.6 | 18.0 | 8.54 | 3.62 | 1.82 | 45.2 | 44.9 | 37.5 |

**[0477] Table 19A**: Day 1 Model Pharmacokinetic Parameters by Treatment; Dose 1 mg (Z)-Endoxifen. N= 5

| Statistic | Day 1 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cmax (ng/mL) | Tmax (hr) | AUCTlast (hr*ng/mL) | Kel (1/hr) | Thalf (hr) | $AUC_{0\text{-inf}}$ (hr*ng/mL) | AUC24hr (hr*ng/mL) | CL/F (L/hr) | Vz/F (L) |
| Mean | 9.6 | 5.62 | 471 | 0.015 | 46.1 | 567 | 158 | 1.82 | 119.9 |
| Std Dev | 1.8 | 2.21 | 76 | 0.002 | 7.3 | 110 | 32 | 0.33 | 27.4 |
| CV (%) | 18.9 | 39.4 | 16.2 | 16.2 | 15.8 | 19.10 | 20.8 | 18.4 | 22.9 |
| Median | 10.0 | 6.0 | 472 | 0.015 | 47.2 | 534 | 171 | 1.87 | 107.6 |
| Min | 7.0 | 2.0 | 367 | 0.013 | 37.5 | 441 | 102 | 1.35 | 102.7 |
| Max | 12.0 | 8.08 | 582 | 0.018 | 54.4 | 739 | 183 | 2.27 | 168.4 |
| GeoMean | 9.5 | 5.11 | 466 | 0.015 | 45.6 | 559 | 155 | 1.79 | 117.8 |
| GeoCV% | 19.9 | 58.2 | 16.5 | 16.2 | 16.2 | 19.1 | 24.0 | 19.1 | 20.6 |



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**[0478] Table 19B**: Day 1 Model Pharmacokinetic Parameters by Treatment; Dose 2 mg

| N | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
|---|---|---|---|---|---|---|---|---|---|
| Mean | 17.7 | 4.28 | 959 | 0.015 | 49.6 | 1105 | 305 | 1.89 | 138.6 |
| Std Dev | 4.1 | 0.96 | 225 | 0.003 | 12.7 | 256 | 55 | 0.46 | 34.9 |
| CV (%) | 23.4 | 22.5 | 23.3 | 23.3 | 25.6 | 23.1 | 17.9 | 24.1 | 25.7 |
| Median | 17.5 | 4.17 | 955 | 0.016 | 44.6 | 1099 | 303 | 1.83 | 118.6 |
| Minimum | 13.6 | 3.06 | 637 | 0.010 | 37.8 | 755 | 249 | 1.34 | 98.2 |
| Maximum | 22.0 | 6.00 | 1137 | 0.018 | 68.1 | 1489 | 389 | 2.65 | 194.8 |
| GeoMean | 17.3 | 4.19 | 862 | 0.015 | 47.7 | 1081 | 301 | 1.85 | 127.3 |
| GeoCV% | 24.1 | 22.2 | 28.7 | 25.3 | 25.3 | 24.0 | 18.0 | 24.6 | 24.7 |

**[0479] Table 19C**: Day 1 Model Pharmacokinetic Parameters by Treatment; Dose 4 mg

| N | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
|---|---|---|---|---|---|---|---|---|---|
| Mean | 32.5 | 5.56 | 1654 | 0.017 | 41.6 | 2017 | 587 | 2.73 | 154.5 |
| Std Dev | 17.0 | 2.47 | 1047 | 0.004 | 9.5 | 1375 | 313 | 1.60 | 79.9 |
| CV (%) | 52.3 | 44.5 | 63.3 | 21.8 | 22.9 | 68.2 | 53.3 | 58.5 | 51.7 |
| Median | 29.5 | 5.08 | 1423 | 0.017 | 39.9 | 1763 | 539 | 2.28 | 136.7 |
| Minimum | 14.0 | 3.00 | 691 | 0.012 | 31.6 | 735 | 358 | 0.87 | 69.9 |
| Maximum | 62.0 | 10.00 | 3574 | 0.022 | 56.0 | 4624 | 1115 | 5.43 | 258.4 |
| GeoMean | 29.1 | 5.15 | 1404 | 0.017 | 40.7 | 1704 | 521 | 2.35 | 137.8 |
| GeoCV% | 55.7 | 43.6 | 64.4 | 22.8 | 22.8 | 69.1 | 57.8 | 69.1 | 56.6 |

**[0480] Table 19D**: Day 21 Model Pharmacokinetic Parameters by Treatment; Dose 1 mg (Z)-Endoxifen. N= 5

| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
|---|---|---|---|---|---|---|---|---|
| Mean | 24.6 | 5.88 | 458 | 19.1 | 0.014 | 52.6 | 2.49 | 181.3 |
| Std Dev | 8.6 | 1.87 | 156 | 6.9 | 0.003 | 10.9 | 1.06 | 64.1 |
| CV (%) | 35.0 | 27.1 | 38.3 | 36.3 | 20.4 | 20.8 | 42.6 | 35.4 |
| Median | 29.0 | 6.00 | 527 | 22.0 | 0.014 | 49.3 | 1.90 | 170.1 |
| Minimum | 14.0 | 4.00 | 248 | 10.3 | 0.011 | 40.6 | 1.57 | 116.7 |
| Maximum | 34.0 | 8.42 | 636 | 26.5 | 0.017 | 65.8 | 4.03 | 286.8 |
| GeoMean | 23.3 | 5.64 | 431 | 17.9 | 0.013 | 51.7 | 2.32 | 173.3 |
| GeoCV% | 40.1 | 32.1 | 42.2 | 42.2 | 20.9 | 20.9 | 42.2 | 33.9 |

**[0481] Table 19E**: Day 21 Model Pharmacokinetic Parameters by Treatment; Dose 2 mg (Z)-Endoxifen.

| N | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
|---|---|---|---|---|---|---|---|---|
| Mean | 58.0 | 4.01 | 911 | 38.0 | 0.016 | 43.4 | 2.27 | 139.1 |
| Std Dev | 11.9 | 1.80 | 179 | 7.5 | 0.003 | 7.4 | 0.44 | 22.7 |
| CV (%) | 23.7 | 44.9 | 19.7 | 19.7 | 18.9 | 17.1 | 19.4 | 16.3 |
| Median | 51.0 | 4.00 | 910 | 37.9 | 0.015 | 45.7 | 2.21 | 131.6 |
| Minimum | 35.0 | 2.00 | 716 | 29.8 | 0.014 | 33.0 | 1.70 | 119.6 |
| Maximum | 65.0 | 6.05 | 1177 | 49.1 | 0.021 | 50.8 | 2.79 | 179.4 |
| GeoMean | 48.8 | 3.54 | 897 | 37.4 | 0.016 | 42.8 | 2.23 | 137.7 |
| GeoCV% | 24.9 | 53.1 | 19.8 | 19.8 | 18.2 | 18.2 | 19.8 | 15.5 |



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**[0482] Table 19F**: Day 21 Model Pharmacokinetic Parameters by Treatment; Dose 4 mg (Z)-Endoxifen.

| N | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
|---|---|---|---|---|---|---|---|---|
| Mean | 115.0 | 5.33 | 2941 | 85.1 | 0.016 | 45.1 | 2.83 | 189.0 |
| Std Dev | 56.3 | 2.73 | 1029 | 42.9 | 0.003 | 6.8 | 2.15 | 156.0 |
| CV (%) | 49.0 | 51.2 | 35.4 | 50.4 | 16.6 | 15.2 | 76.0 | 82.5 |
| Median | 131.0 | 5.00 | 2469 | 102.9 | 0.015 | 45.3 | 1.63 | 186.1 |
| Minimum | 42.0 | 2.00 | 616 | 25.7 | 0.013 | 34.0 | 1.32 | 73.0 |
| Maximum | 178.0 | 10.00 | 3934 | 126.4 | 0.020 | 54.3 | 6.49 | 461.5 |
| GeoMean | 100.5 | 4.75 | 1744 | 72.7 | 0.016 | 44.6 | 2.29 | 147.7 |
| GeoCV% | 67.4 | 58.5 | 78.1 | 78.1 | 15.9 | 15.9 | 78.1 | 84.6 |

**[0483] Table 20**: Mean Ratios of Pharmacokinetic Parameters (Day21)/(Day1)

| **(Z)-Endoxifen Dose** | **Mean Ratios of Pharmacokinetic Parameters (Day 21)/(Day1)** | | |
|---|---|---|---|
| | **$C_{max}$(Day 21)/ $C_{max}$(Day 1)** | **$AUC_{24hr}$(Day 21)/ $AUC_{24hr}$(Day1)** | **$AUC_{24hr}$(Day21)/ $AUC_{0\text{-}inf}$(Day1)** |
| 1 mg (n=5) | 2.74 (SD 1.29) | 3.09 (SD 1.49) | 0.81 (SD 0.20) |
| 2 mg (n=6) | 2.92 (SD 0.88) | 3.04 (SD 0.79) | 0.85 (SD 0.20) |
| 4 mg (n=6) | 3.56 (SD 1.01) | 3.47 (SD 1.08) | 1.08 (SD 0.38) |

**[0484]** The mean accumulation ratios ranged from 2.74 to 3.56 for Cmax and from 3.04 to 3.47 for $AUC_{24hr}$ as the ratio of parameters on Day 21 compared with Day 1. There was no marked trend by dose level in clearance (Cl/F) and volume of distribution (Vd/F) for Day 1 and Day 21.

**[0485]** Time to maximum serum endoxifen levels is achieved by about 10 hours and that there is dose-related increase in serum endoxifen levels (**Fig. 3** and **Fig. 4**). Serum endoxifen levels ranged from about 25 nM to about 80 nM.

**[0486]** Pharmacokinetic assessment of pre-dose trough concentration from Day 8 to Day 21 (**Fig. 4**) showed attainment of straight line after day 14. Steady state levels of serum endoxifen appear to be being achieved by Day 7 with daily dosing. The pre-dose serum concentrations indicate little accumulation after 17 days for 4mg of (Z)-Endoxifen.

**[0487] Table 21**: Parameter estimates of dose linearity for endoxifen

| Pharmacokinetic Parameter (log) | Analyte | Day | β Estimate | Two-sided 95% Confidence Interval | $r^2$ |
|---|---|---|---|---|---|
| Cmax | Endoxifen | 1 | 0.808 | (0.487 – 1.130) | 0.66 |
| | | 21 | 1.055 | (0.655 – 1.455) | 0.68 |
| $AUC_{24hr}$ | Endoxifen | 1 | 0.873 | (0.548 – 1.199) | 0.69 |
| | | 21 | 1.008 | (0.582 – 1.433) | 0.63 |



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**[0488] Table 22**. Comparison of (Z)-endoxifen concentrations (Oral) with published literature.

| (Z)-Endoxifen Dose | Published Literature Result of Average Plasma (Z)-Endoxifen Css | | Study Result of Average Serum (Z)-Endoxifen Css | | % Ratio of Css Study/Literature |
|---|---|---|---|---|---|
| | ng/mL | nM | ng/mL | nM | |
| 1 mg | 12.4 | 33.1 | 19.1 | 51.1 | 154% |
| 2 mg | 18.6 | 49.8 | 38 | 101.7 | 204% |
| 4 mg | 56.8 | 152.1 | 85.1 | 227.9 | 150% |
| 8 mg | 96.8 | 259.2 | - | - | - |

Css = Average Concentration at Steady State (AUCtau/tau)

**[0489]** ***Published literature***

1. Wu X et al. Cancer Res. 2009 Mar 1;69(5):1722-7. PubMed PMID: 19244106

2. Ahmad A et al. Breast Cancer Res Treat. 2010 Jul;122(2):579-84. PubMed PMID:20052538

3. Ahmad A et al. J Clin Oncol 30, 2012 (suppl; abstr 3089)

4. Goetz MP et al. San Antonio Breast Conference 2013 [PD3-4]

5. Goetz MP et al. San Antonio Breast Conference 2015. [PD203]

6. Ahmad A et al. Clin Transl Sci. 2016 Jun 27. doi:10.1111/cts.12407. PubMed PMID: 27346789

7. Lee O et al. Cancer Chemother Pharmacol. 2015 Dec;76(6):1235-46

**[0490]** Thus, data from this study suggest that safety and tolerability of oral endoxifen is generally comparable to oral tamoxifen and that subjects administered with (Z)-endoxifen compositions have plasma endoxifen levels that are within the range that has been shown to have therapeutic effect in the adjuvant setting in women with breast cancer. (Z)-Endoxifen is rapidly absorbed and systemically available and that it displays dose proportionality in peak drug concentrations in serum (C(max)) and area under the concentration-time curve extrapolated from 0 to infinity ($AUC_{0\text{-}inf}$) over the dose range 1mg - 4.0 mg.

## Example 16: *Therapeutic Treatment of Tamoxifen-Refractory Breast Cancer by Oral Administration of Z-Endoxifen Free Base*

**[0491]** An objective of the study is to demonstrate that stable and therapeutic (Z)-endoxifen levels can be achieved in tamoxifen-refractory patients by supplementing tamoxifen with (Z)-endoxifen. Plasma endoxifen levels will be used as a surrogate endpoint to predict clinical benefit as well as the rate of recurrence in this population and to confirm the safety and tolerability of (Z)-endoxifen administration when compared with tamoxifen.

**[0492]** Generally healthy subjects with early stage estrogen receptor positive breast cancer who are on adjuvant therapy of tamoxifen for at least 30 days will be enrolled for the study for up to 6



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months. At least seventy-five tamoxifen-refractory breast cancer subjects will be enrolled in the study to ensure an evaluable population consists of at least 25 tamoxifen and 25 (Z)-endoxifen subjects is achieved. Additional subjects may be enrolled to achieve the desired population of tamoxifen-refractory subjects. These subjects will have been diagnosed with breast cancer and undergone mastectomy or lumpectomy.

**[0493]** After at least 30 days of oral tamoxifen, endoxifen plasma levels will be measured. If the endoxifen level is below 30 or 40 nM, then 1 mg of oral (Z)-endoxifen will be added to the oral tamoxifen adjuvant regimen. Additional (Z)-endoxifen doses will be added until a stable endoxifen of at least 40 nM but not more than 80 nM is achieved. The endpoint is to establish a therapeutically stable endoxifen level in the tamoxifen+endoxifen group for at least 6 months.

**Example 17:** ***Pre-surgical Treatment of Estrogen Receptor Positive Breast Cancer by Oral Administration of Z-Endoxifen-D-gluconate***

**[0494]** An objective is to determine if Z-Endoxifen-D-gluconate reduces tumor activity in pre-surgical estrogen receptor positive breast cancer patients. Upon the initial diagnosis of ER+ breast cancer, 8 patients will be assigned to one of 3 groups, where each patient will receive 1, 2, or 4 mg of (Z)-endoxifen-D-gluconate for 21 days prior to surgery.

**[0495]** The biomarker KI-67 levels of the tumor will be compared from the time of initial biopsy and the surgical sample will be compared to determine if one of the 3 doses results in a decrease in tumor activity.

**Example 18:** ***Therapeutic Treatment of Breast Cancer by Oral Administration of (Z)-Endoxifen D-Gluconate***

**[0496]** An objective of the study is to demonstrate that therapeutic (Z)-endoxifen levels in the subject's plasma can be achieved in tamoxifen-refractory patients initiating adjuvant breast cancer therapy. Plasma endoxifen levels will be used as a surrogate endpoint to predict clinical benefit as well as the rate of recurrence in this population and to confirm the safety and tolerability of oral (Z)-endoxifen D-gluconate administration when compared with tamoxifen.

**[0497]** Generally healthy subjects with estrogen receptor positive breast cancer for whom tamoxifen is indicated as part of their complete treatment regimen will be enrolled for the study for up to 6 months. At least seventy five tamoxifen-refractory breast cancer subjects will be enrolled in the study to ensure an evaluable population consists of at least 25 tamoxifen and 25 (Z)-endoxifen subjects is achieved. Additional subjects may be enrolled to achieve the desired population of tamoxifen-refractory subjects. These subjects will have been diagnosed with breast cancer and undergone mastectomy or lumpectomy.



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**[0498]** Immediately after mastectomy or lumpectomy, 25 subjects will be assigned to the tamoxifen group and administered daily with oral 20 mg Tamoxifen for a period of 3 months. Additional 25 subjects will be assigned to the (Z)-endoxifen group and administered daily with oral 10 mg tablet of (Z)-endoxifen D-gluconate for a period of 3 months. Blood will be drawn from each subject at day 0 (baseline), and on days 7, 14, 21, 28, 60 and 90. Plasma (Z)-endoxifen levels, hematology, chemistry, and coagulation parameters will be taken for both treatment sets on day 0 (baseline measurement), as wells as on days 7, 14, 21, 28, 60 and 90.

**[0499]** The plasma (Z)-endoxifen levels of the two treatment sets will be compared to each other. If the plasma endoxifen levels of the tamoxifen treated subjects are less than 30 nM, then those subjects will be transferred to the (Z)-endoxifen therapy group and the treatment will continue for an additional 6 months. If the plasma endoxifen levels of the tamoxifen treated subjects are above 30 nM, they will continue to be treated with tamoxifen. Bloods samples will continue to be drawn weekly until the end of the study to monitor the subjects' plasma (Z)-endoxifen levels, hematology, chemistry, and coagulation parameters. Recurrence of cancer in the subjects will be monitored and compared between the treatment groups. Safety and efficacy will be evaluated every 3 months until the end of the study.

**[0500]** While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.



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**Inventor(s)**

Steven C. Quay, Seattle, WA;
YaoLin Sun, Kaohsiung City, TAIWAN;
LungHu Wang, Kaohsiung City, TAIWAN;
ChangJung Wu, Kaohsiung City, TAIWAN;
ChuanDer Huang, Tainan City, TAIWAN;

**Applicant(s)**

ATOSSA THERAPEUTICS, INC., Seattle, WA;

**Power of Attorney:** None

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**Foreign Applications** for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
*Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.*

**Permission to Access Application via Priority Document Exchange:** Yes

**Permission to Access Search Results:** Yes

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**If Required, Foreign Filing License Granted:** 03/20/2020

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/641,985**

**Projected Publication Date:** 07/02/2020

**Non-Publication Request:** No

**Early Publication Request:** No
**** SMALL ENTITY ****
**Title**

METHODS FOR MAKING AND USING ENDOXIFEN

**Preliminary Class**

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:** No

## PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

## LICENSE FOR FOREIGN FILING UNDER

## Title 35, United States Code, Section 184

## Title 37, Code of Federal Regulations, 5.11 & 5.15

**GRANTED**

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

**NOT GRANTED**

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

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

| U.S. APPLICATION NO. | FIRST NAMED INVENTOR | ATTY. DOCKET NO. |
|---|---|---|
| 16/641,985 | Steven C. Quay | 38602-758.831 |

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

| INTERNATIONAL APPLICATION NO. | |
|---|---|
| PCT/US18/50272 | |
| I.A. FILING DATE | PRIORITY DATE |
| 09/10/2018 | 09/11/2017 |

**CONFIRMATION NO. 7650**
**371 FORMALITIES LETTER**

*OC000000115614528*

Date Mailed: 03/24/2020

## Notification of Insufficiency Under 37 CFR 1.492 and/or 1.495 (DO/EO/US)

The following items have been submitted by the applicant or the International Bureau to the United States Patent and Trademark Office as a Designated / Elected Office (37 CFR 1.495).

- Indication of Small Entity Status
- Priority Document
- Copy of the International Application filed on 02/25/2020
- Copy of the International Search Report filed on 02/25/2020
- Preliminary Amendments filed on 02/25/2020
- Inventor's Oath or Declaration filed on 02/25/2020
- U.S. Basic National Fees filed on 02/25/2020
- Authorize Access to Search Results filed on 02/25/2020
- Priority Documents filed on 02/25/2020
- Authorization to Permit Access filed on 02/25/2020
- Application Data Sheet (37 CFR 1.76) filed on 02/25/2020

The following items **MUST** be furnished within the period set forth below:

- Additional claim fees of $**8780** as a small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

SUMMARY OF FEES DUE:

Total additional fees required for this application is $**8780** for a Small Entity:

- Total additional claim fee(s) for this application is $**8780**
  - $**920** for **4** independent claims over 3.
  - $**7450** for **149** total claims over 20.
  - $**410** for multiple dependent claim surcharge.

**ALL OF THE ITEMS SET FORTH ABOVE MUST BE SUBMITTED WITHIN TWO (2) MONTHS FROM THE DATE OF THIS NOTICE. FAILURE TO PROPERLY RESPOND WILL RESULT IN ABANDONMENT.**

The time period set above may be extended by filing a petition and fee for extension of time under the provisions of 37 CFR 1.136(a).

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)



FORM PCT/DO/EO/923 (371 Formalities Notice)

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

**If you are not using EFS-Web to submit your reply, you must include a copy of this notice.**

ROSA M WEST

Telephone: (571) 272-1019



FORM PCT/DO/EO/923 (371 Formalities Notice)

## PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/641,985

### APPLICATION AS FILED - PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | SMALL ENTITY RATE($) | SMALL ENTITY FEE($) | OR | OTHER THAN SMALL ENTITY RATE($) | OTHER THAN SMALL ENTITY FEE($) |
|---|---|---|---|---|---|---|---|
| BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | 150 | | N/A | |
| SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | 70 | | N/A | |
| EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | 380 | | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | 169 minus 20 = | * 149 | x 50 = | 7450 | OR | | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | 7 minus 3 = | * 4 | x 230 = | 920 | | | |
| APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | 0.00 | | | |
| MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | 410 | | | |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | TOTAL | 9380 | | TOTAL | |

### APPLICATION AS AMENDED - PART II

| | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | SMALL ENTITY RATE($) | SMALL ENTITY ADDITIONAL FEE($) | OR | OTHER THAN SMALL ENTITY RATE($) | OTHER THAN SMALL ENTITY ADDITIONAL FEE($) |
|---|---|---|---|---|---|---|---|---|---|---|
| AMENDMENT A | Total (37 CFR 1.16(i)) | * | Minus | ** | = | x = | | OR | x = | |
| | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | x = | | OR | x = | |
| | Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| | FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

| | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | SMALL ENTITY RATE($) | SMALL ENTITY ADDITIONAL FEE($) | OR | OTHER THAN SMALL ENTITY RATE($) | OTHER THAN SMALL ENTITY ADDITIONAL FEE($) |
|---|---|---|---|---|---|---|---|---|---|---|
| AMENDMENT B | Total (37 CFR 1.16(i)) | * | Minus | ** | = | x = | | OR | x = | |
| | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | x = | | OR | x = | |
| | Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| | FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

# MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

| Application Number | Filing Date |
|---|---|
| 16641985 | |

Applicant(s) Steven Quay

* May be used for additional claims or amendments

| CLAIMS | AS FILED | | AFTER FIRST AMENDMENT | | AFTER SECOND AMENDMENT | | | * | | * | | * | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Indep | Depend | Indep | Depend | Indep | Depend | | Indep | Depend | Indep | Depend | Indep | Depend |
| 1 | 1 | | | | | | 51 | | ( 1 ) | | | | |
| 2 | | 1 | | | | | 52 | | ( 1 ) | | | | |
| 3 | | 1 | | | | | 53 | | ( 1 ) | | | | |
| 4 | | 1 | | | | | 54 | | ( 1 ) | | | | |
| 5 | | 1 | | | | | 55 | | ( 1 ) | | | | |
| 6 | | 2 | | | | | 56 | | ( 1 ) | | | | |
| 7 | | 1 | | | | | 57 | | ( 1 ) | | | | |
| 8 | | ( 1 ) | | | | | 58 | | ( 1 ) | | | | |
| 9 | | ( 1 ) | | | | | 59 | | ( 1 ) | | | | |
| 10 | | ( 1 ) | | | | | 60 | | ( 1 ) | | | | |
| 11 | | ( 1 ) | | | | | 61 | | ( 1 ) | | | | |
| 12 | | 1 | | | | | 62 | 1 | | | | | |
| 13 | | 1 | | | | | 63 | | ( 1 ) | | | | |
| 14 | | 2 | | | | | 64 | | ( 1 ) | | | | |
| 15 | | 2 | | | | | 65 | | ( 1 ) | | | | |
| 16 | | 2 | | | | | 66 | | ( 1 ) | | | | |
| 17 | | ( 1 ) | | | | | 67 | | ( 1 ) | | | | |
| 18 | | 2 | | | | | 68 | | ( 1 ) | | | | |
| 19 | | ( 1 ) | | | | | 69 | | ( 1 ) | | | | |
| 20 | | ( 1 ) | | | | | 70 | | ( 1 ) | | | | |
| 21 | | ( 1 ) | | | | | 71 | | ( 1 ) | | | | |
| 22 | | ( 1 ) | | | | | 72 | | ( 1 ) | | | | |
| 23 | | 2 | | | | | 73 | | ( 1 ) | | | | |
| 24 | | 2 | | | | | 74 | | ( 1 ) | | | | |
| 25 | | 2 | | | | | 75 | | ( 1 ) | | | | |
| 26 | | ( 1 ) | | | | | 76 | | ( 1 ) | | | | |
| 27 | | 2 | | | | | 77 | | ( 1 ) | | | | |
| 28 | | ( 1 ) | | | | | 78 | | ( 1 ) | | | | |
| 29 | | ( 1 ) | | | | | 79 | | ( 1 ) | | | | |
| 30 | | ( 1 ) | | | | | 80 | | ( 1 ) | | | | |
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| 36 | | ( 1 ) | | | | | 86 | | ( 1 ) | | | | |
| 37 | | ( 1 ) | | | | | 87 | | ( 1 ) | | | | |
| 38 | 1 | | | | | | 88 | | ( 1 ) | | | | |
| 39 | | 1 | | | | | 89 | | ( 1 ) | | | | |
| 40 | | 2 | | | | | 90 | | ( 1 ) | | | | |
| 41 | | ( 1 ) | | | | | 91 | | ( 1 ) | | | | |
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| 50 | | ( 1 ) | | | | | 100 | 1 | | | | | |

# MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

| Application Number | Filing Date |
|---|---|
| 16641985 | |

Applicant(s) Steven Quay

* May be used for additional claims or amendments

| CLAIMS | AS FILED | | AFTER FIRST AMENDMENT | | AFTER SECOND AMENDMENT | |
|---|---|---|---|---|---|---|
| | Indep | Depend | Indep | Depend | Indep | Depend |
| 101 | | ( 1 ) | | | | |
| 102 | | ( 1 ) | | | | |
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| 137 | | 2 | | | | |
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| 149 | | ( 1 ) | | | | |
| 150 | | ( 1 ) | | | | |
| Total Indep | 7 | | 0 | | 0 | |
| Total Depend | 162 | ↵ | 0 | ↵ | 0 | ↵ |
| Total Claims | 169 | | 0 | | 0 | |

| | * | | * | | * | |
|---|---|---|---|---|---|---|
| | Indep | Depend | Indep | Depend | Indep | Depend |
| 151 | 1 | | | | | |
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 10

| Complete if Known | |
|---|---|
| Application Number | 16641985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | QUAY; Steven C. |
| Art Unit | 1629 |
| Examiner Name | Not assigned yet |
| Attorney Docket Number | 38602-758.831 |

## U. S. PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | 001 | US-4851433 | 07-25-1989 | KRAUS; Hans A. [De] et al. | |
| | 002 | US-7485623 | 02-03-2009 | BUA; Jay. | |
| | 003 | US-7507769 | 03-24-2009 | NESTOUR; Elisabeth Le. | |
| | 004 | US-7531578 | 05-12-2009 | FORMAN; Barry. et al. | |
| | 005 | US-7704516 | 04-27-2010 | DROUIN; Dominique Salin. et al. | |
| | 006 | US-7786172 | 08-31-2010 | DE LIGNIERES; Bruno. et al. | |
| | 007 | US-7968532 | 06-28-2011 | LE NESTOUR; Elisabeth. et al. | |
| | 008 | US-8048927 | 11-01-2011 | LE NESTOUR; Elisabeth. | |
| | 009 | US-8063249 | 11-22-2011 | KUSHNER; Peter. et al. | |
| | 010 | US-8119695 | 02-21-2012 | FORMAN; Barry. et al. | |
| | 011 | US-9090640 | 07-28-2015 | BIERBACH; Ulrich. et al. | |
| | 012 | US-9200045 | 12-01-2015 | LIU; David R. et al. | |
| | 013 | US-9220680 | 12-29-2015 | PERUMAL; Omathanu P. et al. | |
| | 014 | US-9333190 | 05-10-2016 | AHMAD; Ateeq. et al. | |
| | 015 | US-20070059288 | 03-15-2007 | DINSMORE; Jonathan H. et al. | |
| | 016 | US-20080138391 | 06-12-2008 | CARRARA; Dario Norberto [Ch] et al. | |
| | 017 | US-20090291134 | 11-26-2009 | AHMAD; Ateeq. et al. | |
| | 018 | US-20100112041 | 05-06-2010 | AHMAD; Ateeq. et al. | |
| | 019 | US-20120164075 | 06-28-2012 | AHMAD; Ateeq [Us] et al. | |

| Examiner Signature | | Date Considered | |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.*

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 10

| Complete if Known | |
|---|---|
| Application Number | 16641985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | QUAY; Steven C. |
| Art Unit | 1629 |
| Examiner Name | Not assigned yet |
| Attorney Docket Number | 38602-758.831 |

## U. S. PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | 020 | US-20140193334 | 07-10-2014 | BIERBACH; Ulrich. et al. | |
| | 021 | US-20140199391 | 07-17-2014 | BIRBARA; Philip J. [Us] et al. | |
| | 022 | US-20150080339 | 03-19-2015 | WANG; Guangdi. et al. | |

## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Foreign Patent Document<br>Country Code[3]-Number[4]-Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| | 001 | WO-2008070463-A2 | 06-12-2008 | JINA PHARMACEUTICALS INC [US], et al. | | ☐ |
| | 002 | WO-2009120999-A2 | 10-01-2009 | OLEMA PHARMACEUTICALS INC [US], et al. | | ☐ |
| | 003 | WO-2011072244-A1 | 06-16-2011 | SINAI SCHOOL MEDICINE [US], et al. | | ☐ |
| | 004 | WO-2012050263-A1 | 04-19-2012 | CJ CHEILJEDANG CORP [KR], et al. | | ☐ |
| | 005 | WO-2014134165-A1 | 09-04-2014 | SLOAN KETTERING INST CANCER [US] | | ☐ |
| | 006 | WO-2014141292-A2 | 09-18-2014 | INTAS PHARMACEUTICALS LTD [IN] | | ☐ |

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 3 of 10

| Complete if Known | |
|---|---|
| Application Number | 16641985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | QUAY; Steven C. |
| Art Unit | 1629 |
| Examiner Name | Not assigned yet |
| Attorney Docket Number | 38602-758.831 |

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|---|---|---|---|---|---|---|
| | 007 | WO-2016168021-A1 | 10-20-2016 | ATOSSA GENETICS INC [US] | | ☐ |
| | 008 | WO-2017070651-A1 | 04-27-2017 | US HEALTH [US], et al. | | ☐ |
| | 009 | WO-2019051416-A1 | 03-14-2019 | ATOSSA GENETICS INC [US] | | ☐ |

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| NON-PATENT LITERATURE DOCUMENTS | | | |
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| | 001 | ACKERMAN, et al. Contrary view: the breast is not an organ per se, but a distinctive region of skin and subcutaneous tissue. Am J Dermatopathol. 2007 Apr;29(2):211-8. | ☐ |
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| | 009 | CHANG, Minsun. Tamoxifen Resistance in Breast Cancer. Biomol. Ther. 20(3), 256-267 (2012). | ☐ |

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| First Named Inventor | QUAY; Steven C. |
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| | 010 | Clinical Trials Gov. Identifier No. NCT01273168. Endoxifen in Adults With Hormone Receptor Positive Solid Tumors. January 10, 2011. | ☐ |
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|---|---|---|---|
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| | 025 | JORDAN, C. New insights into the metabolism of tamoxifen and its role in the treatment and prevention of breast cancer. Steroids. 2007 Nov; 72(13): 829-842. | ☐ |
| | 026 | LAZZERONI, et al. Oral low dose and topical tamoxifen for breast cancer prevention: modern approaches for an old drug. Breast Cancer Res. 2012; 14(5): 214. | ☐ |
| | 027 | Lee et al., in vitro human skin permeation of endoxifen: potential for local transdermal therapy for primary prevention and carcinoma in situ of the breast, Breast Cancer: Targets and Therapy 2011:3, 61-70. | ☐ |

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| First Named Inventor | QUAY; Steven C. |
| Art Unit | 1629 |
| Examiner Name | Not assigned yet |
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|---|---|---|---|
| | 028 | LEE, et al. Local transdermal therapy to the breast for breast cancer prevention and DCIS therapy: preclinical and clinical evaluation. Cancer Chemother Pharmacol. 2015 Dec;76(6):1235-46. doi: 10.1007/s00280-015-2848-y. | ☐ |
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| | 033 | OGAWA, et al. Synthesis and antiestrogenic activity of the compounds related to the metabolites of (E)-4-[1-[4-[2-(dimethylamino)ethoxy]phenyl]- 2-(4-isopropylphenyl)-1-butenyl]phenyl monophosphate (TAT-59) [corrected]. Chem. Pharm. Bull. 39, 911-916, 1991. | ☐ |
| | 034 | OKEN, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group.Am J Clin Oncol. 1982;5:649-655. | ☐ |
| | 035 | PCT/US2018/050193 International Search Report and Written Opinion dated January 4, 2019. | ☐ |
| | 036 | PCT/US2018-050272 International Search Report and Written Opinion dated January 3, 2019. | ☐ |

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| | 037 | ROUANET, et al. Neoadjuvant percutaneous 4-hydroxyTamoxifen decreases breast tumoral cell proliferation: a prospective controlled randomized study comparing three doses of 4-hydroxyTamoxifen gel to oral Tamoxifen. J Clin Oncol. 2005 May 1;23(13):2980-7. | ☐ |
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| | 041 | Yang et al., Dendron-Based Micelles for Topical Delivery of Endoxifen: A Potential Chemo-Preventive Medicine for Breast Cancer Adv. Funct. Mater. 2014, 24, 2442-2449. | ☐ |
| | 042 | ZHAO, et al. A Herceptin-Based Chimeric Antigen Receptor with Modified Signaling Domains Leads to Enhanced Survival of Transduced T Lymphocytes and Antitumor Activity. THE JOURNAL OF IMMUNOLOGY, vol. 183, no. 9, 1 November 2009 (2009-11-01), pages 5563-5574. | ☐ |

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## CERTIFICATION STATEMENT

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☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

## SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| | | | |
|---|---|---|---|
| Signature | /Lisa G Lippert/ | Date (YYYY-MM-DD) | 2020-05-28 |
| Name/Print | Lisa Lippert | Registration Number | 78332 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Inventor: | QUAY; Steven C. et al. | Group Art Unit: | 1629 |
| Serial Number: | 16/641,985 | Examiner: | Not assigned yet |
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| Title: | METHODS FOR MAKING AND USING ENDOXIFEN | | |

**FILED ELECTRONICALLY ON: May 29 , 2020**

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

## INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☒ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☒ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☐ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☐ a fee of $240.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of $240.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No.38602-758.831).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: May 28, 2020

By: /Lisa G Lippert/
Lisa Lippert
Reg. No. 78,332

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

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(71) Applicant *(for all designated States except US)*: **JINA PHARMACEUTICALS, INC.** [US/US]; 28100 North Ashley Circle, Suite 103, Libertyville, IL 60048 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **AHMAD, Ateeq** [US/US]; 4795 West Pebble Beach Drive, Wadsworth, IL 60083 (US). **ALI, Shoukath, M.** [US/US]; 29681 North Waukegan Road, #204, Lake Bluff, IL 60048 (US). **AHMAD, Moghis, U.** [US/US]; 3050 North Forrest Hills Court, Wadsworth, IL 60083 (US). **SHEIKH, Saifuddin** [US/US]; 1059 South West Avenue, Waukegan, IL 60085 (US). **AHMAD, Imran** [US/US]; 4731 West Pebble Beach Drive, Wadsworth, IL 60083 (US).

(74) Agents: **CASIMIR, David, Ann, D.** et al.; Casimir Jones, S.C., 440 Science Drive, Suite 203, Madison, WI 53711 (US).

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(54) **Title:** ENDOXIFEN METHODS AND COMPOSITIONS

(57) **Abstract:** The present invention provides compositions containing endoxifen, formulations and liposomes of endoxifen, methods of preparation of such agents and formulations, and use of such agents and formulations for the treatment of breast cancer and other breast diseases and diseases susceptible to endoxifen. In particular, the compositions of the present invention include liposomes, complexes, vesicles, emulsions, micelles and mixed micelles of endoxifen in which the compositions further contain any of a variety of neutral or charged lipids and desirably, cholesterol and cholesterol derivatives, sterols, *Z*- and *E*- guggulsterones, phospholipids, fatty acids, vitamin D, and vitamin E. The present invention also provides methods of preparing endoxifen. The present invention provides methods for treating and preventing breast cancer and other breast related diseases by administrating novel formulations or compositions comprising a therapeutically effective amount of endoxifen.

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# ENDOXIFEN METHODS AND COMPOSITIONS

This application claims priority to U.S. Provisional Applications Serial No. 60/860,420, filed November 21, 2006, and 60/860,788, filed November 22, 2006, both of which are incorporated herein by reference.

## FIELD OF THE INVENTION

**[0001]** The invention relates to the use of endoxifen in the treatment of mammalian diseases. The invention also relates to liposomes and other formulations such as complexes, vesicles, emulsions, micelles and mixed micelles of endoxifen, methods of preparation, and uses, *e.g.*, in the treatment of human and animal breast diseases. The invention in particular relates to compositions comprising endoxifen–lipid complexes, methods of preparation, and their use for the treatment of breast diseases, in particular benign and malignant breast disease, enhancing disease regression and reducing risk of patients developing breast cancer. The invention further relates to methods of preparing endoxifen and use of endoxifen prepared by inventive method in the treatment of human and animal diseases.

## BACKGROUND OF THE INVENTION

**[0002]** Every year more than 210, 000 women in the United States develop breast cancer. One in eight women in the US will develop breast cancer during their lives. Approximately 70 percent of breast cancers are fueled by estrogen, and many are treated with Tamoxifen, a drug designed to block the effects of estrogen in breast tissue.

**[0003]** Tamoxifen is an anti-estrogenic drug prescribed for long-term, low dose therapy of breast cancer. It has been widely used for more than 30 years for the endocrine treatment of all stages of hormone receptor-positive breast cancer (1-2). Tamoxifen has also been approved for the prevention of breast cancer (3). In women, one of the adverse events associated with Tamoxifen is hot flashes. The risk of hot flashes is two to three-folds higher among women who take Tamoxifen than it is for those who do not (4). Selective serotonin-reuptake inhibitor (SSRI) antidepressants are prescribed to treat hot flashes. However, some SSRIs, such as paroxetine and fluoxetine, are known to inhibit cytochrome P450 (CYP) 2D6 (5), an enzyme that is important for the metabolism of many drugs, including Tamoxifen. Our understanding of Tamoxifen metabolism and effect has changed clinical practice through the wide spread recognition that the co-prescription of drugs that inhibit CYP2D6 may compromise Tamoxifen efficacy. It is known that co-administration



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of paroxetine decreases the plasma concentration of an active metabolite of Tamoxifen, 4-hydroxy-N-desmethyl-Tamoxifen (endoxifen).

**[0004]** Endoxifen is generated via CYP3A4-mediated N-demethylation and CYP2D6 mediated hydroxylation of Tamoxifen (see, *e.g.*, Figure 3). Any drug that can be substrate of CYP3A4 or CYP2D6, especially CYP2D6 *e.g.*, SSRIs, can decrease the level of endoxifen (6) and thus reduce the therapeutic benefits of Tamoxifen. Therefore, to avoid such drug-drug interactions, one should not give them together.

**[0005]** Recently, endoxifen has been shown to be anti-estrogenic in breast cancer cells and to be more potent than Tamoxifen (7). In patients treated with Tamoxifen, endoxifen is present in higher concentration (12.4 ng/mL) than 4-OH-tamoxifen (1 ng/mL) in the human plasma. The majority of genes affected by endoxifen are estrogen-regulated genes (8 -9). Use of endoxifen *e.g.*, in place of Tamoxifen, avoids several metabolic steps that rely on CYP2D6.

**[0006]** A strong need exists for methods to treat and to prevent breast diseases without significant adverse systemic side effects, particularly in the premenoposal population. In particular, there is a need for breast cancer treatments and preventatives that having reduced interactive effect with other medications.

## SUMMARY OF THE INVENTION

**[0007]** The present invention provides methods and compositions for the syntheses and use of active agents such as anticancer agents. The present invention relates to methods and compositions related to the formulations and uses of endoxifen, particularly in applications related to the treatment or prevention of cancer.

**[0008]** In some embodiments, the present invention provides a method of treating a disease, comprising, preparing a composition comprising a therapeutically active amount of endoxifen and administering the composition. In some embodiments, the endoxifen is a free base, or is in the form of a salt. In some preferred embodiments, the endoxifen is in the form of a salt selected from the group of salts consisting of citrate, acetate, formate, oxalate, tartarate, trifluoroacetane, methane sulfonate, phosphate, sulfate, chloride, bromide, iodide, lactate, and formate. In some some embodiments, the endoxifen is predominantly in a form selected from the group consisting of *E*-isomer, *Z*-isomer, and a mixture of *E*- and *Z*-isomer.

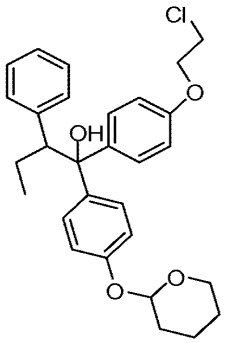
**[0009]** In some embodiments, method comprises preparing a complex comprising an anticancer drug and at least one lipid. In some embodiments, the anticancer drug is



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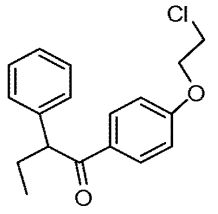
endoxifen. In some embodiments, the compounds of the invention are not complexed with a lipid. In some embodiments, the compound is in the form of a free base or is in the form of a salt.

**[0010]** In some embodiments, the present invention provides methods of preparing endoxifen, comprising reacting a compound of Formula **5** with acid, wherein the compound of formula 5 has the structure:



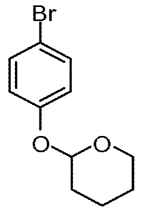

**5**

**[0011]** and, after the reaction of the compound of Formula 5 with acid, reacting the compound with methylamine. In some embodiments, the compound of Formula **5** is prepared by reacting compound of formula **4**




**4**

with a compound of Formula **3**.

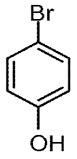



**3**



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**[0012]** In some embodiments, the compound of Formula **3** is prepared by reacting compound of Formula **1**




**1**

with a compound of Formula **2**.




**2**

**[0013]** In some embodiments, the present invention provides methods of purifying the endoxifen as described above, comprising crystallizing the endoxifen and/or chromatographically treating said endoxifen to produce a purified preparation of endoxifen, wherein the purified preparation of endoxifen contains predominantly *E*-isomer, predominantly *Z*-isomer, or mixture of *E*- and *Z*-isomers of endoxifen.

**[0014]** As described above, in some embodiments, the invention provides endoxfen preparations comprising at least one lipid. In preferred embodiments, the at least one lipid is selected from the group consisting of egg phosphatidylcholine (EPC), egg phosphatidylglycerol (EPG), soy phosphatidylcholine (SPC), hydrogenated soy phosphatidylcholine (HSPC), dimyristoylphosphatidylcholine (DMPC), dimyristoylphosphatidylglycerol (DMPG), dipalmitoylphosohatidylcholine (DPPC), disteroylphosphatidylglycerol (DSPG), dipalmitoylphosphatidylglycerol (DMPG), cholesterol (Chol), cholesterol sulfate and its salts (CS), cholesterol hemisuccinate and its salts (Chems), cholesterol phosphate and its salts (CP), cholesterylphosphocholine and other hydroxycholesterol or amino cholesterol derivatives, cholesteryl succinate, cholesteryl oleate, polyethylene glycol derivatives of cholesterol (cholesterol-PEG), coprostanol, cholestanol, cholestane, cholic acid, cortisol, corticosterone, hydrocortisone, and calciferol, *E*-guggulsterone, *Z*-guggulsterone, mixture of *E*-and *Z*-guggulsterone, monoglycerides, diglycerides, triglycerides, carbohydrate-based lipids selected from a group consisting of galactolipid, mannolipid, galactolecithin, β-sitosterol, stigmasterol, stigmastanol, lanosterol, α-spinasterol, lathosterol, campesterol, phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine, phosphatidylserine, phosphatdylinositol, phosphatidic acid, and



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pegylated derivatives of distearoylphosphatidylglycerol, dipalmitoylphosphatidylglycerol, dimyristoylphosphatidylglycerol, and dioleoylphosphatidylglycerol.

**[0015]** In some embodiments, a composition according to the present invention comprises endoxifen, cholesterol and/or cholesterol derivatives, and one or more phospholipids. In some preferred embodiments, the composition comprises a cholesterol derivative, and the cholesterol derivative is cholesteryl sulfate. In some embodiments, at least one of the phospholipids is hydrogenated soy phosphatidylcholine or soy phosphatidylcholine.

**[0016]** In some embodiments of the methods and compositions of the present invention, the composition comprises a form selected from the group consisting of powder, solution, emulsion, micelle, liposome, lipidic particle, gel, and paste form. In some preferred embodiments, the preparing of the composition comprising a complex comprises preparing said complex in a lyophilized form. In some embodiments, the preparing the complex in a lyophilized form comprises using a cryoprotectant, wherein said cryoprotectant comprises one or more sugars selected from the group consisting of trehalose, maltose, lactose, sucrose, glucose, and dextran. In some embodiments, the composition comprises a tablet or a filled capsule, wherein said tablet or filled capsule optionally comprises an enteric coating material.

**[0017]** In some embodiments of the treatment methods of the present invention, the disease is caused by cancer or by cancer-causing agents, while in some embodiments, the disease is benign breast disease.

**[0018]** In some embodiments, the administering comprises oral, intravenous, subcutaneous, percutaneous, parenteral, intraperitoneal, rectal, vaginal, and/or topical delivery said composition to said subject.

**[0019]** In some embodiments, the composition comprises a penetration enhancer, wherein said penetration enhancer comprises at least one saturated or unsaturated fatty acid ester.

**[0020]** In some embodiments, the composition comprising endoxifen is formulated in a hydroalcoholic gel, a hydroalcoholic solution, a patch, a cream, an emulsion, a lotion, an ointment, a powder or an oil.



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**[0021]** In some embodiments, the composition comprising endoxifen is formulated in a hydroalcoholic composition containing a penetration enhancer, an aqueous vehicle, an alcoholic vehicle and a gelling agent.

**[0022]** In some embodiments, the hydroalcoholic composition comprises a neutralizing agent.

**[0023]** In some embodibments, the hydroalcoholic composition comprises endoxifen at about 0.01% to 0.20% by weight; isopropyl myristate at about 0.1% to 2.0%, preferably 0.5% to 2.0% by weight; alcohol at about 50.0% to 80.0%, preferably about 60.0% to 75.0% by weight; aqueous vehicle at about 20.0% to 60.0%, preferably 25.0% to 50.0% by weight; and gelling agent at about 1.0% to 10.0%, preferably about 0.5% to 5.0% by weight. In some embodiments, the wherein the percentage of components is weight to weight of the composition.

**[0024]** In some embodiments, the alcohol is ethanol or isopropanol, and constitutes in absolute form.

**[0025]** In some embodiments, the aqueous vehicle is a phosphate buffered solution.

**[0026]** In some embodiments, the gelling agent is selected from the group consisting of polyacrylic acid, hydroxypropylcellulose and a cellulose derivative other than hydroxypropylcellulose.

**[0027]** In some embodiments, the hydroalcoholic composition further comprises a neutralizing agent, wherein said neutralizing agent is selected from the group consisting of sodium hydroxide, potassium hydroxide, ammonium hydroxide, aminomethylpropanol, arginine, trolamine, and tromethamine, and wherein said neutralizing agent exists at a neutralizing agent/gelling agent ratio of about 1:1 to about 4:1.

**[0028]** In some embodiments, the invention provides methods of delivering endoxifen, comprising: providing any of the above described compositions and delivering the composition so as to expose the composition to a cell.

**[0029]** In some embodiments, the cell is *in vivo*.

**[0030]** In some embodiments of the invention, the host is a mammal.

**[0031]** The present invention also provides methods of inhibiting hormone-dependent breast carcinoma in a mammal comprising administering any of the above compositions to the mammal.

**[0032]** The present invention further provides methods of inhibiting a cancer in a mammal, said cancer including, but not limited to, lung cancer, colon cancer, breast cancer, leukemia, renal cancer, melanoma, cancer or the central nervous system, and prostate cancer



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in a mammal; the method comprising administering any of the above compositions to said mammal (e.g, a human).

**[0033]** The present invention further provides compositions comprising a therapeutically active amount of a complex comprising endoxifen and at least one lipid, wherein said endoxifen is a free base or is in the form of a salt.

**[0034]** In some embodiments, the composition comprising endoxifen is formulated in a hydroalcoholic gel, a hydroalcoholic solution, a patch, a cream, an emulsion, a lotion, an ointment, a powder or an oil.

**[0035]** In some embodiments, the composition comprising endoxifen is formulated in a hydroalcoholic composition containing a penetration enhancer, an aqueous vehicle, an alcoholic vehicle and a gelling agent.

**[0036]** In some embodiments, the hydroalcoholic composition comprises a neutralizing agent.

**[0037]** In some embodibments, the hydroalcoholic composition comprises endoxifen at about 0.01% to 0.20% by weight; isopropyl myristate at about 0.1% to 2.0%, preferably 0.5% to 2.0% by weight; alcohol at about 50.0% to 80.0%, preferably about 60.0% to 75.0% by weight; aqueous vehicle at about 20.0% to 60.0%, preferably 25.0% to 50.0% by weight; and gelling agent at about 1.0% to 10.0%, preferably about 0.5% to 5.0% by weight. In some embodiments, the wherein the percentage of components is weight to weight of the composition.

**[0038]** The present invention is not limited to the compositions and methods described above. It should be understood that variations of the above compositions and methods described elsewhere herein or that are understood by a skilled artisan in view of the present disclosure are included within the invention.

## DESCRIPTION OF THE DRAWINGS

**[0039]** Figure 1 diagrams compound **I.**

**[0040]** Figure 2 diagrams embodiments for synthesis of compounds **3**, **5**, and **I**.

**[0041]** Figure 3 diagrams portions of Tamoxifen metabolic pathways.

## DEFINITIONS

**[0042]** As used herein, the terms "host," "subject" and "patient" refer to any animal, including but not limited to, human and non-human animals (*e.g.*, dogs, cats, cows, horses, sheep, poultry, fish, crustaceans, *etc.*) that is studied, analyzed, tested, diagnosed or treated.



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As used herein, the terms "host," "subject" and "patient" are used interchangeably, unless indicated otherwise.

**[0043]** As used herein, the terms "subject at risk of cancer" refers to a subject identified as being at risk for developing cancer, *e.g.*, by prior health history, genetic data, etc.

**[0044]** As used herein, the term "anticancer drug" refers to an agent used to treat or prevent cancer. Such agents include, but are not limited to, small molecules, drugs, antibodies, pharmaceuticals, and the like.

**[0045]** As used herein, the term "effective amount" refers to the amount of an active composition (*e.g.*, a pharmaceutical compound or composition provided as a component in a lipid formulation) sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications or dosages and is not intended to be limited to a particular formulation or administration route.

**[0046]** As used herein, the terms "active" or "pharmaceutically active" as used in reference to an agent, drug, composition, or compound, refers to an agent that, upon administration or application, causes a beneficial, desired, or expected result. The administration may be in one or more administrations, applications or dosages and is not intended to be limited to a particular formulation or administration route. The term is not limited to any particular level of activity.

**[0047]** The terms "agent" and "compound" are used herein interchangeably to refer to any atom, molecule, mixture, or more complex composition having an attributed feature. For example, an "active agent" or "active compound" refers to any atom, molecule, preparation, mixture, *etc.,* that, upon administration or application, causes a beneficial, desired, or expected result.

**[0048]** As used herein, the term "treating" includes administering therapy to prevent, cure, or alleviate/prevent the symptoms associated with, a specific disorder, disease, injury or condition.

**[0049]** As used herein, the term "treatment" or grammatical equivalents encompasses the improvement and/or reversal of the symptoms of disease (*e.g.*, cancer), or reduction of risk of occurrence of disease. A compound which causes an improvement in any parameter associated with disease when used in the screening methods of the instant invention may thereby be identified as a therapeutic compound. The term "treatment" refers to both therapeutic treatment and prophylactic or preventative measures. For example, those who may benefit from treatment with compositions and methods of the present



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invention include those already with a disease and/or disorder (*e.g.*, cancer, or symptoms or pathologies consistent with cancer) as well as those in which a disease and/or disorder is to be prevented (*e.g.*, using a prophylactic treatment of the present invention).

**[0050]** As used herein, the term "at risk for disease" refers to a subject (*e.g.*, a human) that is predisposed to experiencing a particular disease. This predisposition may be genetic (*e.g.*, a particular genetic tendency to experience the disease, such as heritable disorders), or due to other factors (*e.g.*, age, weight, environmental conditions, exposures to detrimental compounds present in the environment, *etc.*). Thus, it is not intended that the present invention be limited to any particular risk, nor is it intended that the present invention be limited to any particular disease.

**[0051]** As used herein, the term "suffering from disease" refers to a subject (*e.g.*, a human) that is experiencing a particular disease. It is not intended that the present invention be limited to any particular signs or symptoms, nor disease. Thus, it is intended that the present invention encompasses subjects that are experiencing any range of disease (*e.g.*, from sub-clinical manifestation to full-blown disease) wherein the subject exhibits at least some of the indicia (*e.g.*, signs and symptoms) associated with the particular disease.

**[0052]** As used herein, the terms "disease" and "pathological condition" are used interchangeably to describe a state, signs, and/or symptoms that are associated with any impairment of the normal state of a living animal or of any of its organs or tissues that interrupts or modifies the performance of normal functions, and may be a response to environmental factors (such as emotional trauma, physical trauma, malnutrition, industrial hazards, or climate), to specific infective agents (such as worms, bacteria, or viruses), to inherent defect of the organism (such as various genetic anomalies, or to combinations of these and other factors.

**[0053]** As used herein, the term "administration" refers to the act of giving a drug, prodrug, or other active agent, or therapeutic treatment (*e.g.*, compositions of the present invention) to a physiological system (*e.g.*, a subject or *in vivo*, *in vitro*, or *ex vivo* cells, tissues, and organs). Exemplary routes of administration to the human body can be through the eyes (ophthalmic), mouth (oral), skin (transdermal), nose (nasal), lungs (inhalant), rectal, vaginal, oral mucosa (buccal), ear, by injection (*e.g.*, intravenously, subcutaneously, intratumorally, intraperitoneally, *etc.*) and the like. Administration may be in one or more administrations, applications or dosages, and is not intended to be limited to a particular administration route.



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**[0054]** As used herein, the term "co-administration" refers to the administration of at least two agent(s) (*e.g.*, two separate lipid compositions, containing different active compounds) or therapies to a subject. In some embodiments, the co-administration of two or more agents or therapies is concurrent. In other embodiments, a first agent/therapy is administered prior to a second agent/therapy. Those of skill in the art understand that the formulations and/or routes of administration of the various agents or therapies used may vary. The appropriate dosage for co-administration can be readily determined by one skilled in the art. In some embodiments, when agents or therapies are co-administered, the respective agents or therapies are administered at lower dosages than appropriate for their administration alone. Thus, co-administration is especially desirable in embodiments where the co-administration of the agents or therapies lowers the requisite dosage of a potentially harmful (*e.g.*, toxic) agent(s).

**[0055]** As used herein, the term "toxic" refers to any detrimental or harmful effects on a subject, a cell, or a tissue as compared to the same cell or tissue prior to the administration of the toxicant.

**[0056]** As used herein, the term "pharmaceutically purified" refers to a composition of sufficient purity or quality of preparation for pharmaceutical use.

**[0057]** As used herein, the term "purified" refers to a treatment of a starting composition to remove at least one other component (*e.g.*, another component from a starting composition (*e.g.*, plant or animal tissue, an environmental sample *etc.*), a contaminant, a synthesis precursor, or a byproduct, *etc.*), such that the ratio of the purified component to the removed component is greater than in the starting composition.

**[0058]** As used herein, the term "pharmaceutical composition" refers to the combination of an active agent (*e.g.*, an active pharmaceutical compound) with a carrier, inert or active (*e.g.*, a phospholipid), making the composition especially suitable for diagnostic or therapeutic use *in vitro*, *in vivo* or *ex vivo*.

**[0059]** The terms "pharmaceutically acceptable" or "pharmacologically acceptable," as used herein, refer to compositions that do not substantially produce adverse reactions, *e.g.*, toxic, allergic, or immunological reactions, when administered to a subject.

**[0060]** As used herein, the term "topically" refers to application of the compositions of the present invention to the surface of the skin and mucosal cells and tissues (*e.g.*, alveolar, buccal, lingual, masticatory, or nasal mucosa, and other tissues and cells which line hollow organs or body cavities).



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**[0061]** As used herein, the term "pharmaceutically acceptable carrier" refers to any of the standard pharmaceutical carriers including, but not limited to, phosphate buffered saline solution, water, emulsions (*e.g.*, such as an oil/water or water/oil emulsions), and various types of wetting agents, any and all solvents, dispersion media, coatings, sodium lauryl sulfate, isotonic and absorption delaying agents, disintigrants (*e.g.*, potato starch or sodium starch glycolate), and the like.. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers, and adjuvants. (See *e.g.*, Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, Pa. (1975), incorporated herein by reference). Moreover, in certain embodiments, the compositions of the present invention may be formulated for horticultural or agricultural use. Such formulations include dips, sprays, seed dressings, stem injections, sprays, and mists.

**[0062]** As used herein, the term "pharmaceutically acceptable salt" refers to any salt (*e.g.*, obtained by reaction with an acid or a base) of a compound of the present invention that is physiologically tolerated in the target subject (*e.g.*, a mammalian subject, and/or *in vivo* or *ex vivo*, cells, tissues, or organs). "Salts" of the compounds of the present invention may be derived from inorganic or organic acids and bases. Examples of acids include, but are not limited to, hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, sulfonic, naphthalene-2-sulfonic, benzenesulfonic acid, and the like. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

**[0063]** Examples of bases include, but are not limited to, alkali metal (*e.g.*, sodium) hydroxides, alkaline earth metal (*e.g.*, magnesium) hydroxides, ammonia, and compounds of formula $NW_4^+$, wherein W is $C_{1-4}$ alkyl, and the like.

**[0064]** Examples of salts include, but are not limited to: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, flucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, chloride, bromide, iodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, undecanoate, and the like. Other examples of salts include anions of the compounds of the present invention



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compounded with a suitable cation such as $Na^+$, $NH_4^+$, and $NW_4^+$ (wherein W is a $C_{1-4}$ alkyl group), and the like. For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

**[0065]** For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

**[0066]** As used herein, the term "hydroalcoholic" as used in reference to a substance or composition indicates that said substance or composition comprises both water and alcohol.

**[0067]** As used herein, the term "gelling agent" refers to a composition that, when dissolved, suspended or dispersed in a fluid (*e.g.*, an aqueous fluid such as water or a buffer solution), forms a gelatinous semi-solid (*e.g.*, a lubricant gel). Examples of gelling agents include but are not limited to hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl guar, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, carbomer, alginate, gelatin, and poloxamer.

**[0068]** As used herein, the term "dried" as used in reference to a composition refers to removing the solvent component or components to levels that no longer support chemical reactions. The term is also used in reference to a composition that has been dried (*e.g.*, a dried preparation or dried composition). Those of skill in the art will appreciate that a composition may be "dried" while still having residual solvent or moisture content after, *e.g.*, lyophilization, or that a dried composition may, after the end of a drying process, absorb moisture hygroscopically, *e.g.*, from the atmosphere. The term "dried" encompasses a composition with increased moisture content due to hygroscopic absorption.

**[0069]** As used herein, the term "protective agent" refers to a composition or compound that protects the activity or integrity of an active agent (*e.g.*, an anticancer drug) when the active agent is exposed to certain conditions (*e.g.*, drying, freezing). In some embodiments, a protective agent protects an active agent during a freezing process (*i.e.*, it is a "cryoprotectant"). Examples of protective agents include but are not limited to non-fat milk solids, trehalose, glycerol, betaine, sucrose, glucose, lactose, dextran, polyethylene glycol, sorbitol, mannitol, poly vinyl propylene, potassium glutamate, monosodium glutamate, Tween 20 detergent, Tween 80 detergent, and an amino acid hydrochloride.



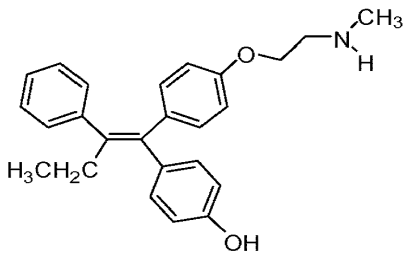
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**[0070]** As used herein, the term "excipient" refers to an inactive ingredient (*i.e.*, not pharmaceutically active) added to a preparation of an active ingredient. The gelling and protective agents described herein may be referred to generally as "excipients."

**[0071]** As used herein, the term "kit" refers to any delivery system for delivering materials. In the context of kinase activity or inhibition assays, such delivery systems include systems that allow for the storage, transport, or delivery of reaction reagents and/or supporting materials (*e.g.*, buffers, written instructions for performing the assay etc.) from one location to another. For example, kits include one or more enclosures (*e.g.*, boxes) containing the relevant reaction reagents and/or supporting materials. As used herein, the term "fragmented kit" refers to delivery systems comprising two or more separate containers that each contains a subportion of the total kit components. The containers may be delivered to the intended recipient together or separately. For example, a first container may contain an agent for use in an assay, while a second container contains standards for comparison to test compounds. The term "fragmented kit" is intended to encompass kits containing Analyte Specific Reagents (ASR's) regulated under section 520(e) of the Federal Food, Drug, and Cosmetic Act, but are not limited thereto. Indeed, any delivery system comprising two or more separate containers that each contains a subportion of the total kit components are included in the term "fragmented kit." In contrast, a "combined kit" refers to a delivery system containing all of the components of a reaction assay in a single container (e.g., in a single box housing each of the desired components). The term "kit" includes both fragmented and combined kits.

## DETAILED DESCRIPTION OF THE INVENTION

**[0072]** The present invention provides compositions and methods for delivering endoxifen of Formula **I**, *e.g.*, to a mammalian host. In some embodiments of the present invention endoxifen is an *E*-isomer, while in other embodiments, it is a *Z*-isomer, while it is still in other embodiments, it is a mixture of *E*- and *Z*-isomers




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**[0073]** An example of the present invention includes endoxifen, analogues of endoxifen, and derivatives of endoxifen, including but not limited to endoxifen, Tamoxifen, and 4-hydroxytamoxifen. The present invention also find use with other antineoplastic agents such as paclitaxel, docetaxel, melphalan, chlormethine, extramustinephosphate, uramustine, ifosfamide, mannomustine, trifosfamide, streptozotocin, mitobronitol, mitoxantrone, methotrexate, fluorouracil, cytarabine, tegafur, idoxide, taxol, paclitaxel, daunomycin, daunorubicin, bleomycin, amphotericin, carboplatin, cisplatin, BCNU, vincristine, camptothecin, SN-38, doxorubicin, and etopside. Also included are steroidal and non-steroidal inhibitors used in cancer treatment, such as bicautamide, exemestane, formestane, letrozole, anastrazole and their analogues.

**[0074]** Endoxifen of Formula **I** can be prepared by any desired method for use in the treatments of the present invention but, in some embodiments, the present invention provides particular methods for the preparation of endoxifen. One preferred method of the present invention is set forth in Figure 2. In this method, 4-bromophenol **1** is reacted with 3,4-dihydropyran **2** in the present of acid (*e.g.*, sulfuric acid and the like), to give compound **3**. Compound **3** is then reacted with magnesium turning in a suitable anhydrous solvent (*e.g.*, tetrahydrofuran and the like). This is followed by reaction with 1-[4-(2-chloroethoxy)phenyl]-2-phenyl-1-butanone **4** to provide compound **5** which, on dehydration/deprotection in presence of acid in a suitable solvent (*e.g.*, methanol and the like), produces compound **6**. Reaction of yielded compound **6** with methylamine in a suitable solvent (*e.g.*, isopropanol and the like) provides endoxifen **I**.

**[0075]** In some embodiments of the present invention, a mixture of *E*- and *Z*-isomers of endoxifen can be separated to provide the purified preparations of *E*- and *Z*-isomer of endoxifen. The separation of *E*- and *Z*- isomers of endoxifen in the present invention can be done, *e.g.*, by crystallization, or purification by liquid column chromatography (LC), or high pressure liquid column chromatography (HPLC).

**[0076]** Suitable solvents that can be employed in present invention for the separation of *E*- and *Z*-isomers of endoxifen include but are not limited to hexanes, heptanes, and the like, benzene; toluene; ethyl acetate; acetonitrile; chlorinating solvents such as methylene chloride, chloroform, 1,2-dichloromethane, and the like, ketones, (*e.g.*, acetone, 2-butanone, and the like), ethers such as diethyl ether, diisopropyl ether, methyl butyl ether, and tetrahydrofuran, alcohols such as methanol, ethyl alcohol, and isopropyl alcohol, and the like, and water. A solvent for crystallization can be used as a single solvent, or as



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mixture of solvents such as hexane-ethyl acetate, chloroform-acetone, chloroform-methanol, dichloromethane-methanol, and the like. When a mixture of two solvents is used in the present invention, examples of ratios of one solvent to another are *e.g.*, in a range such as 9:1 to 1:9, (*e.g.*, 8:2, 7:3; 6:4; 5:5; 4:6; 3:7; 2:8; 1:9, and the like.) However, mixtures for use in the present invention are not limited to these ratios, or to mixtures comprising only two solvents.

**[0077]** Solvents that find use in the preparation of endoxifen according to the present invention include but are not limited to tetrahydrofuran, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, *N,N'*-dimethylformamide, dimethylsulfoxide, toluene, pyridine, methanol, ethanol, isopropanol, acetone, 2-butanone, hexane, heptane, pentane, ethyl acetate, and the like.

**[0078]** Acids that find use in the preparation of endoxifen according to the present invention include, but are not limited to, sulfuric acid, hydrochloric acid, acetic acid, trifluroacetic acid, phosphoric acid, p-toluenesulfonic acid, methanesulfonic acid, nitric acid, and the like.

**[0079]** Intermediates and final products of the present invention can be purified by column chromatography using a single or a mixture of common organic solvents such as hexane pentane, heptane, ethyl acetate, methylene chloride, chloroform, methanol, acetone, and the like.

**[0080]** As noted above, intermediates and final product of the present invention, may, in some embodiments, be purified by crystallization. Solvents that find use in the crystallization of intermediates and products include but are not limited to hydrocarbons such as pentanes, hexanes, heptanes, and the like, benzene; toluene; ethyl acetate; acetonitrile; chlorinating solvents such as methylene chloride, chloroform, 1,2-dichloromethane, and the like; ketones, for example, acetone, 2-butanone, and the like; ethers such as diethyl ether, diisopropyl ether, methyl butyl ether, tetrahydrofuran; alcohols such as methanol, ethyl alcohol, isopropyl alcohol, and the like. A solvent for crystallization can be used as a single solvent or mixture of solvents. Exemplary mixtures include, *e.g.*, hexane-ethyl acetate, chloroform-acetone, chloroform-methanol, dichloromethane-methanol, and the like. When a mixture of two solvents is used in the present invention, examples of ratios of one solvent to another are *e.g.*, in a range such as 9:1 to 1:9, (*e.g.*, 8:2, 7:3; 6:4; 5:5; 4:6; 3:7; 2:8; 1:9, and the like.) However, mixtures for use in the present invention are not limited to these ratios, or to mixtures comprising only two solvents.



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**[0081]** One object of the present invention is to provide *E*-endoxifen or *Z*-endoxifen with at least 80% purity, such as at least 90% pure or at least 95% pure or at least 98% pure or at least 99% pure or at least 100% pure.

**[0082]** Another object of the present invention is to provide solubilized endoxifen in, *e.g.*, aqueous acid. Suitable acids for solubilizing endoxifen include but are not limited to formic acid, acetic acid, propionic acid, butyric acid, trifuloroacetic acid, lactic acid, tartaric acid, oxalic acid, malonic acid, succinic acid, and the like. The pH of the acidic solution comprising endoxifen can be adjusted with suitable base or buffers. Examples of base and buffers include but are not limited to sodium hydroxide, sodium acetate, sodium lactate, sodium succinate, sodium monophosphate, sodium diphosphate, sodium triphosphate, sodium oxalate, sodium tartarate, ammonium hydroxide, ammonium acetate, and the like. In some embodiments, a co-solvent can also be used to solubilize endoxifen. Examples of co-solvent include but are not limited to ethanol, isopropanol, detergents such as Tween 20 and Polysorbate, and the like

**[0083]** In certain preferred embodiments, the pH of a composition containing endoxifen *acco*rding to the present invention are between about 4.0 and about 8.0, and preferably between about 5.0 and about 8.0, and most preferably between about 5.5 and about7.5.

**[0084]** In some embodiments, the present invention relates to compositions and methods for delivery of endoxifen or endoxifen-lipid complexes to a mammalian host. Any suitable amount of endoxifen can be used in complex formation. Suitable amounts of endoxifen are those amounts that can be stably incorporated into the complexes of the present invention.

**[0085]** In some embodiments, the inventive composition comprises a lipid complex with endoxifen in which the complex desirably contains lipid or a mixture of lipids. Complexes can be in the form, *e.g.*, of micelles, vesicles or emulsions without exclusion of other forms. The micelles of the present invention can be in the form of monomeric, dimeric, polymeric or mixed micelles. The complexes including micelles and emulsions are predominately in the size range of 50nm-20 micron, preferably in size range of 50nm-5 micron. In the complexes, the active agent can be bound to the lipid by covalent, hydrophobic, electrostatic, hydrogen, or other bonds, and is considered bound even where the drug is simply entrapped within the interior of lipid structures.

**[0086]** Endoxifen-lipid complexes may contain *e.g.*, cholesterols or cholesterol derivatives or a mixture of cholesterol and cholesterol derivatives. Cholesterol derivatives that find use in the present invention include cholesteryl hemisuccinate, cholesteryl succinate, cholesteryl oleate, cholesteryl linoleate, cholesteryl eicosapentenoate, cholesteryl



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linolenate, cholesteryl arachidonate, cholesteryl palmitate, cholesteryl stearate, cholesteryl myristate, polyethylene glycol derivatives of cholesterol (cholesterol-PEG), water soluble cholesterol (for example, cholesterol methyl-β-cyclodextrin), coprostanol, cholestanol, or cholestane, cholic acid, cortisol, corticosterone or hydrocortisone and 7-dehydrocholesterol.

**[0087]** In some preferred embodiments, the compositions also include α-, β-, γ-tocopherols, vitamin E, calciferol, organic acid derivatives of α-, β-, γ-tocopherols, such as α-tocopherol hemisuccinate (THS), α-tocopherol succinate and/or mixtures thereof.

**[0088]** In other some preferred embodiments, endoxifen-lipid complexes of the present invention contain sterols. Sterols that find use in the present invention include β-sitosterol, stigmasterol, stigmastanol, lanosterol, α-spinasterol, lathosterol, campesterol and/or mixtures thereof.

**[0089]** Compositions of the present invention also include endoxifen complexes with free and/or salts or esters of fatty acid. Preferred fatty acids range from those with carbon chain lengths of about $C_2$ to $C_{34}$, preferably between about $C_4$ and about $C_{24}$, and include tetranoic acid ($C_{4:0}$), pentanoic acid ($C_{5:0}$), hexanoic acid ($C_{6:0}$), heptanoic acid ($C_{7:0}$), octanoic acid ($C_{8:0}$), nonanoic acid ($C_{9:0}$), decanoic acid ($C_{10:0}$), undecanoic acid ($C_{11:0}$), dodecanoic acid ($C_{12:0}$), tridecanoic acid ($C_{13:0}$), tetradecanoic (myristic) acid ($C_{14:0}$), pentadecanoic acid ($C_{15:0}$), hexadecanoic (palmatic) acid ($C_{16:0}$), heptadecanoic acid ($C_{17:0}$), octadecanoic (stearic) acid ($C_{18:0}$), nonadecanoic acid ($C_{19:0}$), eicosanoic (arachidic) acid ($C_{20:0}$), heneicosanoic acid ($C_{21:0}$), docosanoic (behenic) acid ($C_{22:0}$), tricosanoic acid ($C_{23:0}$), tetracosanoic acid ($C_{24:0}$), 10-undecenoic acid ($C_{11:1}$), 11-dodecenoic acid ($C_{12:1}$), 12-tridecenoic acid ($C_{13:1}$), myristoleic acid ($C_{14:1}$), 10-pentadecenoic acid ($C_{15:1}$), palmitoleic acid ($C_{16:1}$), oleic acid ($C_{18:1}$), linoleic acid ($C_{18:2}$), linolenic acid ($C_{18:3}$), eicosenoic acid ($C_{20:1}$), eicosdienoic acid ($C_{20:2}$), eicosatrienoic acid ($C_{20:3}$), arachidonic acid (*cis*-5,8,11,14-eicosatetraenoic acid), and *cis*-5,8,11,14,17-eicosapentaenoic acid, among others. Other fatty acids also can be employed in the compositions. Examples of such include saturated fatty acids such as ethanoic (or acetic) acid, propanoic (or propionic) acid, butanoic (or butyric) acid, hexacosanoic (or cerotic) acid, octacosanoic (or montanic) acid, triacontanoic (or melissic) acid, dotriacontanoic (or lacceroic) acid, tetratriacontanoic (or gheddic) acid, pentatriacontanoic (or ceroplastic) acid, and the like; monoethenoic unsaturated fatty acids such as *trans*-2-butenoic (or crotonic) acid, *cis*-2-butenoic (or isocrotonoic) acid, 2-hexenoic (or isohydrosorbic) acid, 4-decanoic (or obtusilic) acid, 9-decanoic (or caproleic) acid, 4-dodecenoic ( or linderic) acid, 5-dodecenoic (or denticetic) acid, 9-dodecenoic (or lauroleic) acid, 4-tetradecenoic (or tsuzuic) acid, 5-tetradecenoic (or physeteric) acid, 6-



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octadecenoic (or petroselenic) acid, *trans*-9-octadecenoic ( or elaidic) acid, *trans*-11-octadecenoic ( or vaccinic) acid, 9-eicosenoic ( or gadoleic) acid, 11-eicosenoic ( or gondoic) acid, 11-docosenoic ( or cetoleic) acid, 13-decosenoic ( or erucic) acid, 15-tetracosenoic ( or nervonic) acid, 17-hexacosenoic ( or ximenic) acid, 21-triacontenoic ( or lumequeic) acid, and the like; dienoic unsaturated fatty acids such as 2,4-pentadienoic (or β–vinylacrylic) acid, 2,4-hexadienoic (or sorbic) acid, 2,4-decadienoic (or stillingic) acid, 2,4-dodecadienoic acid, 9,12-hexadecadienoic acid, *cis*-9, *cis*-12-octadecadienoic (or α–linoleic) acid, *trans*-9, *trans*-12-octadecadienoic (or linlolelaidic) acid, *trans*-10,*trans*-12-octadecadienoic acid, 11,14-eicosadienoic acid, 13,16-docosadienoic acid, 17,20-hexacosadienoic acid and the like; trienoic unsaturated fatty acids such as 6,10,14-hexadecatrienoic (or hiragonic) acid, 7,10,13-hexadecatrienoic acid, *cis*-6, *cis*-9- *cis*-12-octadecatrienoic (or γ–linoleic) acid, *trans*-8, *trans*-10- *trans*-12-octadecatrienoic (or β–calendic) acid, *cis*-8, *trans*-10- *cis*-12-octadecatrienoic acid, *cis*-9, *cis*-12- *cis*-15-octadecatrienoic (or α–linolenic) acid, *trans*-9, *trans*-12- *trans*-15-octadecatrienoic (or α–linolenelaidic) acid, *cis*-9, *trans*-11- *trans*-13-octadecatrienoic (or α–eleostearic) acid, *trans*-9, *trans*-11- *trans*-13-octadecatrienoic (or β–eleostearic) acid, *cis*-9, *trans*-11- *cis*-13-octadecatrienoic (or punicic) acid, 5,8,11-eicosatrienoic acid, 8,11,14-eicosatrienoic acid and the like; tetraenoic unsaturated fatty acids such as 4,8,11,14-hexadecatetraenoic acid, 6,9,12,15- hexadecatetraenoic acid, 4,8,12,15-octadecatetraenoic (or moroctic) acid, 6,9,12,15- octadecatetraenoic acid, 9,11,13,15- octadecatetraenoic ( or α –or β-parinaric) acid, 9,12,15,18-octadecatetraenoic acid, 4,8,12,16-eicosatetraenoic acid, 6,10,14,18-eicosatetraenoic acid, 4,7,10,13-docasatetraenoic acid, 7,10,13,16-docosatetraenoic acid, 8,12,16,19-docosatetraenoic acid and the like; penta- and hexa-enoic unsaturated fatty acids such as 4,8,12,15,18-eicosapentaenoic (or timnodonic) acid, 4,7,10,13,16-docosapentaenoic acid, 4,8,12,15,19-docosapentaenoic (or clupanodonic) acid, 7,10,13,16,19-docosapentaenoic, 4,7,10, 13,16,19-docosahexaenoic acid, 4,8,12,15,18,21-tetracosahexaenoic (or nisinic) acid and the like; branched-chain fatty acids such as 3-methylbutanoic (or isovaleric) acid, 8-methyldodecanoic acid, 10-methylundecanoic (or isolauric) acid, 11-methyldodecanoic (or isoundecylic) acid, 12-methyltridecanoic (or isomyristic) acid, 13-methyltetradecanoic (or isopentadecylic) acid, 14-methylpentadecanoic (or isopalmitic) acid, 15-methylhexadecanoic, 10-methylheptadecanoic acid, 16-methylheptadecanoic (or isostearic) acid, 18-methylnonadecanoic (or isoarachidic) acid, 20-methylheneicosanoic (or isobehenic) acid, 22-methyltricosanoic (or isolignoceric) acid, 24-methylpentacosanoic (or isocerotic) acid,



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26-methylheptacosanoic (or isomonatonic) acid, 2,4,6-trimethyloctacosanoic (or mycoceranic or mycoserosic) acid, 2-methyl-*cis*-2-butenoic(angelic)acid, 2-methyl-*trans*-2-butenoic (or tiglic) acid, 4-methyl-3-pentenoic (or pyroterebic) acid and the like.

**[0090]** In some preferred embodiments, endoxifen-lipid complexes contain phospholipids. Any suitable phospholipids or mixture of phospholipids can be used. For example, phospholipids can be obtained from natural sources or chemically synthesized. Suitable phospholipids include but are not limited to phosphatidylethanolamine (PE), phosphatidylglycerol (PG), phosphatidylserine (PS), phosphatidylcholine (PC), phosphatidylinositol (PI), phosphatidic acid (PA), sphingomyelin and the like, either used separately or in combination. Phosphatidylglycerols may be having short chain or long chain, saturated or unsaturated such as dimyristoylphosphatidylglycerol, dioleoylphosphatidylglycerol, distearoylphosphatidylglycerol, dipalmitoylphosphatidylglycerol, diarachidonoylphosphatidylglycerol, short chain phosphatidylglycerol ($C_6$-$C_8$), and mixtures thereof. Examples of phosphatidylcholines includes dimyristoylphophatidylcholine, distearoylphosphatidylcholine, dipalmitoylphosphatidylcholine, dioleoylphosphatidylcholine, diarachidonoylphosphatidylcholine, egg phosphatidylcholine, soy phosphatidylcholine or hydrogenated soy phosphatidylcholine can be used, as can mixtures thereof.

**[0091]** According to one aspect, the present invention provides compositions comprising endoxifen and derivatives of mono-, di- and tri-glycerides. Examples of the glycerides include 1-oleoyl-glycerol (monoolein) and 1, 2-dioctanoyl-*sn*-glycerol.

**[0092]** Another aspect of the invention provides forming complexes of endoxifen with functionalized phospholipids including but not limited to phosphatidylethanolamine, preferably dioleoylphosphatidylethanolamine, phosphatidylthioethanol, *N*-biotinylphosphatidylethanolamine and phosphatidylethylene glycol.

**[0093]** Another aspect of the invention provides forming complexes of endoxifen with carbohydrate-based lipids. Examples of carbohydrate-based lipids include but are not limited to galactolipids, mannolipids, galactolecithin and the like.

**[0094]** In other preferred embodiment, endoxifen-lipid complexes comprise sterols. Sterols finding use in the present invention include but are not limited to β-sitosterol, stigmasterol, stigmastanol, lanosterol, α-spinasterol, lathosterol, campesterol and/or mixtures thereof.



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**[0095]** Another aspect of the invention provides forming complexes of endoxifen with guggulipid and any suitable phospholipids. Guggulipid, or *guggul*, is a natural substance derived from the mukul myrrh tree. The mukul myrrh gives off a sticky resin, which is processed to obtain guggulipid. This extract has been used for thousands of years in Aryuvedic medicine to treat arthritis and obesity. The guggulipid is a source of sterol compounds such as *Z*- and *E*-guggulsterones, generally present in an amount of at least 2.5% (10). *Z* and *E*-Guggulsterones can be synthesized chemically and thus can be used in drug formulations where the need is to have pure forms of these sterones. See, *e.g.*, U.S. Application Ser. No. 60/856,952, filed November 6, 2006, and PCT/US07/83832, filed November 6, 2007, both incorporated herein by reference.

**[0096]** Yet another aspect of the invention provides forming complexes of endoxifen with derivatives of phospholipids such as pegylated phospholipids. Examples of pegylated lipids finding use in the present invention include but are not limited to the polyethylene glycol (Pegylated, PEG) derivatives of distearoylphosphatidylglycerol, dimyristoylphosphatidylglycerol, dioleoylphosphatidylglycerol and the like.

**[0097]** In other aspects, the present invention provides compositions comprising endoxifen and polyethyleneglycol (PEG) and one or more lipids.

**[0098]** According to yet other aspects, the present invention provides compositions comprising endoxifen complexes with one or more lipids. Examples include but are not limited to compositions comprising endoxifen, cholesterol or cholesterol derivatives and one or more phospholipids. Other examples of compositions include endoxifen, β-sitosterol, and one or more phospholipids. In some preferred embodiments, compositions of the present invention comprise endoxifen, and hydrogenated soy phosphatidylcholine or soy phosphatidylcholine.

**[0099]** The term "Polyethylene glycol (PEG)" includes polymers of lower alkylene oxide, in particular ethylene oxide (polyethylene glycols) having an esterifiable hydroxyl group at least at one end of the polymer molecule, as well as derivatives of such polymers having esterifiable carboxy groups. Polyethylene glycols of an average molecular weight ranging from 200-20,000 are preferred; those having an average molecular weight ranging from 500-2000 are particularly preferred.

**[00100]** Another aspect of the invention provides forming complexes of endoxifen with carbohydrate-based lipids. Examples of carbohydrate-based lipids include but are not limited to galactolipids, mannolipids, galactolecithin and the like.



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**[00101]** In some embodiments of compositions of the invention, a complex is formed comprising endoxifen and preferably endoxifen in water at a concentration of about 0.5 mg/mL to about 25 mg/mL, such as between 1 mg/mL and about 20 mg/mL or between 1 mg/mL and 10 mg/mL, more preferably between 1 mg/mL and 5 mg/mL.

**[00102]** In some embodiments, compositions of the present invention contain about 2.5% to about 90% of total lipid, preferably about 2.5 to about 50% weight of total lipid or more, preferably about 10% to about 50% weight of total lipid.

**[00103]** In certain embodiments, compositions of the present invention preferably contain endoxifen, and lipid(s) in mole ratio between 1:1 to 1:100 such as in between 1:1 and 1:20 molar ratio or in between 1:1 and 1:30 molar ratio or in between 1:1 and 1:40 molar ratio or in between 1:1 and 1:50 molar ratio, in between 1:1 and 1:60 molar ratio, in between 1:1 and 1:70 molar ratios, and in between 1:1 and 1:80 molar ratios, and 1:90 molar ratios.

**[00104]** Ratios recited herein, *e.g.*, mole ratios of components in a composition, are provided by way of example and do not limit the invention to the precise incremental ratios recited, *e.g.*, to whole number ratios of the components in the composition. For example, a range of ratios of about 1:10 to 1:90 encompasses not only 1:11, 1:25, 1:89, *etc.*, but includes, without limitation, any ratio at or between about 1:10 to 1:90 (*e.g.*, 1:53.637).

**[00105]** In certain embodiments, compositions of the present invention preferably contain endoxifen and hydrogenated soy phosphatidylcholine, or soy phosphatidylcholine, and cholesterol or cholesterol derivative. Such composition includes endoxifen and cholesterol or cholesterol derivative preferably in from about 1:1-1:5 mole ratio, and more preferably at about 1:1 mole ratio to about 1:2 mole ratio.

**[00106]** Yet another aspect of the invention is to form complexes of endoxifen with derivatives of phospholipids, such as pegylated phospholipids. Examples include but are not limited to the polyethylene glycol (PEG) derivatives of distearoylphosphatidylglycerol, dimyristoylphosphatidylglycerol, dioleoylphosphatidylglycerol and the like.

**[00107]** In some preferred embodiments, the mole ratio of endoxifen and hydrogenated soy phosphatidylcholine or soy phosphatidylcholine, in a composition containing endoxifen and hydrogenated soy phosphatidylcholine or phosphatidylcholine is between about 1:10 and 1:90, *e.g.*, between about 1:10 and 1:80 or1:10 and 1:70 or 1:10 and 1:60 or 1:10 and 1:50 or 1:10 and 1:40 and 1:10 and 1:30. Particularly preferred embodiments, the mole ratio of endoxifen and hydrogenated soy phosphatidylcholine or soy phosphatidylcholine is between 1:10 and 1:60.



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**[00108]** In some embodiments, compositions of the present invention preferably contain endoxifen and total lipids having weight to weight ratio between 1:1 to 1:100 ratio such as between 1:1 and 1:20 ratio or between 1:1 and 1:30 ratio or between 1:1 and 1:40 ratio or between 1:1 and 1:50 ratio, or between 1:1 and 1:60 ratio, or between 1:1 and 1:70 ratio, and between 1:1 and 1:80 ratio, or in between 1:1 and 1:90 ratio.

**[00109]** In some embodiments, the method of the present invention comprises solubilizing or suspending endoxifen and lipid(s) together in an aqueous solution, *e.g.*, water. Endoxifen-lipid complex solution can be filtered through suitable filters to control the size distribution of the complexes.

**[00110]** In some embodiments, the method may comprise mixing lipid(s) together in water and then adding endoxifen. Endoxifen-lipid complex solution can be filtered through suitable filters to control the size distribution of the complexes.

**[00111]** In some embodiments, the method also comprises mixing endoxifen and lipid(s) in an organic solvent(s), such as chloroform or ethanol or any other pharmaceutically acceptable solvents, and evaporating the solvent(s) to form a lipid phase or lipid film. The lipid phase is then hydrated with water or an aqueous solution. Examples of aqueous solutions include but are not limited to 0.9% sodium chloride, solutions containing sugars such as dextrose, sucrose, and the like. The hydrated solution can be filtered through suitable filters to control the size distribution of the complexes.

**[00112]** In some embodiments, the method comprises mixing lipid(s) in an organic solvent(s) and evaporating the solvent(s) to form a lipid phase or lipid film. The lipid phase is then hydrated with aqueous solution containing endoxifen. The aqueous solution in addition to endoxifen may further contain sodium chloride or sugars such as dextrose, sucrose and the like. The hydrated solution can be filtered through suitable filters to control the size distribution of the complexes.

**[00113]** In other embodiments, the method of the present invention comprises mixing endoxifen, one or more lipids in any suitable order and in any suitable solvents such that the resulting composition of the present invention contains endoxifen, and one or more lipids.

**[00114]** In some embodiments, the method of preparation of the present invention comprises heating the composition comprising endoxifen, and the lipid(s) at temperatures ranging from 30-100° C preferably between 30 - 80° C and more preferably between 30-60°C.



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**[00115]** In some embodiments, the pH of the composition of invention ranges from about 3 to about 11, while a pH between3.5 to about 8 is preferred and pH of between 4.0 to pH 7.5 are particularly preferred. Aqueous solutions having of a particular pH can be prepared from water having comprising appropriate buffers. Preferred buffers include but are not limited to mixtures of monobasic sodium phosphate and dibasic sodium phosphate, tribasic sodium phosphate, disodium succinate. Other buffers that find use with the present invention include sodium carbonate, sodium bicarbonate, sodium hydroxide, ammonium acetate, sodium citrate, tris (hydroxy-methyl) aminoethane, sodium benzoate, and the like.

**[00116]** The mole ratio of endoxifen and hydrogenated soy phosphatidylcholine or soy phosphatidylcholine in the composition containing endoxifen and hydrogenated soy phosphatidylcholine or soy phosphatidylcholine is in between 1:10 and 1:90 such as in between 1:10 and 1:80 or 1:10 and 1:80 or 1:10 and 1:60 or 1:10 and 1:50 or 1:10 and 1:40 and 1:10 and 1:30. In preferred embodiments, the mole ratio of endoxifen and hydrogenated soy phosphatidylcholine or soy phosphatidylcholine is in between 1:5 and 1:60.

**[00117]** As noted above, compositions can be filtered to obtain a desired size range of complexes particle sizes from the filtrate. Filters that find use in the present invention include those that can be used to obtain the desired size range of the complexes from the filtrate. For example, the complexes can be formed and thereafter filtered through a 5 micron filter to obtain complexes, each particle having a diameter of about 5 micron or less. Alternatively, 1 μm, 500 nm, 200 nm, 100 nm or other filters can be used to obtain complexes having diameters of about 1 μm, 500 nm, 200 nm, 100 nm or any suitable size range, respectively.

**[00118]** When desired, the endoxifen-lipid complex can be dried, *e.g.*, by evaporation or lyophilization. In certain embodiments of the invention, the endoxifen-lipid complex can be lyophilized with one or more cryoprotectants such as sugars. In preferred embodiments, sugars include but are not limited to trehalose, maltose, lactose, sucrose, glucose, and dextran. In particularly preferred embodiments, trehalose and/or sucrose are used. Lyophilization is accomplished under vacuum and can take place either with or without prior freezing of the endoxifen lipid preparation. When desired, the complexes can be resuspended in any desirable solvent including water, saline, dextrose and buffer.

**[00119]** Pharmaceutical preparations that find use with the compositions of the present invention include but are not limited to tablets, capsules, pills, dragees, suppositories, solutions, suspensions, emulsions, ointments, and gels. For the oral mode of



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administration, preferred forms of endoxifen or endoxifen lipid complex include tablets, capsules, lozenges, powders, syrups, aqueous solutions, suspensions and the like. For topical application and suppositories, preferred forms of endoxifen or endoxifen-lipid complex comprise gels, oils, and emulsions, such as are formed by the addition of suitable water-soluble or water-insoluble excipients, for example polyethylene glycols, certain fats, and esters, compounds having a higher content of polyunsaturated fatty acids and derivatives thereof. Derivatives include mono-, di-, and triglycerides and their aliphatic esters (for example, fish oils, vegetable oils etc.) or mixtures of these substances. Suitable excipients are those in which the drug complexes are sufficiently stable to allow for therapeutic use.

**[00120]** When desired, composition containing endoxifen or endoxifen-lipid complex can be encapsulated in enteric-coated capsules to protect it from acids in the stomach. The term "enteric" refers to the small intestine, and enteric coatings prevent release of medication before it reaches the small intestine. Most enteric coatings work by presenting a surface that is stable at acidic pH but breaks down rapidly at higher pH. Enteric coating of capsules filled with composition containing endoxifen or endoxifen-lipid complex can be done as methods known in the art.

**[00121]** The endoxifen -lipid complex of the present invention can be of varying size or can be of substantially uniform size. For example, the complex can have a mean diameter of about 1 mm or less, and more preferably are in the micron or sub-micron range. In some preferred embodiments, the complexes have an average diameter of about 5 μm or less, such as 0.2 μm or less or 0.1 μm or less.

**[00122]** The technology outlined in the present invention may also be used for any other water-insoluble drugs. The methods and compositions of the present invention find use in conjunction with the methods and compositions disclosed in U.S. Application Ser. No. 60/850,446, filed Oct. 10, 2006, PCT Application Ser. No. PCT/US07/80984, filed October 10, 2007, U.S. Application Ser. No. 60/856,952, filed November 6, 2006, PCT Application Ser. No. PCT/US07/83832, filed November 6, 2007, all of which are incorporated by reference herein in their entireties.

**[00123]** The compositions of the present invention can be employed to treat breast cancer and breast related diseases. For example, the compositions of the present invention may be administered to a patient diagnosed with benign breast disease. As used herein, the term" benign breast disease" refers to a constellation of non-malignant aberrations in breast tissue. The aberrations may be proliferative or non-proliferative in nature. The exemplary



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benign breast diseases treatable by the present inventive compositions include adenosis, cysts, duct ectasia, fibroadenoma, fibrosis, hyperplasia, metaplasia and other fibrocystic changes. Each of these diseases, referred as "changes" or "conditions" due to their prevalence, have well-defined histological and clinical characteristics.

**[00124]** "Adenosis" refers to generalized glandular disease of the breast. It typically involves an enlargement of breast lobules, which contain more glands than usual. In "sclerosing adenosis," or "fibrosing adenosis," the enlarged lobules are distorted by scar-like fibrous tissue.

**[00125]** "Cysts" are abnormal sacs filled with fluid or semi-solid material. Cysts in the breast arelined by breast epithelial cells, developing from lobular structures. They begin as excess fluid inside breast glands, but may grow to proportions that stretch surrounding breast tissue, causing pain. "Fibrocysts" are cystic lesions circumscribed by, or situated within, a conspicuous amount of fibrous connective tissue.

**[00126]** "Duct ectasia" refers to a dilation of mammary ducts by lipid and cellular debris. Rupture of the ducts induces infiltration by granulocytes and plasma cells.

**[00127]** "Fibroadenoma" refers to benign tumors that are derived from glandular epithelium and contain a conspicuous stroma of proliferating fibroblasts and connective tissue.

**[00128]** "Fibrosis" simply refers to a prominence of fibrous tissue in the breast.

**[00129]** "Hyperplasia" refers to an overgrowth of cells, where several layers of cells line the basal membrane, without tumor formation. Hyperplasia increases the bulk of mammary tissue. In "epithelial hyperplasia," the cells lining breast ducts and lobules are involved, giving rise to the terms "ductal hyperplasia" and "lobular hyperplasia." Based on a histological determination, hyperplasia may be characterized as "usual" or "atypical".

**[00130]** "Metaplasia" refers to a phenomenon in which a differentiated tissue of one type transforms into a differentiated tissue of another type. Metaplasia often results from an environmental change, and enables cells better to withstand the change.

**[00131]** The compositions of the present invention may be administered in any dosage form and via any system that delivers the active compound endoxifen to breast estrogen receptors *in vivo*. In some embodiments, a composition of present invention is delivered by "percutaneous administration", *e.g.*, delivering the drug from the surface of patient's skin, through the stratum corneum, epidermis, and dermis layers, and into the microcirculations. This is generally accomplished by diffusion down a concentration gradient. The diffusion may occur via intracellular penetration (through the cells),



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intercellular penetration (between the cells), transappendageal penetration (through the hair follicles, sweat, and sebaceous glands), or any combination of the above.

**[00132]** Percutaneous administration of the endoxifen composition of the present invention may be advantageous because this may reduce systemic drug exposure and the risks from non-specifically activating estrogen receptors throughout the body. This is because in topical application of endoxifen will absorb primarily into local tissues. When the composition of invention containing endoxifen will be percutaneously applied to breasts, high concentration will accumulate in the breast tissues presumably due to many estrogen receptors therein. The composition of endoxifen may be applied to any skin surface, preferably to one or both breasts. The daily doses to be administered can initially be estimated based upon the absorption coefficients of endoxifen, the breast tissue concentration that is desired, and the plasma concentration that should not be exceeded. The initial dose may be optimized in each patient, depending on individual responses.

**[00133]** Percutaneous administration can be achieved in different ways, such as (i) by mixing the composition of endoxifen with suitable pharmaceutical carriers and, optionally, penetration enhancers to form ointments, emulsions, gel, lotion, creams or the like, where an amount of said preparation is applied onto a certain area of the skin, (ii) by incorporating the composition of endoxifen into patches or transdermal delivery systems according to the technology known in the art.

**[00134]** The effectiveness of percutaneous drug administration depends on many factors, such as drug concentration, surface area of application, time and duration of application, skin temperature, skin hydration, previous irradiation, physicochemical properties of the drug, and partitioning of the drug between the formulation and the skin. In some embodiments, *e.g.*, to enhance percutaneous effectiveness, the compositions or complexes comprise penetration enhancers that improve percutaneous absorption by reducing the resistance of stratum corneum by reversibly altering its physicochemical properties, changing hydration in the stratum corneum, acting as co-solvent, or changing the organization of lipids or proteins in the intracellular spaces. Such enhancers include but are not limited to organic solvents such as alcohol, acetone, dimethylsulfoxide (DMSO), polyethylene glycol, propoylene glycol, fatty acids and fatty alcohol and their derivatives, hydroxyl acids, pyrrolidones, urea, vegetable oils, essential oils, and mixture thereof. In addition to chemical enhancers, physical methods can increase percutaneous absorption. For example, occlusive bandages induce hydration of the skin. Other physical methods include iontophoresis and sonophoresis, which use electrical fields and high-frequency ultrasound,



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respectively, to enhance absorption of drugs that are poorly absorbed due to their size and ionic characteristics (12-13). Those who are in the pharmaceutical field can easily manipulate the various factors and methods to achieve right efficacious dosage for percutaneous delivery.

**[00135]** For percutaneous administration, the formulation or composition of the invention containing endoxifen may be delivered in the form of ointment, emulsion (lotion), cream, gel, powder, oil or similar formulation. In some embodiments, the formulation comprises excipient additives, including but not limited to vegetable oils such as soybean oil, mustard oil, almond oil, olive oil, groundnut oil, peanut oil, peach kernel oil, groundnut oil, castor oil, canola oil, and the like, animal fats, DMSO, lanolin lipoids, phosphatides, hydrocarbons such as paraffin's, petroleum jelly, waxes, lecithin, detergent emulsifying agents, carotin, alcohols, glycerol, glycerol ether, glycerine, glycol, glycol ethers, polyethylene glycol, polypropylene glycol, non-volatile fatty alcohols, acids, esters, volatile alcoholic compounds, talc, urea, cellulose derivatives, coloring agents, antioxidants and preservatives.

**[00136]** In some embodiments the formulation or composition of the invention containing endoxifen may be delivered as transdermal patch. The patch may comprise (i) a solution-impermeable backing foil, (ii) a layer like element having a cavity, (iii) a microporus or semipermeable membrane, (iv) a self-adhesive layer, and (v) optionally a removable backing film. The layer-like element having a cavity may be formed by the backing foil and the membrane. Alternatively, the patch may comprise(i) a solution-impermeable backing foil.(ii) an open-pored foam, a closed pore foam, a tissue like layer or a fibrous web-like layer as reservoir,(iii) a self adhesive layer, and(iv) optionally a removable backing film.

**[00137]** In some preferred embodiments, the composition of the invention containing endoxifen is formulated in hydro alcoholic gel and the amount of endoxifen may vary from 0.001001 to 1.0 gram per 100grams of gel, most preferably in the range of 0.01-0.20 grams per 100 grams of gel.

**[00138]** In other embodiments, the composition of present invention comprises one or more fatty acid esters as a penetration enhancer. One of the highly preferred examples of a fatty acid ester penetration enhancer is isopropyl myristate. When isopropyl myristate is used in gel, the amount may range e.g., from 0.11 to 5.0 grams per 100 grams of gel, preferably from 0.5 to 2.0grams per 100 grams of gel.



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**[00139]** In another preferred embodiment the composition of invention containing endoxifen may also contain one or more nonaqueous vehicles, such as alcoholic vehicles. Examples of nonaqueous vehicles include ethyl acetate, ethanol, and isopropanol, preferably ethanol and isopropanol. These nonaqueous vehicles may be useful for dissolving both the active agent endoxifen and any other penetration enhancer used. They also preferably have a low boiling point, preferably less than 100° C at atmospheric pressure, to permit rapid evaporation upon contact with skin. In particular, ethanol may effectively contribute to the percutaneous absorption of endoxifen by rapidly evaporating upon contact with skin. The amount of absolute nonaqueous vehicle in a gel formulation ranges from 35% to 99% by weight, preferably between 50% to 85% and more preferably between 60% to 75%.

**[00140]** In another preferred embodiment, the composition or formulation of the invention comprises an aqueous vehicle that permits solubilization of hydrophilic molecules, and promotes moisturization of skin. An aqueous vehicle also can regulate pH. Aqueous vehicles include alkalinizing and basic buffer solutions, including phosphate buffer solutions, including phosphate buffer solutions (e.g., dibasic or monobasic sodium phosphate); citrate buffered solutions (e.g., sodium citrate or potassium citrate) and purified water. The amount of an aqueous vehicle preferably ranges between 0.1% to 65% by weight of the pharmaceutical composition, preferably between 15% to 50%, and more preferably between 25% to 40%.

**[00141]** In other embodiments, the composition of the invention comprises one or more gelling agents to increase the viscosity of the composition or formulation or to function as a solubilizing agent. It may constitute between 0.1% to 20% by weight of formulation depending on the nature of gelling agent, preferably between 0.5% to 10% and more preferably between 0.5% to 5%. The gelling agents may be carbomers, cellulose derivatives, poloxamers and poloxamines. The preferred gelling agents are chitosan, dextran, pectins, natural gums and cellulose derivatives such as ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and the like. The most preferred gelling agent is hydroxypropyl cellulose.

**[00142]** The composition of invention may comprise a gelling agent as described above, in particular a non-preneutralized acrylic polymer and also comprise a neutralizing agent. The ratio of neutralizing agent/gelling agent varies in between 10:1 to 0.1:1, preferably between 7:1 to 0.5:1, and more preferably between 4:1 to1:1.A neutralizing agent



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in the presence of polymer should form salts that are soluble in the vehicle. A neutralizing agent also should permit optimum swelling of polymer chains during neutralization of charges and formation of polymer salts. The neutralizing agents include ammonium hydroxide, potassium hydroxide, sodium hydroxide, aminomethylpropanol, trolamine, and tromethamine. Those skilled in the art will select a neutralizing agent according to the type of geling agent used in the composition or formulation. However, no neutralizing agent is required when a cellulose derivative will be used as geling agents.

**[00143]** In some embodiments, the compositions of present invention are employed to treat other diseases, and the medication is selected from a lipophilic or a compound made lipophilic by derivatization of the group consisting of antiasthama, antiarrhythmic, antifungals, antihypertensive, anticancer, antibiotics, antidiabetics, antihistamines, antiparasitics, antivirals, cardiac glycosides, hormones, immunotherapies, antihypotensives, steroids, sedatives and analgesics, tranquilizers, vaccines, and cell surface receptor blockers.

**[00144]** All references, including publications, patent applications, and patent cited herein, including those in the list below and otherwise cited in this specification, are hereby incorporated by reference to the same extent as if each reference was individually and specifically indicated to be incorporated by reference and were set forth in the entirely herein.

**[00145]** The use of terms "a" and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising", "including", "having", and "containing" are to be construed as open-ended terms (i.e. meaning "including but not limited to") unless otherwise noted. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specifications should be constructed as indicating any non-claimed element as essential to the practice of the invention.

**[00146]** Preferred embodiments of this invention are described, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments can become apparent to those of ordinary skilled artisans to employ such variations as appropriate, and the inventors intend for the inventions to be practiced otherwise than specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as



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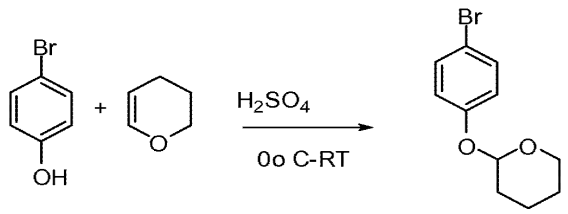
permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

## EXAMPLES

**[00147]** The following examples further illustrate the invention and are not to be construed as in any way as limiting its scope.

### EXAMPLE 1

### Synthesis of Compound 3




**1** **2** **3**

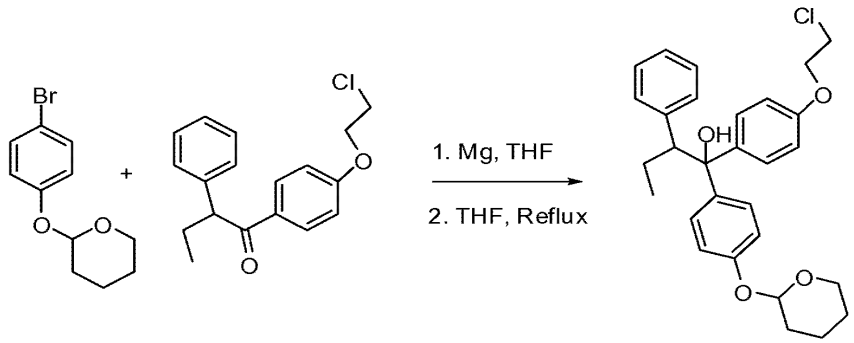
**[00148]** 4-Bromophenol (**1**, 1 kg) and 3, 4-dihydro-2H-pyran (**2**, 1.5 L) was mixed together in a round bottom flask and cooled to 0°C. Conc. Sulfuric acid (1 mL) was added drop wise while maintaining the temperature below room temperature. The solution was stirred at RT for 1 hr. The reaction solution was diluted with hexane and washed with water (1 L) followed by 5% sodium bicarbonate solution (1 L). The organic layer was dried over sodium sulfate, filtered and evaporated *in vacuo* at 50-55° C to give an oil (1.55 Kg). Hexane (300 mL) was added to the oil and triturated to give white solid **3**. The suspension was cooled to 0°C and stirred for 30 min before it was filtered and washed with cold hexane (100 mL) and dried. Yield 1.32 Kg.



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## EXAMPLE 2

### Synthesis of Compound 5




3 4 5

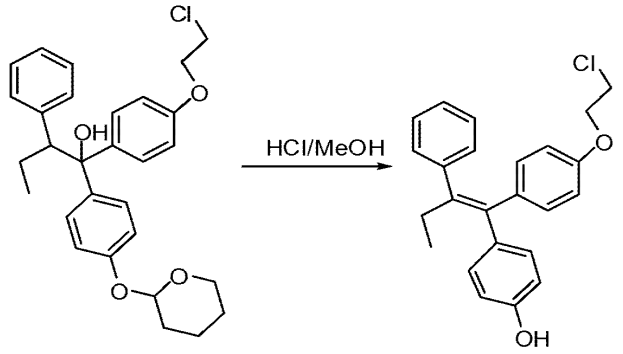
**[00149]** Magnesium turnings (115 g) were added to a 10_L 4-neck round bottom flask containing anhydrous tetrahydrofuran (1 L). The mixture was heated to 55°C. Iodine chips (approx. 5) were added in one lot followed by ethyl bromide (5 mL). Compound **3** (1.1 kg) was dissolved in THF (2 L). 200 mL of this solution was added at once to Mg-THF suspension. The reaction was initiated after 30 mins and reflux started. Remaining solution of compound 3 was added drop wise maintaining the reflux temperature over a period of 1.5 h. The reaction mixture was further refluxed for 2 hr and the cooled to RT. (2-Chloroethoxyphenyl) phenyl butanone (**4**, 870 g) in THF (1.5 L) was added drop wise over a period of 1 h maintaining the temperature between 30-35° C. The reaction mixture was refluxed for 4h and cooled to RT. The reaction mixture was poured into ice cold 50% hydrochloric acid (3L). The organic layer was separated and the aqueous layer was extracted with THF (3 x 500 mL). The organic layers were combined, dried over sodium sulfate, filtered and concentrated to give **5** as oil which was carried over to next step without further purification. Yield – 1.57 kg.



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## EXAMPLE 3

### Synthesis of Compound 6

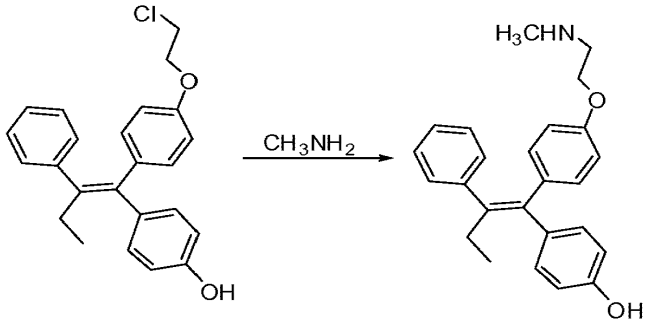



**5** **6**

**[00150]** Compound (**5**, 1.57 kg) was dissolved in methanol (6 L) and conc. hydrochloric acid (1.57 kg) was added. The solution was refluxed for 5 h. Methanol was removed *in vacuo* and dichloromethane (5 L) was added. The organic layer was separated. The aqueous layer was extracted with dichloromethane (2 x 500 mL). The organic layers were combined and washed with water (2 L), 5% aq. NaHCO3 (2 L), water (2L), dried over sodium sulfate. Charcoal was added and filtered. The solvent was removed under vacuum to give oil (1.38 kg). The oil was triturated with hexane (5 L) with vigorous stirring to yield **6** as solid product which was filtered and dried. Yield 1.07 kg.

## EXAMPLE 4

### Synthesis of Compound I




**6** **I**

**[00151]** To a solution of compound **6** (50 g) in isopropanol (500 mL), monomethyl amine (300 mL) was added and heated for 24 h maintaining the temperature between 70-



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75°C. The completion of reaction was monitored by TLC (toluene:triethylamine, 7:3). The solvent was removed *in vacuo*. Water (500 mL) was added to the residue and extracted with diisopropyl ether (DIPE, 500 mL). The organic layer was separated and the aqueous layer was back extracted with DIPE (200 mL). The organic layers were combined and washed with water (500 mL), 5% aq. sodium bicarbonate (500 mL), dried over sodium sulfate and filtered. The solvent was removed *in vacuo* to give a gummy residue. Ethyl acetate (50 mL) was added and heated to dissolve the residue completely. The solution was cooled to RT and hexane (50 mL) was added and stirred for 12 h. The solid was filtered and washed with cold ethyl acetate-hexane (1:1, 10 mL) mixture. Product I was dried overnight under high vacuum. Yield 25 g.

## EXAMPLE 5

### Endoxifen Solution

**[00152]** Endoxifen solution (1 mg/mL) was prepared by solubilizing endoxifen (10.3 mg) in 0.2% glacial acetic acid (10 mL). The pH (~5.75)of the solution was adjusted with 1N sodium hydroxide (300 µL).

## EXAMPLE 6

### Endoxifen Solution

**[00153]** Endoxifen solution (5 mg/mL) was prepared by solubilizing endoxifen (100 mg) in 2% glacial acetic acid (8.6 mL). The solution was diluted with 5% dextrose (10.97 mL). The pH (~5.56) of the solution was adjusted with 5N sodium hydroxide (430 µL).

## EXAMPLE 7

### Endoxifen Complexes

**[00154]** A suspension of endoxifen, cholesteryl sulfate, and soy lecithin, is produced by mixing the components together in water and homogenizing using. *e.g.*, a high pressure homogenizer. The resulting suspension can be filtered through 0.2 µm filter and then mixed with 7.5% sucrose solution and lyophilized in either vials or in bulk. The particle size of the resulting complexes is determined using standard procedures, *e.g.*, using a Nicomp particle sizer 380.



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## EXAMPLE 8

### Endoxifen Complexes

**[00155]** A suspension of endoxifen and soy lecithin is produced by mixing the components together in water and homogenizing using, *e.g.*, a high pressure homogenizer.. The resulting suspension can be filtered through 0.2 μm filter and then mixed with 7.5% sucrose solution and lyophilized in eithervials or in bulk. The particle size is determined using standard procedures, *e.g.*, using a Nicomp particle sizer 380.

## EXAMPLE 9

### Toxicity Testing

**[00156]** Endoxifen was formulated according to Example 6 and was tested for toxicity in male Balb/c mice. A single test dose at 100 mg/kg or 50 mg/kg was intravenously administered to mice. All the mice died at the100 mg/kg dose level whereas all animals survived at the 50 mg/kg dose level with no significant loss of body weight. The mice also survived in the control group with a vehicle control that lacked endoxifen. Repeat dose toxicity study was conducted with a dose of 25 mg/kg administered consecutively for 3 days with accumulated dose of 75 mg/kg. All the animals in this group survived. The results are reported in the table below as the number of mice surviving per total.

| Treatment | Dose (mg/kg) | Survival/Total |
|---|---|---|
| Single dose | 100 | 0/2 |
| | 50 | 4/4 |
| Repeat dose | 25 | 4/4 |

## EXAMPLE 10

### Endoxifen exhibits anti-proliferative activity against different tumor cells

**[00157]** Endoxifen was tested for antiproliferation activity against various cancer cell lines from Non Small Lung Cancer, Breast Cancer, Prostate Cancer, Melanoma Cancer, Ovarian Cancer, CNS Cancer, Renal Cancer and Colon Cancers. The cells were incubated for multiple days (3 - 7) with Endoxifen (10 nM to 10 μM) and the inhibition of growth were measured by SRB or MTT staining method. The results indicated significant growth inhibition of cells in the presence of Endoxifen ranging from 10 to 100%. Endoxifen induce



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growth inhibition or cell killing in different tumor cells indicates the usefulness of Endoxifen in the treatment of cancers in humans.

## EXAMPLE 11

### Endoxifen Inhibits Estradiol Dependent Breast Tumor Growth

**[00158]** It is known that Tamoxifen antagonizes estradiol-dependent breast cancer xenograft growth (15). Endoxifen base and endoxifen-citrate in oral dosage form can be similarly be tested for inhibition of estradiol dependent MCF-7 xenograft growth. For the animal experiments, female nude mice (Bom: NMRI-*nu/nu*) per xenograft experiment, ages 4 to 6 weeks and weighing 20 to 24 g, are used according to standard protocols. An example of such a procedure is as follows:

**[00159]** MCF-7 xenografts are developed by passage of transplantable tumor from a parent tumor established in oophorectomized athymic nude mice treated with estradiol (16-17).

**[00160]** Randomly bred female athymic mice are bilaterally ovriectomized and allowed a 2-week recovery period before the implantation of tumor material. The s.c. transplantation of the MCF-7 tumor fragments (size, 1x 1 x 1 $mm^3$) is done under anesthesia. The diameter of the tumors is measured regularly, *e.g.*, once weekly, using a caliper-like mechanical instrument and the tumor volume ($V$) is calculated according to the empirical equation $V = (\text{length} \times \text{width}^2)/2$. The median volumes of each group are normalized to the initial tumor volume resulting in the relative tumor volume. In all the experiments, tumor-bearing mice receive estradiol supplementation [estradiol valeriate (E2D), 0.5 mg/kg once/wk i.m.]. This supplementation leads to physiologic levels of serum E2 (25-984 pg/mL) that are comparable to the human situation (25–600 pg/mL depending on the follicular phase).

**[00161]** Substances**:** The following substances are used: E2D, Tamoxifen and endoxifen.

**[00162]** Treatment Modalities: All MCF-7 transplanted animals receive E2D (0.5 mg/kg) injections once a week. After 4 weeks, when hormone-supplemented tumors have grown to ~0.7-0.8 cm in diameter (180-250 $mm^3$ ), the mice are randomized into 4 treatment groups of 5-10 mice each. The 5-10 mice are sacrificed as baseline controls for E2D alone.

**[00163]** The treatment groups are**:** (i) E2D support (0.5mg/kg once/wk i.m); (ii) E2D support (0.5mg/kg once/wk i.m) plus Tamoxifen (0.5mg-2mg)/mouse per day, 5



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days/week by gavage ; (iii) E2D support (0.5mg/kg once/wk i.m) plus endoxifen (0.5mg-2mg)/mouse per day, 5 days /week by gavage; (iv) withdrawal of E2D support.

**[00164]** Suppression of tumor growth in this breast cancer tumor model is indicative of therapeutic effect in the treatment of breast cancer in humans (15).

## EXAMPLE 12

### Endoxifen Minimizes Uterotrophic Effect of Estrogen

**[00165]** It is known that Tamoxifen is a non-steroidal agent with potent anti-estrogenic effect in animal and *in vitro* models. This pharmacologic property is related to the drug's ability to compete with estrogen for estrogen receptors in breast tissues, and to inhibit the stimulatory effect of estrogen on the uterus, vagina and ovaries (18).

**[00166]** Endoxifen (0.1 mg-2 mg) is administered orally once daily for 28 days to determine the reduction in utertrophic effect of estradiol; Female BALB/c mice approximately 50 days old and weighing 19-20 g are obtained (*e.g.*, from Charles-River, Inc.) and housed four to five per cage at a temperature (23+_ 1 C) and light (12 h light/ day). The atrophic changes are observed in the mice. There will be three groups such as vehicle control, Tamoxifen and endoxifen. The animals (5-10 mice) are randomly assigned to each group. Daily treatments of intact mice with a dose (*e.g.*, 0.1 mg-2mg) by gavage of Tamoxifen or endoxifen are expected to lead to progressive inhibition of uterine and vaginal weight.

**[00167]** Such results will show that endoxifen has better minimizing uterotrophic effect of estrogen than Tamoxifen, and that endoxifen finds use as an effective anti-estrogen. Endoxifen blocking of uterine weight gain stimulated by estrogen can also be demonstrated in immature rats. Endoxifen preparations showing the effects described above find use in the treatment of breast cancer as well as other estrogen-sensitive conditions, such as endometriosis, leiomyomata, and benign breast disease, as well as other estrogen-responsive conditions in men and women.

## EXAMPLE 13

### Endoxifen-Caused Decrease of Ki-67 Antigen Expression in Proliferating Breast Cancer Cells

**[00168]** Ki-67 is a nuclear non-histone protein. This antigen is absent in quiescent cells and is expressed in proliferating cells and is used as a biomarker (19-20). Endoxifen



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base or endoxifen-citrate in oral or injectable form are given to xenograft breast cancer tumor models (*e.g.*, as described above), as well as to breast cancer patients. Immunochemical determination of Ki-67 is done in tumor cells from breast cancer tissues from patients, as well as from mice bearing tumors as described in Example 11. The MIB-1 or similar antibody available from commercial sources such as DAKO, Carpenteria, CA is used for immunochemical localization of antigen. Decrease in Ki-67 antigen expression in animals and/or breast cancer patients demonstrate the applicability of endoxifen in treating breast cancers.

## EXAMPLE 14

### Endoxifen reduces IGF-1 levels in Breast Cancer

**[00169]** It is known for humans that Tamoxifen reduces the levels of circulating insulin-like growth factor I (IGF-1). IGF-1 has been used as a surrogate biomarker and predicts the effectiveness of Tamoxifen in treatments of breast cancer patients (21). To test the effects of endoxifen preparations of the present invention, endoxifen base or endoxifen-citrate are given orally or injected to experimental animals bearing breast cancer tumors. The concentration of IGF-1 levels in control and xenografted breast tumor is monitored by established assays (*e.g.*, ELISA Kit from Diagnostics Systems Laboratories, London, UK or DAKO, Carpenteria, CA). Endoxifen is administered by gavages at 0.5mg-2mg per mouse per day, 5 days/week. Decrease of IGF-1 levels and tumor growth reduction indicates the usefulness of IGF-1 as a surrogate marker for breast cancer.

## EXAMPLE 15

### Endoxifen Prevents Development of Bicalutamide –induced Gynecomastia and Breast Pain

**[00170]** Bicalutamide (CasodexR) is used for treating prostate cancer in men. There is growing evidence that IGF-1 may be involved in prostate cancer promotion and progression. It is also known that anti-estrogen agents such as Tamoxifen decrease IGF-1 levels and prevent biculatamide –induced gynecomastia in prostate cancer patients (22). Since, endoxifen is an active metabolite of the Tamoxifen anti-estrogen, the silastic slow-release capsules containing endoxifen for implant or oral doses of endoxifen (1mg-10mg/day) with biculatamide are expected to prevent development of biclutamide –induced gynecomastia and breast pain.



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## CLAIMS

1. A method of treating a disease comprising, preparing a composition comprising a therapeutically active amount of a complex comprising an anticancer drug and with or without at least one lipid.

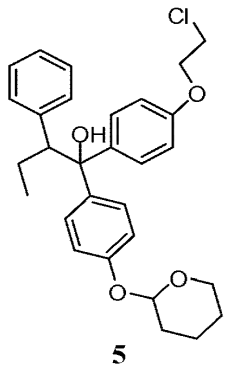
2. The method of claim 1, wherein the anticancer drug is endoxifen, and wherein said endoxifen is a free base or is in the form of a salt.

3. The method of claim 2 wherein said endoxifen is in the form of a salt selected from the group of salts consisting of citrate, acetate, formate, oxalate, tartarate, trifluoroacetane, methane sulfonate, phosphate, sulfate, chloride, bromide, iodide, lactate, and formate.

4. The method of claim 2 or 3, wherein said endoxifen is predominantly in a form selected from the group consisting of *E*-isomer, *Z*-isomer, and a mixture of *E*- and *Z*-isomer.

5. A method of preparing endoxifen, comprising:

i. reacting a compound of Formula **5** with acid, wherein the compound of formula 5 has the structure:




**5**

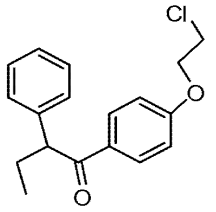
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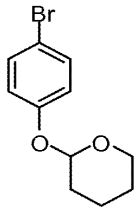
i. after said reaction of said compound of Formulat5 with acid, reacting said compound with methylamine.

6. The method of claim 5, wherein said compound of Formula **5** is prepared by reacting compound of formula **4**



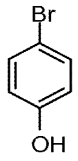

**4**

with a compound of Formula **3**.




**3**

7. The method of claim 6, wherein said compound of Formula **3** is prepared by reacting compound of Formula **1**




**1**

with a compound of Formula **2**.




**2**

8. A method of purifying the endoxifen of claim 5, comprising:

a. crystallizing said endoxifen; and/or



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b.chromatographically treating said endoxifen;

to produce a purified preparation of endoxifen, wherein said purified preparation of endoxifen contains predominantly *E*-isomer, predominantly *Z*-isomer, or a mixture of *E*- and *Z*-isomers of endoxifen.

9. The method of claim 1 or 2, wherein said at least one lipid is selected from the group consisting of egg phosphatidylcholine (EPC), egg phosphatidylglycerol (EPG), soy phosphatidylcholine (SPC), hydrogenated soy phosphatidylcholine (HSPC), dimyristoylphosphatidylcholine (DMPC), dimyristoylphosphatidylglycerol (DMPG), dipalmitoylphosohatidylcholine (DPPC), disteroylphosphatidylglycerol (DSPG), dipalmitoylphosphatidylglycerol (DMPG), cholesterol (Chol), cholesterol sulfate and its salts (CS), cholesterol hemisuccinate and its salts (Chems), cholesterol phosphate and its salts (CP), cholesterylphosphocholine and other hydroxycholesterol or amino cholesterol derivatives, cholesteryl succinate, cholesteryl oleate, polyethylene glycol derivatives of cholesterol (cholesterol-PEG), coprostanol, cholestanol, cholestane, cholic acid, cortisol, corticosterone, hydrocortisone, and calciferol, *E*-guggulsterone, *Z*-guggulsterone, mixture of *E*-and *Z*-guggulsterone, monoglycerides, diglycerides, triglycerides, carbohydrate-based lipids selected from a group consisting of galactolipid, mannolipid, galactolecithin, β-sitosterol, stigmasterol, stigmastanol, lanosterol, α-spinasterol, lathosterol, campesterol, phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine, phosphatidylserine, phosphatdylinositol, phosphatidic acid, and pegylated derivatives of distearoylphosphatidylglycerol, dipalmitoylphosphatidylglycerol, dimyristoylphosphatidylglycerol, and dioleoylphosphatidylglycerol.

10. The method of claim 2, wherein said composition comprises endoxifen, cholesterol and/or cholesterol derivatives, and one or more phospholipids.

11. The method of claim 10, wherein said composition comprises a cholesterol derivative, wherein the cholesterol derivative is cholesteryl sulfate.

12. The method of claim 10, wherein at least one of said phospholipids is hydrogenated soy phosphatidylcholine or soy phosphatidylcholine.



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13. The method of claim 1, wherein said composition comprises a form selected from the group consisting of powder, solution, emulsion, micelle, liposome, lipidic particle, gel, and paste form.

14. The method of claim 1 or 13, wherein said preparing of said composition comprising a complex comprises preparing said complex in a lyophilized form.

15. The method of claim 14, wherein said preparing said complex in a lyophilized form comprises using a cryoprotectant, wherein said cryoprotectant comprises one or more sugars selected from the group consisting of trehalose, maltose, lactose, sucrose, glucose, and dextran.

16. The method of claim 1 or 2, wherein, said composition comprises a tablet or a filled capsule, wherein said tablet or filled capsule optionally comprises an enteric coating material.

17. The method of claim 1 or 2, wherein said disease is cancer or caused by cancer-causing agents.

18. The method of claim 1 or 2, wherein said disease is benign breast disease.

19. The method of claim 1 or 2, wherein said administering comprises oral, intravenous, subcutaneous, percutaneous, parenteral, intraperitoneal, rectal, vaginal, and/or topical delivery said composition to said subject.

20. The method of claim 1 or 2, wherein said composition comprises a penetration enhancer, wherein said penetration enhancer comprises at least one saturated or unsaturated fatty acid ester.

21. The method of claim 2, wherein said composition comprising endoxifen is formulated in a hydroalcoholic gel, a hydroalcoholic solution, a patch, a cream, an emulsion, a lotion, an ointment, a powder or an oil.



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22. The method of claim 21, wherein said composition comprising endoxifen is formulated in a hydroalcoholic composition containing a penetration enhancer, an aqueous vehicle, an alcoholic vehicle and a gelling agent.

23. The method of claim 21, wherein said hydroalcoholic composition comprises a neutralizing agent.

24. The method of claim 21, wherein said hydroalcoholic composition comprises

(i) endoxifen at about 0.01% to 0.20% by weight;

(ii) isopropyl myristate at about 0.1% to 2.0%, preferably 0.5% to 2.0% by weight;

(iii) alcohol at about 50.0% to 80.0%, preferably about 60.0% to 75.0% by weight

(iv) aqueous vehicle at about 20.0% to 60.0%, preferably 25.0% to 50.0% by weight; and

(v) gelling agent at about 1.0% to 10.0%, preferably about 0.5% to 5.0% by weight.

wherein the percentage of components is weight to weight of the composition.

25. The method of claim 24, wherein said alcohol is ethanol or isopropanol, and constitutes in absolute form.

26. The method of claim 24, wherein said aqueous vehicle is a phosphate buffered solution.

27. The method of claim 24, wherein said gelling agent is selected from the group consisting of polyacrylic acid, hydroxypropylcellulose and a cellulose derivative other than hydroxypropylcellulose.

28. The method of claim 24, wherein said hydroalcoholic composition further comprises a neutralizing agent, wherein said neutralizing agent is selected from the group consisting of sodium hydroxide, potassium hydroxide, ammonium hydroxide, aminomethylpropanol, arginine, trolamine, and tromethamine, and wherein said



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neutralizing agent exists at a neutralizing agent/gelling agent ratio of about 1:1 to about 4:1.

29. A method of delivering endoxifen, comprising providing a composition according to any of the claims 1-28 and delivering said composition so as to expose the composition to a cell.

30. The method of claim 29, wherein the cell is *in vivo*.

31. The method of claims 1 and 30, wherein the host is a mammal.

32. A method of inhibiting hormone-dependent breast carcinoma in a mammal comprising administering composition of claim 1, 2 and 24 to said mammal.

33. A method of inhibiting a cancer in a mammal, said cancer selected from the group consisting of lung cancer, colon cancer, breast cancer, leukemia, renal cancer, melanoma, cancer or the central nervous system, and prostate cancer in a mammal, comprising administering a composition of claim 1, 2 or 24 to said mammal.

34. The method of claim 31, 32 or 33 wherein said mammal is human.

35. A composition comprising a therapeutically active amount of a complex comprising endoxifen and at least one lipid, wherein said endoxifen is a free base or is in the form of a salt.

36. The composition of claim 35, wherein said composition comprising endoxifen is formulated in a hydroalcoholic gel, a hydroalcoholic solution, a patch, a cream, an emulsion, a lotion, an ointment, a powder or an oil.

37. The composition of claim 36, wherein said composition comprising endoxifen is formulated in a hydroalcoholic composition containing a penetration enhancer, an aqueous vehicle, an alcoholic vehicle and a gelling agent.



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38. The composition of claim 36, wherein said hydroalcoholic composition comprises a neutralizing agent.

39. The composition of claim 36, wherein said hydroalcoholic composition comprises

(i) endoxifen at about 0.01% to 0.20% by weight;

(ii) isopropyl myristate at about 0.1% to 2.0%, preferably 0.5% to 2.0% by weight;

(iii) alcohol at about 50.0% to 80.0%, preferably about 60.0% to 75.0% by weight

(iv) aqueous vehicle at about 20.0% to 60.0%, preferably 25.0% to 50.0% by weight; and

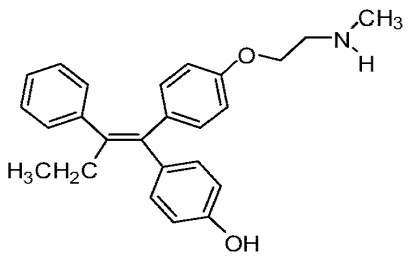
(v) gelling agent at about 1.0% to 10.0%, preferably about 0.5% to 5.0% by weight.

wherein the percentage of components is weight to weight of the composition.



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**Figure 1**

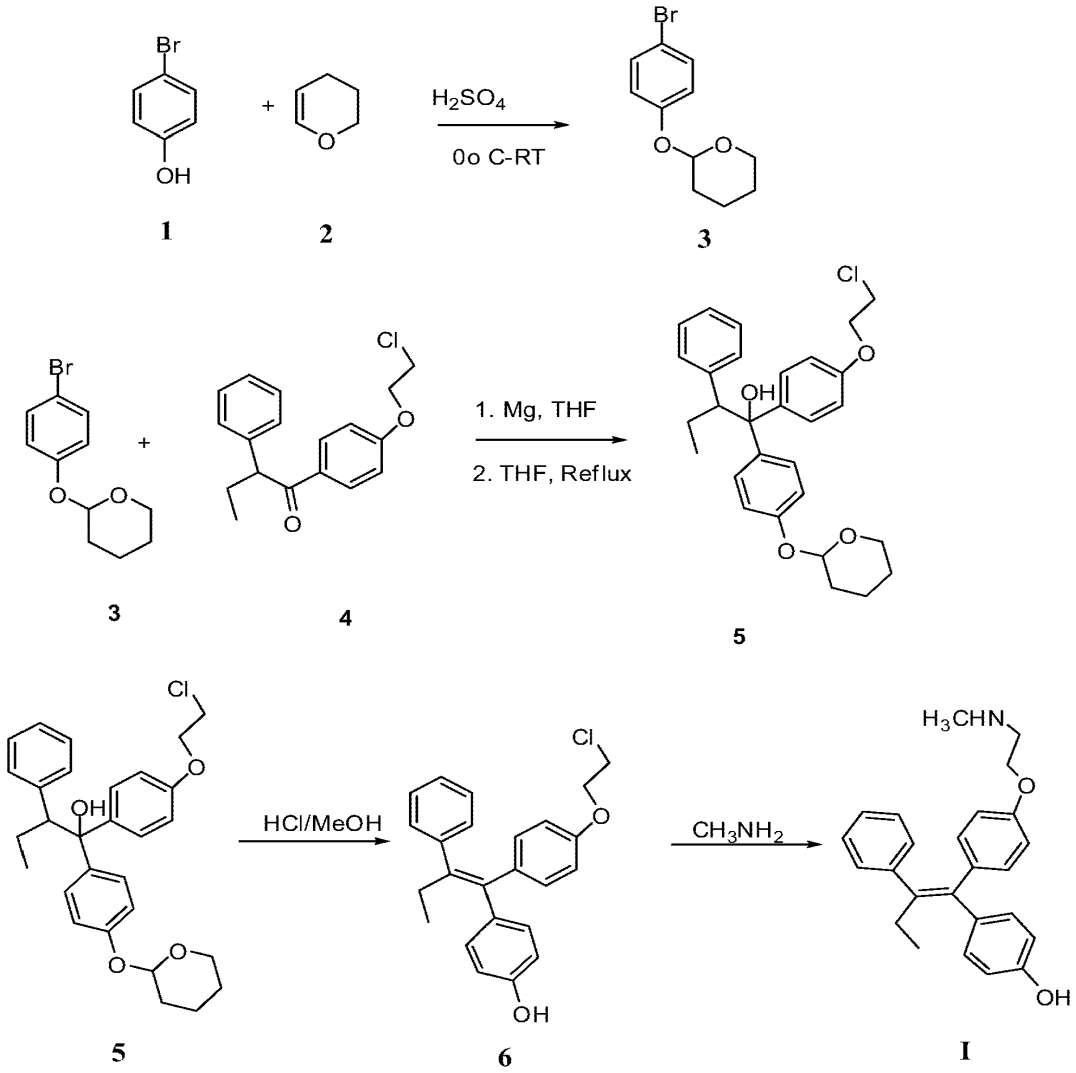



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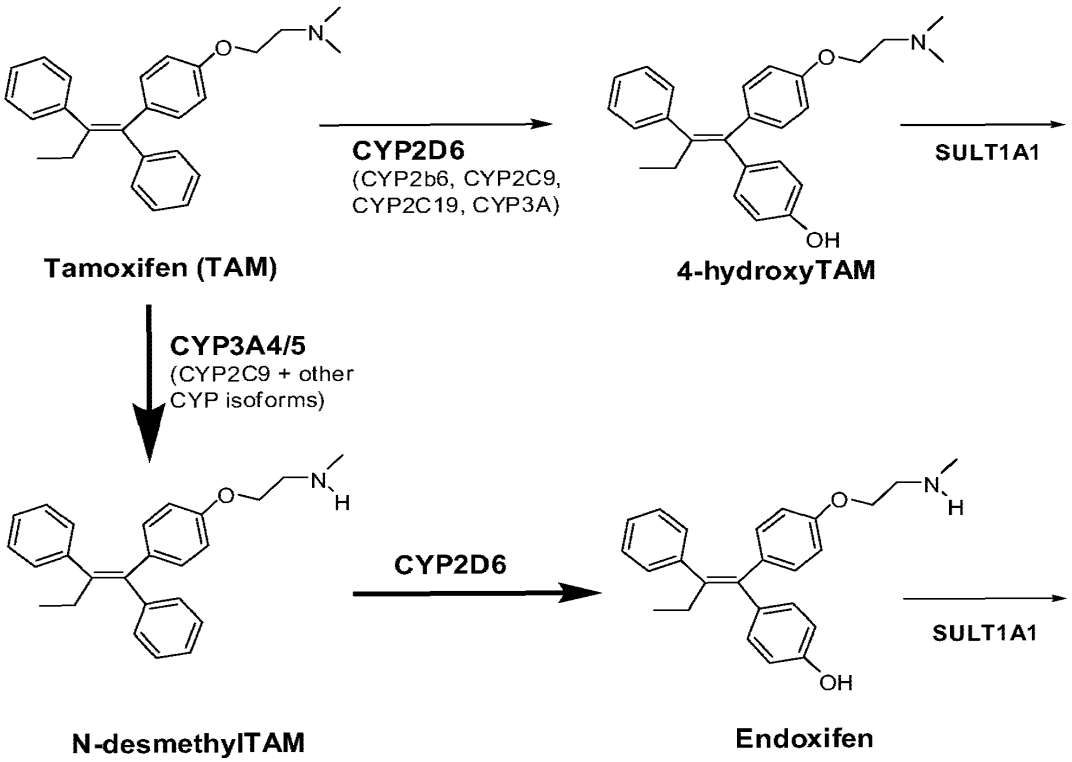
**Figure 2**






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Figure 3






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(71) **Applicant** *(for all designated States except US)*: **OLEMA PHARMACEUTICALS, INC.** [US/US]; 665 Third Street, Suite 250, San Francisco, CA 94107 (US).

(72) **Inventors; and**
(75) **Inventors/Applicants** *(for US only)*: **KUSHNER, Peter** [US/US]; 1362 6th Avenue, San Francisco, CA 94122 (US). **HARMON, Cyrus** [US/US]; 726 Euclid Ave, Berkeley, CA 94708 (US). **MYLES, David** [US/US]; 1665 Thousand Oaks Boulevard, Berkeley, CA 94707 (US). **PHILLIPS, James, G.** [US/US]; 552 Bradley Rd, Bay Village, OH 44140 (US).

(74) **Agent**: **WILLIS, Michael, A.**; King & Spalding LLP, 1185 Avenue of The Americas, New York, NY 10036 (US).

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(54) **Title**: USE OF AN ENDOXIFEN PRODRUG FOR TREATMENT OF BREAST CANCER

(57) **Abstract**: The present invention is directed to compounds, compositions thereof, and the use of the compounds and compositions for the treatment and prevention of breast cancer. In one embodiment, the present invention relates to the use of a prodrug of endoxifen or a related compound for the treatment of breast cancer in mono-therapy or in combination therapy, or for a reduction in the recurrence rate of previously-treated breast cancer.

# USE OF AN ENDOXIFEN PRODRUG FOR TREATMENT OF BREAST CANCER

**[0001]** This application claims priority to US provisional patent applications 61/040,553, filed March 28, 2008, and 61/076,557, filed June 27, 2008, and the entire contents of each of the priority applications are incorporated by reference.

## 1. FIELD OF THE INVENTION

**[0002]** The present invention is directed to compounds, compositions thereof, and the use of the compounds and compositions for the treatment and prevention of breast cancer. In one embodiment, the present invention relates to the use of a prodrug of endoxifen or a related compound for the treatment of breast cancer in mono-therapy or in combination therapy, or for a reduction in the recurrence rate of previously-treated breast cancer. In an alternative embodiment, intermediates are presented for the synthesis of compounds and compositions for the treatment and prevention of breast cancer.

## 2. BACKGROUND OF THE INVENTION

**[0003]** Among women in the U.S., breast cancer is the most common cancer and the second-most common cause of cancer death. Estrogen Receptor (ER)-positive breast cancer is treated with agents designed to block the pro-proliferative action of the estrogen receptor. One such agent is the antiestrogen tamoxifen.

**[0004]** Tamoxifen itself binds very poorly to the ER. However, when activated by metabolic action, tamoxifen gives rise to derivatives that bind very tightly to the ER and put it in an inactive state that prevents it from modulating transcription of pro-proliferative genes. The tamoxifen is activated to inhibit ER action by metabolizing enzymes that convert the tamoxifen to 4-hydroxy tamoxifen (4-OHT) or to 4-hydroxy N-desmethyl tamoxifen (also known as endoxifen). These later compounds bind with high affinity to the ER, with binding constants roughly equal to that of estradiol. See Jordan, V.C., "New insights into the metabolism of



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tamoxifen and its role in the treatment and prevention of breast cancer," Steroids, vol. 72, issue 13, pp. 829-842, November 2007.

**[0005]** Some women have defects in the activating enzymes of tamoxifen metabolism, especially the cytochrome p450 enzyme Cyp2D6, resulting in lowered levels of active tamoxifen metabolites in their circulation. See Lim, H.-S. et al., "Clinical Implications of CYP2D6 Genotypes Predictive of Tamoxifen Pharmacokinetics in Metastatic Breast Cancer," Journal of Clinical Oncology, vol. 25, no. 25, pp. 3837-3845, September 1, 2007; Schroth, W. et al., "Breast Cancer Treatment Outcome With Adjuvant Tamoxifen Relative to Patient CYP2D6 and CYP2C19 Genotypes," Journal of Clinical Oncology, vol. 25, no. 33, pp. 5187-5193, November 20, 2007; and Kiyotani, K. et al., "Impact of CYP2D6*10 on recurrence-free survival in breast cancer patients receiving adjuvant tamoxifen therapy," Cancer Science, Online Early Articles, pp. 1-5, published online February 24, 2008. Women with such defects have a poorer response to tamoxifen therapy and reduced tumor-free survival. In contrast, women with super-fast metabolism of tamoxifen and increased endoxifen levels have a superior clinical response to tamoxifen. See Schroth, W. et al., "Breast Cancer Treatment Outcome With Adjuvant Tamoxifen Relative to Patient CYP2D6 and CYP2C19 Genotypes," Journal of Clinical Oncology, vol. 25, no. 33, pp. 5187-5193, November 20, 2007. In addition to these genetic factors, it is also known that certain drugs, especially selective serotonin reuptake inhibitors (SSRIs) such as PAXIL®, also interfere with Cyp2d6 activity including the conversion of tamoxifen to active metabolites (discussed in Jordan, V.C., "New insights into the metabolism of tamoxifen and its role in the treatment and prevention of breast cancer," Steroids, vol. 72, issue 13, pp. 829-842, November 2007). Additional information can be found in Goetz et al., "Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes," J Clin Oncol, 2005, 23, 9312-9318; Goetz et al., "The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen" Breast Cancer Res Treat, 2007, 101, 113-121; and Schroth et al, "Breast cancer treatment outcome with adjuvant tamoxifen relative to patient CYP2D6 and CYP2C19 genotypes" J Clin Oncol, 2007, 25, 5187-5193.



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**[0006]** The activity of tamoxifen, 4-hydroxytamoxifen, and endoxifen are affected by their rates of processing in the body. Endoxifen and 4-hydroxytamoxifen have hydroxy groups that are reported to be substrates for O-glucuronidation by two UGTs: 1A8 and 1A10. See Sun, D. et al., "Glucuronidation of Active Tamoxifen Metabolites by the Human UDP Glucuronosyltransferases," Drug Metabolism and Disposition, vol. 35, no. 11, pp. 2006-2014, November 2007. These enzymes are present in both the gut and liver as well as other extrahepatic tissues and may possibly inactivate endoxifen by O-linked glucuronidation at the hydroxyl group. For example, it has been reported that glucuronated endoxifen can no longer bind to the ER (Zheng, Y. et al., "Elimination of Antiestrogenic Effects of Active Tamoxifen Metabolites by Glucuronidation," Drug Metabolism and Disposition, vol. 35, no. 10, pp. 1942-1948, October 2007). Thus, the current treatment of breast cancer with tamoxifen has an uneven effect on different patients due in part to variations in the manner in which patients metabolize tamoxifen or its metabolite endoxifen.

## 3. SUMMARY OF THE INVENTION

**[0007]** To overcome these and other problems with breast cancer therapy, we have designed compounds that are prodrugs of endoxifen or related compounds that do not require activation by Cyp2D6 or other oxidative metabolism. Compounds according to the invention may result in improved endoxifen serum levels for patients non-responsive to tamoxifen therapy due to the cytochrome p450 enzyme Cyp2D6. Compounds according to the invention may have improved bioavailability in that they are no longer substrates for UGTs in the gut, or may be more readily absorbed than endoxifen. Endoxifen prodrugs according to the invention may include, for example, endoxifen phosphate in which the hydroxyl moiety is modified to a phosphate, where the phosphate may lead to more efficient absorption when it is converted to endoxifen at high concentration at the apical cell surface. These and other advantages are more fully described below.

**[0008]** The present invention is directed to compounds, compositions thereof, and the use of the compounds and compositions for the treatment and prevention of breast cancer. Compounds according to the invention may be considered prodrugs of endoxifen and related compounds. The compounds may be used for the treatment of

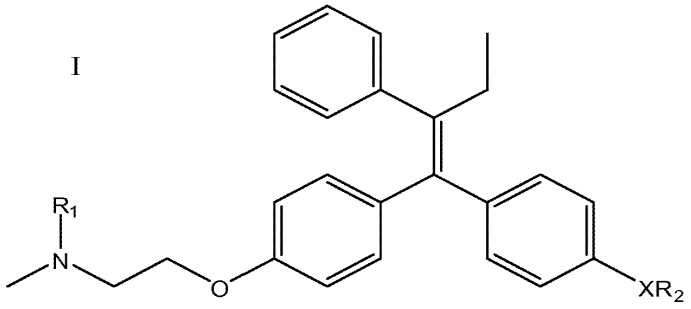


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breast cancer, or for a reduction in the recurrence rate or severity of previously-treated breast cancer. The compounds may be used in the manufacture of a medicament for the treatment of breast cancer. In an alternative embodiment, intermediate compounds according to the invention are used for the synthesis of an anti-cancer agent.

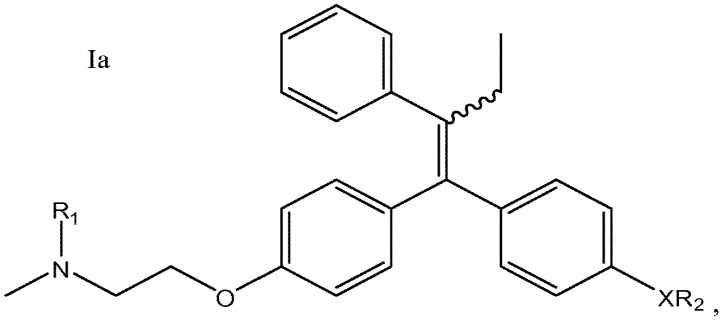
**[0009]** In one embodiment, the compounds according to the invention are compounds of the following formula I:

I




and pharmaceutically-acceptable salts thereof, where X is O or S; $R_1$ may be H, lower alkyl, cyclic alkyl (by replacing the methyl group on the nitrogen or by creating a quaternary ammonium), or a prodrug moiety, and where $R_2$ may be H or a prodrug moiety, with the understanding that at least one of $R_1$ and $R_2$ is a prodrug moiety. Known compounds 4-hydroxy-tamoxifen and endoxifen are not encompassed within compounds according to the invention. While the compound of Formula I is drawn with a specific orientation around the double bond, both E and Z configurations around the double bond are encompassed by the invention, for example, as represented by Formula Ia:

Ia



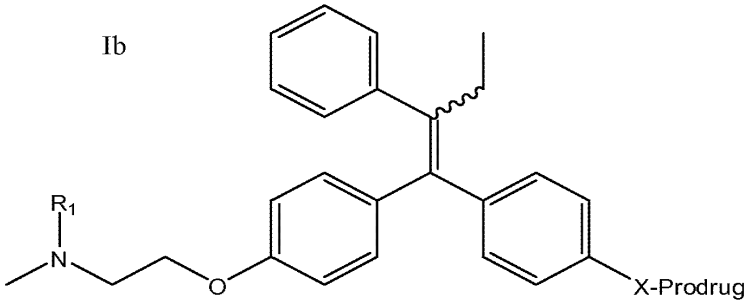



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where the wavy bond indicates unspecified stereochemistry for the ethyl and phenyl substituents, such that the structure has either an E or Z configuration around the double bond.

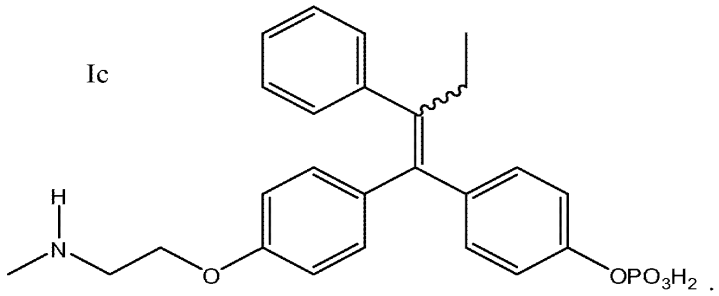
**[0010]** In one embodiment, the compounds according to the invention are compounds of the following formula:

Ib




and pharmaceutically-acceptable salts thereof, where X is O, and $R_1$ may be H or $CH_3$. where the wavy bond indicates unspecified stereochemistry for the ethyl and phenyl substituents, such that the structure has either an E or Z configuration around the double bond. Such compounds may be referred to as O-Pro-Endoxifens, when $R_1$ is H. In one embodiment, the compound according to the invention has the following formula:

Ic

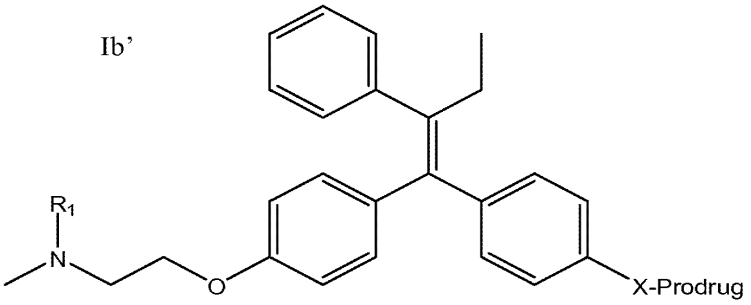



**[0011]** In one embodiment, the compounds according to the invention are compounds of the following formula:



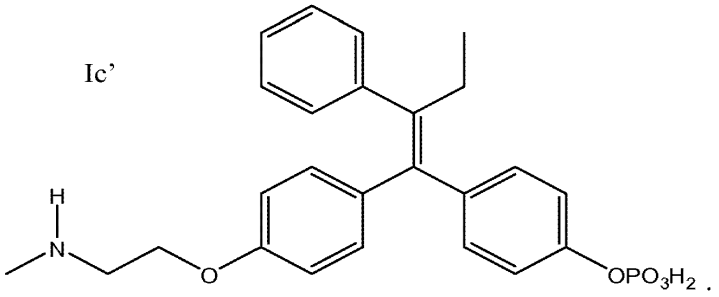
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Ib'



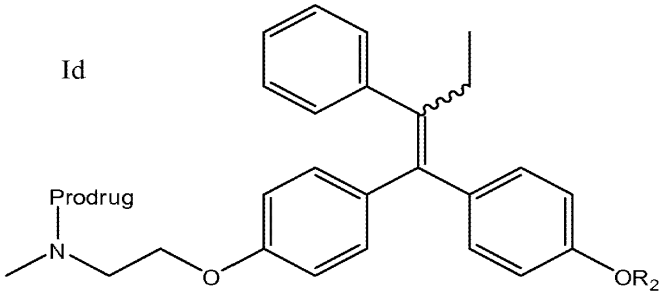

and pharmaceutically-acceptable salts thereof, where X is O, and $R_1$ may be H or $CH_3$. In one embodiment, the compound according to the invention has the following formula:

Ic'




**[0012]** In one embodiment, the compounds according to the invention are compounds of the following formula:

Id



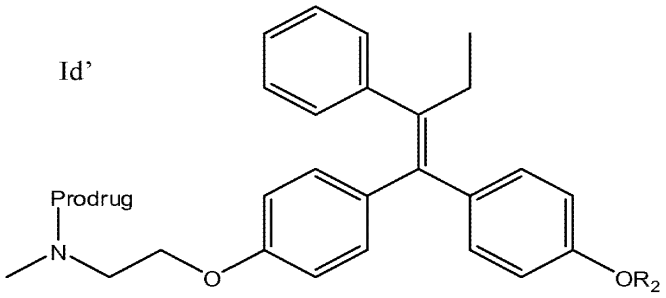

and pharmaceutically-acceptable salts thereof, where $R_2$ is an H, where the wavy bond indicates unspecified stereochemistry for the ethyl and phenyl substituents, such that the structure has either an E or Z configuration around the double bond. Such compounds may be referred to N-Pro-Endoxifens.



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**[0013]** In one embodiment, the compounds according to the invention are compounds of the following formula:

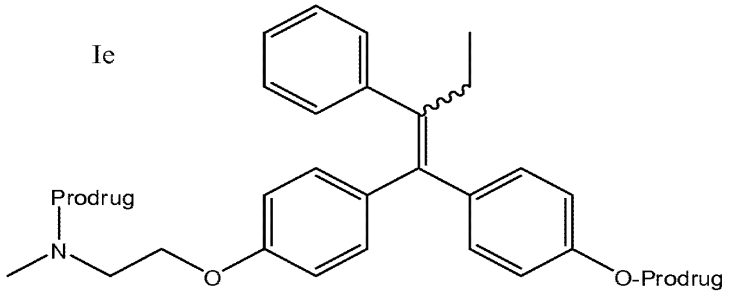
Id'




and pharmaceutically-acceptable salts thereof, where $R_2$ is an H.

**[0014]** In one embodiment, the compounds according to the invention are compounds of the following formula:

Ie



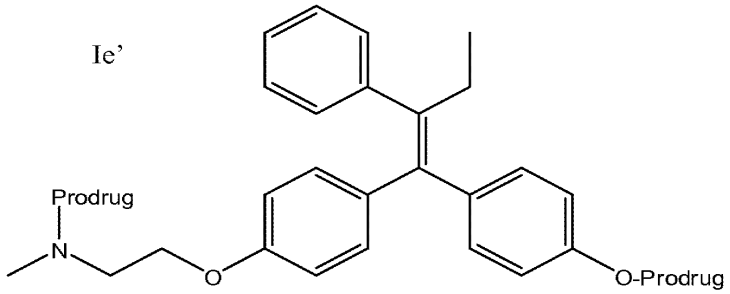

and pharmaceutically-acceptable salts thereof, where the wavy bond indicates unspecified stereochemistry for the ethyl and phenyl substituents, such that the structure has either an E or Z configuration around the double bond. Such compounds may be referred to as N,O-di-Pro-Endoxifens.

**[0015]** In one embodiment, the compounds according to the invention are compounds of the following formula:



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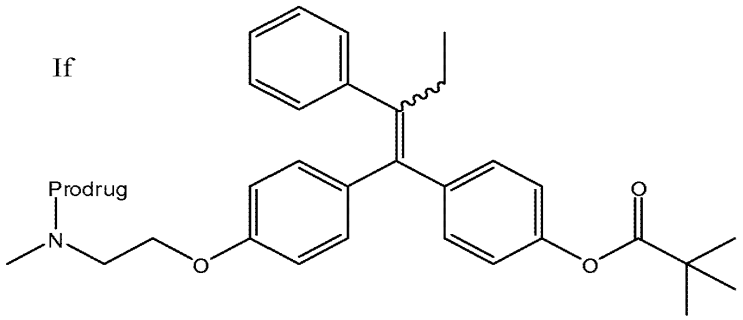
Ie'




and pharmaceutically-acceptable salts thereof.

**[0016]** In one embodiment, the compounds according to the invention are compounds of the following formula:

If



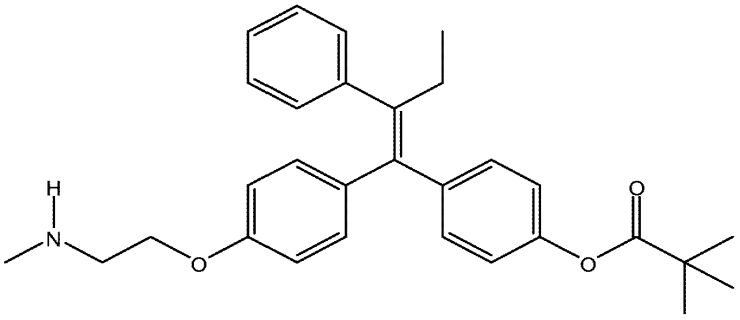

and pharmaceutically-acceptable salts thereof, where the wavy bond indicates unspecified stereochemistry for the ethyl and phenyl substituents, such that the structure has either an E or Z configuration around the double bond. Such compounds may be referred to as N-Pro-Endoxifen Pivalate Ester.

**[0017]** In one embodiment, the compounds according to the invention are compounds of the following formula:

If'



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and pharmaceutically-acceptable salts thereof.

**[0018]** In one embodiment, compounds according to the above formulas are capable of being metabolized *in vivo* to endoxifen in one or more steps. Those compounds which are metabolized *in vivo* to endoxifen may be referred to as endoxifen prodrugs. For example, the compounds may be metabolized through a pathway that does not involve liver enzymes, or does not specifically involve Cyp2D6, such as hydrolysis in the stomach. In one embodiment, the compounds are resistant to glucuronidation at either the O- or N-position. Alternatively, the compounds according to the invention may have improved bioavailability by virtue of improved oral adsorption compared to endoxifen or related compounds. In an alternative embodiment, the compounds according to the invention may have more consistent or reliable bioavailability among populations of patients compared to endoxifen or related compounds.

**[0019]** In one embodiment, the invention encompasses methods of making compounds according to the above formulas. In another aspect, the invention includes compositions comprising a pharmaceutically acceptable carrier and a compound according to the above formula. Such compositions may be pharmaceutical formulations themselves, or may be formulated with additional ingredients at a later time prior to administration to yield the actual pharmaceutical formulation. Compositions comprising mixtures of E/Z isomers are also envisioned. Such mixtures may be equimolar or enriched in either the E or the Z isomer. Compositions according to the invention may have a physical form of the compound selected from the group consisting of an anhydrous form, a single crystalline form, a mixture of polymorphic forms, a hydrated form, and mixtures thereof. Alternatively, the



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invention encompasses methods of making a medicament comprising the addition of a compound according to the above formula to a pharmaceutically-acceptable carrier. The present invention also provides pharmaceutical compositions comprising or consisting essentially of the compounds described herein, as well as kits comprising the compositions and combinations thereof.

**[0020]** In one embodiment, the invention encompasses methods of treating breast cancer, or of reducing the rate or severity of recurrence of breast cancer in previously-treated breast cancer patients. Treating includes management of, amelioration of symptoms of, and slowing the progression of the condition. Methods according to the invention comprise administering to a patient in need thereof a therapeutically effective amount of the compound as an active agent. In one embodiment, the breast cancer is estrogen receptor (ER) positive. Treatment may be directed to those patients that will benefit the most from a compound according to the invention as an alternative to tamoxifen. For example, treatment may be directed at human females who are resistant or non-responsive to tamoxifen treatment. Non-responsiveness may be found empirically through dosage with tamoxifen, or it may be inferred through genetic, enzymatic, or other assay of samples from the patient. Alternatively, non-responsiveness to tamoxifen may be a transient or induced condition. For example, non-responsiveness to tamoxifen may be due to administration of one or more drugs for a condition other than breast cancer, such as SSRIs or monoamine oxidase inhibitors used in psychiatric or other types of patients. Non-responsiveness to tamoxifen may be due to inability to convert tamoxifen to endoxifen *in vivo*, or may be due to resistance by overexpression of HER2/neu by the cancer cells, or due to some other mechanism. In some embodiments, the subject has previously undergone treatment, and in some cases, the previous therapy has failed. In some embodiments, the subject is in remission. In some embodiments, the subject is post-menopausal. In some embodiments, the subject is at risk for breast cancer. Subjects are mammalian, and preferably are human, and more preferably are human females. In one embodiment, treatment is for patients that are non-responsive to tamoxifen, wherein non-responsiveness may be determined by a method selected from the group consisting of liver enzyme assay, genotyping Cyp2D6 for one or more copies of a partly or completely defective allele, for example the *10 allele, detecting the presence, absence, or levels of endoxifen in biological fluids,



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determining if the patient is taking drugs that interfere with tamoxifen metabolism, and combinations thereof.

**[0021]** In some embodiments, the breast cancer to be treated is ER positive. In some embodiments, the breast cancer is tamoxifen resistant or overexpresses Her2/Neu. In some embodiments, the breast cancer is recurring. In some embodiments, the breast cancer progression rate from ductal carcinoma in situ (DCIS) or atypical hyperplasia is reduced or delayed. The compounds may be used for the treatment of breast cancer, or for a reduction in the recurrence rate or severity of previously-treated breast cancer.

**[0022]** In one embodiment, the compound is administered as mono-therapy, where the compound according to the invention is the only agent active against breast cancer. In one embodiment, the monotherapeutically effective amount of compound according to the invention is bioequivalent to oral tamoxifen of 5-80 mg per day.

**[0023]** In one embodiment, the invention encompasses methods of treating breast cancer using a combination of two or more drugs. In combinations, each drug may be active individually against the breast cancer, or one or more drugs may be active against the breast cancer, and one or more additional drugs may serve to improve the efficacy of the active drug(s) by reducing side effects, increasing potency of the active drug(s), or some other mechanism. With regard to combination therapy, the two or more compounds (e.g., two, three, four, five, or more compounds) may be administered in combination, e.g., in the same formulation, or may be administered in separate formulations at the same or at different times. Pharmaceutical formulations of all combinations listed herein are also contemplated.

**[0024]** In one embodiment, compounds according to the invention are used in combination therapy with HDAC inhibitors such as valproic acid, trichostatin A, or SAHA; and/or IGF receptor inhibitors such as EGCG; and/or mTOR inhibitors such as rapamycin and/or sulforaphane; an EGFR inhibitor; and/or tamoxifen and related compounds; other chemotherapeutic agent, biologic, radiation therapy, or other agents and procedures useful in the treatment of cancer; and combinations thereof. In one embodiment, formula I, a HDAC inhibitor, and an IGF receptor inhibitor are



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administered. In another embodiment, the IGF receptor inhibitor is EGCG. In another embodiment, sulforaphane is also administered. In another embodiment, the breast cancer is ER positive.

**[0025]** In certain of the embodiments, the IGF-1R inhibitor can be picropodophyllin (see, e.g., Girnita, A. et al., Cancer Res., 2004. 64(1): 236-242) or the green tea polyphenol, EGCG (see, e.g., Shimizu, M. et al, Biochem. Biophys. Res. Commun., 2005. 334(3): 947-953; Li, M. et al., Cancer Epidemiol. Biomarkers Prev., 2007. 16(3): 598-605. An EGFR inhibitor may be gefitinib, and the mTOR inhibitor may be rapamycin or rapamycin derivatives (see, e.g., Johnston, S.R., Clin. Cancer Res., 2006. 12(3 Pt. 2): 1061-1069s). The skilled practitioner will be able to use a variety of IGF-1R, EGFR, and mTOR inhibitors in the invention, to provide therapeutically effective combinations.

**[0026]** Embodiments of the above combinations include administering formula I, EGCG, and sulforaphane; formula I, rapamycin, and sulforaphane; and formula I, EGCG, rapamycin, and sulforaphane. Sulforaphane may be administered at 01.-10 micromolar, 0.5-5 micromolar, 0.5-2 micromolar, or about 1 micromolar amounts. Additional embodiments include administering formula I and valproic acid; formula I, valproic acid, and EGCG; formula I, valproic acid, and rapamycin; and formula I, valproic acid, EGCG, and rapamycin. Embodiments of the above combinations include administering formula 1 and trichostatin A; formula I, trichostatin A, and EGCG; formula I, trichostatin A, and rapamycin; and formula I, trichostatin A, EGCG, and rapamycin. Embodiments of the above combinations include administering formula I and EGCG; formula I and rapamycin; and formula I, EGCG, and rapamycin.

**[0027]** When combinations are administered, dosages may be adjusted accordingly. In one embodiment, the daily dose of valproic acid is from about 15/mg/kg to about 60 mg/kg. In one embodiment, the daily dose of valproic acid is sufficient to achieve about 300 to about 867 micromolar in patient serum. In another embodiment, the daily dose of valproic acid is sufficient to achieve about 300 to about 1000 micromolar in patient serum, and in another embodiment, the daily dose of valproic acid is sufficient to achieve about 500 to about 1000 micromolar in patient



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serum. In some embodiments, the dose of SAHA is from about 200 mg/day to about 600 mg/day. In another embodiment, the dose of SAHA is about 400 mg/day. In one embodiment, the dose of EGCG is from about 300 mg/day to about 800 mg/day. In one embodiment, the dose of rapamycin is from about 0.125 mg/day to about 1 mg/day. In one embodiment, the dose of gefitinib is from about 200 mg/day to about 300 mg/day. In another embodiment, the dose of gefitinib is about 250 mg/day. In one embodiment, the dose of erlotinib is from about 100 mg/day to about 150 mg/day. In some embodiments, compounds are administered in combination, with ratios of those compounds which preserve the recommended daily doses of the compounds. In some embodiments, compounds are administered in combination, with ratios of those compounds which preserve the ranges of doses as described herein.

**[0028]** In another aspect, the invention provides a method of treating, reducing the recurrence rate, or reducing the severity of recurrence of breast cancer, the method comprising the step of administering a therapeutically effective amount of a compound according to the invention and a compound selected from the group consisting of a HDAC inhibitor or an IGF receptor inhibitor. In another aspect, the invention provides a method of treating, reducing the recurrence rate, or reducing the severity of recurrence of breast cancer, the method comprising the step of administering a therapeutically effective amount of a compound according to the invention and valproic acid. In another aspect, the invention provides a method of treating, reducing the recurrence rate, or reducing the severity of recurrence of breast cancer, the method comprising the step of administering a therapeutically effective amount of a compound according to the invention and sulforaphane.

**[0029]** In another aspect, the invention provides a method of treating, reducing the recurrence rate, or reducing the severity of recurrence of breast cancer, without attendant increase in risk of uterine cancer, the method comprising the step of administering a therapeutically effective amount of compound according to the invention with an HDAC inhibitor. In one embodiment, the HDAC inhibitor is VPA, TSA, sulforaphane, or SAHA. In another aspect, the invention provides a method of treating, reducing the recurrence rate, or reducing the severity of recurrence of breast cancer, without attendant increase in risk of uterine cancer, the method comprising the step of administering a therapeutically effective amount of compound according to the



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invention with an HDAC inhibitor, wherein the compound according to the invention has an estrogen-like effect on the uterus. Attendant risk of uterine cancer refers to reducing or eliminating the risk of uterine cancer that typically exists with anti-estrogen therapy alone. In some embodiments, this risk is reduced by 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or it is virtually or wholly eliminated. Prevention of breast cancer is also envisioned.

**[0030]** In one embodiment, the compound according to the invention is administered as part of a hormonal therapy. For example, hormonal therapy may be an antiestrogen therapy or aromatase inhibitor therapy. The hormonal therapy can also be estrogen ablation therapy, including an aromatase inhibitor. According to the invention, the aromatase inhibitor can be, but is not limited to, exemestane, letrozole, or anastrozole. In one embodiment, the dose of letrozole is from about 1 mg/day to about 5 mg/day. In another embodiment, the dose of letrozole is about 2.5 mg/day. In one embodiment, the dose of exemestane is from about 10 mg/day to about 40 mg/day. In another embodiment, the dose of exemestane is about 25 mg/day. In yet another embodiment, the dose of anastrozole is from about 0.5 mg/day to about 3 mg/day. In another embodiment, the dose of anastrozole is about 1 mg/day.

**[0031]** In one embodiment, the compound according to the invention is administered in combination with 4-hydroxytamoxifen or a prodrug of 4-hydroxytamoxifen. In one aspect, combinations of the compound according to the invention and 4-hydroxytamoxifen (or prodrug thereof) are administered to those patients that are non-responsive to tamoxifen, and the administered ratio of compound according to the invention and 4-hydroxytamoxifen or 4-hydroxytamoxifen prodrug (which may also be a compound according to the invention) results in *in vivo* levels of endoxifen and 4-hydroxytamoxifen that mimic the levels of endoxifen and 4-hydroxytamoxifen following administration of tamoxifen to responsive patients. The *in vivo* levels may correlate with serum levels or may be measured at the site of action, or by other manner, such as by plural effusion. In one embodiment, the ratio of compound according to the invention to 4-hydroxytamoxifen or prodrug thereof is the bioequivalent of from about 0.5 to about 10 times endoxifen to 4-hydroxytamoxifen. In one embodiment, levels of endoxifen are about 4 times the level of 4-hydroxytamoxifen up to endoxifen levels of about 6 times the level of 4-



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hydroxytamoxifen. Bioequivalence may be determined by assay of serum levels, or by levels in plural effusion, among other methods of determining bioequivalence. Prevention of breasts cancer is also envisioned.

**[0032]** In some embodiments, the present invention encompasses methods and compositions for reducing the incidence of breast cancer or delaying the progression of pre-cancerous conditions, including in subjects who are at risk for breast cancer that is greater than the average risk for breast cancer. Risk factors considered in preventing breast cancer in subjects include family history of breast cancer (relatives with breast cancer), genetic markers for breast cancer such as BRCA1 and BRCA2, age at menarche, age at first live birth, the number of breast biopsies, presence of atypical hyperplasia on breast biopsy, population rates of breast cancer and death from other causes. The present invention also provides methods and compositions for reducing the rate of progression of breast cancer to a later stage for those who already have breast cancer or precancerous indicators, as well as reducing the rate and/or severity of the recurrence of breast cancer for those in remission from breast cancer.

**[0033]** In some embodiments, the invention contemplates methods of delaying the progression of DCIS to breast cancer, and methods of delaying the progression of atypical hyperplasia to breast cancer. In some preferred embodiments, the invention encompasses treating estrogen receptor positive breast cancer. In yet another embodiment, the present invention encompasses treating DCIS and, in another embodiment, the present invention encompasses treating atypical hyperplasia.

**[0034]** The present invention further contemplates that the combination therapies as described herein can also reduce or eliminate other side effects of treatment, at least in part because lower doses of compounds can be used in treatment or prevention protocols.

**[0035]** It is within the scope of the invention to treat breast cancer that is tamoxifen resistant, as well as to treat breast cancer that overexpresses Her2/Neu. The invention also contemplates treating subjects with breast cancer for whom previous therapy has failed, or for whom the cancer is recurring. In some embodiments of the invention, the invention is to treat subjects with breast cancer



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who are post-menopausal, and in some embodiments, the invention contemplates treating subjects who are genetically predisposed to breast cancer or otherwise at increased risk. The invention also encompasses methods of treating subjects to prevent progression of breast cancer, and in some embodiments, the invention encompasses treating or preventing breast cancer in patients with pre-cancerous growths or benign tumors. It is within the scope of the invention to treat subjects that are in remission from breast cancer, and to treat subjects with breast cancer that have previously undergone treatment.

**[0036]** In one embodiment, intermediates are presented for the synthesis of compounds and compositions for the treatment and prevention of breast cancer. The intermediates may be immediate precursors of the compounds to be administered to the patient, or the intermediates may require two or more synthetic steps to be converted into a compound to be administered to a patient.

## 4. BRIEF DESCRIPTION OF THE FIGURES

**[0037]** FIG. 1 shows the chemical structures for tamoxifen, 4-hydroxy-tamoxifen, endoxifen, and 4-hydroxytoremifene.

**[0038]** FIG. 2 shows a proposed synthetic scheme for endoxifen phosphate.

**[0039]** FIG. 3 shows additional synthetic options for access to O-Pro-endoxifens.

**[0040]** FIG. 4 shows a direct activation of the phenol-OH.

**[0041]** FIG. 5 shows a route to O-Pro-endoxifen via a protected amine.

**[0042]** FIG. 6 shows additional options for access to O-Pro-endoxifens.

**[0043]** FIG. 7 shows additional classes of phenol prodrugs.

**[0044]** FIG. 8 shows proposed synthetic options for access to N-Pro-endoxifens.

**[0045]** FIG. 9 shows the effect of tamoxifen metabolites on ER beta.

**[0046]** FIG. 10 shows a synthetic scheme for endoxifen via an aldehyde precursor. The -OR groups form an acetal, and may be, for example, -OMe or -OEt.

**[0047]** FIG. 11 shows a synthetic scheme of a pivalate ester and an endoxifen phosphate via a common precursor. The -OR groups form an acetal, and may be, for example, -OMe or -OEt.



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## 5. DETAILED DESCRIPTION OF THE INVENTION

**[0048]** While not wishing to be bound by theory, it is believed that the compounds, compositions, and methods of the instant invention overcome the deficiencies of the prior art with regard to non-responsiveness to tamoxifen. Again, while not wishing to be bound by theory, it is believed that non-responsiveness in some cases may be due to lack of the proper enzymatic machinery for the *in vivo* conversion of tamoxifen into endoxifen, and/or the poor bioavailability of endoxifen resulting from possible glucuronidation. Alternatively, endoxifen may have highly variable bioavailability among patient groups or subpopulations. The present inventors find that these and other problems can be overcome by appropriate chemical modification and/or *de novo* synthesis of endoxifen-related prodrugs. In a preferred example, a phosphate group is attached at the 4-hydroxy position of endoxifen. While not wishing to be bound by theory, it is believed that this modification and other modifications can lead to improved clinical outcomes for breast cancer patients.

### 5.1 Definitions

**[0049]** As used herein, the term "prodrug" means a compound with a temporary modification of a functional group of a drug in order to improve the pharmaceutical utility of the drug. Prodrug may refer to the entire compound, or it may refer to the chemical modification, in the context of a prodrug moiety being the chemical modification. In some embodiments, the functional group of the drug is a handle for the introduction of a moiety that confers on the new entity some desirable characteristic. In other embodiments, the prodrug moiety is intimately connected with the pharmaceutical deficiency of the parent drug, and the presence of the prodrug moiety directly addresses the deficiency. In some embodiments, prodrugs rely on *in vivo* enzymatic activation for conversion to active form of the drug for example by cleavage of the prodrug moiety by an enzyme. In other embodiments, prodrugs rely on physiological chemical conditions for release of the drug, for example through a change in pH. The benefits of a prodrug are not limited to improved *in vivo* benefits compared to the parent drug, but may also include improved processing or storage characteristics or economic considerations prior to administration to the patient.



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**[0050]** As used herein, the term "cancer" refers to a disease involving cells that have the potential to metastasize to distal sites and exhibit phenotypic traits that differ from those of non-cancer cells. Cancer cells acquire a characteristic set of functional capabilities during their development, albeit through various mechanisms. Such capabilities include evading apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals, tissue invasion/metastasis, limitless replicative potential, and sustained angiogenesis. The term "cancer cell" is meant to encompass both pre-malignant and malignant cancer cells.

**[0051]** "Estrogen receptor positive breast cancer" refers to breast cancers that are in the positive or intermediate range for the estrogen receptor protein. For example, when estrogen receptor protein can be measured as femtomoles per milligram of cytosol protein. In this assay, values above 10 are positive, values from 3 to 10 are intermediate, and values less than 3 are negative. Other assays known in the art can be used to determined if the breast cancer is estrogen receptor positive, in particular assays based on antibodies to estrogen receptors alpha and beta and their use in biochemical or histological assays.

**[0052]** The terms "histone deacetylase inhibitor" and "inhibitor of histone deacetylase" mean a compound which is capable of interacting with a histone deacetylase and inhibiting its enzymatic activity, abbreviated as HDAC inhibitors. "Inhibiting histone deacetylase enzymatic activity" means reducing the ability of a histone deacetylase to remove an acetyl group from a histone. (see, e.g., Minucci et al., Nature 6:38-51 (2006). In some preferred embodiments, such reduction of histone deacetylase activity is at least about 50%, more preferably at least about 75%, and still more preferably at least about 90%. In other preferred embodiments, histone deacetylase activity is reduced by at least 95% and more preferably by at least 99%. Assays for determining inhibition are described in Phiel, C.J., et al., J Biol Chem., 2001. 276(39): p. 36734-41 and Gottlicher, M., et al., Embo J., 2001. 20(24): p. 6969-78.

**[0053]** Preferably, such inhibition is specific, i.e., the histone deacetylase inhibitor reduces the ability of a histone deacetylase to remove an acetyl group from a



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histone at a concentration that is lower than the concentration of the inhibitor that is required to produce another, unrelated biological effect. Preferably, the concentration of the inhibitor required for histone deacetylase inhibitory activity is at least 2-fold lower, more preferably at least 5-fold lower, even more preferably at least 10-fold lower, and most preferably at least 20-fold lower than the concentration required to produce an unrelated biological effect.

**[0054]** As used herein, the term "active ingredient" includes having a therapeutic or prophylactic effect on breast cancer in the combinations. This does not include inactive ingredients such as pharmaceutical carriers, excipients, and the like.

**[0055]** "Mammalian target of rapamycin protein inhibitor" or "mTOR inhibitor" includes drugs such as rapamycin, temsirolimus, and everolimus that selectively inhibit the mammalian target of rapamycin (mTOR).

**[0056]** "IGF-1 receptor inhibitor" refers to drugs such as picrophodophyllin and podophyllotoxin that selectively inhibit the IGF-1 receptor.

**[0057]** "EGF receptor inhibitor" of "EGFR inhibitor" refers to drugs such as gefitinib and erlotinib that selectively inhibit the EGF receptor.

**[0058]** "Insufficient to fully prevent production of estrogen" refers to the inability of an aromatase inhibitor to fully prevent a tumor cell from converting an estrogen precursor into a functional estrogen that can stimulate tumor proliferation.

**[0059]** "Less than estrogen receptor-saturating amounts" refers to amounts of fulvestrant less than 100 fold molar excess to the amounts of estradiol or less than 10 nanomolar in patient circulation.

**[0060]** "Hormonal therapy" refers to drugs or treatments that block the effect of, or reduce the levels of hormones, and in particular which block the effect of estrogen or lower estrogen levels, including anti-estrogen therapy and estrogen ablation therapy.



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**[0061]** As used herein, the terms "prevent," "preventing" and "prevention" refer to the prevention of the recurrence, worsening, or spread of a disease in a subject resulting from the administration of a prophylactic or therapeutic agent.

**[0062]** The terms "overexpress," "overexpression" or "overexpressed" interchangeably refer to a protein or nucleic acid (RNA) that is translated or transcribed at a detectably greater level, usually in a cancer cell, in comparison to a normal cell. The term includes overexpression due to transcription, post transcriptional processing, translation, post-translational processing, cellular localization (*e.g.*, organelle, cytoplasm, nucleus, cell surface), and RNA and protein stability, as compared to a normal cell. Overexpression can be detected using conventional techniques for detecting mRNA (*i.e.*, RT-PCR, PCR, hybridization, microarray) or proteins (i.e., ELISA, immunohistochemical techniques). Overexpression can be 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a normal cell. In certain instances, overexpression is 1-fold, 2-fold, 3-fold, 4-fold or more higher levels of transcription or translation in comparison to a normal cell.

**[0063]** As used herein, the term "in combination" refers to the use of more than one prophylactic and/or therapeutic agents. The use of the term "in combination" does not restrict the order in which prophylactic and/or therapeutic agents are administered to a subject with cancer, especially breast cancer. A first prophylactic or therapeutic agent can be administered prior to (e.g., 1 minute, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 1 minute, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second prophylactic or therapeutic agent to a subject which had, has, or is susceptible to cancer, especially breast cancer. The prophylactic or therapeutic agents are administered to a subject in a sequence and within a time interval such that the agent of the invention can act together with the other agent to provide an increased benefit than if they were administered otherwise. Any additional prophylactic or therapeutic



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agent can be administered in any order with the other additional prophylactic or therapeutic agents.

**[0064]** As used herein, the term "combine effectively" refers to a combination of therapies (e.g., a combination of prophylactic or therapeutic agents) which is more effective than any single agent administered alone. Combining effectively may also refer to combinations of therapies that are not less effective than any single agent or even less effective than any single agent, but which also eliminate or reduce the adverse effects of one or more of the agents, such as eliminating or reducing the risk of uterine cancer associated with one or more of the agents.

**[0065]** As used herein, the term "synergistic" refers to a combination of therapies (e.g., a combination of prophylactic or therapeutic agents) which is more effective than the additive effects of any two or more single agents. A synergistic effect of a combination of therapies permits the use of lower dosages of one or more of the therapies and/or less frequent administration of said therapies (e.g., agents) to a subject with a disease or disorder, in particular, cancer, or a condition or symptom associated therewith. The ability to utilize lower dosages of therapies and/or to administer said therapies less frequently reduces the toxicity associated with the administration of said therapies to a subject without reducing the efficacy of said therapies in the prevention, management, or treatment of a disease or disorder, in particular, cancer or a condition or symptom associated therewith. In addition, a synergistic effect can result in improved efficacy of therapies in the prevention, management, or treatment of a disease or disorder, in particular, cancer or a condition or symptom associated therewith. Finally, the synergistic effect of a combination of therapies may avoid or reduce adverse or unwanted side effects associated with the use of any single therapy.

**[0066]** As used herein, the phrase "side effects" encompasses unwanted and adverse effects of a prophylactic or therapeutic agent. Adverse effects are always unwanted, but unwanted effects are not necessarily adverse. An adverse effect from a prophylactic or therapeutic agent might be harmful or uncomfortable or risky. Side effects can refer specifically to an increase in uterine cell proliferation, as well as to an increase in the frequency of uterine cancer and an increase in the risk of



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developing uterine cancer. Side effects from chemotherapy include, but are not limited to, gastrointestinal toxicity such as, but not limited to, early and late-forming diarrhea and flatulence, nausea, vomiting, anorexia, leukopenia, anemia, neutropenia, asthenia, abdominal cramping, fever, pain, loss of body weight, dehydration, alopecia, dyspnea, insomnia, dizziness, mucositis, xerostomia, and kidney failure, as well as constipation, nerve and muscle effects, temporary or permanent damage to kidneys and bladder, flu-like symptoms, fluid retention, and temporary or permanent infertility. Side effects from radiation therapy include but are not limited to fatigue, dry mouth, and loss of appetite. Side effects from biological therapies/immunotherapies include but are not limited to rashes or swellings at the site of administration, flu-like symptoms such as fever, chills and fatigue, digestive tract problems and allergic reactions. Side effects from hormonal therapies include but are not limited to nausea, fertility problems, depression, loss of appetite, eye problems, headache, and weight fluctuation. Additional undesired effects typically experienced by patients are numerous and known in the art. Many are described in the Physicians' Desk Reference ($56^{th}$ ed., 2002).

**[0067]** "Without attendant risk in increase of uterine cancer" refers to a lowered or eliminated risk of developing uterine cancer as compared to patients who have an increased risk for developing uterine cancer due to a course of anti-estrogen therapy.

**[0068]** By "therapeutically effective amount or dose" or "therapeutically sufficient amount or dose" or "effective or sufficient amount or dose" herein is meant a dose that produces therapeutic effects for which it is administered, in the context of the combination therapy in which it is administered. Often, the therapeutically effective or sufficient amount or dose of the compounds comprising the pharmaceutical compositions of the invention will be lower when administered in the specific combinations, than the doses that would be therapeutically effective or sufficient when the compounds are administered separately. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see, e.g.*, Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and Remington. *The*



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*Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins). In some embodiments, a therapeutically effective amount refers to that amount of the therapeutic agent sufficient to destroy, modify, control or remove primary, regional or metastatic cancer tissue. A therapeutically effective amount may refer to the amount of therapeutic agent sufficient to delay or minimize the spread of cancer. A therapeutically effective amount may also refer to the amount of the therapeutic agent that provides a therapeutic benefit in the treatment or management of cancer. Further, a therapeutically effective amount with respect to a therapeutic agent of the invention means that amount of therapeutic agent alone, or in combination with other therapies, that provides a therapeutic benefit in the treatment or management of cancer. In sensitized cells, the therapeutically effective dose can often be lower than the conventional therapeutically effective dose for non-sensitized cells. In some embodiments, a therapeutically effective amount refers to the amount of a therapeutic agent that, e.g., reduces the proliferation of cancer cells, increases the death of cancer cells or, reduces the size of a tumor or spread of a tumor in a subject. Preferably, a therapeutically effective amount of a therapeutic agent reduces the size of a tumor or the spread of a tumor in a subject by at least 5%, preferably at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, ate least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99% relative to a control such as PBS. In some embodiments, a therapeutically effective amount refers to the amount of a therapeutic agent that increases survival by 1 month, 2 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, or more. In some embodiments, a therapeutically effective amount refers to the amount of a therapeutic agent that prevents the progression from DCIS or atypical hyperplasia to breast cancer.

**[0069]** The term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant (e.g., Freund's adjuvant (complete and incomplete)), excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin,



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such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin. Such compositions will contain a prophylactically or therapeutically effective amount of a prophylactic or therapeutic agent preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration. In a preferred embodiment, the pharmaceutical compositions are sterile and in suitable form for administration to a subject, preferably an animal subject, more preferably a mammalian subject, and most preferably a human subject.

**[0070]** As used herein, the term "intermediates" encompasses compounds used in the synthesis of prodrug compounds according to the invention. Such intermediates may have activity in their own right, or may be biologically inactive.

5.2 Pharmaceutical Formulations

**[0071]** Pharmaceutically acceptable carriers are determined in part by the particular composition being administered, as well as by the particular method used to administer the composition. Accordingly, there are a wide variety of suitable formulations of pharmaceutical compositions of the present invention (*see, e.g.*, *Remington's Pharmaceutical Sciences*, 20$^{th}$ ed., 2003).



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**[0072]** It may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion, by injection, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering one or more prophylactic or therapeutic agents, care must be taken to use materials to which the prophylactic or therapeutic agents do not absorb.

**[0073]** The invention can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, pp. 317-327; see generally above).

**[0074]** The composition can be delivered in a controlled release or sustained release system. In one embodiment, a pump may be used to achieve controlled or sustained release (see Langer, supra; Sefton, 1987, CRC Crit. Ref. Biomed. Eng. 14:20; Buchwald et al., 1980, Surgery 88:507; Saudek et al., 1989, N. Engl. J. Med. 321:574). In another embodiment, polymeric materials can be used to achieve controlled or sustained release of the antibodies of the invention or fragments thereof (see e.g., Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla. (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, N.Y. (1984); Ranger and Peppas, 1983, J., Macromol. Sci. Rev. Macromol. Chem. 23:61; see also Levy et al., 1985, Science 228:190; During et al., 1989, Ann. Neurol. 25:351; Howard et al., 1989, J. Neurosurg. 7 1:105); U.S. Pat. No. 5,679,377; U.S. Pat. No. 5,916,597; U.S. Pat. No. 5,912,015; U.S. Pat. No. 5,989,463; U.S. Pat. No. 5,128,326; International Publication No. WO 99/15154; and International Publication No. WO 99/20253. Examples of polymers used in sustained release formulations include, but are not limited to, poly(2-hydroxy ethyl methacrylate), poly(methyl methacrylate), poly(acrylic acid), poly(ethylene-co-vinyl acetate), poly(methacrylic acid), polyglycolides (PLG), polyanhydrides, poly(N-vinyl pyrrolidone), poly(vinyl alcohol), polyacrylamide, poly(ethylene glycol), polylactides (PLA), poly(lactide-co-glycolides) (PLGA), and polyorthoesters. In a preferred embodiment, the polymer used in a sustained release formulation is inert, free of leachable impurities, stable on storage, sterile, and



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biodegradable. In yet another embodiment, a controlled or sustained release system can be placed in proximity of the therapeutic target, i.e., the lungs, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)).

**[0075]** Controlled release systems are discussed in the review by Langer (1990, Science 249:1527-1533). Any technique known to one of skill in the art can be used to produce sustained release formulations comprising one or more antibodies of the invention or fragments thereof. See, e.g., U.S. Pat. No. 4,526,938, International publication No. WO 91/05548, International publication No. WO 96/20698, Ning et al., 1996, "Intratumoral Radioimmunotheraphy of a Human Colon Cancer Xenograft Using a Sustained-Release Gel," Radiotherapy & Oncology 39:179-189, Song et al., 1995, "Antibody Mediated Lung Targeting of Long-Circulating Emulsions," PDA Journal of Pharmaceutical Science & Technology 50:372-397, Cleek et al., 1997, "Biodegradable Polymeric Carriers for a bFGF Antibody for Cardiovascular Application," Pro. Int'l. Symp. Control. Rel. Bioact. Mater. 24:853-854, and Lam et al., 1997, "Microencapsulation of Recombinant Humanized Monoclonal Antibody for Local Delivery," Proc. Int'l. Symp. Control Rel. Bioact. Mater. 24:759-760, each of which is incorporated herein by reference in their entirety.

**[0076]** A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of suitable routes of administration include, but are not limited to, ingestion, parenteral (e.g., intravenous, intramuscular, intradermal, intra-tumoral, intra-synovial, and subcutaneous), oral (e.g., inhalation, ingestion), intranasal, transdermal (topical), transmucosal, intra-tumoral, intra-synovial, vaginal, and rectal administration. In a specific embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous, subcutaneous, intramuscular, oral, e.g. ingestion, intra-tumoral, intra synovial, intranasal or topical administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection.



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**[0077]** If the compositions of the invention are to be administered topically, the compositions can be formulated in the form of, e.g., a toothpaste, ointment, cream, transdermal patch, lotion, gel, oral gel, shampoo, spray, aerosol, solution, emulsion, or other form well-known to one of skill in the art. See, e.g., Remington's Pharmaceutical Sciences and Introduction to Pharmaceutical Dosage Forms, 4th ed., Lea & Febiger, Philadelphia, Pa. (1985). For non-sprayable topical dosage forms, viscous to semi-solid or solid forms comprising a carrier or one or more excipients compatible with topical application and having a dynamic viscosity preferably greater than water are typically employed. Suitable formulations include, without limitation, solutions, suspensions, emulsions, creams, ointments, powders, liniments, salves, and the like, which are, if desired, sterilized or mixed with auxiliary agents (e.g., preservatives, stabilizers, wetting agents, buffers, or salts) for influencing various properties, such as, for example, osmotic pressure. Other suitable topical dosage forms include sprayable aerosol preparations wherein the active ingredient, preferably in combination with a solid or liquid inert carrier, is packaged in a mixture with a pressurized volatile (e.g., a gaseous propellant, such as Freon), or in a squeeze bottle. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well-known in the art.

**[0078]** If the compositions of the invention are to be administered intranasally, the compositions can be formulated in an aerosol form, spray, mist or in the form of drops. In particular, prophylactic or therapeutic agents for use according to the present invention can be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

**[0079]** If the compositions of the invention are to be administered orally, the compositions can be formulated orally in the form of, e.g., gum, tablets, capsules,



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cachets, gelcaps, solutions, suspensions and the like. Tablets or capsules can be prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well-known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavoring, coloring and sweetening agents as appropriate. Preparations for oral administration may be suitably formulated for slow release, controlled release or sustained release of a prophylactic or therapeutic agent(s).

**[0080]** The compositions of the invention may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

**[0081]** The compositions of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

**[0082]** In addition to the formulations described previously, the compositions of the invention may also be formulated as a depot preparation. Such long acting



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formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compositions may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

**[0083]** Generally, the ingredients of compositions of the invention are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

5.3 Kits

**[0084]** The invention provides a pharmaceutical pack or kit comprising one or more containers filled with individual components (in pharmaceutical formulations) of the combination therapies described herein; for example, contained filled with an HDAC inhibitor and one or more hormonal therapy agents, and/or one or more therapeutic or prophylactic agents such as an IGF-1R inhibitor, an EGFR inhibitor, an mTOR inhibitor, or another active ingredient. Containers may also be filled with an HDAC inhibitor, and one or more therapeutic or prophylactic agents such as an IGF-1R inhibitor, an EGFR inhibitor, an mTOR inhibitor, and/or another active ingredient. The pharmaceutical pack or kit may further comprises one or more other prophylactic or therapeutic agents useful for the treatment of a disease or disorder. The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.



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**[0085]** The present invention provides pharmaceutical packs or kits that can be used in the above methods. The kit may further comprises one or more other prophylactic or therapeutic agents, or active ingredients useful for the treatment of cancer in one or more containers. In other embodiments, the kit may comprise at least one compound according to the invention, at least one HDAC inhibitor, and one or more of at least one or more of an IGF-1R inhibitor, an EGFR inhibitor or mTOR inhibitor. Examples of such agents and compounds are disclosed above.

5.4 Articles of Manufacture

**[0086]** The present invention also encompasses a finished packaged and labeled pharmaceutical product. This article of manufacture includes the appropriate unit dosage form in an appropriate vessel or container such as a glass vial or other container that is hermetically sealed. In the case of dosage forms suitable for parenteral administration the active ingredient is sterile and suitable for administration as a particulate free solution. In other words, the invention encompasses both parenteral solutions and lyophilized powders, each being sterile, and the latter being suitable for reconstitution prior to injection. Alternatively, the unit dosage form may be a solid suitable for oral, transdermal, intratumoral, intra-synovial, topical or mucosal delivery.

**[0087]** In a specific embodiment, the unit dosage form is suitable for intravenous, intramuscular, intratumoral, intra-synovial, or subcutaneous delivery. Thus, the invention encompasses solutions, preferably sterile, suitable for each delivery route.

**[0088]** As with any pharmaceutical product, the packaging material and container are designed to protect the stability of the product during storage and shipment. Further, the products of the invention include instructions for use or other informational material that advise the physician, technician or patient on how to appropriately prevent or treat the disease or disorder in question. In other words, the article of manufacture includes instruction means indicating or suggesting a dosing regimen including, but not limited to, actual doses, monitoring procedures (such as



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methods for monitoring mean absolute lymphocyte counts, tumor cell counts, calcium concentration, and tumor size) and other monitoring information.

**[0089]** More specifically, the invention provides an article of manufacture comprising packaging material, such as a box, bottle, tube, vial, container, sprayer, insufflator, intravenous (i.v.) bag, envelope and the like; and at least one unit dosage form of a pharmaceutical agent contained within said packaging material.

**[0090]** In a specific embodiment, an article of manufacture comprises packaging material and a pharmaceutical agent and instructions contained within said packaging material, and a pharmaceutically acceptable carrier, and said instructions indicate a dosing regimen for preventing, treating or managing a subject with cancer. In another embodiment, an article of manufacture comprises packaging material and a pharmaceutical agent and instructions contained within said packaging material, and said instructions indicate a dosing regimen for preventing, treating or managing a subject with a cancer.

**[0091]** In therapeutic use for the treatment of cancer, the compounds utilized in the pharmaceutical method of the invention are administered at the initial dosage of about 0.001 mg/kg to about 100 mg/kg daily. A daily dose range of about 0.01 mg/kg to about 50 mg/kg, or about 0.1 mg/kg to about 20 mg/kg, or about 1 mg/kg to about 10 mg/kg, or about 1 mg/kg to about 5 mg/kg, can be used. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. For example, dosages can be empirically determined considering the type and stage of cancer diagnosed in a particular patient. The dose administered to a patient, in the context of the present invention should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects that accompany the administration of a particular compound in a particular patient. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. For convenience, the total daily dosage may be divided and



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administered in portions during the day, if desired. Doses can be given daily, or on alternate days, as determined by the treating physician.

5.5 Characterization and Demonstration of Therapeutic or Prophylactic Utility

**[0092]** Toxicity and efficacy of the prophylactic and/or therapeutic treatments and protocols of the instant invention can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the $LD_{50}$ (the dose lethal to 50% of the population) and the $ED_{50}$ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio $LD_{50}/ED_{50}$. Prophylactic and/or therapeutic agents that exhibit large therapeutic indices are preferred. While prophylactic and/or therapeutic agents that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such agents to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

**[0093]** The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage of the prophylactic and/or therapeutic agents for use in humans. The dosage of such agents lies preferably within a range of circulating concentrations that include the $ED_{50}$ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any agent used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the $IC_{50}$ (i.e., the concentration of the test compound that achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

**[0094]** In order to determine therapeutic or prophylactic utility, it is encompassed by the present invention to use any of the assays described herein, as well as those known in the art. Also encompassed by the invention to determine



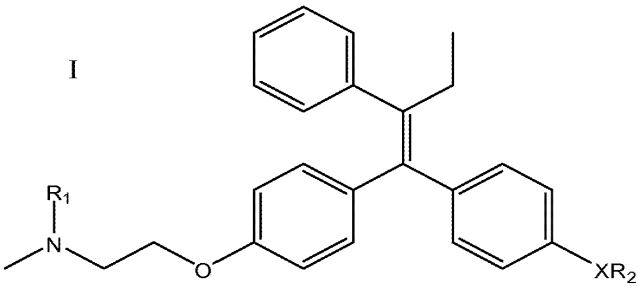
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therapeutic or prophylactic utility are any relevant cancer, and more specifically, breast cancer animal models. For example, one may utilize a an MCF-7 xenograft model, or a modified MCF-7 xenograft model (Hale L.V. et al., 1997, Lab Anim Sci.,47(1):82-85). Further encompassed by the invention, pending safety and efficacy, are clinical trials to assess the compounds and methods of the present invention.

5.6 Embodiments

**[0095]** The present invention is directed to compounds, compositions thereof, and the use of the compounds and compositions for the treatment and prevention of breast cancer. Compounds according to the invention may be considered prodrugs of endoxifen and related compounds. The compounds may be used for the treatment of breast cancer, or for a reduction in the recurrence rate or severity of previously-treated breast cancer.

**[0096]** In one embodiment, the compounds according to the invention are compounds of the following formula I:



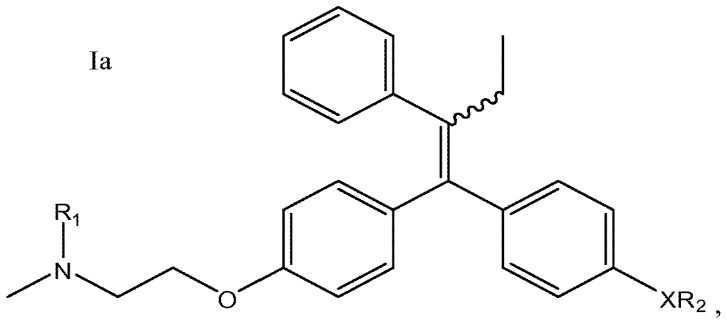

and pharmaceutically-acceptable salts thereof, where X is O or S; $R_1$ may be H, lower alkyl, cyclic alkyl (by replacing the methyl group on the nitrogen or by creating a quaternary ammonium), or a prodrug moiety, and where $R_2$ may be H or a prodrug moiety, with the understanding that at least one of $R_1$ and $R_2$ is a prodrug moiety. Known compounds 4-hydroxy-tamoxifen and endoxifen are not encompassed within compounds according to the invention. While the compound of Formula I is drawn with a specific orientation around the double bond, both E and Z configurations



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around the double bond are encompassed by the invention, for example, as represented by Formula Ia:

Ia

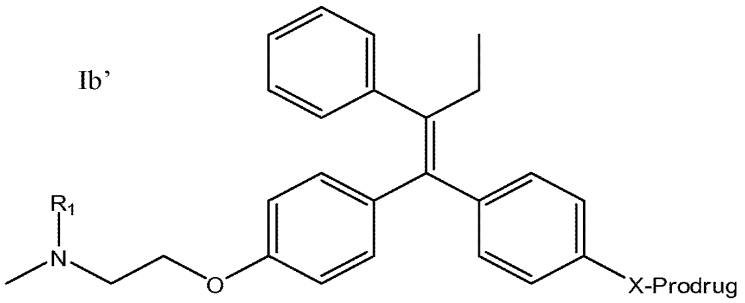



where the wavy bond indicates unspecified stereochemistry for the ethyl and phenyl substituents, such that the structure has either an E or Z configuration around the double bond.

**[0097]** In one embodiment, when $R_1$ is $CH_3$, $XR_2$ is not $OPO_3H_2$.

**[0098]** In one embodiment, the compounds according to the invention are compounds of the following formula:

Ib'

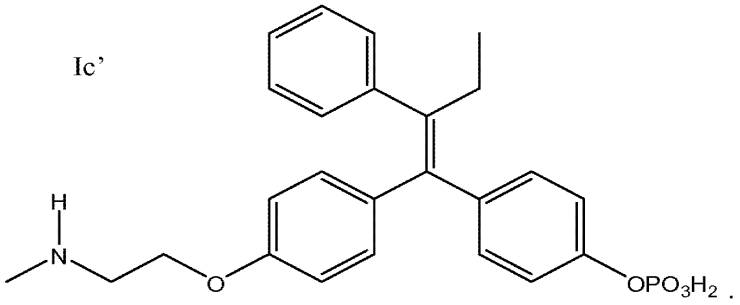



and pharmaceutically-acceptable salts thereof, where X is O, and where $R_1$ may be H or $CH_3$. Such compounds may be referred to as O-Pro-Endoxifens, when $R_1$ is H. In one embodiment, the compound according to the invention has the following formula:



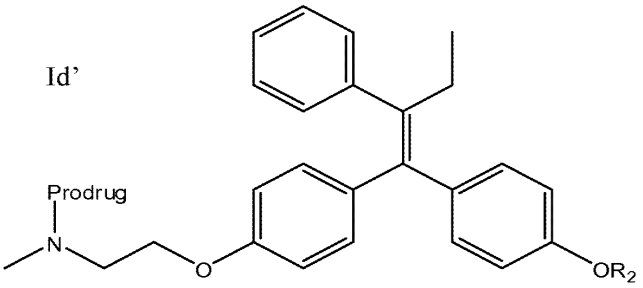
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Ic'




**[0099]** In one embodiment, the compounds according to the invention are compounds of the following formula:

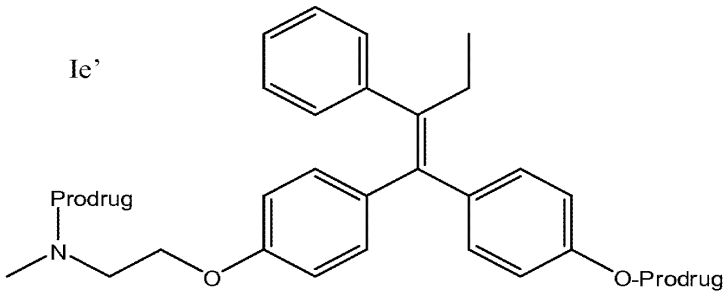
Id'




and pharmaceutically-acceptable salts thereof, where $R_2$ is an H. Such compounds may be referred to N-Pro-Endoxifens.

**[00100]** In one embodiment, the compounds according to the invention are compounds of the following formula:

Ie'



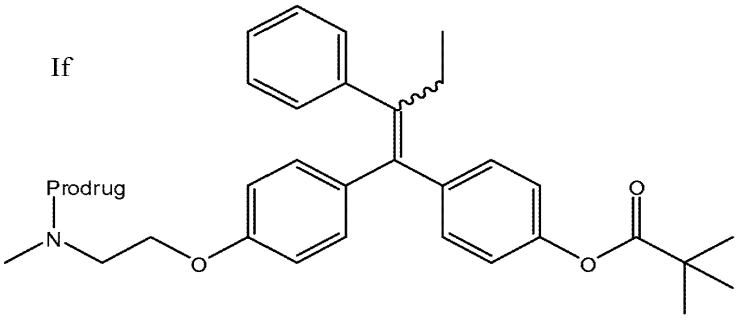

and pharmaceutically-acceptable salts thereof. Such compounds may be referred to as N,O-di-Pro-Endoxifens.



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**[00101]** In one embodiment, the compounds according to the invention are compounds of the following formula:

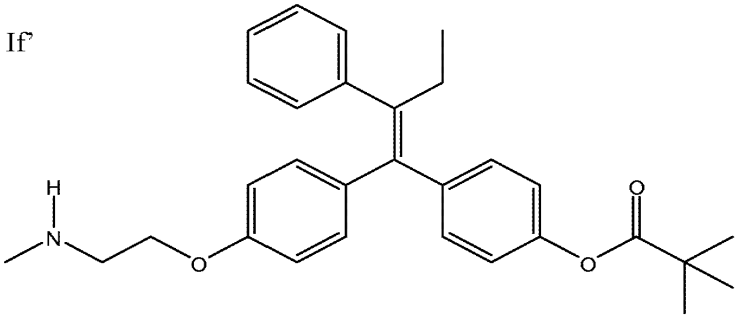
If




and pharmaceutically-acceptable salts thereof, where the wavy bond indicates unspecified stereochemistry for the ethyl and phenyl substituents, such that the structure has either an E or Z configuration around the double bond. Such compounds may be referred to as N-Pro-Endoxifen Pivalate Ester.

**[00102]** In one embodiment, the compounds according to the invention are compounds of the following formula:

If'




and pharmaceutically-acceptable salts thereof.

**[00103]** In various embodiments, $R_1$ and $R_2$ are each independently selected from the following groups:

**[00104]** Alkyl groups preferably having from 1 to 12 carbon atoms. A preferred class of alkyl groups has 1 to about 8 carbon atoms, still more preferably 1 to about 6 carbon atoms, and most preferably 1, 2, 3 or 4 carbon atoms. Methyl, ethyl and propyl including isopropyl are particularly preferred alkyl groups in the compounds of the present invention. As used herein, the term alkyl, unless otherwise modified, refers to



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both cyclic and noncyclic groups, although cyclic groups will comprise at least three carbon ring members. Lower alkyl groups refers may refer to alkyl groups with 1 to 6 carbon atoms.

**[00105]** Alkenyl and alkynyl groups having one or more unsaturated linkages and from 2 to about 12 carbon atoms, more preferably 2 to about 8 carbon atoms, still more preferably 2 to about 6 carbon atoms, even more preferably 2, 3 or 4 carbon atoms. The terms alkenyl and alkynyl as used herein refer to both cyclic and noncyclic groups, although straight or branched noncyclic groups are generally more preferred.

**[00106]** Alkylidene groups, branched or unbranched, and preferably having from 1 to 12 carbon atoms. One more preferred class of alkylidene groups has from 1 to about 8 carbon atoms, yet more preferably from 1 to about 6 carbon atoms, and most preferably 1, 2, 3 or 4 carbon atoms. Methylidene, ethylidene and propylidene including isopropylidene are particularly preferred alkylidene groups in the compounds of the present invention.

**[00107]** Alkylsulfinyl groups having one or more sulfoxide (SO) groups and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms. Alkylsulfinyl groups having 1, 2, 3 or 4 carbon atoms are particularly preferred.

**[00108]** Alkylsulfonyl groups having one or more sulfonyl ($SO_2$) groups and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms. Alkylsulfonyl groups having 1, 2, 3 or 4 carbon atoms are particularly preferred.

**[00109]** Aminoalkyl groups having one or more primary, secondary and/or tertiary amine groups, and from 1 to about 12 carbon atoms, more preferably 1 to about 8 carbon atoms, still more preferably 1 to about 6 carbon atoms, even more preferably 1, 2, 3 or 4 carbon atoms. Secondary and tertiary amine groups are generally more preferred than primary amine moieties.



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**[00110]** Heterocyclic groups including heteroaromatic and heteroalicyclic groups. Suitable heteroaromatic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., coumarinyl including 8-coumarinyl, quinolinyl including 8-quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, indolyl, benzofuranyl and benzothiazol. Suitable heteroalicyclic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolidinyl groups.

**[00111]** Aryl groups including single and multiple ring compounds, including multiple ring compounds that contain separate and/or fused aryl groups. Typical aryl groups contain from 1 to 3 separated or fused rings and from 6 to about 18 carbon ring atoms. Specifically preferred aryl groups include substituted or unsubstituted phenyl, naphthyl, biphenyl, phenanthryl, and anthracyl.

**[00112]** References herein to substituted groups in the compounds of the present invention refer to the specified moiety, typically alkyl or alkenyl, that may be substituted at one or more available positions by one or more suitable groups, e.g., halogen such as fluoro, chloro, bromo and iodo; cyano; hydroxyl; nitro; azido; carboxamido; alkyl groups including those groups having 1 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms and more preferably 1-3 carbon atoms; alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 12 carbon or from 2 to about 6 carbon atoms; alkoxy groups having those having one or more oxygen linkages and from 1 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms; aryloxy such as phenoxy; alkylthio groups including those moieties having one or more thioether linkages and from 1 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms; alkylsulfinyl groups including those moieties having one or more sulfinyl linkages and from 1 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms; alkylsulfonyl groups including those moieties having one or more sulfonyl linkages and from 1 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms; aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms; aryl having 6 or more carbons, particularly



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phenyl; aralkyl such as benzyl; heterocyclic groups including heteroalicyclic and heteroaromatic groups, especially with 5 to 10 ring atoms of which I to 4 are heteroatoms, more preferably heterocyclic groups with 5 or 6 ring atoms and 1 or 2 heteroatoms or with 10 ring atoms and 1 to 3 heteroatoms.

**[00113]** Preferred R groups include alkyl, alkenyl and alkynyl that may be substituted at one or more available positions by one or more suitable groups, e.g., halogen such as fluoro, chloro, bromo and iodo, especially ω-chloro or perfluoro; aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms; aryl having 6 or more carbons, particularly phenyl; aralkyl such as benzyl; heterocyclic groups including heteroalicyclic and heteroaromatic groups, especially with 5 to 10 ring atoms of which 1 to 4 are heteroatoms, more preferably heterocyclic groups with 5 or 6 ring atoms and 1 or 2 heteroatoms or with 10 ring atoms and 1 to 3 heteroatoms, the heterocyclic groups optionally being substituted with one or more of the substituents, especially amino such as dimethylamino or with keto.

**[00114]** Various prodrugs are known in the art. For example, see Simplicio et al., "Prodrugs for Amines," Molecules, vol. 13, iss. 3, pp. 519-547, March 2008, available from the internet at <<http://www.mdpi.org>>; see also Larsen, C.S., et al., "Chapter 14: Design and application of prodrugs" from Textbook of Drug Design and Discovery, Third Edition, edited by Krogsgaard-Larsen, P. et al., pages 410-458, 2002. The contents of each publication are incorporated by reference.

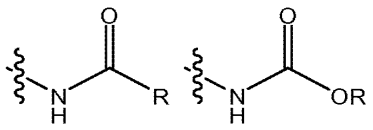
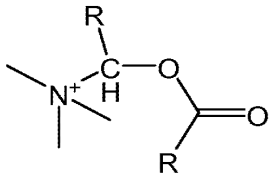
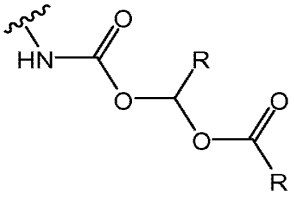
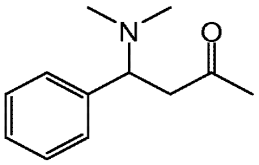
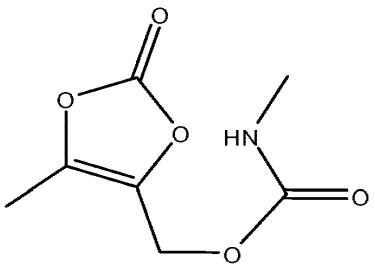
**[00115]** In some embodiments, the prodrug moiety may be selected from Table 1, as adapted from Simplicio, in particular for a prodrug moiety to be attached to a nitrogen:

Table 1

| Prodrug type | mechanism of transformation | advantages | disadvantages |
|---|---|---|---|

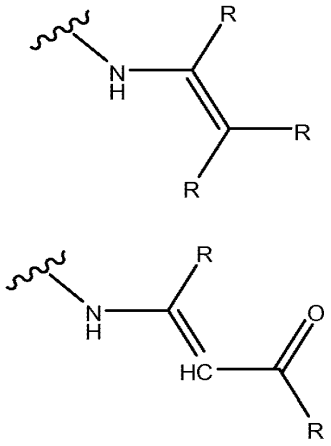
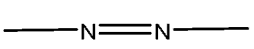
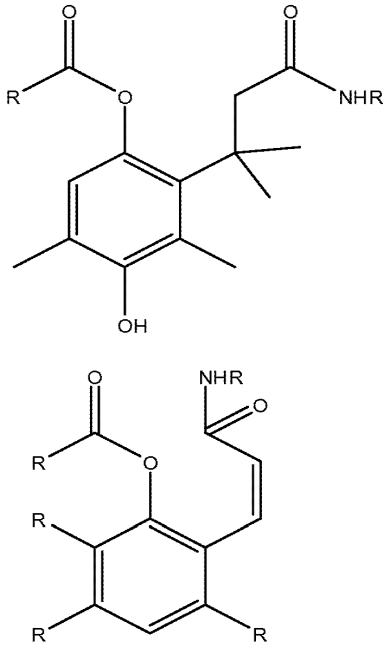


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| Prodrug type | mechanism of transformation | advantages | disadvantages |
|---|---|---|---|
|  amides and carbamates | enzymatic, pH activated | lipid solubility may be improved slow release | Needs to be activated by an electron withdrawing substitute |
|  N-acyloxyalkylderivatives | enzymatic followed by spontaneous | improved lipophilicity | only applicable to tertiary amines |
|  N-acyloxyalkoxy carbonyl derivatives | enzymatic followed by spontaneous | produces neutral compounds | usually not suitable for primary amines |
|  β-aminoketones | pH activated | lowers pKa increases lipophilicity | easily hydrolyzed in aqueous solution |
|  (oxodioxolenyl)methyl derivatives | base catalysis and/or enzymatic | also applicable to primary amines | |

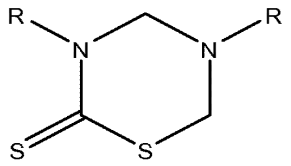
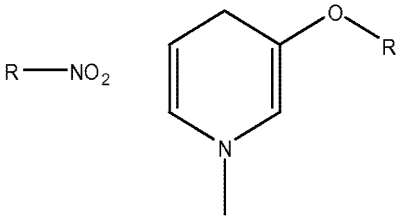


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| Prodrug type | mechanism of transformation | advantages | disadvantages |
|---|---|---|---|
|  enamines and enaminones | chemical | lowers pKa improved lipophilicity | not stable enough at low pH |
|  azo compounds | azo-reductases | possibility of targeting | only applicable to aromatic amines |
|  lactonization systems | enzymatic followed by spontaneous | possible to manipulate phys/chem characteristics | poor aqueous solubility in most cases |



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| Prodrug type | mechanism of transformation | advantages | disadvantages |
|---|---|---|---|
|  THTT | enzymatic and chemical | improved lipophilicity | only applicable to primary amines |
|  redox systems | chemical or enzymatic activation | possibility of targeting | oxidation in solid state |
| PEG | chemical and enzymatic activation | improved solubility | need association with other systems |

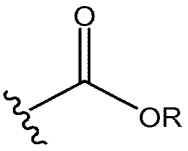
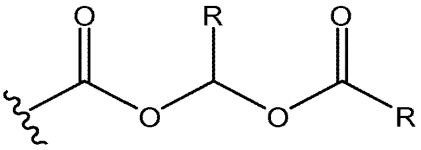
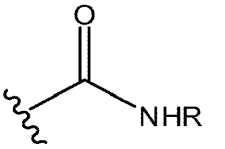
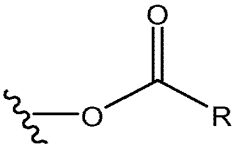
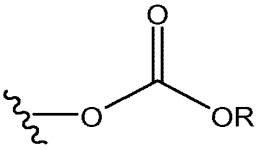
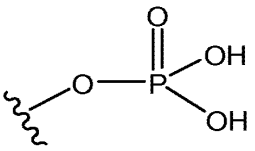
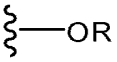
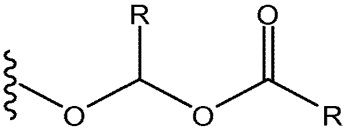
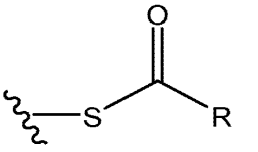
**[00116]** In some embodiments, the prodrug moiety may be selected from Table 2, as adapted from Larsen, in particular for a prodrug moiety to be attached to an oxygen:

Table 2

| *Functional group* | *Prodrug form* |
|---|---|



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| *Functional group* | *Prodrug form* | |
|---|---|---|
| -COOH |  | Esters |
| |  | α-Acyloxyalkyl esters |
| |  | Amides |
| -OH |  | Esters |
| |  | Carbonate esters |
| |  | Phosphate esters |
| |  | Ethers |
| |  | α-Acyloxyalkyl ethers |
| -SH |  | Thioesters |



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**[00117]** In various embodiments, a prodrug moiety may be adapted from Tables 1 or 2, Examples 1-7 below, or from Figures 2-8. Such prodrugs may include R groups (including $R_1$, etc.) as defined above for Formula I. The synthesis of prodrugs according to the invention may be adapted from Examples 1-7 below, from Figures 2-8, and from standard transformations available to the practitioner in the art. For example, see Simplicio et al., "Prodrugs for Amines," Molecules, vol. 13, iss. 3, pp. 519-547, March 2008, available from the internet at <<http://www.mdpi.org>>; see also Larsen, C.S., et al., "Chapter 14: Design and application of prodrugs" from Textbook of Drug Design and Discovery, Third Edition, edited by Krogsgaard-Larsen, P. et al., pages 410-458, 2002. See also March, J., Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Fourth Edition, John Wiley & Sons, Inc., publishers, 1992; Greene, T.W., Protective Groups in Organic Synthesis, John Wiley & Sons, Inc., publishers, 1981; and Larock, R.C., Comprehensive Organic Transformations: A Guide to Functional Group Preparations, John Wiley & Sons, Inc., publishers, November 1999. The contents of each publication are incorporated by reference. Substituents for the generic groups in Tables 1 and 2 may be as understood in the art, including substituted or unsubstituted derivatives thereof. In one embodiment, any R group (including $R_1$, $R_2$, etc.) in Table 1 or 2 is independently a $C_1$-$C_6$ alkyl group.

**[00118]** As discussed above, the term "prodrug" means a compound with a temporary modification of a functional group of a drug in order to improve the pharmaceutical utility of the drug. Prodrug may refer to the entire compound, or it may refer to the chemical modification, in the context of a prodrug moiety being the chemical modification. In some embodiments, the functional group of the drug is a handle for the introduction of a moiety that confers on the new entity some desirable characteristic. In other embodiments, the prodrug moiety is intimately connected with the pharmaceutical deficiency of the parent drug, and the presence of the prodrug moiety directly addresses the deficiency. In some embodiments, prodrugs rely on *in vivo* enzymatic activation for conversion to active form of the drug for example by cleavage of the prodrug moiety by an enzyme. In other embodiments, prodrugs rely on physiological chemical conditions for release of the drug, for example through a change in pH. The benefits of a prodrug are not limited to improved *in vivo* benefits compared to the parent drug, but may also include improved processing or storage



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characteristics or economic considerations prior to administration to the patient. In various embodiments, the advantages of the prodrug moiety may be selected from the group consisting of improved biomembrane passage and bioavailability (including improved oral absorption, dermal absorption, ocular absorption, gastro-intestinal absorption, and/or reduced first-pass metabolism), site-directed drug delivery, site-specific bioactivation, improvement of drug formulation, and combinations thereof.

**[00119]** In one embodiment, an endoxifen prodrug according to the invention is administered in a manner to avoid exposure of the colon to high levels of endoxifen. While not wishing to be bound by theory, it is thought that endoxifen may have low (less than 20%) oral absorption, leading to exposure of the colon to high levels of endoxifen. As women have a lower incidence of colon cancer than men, one possible mechanism for this difference is the protective action of estrogen on the colon. By interacting with estrogen receptors, such as estrogen receptor beta, in the colon, estrogen may serve to protect women from colon cancer. Interaction with such receptors by endoxifen may have the potential to otherwise increase colon cancer rates by antagonizing the protective action of estrogen. As such, an endoxifen prodrug with decreased activity compared to endoxifen, but which is converted to endoxifen upon absorption or following absorption, may avoid the exposing the colon the high levels of antiestrogen activity, and therefore preserve any estrogen-related protective effect related to colon cancer. Alternatively, an endoxifen prodrug according to the invention may be more active than endoxifen, but also absorbed more completely prior to reaching the colon, thereby achieving the same effect, which is to reduce delivery of an antiestrogen agent to the colon.

**[00120]** Figure 9 provides data showing that endoxifen antagonizes Estrogen Receptor Beta (ERβ). In Figure 9, HeLa cells were transiently transfected with an ERβ expression vector along with a luciferase reporter gene (ERE-tk109-Luc). Transfected cells were treated with 5 nM hydroxytamoxifen (OH-Tam) or Endoxifen (Endox), in the presence and absence of 100 pM 17β-estradiol (E2). Luciferase activity was assayed after 18 hours of ligand treatment. Bars represent the mean relative light units obtained from triplicate wells with error bars representing S.E.M.



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**[00121]** The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc. Pharmaceutically acceptable non-toxic salts may include the base addition salts (formed with free carboxyl or other anionic groups) which may be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino-ethanol, histidine, procaine, and the like. Such salts may also be formed as acid addition salts with any free cationic groups and will generally be formed with inorganic acids such as, for example, hydrochloric, sulfuric, or phosphoric acids, or organic acids such as acetic, p-toluenesulfonic, methanesulfonic acid, oxalic, tartaric, mandelic, and the like. Salts of the invention include amine salts formed by the protonation of an amino group with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like. Salts of the invention also include amine salts formed by the protonation of an amino group with suitable organic acids, such as p-toluenesulfonic acid, acetic acid, and the like. Additional salt-forming excipients which are contemplated for use in the practice of the present invention are those available to those of ordinary skill in the art, for example, those found in the United States Pharmacopeia Vol. XXII and National Formulary Vol. XVII, U.S. Pharmacopeia Convention, Inc., Rockville, Md. (1989), the relevant contents of which is incorporated herein by reference.

**[00122]** Any therapy (e.g., chemotherapies, radiation therapies, hormonal therapies, and/or biological therapies/immunotherapies) which is known to be useful, or which has been used or is currently being used for the prevention, treatment, management or amelioration of cancer or one or more symptoms thereof can be used in accordance with the invention, and may be combined with any of the compositions described herein, and may encompass the other active ingredient described for some of the combination therapies herein.



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**[00123]** In some embodiments, the anti-cancer agents contemplated in the methods and compositions of the present invention, which can be administered in combination with the compositions of the present invention include, but are not limited to doxorubicin, epirubicin, the combination of doxorubicin and cyclophosphamide (AC), the combination of cyclophosphamide, doxorubicin and 5-fluorouracil (CAF), the combination of cyclophosphamide, epirubicin and 5-fluorouracil (CEF), herceptin, tamoxifen, the combination of tamoxifen and cytotoxic chemotherapy, taxanes (such as docetaxel and paclitaxel). In a further embodiment, the combinations of the invention can be administered with taxanes plus standard doxorubicin and cyclophosphamide for adjuvant treatment of node-positive, localized breast cancer.

**[00124]** In one embodiment, the dose of doxorubicin hydrochloride (i.v.) is 60-75 $mg/m^2$ on day 1 of treatment. In another embodiment, the dose of epirubicin (i.v.) is 100-120 $mg/m^2$ on day 1 of each cycle or divided equally and given on days 1-8 of the treatment cycle. In yet another embodiment, the dose of docetaxel (i.v.) is 60-100 $mg/m^2$ over 1 hour. In another embodiment, the dose of paclitaxel (i.v.) is 175 $mg/m^2$ over 3 hours.

**[00125]** The present invention can be used to treat a patient with any type of breast cancer. Breast cancers may include carcinoma in situ, infiltrating (or invasive) ductal carcinoma, infiltrating (or invasive) lobular carcinoma, medullary carcinoma, colloid carcinoma, tubular carcinoma, and inflammatory carcinoma.

**[00126]** In addition to the different types of breast cancer, there are also different stages of breast cancer, referred to as stages 0-IV. The system most often used to describe the growth and spread of breast cancer is the TNM staging system, also known as the American Joint Committee on Cancer (AJCC) system. In TNM staging, information about the tumor, nearby lymph nodes, and distant organ metastases is combined and a stage is assigned to specific TNM groupings. The grouped stages are described using Roman numerals from I to IV. The clinical stage is determined by results from physical examination and tests. The pathologic stage includes the findings of the pathologist after surgery. Most of the time, pathologic stage is the most important stage because usually the cancer isn't known to have



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spread to lymph nodes until the pathologist examines them under the microscope. In the TNM staging system, T stands for the size of the cancer (measured in centimeters; 2.54 centimeters 1 inch); N stands for spread to lymph nodes in the area of the breast, and M is for metastasis (spread to distant organs of the body).

**[00127]** The T category describes the original (primary) tumor. Tis: Tis is used only for carcinoma in situ or noninvasive breast cancer such as ductal carcinoma in situ, (DCIS) or lobular carcinoma in situ (LCIS). T1: The cancer is 2 cm in diameter (about 3/4 inch) or smaller. T2: The cancer is more than 2 cm but not more than 5 cm in diameter. T3: The cancer is more than 5 cm in diameter. T4: The cancer is any size and has spread to the chest wall, the skin, or lymphatics.

**[00128]** The N category is based on which of the lymph nodes near the breast, if any, are affected by the cancer. N0: The cancer has not spread to lymph nodes. N1: The cancer has spread to lymph nodes under the arm on the same side as the breast cancer. Lymph nodes have not yet attached to one another or to the surrounding tissue. N2: The cancer has spread to lymph nodes under the arm on the same side as the breast cancer and are attached to one another or to the surrounding tissue or enlarged. Or, the cancer can be seen to have spread to the internal mammary lymph nodes (next to the sternum), but not to the lymph nodes under the arm. N3: The cancer has spread to lymph nodes above or just below the collarbone on the same side as the cancer, and may or may not have spread to lymph nodes under the arm. Or, the cancer has spread to internal mammary lymph nodes and lymph nodes under the arm, both on the same side as the cancer.

**[00129]** M categories: The M category depends on whether the cancer has spread to any distant tissues and organs. M0: No distant cancer spread. M1: Cancer has spread to distant organs.

**[00130]** There are different types of staging. Clinical staging estimates how much cancer there is based on the results of the physical exam, imaging tests (x-rays, CT scans, etc.) and sometimes biopsies of affected areas. For certain cancers the results of other tests, such as blood tests, are also used in staging. Pathologic staging can only be done on patients who have had surgery to remove or explore the extent of



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the cancer. It combines the results of clinical staging (physical exam, imaging tests, etc.) with the results from the surgery. In some cases, the pathologic stage may be different from the clinical stage (for example, if the surgery shows the cancer is more extensive than it was previously thought to be). Restaging is sometimes used to determine the extent of the disease if a cancer recurs (comes back) after treatment.

**[00131]** In one embodiment, the methods and compositions of the present invention are used to treat patients with stage I breast cancer.

**[00132]** In one embodiment, the methods and compositions of the present invention are used to treat patients with stage II breast cancer.

**[00133]** In one embodiment, the methods and compositions of the present invention are used to treat patients with stage III breast cancer.

**[00134]** In one embodiment, the methods and compositions of the present invention are used to treat patients with stage IV breast cancer, i.e. patients with metastatic cancer.

**[00135]** In another embodiment, the patient having breast cancer has already failed other treatment regimens such as chemotherapy.

**[00136]** In one embodiment, the methods and pharmaceutical compositions of the present invention may be used to prevent the development of a cancer, particularly in an individual at higher risk than average to develop such cancer than other individuals, or to treat a patient afflicted with breast cancer.

**[00137]** There are a number of ways to assess an individual's risk for breast cancer, and any means of risk assessment is contemplated by the present invention as determining which subjects are at risk for breast cancer and can undergo treatment via the methods and compositions of the present invention. The invention contemplates treatment for individuals with a higher than average lifetime risk for breast cancer, the average being about one in eight women in the U.S.



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**[00138]** The invention provides methods treating asymptomatic patients who have a likelihood of benefiting from therapeutic treatment of breast cancer. The asymptomatic patients can comprise patients in any of the many high risk groups for breast cancer. The high risk groups can include e.g. patients with a family history of breast cancer, patients of increasing age (e.g., patients 40 years of age or older), menopausal patients, patients having at least one high risk parity factor (e.g. early start of menses, late onset of menopause, no pregnancies, or late-age pregnancy), patients having high risk gene status (e.g. patients testing positive for a mutation in *BRCA1* or *BRCA2* genes, or others, as described below), patients having at least one previous breast biopsy (benign or otherwise), patients having a previous diagnosis of breast cancer, and patients having any other risk factor for breast cancer. Other risk factors are continually being defined and can include such considerations, as geographic location (e.g. where women living in a particular region have been found to have a higher incidence of breast cancer). Diet is also thought to play a role in breast cancer risk; specifically women who include more fat in their diet may be more likely to develop breast cancer (see Kniget et al. Cancer Epidemiol Biomarkers Prev 8(2):123-8, 1999).

**[00139]** The Gail model is a common means of determining risk for breast cancer, and was developed based on the Breast Cancer Detection Demonstration Project (see Gail, M. et al, J Natl Cancer Inst., 1989. 81: p. 1879-86). The risk factors used in the Gail model are age, age at menarche, age at first live birth, number of previous breast biopsies, number of first-degree relatives with breast cancer. These risk factors are broadly consistent with those selected from other large population-based studies. A revised Gail model also incorporates race, presence of atypical hyperplasia on breast biopsy, and 1987 population rates of breast cancer and death from other causes.

**[00140]** Another commonly used prediction model is the Claus model, based on the Cancer and Steroid Hormone Study (see Claus E. et al., Cancer, 1994. 73: 643-51) and incorporates more extensive information about family history. The Claus model provides individual estimates of breast-cancer risk according to decade from 29-79 years of age. It takes into account factors such as the number of first-degree



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and number of second-degree relatives with breast cancer, as well as different combinations of different degree relatives with breast cancer.

**[00141]** The invention also contemplates treatment for early stages of cancer, for recurrent cancer, and for those in remission from cancer.

**[00142]** The present invention also encompasses treatment for subjects with markers for breast cancer, including, but not limited to having mutations or other alterations in the genes, *BRCA1*, *BRCA2*, *P53*, *P65*, *ATM*, or *pS2*, or a changed ratio of the expression of the genes *HOXB13* and *IL17BR,* amplification of the *AIB1/pCIP* coactivator gene, overproduction of HER2 protein and/or gene, and alterations in levels of hormones, such as estrogen and progesterone, or their receptors.

**[00143]** Markers can also include neoplastic ductal epithelial cells, transforming growth factor-β, carcinoma embryonic antigen (CEA), prostate specific antigen (PSA), Erb B2 antigen, gross cystic disease fluid protein-15 (GCDFP-15), lactose dehydrogenase (LDH), measured in the ductal fluid, or a chromosomal abnormality in the ductal epithelial cells. Where the marker is neoplastic ductal epithelial cells, the cells can be at a stage including hyperplasia, atypical hyperplasia, low grade ductal carcinoma in situ (LG-DCIS), high grade ductal carcinoma in situ (HG-DCIS) or invasive carcinoma. The present invention encompasses providing the pharmaceutical compositions described herein to treat subjects with any of the described markers, and also to prevent the progression from DCIS and from atypical hyperplasia to breast cancer.

**[00144]** The compositions of the invention may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs.

**[00145]** The methods and compositions of the present invention may be used advantageously in combination with any other treatment regimen for breast cancer. Treatments for breast cancer are well known in the art and continue to be developed. Treatments include but are not limited to surgery, including axillary dissection, sentinel lymph node biopsy, reconstructive surgery, surgery to relieve symptoms of



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advanced cancer, lumpectomy (also called breast conservation therapy), partial (segmental) mastectomy, simple or total mastectomy, modified radical mastectomy, and radical mastectomy; immunotherapy, e.g. using Herceptin™ (trastuzumab), an anti-HER2 humanized monoclonal antibody developed to block the HER2 receptor; bone marrow transplantation; peripheral blood stem cell therapy; bisphosphonates; additional chemotherapy agents; radiation therapy; acupressure; and acupuncture. Any combination of therapies may be used in conjunction with the present invention.

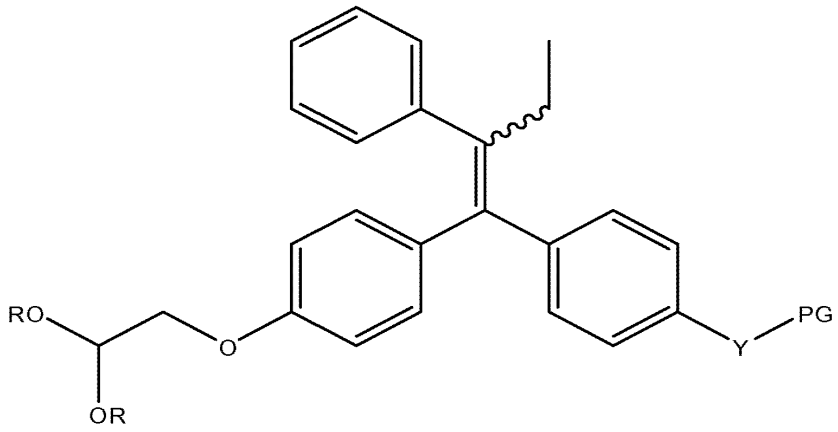
**[00146]** The methods and compositions comprising the combination therapies described herein may also be used to reduce the proliferation of cancer cells, increase the death of cancer cells or, reduces the size of a tumor or spread of a tumor in a subject. It is contemplated by the present invention that the combination therapies described herein may reduce the size of a tumor or the spread of a tumor in a subject by at least 5%, preferably at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99% relative to a control such as PBS. In some embodiments, the combination therapies described herein may increase survival by 1 month, 2 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, or more, it may render the subject disease-free, or it may prevent the progression from DCIS or atypical hyperplasia to breast cancer.

**[00147]** In one embodiment, intermediates are presented for the synthesis of compounds and compositions for the treatment and prevention of breast cancer. The intermediates may be immediate precursors of the compounds to be administered to the patient, or the intermediates may require two or more synthetic steps to be converted into a compound to be administered to a patient. In one embodiment, the intermediates are converted into compounds of Formula I, Ia, Ib, Ib', Ic, Ic', Id, Id', Ie, or Ie'.

**[00148]** In one embodiment, an intermediate according to the invention is a compound of Formula II:



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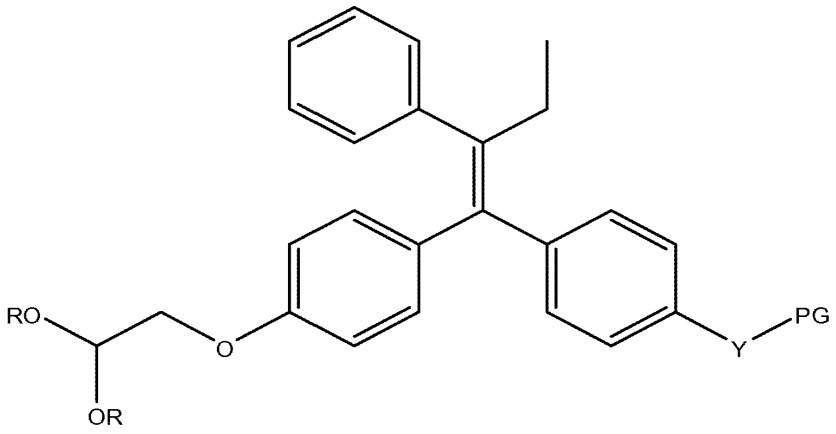



where the two OR groups form an acetal, or where the R groups optionally form a ring, where Y is an oxygen or sulfur atom, and where PG is a hydrogen atom or a protecting group, and where the wavy bond indicates unspecified stereochemistry for the ethyl and phenyl substituents, such that the structure has either an E or Z configuration around the double bond. Protecting groups for O or S atoms and acetals are known in the art, for example, as described in Greene, Protective Groups in Organic Synthesis, 1981, the contents of which are hereby incorporated by reference in their entirety. Where Y is oxygen, representative protecting groups may be ethers (MOM, MEM, MTM, tetrahydropyranyl, phenacyl, cyclopropylmethyl, allyl, isopropyl, cyclohexyl, t-butyl, benzyl, 4-methoxybenzyl, o-nitrobenzyl, 9-anthrylmethyl, 4-picolyl, silyl, trimethylsilyl, t-butyldimethylsilyl, and the like), esters (acetate, pivalate, benzoate, 9-fluorenecarboxylate, and the like), carbonates (methyl, 2,2,2-trichloroethyl, vinyl, benzyl), arylcarbonates, sulfonates (methanesulfonate, toluenesulfonate), cyclic acetals, and cyclic esters. In one embodiment, Y is oxygen, and PG is 4-methoxybenzyl ether. In another embodiment, Y is oxygen, and PG is the pivalate ester. In a preferred embodiment, the protecting group at Y is orthogonal to the acetal formed by the R groups. In one embodiment, the R groups forming an acetal are each independently a $C_1$ through $C_6$ alkyl group, such as methyl, ethyl, propyl, butyl, pentyl, hexyl, 2-isopropyl, t-butyl, or 2,2,2-trichloroethyl group. In one embodiment, the acetal is a cyclic acetal, such as a 1,3-dioxane, or a 1,3-dioxolane. In one embodiment, the two R groups form a dibenzyl or a diacetyl acetal. In one embodiment, the two R groups form a dimethyl acetal. In another embodiment, the two R groups form a diethyl acetal.



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**[00149]** In one embodiment, the intermediate according to the invention is a compound of Formula IIa:

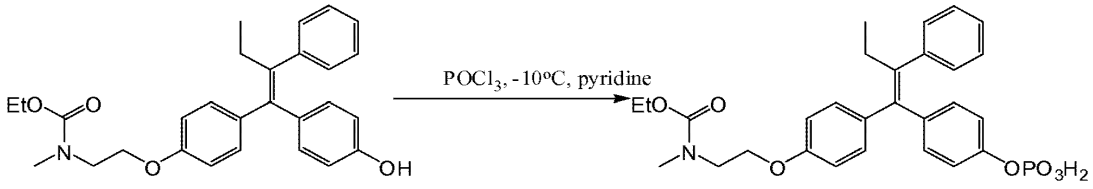



where the two OR groups form a dimethyl or diethyl acetal, Y is oxygen, and PG is selected from a 4-methoxybenzyl group or a pivalate group.

6. EXAMPLES

**[00150]** The following series of Examples are presented for purposes of illustration and not by way of limitation on the scope of the invention. Isomerization between E and Z isomers for intermediates and final products may occur. As such, mixtures of E and Z isomers are envisioned, and may be retained or, if desired, specific isomers may be enriched to the point of purity.

**[00151]** Example 1. (Z)-Endoxifen phosphate ethyl carbamate ((Z)-ethyl methyl(2-(4-(2-phenyl-1-(4-(phosphonooxy)phenyl)but-1-enyl)phenoxy)ethyl)carbamate)



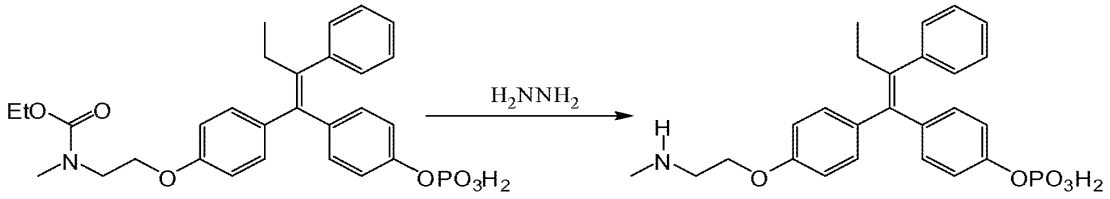

**[00152]** Phosphorous oxychloride (0.8-2 equiv) is added to dry pyridine (0.1-12 M/L) at -10C. To this mixture is added gradually (E)-ethyl 2-(4-(1-(4-



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hydroxyphenyl)-2-phenylbut-1-enyl)phenoxy)ethyl(methyl)carbamate (N-carbonylethoxy-(E)-endoxifen) (1 equiv). The mixture is stirred with cooling for 1-8 h and then allowed to warm slowly to room temperature and stirred at room temperature for 1-5 h. This reaction mixture is then added gradually to a mixture of 2-10% aqueous sodium bicarbonate and ice. The mixture is then allowed to stir for 1-5 h after which time, the pH of the mixture is slowly adjusted to ca. 2 using hydrochloric acid. At that time, a precipitate is formed. This mixture is filtered to yield among other products N-carbonylethoxy-(Z)-endoxifen phosphate.

**[00153]** Example 2. (Z)-Endoxifen phosphate ((Z)-4-(1-(4-(2-(methylamino)ethoxy)phenyl)-2-phenylbut-1-enyl)phenyl dihydrogen phosphate)

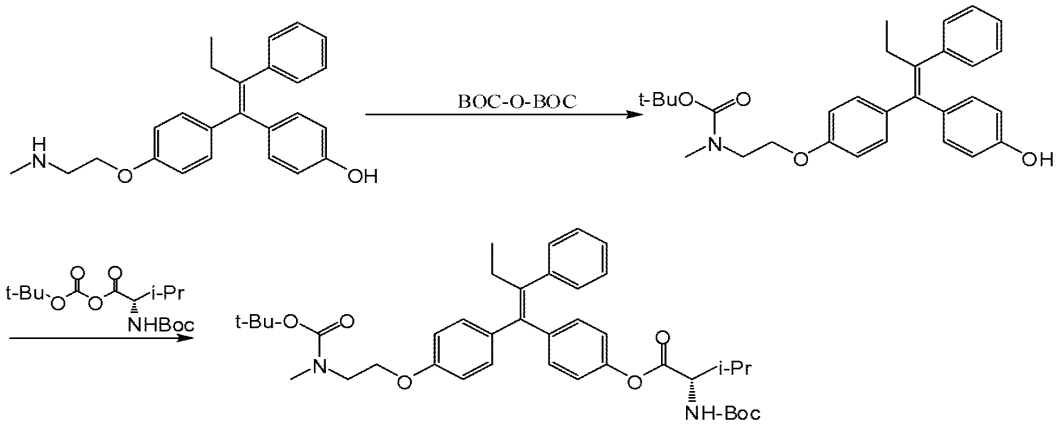



**[00154]** The product from example 1 is suspended in ethylene glycol (0.05-2 M). To this suspension are added hydrazine hydrate and potassium hydroxide. The resulting mixture is warmed to 80-150C for 1-8 h. The reaction mixture is then added water at 0C or a mixture of water and ice. The cooled mixture is extracted with ether or other lipophilic organic solvent. The organic extracts may be washed with brine and then dried over a suitable desiccant (e.g. magnesium sulfate anh. or sodium sulfate anh.). The mixture is then filtered. Removal of the organic solvent furnishes among other products the Z isomer of endoxifen phosphate.

**[00155]** Example 3. (Z)-Endoxifen valine ester t-butyl carbamate ((S,Z)-4-(1-(4-(2-(tert-butoxycarbonyl(methyl)amino)ethoxy)phenyl)-2-phenylbut-1-enyl)phenyl 2-(tert-butoxycarbonylamino)-3-methylbutanoate)



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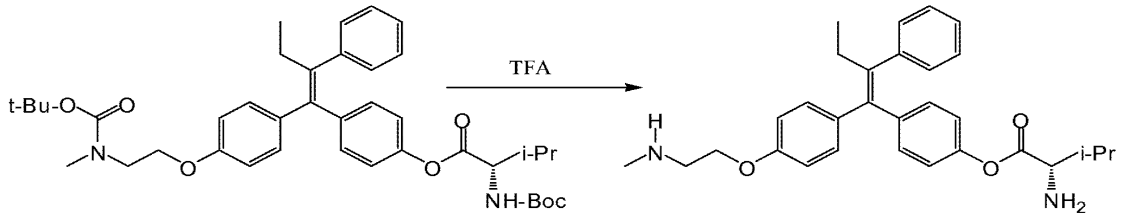

**[00156]** A. (E)-Endoxifen is dissolved in dichloromethane or other suitable organic solvent. To this solution is added triethyl amine or other suitable base. This solution may be cooled. To this solution is added Boc-O-Boc. The mixture is stirred for 1-12 h, at which time the reaction is quenched by addition of aqueous sodium bicarbonate or other quenching reagent. The mixture is then washed with dilute HCl (aq.). The mixture is then extracted with ethyl acetate or other suitable organic solvent. The combined organic extracts are then dried over a suitable desiccant (e.g. magnesium sulfate anh.). The mixture is then filtered and the organic solvent removed to furnish among other things N-Boc-(E)-endoxifen.

**[00157]** B. The product of the previous step is dissolved in dichloromethane or other suitable organic solvent. To this solution is added triethyl amine or other suitable base. This solution may be cooled. To this solution is added an activated form of N-Boc-valine (e.g. O-t-butyloxycarbonyl valine). The mixture is stirred for 1-12 h, at which time the reaction is quenched by addition of aqueous sodium bicarbonate or other quenching reagent. The mixture is then washed with dilute HCl (aq.) The mixture is then extracted with ethyl acetate or other suitable organic solvent. The combined organic extracts are then dried over a suitable desiccant (e.g. magnesium sulfate anh.). The mixture is then filtered and the organic solvent removed to furnish among other products bis-N-Boc-(Z)-endoxifen valine ester.

**[00158]** Example 4. (Z)-Endoxifen Valine ester ((S,Z)-4-(1-(4-(2-(methylamino)ethoxy)phenyl)-2-phenylbut-1-enyl)phenyl 2-amino-3-methylbutanoate)

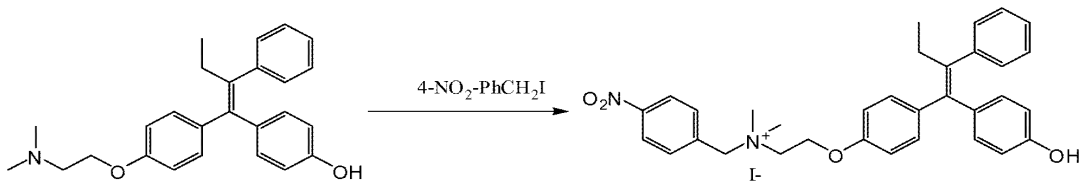


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**[00159]** The product from example 3 is dissolved in dichloromethane or other suitable organic solvent. This solution may be cooled. To this solution is added trifluoroacetic acid. This mixture is stirred for 1-12 h, at which time the reaction is quenched by addition of aqueous sodium bicarbonate or other quenching reagent. The mixture is then extracted with ethyl acetate or other suitable organic solvent. The combined organic extracts are then dried over a suitable desiccant (e.g. magnesium sulfate anh.). The mixture is then filtered and the organic solvent removed to furnish among other products the Z isomer of endoxifen valine ester.

**[00160]** Example 5. N-(4-nitrobenzyl)-4-hydroxy-tamoxifen iodide ((E)-2-(4-(1-(4-hydroxyphenyl)-2-phenylbut-1-enyl)phenoxy)-N,N-dimethyl-N-(4-nitrobenzyl)ethanaminium iodide)

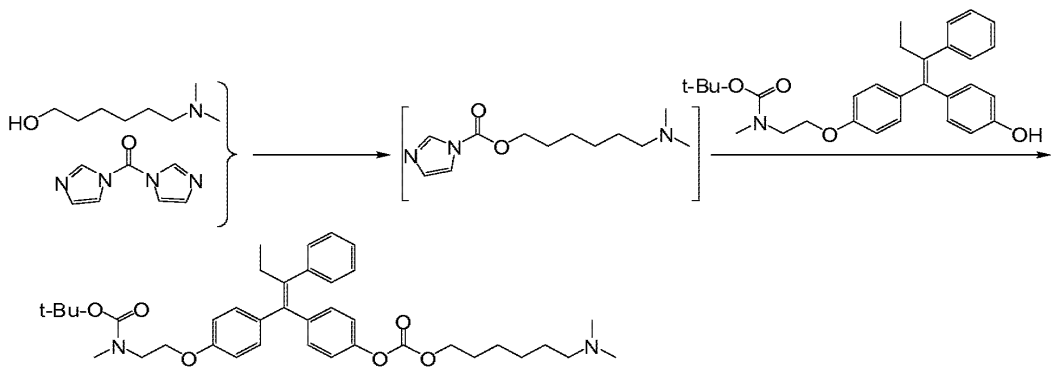



**[00161]** (E)-4-Hydroxy-tamoxifen is dissolved in toluene or other suitable organic solvent. To this mixture is added an alkylating agent such as 4-nitrobenzyl iodide. This mixture may be heated. After starting material is completely consumed, volatile organics are removed to afford among other products the separable E isomer of N-(4-nitrobenzyl)-4-hydroxy-tamoxifen iodide.

**[00162]** Example 6. (Z)-Endoxifen-(6-N,N-dimethylamino)-1-hexyl carbonate t-butyl carbamate ((Z)-tert-butyl 2-(4-(1-(4-((6-(dimethylamino) hexyloxy)carbonyloxy)phenyl)-2-phenylbut-1-enyl)phenoxy)ethyl(methyl)carbamate)



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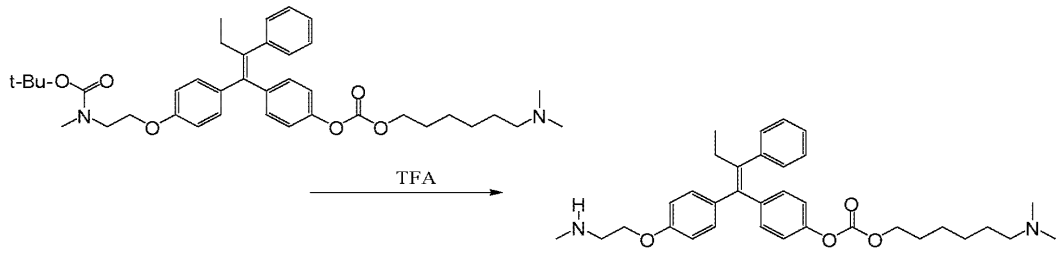



**[00163]** 6-(N,N-dimethylamino)-1-hexanol is dissolved in dichloromethane or other suitable organic solvent. To this solution may be added triethyl amine or other suitable base. This solution may be cooled. To this solution is added carbonyl diimidazole or other suitable phosgene equivalent or phosgene. The mixture is stirred for 1-12 h, at which time N-Boc-(E)-endoxifen (product of example 3, step A). The mixture is then stirred for 1-12 h. The reaction is quenched by addition of aqueous sodium bicarbonate or other quenching reagent. The mixture is then washed with dilute HCl (aq.). The mixture is then extracted with ethyl acetate or other suitable organic solvent. The combined organic extracts are then dried over a suitable desiccant (e.g. magnesium sulfate anh.). The mixture is then filtered and the organic solvent removed to furnish among other things N-Boc-(Z)-endoxifen (6-N,N-dimethylamino)-1-hexyl carbonate.

**[00164]** Example 7. (Z)-Endoxifen-(6-N,N-dimethylamino)-1-hexyl carbonate ((Z)-6-(dimethylamino)hexyl 4-(1-(4-(2-(methylamino)ethoxy)phenyl)-2-phenylbut-1-enyl)phenyl carbonate)

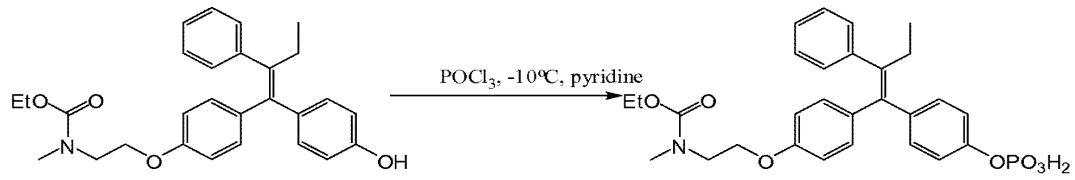


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**[00165]** The product from example 6 is dissolved in dichloromethane or other suitable organic solvent. This solution may be cooled. To this solution is added trifluoroacetic acid. This mixture is stirred for 1-12 h, at which time the reaction is quenched by addition of aqueous sodium bicarbonate or other quenching reagent. The mixture is then extracted with ethyl acetate or other suitable organic solvent. The combined organic extracts are then dried over a suitable desiccant (e.g. magnesium sulfate anh.). The mixture is then filtered and the organic solvent removed to furnish among other products the separable Z isomer of endoxifen 6-N,N-dimethylamino-1-hexyl carbonate.

**[00166]** Example 8. Endoxifen phosphate ethyl carbamate ((E)-ethyl methyl(2-(4-(2-phenyl-1-(4-(phosphonooxy)phenyl)but-1-enyl)phenoxy)ethyl)carbamate)



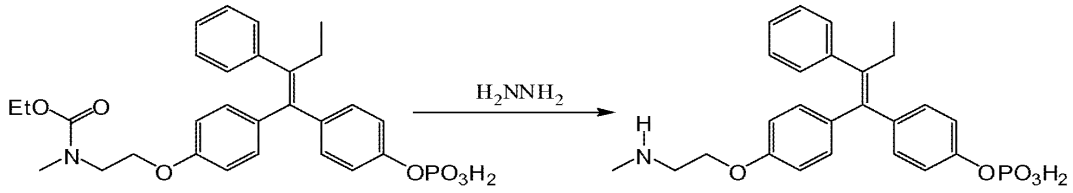

**[00167]** Phosphorous oxychloride (0.8-2 equiv) is added to dry pyridine (0.1-12 M/L) at -10C. To this mixture is added gradually (Z)-ethyl 2-(4-(1-(4-hydroxyphenyl)-2-phenylbut-1-enyl)phenoxy)ethyl(methyl)carbamate (N-carbonylethoxy-endoxifen) (1 equiv). The mixture is stirred with cooling for 1-8 h and then allowed to warm slowly to room temperature and stirred at room temperature for 1-5 h. This reaction mixture is then added gradually to a mixture of 2-10% aqueous sodium bicarbonate and ice. The mixture is then allowed to stir for 1-5 h after which time, the pH of the mixture is slowly adjusted to ca. 2 using hydrochloric



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acid. At that time, a precipitate is formed. This mixture is filtered to yield among other products N-carbonylethoxy-endoxifen phosphate.

**[00168]** Example 9. Endoxifen phosphate ((E)-4-(1-(4-(2-(methylamino)ethoxy)phenyl)-2-phenylbut-1-enyl)phenyl dihydrogen phosphate)

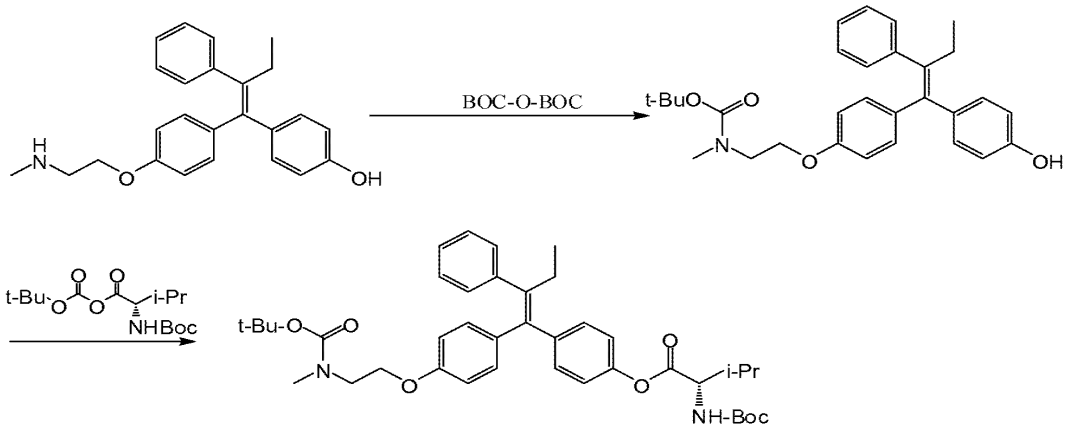



**[00169]** The product from example 8 is suspended in ethylene glycol (0.05-2 M). To this suspension are added hydrazine hydrate and potassium hydroxide. The resulting mixture is warmed to 80-150C for 1-8 h. The reaction mixture is then added water at 0C or a mixture of water and ice. The cooled mixture is extracted with ether or other lipophilic organic solvent. The organic extracts may be washed with brine and then dried over a suitable desiccant (e.g. magnesium sulfate anh. or sodium sulfate anh.). The mixture is then filtered. Removal of the organic solvent furnishes among other products the separable E isomer of endoxifen phosphate.

**[00170]** Example 10. Endoxifen valine ester t-butyl carbamate ((S,E)-4-(1-(4-(2-(tert-butoxycarbonyl(methyl)amino)ethoxy)phenyl)-2-phenylbut-1-enyl)phenyl 2-(tert-butoxycarbonylamino)-3-methylbutanoate)



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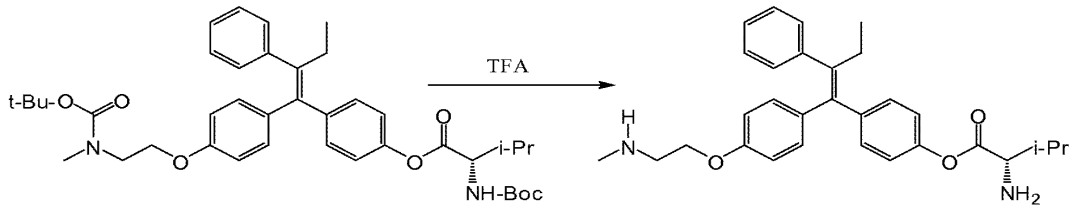

**[00171]** A. Endoxifen is dissolved in dichloromethane or other suitable organic solvent. To this solution is added triethyl amine or other suitable base. This solution may be cooled. To this solution is added Boc-O-Boc. The mixture is stirred for 1-12 h, at which time the reaction is quenched by addition of aqueous sodium bicarbonate or other quenching reagent. The mixture is then washed with dilute HCl (aq.). The mixture is then extracted with ethyl acetate or other suitable organic solvent. The combined organic extracts are then dried over a suitable desiccant (e.g. magnesium sulfate anh.). The mixture is then filtered and the organic solvent removed to furnish among other things N-Boc-endoxifen.

**[00172]** B. The product of the previous step is dissolved in dichloromethane or other suitable organic solvent. To this solution is added triethyl amine or other suitable base. This solution may be cooled. To this solution is added an activated form of N-Boc-valine (e.g. O-t-butyloxycarbonyl valine). The mixture is stirred for 1-12 h, at which time the reaction is quenched by addition of aqueous sodium bicarbonate or other quenching reagent. The mixture is then washed with dilute HCl (aq.) The mixture is then extracted with ethyl acetate or other suitable organic solvent. The combined organic extracts are then dried over a suitable desiccant (e.g. magnesium sulfate anh.). The mixture is then filtered and the organic solvent removed to furnish among other products bis-N-Boc-endoxifen valine ester.



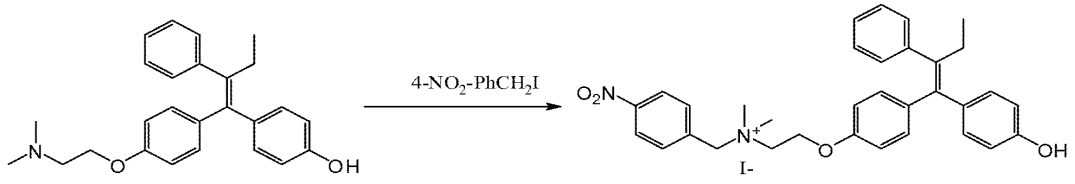
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**[00173]** Example 11. Endoxifen Valine ester ((S,E)-4-(1-(4-(2-(methylamino)ethoxy)phenyl)-2-phenylbut-1-enyl)phenyl 2-amino-3-methylbutanoate)




**[00174]** The product from example 3 is dissolved in dichloromethane or other suitable organic solvent. This solution may be cooled. To this solution is added trifluoroacetic acid. This mixture is stirred for 1-12 h, at which time the reaction is quenched by addition of aqueous sodium bicarbonate or other quenching reagent. The mixture is then extracted with ethyl acetate or other suitable organic solvent. The combined organic extracts are then dried over a suitable desiccant (e.g. magnesium sulfate anh.). The mixture is then filtered and the organic solvent removed to furnish among other products the separable E isomer of endoxifen valine ester.

**[00175]** Example 12. N-(4-nitrobenzyl)-4-hydroxy-tamoxifen iodide ((Z)-2-(4-(1-(4-hydroxyphenyl)-2-phenylbut-1-enyl)phenoxy)-N,N-dimethyl-N-(4-nitrobenzyl)ethanaminium iodide)



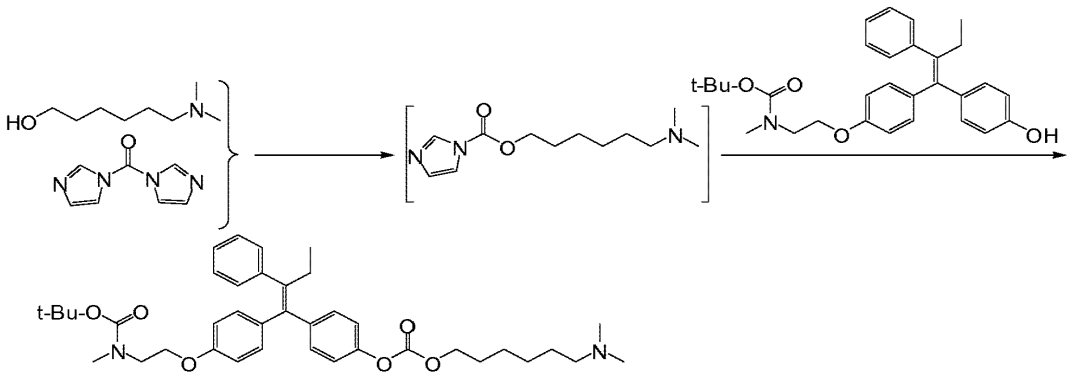

**[00176]** 4-Hydroxy-tamoxifen is dissolved in toluene or other suitable organic solvent. To this mixture is added an alkylating agent such as 4-nitrobenzyl iodide. This mixture may be heated. After starting material is completely consumed, volatile



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organics are removed to afford among other products the separable Z isomer of N-(4-nitrobenzyl)-4-hydroxy-tamoxifen iodide.

**[00177]** Example 13. Endoxifen-(6-N,N-dimethylamino)-1-hexyl carbonate t-butyl carbamate ((E)-tert-butyl 2-(4-(1-(4-((6-(dimethylamino) hexyloxy)carbonyloxy)phenyl)-2-phenylbut-1-enyl)phenoxy)ethyl(methyl)carbamate)

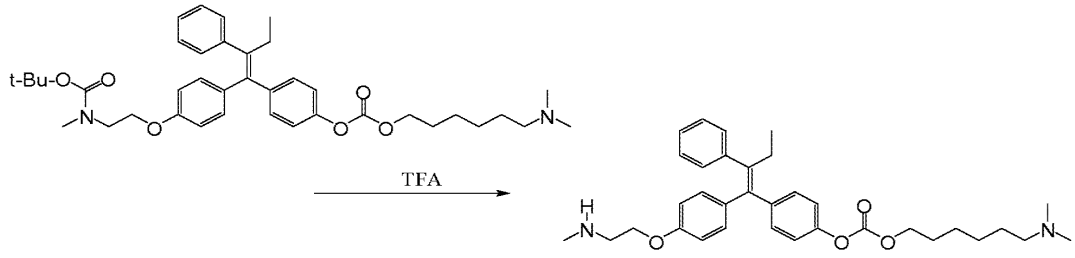



**[00178]** 6-(N,N-dimethylamino)-1-hexanol is dissolved in dichloromethane or other suitable organic solvent. To this solution may be added triethyl amine or other suitable base. This solution may be cooled. To this solution is added carbonyl diimidazole or other suitable phosgene equivalent or phosgene. The mixture is stirred for 1-12 h, at which time N-Boc-endoxifen (product of example 10, step A). The mixture is then stirred for 1-12 h. The reaction is quenched by addition of aqueous sodium bicarbonate or other quenching reagent. The mixture is then washed with dilute HCl (aq.). The mixture is then extracted with ethyl acetate or other suitable organic solvent. The combined organic extracts are then dried over a suitable desiccant (e.g. magnesium sulfate anh.). The mixture is then filtered and the organic solvent removed to furnish among other things N-Boc-endoxifen (6-N,N-dimethylamino)-1-hexyl carbonate.

**[00179]** Example 14. Endoxifen-(6-N,N-dimethylamino)-1-hexyl carbonate ((E)-6-(dimethylamino)hexyl 4-(1-(4-(2-(methylamino)ethoxy)phenyl)-2-phenylbut-1-enyl)phenyl carbonate)

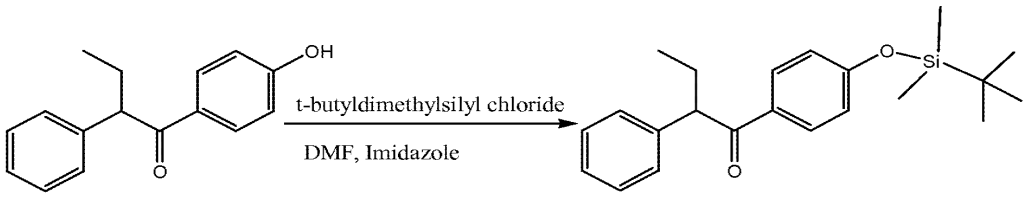


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**[00180]** The product from example 13 is dissolved in dichloromethane or other suitable organic solvent. This solution may be cooled. To this solution is added trifluoroacetic acid. This mixture is stirred for 1-12 h, at which time the reaction is quenched by addition of aqueous sodium bicarbonate or other quenching reagent. The mixture is then extracted with ethyl acetate or other suitable organic solvent. The combined organic extracts are then dried over a suitable desiccant (e.g. magnesium sulfate anh.). The mixture is then filtered and the organic solvent removed to furnish among other products the separable E and Z isomers of endoxifen 6-N,N-dimethylamino)-1-hexyl carbonate.

**[00181]** Example 15. Ketone **2.**




**1** **2**

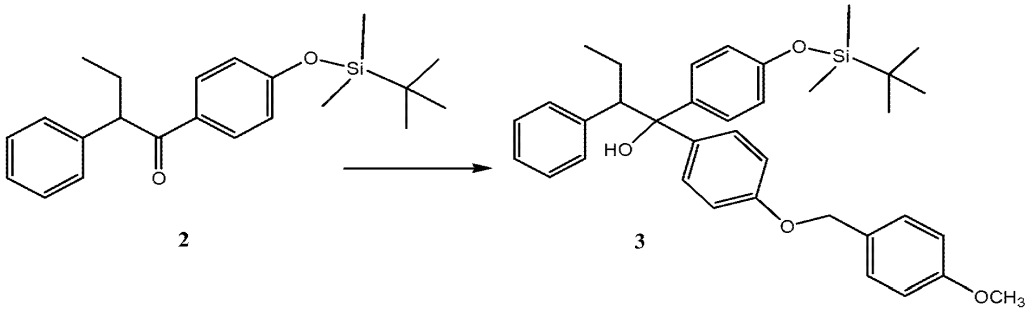
**[00182]** Phenol **1** (10g, 0.041 moles) was dissolved in dry DMF (40 ml) at room temperature under $N_2$. Imidazole (5.67g, 0.083 moles) was added followed by tert-butyldimethylsilyl chloride ( 6.91g, 0.0458 moles). The reaction was stirred for 2 hours, added to saturated sodium chloride solution (200 ml) and extracted with ethyl acetate (250 ml). The ethyl acetate layer was separated, washed 3 times with NaCl solution (100 ml), separated, dried over sodium sulfate, filtered through a small pad of silica gel with the aid of ethyl acetate, and concentrated to give 14 grams (95%) of a



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brown viscous oil containing ketone **2** among other products. A TLC system of ethyl acetate/hexanes (3:7) was used to follow the progress of the reaction.

**[00183]** Example 16. Adduct **3**.



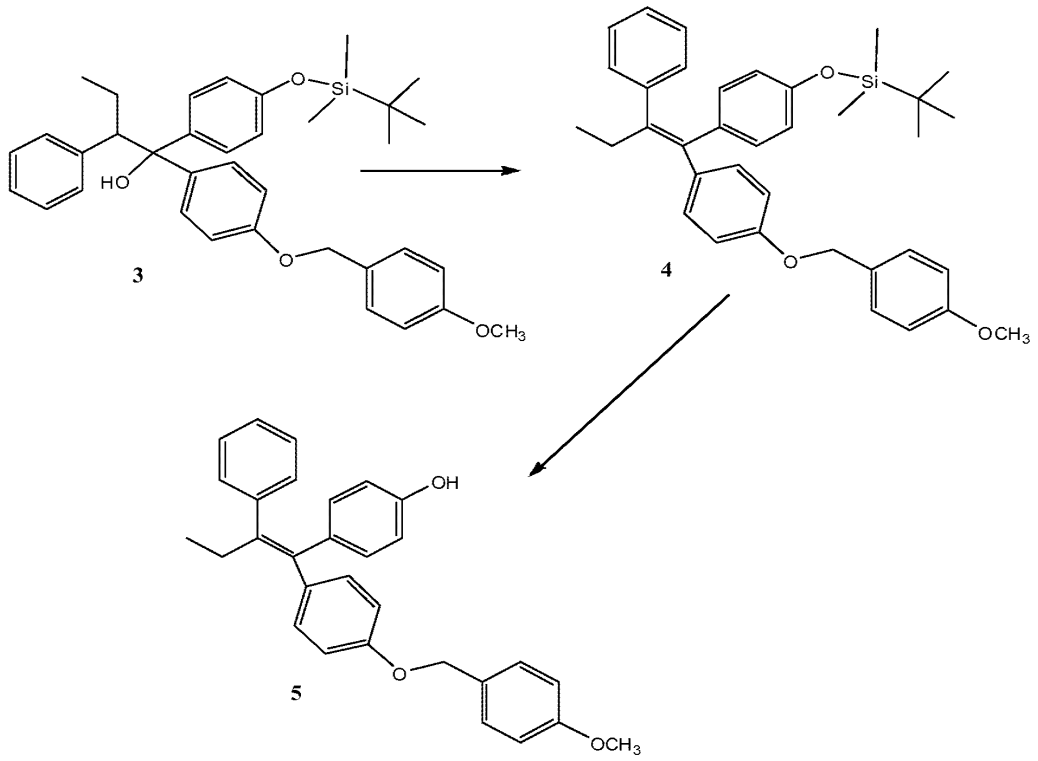

2 3

**[00184]** Ketone **2** ( 2.75g, 7.76 mmoles) was dissolved in dry THF (20 ml) at room temperature under $N_2$. Anhydrous $CeCl_3$ (2.3g, 9.33 mmoles) was added and the suspension stirred for 5 hours. 4-Bromophenol-p-methoxybenzyl ether (2.73g, 9.32 mmoles) was dissolved in dry THF (35 ml) in a separate flask and cooled to -78°C (forming a paste at this temperature) under $N_2$. Addition of n-butyllithium (3.73 ml, 2.5M in hexanes, 9.32 mmoles) dropwise in 10 minutes to 4-Bromophenol-p-methoxybenzyl ether gave a homogeneous solution which was stirred for 40 minutes. This solution was added via cannula to the $CeCl_3$-ketone **2** suspension which had been cooled to -10°C. The reaction mixture was allowed to warm to rt and stirred for 16 hours. The reaction was quenched with 1N aqueous HCl solution and extracted with MTBE (2 x 100 ml). The organic layer was separated, dried over sodium sulfate, filtered, concentrated, and purified by flash chromatography. Purification using ethyl acetate/hexanes gave 2.55 g (58%) of a light yellow foam containing adduct **3** among other products.

**[00185]** Example 17. Phenol **5**.



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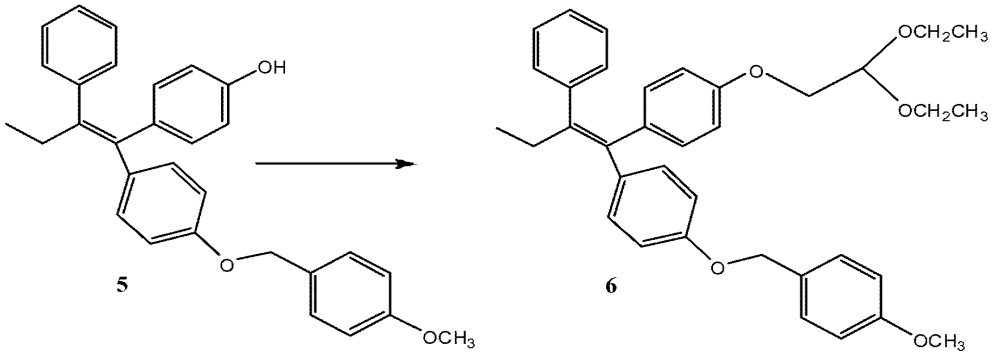



**[00186]** Adduct **3** (2.3g, 4.05 mmoles) was dissolved in ethanol (25 ml) at rt. PPTS ( 0.31g, 1.19 mmoles) was added and the reaction stirred for 17 hours at rt giving predominantly a mixture of (55:45) E/Z olefins with the tert-butyldimethyl silyl group still attached. Ethanol was evaporated and the crude redissolved in dry THF (20 ml). Tetra-n-butyl ammonium fluoride solution (1M in THF, 8.1 mmoles) was added. The reaction was stirred for 1 hour at room temperature, the THF evaporated, and the crude purified by flash silica chromatography using ethyl acetate/hexanes to give 1.7 g (93%) of phenol **5** as a light yellow viscous oil containing E and Z isomers among other products.

**[00187]** Example 18. Ether **6**.

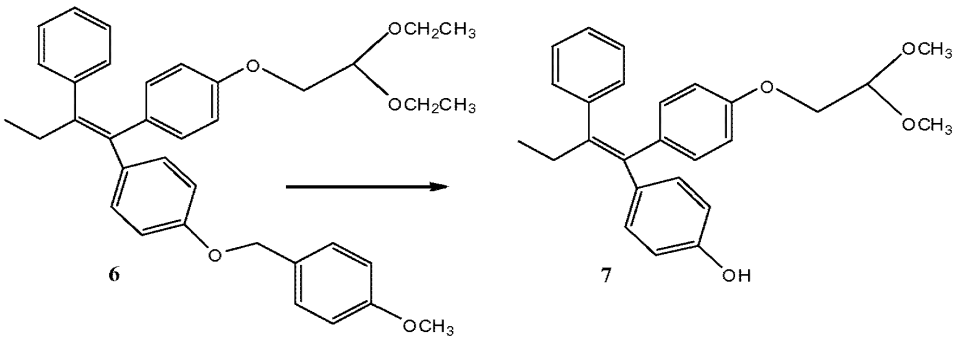


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**[00188]** Phenol **5** (1.69g, 3.87 mmoles) was dissolved in dry DMF (14 ml). The solution was cooled to 0°C under $N_2$ and NaH (0.193g, 4.82 mmoles) was added. After 30 minutes, bromoacetaldehyde diethyl acetal (0.80g, 4.06 mmoles) was added and the reaction mixture heated at 55°C for 20 hours. The reaction was cooled, added to saturated NaCl solution (50 ml), and extracted with ethyl acetate (75 ml). The organic layer was separated, washed 3 times with saturated NaCl solution (50 ml), dried over sodium sulfate, filtered, and concentrated. Purification by flash chromatography using ethyl acetate/hexanes gave 1.86g (87%) of ether **6** as a light yellow oil containing E and Z isomers among other products.

**[00189]** Example 19. Phenol **7**.



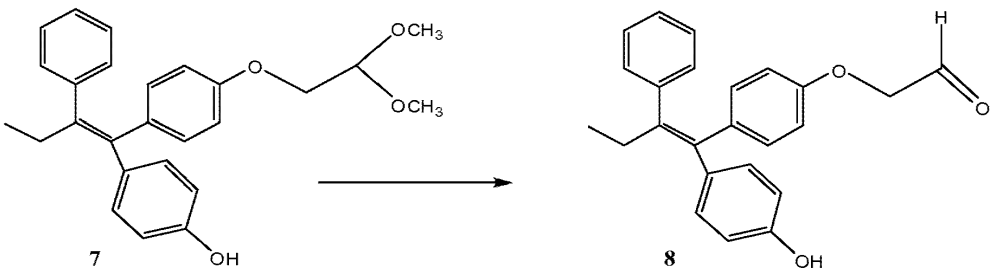

**[00190]** To ether 6 (2.0g, 3.62 mmoles) dissolved in dry methanol (90 ml) was added 0.3g of camphorsulfonic acid. The reaction was heated at reflux for 16 hours,



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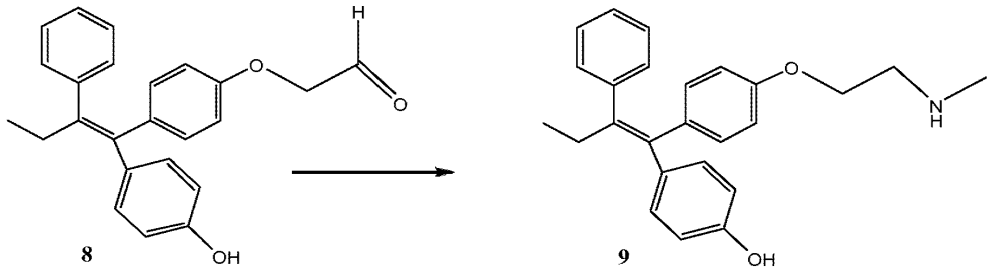
cooled, and concentrated. The crude was partitioned between ethyl acetate (50 ml) and water (50 ml), the organic layer separated, dried over sodium sulfate, filtered, and evaporated. Purification by flash chromatography using ether/hexanes gave 1.50 grams (approx 100%) of phenol **7** as a light yellow oil containing E and Z isomers among other products.

**[00191]** Example 20. Aldehyde **8**.




**[00192]** Phenol **7** (1.69g, 4.18 mmoles, calculated for dimethyl acetal) was dissolved in THF (18 ml) at room temperature. 3M HCl (18 ml) was added. The reaction was heated at 50°C for 17 hours. After cooling, the reaction mixture was added to ethyl acetate (50 ml), the organic layer separated, dried over sodium sulfate, filtered and concentrated to give 1.59 g of crude aldehyde **8** containing E and Z isomers among other products.

**[00193]** Example 21. Endoxifen (**9**).

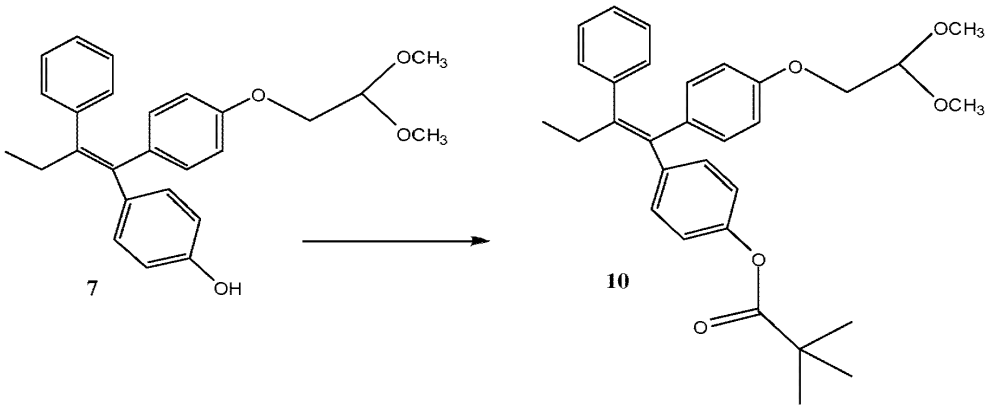





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**[00194]** Aldehyde **8** (0.872g, 2.43 mmoles) was dissolved in dry THF (6 ml) at room temperature. $MgSO_4$ (6g) was added, followed by methylamine (2.67 ml, 5.34 mmoles, 2.0M solution in THF). The reaction was stirred for 16 hours, filtered, and concentrated. The crude imine was redissolved in anhydrous ethanol (20 cc) and the solution cooled to 0°C. $NaBH_4$ (0.11g) was added portionwise, the reaction mixture stirred for 1 hour with warming to rt. Water was added and the mixture was extracted with ethyl acetate (50 ml). The organic layer was separated, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography using $CH_2Cl_2$/methanol/aqueous $NH_3$ and to yield 0.150 g of a light pink foam containing an (E/Z) mixture of endoxifen (**9**).

**[00195]** Example 22. Ester **10**.

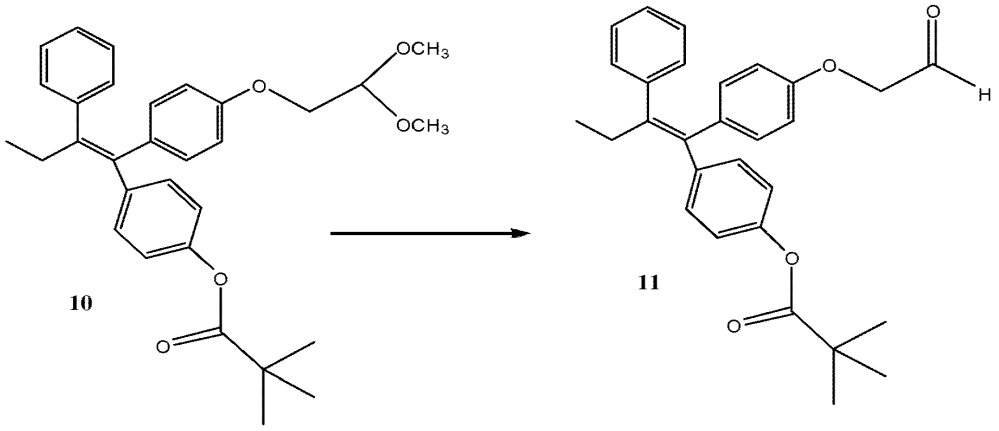



**[00196]** Phenol **7** (0.414g, 1.02 mmoles) and dimethylaminopyridine ( 0.226, 1.85 mmoles) was dissolved in dry dichloromethane (10 ml) and the solution cooled to 0°C under $N_2$. Pivaloyl chloride (0.21g, 1.73 mmoles) was added dropwise via syringe and the reaction was then allowed to warm to room temperature. After 6 hours, 1N aqueous HCl was added and additional dichloromethane (50 ml) was added. The organic layer was separated, dried over $Na_2SO_4$, filtered, and concentrated. Purification by flash chromatography using ethyl acetate/hexanes gave 0.32 grams of ester **10** as a light yellow oil containing E and Z isomers among other products.



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**[00197]** Example 23. Aldehyde **11**.

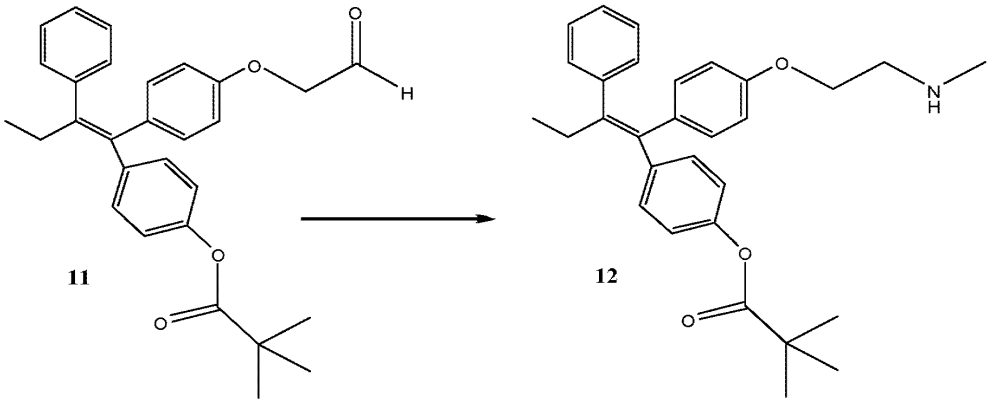



**[00198]** Dimethyl acetal **10** (0.32g, 0.63 mmoles) was dissolved in 10 ml of THF at room temperature. 6 ml of 3N HCl was added and the reaction mixture heated at 45-50°C for 15 hours. After cooling, the mixture was added to water and ethyl acetate (1:1, 50 ml). The organic layer was separated, dried over $Na_2SO_4$, filtered, and concentrated to give 0.23 grams of crude aldehyde **11** as a light yellow oil containing E and Z isomers among other products.

**[00199]** Example 24. Pivalate ester **12**.



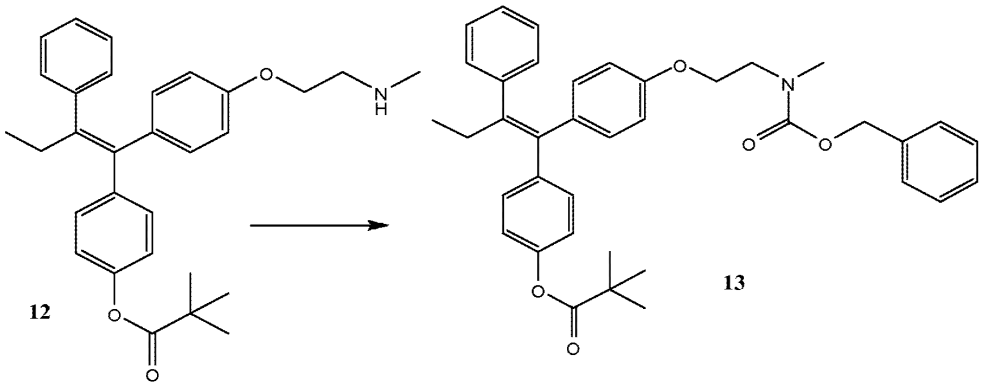
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11 12

**[00200]** Aldehyde **11** (0.273g, 0.52 mmoles) was dissolved in dry THF (10 ml) at rt. $MgSO_4$ (1.33g) was added, followed by methylamine (0.52 ml, 1.04 mmoles, 2.0M solution in THF). The reaction was stirred for 16 hours, filtered, and concentrated. The crude imine was redissolved in anhydrous ethanol (10 cc) and the solution cooled to 0°C. $NaBH_4$ (0.02g) was added, the reaction mixture stirred for 1 hour with warming to rt. Water was added and the mixture extracted with ethyl acetate (20 ml). The organic layer was separated, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography using $CH_2Cl_2$/methanol/aqueous $NH_3$ and gave 0.07 g of pivalate ester **12** as a light pink oil containing a mixture (E/Z) isomers among other products.

**[00201]** Example 25. Ester **13**.



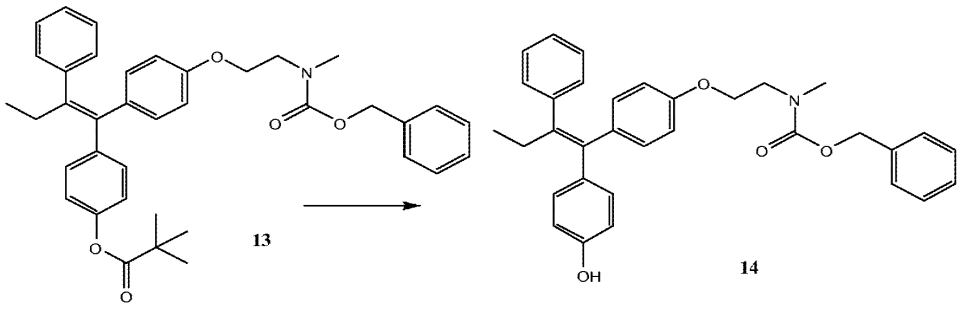
12 13



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**[00202]** Pivalate ester **12** (E/Z mixture) (0.059g, 0.128 mmoles) was dissolved in 1 ml of THF. Aqueous NaOH (2M, 96 µl) was added and the reaction mixture cooled to 0°C. Benzyl chloroformate (0.033g, 0.19 mmoles) was added. The reaction was allowed to warm to rt and, when determined to be complete by tlc, added to water (10 ml) and extracted with ethyl acetate (20 ml). The organic layer was washed with saturated aqueous sodium bicarbonate solution, separated, dried over $MgSO_4$, filtered through a small pad of silica with the aid of ethyl acetate and concentrated to give 81 mg of a light yellow oil **13**. Crude **13** was used without further purification.

**[00203]** Example 26. Compound **14**.

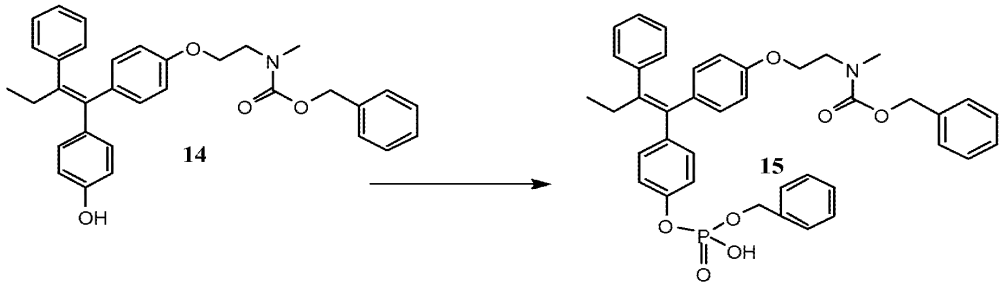



**[00204]** Carbamate **13** (0.081g, 0.13 mmoles) was dissolved in 4 ml of dry THF. The solution was cooled to 0°C under $N_2$. $LiAlH_4$ (0.026g, 0.70 mmoles) was added. The reaction mixture was stirred for 30 minutes and then water (39 µl) added. The mixture was filtered through celite with the aid of THF (15 ml) and ethyl acetate (15 ml). The filtrate was dried over $MgSO_4$, filtered, and concentrated to give 45 mg of **14**.

**[00205]** Example 27. Compound **15**.

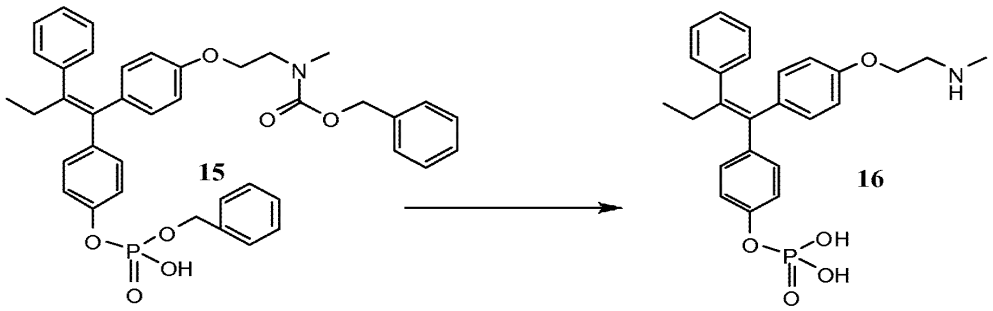


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**[00206]** Phenol **14** was dried prior to reaction by treatment with 3 x 10 ml of dry acetonitrile followed by rotary evaporation. The phenol **14** (0.045g, 0.087 mmoles) was then dissolved in dry acetonitrile (1.5 ml) and then cooled to -10°C under $N_2$. $CCl_4$ (0.068g, 0.44 mmoles) was added and the suspension stirred for 10 minutes. Hunig's base ( 0.024g, 0.18 mmoles) and N,N-dimethylaminopyridine (1 mg) were added. After 1 minute, dibenzyl phosphate (0.034g, 0.12 mmoles) was added. Stirring was continued for 1 hour and 15 minutes, then aqueous $KH_2PO_4$ solution (1 ml, 0.5M) was added, the mixture warmed to rt and extracted with ethyl acetate (25 ml). The organic layer was separated, dried over $Na_2SO_4$, filtered, and concentrated to give crude **15**. Purification by flash chromatography using dichloromethane/methanol 9:1 gave 20 mg of **15**.

**[00207]** Example 28. Compound **16**.




**[00208]** Phosphate **15** (0.040g, 0.052 mmoles) is dissolved in 20 ml of ethanol. Pd on carbon (10%, 30 mg) is added. The mixture is hydrogenated at rt and 40 psi for



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5 hours. The catalyst is removed by filtration through celite and the filtrate concentrated to give **16**.

**[00209]** The invention described and claimed herein is not to be limited in scope by the specific embodiments herein disclosed since these embodiments are intended as illustrations of several aspects of the invention. Any equivalent embodiments are intended to be within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described therein will become apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. All publications cited herein are incorporated by reference in their entirety.

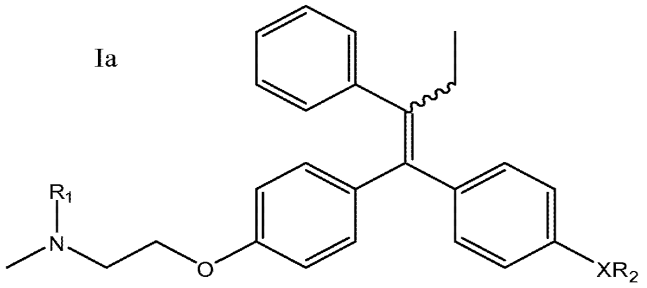


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CLAIMS

1. A compound of the following formula Ia:

Ia




and pharmaceutically acceptable salts thereof, wherein

X is O or S;

$R_1$ is H, $CH_3$, a lower alkyl group, a divalent cyclic alkyl (either replacing the existing methyl group or forming a quaternary ammonium), or a prodrug moiety;

$R_2$ is H or a prodrug moiety;

with the proviso that at least one of $R_1$ and $R_2$ is a prodrug moiety, and

with the proviso that when $R_1$ is $CH_3$, $XR_2$ is not $OPO_3H_2$,

wherein the wavy bond indicates unspecified stereochemistry for the ethyl and phenyl substituents, such that the structure has either an E or Z configuration around the double bond.

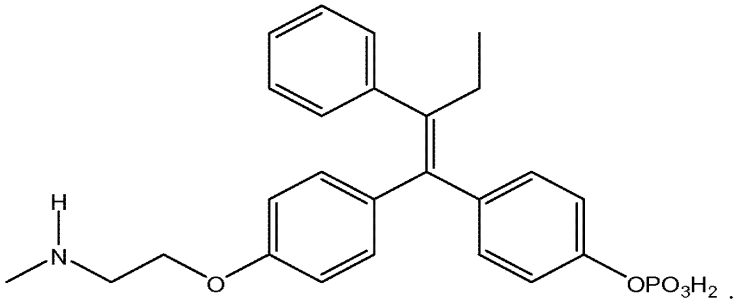
2. A compound according to claim 1, wherein $R_1$ is independently selected from amides and carbamates, N-acyloxyalkyl derivatives, N-acylalkoxy carbonyl derivatives, beta-aminoketones, (oxodioxolenyl)methyl derivatives, N-Mannich bases, imines (Schiff bases), enamines and enaminones, azo compounds, lactonization systems, THTT, redox systems, and PEG.



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3. A compound according to any of claims 1-2, wherein X is O, and $R_2$ is independently selected from the group consisting of esters, carbonate esters, phosphate esters, diphosphate esters, triphosphate esters, ethers, and alpha-acyloxyalkyl ethers.

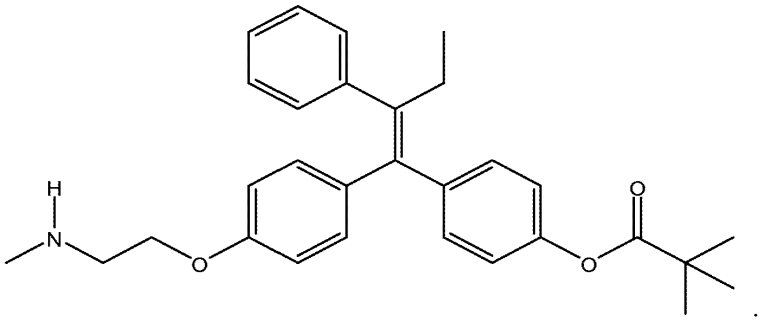
4. A compound according to any of claims 1-3, wherein the compound is




.

5. A compound according to any of claims 1-3, wherein $XR_2$ is a pivalate ester.

6. A compound according to any of claims 1-3, wherein the compound is




.

7. A compound according to any of claims 1-6, wherein the compound is capable of being metabolized *in vivo* in a human to produce endoxifen.



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8. Use of a compound according to any of claims 1-7 for the manufacture of a medicament for the treatment of breast cancer.

9. A composition comprising a compound according to any of claims 1-7 and a pharmaceutically acceptable carrier, wherein the composition includes the E isomer, or the Z isomer, or an equimolar or non-equimolar mixture of E and Z isomers.

10. A composition according to claim 9, wherein the physical form of the compound is selected from the group consisting of an anhydrous form, a single crystalline form, a mixture of polymorphic forms, a hydrated form, and mixtures thereof.

11. A method of treating breast cancer in a human in need thereof comprising administering a compound according to any of claims 1-7 to said human.

12. A method according to claim 11, wherein the human is female.

13. A method according to claim 11, wherein the female is non-responsive to treatment with tamoxifen.

14. The method according to claim 13, wherein non-responsiveness is determined by a method selected from the group consisting of liver enzyme assay, genotyping Cyp2D6 for one or more copies of a partly or completely defective allele, detecting the presence, absence, or levels of endoxifen in biological fluids, determining if the patient is taking drugs that interfere with tamoxifen metabolism, and combinations thereof.



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15. The method according to claim 13, wherein non-responsiveness is determined by an assay of Cyp2D6 activity.

16. The method according to any of claims 11-15, further comprising administration of one or more additional compounds.

17. The method according to claim 16, wherein the one or more additional compounds is selected from the group consisting of 4-hydroxytamoxifen or a prodrug thereof, wherein the prodrug thereof is optionally within Formula I, wherein following administration, the mixture produces an *in vivo* ratio of endoxifen to 4-hydroxytamoxifen that is similar to the ratio of endoxifen to 4-hydroxytamoxifen produced *in vivo* following administration of tamoxifen to a patient that is responsive to tamoxifen, wherein the method is for the treatment of breast cancer or for the reduction in severity or rate of recurrence of breast cancer in patients previously treated for breast cancer.

18. The method according to any of claims 11-17, wherein the breast cancer is ER-positive.

19. The method according to any of claims 11-18, wherein the human is concurrently being administered a selective serotonin reuptake inhibitor or a monoamine oxidase inhibitor.



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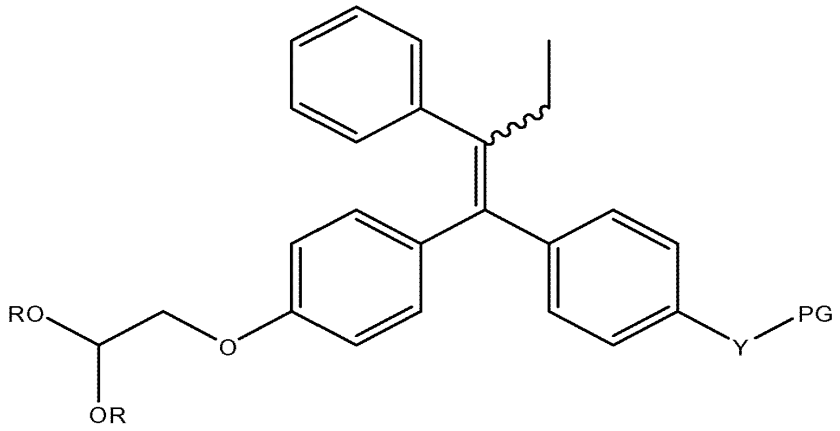
20. The method according to any of claims 11-19, wherein the dose of compound is bioequivalent to an oral tamoxifen dose of between about 2 to about 40 mg per day.

21. The method according to claim 20, where bioequivalence is determined by serum level assay.

22. A method of reducing the rate or severity of recurrence of breast cancer in a human previously treated for breast cancer comprising administering a compound according to any of claims 1-7 to said human.

23. The method according to claim 22, further comprising administration of one or more additional active agents.

24. A compound of Formula II:




wherein the two OR groups form an acetal, or the R groups optionally form a ring;

wherein Y is an oxygen or sulfur atom;

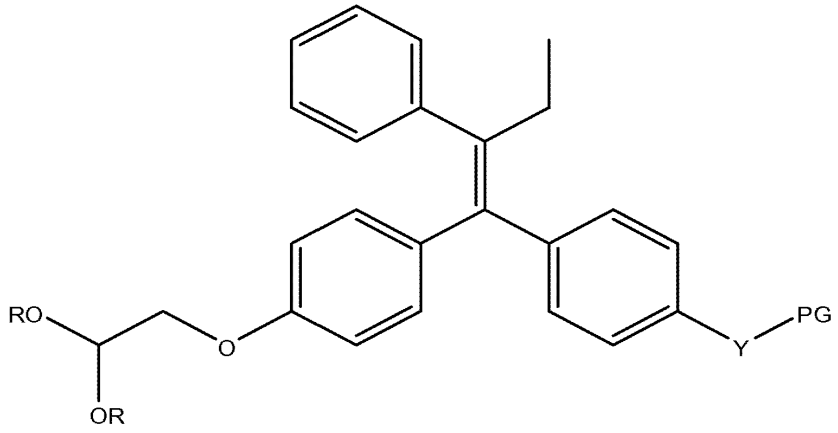
wherein PG is a hydrogen atom or a protecting group; and



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wherein the wavy bond indicates unspecified stereochemistry for the ethyl and phenyl substituents, such that the structure has either an E or Z configuration around the double bond.

25. A compound according to claim 24, wherein the compound is a compound of Formula IIa:




wherein the two OR groups form a dimethyl or diethyl acetal;
Y is oxygen; and
PG is selected from a 4-methoxybenzyl group or a pivalate group.

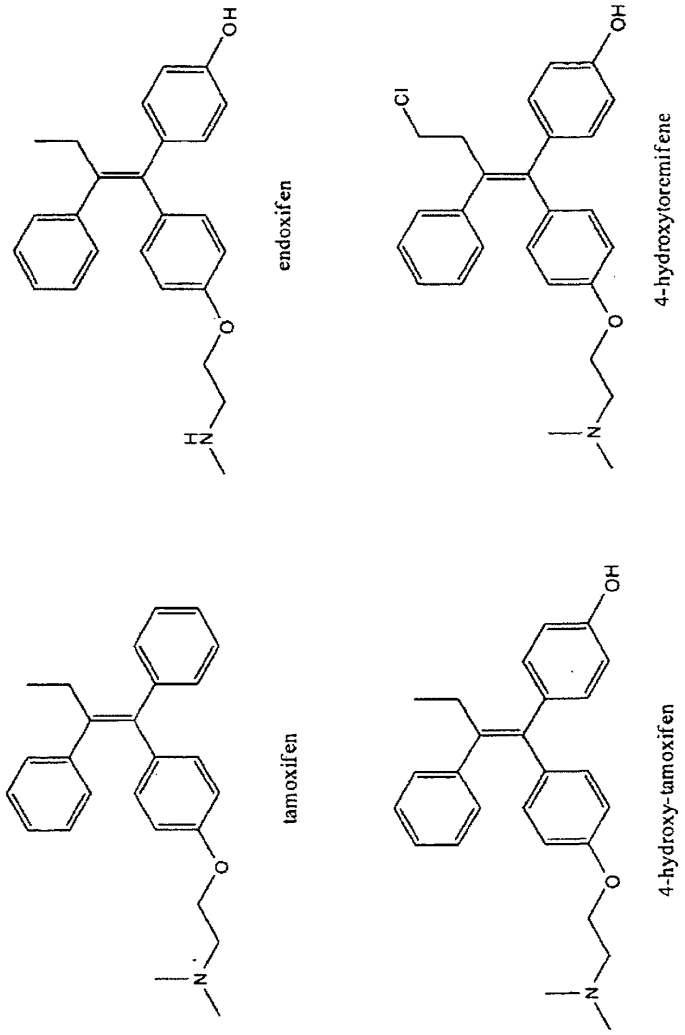
26. A compound according to claim 25, wherein PG is pivalate.

27. Use of a compound according to any of claims 24-26 for the synthesis of an anticancer agent.



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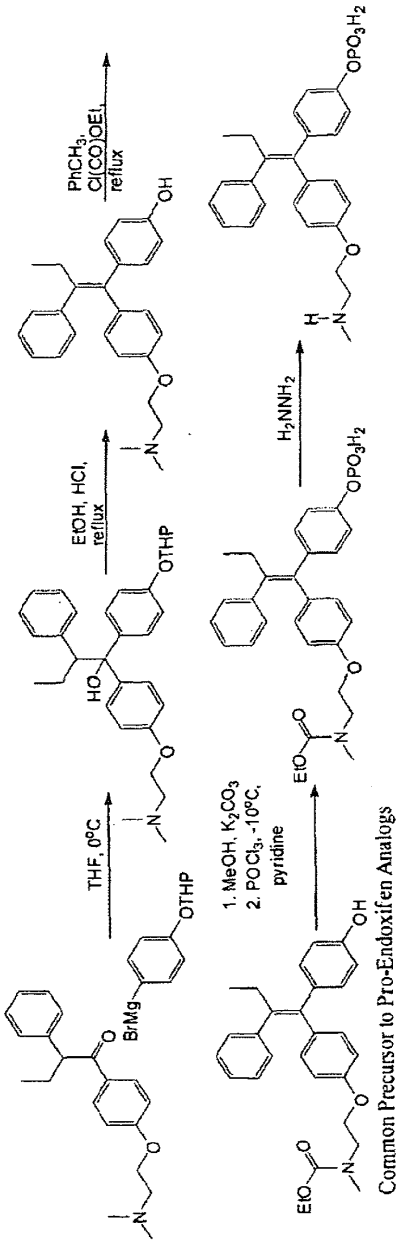
FIGURE 1






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FIGURE 2



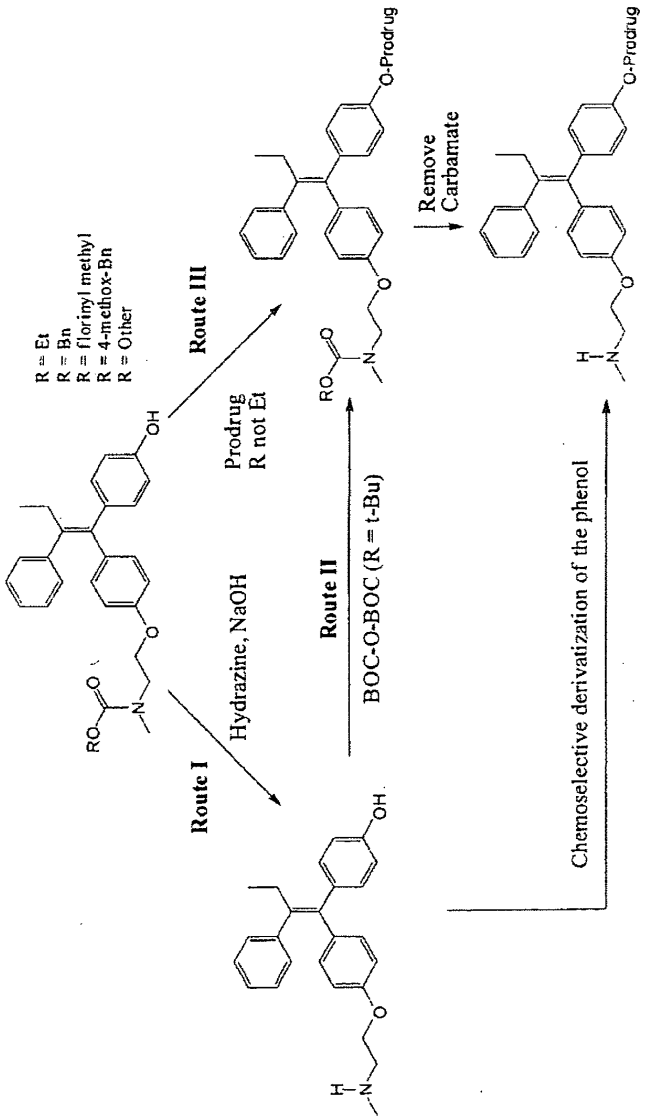



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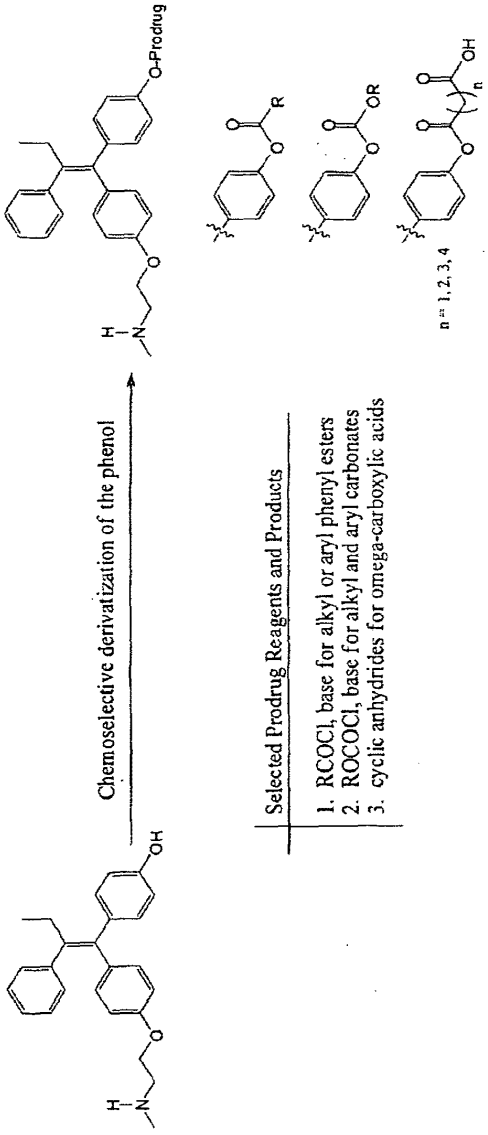
FIGURE 3



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FIGURE 4



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FIGURE 5

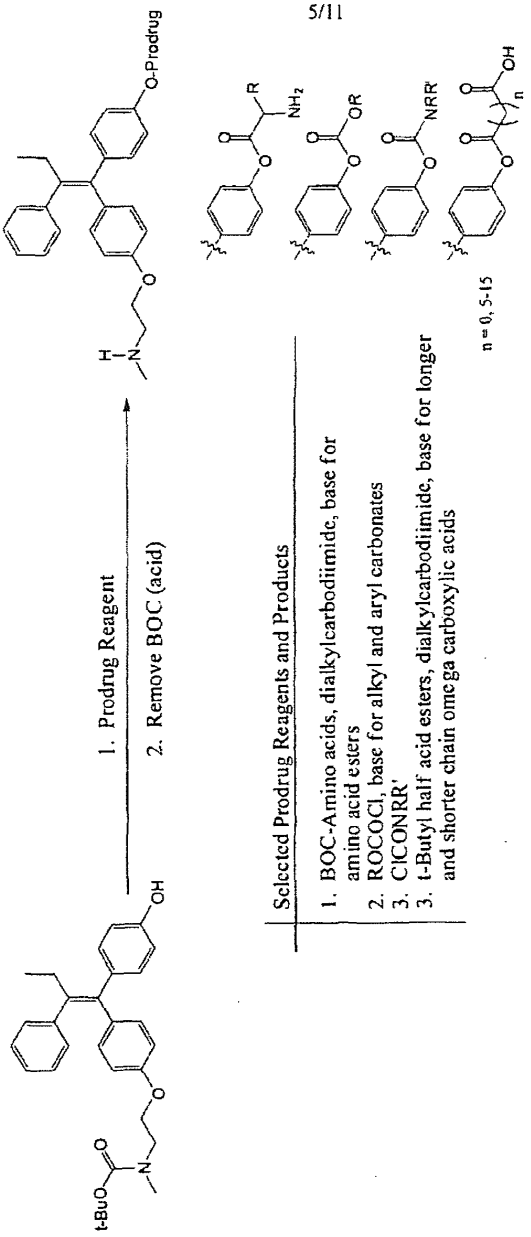


FIGURE 6




Notes:

1. R groups are selected to compliment the mildly acidic cleavage conditions of the BOC protecting group used in Route II
2. Benzyloxy carbonyls (CBZ) are cleaved reductively and nucleophilically
3. Florinylmethyl oxycarbonyls (FMOC) are cleaved under basic conditions
4. 4-OMeBOC carbamates are cleaved under acidic or oxidative conditions

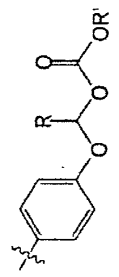




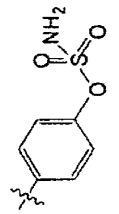
SUBSTITUTE SHEET (RULE 26)

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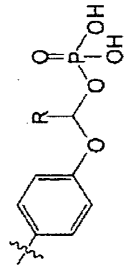
FIGURE 7



methyl (R = H) or ethylene carbonates



sulfamate ester



phosphonooxylmethyl (R = H) or ethyl (R = Me)



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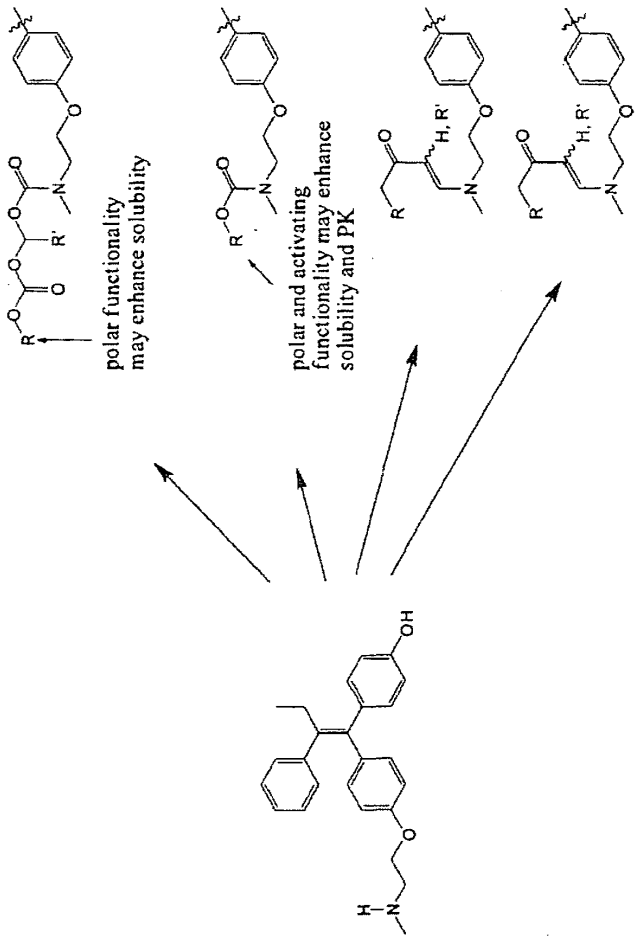



FIGURE 8



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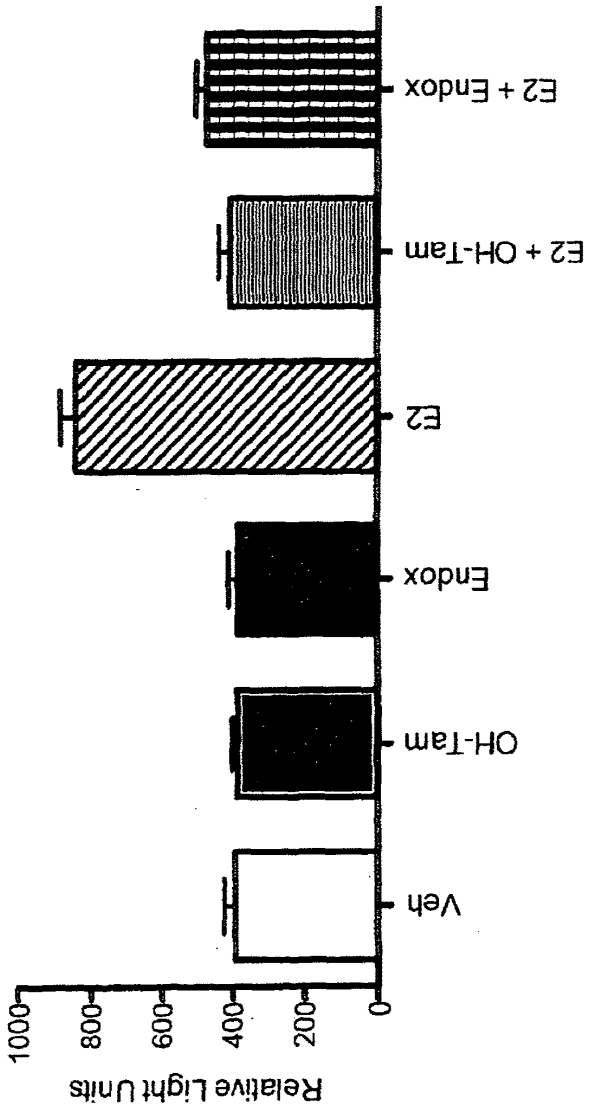
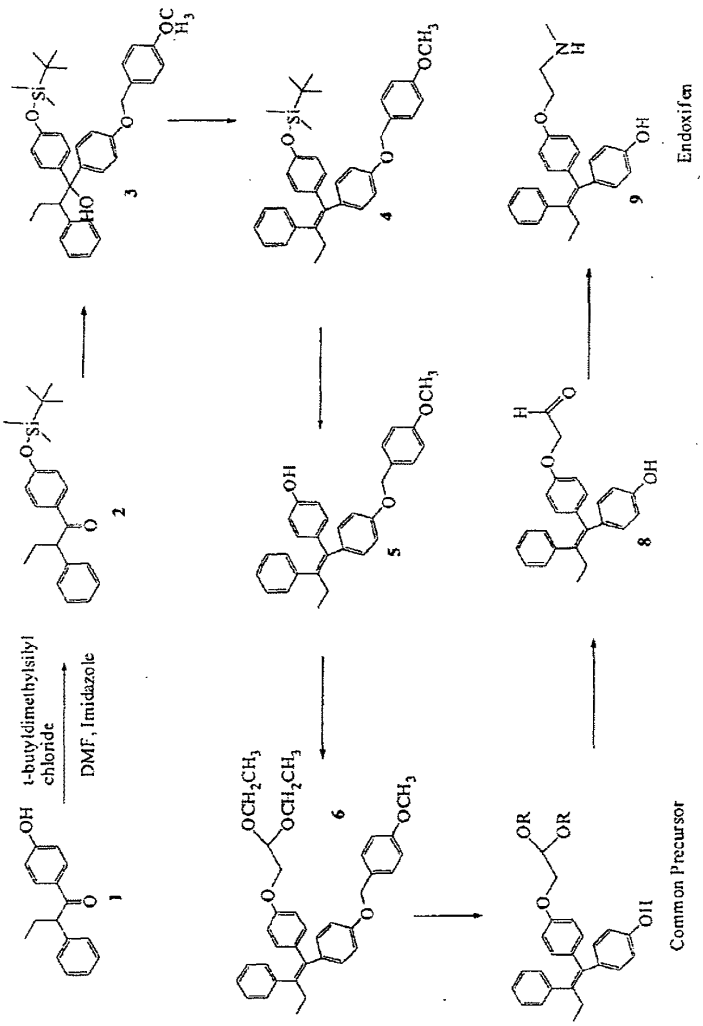



FIGURE 9



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FIGURE 10






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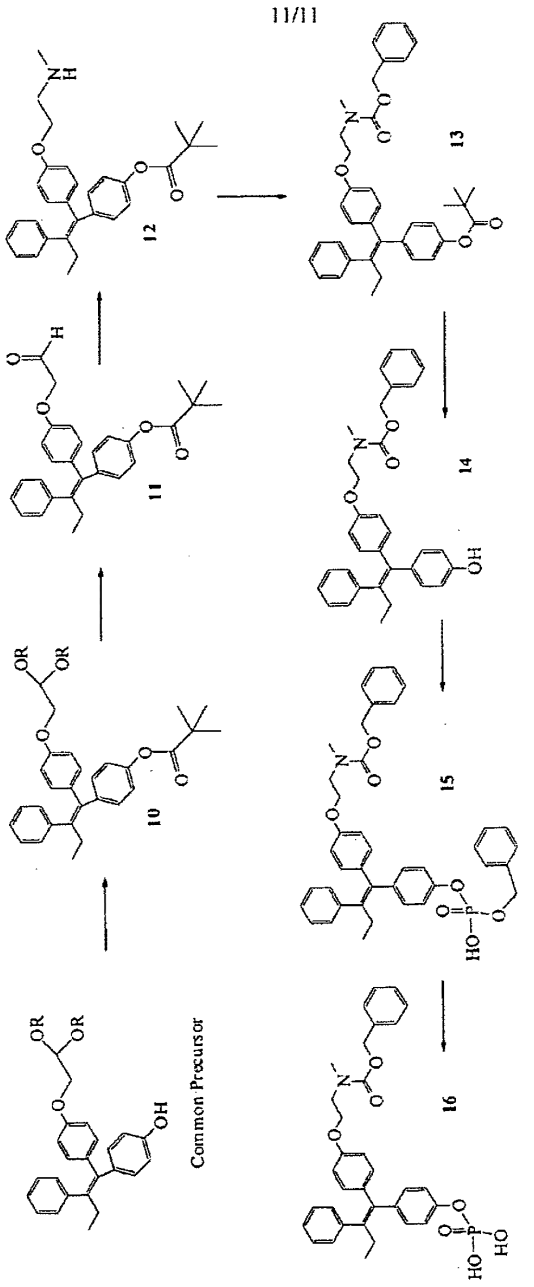



FIGURE 11

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: JUAN ZHENG
CHRISTENSEN O'CONNOR JOHNSON
KINDNESS PLLC
1201 THIRD AVENUE, SUITE 3600
SEATTLE, WA 98101

# PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

| | |
|---|---|
| | Date of mailing *(day/month/year)* 04 JAN 2019 |
| Applicant's or agent's file reference ATGI167262 | **FOR FURTHER ACTION** See paragraphs 1 and 4 below |
| International application No. PCT/US 18/50193 | International filing date *(day/month/year)* 10 September 2018 (10.09.2018) |
| Applicant ATOSSA GENETICS INC. | |

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   **Filing of amendments and statement under Article 19:**
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   **When?** The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   **How?** Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   **For more detailed instructions,** see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **22 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

| | |
|---|---|
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-8300 | Authorized officer<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>Telephone No. PCT OSP: 571-272-7774 |

Form PCT/ISA/220 (July 2014)

PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference ATGI167262 | FOR FURTHER ACTION | see Form PCT/ISA/220 as well as, where applicable, item 5 below. |
|---|---|---|
| International application No. PCT/US 18/50193 | International filing date *(day/month/year)* 10 September 2018 (10.09.2018) | (Earliest) Priority Date *(day/month/year)* 11 September 2017 (11.09.2017) |
| Applicant ATOSSA GENETICS INC. | | |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

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

☒ the text is approved as submitted by the applicant.

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

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

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. 2D

☒ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

**INTERNATIONAL SEARCH REPORT**

International application No.
PCT/US 18/50193

**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.: 5-26, 30
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:

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.:

**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.

**INTERNATIONAL SEARCH REPORT**

International application No.
PCT/US 18/50193

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/138; A61K 9/00 (2018.01)
CPC - A61K 31/138; A61K 9/0034; A61K 9/0036; A61K 9/02; A61K 9/2018

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
See Search History Document

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<br>--<br>Y | US 4,851,433 A (Kraus) 25 July 1989 (25.07.1989); col 1, ln 39-41, col 2, ln 66-67, col 3, ln 42-44, col 4, ln 20-25, 58-59 | 1, 3, 4/(1, 3)<br>---<br>2, 4/2 |
| X | WO 2016/168021 A1 (ATOSSA GENETICS, INC) 20 October 2016 (20.10.2016); para [0080], [0084], [0189], [0305], [0310], [0313], claim 37 | 27-29 |
| Y | US 2008/0138391 A1 (Carrara et al.) 12 June 2008 (12.06.2008); para [0066], [0072], [0078] | 2, 4/2 |
| A | US 2014/0199391 A1 (API Genesis, LLC) 17 July 2014 (17.07.2014); entire document | 1-4, 27-29 |

☐ 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 | Date of mailing of the international search report |
|---|---|
| 12 December 2018 | 04 JAN 2019 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-8300 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

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

# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: JUAN ZHENG
CHRISTENSEN O'CONNOR JOHNSON
KINDNESS PLLC
1201 THIRD AVENUE, SUITE 3600
SEATTLE, WA 98101

# PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 04 JAN 2019 |
| Applicant's or agent's file reference<br>ATGI167262 | **FOR FURTHER ACTION**<br>See paragraph 2 below |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US 18/50193 | 10 September 2018 (10.09.2018) | 11 September 2017 (11.09.2017) |

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/138; A61K 9/00 (2018.01)
CPC - A61K 31/138; A61K 9/0034; A61K 9/0036; A61K 9/02; A61K 9/2018

Applicant ATOSSA GENETICS INC.

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

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

| Name and mailing address of the ISA/US | Date of completion of this opinion | Authorized officer |
|---|---|---|
| Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-8300 | 12 December 2018 | Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/237 (cover sheet) (January 2015)

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US 18/50193

**Box No. I Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a)).

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US 18/50193

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 5-26, 30

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 5-26, 30 are so unclear that no meaningful opinion could be formed *(specify)*:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 5-26, 30

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US 18/50193

**Box No. V** **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 2, 4/2 | YES |
| | Claims | 1, 3, 4/(1, 3), 27-29 | NO |
| Inventive step (IS) | Claims | NONE | YES |
| | Claims | 1-4, 27-29 | NO |
| Industrial applicability (IA) | Claims | 1-4, 27-29 | YES |
| | Claims | NONE | NO |

2. Citations and explanations:

Claims 1, 3 and 4/(1, 3) lack novelty under PCT Article 33(2) as being anticipated by US 4,851,433 A to Kraus.

Regarding Claim 1, Kraus discloses a topical composition (col 3, ln 42-44: typical cream formulations for topical use) for administration to a subject (col 1, ln 39-41) in need thereof, the composition comprising: a. tamoxifen and salts thereof (col 2, ln 66-67: topical administration contains tamoxifen D-gluconate; col 4, ln 20: active ingredient); b. a first compound which is stearic acid (col 4, ln 20-25); and c. a second compound which is cetyl alcohol (col 4, ln 20-25); and wherein the first compound and second compound are different, and each is selected from the group consisting of cetyl alcohol and stearic acid (col 4, ln 20-25).

Regarding Claim 3, Kraus discloses the topical composition of Claim 1 (col 3, ln 42-44), wherein the first compound comprises DMSO (col 4, ln 58-59: The above formulations may optionally contain 0.5 to 5.0% of a penetration enhancer such as dimethylsulphoxide), wherein the second compound comprises a permeation enhancer which is cetyl alcohol/stearic acid (col 4, ln 20-25).

Regarding Claim 4/(1, 3), Kraus discloses the topical composition of Claims 1 and 3 (as disclosed above), and further discloses wherein the total concentration of the first compound and the second compound is up to about 5% w/w of the topical composition (col 4, ln 20-25: Cetyl alcohol 2.5; Stearic acid 1.5; col 4, ln 58-59: The above formulations may optionally contain 0.5 to 5.0% of a penetration enhancer such as dimethylsulphoxide).

Claims 27-29 lack novelty under PCT Article 33(2) as being anticipated by WO 2016/168021 A1 to ATOSSA GENETICS, INC (hereinafter Atossa).

Regarding Claim 27, Atossa discloses a kit (para [0305]) for treatment or prevention of hormone-dependent breast disorder (para [0080]: the compositions disclosed herein may be used to treat breast disorders... ER-positive (ER+) breast cancer, ER- negative (ER-) breast cancer, HER2+ breast cancer), in a subject in need thereof comprising: (a) a composition comprising at least one active agent which is N-desmethyl-tamoxifen (para [0189]: desmethyltamoxifen); (b) a sealed container for housing the composition (para [0313]: closed container containing a composition); and c) instructions for use of the composition (para [0305]: instructions).

Regarding Claim 28, Atossa discloses the kit of Claim 27 (para [0305]), wherein the kit further comprises a means for administering the composition (para [0310]: delivering the pharmaceutical compositions).

Regarding Claim 29, Atossa discloses the kit of Claims 27-28, as disclosed above, and further discloses wherein the kit further comprises a second therapeutic agent which is trastuzumab (para [0084]: the compositions may comprise an additional medication such as a cytotoxic agent such as trastuzumab; claim 37: wherein the at least one additional medication is trastuzumab).

Claims 2 and 4/2 lack an inventive step under PCT Article 33(3) as being obvious over Kraus in view of US 2008/0138391 A1 to Carrara et al. (hereinafter Carrara).

Regarding Claim 2, Kraus discloses the topical composition of Claim 1 col 3, (ln 42-44), wherein the second compound comprises a permeation enhancer which is DMSO (col 4, ln 58-59: The above formulations may optionally contain 0.5 to 5.0% of a penetration enhancer such as dimethylsulphoxide), but does not disclose wherein the first compound comprises diethyleneglycol monoethyl ether. However, Carrara discloses similar topical compositions (para [0072]: topically transdermally or transmucosally administered) for various pharmaceutical agents including tamoxifen (para [0066]: tamoxifen); and various penetration enhancers such as diethyleneglycol monoethyl ether (para [0078]: Compounds that have been used to enhance skin permeability include... diethylene glycol monoethyl ether). It would have been obvious to one with skill in the art to utilize the composition disclosed by Kraus utilizing various permeation enhancers utilized in similar topical compositions comprising the same active agent in order to optimize bioavailability of said active agent.

Regarding Claim 4/2, Kraus in view of Carrara discloses the topical composition of Claim 2 (col 3, ln 42-44), but does not disclose wherein the total concentration of the first compound and the second compound is up to about 5% w/w of the topical composition. It would have been obvious to one with skill in the art to utilize the disclosed composition utilizing various amount of permeation enhancer compounds, such as up to 5% w/w, in order to optimize bioavailability of the disclosed active agent.

Claims 1-4 and 27-29 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 18/50193

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
Claim 27 lacks clarity regarding "In some embodiments, the topical composition comprises 0.01% to 20% (w/w) of the at least one active agent or a salt or a solvate thereof..."; for the purpose of this ISR, claim 27 is assumed to be wherein "optionally, the topical composition comprises 0.01% to 20% (w/w) of the at least one active agent or a salt or a solvate thereof...".

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 39574111 |
| **Application Number:** | 16641985 |
| **International Application Number:** | |
| **Confirmation Number:** | 7650 |
| **Title of Invention:** | METHODS FOR MAKING AND USING ENDOXIFEN |
| **First Named Inventor/Applicant Name:** | Steven C. Quay |
| **Customer Number:** | 21971 |
| **Filer:** | Payal Vrajesh Vyas/Cheuk Hei Ho |
| **Filer Authorized By:** | Payal Vrajesh Vyas |
| **Attorney Docket Number:** | 38602-758.831 |
| **Receipt Date:** | 29-MAY-2020 |
| **Filing Date:** | 25-FEB-2020 |
| **Time Stamp:** | 12:55:58 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

| | |
|---|---|
| Submitted with Payment | no |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | | IDS38602-758-831-5-27-2020.pdf | 506235<br>1864383c384541b896b26e31fccd16bfd1e8aa70 | yes | 14 |

| | Multipart Description/PDF files in .zip description | | | | |
|---|---|---|---|---|---|
| | Document Description | | Start | End | |
| | Information Disclosure Statement (IDS) Form (SB08) | | 5 | 14 | |
| | Transmittal Letter | | 1 | 4 | |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Foreign Reference | WO2008070463A2_EFS.PDF | 2470890<br>9ae81a05a5eeffb2e79b8026154d90dbce0623d6 | no | 52 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Foreign Reference | WO2009120999A2_EFS.PDF | 3472512<br>815a1464669d99c5b431da6b2dc514379892320c | no | 92 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Foreign Reference | WO2011072244A1_EFS.PDF | 1413455<br>291aba03afa6280e6cce8d6704678400aa9c4ef8 | no | 31 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | Foreign Reference | WO2012050263A1_EFS.PDF | 872984<br>352902d29db5ebbcaad03fea4527b6ae934b40e9 | no | 19 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 6 | Foreign Reference | WO2014134165A1_EFS.PDF | 7022458<br>4582b98c2db10fbc1a91c7965d9ac597e71b6b08 | no | 136 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 7 | Foreign Reference | WO2014141292A2_EFS.PDF | 588684<br>fe8be886f3e9a9d3ceaef3834ec146bf5212d951 | no | 20 |
| **Warnings:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Information:** | | | | | |
| 8 | Foreign Reference | WO2016168021A1_EFS.PDF | 7572025<br>5f89de47bfe5759199d3eebc6ebb0498d19b4a0e | no | 133 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 9 | Foreign Reference | WO2017070651A1_EFS.PDF | 1188691<br>ce09becd87288e28556a075b1b874fde4437e5f1 | no | 27 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 10 | Foreign Reference | WO2019051416A1_EFS.PDF | 8124455<br>179cb2c27acf804c32ff9f875526f4259975bf34 | no | 148 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 11 | Non Patent Literature | ACKERMAN-CONTRARY-2007.PDF | 1469445<br>f2fe867f880acbef4cdd8d3019d22099f61ceb8b | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 12 | Non Patent Literature | AHMAD-ENDOXIFEN-2012.PDF | 3364920<br>107997ffc1298a786329a588bad2eb80417dad22 | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 13 | Non Patent Literature | AHMAD-ENDOXIFEN-A-NEW-2010.PDF | 221018<br>5661b9c42f677a95d237edf8631345017ada9388 | no | 4 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 14 | Non Patent Literature | AHMAD-ENDOXIFEN-A-NEW-2016.PDF | 3104412<br>5a234cf39a42ace56470732e4f45cbbf1bb80ef8 | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 15 | Non Patent Literature | AHMAD-ORALLY-2010.PDF | 3191866<br>6e5795917f4fbd61e02fdee44d242ec513a8a6ff | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 16 | Non Patent Literature | ANONYMOUS-HISTORY-2015.PDF | 1276341<br>0e71703c4984312ff94a2550777f75ac65536b9c | no | 4 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 17 | Non Patent Literature | BHATNAGAR-TUMOR-2014.PDF | 1869235<br>f69e207e3886a2ca7f5b50df470cf7be91e379e3 | no | 21 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 18 | Non Patent Literature | CABRERA-GALENA-KI67-2018.PDF | 11610690<br>6d9538fd4aabef5140c6bf0350da88d44e986ae7 | no | 9 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 19 | Non Patent Literature | CHANG-TAMOXIFEN-2012.PDF | 12175135<br>5cb329c39065fc321f99a1885e72b186105b8e3a | no | 12 |
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| **Information:** | | | | | |
| 20 | Non Patent Literature | CLINICAL-NCT01273168.PDF | 390985<br>a6aac0da7389a3010aecab36dfd04488b016c241 | no | 10 |
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| 21 | Non Patent Literature | CLINICAL-NCT02311933.PDF | 455192<br>dd2943173b996841e1e1b06c523ac1987685b027 | no | 13 |
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| **Information:** | | | | | |

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| 22 | Non Patent Literature | DICKSCHEN-PHYSIOLOGICALLY-2012.PDF | 8887313<br>31e0d36f44be94c4bde0d5f8d0e664e53a6f025c | no | 15 |
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| **Information:** | | | | | |
| 23 | Non Patent Literature | DONNEYONG-RISK-2016.PDF | 10240002<br>de95393aaf04c952f56e97887c0d73d06e0fe28e | no | 20 |
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| 24 | Non Patent Literature | ESR-3-24-2020-EP17857260.PDF | 571262<br>c9895e288b7652da61f68b584c6c8013c857e697 | no | 16 |
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| 25 | Non Patent Literature | FASCHING-KI67-2011.PDF | 7289555<br>f4a8db8c5280ea9f1f5e2dc96d10d2b886b9e8ab | no | 13 |
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| **Information:** | | | | | |
| 26 | Non Patent Literature | GAUTHIER-NEW-1996.PDF | 284136<br>2372235a285ce979262b00bd79505b0933ba6c8c | no | 4 |
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| **Information:** | | | | | |
| 27 | Non Patent Literature | GOETZ-A-FIRST-2013.PDF | 3668096<br>601050c592639ddb7a29fe7142d63ee5a047b747 | no | 4 |
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| 28 | Non Patent Literature | GOETZ-FINAL-PD2-03-2015.PDF | 26420<br>dc439e16d62f92bc253935eacbea48bb6a874669 | no | 1 |
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| 29 | Non Patent Literature | GOETZ-FIRST-IN-HUMAN-PHASE-2017.PDF | 5864245<br>90321f8b5b107dfa2c6b0131ce03b8218ff6dcff | no | 16 |
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| 30 | Non Patent Literature | HAWSE-ENDOXIFEN-MOLECULAR-MECHANISM.PDF | 1440869<br>3a4244729a6ae9ccfd0416aa6081becf0a35be4d | no | 18 |
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| 31 | Non Patent Literature | HENDERSON-PROFOUND-REDUCTION-2016.PDF | 6449569<br>5edfd2a16b1327860278d9d4e0809182704eced8 | no | 6 |
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| 32 | Non Patent Literature | ISR-01-3-2019-PCT-US2018-050272.PDF | 647613<br>97da80eb9d0586c98be5c7c41e674b145abb163f | no | 12 |
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| 33 | Non Patent Literature | ISR-01-04-2019-PCT-US2018-050193.PDF | 549851<br>7e68dc470e091fd6c70963577fd834db77510d40 | no | 9 |
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| 34 | Non Patent Literature | JOHNSON-GYNECOMASTIA-2011.PDF | 1999717<br>1d4604e9508cf4e1b1e0327a87137cdb977f5c31 | no | 4 |
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| 35 | Non Patent Literature | JOHNSON-PHARMACOLOGICAL-2004.PDF | 3918623<br>af58cb247b326d3579ca81a3a2dc730c3209a356 | no | 9 |
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| 36 | Non Patent Literature | JORDAN-NEW-2007.PDF | 17032568<br>ec8c43337d83432c700c676b9bc6a1123583ee3a | no | 26 |
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| 37 | Non Patent Literature | LAZZERONI-ORAL-2012.PDF | 8013144<br>f81370d77a483160875b98166d0c0ae255747059 | no | 11 |
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| 38 | Non Patent Literature | LEE-IN-VITRO-HUMAN-2011.PDF | 934194<br>39c09e7b87520d9eaca8b092180093c87b89f7a5 | no | 10 |
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| 39 | Non Patent Literature | LEE-LOCAL-2015.PDF | 446104<br>8d2b87c88b331b85b835afb897e6100249554d283 | no | 12 |
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| 40 | Non Patent Literature | LI-PROGNOSTIC-2017.PDF | 822646<br>6fa59082cde14a65b4c0d9d1050450b4b0597623 | no | 14 |
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| 41 | Non Patent Literature | MANSEL-A-PHASE-2007.PDF | 139103<br>f5f883d3332fdbc8f8776a53f4afb9b141437c2f | no | 9 |
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| 42 | Non Patent Literature | MAXIMOV-STRUCTURE-FUNCTION-2010.PDF | 776148<br>0e984bd2fc31dddc10c963d415260f5109b52862 | no | 11 |
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| 43 | Non Patent Literature | MELNIKOW-PREFERENCES-2005.PDF | 986695<br>8446ed7f72819560ac2ebe5e556110d828200d5d | no | 10 |
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| 44 | Non Patent Literature | OGAWA-SYNTHESIS-1991.PDF | 379142<br>d966adf151c7808415dd71811e93784fc16c457d | no | 6 |
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| 45 | Non Patent Literature | OKEN-TOXICITY-1982.PDF | 384543<br>72f24a6c2dab46f2991b83acbf9c272218201d1b | no | 7 |
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| 46 | Non Patent Literature | ROUANET-NEOADJUVANT-2005.PDF | 508404<br>8d8131faebe69663df044b7d43df110fa5163afc | no | 8 |
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| 47 | Non Patent Literature | STEARNS-ACTIVE-2003.PDF | 12568173<br>b44040200ac71a23790e5ecddcc6efbcd3b2fe5a | no | 7 |
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| 48 | Non Patent Literature | SUN-CONSTRUCTION-2014.PDF | 589012<br>5e371fe1bdeebb185dcf2980fc6a42f18c3a2cac | no | 10 |
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| 49 | Non Patent Literature | WU-THE-TAMOXIFEN-2009.PDF | 11836837<br>a77eb26acb545d732053139b3d2f75018fe5c942 | no | 7 |
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| 50 | Non Patent Literature | YANG-DENDRON-BASED-2014.PDF | 469624<br>25ff8c318b5de9c250902f6727a9fe0dd5793543 | no | 8 |
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| 51 | Non Patent Literature | Z-FAUQ-A-CONVENIENT-3036.PDF | 160242<br>06ea524e54c42fb7d0d480c645ae6864b32ab535 | no | 3 |
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| 52 | Non Patent Literature | ZHAO-A-HERCEPTIN-2009.PDF | 4852961<br>d0517ec56bab15a3958006986067aa5a499df3d8 | no | 14 |
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| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 185098439 | | |

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**<u>New Applications Under 35 U.S.C. 111</u>**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**
**<u>National Stage of an International Application under 35 U.S.C. 371</u>**
**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**
**<u>New International Application Filed with the USPTO as a Receiving Office</u>**
**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 38602-758.831 |
|---|---|---|
| | Application Number | |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

## Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

## Inventor Information:

**Inventor 1** Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | Steven | C. | Quay | |

**Residence Information (Select One)** ◉ US Residency ○ Non US Residency ○ Active US Military Service

| City | Seattle | State/Province | WA | Country of Residence | US |
|---|---|---|---|---|---|

**Mailing Address of Inventor:**

| Address 1 | 107 Spring Street | | |
|---|---|---|---|
| Address 2 | | | |
| City | Seattle | State/Province | WA |
| Postal Code | 98104 | Country | US |

**Inventor 2** Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | YaoLin | | Sun | |

**Residence Information (Select One)** ○ US Residency ◉ Non US Residency ○ Active US Military Service

| City | Kaohsiung City | Country of Residence | TW |
|---|---|---|---|

**Mailing Address of Inventor:**

| Address 1 | 13F., No. 339-12, Sec. 2, Guangfu Rd. | | |
|---|---|---|---|
| Address 2 | Fengshan Dist. | | |
| City | Kaohsiung City | State/Province | |
| Postal Code | 830 | Country | TW |

**Inventor 3** Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | LungHu | | Wang | |

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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 38602-758.831 |
|---|---|---|
| | Application Number | |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

**Residence Information (Select One)** ○ US Residency ◉ Non US Residency ○ Active US Military Service

| City | Kaohsiung City | Country of Residence [i] | TW |
|---|---|---|---|

**Mailing Address of Inventor:**

| Address 1 | No. 102-2, Beishan Ln. | | |
|---|---|---|---|
| Address 2 | Qijin Dist. | | |
| City | Kaohsiung City | State/Province | |
| Postal Code | 805 | Country [i] | TW |

**Inventor 4** Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | ChangJung | | Wu | |

**Residence Information (Select One)** ○ US Residency ◉ Non US Residency ○ Active US Military Service

| City | Kaohsiung City | Country of Residence [i] | TW |
|---|---|---|---|

**Mailing Address of Inventor:**

| Address 1 | No. 28, Ln. 150, Youchang St. | | |
|---|---|---|---|
| Address 2 | Nanzi Dist. | | |
| City | Kaohsiung City | State/Province | |
| Postal Code | 811 | Country [i] | TW |

**Inventor 5** Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | ChuanDer | | Huang | |

**Residence Information (Select One)** ○ US Residency ◉ Non US Residency ○ Active US Military Service

| City | Tainan City | Country of Residence [i] | TW |
|---|---|---|---|

**Mailing Address of Inventor:**

| Address 1 | No. 21, Aly. 11, Ln. 176, Sec. 1 Bei'an Rd. | | |
|---|---|---|---|
| Address 2 | North Dist. | | |
| City | Tainan City | State/Province | |
| Postal Code | 704 | Country [i] | TW |

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 38602-758.831 |
|---|---|---|
| | Application Number | |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

## Correspondence Information:

**Enter either Customer Number or complete the Correspondence Information section below.**
**For further information see 37 CFR 1.33(a).**

☐ **An Address is being provided for the correspondence Information of this application.**

| | | | |
|---|---|---|---|
| **Customer Number** | 021971 | | |
| **Email Address** | patentdocket@wsgr.com | Add Email | Remove Email |

## Application Information:

| | | | |
|---|---|---|---|
| **Title of the Invention** | METHODS FOR MAKING AND USING ENDOXIFEN | | |
| **Attorney Docket Number** | 38602-758.831 | **Small Entity Status Claimed** | ☒ |
| **Application Type** | Nonprovisional | | |
| **Subject Matter** | Utility | | |
| **Total Number of Drawing Sheets (if any)** | 13 | **Suggested Figure for Publication (if any)** | 1 |

## Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

| Application number of the previously filed application | Filing date (YYYY-MM-DD) | Intellectual Property Authority or Country |
|---|---|---|
| | | |

## Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

## Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

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| **Application Data Sheet 37 CFR 1.76** | Attorney Docket Number | 38602-758.831 |
|---|---|---|
| | Application Number | |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

| Please Select One: | ◉ Customer Number | ○ US Patent Practitioner | ○ Limited Recognition (37 CFR 11.9) |
|---|---|---|---|
| Customer Number | 021971 | | |

## Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

| Prior Application Status | Pending | | Remove |
|---|---|---|---|
| Application Number | Continuity Type | Prior Application Number | Filing or 371(c) Date (YYYY-MM-DD) |
| | a 371 of international | PCT/US2018/050272 | 2018-09-10 |
| Prior Application Status | Expired | | Remove |
| Application Number | Continuity Type | Prior Application Number | Filing or 371(c) Date (YYYY-MM-DD) |
| PCT/US2018/050272 | Claims benefit of provisional | 62/556799 | 2017-09-11 |
| Prior Application Status | Expired | | Remove |
| Application Number | Continuity Type | Prior Application Number | Filing or 371(c) Date (YYYY-MM-DD) |
| PCT/US2018/050272 | Claims benefit of provisional | 62/556884 | 2017-09-11 |
| Prior Application Status | Expired | | Remove |
| Application Number | Continuity Type | Prior Application Number | Filing or 371(c) Date (YYYY-MM-DD) |
| PCT/US2018/050272 | Claims benefit of provisional | 62/624787 | 2018-01-31 |
| Prior Application Status | Expired | | Remove |
| Application Number | Continuity Type | Prior Application Number | Filing or 371(c) Date (YYYY-MM-DD) |
| PCT/US2018/050272 | Claims benefit of provisional | 62/693885 | 2018-07-03 |

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

## Foreign Priority Information:

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| **Application Data Sheet 37 CFR 1.76** | Attorney Docket Number | 38602-758.831 |
|---|---|---|
| | Application Number | |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

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| Application Number | Country[i] | Filing Date (YYYY-MM-DD) | Access Code[i] (if applicable) |
|---|---|---|---|
| | | | |

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## Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 38602-758.831 |
|---|---|---|
| | Application Number | |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

## Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

**NOTE**: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

**1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)**

**A. Priority Document Exchange (PDX)** - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

**B. Search Results from U.S. Application to EPO** - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

**2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)**

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

**NOTE:** Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 38602-758.831 |
|---|---|---|
| | Application Number | |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

## Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

**Applicant 1**

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

| | | |
|---|---|---|
| ◉ Assignee | ○ Legal Representative under 35 U.S.C. 117 | ○ Joint Inventor |
| ○ Person to whom the inventor is obligated to assign. | ○ Person who shows sufficient proprietary interest | |

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

| | |
|---|---|
| Name of the Deceased or Legally Incapacitated Inventor: | |

If the Applicant is an Organization check here. ☒

| | |
|---|---|
| Organization Name | ATOSSA THERAPEUTICS, INC. |

**Mailing Address Information For Applicant:**

| | | | |
|---|---|---|---|
| **Address 1** | 107 Spring Street | | |
| Address 2 | | | |
| **City** | Seattle | **State/Province** | WA |
| **Country** | US | Postal Code | 98104 |
| Phone Number | | Fax Number | |
| Email Address | | | |

Additional Applicant Data may be generated within this form by selecting the Add button.

## Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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| **Application Data Sheet 37 CFR 1.76** | Attorney Docket Number | 38602-758.831 |
|---|---|---|
| | Application Number | |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

**Assignee 1**

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

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| **Country** i | | Postal Code | |
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| Email Address | | | |

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## Signature:

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See 37 CFR 1.4(d) for the manner of making signatures and certifications.

| **Signature** | /Lisa G Lippert/ | | | Date (YYYY-MM-DD) | 2020-02-25 |
|---|---|---|---|---|---|
| First Name | Lisa G. | Last Name | Lippert, Ph.D. | Registration Number | 78332 |

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| **Application Data Sheet 37 CFR 1.76** | Attorney Docket Number | 38602-758.831 |
|---|---|---|
| | Application Number | |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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| **EFS ID:** | 39574111 |
| **Application Number:** | 16641985 |
| **International Application Number:** | |
| **Confirmation Number:** | 7650 |
| **Title of Invention:** | METHODS FOR MAKING AND USING ENDOXIFEN |
| **First Named Inventor/Applicant Name:** | Steven C. Quay |
| **Customer Number:** | 21971 |
| **Filer:** | Payal Vrajesh Vyas/Cheuk Hei Ho |
| **Filer Authorized By:** | Payal Vrajesh Vyas |
| **Attorney Docket Number:** | 38602-758.831 |
| **Receipt Date:** | 29-MAY-2020 |
| **Filing Date:** | 25-FEB-2020 |
| **Time Stamp:** | 12:55:58 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

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| Submitted with Payment | no |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | | IDS38602-758-831-5-27-2020.pdf | 506235<br>1864383c384541b896b26e31fccd16bfd1e8aa70 | yes | 14 |

| | Multipart Description/PDF files in .zip description | | | | |
|---|---|---|---|---|---|
| | **Document Description** | **Start** | **End** | | |
| | Information Disclosure Statement (IDS) Form (SB08) | 5 | 14 | | |
| | Transmittal Letter | 1 | 4 | | |
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| 2 | Foreign Reference | WO2008070463A2_EFS.PDF | 2470890<br>9ae81a05a5eeffb2e79b8026154d90dbce0623d6 | no | 52 |
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| 3 | Foreign Reference | WO2009120999A2_EFS.PDF | 3472512<br>815a1464669d99c5b431da6b2dc514379892320c | no | 92 |
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| 12 | Non Patent Literature | AHMAD-ENDOXIFEN-2012.PDF | 3364920<br>107997ffc1298a786329a588bad2eb80417dad22 | no | 3 |
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| 13 | Non Patent Literature | AHMAD-ENDOXIFEN-A-NEW-2010.PDF | 221018<br>5661b9c42f677a95d237edf8631345017ada9388 | no | 4 |
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| 14 | Non Patent Literature | AHMAD-ENDOXIFEN-A-NEW-2016.PDF | 3104412<br>5a234cf39a42ace56470732e4f45cbbf1bb80ef8 | no | 8 |
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| 15 | Non Patent Literature | AHMAD-ORALLY-2010.PDF | 3191866<br>6e5795917f4fbd61e02fdee44d242ec513a8a6ff | no | 6 |
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| 16 | Non Patent Literature | ANONYMOUS-HISTORY-2015.PDF | 1276341<br>0e71703c4984312ff94a2550777f75ac65536b9c | no | 4 |
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| 17 | Non Patent Literature | BHATNAGAR-TUMOR-2014.PDF | 1869235<br>f69e207e3886a2ca7f5b50df470cf7be91e379e3 | no | 21 |
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| 24 | Non Patent Literature | ESR-3-24-2020-EP17857260.PDF | 571262<br>c9895e288b7652da61f68b584c6c8013c857e697 | no | 16 |
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| 25 | Non Patent Literature | FASCHING-KI67-2011.PDF | 7289555<br>f4a8db8c5280ea9f1f5e2dc96d10d2b886b9e8ab | no | 13 |
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| 27 | Non Patent Literature | GOETZ-A-FIRST-2013.PDF | 3668096<br>601050c592639ddb7a29fe7142d63ee5a047b747 | no | 4 |
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| 28 | Non Patent Literature | GOETZ-FINAL-PD2-03-2015.PDF | 26420<br>dc439e16d62f92bc253935eacbea48bb6a874669 | no | 1 |
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| 30 | Non Patent Literature | HAWSE-ENDOXIFEN-MOLECULAR-MECHANISM.PDF | 1440869<br>3a4244729a6ae9ccfd0416aa6081becf0a35be4d | no | 18 |
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| 33 | Non Patent Literature | ISR-01-04-2019-PCT-US2018-050193.PDF | 549851<br>7e68dc470e091fd6c70963577fd834db77510d40 | no | 9 |
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| 37 | Non Patent Literature | LAZZERONI-ORAL-2012.PDF | 8013144<br>f81370d77a483160875b98166d0c0ae255747059 | no | 11 |
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| 38 | Non Patent Literature | LEE-IN-VITRO-HUMAN-2011.PDF | 934194<br>39c09e7b87520d9eaca8b092180093c87b89f7a5 | no | 10 |
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| 39 | Non Patent Literature | LEE-LOCAL-2015.PDF | 446104<br>8d2b87c88b331b85b835afb897e6100249554d283 | no | 12 |
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| 41 | Non Patent Literature | MANSEL-A-PHASE-2007.PDF | 139103<br>f5f883d3332fdbc8f8776a53f4afb9b141437c2f | no | 9 |
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| 42 | Non Patent Literature | MAXIMOV-STRUCTURE-FUNCTION-2010.PDF | 776148<br>0e984bd2fc31dddc10c963d415260f5109b52862 | no | 11 |
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| 48 | Non Patent Literature | SUN-CONSTRUCTION-2014.PDF | 589012<br>5e371fe1bdeebb185dcf2980fc6a42f18c3a2cac | no | 10 |
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| 49 | Non Patent Literature | WU-THE-TAMOXIFEN-2009.PDF | 11836837<br>a77eb26acb545d732053139b3d2f75018fe5c942 | no | 7 |
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| APPLICATION NUMBER | FILING OR 371(C) DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO./TITLE |
|---|---|---|---|
| 16/641,985 | 02/25/2020 | Steven C. Quay | 38602-758.831 |

**CONFIRMATION NO. 7650**

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

**PUBLICATION NOTICE**

*OC00000018199188*

**Title:**METHODS FOR MAKING AND USING ENDOXIFEN

**Publication No.**US-2020-0207704-A1
**Publication Date:**07/02/2020

## NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

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In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

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Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on July 23, 2020

WILSON SONSINI GOODRICH & ROSATI

By: /Lori Ford/

Attorney Docket No.: 38602-758.831

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re Application of: | Confirmation No.: 7650 |
| Steven C. QUAY, et al. | |
| Application No.: 16/641,985 | Examiner: Unassigned |
| Filed: February 25, 2020 | Art Unit: 1629 |
| For: METHODS FOR MAKING AND USING ENDOXIFEN | PRELIMINARY AMENDMENT AND RESPONSE TO NOTIFICATION OF INSUFFICIENCY UNDER 37 C.F.R. 1.492 AND/OR 1.495 (DO/EO/US) |
| Customer No.: 21971 | |

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

Commissioner:

This paper responds to the Notification of Insufficiency dated March 24, 2020, the time period for response set for May 24, 2020. With payment of a two-month extension of time fee, the due date for response has been extended to July 24, 2020, and the Response is therefore timely. Applicant respectfully requests entry of the proposed amendments prior to examination and allowance of the pending claims.

**Amendments to the Claims** begin on page **2**.

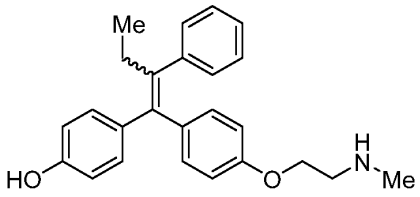
**Remarks** begin on page **8**.

**Amendments to Claims**

This listing of claims replaces all prior versions and listing of claims in the above-referenced patent application:

**Listing of Claims:**

1. (Currently Amended) A composition comprising a crystalline form of a compound of Formula (III):




Formula (III),

wherein at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer and the crystalline form of the compound of Formula (III) is Form I.

2-3. (Canceled)

4. (Currently Amended) The composition of claim [[3]]1, wherein the crystalline form is characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta.

5. (Original) The composition of claim 4, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from 16.0 ± 0.3°, 18.8 ± 0.3° and 26.5 ± 0.3 two theta.

6. (Currently Amended) The composition of claim 4 ~~or 5~~, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from 12.3 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta.



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7. (Original) The composition of claim 4, wherein the x-ray powder diffraction pattern further comprises peaks at 12.3 ± 0.3°, 16.0 ± 0.3°, 18.8 ± 0.3°, 26.5 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta.

8. (Currently Amended) The composition of ~~any one of claims 3 to 7~~ claim 1, wherein the crystalline form is characterized by an x-ray powder diffraction pattern substantially as set forth in Fig. 9 or Fig. 10.

9. (Currently Amended) The composition of claim 1 ~~any one of claims 3 to 8~~, wherein greater than 90%~~, 95% or 99%~~ by weight of the compound of Formula (III) in the composition is crystalline Form I.

10-31. (Canceled)

32. (Currently Amended) ~~A pharmaceutical~~ The composition of claim 1, further comprising a pharmaceutically acceptable carrier or diluent ~~and the composition of any one of the preceding claims~~.

33. (Currently Amended) The composition of ~~any one of the preceding claims~~ claim 32, wherein the composition is formulated for oral, parenteral, topical, or intraductal delivery.

34. (Currently Amended) The composition of ~~any one of the preceding claims~~ claim 32, wherein the composition is formulated for oral delivery as a tablet, a caplet, a capsule, or a pill.

35. (Currently Amended) The composition of ~~any one of the preceding claims~~ claim 32, wherein a mean half-life of endoxifen in a subject treated with the composition is between 30 hours to 60 hours.

36-37. (Canceled)



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38. (Currently Amended) The composition of claim 1, formulated as [[An]]an oral ~~composition~~ dosage form comprising 1 mg to 200 mg per unit dose of the composition ~~of any one of the preceding claims for administration to a subject in need thereof,~~ , and wherein daily administration of the oral ~~composition~~ dosage form achieves in [[the]]a subject in need thereof one or more of:

a steady state plasma level of endoxifen within 7 to 21 days;

a steady state plasma level of endoxifen ranging from 25 nM to 300 nM;

a steady state plasma level of endoxifen greater than 30 nM; or

maximal plasma levels of endoxifen within 2 to 10 hours after administering~~; or any combination thereof~~.

39. (Currently Amended) The ~~oral~~ composition of claim 38, wherein a mean half-life of endoxifen in a subject treated with the ~~composition~~ oral dosage form is between 40 hours to 55 hours.

40. (Currently Amended) The ~~oral~~ composition of claim 38 [[ or 39]], wherein the ~~composition~~ oral dosage form is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

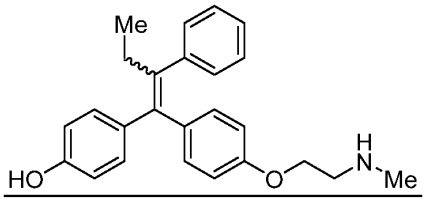
41. (Currently Amended) The composition of claim 38 ~~any one of the preceding claims~~, wherein ~~at least 40%, at least 50%, at least 60%, at least 70%,~~ at least 80%~~, or at least 90%~~ of endoxifen in the ~~composition~~ oral dosage form is released in the intestines of a subject treated with the oral dosage form.

42. (Currently Amended) The composition of claim 38 ~~any one of the preceding claims~~, having a mean area under the curve extrapolated to time infinity ($AUC_{0\text{-}inf}$) of endoxifen of 200 hr*ng/mL to 10000 hr*ng/mL~~, of 300 hr*ng/mL to 8000 hr*ng/mL, of 400 hr*ng/mL to 6000 hr*ng/mL or of 700 hr*ng/mL to 6000 hr*ng/mL~~.



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43. (Currently Amended) A method of treating a subject in need thereof, the method comprising administering to the subject ~~the composition of any one of claims 1 to 0~~ a composition comprising a crystalline form of a compound of Formula (III):




Formula (III),

wherein at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer and the crystalline form of the compound of Formula (III) is Form I.

44. (Original) The method of claim 43, wherein the subject has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both.

45. (Canceled)

46. (Currently Amended) The method of claim 43 ~~any one of claims 43 to 45~~, wherein the subject has prostate cancer and wherein the subject further has or is at risk of having gynecomastia.

47. (Currently Amended) The method of claim 43 ~~any one of claims 43 to 46~~, wherein the subject has tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder.

48. (Canceled)

49. (Currently Amended) The method of claim 43 ~~any one of claims 43 to 48~~, wherein the composition comprises 0.01 mg to 200 mg of (Z)-endoxifen.

50-51. (Canceled)



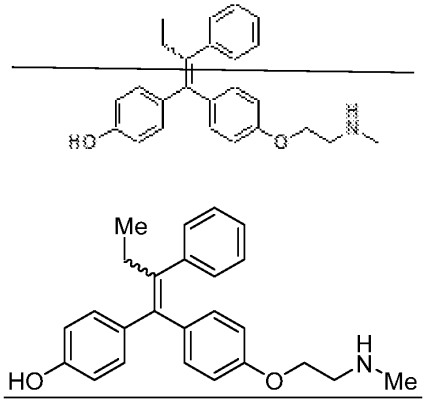
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52. (Currently Amended) The method of claim 43 ~~any one of claims 43 to 51~~, wherein ~~the~~ a steady state plasma level of endoxifen is achieved within 7 to 21 days of the first administration of the composition and the steady state plasma level of endoxifen in the subject is greater than 30 nM.

53-61. (Canceled)

62. (Currently Amended) An industrially scalable process for manufacturing (Z)-endoxifen, comprising the steps of:

[[(a)]] subjecting a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), represented by:




to fractional crystallization from a first solvent to form a first crystalline solid and first mother liquor, wherein the first mother liquor has an E/Z ratio of at least 50% higher (Z) endoxifen as compared with the E/Z ratio of the mixture of (E)-endoxifen and (Z)-endoxifen;

[[(b)]] subjecting the first mother liquor 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 the second solvent one or more times, to form a second crystalline solid and a second mother liquor, wherein the second crystalline solid is ≥ 90% (Z)-endoxifen; and

[[(c)]] optionally, subjecting the second crystalline solid to recrystallization from a third solvent or chromatographic treatment one or more times to form a third crystalline solid.



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63-157. (Canceled)



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## REMARKS

### Amendments to the Claims

Upon entry of this amendment, claims 1, 4-9, 32-35, 38-44, 46, 47, 49, 52, and 62 will be pending in the present application. Claims 2, 3, 10-31, 36, 37, 45, 48, 50, 51, 53-61, 63-157 have been cancelled without prejudice or disclaimer. Applicant reserves the right to pursue the subject matter of the cancelled claims in this or any other appropriate patent application. Claims 1, 4, 6, 8, 9, 32-35, 38-43, 46-47, 49, 52, and 62 have been amended.

Support for the amendments to the claims is found in the original claims and throughout the specification. For example, support for amended claim 1 can be found at least at original claims 2 and 3, support for amended claim 43 can be found at least at original claims 1-3, and support for amended claim 52 can be found at least at original claim 51. No new matter is added by any amendment made herein. Consideration is respectfully requested.

### Response to Notification of Insufficiency

In response to the Notification of Insufficiency dated March 24, 2020 (the "Notice"), Applicant respectfully submits the following fees totaling $450.00 for small entity:

1. $150.00 for three additional dependent claims over 20;
2. $300.00 for two-month extension of time.

## 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 associated with this paper or during the pendency of this application, or credit any overpayment, to Deposit Account No. 23-2415.

If the Examiner believes a telephone conference would expedite prosecution of this application, the Examiner is encouraged to telephone the undersigned at (206) 883-2500.

Respectfully submitted,

Dated: July 23, 2020

/Lisa G Lippert/

Lisa G. Lippert, Ph.D.
Reg. No. 78,332

WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304-1050
Phone 650-493-9300
Fax 650-493-6811



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# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 16641985 |
| **Filing Date:** | 25-Feb-2020 |
| **Title of Invention:** | METHODS FOR MAKING AND USING ENDOXIFEN |
| **First Named Inventor/Applicant Name:** | Steven C. Quay |
| **Filer:** | Lisa Gail Lippert/Lori Ford |
| **Attorney Docket Number:** | 38602-758.831 |

Filed as Small Entity

**Filing Fees for U.S. National Stage under 35 USC 371**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| CLAIMS IN EXCESS OF 20 | 2615 | 3 | 50 | 150 |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
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| Extension - 2 months with $0 paid | 2252 | 1 | 300 | 300 |
| **Miscellaneous:** | | | | |
| | | **Total in USD ($)** | | **450** |

# Electronic Acknowledgement Receipt

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|---|---|
| **EFS ID:** | 40091945 |
| **Application Number:** | 16641985 |
| **International Application Number:** | |
| **Confirmation Number:** | 7650 |
| **Title of Invention:** | METHODS FOR MAKING AND USING ENDOXIFEN |
| **First Named Inventor/Applicant Name:** | Steven C. Quay |
| **Customer Number:** | 21971 |
| **Filer:** | Lisa Gail Lippert/Lori Ford |
| **Filer Authorized By:** | Lisa Gail Lippert |
| **Attorney Docket Number:** | 38602-758.831 |
| **Receipt Date:** | 23-JUL-2020 |
| **Filing Date:** | 25-FEB-2020 |
| **Time Stamp:** | 19:24:28 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

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| Submitted with Payment | yes |
| Payment Type | DA |
| Payment was successfully received in RAM | $450 |
| RAM confirmation Number | E20207MJ24592449 |
| Deposit Account | |
| Authorized User | |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | | 38602-758-831-ResponseNotificationInsufficiency.pdf | 141773<br>f82ba2c55f1c07fae83f6d8e836aef9822576ed8 | yes | 9 |

**Multipart Description/PDF files in .zip description**

| Document Description | Start | End |
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| Applicant Response to Pre-Exam Formalities Notice | 1 | 1 |
| Claims | 2 | 7 |
| Applicant Arguments/Remarks Made in an Amendment | 8 | 9 |

**Warnings:**

**Information:**

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| 2 | Fee Worksheet (SB06) | fee-info.pdf | 32451<br>a01ee3f425b5e0d3df92daa34d97c354fb9fc8bf | no | 2 |

**Warnings:**

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**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**

**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**

**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

# MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

| Application Number | Filing Date |
|---|---|
| 16641985 | |

Applicant(s) Steven Quay

* May be used for additional claims or amendments

| CLAIMS | AS FILED | | AFTER FIRST AMENDMENT | | AFTER SECOND AMENDMENT | |
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# MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

| Application Number | Filing Date |
|---|---|
| 16641985 | |

Applicant(s) Steven Quay

* May be used for additional claims or amendments

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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 NUMBER | FILING or 371(c) DATE | GRP ART UNIT | FIL FEE REC'D | ATTY.DOCKET.NO | TOT CLAIMS | IND CLAIMS |
|---|---|---|---|---|---|---|
| 16/641,985 | 02/25/2020 | 1629 | 750 | 38602-758.831 | 23 | 3 |

**CONFIRMATION NO. 7650**

**UPDATED FILING RECEIPT**

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

OC000000119159305

Date Mailed: 08/14/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

**Please verify the accuracy of the data presented on this receipt.** If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

**Inventor(s)**

Steven C. Quay, Seattle, WA;
YaoLin Sun, Kaohsiung City, TAIWAN;
LungHu Wang, Kaohsiung City, TAIWAN;
ChangJung Wu, Kaohsiung City, TAIWAN;
ChuanDer Huang, Tainan City, TAIWAN;

**Applicant(s)**

ATOSSA THERAPEUTICS, INC., Seattle, WA;

**Power of Attorney:** None

**Domestic Priority data as claimed by applicant**

This application is a 371 of PCT/US18/50272 09/10/2018
which claims benefit of 62/556,799 09/11/2017
and claims benefit of 62/556,884 09/11/2017
and claims benefit of 62/624,787 01/31/2018
and claims benefit of 62/693,885 07/03/2018

**Foreign Applications** for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
*Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.*

**Permission to Access Application via Priority Document Exchange:** Yes

**Permission to Access Search Results:** Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

**If Required, Foreign Filing License Granted:** 03/20/2020

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/641,985**

**Projected Publication Date:** Not Applicable

**Non-Publication Request:** No

**Early Publication Request:** No

**** SMALL ENTITY ****

**Title**

METHODS FOR MAKING AND USING ENDOXIFEN

**Preliminary Class**

514

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:** No

## PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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## Title 35, United States Code, Section 184

## Title 37, Code of Federal Regulations, 5.11 & 5.15

**GRANTED**

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

**NOT GRANTED**

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

---

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The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor

community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

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

| U.S. APPLICATION NO. | FIRST NAMED INVENTOR | ATTY. DOCKET NO. |
|---|---|---|
| 16/641,985 | Steven C. Quay | 38602-758.831 |

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

| INTERNATIONAL APPLICATION NO. | |
|---|---|
| PCT/US18/50272 | |
| I.A. FILING DATE | PRIORITY DATE |
| 09/10/2018 | 09/11/2017 |

**CONFIRMATION NO. 7650**
**371 ACCEPTANCE LETTER**

*OC000000119159306*

Date Mailed: 08/14/2020

## NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office, in its capacity as a Designated / Elected Office (37 CFR 1.495), has ACCEPTED the above identified international application for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above. A Filing Receipt will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE "FILING DATE or 371(c) DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 (c)(1) and (c)(2) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN BELOW.** The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363)

02/25/2020
DATE OF RECEIPT OF 35 U.S.C.
371(c)(1) and (c)(2) REQUIREMENTS

The following items have been received:

- Indication of Small Entity Status
- Copy of the International Application filed on 02/25/2020
- Copy of the International Search Report filed on 02/25/2020
- Preliminary Amendments filed on 02/25/2020
- Information Disclosure Statements filed on 05/29/2020
- Inventor's Oath or Declaration filed on 02/25/2020
- U.S. Basic National Fees filed on 02/25/2020
- Authorize Access to Search Results filed on 02/25/2020
- Priority Documents filed on 02/25/2020
- Authorization to Permit Access filed on 02/25/2020
- Application Data Sheet (37 CFR 1.76) filed on 02/25/2020



FORM PCT/DO/EO/903 (371 Acceptance Notice)

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

ROSA M WEST

Telephone: (571) 272-1019



FORM PCT/DO/EO/903 (371 Acceptance Notice)

## PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/641,985

### APPLICATION AS FILED - PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | SMALL ENTITY RATE($) | SMALL ENTITY FEE($) | OR | OTHER THAN SMALL ENTITY RATE($) | OTHER THAN SMALL ENTITY FEE($) |
|---|---|---|---|---|---|---|---|
| BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | 150 | | N/A | |
| SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | 70 | | N/A | |
| EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | 380 | | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | 23 minus 20 = | * 3 | x 50 = | 150 | OR | | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | 3 minus 3 = | * | x 230 = | 0.00 | | | |
| APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | 0.00 | | | |
| MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | 0.00 | | | |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | TOTAL | 750 | | TOTAL | |

### APPLICATION AS AMENDED - PART II

| | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | SMALL ENTITY RATE($) | SMALL ENTITY ADDITIONAL FEE($) | OR | OTHER THAN SMALL ENTITY RATE($) | OTHER THAN SMALL ENTITY ADDITIONAL FEE($) |
|---|---|---|---|---|---|---|---|---|---|---|
| AMENDMENT A | Total (37 CFR 1.16(i)) | * | Minus | ** | = | x = | | OR | x = | |
| | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | x = | | OR | x = | |
| | Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| | FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

| | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | SMALL ENTITY RATE($) | SMALL ENTITY ADDITIONAL FEE($) | OR | OTHER THAN SMALL ENTITY RATE($) | OTHER THAN SMALL ENTITY ADDITIONAL FEE($) |
|---|---|---|---|---|---|---|---|---|---|---|
| AMENDMENT B | Total (37 CFR 1.16(i)) | * | Minus | ** | = | x = | | OR | x = | |
| | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | x = | | OR | x = | |
| | Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| | FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
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# TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

| | |
|---|---|
| Application Number | 16/641,985 |
| Filing Date | February 25, 2020 |
| First Named Inventor | Steven C. Quay |
| Title | METHODS FOR MAKING AND USING ENDOXIFEN |
| Art Unit | 1629 |
| Examiner Name | Unassigned |
| Attorney Docket Number | 109559-669805 |

**SIGNATURE of Applicant or Patent Practitioner**

| | | | |
|---|---|---|---|
| Signature | /Lisa G Lippert/ | Date (Optional) | November 12, 2020 |
| Name | Lisa G. Lippert, Ph.D. | Registration Number | 78332 |
| Title (if Applicant is a juristic entity) | | | |
| Applicant Name (if Applicant is a juristic entity) | | | |

**NOTE:** This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Document Description: Power of Attorney

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# POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

| Application Number | Filing Date |
|---|---|
| | |

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 27148

**OR**

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

**Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:**

☑ The address associated with the above-mentioned Customer Number

**OR**

☐ The address associated with Customer Number:

**OR**

| | | | | | |
|---|---|---|---|---|---|
| ☐ Firm or Individual Name | | | | | |
| Address | | | | | |
| City | | State | | Zip | |
| Country | | | | | |
| Telephone | | Email | | | |

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Atossa Therapeutics, Inc.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

**SIGNATURE of Applicant for Patent**

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

| | | | |
|---|---|---|---|
| Signature | Kyle Guse | Date (Optional) | 9/24/2020 |
| Name | Kyle Guse | | |
| Title | Chief Financial Officer and General Counsel | | |

**NOTE:** Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ Total of forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 41105757 |
| **Application Number:** | 16641985 |
| **International Application Number:** | |
| **Confirmation Number:** | 7650 |
| **Title of Invention:** | METHODS FOR MAKING AND USING ENDOXIFEN |
| **First Named Inventor/Applicant Name:** | Steven C. Quay |
| **Customer Number:** | 21971 |
| **Filer:** | Lisa Gail Lippert/Lori Ford |
| **Filer Authorized By:** | Lisa Gail Lippert |
| **Attorney Docket Number:** | 38602-758.831 |
| **Receipt Date:** | 12-NOV-2020 |
| **Filing Date:** | 25-FEB-2020 |
| **Time Stamp:** | 13:38:47 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

| | |
|---|---|
| Submitted with Payment | no |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Power of Attorney | 109559-669805-POA.pdf | 288522<br>f3b058282912535d6ca812f16f0b9b9c2a01630d | no | 2 |

**Warnings:**

| Information: | |
|---|---|
| Total Files Size (in bytes): | 288522 |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**
**National Stage of an International Application under 35 U.S.C. 371**
**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**
**New International Application Filed with the USPTO as a Receiving Office**
**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

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www.uspto.gov

| APPLICATION NUMBER | FILING OR 371(C) DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO./TITLE |
|---|---|---|---|
| 16/641,985 | 02/25/2020 | Steven C. Quay | 109559-669805 |

**CONFIRMATION NO. 7650**

27148
POLSINELLI PC
900 WEST 48TH PLACE
SUITE 900
KANSAS CITY, MO 64112-1895

**POA ACCEPTANCE LETTER**

*OC000000121350431*

Date Mailed: 11/17/2020

## NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 11/12/2020.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/atesfai/

PTO/SB/08a (02-18)
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 16641985 |
| Filing Date | 2020-02-25 |
| First Named Inventor | STEVEN; C. Quay |
| Art Unit | 1629 |
| Examiner Name | - |
| Attorney Docket Number | 109559-669805 |

**U.S.PATENTS** Remove

| Examiner Initial* | Cite No | Patent Number | Kind Code[1] | Issue Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | None | | | | |

If you wish to add additional U.S. Patent citation information please click the Add button. Add

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| Examiner Initial* | Cite No | Publication Number | Kind Code[1] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | 20120301541 | | 2012-11-29 | HARONSKY; Elina et al. | |

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| Examiner Initial* | Cite No | Foreign Document Number[3] | Country Code[2] i | Kind Code[4] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear | T[5] |
|---|---|---|---|---|---|---|---|---|
| | 1 | None | | | | | | |

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**NON-PATENT LITERATURE DOCUMENTS** Remove

| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published. | T[5] |
|---|---|---|---|

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 16641985 |
| | Filing Date | 2020-02-25 |
| | First Named Inventor | STEVEN; C. Quay |
| | Art Unit | 1629 |
| | Examiner Name | - |
| | Attorney Docket Number | 109559-669805 |

| | | | |
|---|---|---|---|
| | 1 | Extended European Search Report for European Application No. EP18853361.6, dated May 28, 2021, 5 pages. | |
| | 2 | FOREFRONT., "Endoxifen Shows Promise As Breast Cancer Treatment", Mayo Clinic Cancer Center's Online Magazine, Vol. 3, Issue 1, 2014, 3 pages. | |
| | 3 | LOVE et al., "A Feasibility Study of the Intraductal Administration of Chemotherapy", Cancer Prevention Research, Vol. 6, No. 1, January 2013, pp. 51-58. | |
| | 4 | Search Report and Written Opinion for Singapore Patent Application No. SG11202002105W mailed April 21, 2021, 8 pages. | |

If you wish to add additional non-patent literature document citation information please click the Add button Add

**EXAMINER SIGNATURE**

| Examiner Signature | | Date Considered | |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 16641985 |
| | Filing Date | 2020-02-25 |
| | First Named Inventor | STEVEN; C. Quay |
| | Art Unit | 1629 |
| | Examiner Name | - |
| | Attorney Docket Number | 109559-669805 |

**CERTIFICATION STATEMENT**

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

**SIGNATURE**

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| Signature | /Lisa G Lippert/ | Date (YYYY-MM-DD) | 2021-06-29 |
|---|---|---|---|
| Name/Print | Lisa G. Lippert, Ph.D. | Registration Number | 78,322 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

## Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 43126521 |
| **Application Number:** | 16641985 |
| **International Application Number:** | |
| **Confirmation Number:** | 7650 |
| **Title of Invention:** | METHODS FOR MAKING AND USING ENDOXIFEN |
| **First Named Inventor/Applicant Name:** | Steven C. Quay |
| **Customer Number:** | 27148 |
| **Filer:** | Lisa Gail Lippert/Lori Ford |
| **Filer Authorized By:** | Lisa Gail Lippert |
| **Attorney Docket Number:** | 109559-669805 |
| **Receipt Date:** | 29-JUN-2021 |
| **Filing Date:** | 25-FEB-2020 |
| **Time Stamp:** | 20:21:21 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

| | |
|---|---|
| Submitted with Payment | no |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Transmittal Letter | 109559_669805_IDS_Transmittal.pdf | 128216<br>d54c5fdc460bd96490d45f9b3d5b9a09ed53ace9 | no | 4 |

**Warnings:**

| | | | | | |
|---|---|---|---|---|---|
| **Information:** | | | | | |
| 2 | Non Patent Literature | LOVE_A_Feasibility_Study_2013_pp_51_58_EFS.pdf | 2302173<br>6a8dfed88ad10b46613be75df5c62f17fabb88ab | no | 10 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Non Patent Literature | SR_WO_SG11202002105W_21Apr2021_Pgs_8_EFS.pdf | 871092<br>375db430f30e6a53bdb95c3d262e2e8a6101de38 | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Non Patent Literature | EESR_EP18853361_28May2021_5pgs_EFS.pdf | 979226<br>e4e80ba76ecb0d27771b6a7b4da1fbed37775e16 | no | 5 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | Non Patent Literature | FOREFRONT_ENDOXIFEN_BREAST_2014_3pgs_EFS.pdf | 1024517<br>77fc55c148f609ca5c0a32545b1f58a91cce1dbd | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 6 | Information Disclosure Statement (IDS) Form (SB08) | 109559-669805_0_IDS_20210629164429.pdf | 1053536<br>9a44d8ab139e6a6ce656f76668426bdaee3d54c3 | no | 4 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 6358760 | | |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**

**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**

**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**

**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Inventor: | Steven C. Quay | Group Art Unit: | 1629 |
| Serial Number: | 16/641,985 | Examiner: | Unassigned |
| Filing or 371 (c) Date: | 2/25/2020 | **CONFIRMATION NO:** | **7650** |
| Title: | METHODS FOR MAKING AND USING ENDOXIFEN | CUST. NO.: 27148 | |

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

## INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☒ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☒ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☐ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☐ a fee of $260.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of $260.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☐ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 501662 (Docket No. 109559-669805).

Respectfully submitted,

Dated: June 29, 2021

/Lisa G Lippert/

Lisa G. Lippert, Ph.D.
Registration No. 78,332

POLSINELLI PC
900 W. 48th Place, Suite 900
Kansas City, MO 64112
Tel: (816) 753-1000
Fax: (816) 753-1536
CUSTOMER NO.: 27148

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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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

POLSINELLI PC
PO Box 140310
KANSAS CITY, MO 64114-0310

| EXAMINER |
|---|
| DAVIS, BRIAN J |

| 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 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 <u>of the (Z)-isomer</u> 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, 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.)

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 ≥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$^{th}$ 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

| Notice of References Cited | Application/Control No. 16/641,985 | Applicant(s)/Patent Under Reexamination Quay et al. | |
|---|---|---|---|
| | Examiner BRIAN J DAVIS | Art Unit 1612 | Page 1 of 1 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | CPC Classification | US Classification |
|---|---|---|---|---|---|---|
| | A | | | | | |
| | B | | | | | |
| | C | | | | | |
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**FOREIGN PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Country | Name | CPC Classification |
|---|---|---|---|---|---|---|
| | N | WO2017/080770A1 | 05-2017 | WIPO | HEINKELE et al. | C07C 43/225 |
| | O | WO2017/080770A1( MA.TRAN) | 05-2017 | WIPO | HEINKELE et al. | C07C 43/225 |
| | P | | | | | |
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**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
|---|---|---|
| | U | |
| | V | |
| | W | |
| | X | |

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 16/641,985 | Quay et al. |
| | Examiner | Art Unit |
| | BRIAN J DAVIS | 1612 |

| CPC - Searched* | | |
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| CPC Combination Sets - Searched* | | |
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| US Classification - Searched* | | | |
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* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

| Search Notes | | |
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| Search Notes | Date | Examiner |
| Structure/Research Topic searches in CAS SciFinder (see search history printout) | 08/29/2021 | /BJD/ |
| Global Dossier | 08/29/2021 | /BJD/ |
| Inventor name searches in PE2E | 08/29/2021 | /BJD/ |

| Interference Search | | | |
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| US Class/CPC Symbol | US Subclass/CPC Group | Date | Examiner |
| | | | |

| /BRIAN J DAVIS/<br>Primary Examiner, Art Unit 1612 | 8/31/2021 |
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| | Examiner | Art Unit |
| | BRIAN J DAVIS | 1612 |

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**CLAIMS**

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
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| | **Examiner** | **Art Unit** |
| | BRIAN J DAVIS | 1612 |

| CLAIM | | DATE | | | | | | | | |
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| Final | Original | 08/31/2021 | | | | | | | | |
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| | Examiner | Art Unit |
| | BRIAN J DAVIS | 1612 |

| CLAIM | | DATE | | | | | | | | |
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| Final | Original | 08/31/2021 | | | | | | | | |
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| | **Examiner** | **Art Unit** |
| | BRIAN J DAVIS | 1612 |

| CLAIM | | DATE | | | | | | | | |
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| Final | Original | 08/31/2021 | | | | | | | | |
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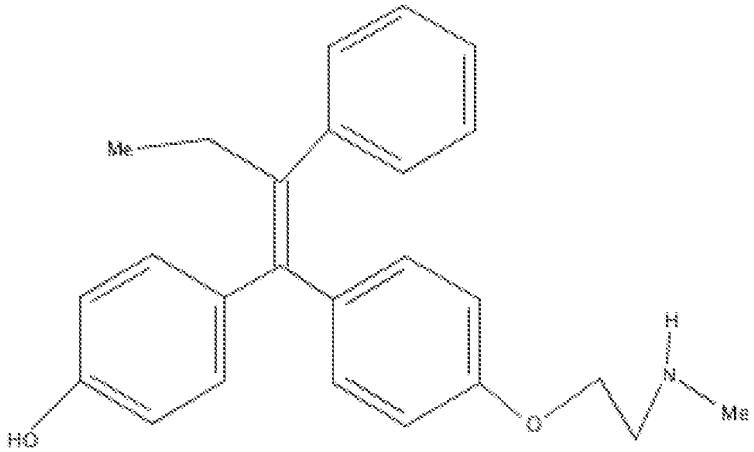


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**Session Began August 29, 2021 at 07:41 PM**

**Task Began August 29, 2021 07:43 PM**

**Explore substances by SUBSTRUCTURE ID(1)**




| | |
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*Answer Type:* *Substances*

*Result Count:* *116*

**Retrieve reference information in 1 substance (ID 2)**

From ID: 1

*Answer Type:* *References*

*Result Count:* *664*

**Refine by research topic (ID 3)**

Research Topic: polymorph
From ID: 2

*Answer Type:* *References*

*Result Count:* *134*

**Detailed display**

From ID: 3

Type: Preparation of endoxifen citrate polymorph

Exported as Reference_08_29_2021_194527.pdf

**Detailed display**

From ID: 3

Type: Preparation of endoxifen citrate polymorph

**Detailed display**

From ID: 3

Type: Preparation of Z-endoxifen and salts thereof and topical compositions containing them for the treatment and prevention of cancers and reproductive tract disorders

**Refine by research topic (ID 4)**

Research Topic: form
From ID: 2

*Answer Type:* *References*

*Result Count:* *66*

**Detailed display**

From ID: 4

Type: method for preparation of Z-form endoxifen

Exported as Reference_08_29_2021_195138.pdf

**Detailed display**

From ID: 4

Type: Method for preparation of Z-form endoxifen

**Detailed display**

From ID: 4

Type: Preparation of endoxifen citrate polymorph

**Task Began August 29, 2021 07:55 PM**

**Explore references by research topic: endoxifen**

Research Topic: endoxifen
Result Count: 2

**Candidates Selected (ID 5)**

843 references were found containing "endoxifen" as entered.

933 references were found containing the concept "endoxifen".

*Answer Type:* *References*

*Result Count:* *933*

**Refine by research topic (ID 6)**

Research Topic: Z
From ID: 5

*Answer Type:* *References*

*Result Count:* *141*

**Detailed display**

From ID: 6

Type: A convenient synthesis of (Z)-4-hydroxy-N-desmethyltamoxifen (endoxifen)

Exported as Reference_08_29_2021_195650.pdf

**Detailed display**

From ID: 6

Type: preparation of 4-hydroxytoremifene prodrugs for treating and preventing breast cancer

Exported as Reference_08_29_2021_195826.pdf

**Detailed display**

From ID: 6

Type: Characterization of the isomeric configuration and impurities of (Z)-endoxifen by 2D NMR, high resolution LC MS, and quantitative HPLC analysis

Exported as Reference_08_29_2021_200126.pdf

**Detailed display**

From ID: 6

Type: Process for preparing (Z)-endoxifen hydrochloride

Exported as Reference_08_29_2021_200307.pdf

**Detailed display**

From ID: 6

Type: A process for the preparation of (Z)-endoxifen

Exported as Reference_08_29_2021_200453.pdf

**Detailed display**

From ID: 6

Type: A multi-gram-scale stereoselective synthesis of Z-endoxifen

Exported as Reference_08_29_2021_200548.pdf

**Detailed display**

From ID: 6

Type: Preparation of Z-endoxifen and salts thereof and topical compositions containing them for the treatment and prevention of cancers and reproductive tract disorders

**Detailed display**

From ID: 6

Type: Preparation of endoxifen isoforms and salts thereof and topical compositions containing them for the treatment and prevention of cancers and reproductive tract disorders

**Refine by research topic (ID 7)**

Research Topic: isoform
From ID: 5

*Answer Type:* *References*

*Result Count:* *33*

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Sheet 1 of 10

| Complete if Known | |
|---|---|
| Application Number | 16641985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | QUAY; Steven C. |
| Art Unit | 1629 |
| Examiner Name | Not assigned yet |
| Attorney Docket Number | 38602-758.831 |

## U. S. PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Document Number Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
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| Complete if Known | |
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| Application Number | 16641985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | QUAY; Steven C. |
| Art Unit | 1629 |
| Examiner Name | Not assigned yet |
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| Application Number | 16641985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | QUAY; Steven C. |
| Art Unit | 1629 |
| Examiner Name | Not assigned yet |
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|---|---|---|---|---|---|---|
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|---|---|
| Application Number | 16641985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | QUAY; Steven C. |
| Art Unit | 1629 |
| Examiner Name | Not assigned yet |
| Attorney Docket Number | 38602-758.831 |

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| Examiner Signature | /BRIAN J DAVIS/ | Date Considered | 08/29/2021 |
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| Application Number | 16641985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | QUAY; Steven C. |
| Art Unit | 1629 |
| Examiner Name | Not assigned yet |
| Attorney Docket Number | 38602-758.831 |

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| Application Number | 16641985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | QUAY; Steven C. |
| Art Unit | 1629 |
| Examiner Name | Not assigned yet |
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| | 027 | ~~Lee et al., in vitro human skin permeation of endoxifen: potential for local transdermal therapy~~ for primary prevention and carcinoma in situ of the breast, Breast Cancer: Targets and Therapy 2011:3, 61-70. | ☐ |

| Examiner Signature | /BRIAN J DAVIS/ | Date Considered | 08/29/2021 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
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Substitute for form 1449/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 7 of 10

| Complete if Known | |
|---|---|
| Application Number | 16641985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | QUAY; Steven C. |
| Art Unit | 1629 |
| Examiner Name | Not assigned yet |
| Attorney Docket Number | 38602-758.831 |

| NON-PATENT LITERATURE DOCUMENTS | | | |
|---|---|---|---|
| Examiner Initials* | Cite No.[1] | Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published. | T[2] |
| | 028 | ~~LEE, et al. Local transdermal therapy to the breast for breast cancer prevention and DCIS therapy: preclinical and clinical evaluation. Cancer Chemother Pharmacol. 2015 Dec;76(6):1235-46. doi: 10.1007/s00280-015-2848-y.~~ | ☐ |
| | 029 | LI, et al. Prognostic values of Ki-67 in neoadjuvant setting for breast cancer: a systematic review and meta-analysis. Future Oncol. 2017 May;13(11):1021-1034. | ☐ |
| | 030 | ~~MANSEL, et al. A phase II trial of Afimoxifene (4-hydroxyTamoxifen gel) for cyclical mastalgia in premenopausal women. Breast Cancer Res Treat. 2007 Dec;106(3):389-97.~~ | ☐ |
| | 031 | Maximov et al., Structure-Function Relationships of Estrogenic Triphenylethylenes Related to Endoxifen and 4-Hydroxytamoxifen. J Med. Chem. 22 April 2010; 53(8): 3273-3283. | ☐ |
| | 032 | MELNIKOW, et al. Preferences of Women Evaluating Risks of Tamoxifen (POWER) study of preferences for Tamoxifen for breast cancer risk reduction. Cancer. 2005 May 15;103(10):1996-2005. | ☐ |
| | 033 | OGAWA, et al. Synthesis and antiestrogenic activity of the compounds related to the metabolites of (E)-4-[1-[4-[2-(dimethylamino)ethoxy]phenyl]- 2-(4-isopropylphenyl)-1-butenyl]phenyl monophosphate (TAT-59) [corrected]. Chem. Pharm. Bull. 39, 911-916, 1991. | ☐ |
| | 034 | OKEN, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group.Am J Clin Oncol. 1982;5:649-655. | ☐ |
| | 035 | PCT/US2018/050193 International Search Report and Written Opinion dated January 4, 2019. | ☐ |
| | 036 | PCT/US2018-050272 International Search Report and Written Opinion dated January 3, 2019. | ☐ |

| Examiner Signature | /BRIAN J DAVIS/ | Date Considered | 08/29/2021 |
|---|---|---|---|

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 8 of 10

| Complete if Known | |
|---|---|
| Application Number | 16641985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | QUAY; Steven C. |
| Art Unit | 1629 |
| Examiner Name | Not assigned yet |
| Attorney Docket Number | 38602-758.831 |

**NON-PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| | 037 | ROUANET, et al. Neoadjuvant percutaneous 4-hydroxyTamoxifen decreases breast tumoral cell proliferation: a prospective controlled randomized study comparing three doses of 4-hydroxyTamoxifen gel to oral Tamoxifen. J Clin Oncol. 2005 May 1;23(13):2980-7. | ☐ |
| | 038 | STEARNS, et al. Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. J Natl Cancer Inst. 2003 Dec 3;95(23):1758-64. | ☐ |
| | 039 | SUN, et al. Construction and evaluation of a novel humanized HER2-specific chimeric receptor.Breast Cancer Research: BCR 16.3 (2014): R61. | ☐ |
| | 040 | WU, et al. The Tamoxifen metabolite, Endoxifen, is a potent antiestrogen that targets estrogen receptor alpha for degradation in breast cancer cells. Cancer Res. 2009 Mar 1;69(5):1722-7. doi: 10.1158/0008-5472.CAN-08-3933. | ☐ |
| | 041 | Yang et al., Dendron-Based Micelles for Topical Delivery of Endoxifen: A Potential Chemo-Preventive Medicine for Breast Cancer Adv. Funct. Mater. 2014, 24, 2442-2449. | ☐ |
| | 042 | ZHAO, et al. A Herceptin-Based Chimeric Antigen Receptor with Modified Signaling Domains Leads to Enhanced Survival of Transduced T Lymphocytes and Antitumor Activity. THE JOURNAL OF IMMUNOLOGY, vol. 183, no. 9, 1 November 2009 (2009-11-01), pages 5563-5574. | ☐ |

| Examiner Signature | /BRIAN J DAVIS/ | Date Considered | 08/29/2021 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 16641985 |
| Filing Date | 2020-02-25 |
| First Named Inventor | STEVEN; C. Quay |
| Art Unit | 1629 |
| Examiner Name | - |
| Attorney Docket Number | 109559-669805 |

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|---|---|---|---|---|---|---|
| | 1 | 20120301541 | | 2012-11-29 | HARONSKY; Elina et al. | |

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| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 16641985 |
| | Filing Date | 2020-02-25 |
| | First Named Inventor | STEVEN; C. Quay |
| | Art Unit | 1629 |
| | Examiner Name | - |
| | Attorney Docket Number | 109559-669805 |

| | | | |
|---|---|---|---|
| | 1 | Extended European Search Report for European Application No. EP18853361.6, dated May 28, 2021, 5 pages. | |
| | 2 | FOREFRONT., "Endoxifen Shows Promise As Breast Cancer Treatment", Mayo Clinic Cancer Center's Online Magazine, Vol. 3, Issue 1, 2014, 3 pages. | |
| | 3 | LOVE et al., "A Feasibility Study of the Intraductal Administration of Chemotherapy", Cancer Prevention Research, Vol. 6, No. 1, January 2013, pp. 51-58. | |
| | 4 | Search Report and Written Opinion for Singapore Patent Application No. SG11202002105W mailed April 21, 2021, 8 pages. | |

If you wish to add additional non-patent literature document citation information please click the Add button Add

**EXAMINER SIGNATURE**

| Examiner Signature | /BRIAN J DAVIS/ | Date Considered | 08/29/2021 |
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PTO/SB/06 (09-11)
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| **PATENT APPLICATION FEE DETERMINATION RECORD**<br>Substitute for Form PTO-875 | Application or Docket Number<br>16/641,985 | Filing Date<br>02/25/2020 | ☐ To be Mailed |
|---|---|---|---|

**ENTITY:** ☐ LARGE ☑ SMALL ☐ MICRO

## APPLICATION AS FILED - PART I

| FOR | (Column 1)<br>NUMBER FILED | (Column 2)<br>NUMBER EXTRA | | RATE ($) | FEE ($) |
|---|---|---|---|---|---|
| ☐ BASIC FEE<br>(37 CFR 1.16(a), (b), or (c)) | N/A | N/A | | N/A | |
| ☐ SEARCH FEE<br>(37 CFR 1.16(k), (i), or (m)) | N/A | N/A | | N/A | |
| ☐ EXAMINATION FEE<br>(37 CFR 1.16(o), (p), or (q)) | N/A | N/A | | N/A | |
| TOTAL CLAIMS<br>(37 CFR 1.16(i)) | minus 20 = | * | | x $50 = | |
| INDEPENDENT CLAIMS<br>(37 CFR 1.16(h)) | minus 3 = | * | | x $230 = | |
| ☐ APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | | |
| ☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | | |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | | TOTAL | |

## APPLICATION AS AMENDED - PART II

| AMENDMENT | 10/15/2021 | (Column 1)<br>CLAIMS REMAINING AFTER AMENDMENT | | (Column 2)<br>HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3)<br>PRESENT EXTRA | | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|---|
| | Total<br>(37 CFR 1.16(i)) | * 21 | Minus | ** 23 | = 0 | | x $50 = | 0 |
| | Independent<br>(37 CFR 1.16(h)) | * 2 | Minus | *** 3 | = 0 | | x $240 = | 0 |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | |
| | | | | | | | TOTAL ADD'L FEE | 0 |

| AMENDMENT | | (Column 1)<br>CLAIMS REMAINING AFTER AMENDMENT | | (Column 2)<br>HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3)<br>PRESENT EXTRA | | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|---|
| | Total<br>(37 CFR 1.16(i)) | * | Minus | ** | = | | x $0 = | |
| | Independent<br>(37 CFR 1.16(h)) | * | Minus | *** | = | | x $0 = | |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | |
| | | | | | | | TOTAL ADD'L FEE | |

| | |
|---|---|
| * If the entry in column 1 is less than the entry in column 2, write "0" in column 3. | LIE |
| ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". | /YOLANDA CHADWICK/ |
| *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". | |
| The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1. | |

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# SCORE Placeholder Sheet for IFW Content

Application Number: 16641985 Document Date: 10/15/2021

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POLSINELLI PC

By: October 15, 2021

Attorney Docket No.: 109559-669805

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re Application of: | Confirmation No. 7650 |
| Steven C. QUAY et al. | |
| Application No.: 16/641,985 | Examiner: Brian J. Davis |
| Filed: February 25, 2020 | Art Unit: 1612 |
| For: METHODS FOR MAKING AND USING ENDOXIFEN | AMENDMENT |
| Customer No. 27148 | |

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.



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**Intas Exhibit 1002**
**Page 459 of 598**
**IPR2025-00799**

**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.

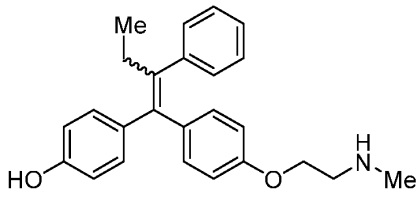
Attachment: Replacement Sheets

**Amendments 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 composition comprising a crystalline form of a compound of Formula (III):




Formula (III),

wherein at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer [[and]], and wherein the crystalline form of the (Z)-isomer ~~compound of Formula (III)~~ is Form I, characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta.

2-3. (Canceled)

4. (Canceled) ~~The composition of claim 1, wherein the crystalline form is characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta.~~

5. (Currently Amended) The composition of claim [[4]]1, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from 16.0 ± 0.3°, 18.8 ± 0.3° and 26.5 ± 0.3 two theta.

6. (Currently Amended) The composition of claim [[4]]1, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from 12.3 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta.

7. (Currently Amended) The composition of claim [[4]]1, wherein the x-ray powder diffraction pattern further comprises peaks at 12.3 ± 0.3°, 16.0 ± 0.3°, 18.8 ± 0.3°, 26.5 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta.

8. (Currently Amended) The composition of claim 1, wherein the crystalline form of the (Z)-isomer is characterized by an x-ray powder diffraction pattern substantially as set forth in Fig. 9 or Fig. 10.

9. (Currently Amended) The composition of claim 1, wherein greater than 90% by weight of the (Z)-isomer ~~compound of Formula (III)~~ in the composition is crystalline Form I.

10-31. (Canceled)

32. (Previously Presented) The composition of claim 1, further comprising a pharmaceutically acceptable carrier or diluent.

33. (Previously Presented) The composition of claim 32, wherein the composition is formulated for oral, parenteral, topical, or intraductal delivery.

34. (Previously Presented) The composition of claim 32, wherein the composition is formulated for oral delivery as a tablet, a caplet, a capsule, or a pill.

35. (Currently Amended) The composition of claim 32, wherein a mean half-life of the compound of Formula (III) ~~endoxifen~~ in a subject treated with the composition is between 30 hours to 60 hours.

36-37. (Canceled)

38. (Currently Amended) The composition of claim 1, formulated as an oral dosage form comprising 1 mg to 200 mg per unit dose of the composition, and wherein daily

administration of the oral dosage form achieves in a subject ~~in need thereof~~ treated with the composition one or more of:

a steady state plasma level of the compound of Formula (III) ~~endoxifen~~ within 7 to 21 days;

a steady state plasma level of the compound of Formula (III) ~~endoxifen~~ ranging from 25 nM to 300 nM;

a steady state plasma level of the compound of Formula (III) ~~endoxifen~~ greater than 30 nM; or

maximal plasma levels of the compound of Formula (III) ~~endoxifen~~ within 2 to 10 hours after administering.

39. (Currently Amended) The composition of claim 38, wherein a mean half-life of the compound of Formula (III) ~~endoxifen~~ in [[a]] the subject ~~treated with the oral dosage form~~ is between 40 hours to 55 hours.

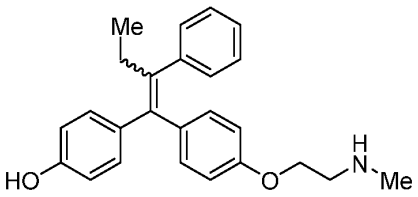
40. (Previously Presented) The composition of claim 38, wherein the oral dosage form is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

41. (Currently Amended) The composition of claim 38, wherein at least 80% of the compound of Formula (III) ~~endoxifen~~ in the oral dosage form is released in the intestines of [[a]] the subject ~~treated with the oral dosage form~~.

42. (Currently Amended) The composition of claim 38, having a mean area under the curve extrapolated to time infinity ($AUC_{0\text{-}inf}$) of the compound of Formula (III) ~~endoxifen~~ of 200 hr*ng/mL to 10000 hr*ng/mL.

43. (Currently Amended) A method of treating or preventing a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in a subject ~~in need thereof~~,

the method comprising administering to the subject a composition comprising a crystalline form of a compound of Formula (III):




Formula (III),

wherein at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer [[and]], and wherein the crystalline form of the (Z)-isomer ~~compound of Formula (III)~~ is Form I, characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta, thereby treating or preventing the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder.

44. (Canceled) ~~The method of claim 43, wherein the subject has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both.~~

45. (Canceled)

46. (Previously Presented) The method of claim 43, wherein the subject has prostate cancer and wherein the subject further has or is at risk of having gynecomastia.

47. (Previously Presented) The method of claim 43, wherein the subject has tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder.

48. (Canceled)

49. (Currently Amended) The method of claim 43, wherein the composition comprises 0.01 mg to 200 mg of the (Z)-isomer ~~(Z) endoxifen~~.

50-51. (Canceled)

52. (Currently Amended) The method of claim 43, wherein a steady state plasma level of the compound of Formula (III) ~~endoxifen~~ is achieved within 7 to 21 days of the first administration of the composition to the subject, and wherein the steady state plasma level of the compound of Formula (III) ~~endoxifen~~ in the subject is greater than 30 nM.

53-157. (Canceled)

158. (New) The composition of claim 1, wherein the composition is stable for at least 9 months at 5 °C and 60% relative humidity or at 25 °C and 60% relative humidity.

## 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 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° 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

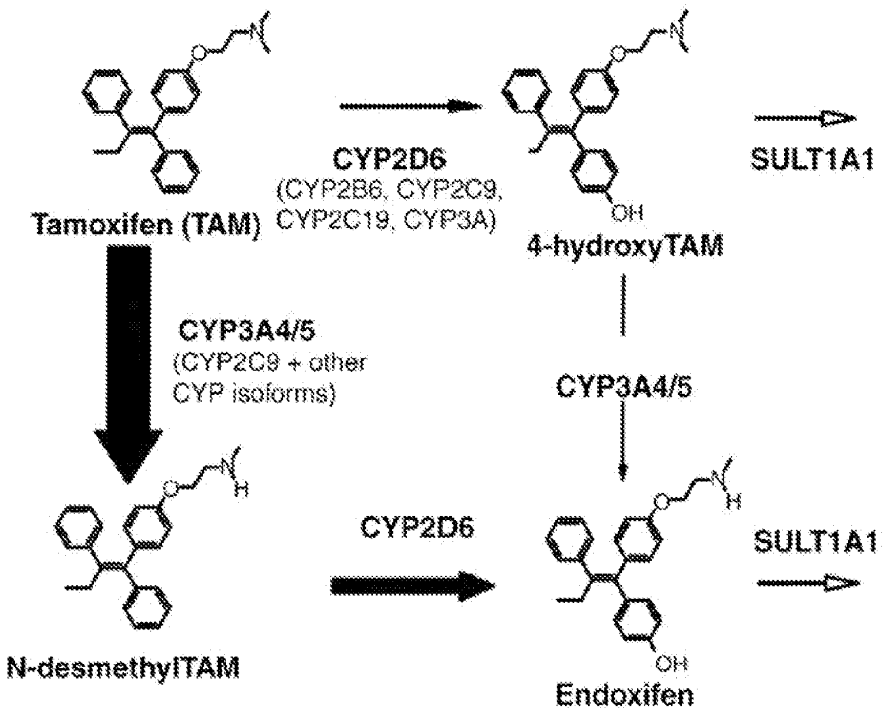
/Lisa G Lippert/

Lisa G. Lippert, Ph.D.
Registration No. 78,332

POLSINELLI PC
900 W. 48th Place, Suite 900
Kansas City, MO 64112
Tel: 816-753-1000
Fax: 816-753-1536

REPLACEMENT SHEET

**Fig. 1**




# PRIOR ART

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 16641985 |
| **Filing Date:** | 25-Feb-2020 |
| **Title of Invention:** | METHODS FOR MAKING AND USING ENDOXIFEN |
| **First Named Inventor/Applicant Name:** | Steven C. Quay |
| **Filer:** | Lisa Gail Lippert/Megan Thornton |
| **Attorney Docket Number:** | 109559-669805 |

Filed as Small Entity

**Filing Fees for U.S. National Stage under 35 USC 371**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Miscellaneous:** | | | | |
| SUBMISSION- INFORMATION DISCLOSURE STMT | 2806 | 1 | 130 | 130 |
| | | **Total in USD ($)** | | **130** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 44045115 |
| **Application Number:** | 16641985 |
| **International Application Number:** | |
| **Confirmation Number:** | 7650 |
| **Title of Invention:** | METHODS FOR MAKING AND USING ENDOXIFEN |
| **First Named Inventor/Applicant Name:** | Steven C. Quay |
| **Customer Number:** | 27148 |
| **Filer:** | Lisa Gail Lippert/Megan Thornton |
| **Filer Authorized By:** | Lisa Gail Lippert |
| **Attorney Docket Number:** | 109559-669805 |
| **Receipt Date:** | 15-OCT-2021 |
| **Filing Date:** | 25-FEB-2020 |
| **Time Stamp:** | 17:51:03 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | DA |
| Payment was successfully received in RAM | $130 |
| RAM confirmation Number | E20210EH51562474 |
| Deposit Account | 501662 |
| Authorized User | Megan Thornton |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:<br>37 CFR 1.17 (Patent application and reexamination processing fees)<br>37 CFR 1.19 (Document supply fees) | |

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

37 CFR 1.492(a) (Basic national fee only)

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Transmittal Letter | 109559-669805-IDS-Transmittal.pdf | 163334<br>cd4108736adf5fbdefa3df313cb2b27b25fcd692 | no | 4 |
| **Warnings:** | | | | | |
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| 2 | Information Disclosure Statement (IDS) Form (SB08) | 109559-669805_IDS_20211014125321.pdf | 171276<br>2a552826b5470dfc3280982046d7c024e9a8b455 | no | 8 |
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| This is not an USPTO supplied IDS fillable form | | | | | |
| 3 | Foreign Reference | WO0174366A1_EFS.pdf | 1385726<br>3951e54c6623660ebd27ff49d8bc44f78cf46829 | no | 31 |
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| 4 | Foreign Reference | EP3202420A1_EFS.pdf | 1586753<br>d98590f7025b5ec39fe6258cf02ff83dd7c2bce3 | no | 28 |
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| 5 | Foreign Reference | WO2015138340A1_EFS.pdf | 703141<br>f7769da9e95d71af0a6abd7f6179de6dfb9eefa0 | no | 18 |
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| 6 | Foreign Reference | EP2350111A1_EFS.pdf | 15139<br>daa8fc543eec1964963fbe3d5e9073bc9a00bb2f | no | 1 |
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| 7 | Foreign Reference | WO2009069140A1_EFS.pdf | 1936432<br>21004f85a6693365ba0b1fcd64bed2bf3ae22c30 | no | 54 |
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| 8 | Foreign Reference | WO2009032699A1_EFS.pdf | 4915622<br>4b65ab11da87155740c500ac48eeadba954fedad | no | 89 |
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| 9 | Foreign Reference | WO2015106094A1_EFS.pdf | 2279983<br>4efee717e5cc0a09b169ca331701d6a48798185c | no | 39 |
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| 10 | Foreign Reference | WO2017011623A1_EFS.pdf | 3691076<br>c51c18425903ea88a969926d815694e93f0c9f47 | no | 63 |
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| 11 | Foreign Reference | WO2013-050280.pdf | 2281878<br>caea791c4c39c04e4032eae8b74363292713845e | no | 57 |
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| 12 | Foreign Reference | WO0064416A3_EFS.pdf | 134700<br>0c9e5e4ed7ac63fd44fc16ec534c46ca496ea2ed | no | 4 |
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| 13 | Foreign Reference | WO2014060640A8_EFS.pdf | 49753<br>38e5c4720814e58c18a2a2799527415b5b2af797 | no | 1 |
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| 14 | Foreign Reference | EP1709062B9_EFS.pdf | 1001716<br>f2f9ffa2cb1ed80bd5ade74d71ee97c64f2985ae | no | 27 |
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| 15 | Non Patent Literature | Ikeda_2011_pp_2038_2042_EFS.pdf | 3197594<br>f6ce7c416b1dd1759c28125ad262414922af4e7c | no | 5 |
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| 16 | Foreign Reference | CN104230723B_EFS.pdf | 1706447<br>1baec466992e056712f729eacf33116d1a0606bc | no | 23 |
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| 17 | Non Patent Literature | AYDINER_MetaAnalysis_29July2008_9pgs_EFS.pdf | 4331423<br>5dd7f4aae3e91c57eac250c16f305be6ba68a733 | no | 9 |
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| 18 | Non Patent Literature | BAO_Clinicalpharmacology_2011_3pgs_EFS.pdf | 2146458<br>33d788f50701d37c0d69e69f99f804976915f92b | no | 3 |
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| 19 | Non Patent Literature | BATHINI_Improvedsysnthesis_2014_4pgs_EFS.pdf | 1731479<br>841af24196c85bf6f6a2e149cab4f0192e4c6aa8 | no | 4 |
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| 20 | Non Patent Literature | DAVISON_InVitro_11Nov2008_10pgs_EFS.pdf | 5784393<br>6ab5c0aaaa2d7dd28675202a4b3b5f619f8701ae | no | 10 |
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| 21 | Non Patent Literature | DOWSETT_Effect_Anastrozole_1999_5pgs_EFS.pdf | 3034292<br>c98363f0002afeb524ce0467b52f001a4e7351df | no | 5 |
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| 22 | Non Patent Literature | FORBES_Anastrozole_27Feb2016_8pgs_EFS.pdf | 5257248<br>3ee5a3a574373057210c660cae03252b874d9ad4 | no | 8 |
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| 23 | Non Patent Literature | GELMON_Targeting_2012_12pgs_EFS.pdf | 8318918<br>f8417efae79b056992e3ec1b5d0d0ce1818dad49 | no | 12 |
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| 24 | Non Patent Literature | HERSHMAN_EARLYDiscontinuation_20Sept2010_9pgs_EFS.pdf | 5237002<br>825c48db89097c7b30fc389caf0080550b629620 | no | 9 |
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| 25 | Non Patent Literature | INGLE_Variation_15Apr2010_17pgs_EFS.pdf | 6194752<br>3bff24a73d1296603ae0b84f03225dde93d7b673 | no | 17 |
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| 26 | Non Patent Literature | JANSEN_Highmir26a_2012_11pgs_EFS.pdf | 6137353<br>2d28d298358f99d4785f3d68873ff7efd5dd71c | no | 11 |
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| 27 | Non Patent Literature | KAMDEM_Oxidative_2010_16pgs_EFS.pdf | 9868933<br>8e203965cb9971ec826cb967be13965cf1237eab | no | 16 |
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| 28 | Non Patent Literature | KAUR_Designsynthesis_30Oct2014_8pgs_EFS.pdf | 4585293<br>829249e13f36a44def99492967c80f4e598e6afb | no | 8 |
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| 29 | Non Patent Literature | KEBAMO_Biotransformation_2015_13pgs_EFS.pdf | 8225959<br>1682f17a7fda392a336e5fbbd213d7bfe2a1e1af | no | 13 |
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| 30 | Non Patent Literature | LANCET_Aromatase_Oct2015_12pgs_EFS.pdf | 6925316<br>7084e906fc7dbaffe4d17001c1d874d985e84880 | no | 12 |
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| 31 | Non Patent Literature | MILLER_Stereospecific_1985_3PGS_EFS.pdf | 1257109<br>2593b9770c80909b29d2f0f20e342dc8a1a7a676 | no | 3 |
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| 32 | Non Patent Literature | LIBY_Combination_LG100268_Oct2006_9pgs_EFS.pdf | 5535038<br>0510d5629de062f73c2ffe97e1767ba8fce39cec | no | 9 |
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| 33 | Non Patent Literature | LEMAINE_Gynecomastia_Feb2013_6pgs_EFS.pdf | 3349040<br>63d704e241d62cd74f9f906f9f792496b183be09 | no | 6 |
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| 34 | Non Patent Literature | LARI_Biological_2011_30pgs_EFS.pdf | 15446125<br>6794a41b033e0254104e491821832c8bcff97bac | no | 30 |
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| 35 | Non Patent Literature | PARTRIDGE_Initial_Adjuvant_01Feb2008_7pgs_EFS.pdf | 3473927<br>32a3fafc84946456732a759860b2c45facc6d6cf | no | 7 |
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| 36 | Non Patent Literature | ROBERTSON_Advanced_Cancer_2004_10pgs_EFS.pdf | 3821453<br>b1d35263f0ef767206c2624588282551836 8643f | no | 10 |
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| 37 | Non Patent Literature | ROBERTSON_Pharmacokinetics_Pharmacology_2004_4pgs_EFS.pdf | 2329362<br>d4ababedc567636dc80e40e9f0a32d70699 26b48 | no | 4 |
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| 38 | Non Patent Literature | SANO_Synthesis_Coupling_Reaction_2006_5pgs_EFS.pdf | 5889563<br>40c3aa012bd4176b27d1cbb374e14e2d0e 5c11cc | no | 5 |
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| 39 | Non Patent Literature | UMAREDDY_Improved_Process_2015_6pgs_EFS.pdf | 2327871<br>344a541a66d4c1ab13283eb124515a3dd3 b1a096 | no | 6 |
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| 40 | Non Patent Literature | UMAREDDY_Total_Synthesis_2015_5pgs_EFS.pdf | 1863078<br>38fad82b0bc38801db208775bdeb48ffde0 ab430 | no | 5 |
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| 41 | Non Patent Literature | VERGOTE_Fulvestrant_Clinical_TRials_2004_4pgs_EFS.pdf | 2323034<br>4f3e42526e6e85df52b9f286586e47668301 aa98 | no | 4 |
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| 42 | Non Patent Literature | WELSH_Induction_Cancer_1994_9pgs_EFS.pdf | 888413<br>75aaa2ac8107296297c1304e023af2a26dd6aac9 | no | 9 |
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| 43 | Non Patent Literature | YAO_Synthesis_Reactivity_2001_11pgs_EFS.pdf | 5892310<br>51bf64ed94356b79c09f2737dac294e2a161e3c5 | no | 11 |
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| 44 | Non Patent Literature | ZHANG_Safety_Parameters_09Sep2014_9pgs_EFS.pdf | 3233518<br>1c7cadc9048e64a05f3883340eddaeaffb1b29aa | no | 9 |
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| 45 | Non Patent Literature | MAH_Miniaturized_Flow_2013_8pgs_EFS.pdf | 4262062<br>a917a81e855b14b536229b6e906a25c66450e55d | no | 8 |
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| 46 | Non Patent Literature | PARTRIDGE_NonAdherence_Therapy_15Feb2003_5pgs_EFS.pdf | 3787018<br>38d87cb1384b2aef104f99795872ab5d9a41cf9e | no | 5 |
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| 47 | Non Patent Literature | YONEYA_Thiochroman_Estrogen_2010_6pgs_EFS.pdf | 3556299<br>c416d7e0ff24c4bb0da922d4a984fbd0b222e1df | no | 6 |
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| 48 | Non Patent Literature | MANNI_Combination_of_Antiestrogens_2015_Pgs10_EFS.pdf | 2324443<br>2dc38553b5915023b922c7e6e1d2cf0086e027da | no | 10 |
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| 49 | Foreign Reference | WO2013134230A1_EFS.pdf | 1951513<br>0235d0f72842bda30507d8377de343d98d48fd1d | no | 58 |
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| 50 | Non Patent Literature | AHAMAD_Endoxifen_A_New_Cornerstone_2010_pp_814_817_EFS.pdf | 2346789<br>7fcea34fac2713029c019c3e2bef60250eef9f88 | no | 4 |
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| 51 | Non Patent Literature | GAUTHIER_New_Highly_Stereoselective_1996_pp_3890_3893_EFS.pdf | 2241792<br>0d2a2a105ef54641733bb8c13938ee2ec9bbcaa6 | no | 4 |
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| 52 | Non Patent Literature | LEE_In_Vitro_Human_Skin_2011_pp_61_70_EFS.pdf | 4388582<br>54c568e4d849b2e770ec96ae54fada5334b4ca73 | no | 10 |
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| 53 | Non Patent Literature | LEE_Local_Transdermal_Therapy_2015_pp_1235_1246_EFS.pdf | 5734730<br>77d7e89f716bf6681766fb249ddf7d333550286e | no | 12 |
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| 54 | Non Patent Literature | MANSEL_A_Phase_II_Trial_2007_pp_389_397_EFS.pdf | 4327196<br>8939df28d493a656e33480eb693e92b9496b8a0d | no | 9 |
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| 55 | | 109559-669805-NFOA-Response-AMENDMENT.pdf | 184256<br>9ff60eec22178a4c10e9077f7f7bf253363b75be | yes | 12 |
| | **Multipart Description/PDF files in .zip description** | | | | |
| | **Document Description** | | **Start** | **End** | |

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| | Amendment/Req. Reconsideration-After Non-Final Reject | | 1 | 1 | |
| | Drawings-other than black and white line drawings | | 2 | 2 | |
| | Claims | | 3 | 7 | |
| | Applicant Arguments/Remarks Made in an Amendment | | 8 | 12 | |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 56 | Drawings-only black and white line drawings | 109559-669805-Figure-1-Replacement-Sheet-NFOA.pdf | 107032<br>f28e4a119fe2f7f844ff3523aef80472787439<br>7d | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 57 | Fee Worksheet (SB06) | fee-info.pdf | 38232<br>2775281b187f1d246f9ea2b3c013a9a97af3<br>8719 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 195879174 | | |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**

**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**

**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**

**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Inventor: | Steven C. Quay | Group Art Unit: | 1612 |
| Serial Number: | 16/641,985 | Examiner: | Brian J. Davis |
| Filing or 371 (c) Date: | February 25, 2020 | **CONFIRMATION NO:** | **7650** |
| Title: | METHODS FOR MAKING AND USING ENDOXIFEN | CUST. NO.: | 27148 |

**FILED ELECTRONICALLY ON October 15, 2021**

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

## INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☒ a fee of $130.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of $260.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $130.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 501662 (Docket No. 50-1662).

Respectfully submitted,

Dated: October 15, 2021,

/Lisa G Lippert/
Lisa G. Lippert, Ph.D.
Registration No. 78,332

POLSINELLI PC
900 W. 48th Place, Suite 900
Kansas City, MO 64112
Tel: (816) 753-1000
Fax: (816) 753-1536
CUSTOMER NO.: 27148

Substitute for form 1449/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 8

| Complete if Known | |
|---|---|
| Application Number | 16/641,985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | STEVEN; C. Quay |
| Art Unit | 1612 |
| Examiner Name | DAVIS, BRIAN J |
| Attorney Docket Number | 109559-669805 |

**U. S. PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | 001 | US-3848030 | 11-12-1974 | VITERBO; R. et al. | |
| | 002 | US-6774122 | 08-10-2004 | EVANS; John R. et al. | |
| | 003 | US-7384418 | 06-10-2008 | HUNG; David et al. | |
| | 004 | US-7705159 | 04-27-2010 | MACDONALD; Peter Lindsay et al. | |
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| | 007 | US-8436029 | 05-07-2013 | HICKEY; Magali Bourghol et al. | |
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| | 010 | US-8822511 | 09-02-2014 | COMBS; Andrew P. et al. | |
| | 011 | US-8993605 | 03-31-2015 | COMBS; Andrew P. et al. | |
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| | 013 | US-9308181 | 04-12-2016 | KISAK; Edward T. et al. | |
| | 014 | US-20020025543 | 02-28-2002 | SERRERO; Ginette | |
| | 015 | US-20030021787 | 01-30-2003 | HUNG; David et al. | |
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| | 019 | US-20070190019 | 08-16-2007 | GUO; Chunfeng et al. | |
| | 020 | US-20080319092 | 12-25-2008 | SINGH; Jagat | |
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| | 022 | US-20090098069 | 04-16-2009 | VACCA; Rita Downard | |
| | 023 | US-20090208944 | 08-20-2009 | GOETZ; Matthew P. et al. | |
| | 024 | US-20090281063 | 11-12-2009 | INAGI; Toshio et al. | |
| | 025 | US-20090291102 | 11-26-2009 | FORTIN; Samuel | |

| Examiner Signature | | Date Considered | |
|---|---|---|---|

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 8

| Complete if Known | |
|---|---|
| Application Number | 16/641,985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | STEVEN; C. Quay |
| Art Unit | 1612 |
| Examiner Name | DAVIS, BRIAN J |
| Attorney Docket Number | 109559-669805 |

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|---|---|---|---|---|---|
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| | 028 | US-20100069781 | 03-18-2010 | JOHANSEN; Jerald A. et al. | |
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| | 032 | US-20130046171 | 02-21-2013 | JOHANSEN; Jerald A. et al. | |
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| | 035 | US-20160346230 | 12-01-2016 | AHMAD; Ateeq et al. | |
| | 036 | US-20160375234 | 12-29-2016 | STEVEN; C. Quay | |
| | 037 | US-20170145515 | 05-25-2017 | CHEN; Shu-Chih et al. | |
| | 038 | US-20180049999 | 02-22-2018 | QUAY; Steven C. | |
| | 039 | US-20180200206 | 07-19-2018 | QUAY; Steven C. | |

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| Examiner Initials* | Cite No.[1] | Foreign Patent Document<br>Country Code[3]-Number[4]-Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| | 001 | CN-104230723-B | 08-24-2016 | ASYMCHEM LAB TIANJIN CO LTD. | | ☒ |
| | 002 | EP-1709062-B9 | 02-13-2013 | CEDARBURG PHARMACEUTICALS INC [US] | | ☐ |
| | 003 | EP-2350111-A1 | 08-03-2011 | SYNTHON BV [NL] | | ☐ |

| Examiner Signature | | Date Considered | |
|---|---|---|---|

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 3 of 8

| Complete if Known | |
|---|---|
| Application Number | 16/641,985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | STEVEN; C. Quay |
| Art Unit | 1612 |
| Examiner Name | DAVIS, BRIAN J |
| Attorney Docket Number | 109559-669805 |

## FOREIGN PATENT DOCUMENTS

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|---|---|---|---|---|---|---|
| | 004 | EP-3202420-A1 | 08-09-2017 | BESINS HEALTHCARE LU SARL [LU] | | ☐ |
| | 005 | WO-0064416-A3 | 03-08-2001 | LILLY CO ELI [US], et al. | | ☐ |
| | 006 | WO-0174366-A1 | 10-11-2001 | ASTRAZENECA AB [SE], et al. | | ☐ |
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| | 008 | WO-2009069140-A1 | 06-04-2009 | DABUR PHARMA LTD [IN], et al. | | ☐ |
| | 009 | WO-2013050280-A1 | 04-11-2013 | COMMISSARIAT ENERGIE ATOMIQUE [FR] | | ☐ |
| | 010 | WO-2013134230-A1 | 09-12-2013 | XAVIER UNIVERSITY [US] | | ☐ |
| | 011 | WO-2014060640-A8 | 05-07-2015 | FERMION OY [FI] | | ☐ |
| | 012 | WO-2015106094-A1 | 07-16-2015 | ATOSSA GENETICS INC [US] | | ☐ |
| | 013 | WO-2015138340-A1 | 09-17-2015 | REPROS THERAPEUTICS INC [US] | | ☐ |
| | 014 | WO-2017011623-A1 | 01-19-2017 | ATOSSA GENETICS INC [US] | | ☐ |

| Examiner Signature | | Date Considered | |
|---|---|---|---|

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 4 of 8

| Complete if Known | |
|---|---|
| Application Number | 16/641,985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | STEVEN; C. Quay |
| Art Unit | 1612 |
| Examiner Name | DAVIS, BRIAN J |
| Attorney Docket Number | 109559-669805 |

**NON-PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published. | T[2] |
|---|---|---|---|
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| | 002 | AYDINER, et al., "Meta-Analysis of Trials Comparing Anastrozole and Tamoxifen for Adjuvant Treatment of Oostmenopausal Women with Early Breast Cancer," Trials, Vol. 9 (47), 29 July 2008, pp. 1-9. | ☐ |
| | 003 | BAO, et al., "The Clinical Pharmacology of Anastrozole," European Oncology and Hematology, Vol. 7 (2), 2011, pp. 106-108. | ☐ |
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| | 009 | GELMON, et al., "Targeting Triple-Negative Breast Cancer: Optimizing Therapeutic Outcomes," Annals of Oncology, Vol. 23 (9), September 2012, pp. 2223-2234. | ☐ |

| Examiner Signature | | Date Considered | |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 5 of 8

| Complete if Known | |
|---|---|
| Application Number | 16/641,985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | STEVEN; C. Quay |
| Art Unit | 1612 |
| Examiner Name | DAVIS, BRIAN J |
| Attorney Docket Number | 109559-669805 |

**NON-PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| | 010 | HERSHMAN, et al., "Early Discontinuation and Non-adherence to Adjuvant Hormonal Therapy in a Cohort of 8, 769 early Stage Breast Cancer Patients," Journal of Clinical Oncology, Vol. 26(27), 20 September 2010. | ☐ |
| | 011 | IKEDA H., et al., "Combination Treatment with Fulvestrant and various Cytotoxic Agents (Doxorubicin, Paclitaxel, Docetaxel, Vinorelbine, and 5-Fluorouracil) has a Synergistic Effect in Estrogen Receptor-Positive Breast Cancer," Cancer Science, Vol. 102 (11), November 2011, pp. 2038-2042, 5 Pages. | ☐ |
| | 012 | INGLE, et al., "Variation in Anastrozole Metabolism and Pharmacodynamics in Women with Early Breast Cancer," Cancer Research, Vol. 70 (8), 15 April 2010, pp. 3278-3286. | ☐ |
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| | 015 | KAUR, et al., "Design, Synthesis and Evaluation of Ospemifene Analogs as Anti-Breast Cancer Agents," European Journal of Medicinal Chemistry, Vol. 86, 30 October 2014, pp. 211-218. | ☐ |
| | 016 | KEBAMO., et al., "The Role of Biotransformation in Drug Discovery and Development," Journal of Drug Metabolism and Toxicology, Vol. 6 (5), 2015, pp. 1-13. | ☐ |
| | 017 | LANCET, "Aromatase Inhibitors Versus Tamoxifen in Early Breast Cancer: Patient-Level Meta-Analysis of the Randomised Trials," Vol. 386, 2015, pp. 1341-1352. | ☐ |
| | 018 | LARI, et al., "Biological Markers in DCIS and Risk of Breast Recurrence: A Systematic Review," Journal of Cancer, Vol. 2, 2011, pp. 232- 261. | ☐ |
| | 019 | LEE O., et al., "In Vitro Human Skin Permeation of Endoxifen: Potential for Local Transdermal Therapy for Primary Prevention and Carcinoma in Situ of the Breast," Breast Cancer: Targets and Therapy, Vol. 3, 2011, pp. 61-70. | ☐ |

| Examiner Signature | | Date Considered | |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 6 of 8

| Complete if Known | |
|---|---|
| Application Number | 16/641,985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | STEVEN; C. Quay |
| Art Unit | 1612 |
| Examiner Name | DAVIS, BRIAN J |
| Attorney Docket Number | 109559-669805 |

**NON-PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| | 020 | LEE O., et al., "Local Transdermal Therapy to the Breast for Breast Cancer Prevention and DCIS Therapy: Preclinical and Clinical Evaluation," Cancer Chemother Pharmacol, Vol. 76(6), December 2015, pp. 1235-1246. | ☐ |
| | 021 | LEMAINE, et al., "Gynecomastia in Adolescent Males," Seminars Plastic Surgery, Vol. 27 (1), Febraury 2013, pp. 56-61. | ☐ |
| | 022 | LIBY, et al., "The Combination of the Rexinoid, LG100268, and a Selective Estrogen Receptor Modulator, Either Arzoxifene or A colbifene, Synergizes in the Prevent and Treatment of Mammary Tumors in an Estrogen Receptor-Negative Model of Breast Cancer," Clinical Cancer Research, Vol. 12 (19), October 2006, pp. 5902-5909. | ☐ |
| | 023 | MAH, et al., "A Miniaturized Flow-through Cell to Evaluate Skin Permeation of Endoxifen," International Journal of pharmaceutics, Vol. 441, 2013, pp. 433-440. | ☐ |
| | 024 | MANNI, et al., "Combination of Antiestrogens and Omega-3 Fatty Acids for Breast Cancer Prevention," Biomed Research International, 1 January 2015, 10 pages. | ☐ |
| | 025 | MANSEL R., et al., "A Phase II Trial of Afimoxifene (4-hydroxyTamoxifen gel) for Cyclical Mastalgia in Premenopausal Women," Breast Cancer Research Treatment, December 2007, Vol. 106 (3), pp. 389-397. | ☐ |
| | 026 | MILLER, et al., "Stereospecific Synthesis of (Z)-Tamoxifen via Carbometallation of Alkynylsilanes," The Journal of Organic Chemistry, Vol. 50 (12), 1985, pp. 2121-2123. | ☐ |
| | 027 | PARTRIDGE, et al., "Adherence to Initial Adjuvant Anastrozole Therapy among Women with Early Stage Breast Cancer," Journal Clinical Oncology, 01 Febuary 2008, Vol. 26 (4). | ☐ |
| | 028 | PARTRIDGE, et al., "Nonadherence to Adjuvant Tamoxifen Therapy in Women with Primary Breast Cancer," Journal of Clinical Oneology, 15 Febuary 2003, Vol. 21. | ☐ |
| | 029 | ROBERTSON, et al., "Fulvestrant: Pharmacokinetics and Pharmacology," British Journal of Cancer, 2004, Vol. 90, pp. S7-S10. | ☐ |
| | 030 | ROBERTSON, et al., "Pharmacokinetic Profile of Intramuscular Fulvestrant in Advanced Breast Cancer," Clinical Pharmacokinetics, 2004, Vol. 43 (8), pp. 529-538. | ☐ |

| Examiner Signature | | Date Considered | |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

Substitute for form 1449/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 7 of 8

| Complete if Known | |
|---|---|
| Application Number | 16/641,985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | STEVEN; C. Quay |
| Art Unit | 1612 |
| Examiner Name | DAVIS, BRIAN J |
| Attorney Docket Number | 109559-669805 |

**NON-PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| | 031 | SANO, et al., "Short-step Synthesis of Droloxifene via the Three-Component Coupling Reaction among Aromatic Aldehyde, Cinnamyltrimethylsilane, and 13-Chlorophenetole," Tetrahedron Letters, 6 March 2006, Vol. 47 (10), pp. 1631-1635. | ☐ |
| | 032 | UMAREDDY, et al., "Improved Process for Centchroman, A Selective Estrogen Receptor Modulator (SERM)," Journal of Chemical and Pharmaceutical Research, 2015, Vol. 7 (7), pp. 736-741. | ☐ |
| | 033 | UMAREDDY, et al., "Total Synthesis of Lasofoxifene and Nafoxidine," An International Journal for Rapid Communication of Synthetic Organic Chemistry, 2016, Vol. 46 (4), pp. 309-313. | ☐ |
| | 034 | VERGOTE, et al., "Fulvestrant is an Effective and Well-Tolerated Endocrine Therapy for Postmenopausal Women with Advanced Breast Cancer," Results from Clinical Trials, British Journal of Cancer, 90 (Suppl), 2004, pp. S11-S14. | ☐ |
| | 035 | WELSH J., "Induction of Apoptosis in Breast Cancer Cells in Response to Vitamin D and Antiestrogens," Biochemistry and Cell Biology, 1994, Vol. 72 (11-12), pp. 537-545. | ☐ |
| | 036 | YAO, et al., "Synthesis and Reactivity of Potential Toxic Metabolites of Tamoxifen Analogues: Droloxifene and Toremifene a-Quinones," Chemical Research in Toxicology, 2001, Vol. 14 (12), pp. 1643-1653. | ☐ |
| | 037 | YONEYA, et al., "Thiochroman Derivative CH4986399, A New Nonsteroidal Estrogen Receptor Down-regulator, Is effective in Breast Cancer Models," Anticancer Research, 2010, Vol. 30, pp. 873-878. | ☐ |
| | 038 | ZHANG B., et al., "The Safety Parameters of the Study on Intraductal Cytotoxic Agent Delivery to the Breast Before Mastectomy," http://dx.doi.org/10.3978/j.issn.1000-9604.2014.10.06, September 09, 2014, Chinese Journal of Cancer Research, Vol. 26(5), pp: 579-587. | ☐ |

| Examiner Signature | | Date Considered | |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

| Substitute for form 1449/PTO | | | | Complete if Known | |
|---|---|---|---|---|---|
| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary) | | | | Application Number | 16/641,985 |
| | | | | Filing Date | 02-25-2020 |
| | | | | First Named Inventor | STEVEN; C. Quay |
| | | | | Art Unit | 1612 |
| | | | | Examiner Name | DAVIS, BRIAN J |
| Sheet | 8 | of | 8 | Attorney Docket Number | 109559-669805 |

**CERTIFICATION STATEMENT**

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

**SIGNATURE**

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| Signature | /Lisa G Lippert/ | Date (YYYY-MM-DD) | 2021-10-15 |
|---|---|---|---|
| Name/Print | Lisa G. Lippert | Registration Number | 78332 |

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| 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 10/26/2021

POLSINELLI PC
PO Box 140310
KANSAS CITY, MO 64114-0310

| EXAMINER | |
|---|---|
| DAVIS, BRIAN J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1612 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 10/26/2021 | 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 10/15/2021.

☐ 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) 1,5-9,32-35,38-43,46-47,49,52 and 158 is/are pending in the application.

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

6) ☑ Claim(s) 1,5-9,32-35,38-42 and 158 is/are allowed.

7) ☑ Claim(s) 43,46-47,49 and 52 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 15 October 2021 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 10/15/2021.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.



**Intas Exhibit 1002**
**Page 497 of 598**
**IPR2025-00799**

## 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.

### *Drawings*

The objection to the drawing, outlined in the previous Office Action, has been overcome by inventor's amendment. The amendment supplies the appropriate drawing label.

### *112(b) Rejections Withdrawn*

The rejections of claims 1, 4-9, 32-35, 38-44, 46, 47, 49, 52 and 62 under 35 USC 112(b) or 35 USC 112 (pre-AIA), second paragraph, outlined in the previous Office Action, have been overcome by inventor's amendment. With respect to claims 1, 35, 38, 39, 41-43, 49 and 52, the amendment clarifies the claims as appropriate. With respect to claim 62, the amendment cancels the claim. With respect to claims 4-9, 32-43, 40, 44, 46 and 47 (indefinite from indefinite), the rejection is moot. (The amendment also cancels claims 4 and 44.)

### *Claim Rejections - 35 USC § 112(a), NEW*

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it

> is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43, 46, 47, 49 and 52 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, because the specification, while **being enabling for a method of treating a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder**, does not reasonably provide enablement for *preventing* such disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

With regard to rejections under 35 USC 112(a) or 35 USC 112, first paragraph, the following factors are considered (*In re Wands* 8 USPQ 2d 1400, 1404 (CAFC 1988)): a) Breadth of claims; b) Nature of invention; c) State of the prior art; d) Level of ordinary skill in the art; e) Level of predictability in the art; f) Amount of direction and guidance provided by the inventor; g) Working examples and; h) Level of experimentation needed to make or use the invention based on the content of the disclosure.

a) The claims are extraordinarily broad: "A method of treating or preventing a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in a subject the method comprising administering to the subject a composition

comprising a crystalline form of the compound of Formula (III) wherein at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer and wherein the crystalline form of the (Z)-isomer is Form (I), characterized by an x-ray powder diffraction pattern comprising major peaks at…thereby treating or preventing the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder" (claim 43). Dependent claims 46 and 47 further define the disorder. Dependent claim 49 teaches an amount of the (Z)-isomer in the composition. Dependent claim 52 teaches parameters related to steady state plasma levels of the compound of Formula (III).

The examiner notes for clarity of the record that the specification explicitly teaches that the limitations "hormone-dependent breast disorder" and "hormone-dependent reproductive tract disorder" encompass breast cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, vulvar cancer and prostate cancer and also when these cancers are tamoxifen-refractory or tamoxifen-resistant (specification page 11, [0039]-[0041]).

b,c) The nature of the invention is determined in part by the state of the prior art.

The practitioner is imputed to possess full knowledge of the prior art in his field of endeavor. *In re Winslow*, 365 F.2d 1017, 1020, 151 USPQ 48, 51 (CCPA 1956). Additionally, the practitioner is also imputed to possess knowledge in related fields which are pertinent to his particular problems. *In re Antle*, 444 F.2d, 1168, 1171-72, 170 USPQ 285, 287-88 (CCPA 1971). That being the case, inventor is presumed to be aware that even a cursory perusal of the teachings of the medicinal arts reveals that

they have not advanced to the point where complex diseases with a significant genetic component, such as breast cancer, ovarian cancer, etc., can be said to be preventable.

d) The level of skill in the art is considered to be relatively high.

e) The level of predictability in the art is considered to be relatively low.

The basis of all modern medicine and biology is, of course, chemistry. Yet even under the best of circumstances, and more than two hundred years after Lavoisier laid the foundations of its modern practice, chemistry remains an experimental science. Neither the medicinal/biological arts nor the chemical arts upon which they are based have advanced to the point where certainty has replaced the need for clinical and/or laboratory experimentation.

Cancer is neither a simple disease, nor a single disease. While some cancers can be treated in some hosts using specific compounds, the effective treatment - let alone prevention - of various forms of cancer remains highly unpredictable in the art.

Note that the enabled scope varies inversely with the degree of unpredictability in the art. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d, 833, 839, 166 USPQ 18, 24 (1970).

f,g) The amount of direction provided by the inventor is considered to be determined by the specification and the working examples. Inventor's data do not demonstrate that the instant composition prevents breast cancer, ovarian cancer, etc.

h) It would clearly require an undue amount of experimentation in order to determine if, in fact, the instant composition is actually efficacious in the prevention of breast cancer, ovarian cancer, etc. However, the specification must teach how to make

and use the invention, not teach how to figure out for oneself how to make and use the invention. *In re Gardner*, 166 USPQ 138 (CCPA 1970).

But, regardless of the amount of experimentation involved, inventor's claims to the prevention of hormone-dependent breast and reproductive tract disorders which encompass cancers are simply not believable in light of the present understanding in the contemporary medicinal arts. It is settled case law that allegations of utility that are not believable in light of the contemporary knowledge in the art must be substantiated by acceptable evidence or stricken from the specification. *In re Ferns*, 163 USPQ 609 (CCPA 1969; *Ex Parte Moore*, 128, USPQ 8 (BPAI 1960); *In re Hozumi*, 226, USPQ 353 (Comr. Dec. 1985); MPEP 706.03(c).

Note that a patent is not a hunting license, nor a reward for search. But rather is compensation for a search's successful conclusion. Protection is granted in return for an enabling disclosure, not for vague intimations of general ideas which may or may not be workable. *Genetech Inc. v. Nova Nordisk*, 108 F.3d 1361, 42 USPQ 2d 1001, Fed. Circuit 1997.

The examiner respectfully suggests deleting limitations from claim 43 (the independent claim) with respect to *prevention*.

***103 Rejections Withdrawn***

The rejection of claim 62 under 35 USC 103, outlined in the previous Office Action, has been overcome by inventor's amendment. The amendment cancels the claim.

***Allowable Subject Matter***

Claims 1, 5-9, 32-35, 38-42 and 158 are allowed for reasons of record (9/7/2021).

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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 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 published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BRIAN J DAVIS/
Primary Examiner, Art Unit 1612
10/22/2021

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 16/641,985 | Quay et al. |
| | Examiner | Art Unit |
| | BRIAN J DAVIS | 1612 |

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|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

**CLAIMS**

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
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Intas Exhibit 1002
Page 505 of 598
IPR2025-00799

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 16/641,985 | Quay et al. |
| | **Examiner** | **Art Unit** |
| | BRIAN J DAVIS | 1612 |

| CLAIM | | DATE | | | | | | | | |
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| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 16/641,985 | Quay et al. |
| | **Examiner** | **Art Unit** |
| | BRIAN J DAVIS | 1612 |

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 08/31/2021 | 10/22/2021 | | | | | | | |
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| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
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| | **Examiner** | **Art Unit** |
| | BRIAN J DAVIS | 1612 |

| CLAIM | | DATE | | | | | | | | |
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| Final | Original | 08/31/2021 | 10/22/2021 | | | | | | | |
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| | Examiner | Art Unit |
| | BRIAN J DAVIS | 1612 |

| CPC - Searched* | | |
|---|---|---|
| **Symbol** | **Date** | **Examiner** |
| C07C 217/18 (EAST, cursory, 8/2021 to date) | 10/22/2021 | /BJD/ |

| CPC Combination Sets - Searched* | | |
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| **Symbol** | **Date** | **Examiner** |
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| US Classification - Searched* | | | |
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| **Class** | **Subclass** | **Date** | **Examiner** |
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* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

| Search Notes | | |
|---|---|---|
| **Search Notes** | **Date** | **Examiner** |
| Global Dossier | 10/22/2021 | /BJD/ |
| Inventor name searches in PE2E | 10/22/2021 | /BJD/ |

| Interference Search | | | |
|---|---|---|---|
| **US Class/CPC Symbol** | **US Subclass/CPC Group** | **Date** | **Examiner** |
| | | | |

| /BRIAN J DAVIS/<br>Primary Examiner, Art Unit 1612 | 10/22/2021 |
|---|---|



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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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| Complete if Known | |
|---|---|
| Application Number | 16/641,985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | STEVEN; C. Quay |
| Art Unit | 1612 |
| Examiner Name | DAVIS, BRIAN J |
| Attorney Docket Number | 109559-669805 |

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| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
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| Examiner Signature | /BRIAN J DAVIS/ | Date Considered | 10/22/2021 |
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| Examiner Signature | /BRIAN J DAVIS/ | Date Considered | 10/22/2021 |
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| Application Number | 16/641,985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | STEVEN; C. Quay |
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| Examiner Signature | /BRIAN J DAVIS/ | Date Considered | 10/22/2021 |
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| | | | | First Named Inventor | STEVEN; C. Quay |
| | | | | Art Unit | 1612 |
| | | | | Examiner Name | DAVIS, BRIAN J |
| Sheet | 4 | of | 8 | Attorney Docket Number | 109559-669805 |

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|---|---|---|---|
| Examiner Initials* | Cite No.[1] | Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published. | T[2] |
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| Examiner Signature | /BRIAN J DAVIS/ | Date Considered | 10/22/2021 |
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| | | | | Art Unit | 1612 |
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| Examiner Signature | /BRIAN J DAVIS/ | Date Considered | 10/22/2021 |
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| | 030 | ROBERTSON, et al., "Pharmacokinetic Profile of Intramuscular Fulvestrant in Advanced Breast Cancer," Clinical Pharmacokinetics, 2004, Vol. 43 (8), pp. 529-538. | ☐ |

| Examiner Signature | /BRIAN J DAVIS/ | Date Considered | 10/22/2021 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /B.J.D/

Substitute for form 1449/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 7 of 8

| Complete if Known | |
|---|---|
| Application Number | 16/641,985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | STEVEN; C. Quay |
| Art Unit | 1612 |
| Examiner Name | DAVIS, BRIAN J |
| Attorney Docket Number | 109559-669805 |

**NON-PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| | 031 | SANO, et al., "Short-step Synthesis of Droloxifene via the Three-Component Coupling Reaction among Aromatic Aldehyde, Cinnamyltrimethylsilane, and 13-Chlorophenetole," Tetrahedron Letters, 6 March 2006, Vol. 47 (10), pp. 1631-1635. | ☐ |
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| | 034 | VERGOTE, et al., "Fulvestrant is an Effective and Well-Tolerated Endocrine Therapy for Postmenopausal Women with Advanced Breast Cancer," Results from Clinical Trials, British Journal of Cancer, 90 (Suppl), 2004, pp. S11-S14. | ☐ |
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| | 036 | YAO, et al., "Synthesis and Reactivity of Potential Toxic Metabolites of Tamoxifen Analogues: Droloxifene and Toremifene a-Quinones," Chemical Research in Toxicology, 2001, Vol. 14 (12), pp. 1643-1653. | ☐ |
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| Examiner Signature | /BRIAN J DAVIS/ | Date Considered | 10/22/2021 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

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| Substitute for form 1449/PTO | | | | Complete if Known | |
|---|---|---|---|---|---|
| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary) | | | | Application Number | 16/641,985 |
| | | | | Filing Date | 02-25-2020 |
| | | | | First Named Inventor | STEVEN; C. Quay |
| | | | | Art Unit | 1612 |
| | | | | Examiner Name | DAVIS, BRIAN J |
| Sheet | 8 | of | 8 | Attorney Docket Number | 109559-669805 |

**CERTIFICATION STATEMENT**

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

**SIGNATURE**

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| | | | |
|---|---|---|---|
| Signature | /Lisa G Lippert/ | Date (YYYY-MM-DD) | 2021-10-15 |
| Name/Print | Lisa G. Lippert | Registration Number | 78332 |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /B.J.D/

**EAST Search History**

**EAST Search History (Prior Art)**

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | Time Stamp |
|---|---|---|---|---|---|---|
| L1 | 82 | C07C217/18.cpc. | USPAT | OR | ON | 2021/10/22 04:38 |
| L2 | 74 | C07C217/18.cpc. | US-PGPUB | OR | ON | 2021/10/22 04:39 |

10/22/2021 4:40:00 AM
C:\Users\bdavis\Documents\EAST\Workspaces\~auto.07062018.040755.wsp

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on October 27, 2021.

POLSINELLI PC

By: /Megan Thornton/

Attorney Docket No.: 109559-669805

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re Application of: | Confirmation No. 7650 |
| Steven C. Quay et al. | |
| Application No.: 16/641,985 | Examiner: BRIAN J DAVIS |
| Filed: February 25, 2020 | Art Unit: 1612 |
| For: METHODS FOR MAKING AND USING ENDOXIFEN | AMENDMENT |
| Customer No. 27148 | |

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

Commissioner:

In response to the Office Action mailed October 26, 2021, please enter the following amendments and remarks.

**Amendments to the Claims** are reflected in the listing of claims which begins on page 2 of this paper.

**Remarks** begin on page 7 of this paper.



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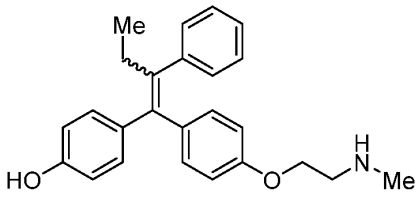
**Intas Exhibit 1002**
**Page 519 of 598**
**IPR2025-00799**

**Amendments to the Claims:**

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

**Listing of Claims:**

1. (Previously Presented) A composition comprising a crystalline form of a compound of Formula (III):




Formula (III),

wherein at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer, and 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 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta.

2-4. (Canceled)

5. (Previously Presented) The composition of claim 1, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from 16.0 ± 0.3°, 18.8 ± 0.3° and 26.5 ± 0.3 two theta.

6. (Previously Presented) The composition of claim 1, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from 12.3 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta.

7. (Previously Presented) The composition of claim 1, wherein the x-ray powder diffraction pattern further comprises peaks at 12.3 ± 0.3°, 16.0 ± 0.3°, 18.8 ± 0.3°, 26.5 ± 0.3°, 28.0 ± 0.3°



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IPR2025-00799

and 29.0 ± 0.3° two theta.

8. (Previously Presented) The composition of claim 1, wherein the crystalline form of the (Z)-isomer is characterized by an x-ray powder diffraction pattern substantially as set forth in Fig. 9 or Fig. 10.

9. (Previously Presented) The composition of claim 1, wherein greater than 90% by weight of the (Z)-isomer in the composition is crystalline Form I.

10-31. (Canceled)

32. (Previously Presented) The composition of claim 1, further comprising a pharmaceutically acceptable carrier or diluent.

33. (Previously Presented) The composition of claim 32, wherein the composition is formulated for oral, parenteral, topical, or intraductal delivery.

34. (Previously Presented) The composition of claim 32, wherein the composition is formulated for oral delivery as a tablet, a caplet, a capsule, or a pill.

35. (Previously Presented) The composition of claim 32, wherein a mean half-life of the compound of Formula (III) in a subject treated with the composition is between 30 hours to 60 hours.

36-37. (Canceled)

38. (Previously Presented) The composition of claim 1, formulated as an oral dosage form comprising 1 mg to 200 mg per unit dose of the composition, and wherein daily administration of the oral dosage form achieves in a subject treated with the composition one or more of:



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**IPR2025-00799**

a steady state plasma level of the compound of Formula (III) within 7 to 21 days;
a steady state plasma level of the compound of Formula (III) ranging from 25 nM to 300 nM;
a steady state plasma level of the compound of Formula (III) greater than 30 nM; or
maximal plasma levels of the compound of Formula (III) within 2 to 10 hours after administering.

39. (Previously Presented) The composition of claim 38, wherein a mean half-life of the compound of Formula (III) in the subject is between 40 hours to 55 hours.

40. (Previously Presented) The composition of claim 38, wherein the oral dosage form is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

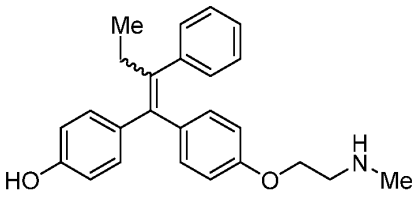
41. (Previously Presented) The composition of claim 38, wherein at least 80% of the compound of Formula (III) in the oral dosage form is released in the intestines of the subject.

42. (Previously Presented) The composition of claim 38, having a mean area under the curve extrapolated to time infinity ($AUC_{0\text{-}inf}$) of the compound of Formula (III) of 200 hr*ng/mL to 10000 hr*ng/mL.

43. (Currently Amended) A method of treating ~~or preventing~~ a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in a subject, the method comprising administering to the subject a composition comprising a crystalline form of a compound of Formula (III):



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Formula (III),

wherein at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer, and 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 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta, thereby treating ~~or preventing~~ the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder.

44-45. (Canceled)

46. (Previously Presented) The method of claim 43, wherein the subject has prostate cancer and wherein the subject further has or is at risk of having gynecomastia.

47. (Previously Presented) The method of claim 43, wherein the subject has tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder.

48. (Canceled)

49. (Previously Presented) The method of claim 43, wherein the composition comprises 0.01 mg to 200 mg of the (Z)-isomer.

50-51. (Canceled)



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IPR2025-00799

52. (Previously Presented) The method of claim 43, wherein a steady state plasma level of the compound of Formula (III) is achieved within 7 to 21 days of the first administration of the composition to the subject, and wherein the steady state plasma level of the compound of Formula (III) in the subject is greater than 30 nM.

53-157. (Canceled)

158. (Previously Presented) The composition of claim 1, wherein the composition is stable for at least 9 months at 5 °C and 60% relative humidity or at 25 °C and 60% relative humidity.



**Intas Exhibit 1002**
**Page 524 of 598**
**IPR2025-00799**

## 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 1, 5-9, 32-35, 38-42 and 158 are allowed. Applicant reserves the right to pursue any canceled subject matter in a related, future application. Claim 43 has been amended. Support for the amendments can be found in the specification as originally filed. Accordingly, no new matter has been added. Reconsideration is respectfully requested.

### Allowable Subject Matter

Applicant thanks the Examiner for indicating that claims 1, 5-9, 32-35, 38-42 and 158 are allowed.

### Claim Rejections – 35 USC § 112

Claims 43, 46, 47, 49 and 52 stand rejected under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner alleges that "the specification, while **being enabling for a method of treating a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder**, dose not reasonably provide enablement for *preventing* such disorders," (Office Action at p. 3).

Without conceding on the merits of the rejection, claim 43 has been amended to recite, in part, "[a] method of treating a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in a subject."

Applicant thanks the Examiner for acknowledging that the specification is enabling for a method of treating a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder and for the suggestion to delete limitations from claim 43 with respect for prevention. As suggested, claim 43 has been amended to delete limitations with respect to prevention. Therefore, Applicant submits that amended claim 43, and claims dependent

therefrom, are fully enabled by the specification. Accordingly, withdrawal of the rejection of claims 43, 46, 47, 49 and 52 under 35 U.S.C. § 112 is respectfully requested.

## CONCLUSION

In view of the foregoing, Applicants believe 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 27, 2021

/Lisa G Lippert/

Lisa G. Lippert, Ph.D.
Registration No. 78332

POLSINELLI PC
900 W. 48th Place, Suite 900
Kansas City, MO 64112
Tel: (816) 753-1000
Fax: (816) 753-1536
CUSTOMER NO.: 27148
Fax 650-493-6811

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 44140784 |
| **Application Number:** | 16641985 |
| **International Application Number:** | |
| **Confirmation Number:** | 7650 |
| **Title of Invention:** | METHODS FOR MAKING AND USING ENDOXIFEN |
| **First Named Inventor/Applicant Name:** | Steven C. Quay |
| **Customer Number:** | 27148 |
| **Filer:** | Lisa Gail Lippert/Megan Thornton |
| **Filer Authorized By:** | Lisa Gail Lippert |
| **Attorney Docket Number:** | 109559-669805 |
| **Receipt Date:** | 27-OCT-2021 |
| **Filing Date:** | 25-FEB-2020 |
| **Time Stamp:** | 17:31:00 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

| | |
|---|---|
| Submitted with Payment | no |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | | 109559-669805-Response-to-Final-OA-Amendment.pdf | 166549<br>97e0e5f61e4a03cc64bf1500765530253b811a88 | yes | 9 |

| | Multipart Description/PDF files in .zip description | | |
|---|---|---|---|
| | **Document Description** | **Start** | **End** |
| | Response After Final Action | 1 | 1 |
| | Claims | 2 | 6 |
| | Applicant Arguments/Remarks Made in an Amendment | 7 | 9 |
| **Warnings:** | | | |
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**New Applications Under 35 U.S.C. 111**

**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**

**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**

**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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| **PATENT APPLICATION FEE DETERMINATION RECORD**<br>Substitute for Form PTO-875 | Application or Docket Number<br>16/641,985 | Filing Date<br>02/25/2020 | ☐ To be Mailed |
|---|---|---|---|

**ENTITY:** ☐ LARGE ☑ SMALL ☐ MICRO

## APPLICATION AS FILED - PART I

| FOR | (Column 1)<br>NUMBER FILED | (Column 2)<br>NUMBER EXTRA | | RATE ($) | FEE ($) |
|---|---|---|---|---|---|
| ☐ BASIC FEE<br>(37 CFR 1.16(a), (b), or (c)) | N/A | N/A | | N/A | |
| ☐ SEARCH FEE<br>(37 CFR 1.16(k), (i), or (m)) | N/A | N/A | | N/A | |
| ☐ EXAMINATION FEE<br>(37 CFR 1.16(o), (p), or (q)) | N/A | N/A | | N/A | |
| TOTAL CLAIMS<br>(37 CFR 1.16(i)) | minus 20 = | * | | x $50 = | |
| INDEPENDENT CLAIMS<br>(37 CFR 1.16(h)) | minus 3 = | * | | x $230 = | |
| ☐ APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | | |
| ☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | | |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | | TOTAL | |

## APPLICATION AS AMENDED - PART II

| | | (Column 1) | | (Column 2) | (Column 3) | | | |
|---|---|---|---|---|---|---|---|---|
| AMENDMENT | 11/08/2021 | CLAIMS REMAINING AFTER AMENDMENT | | HIGHEST NUMBER PREVIOUSLY PAID FOR | PRESENT EXTRA | | RATE ($) | ADDITIONAL FEE ($) |
| | Total<br>(37 CFR 1.16(i)) | * 21 | Minus | ** 23 | = 0 | | x $50 = | 0 |
| | Independent<br>(37 CFR 1.16(h)) | * 2 | Minus | *** 3 | = 0 | | x $240 = | 0 |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | |
| | | | | | | | TOTAL ADD'L FEE | 0 |

| | | (Column 1) | | (Column 2) | (Column 3) | | | |
|---|---|---|---|---|---|---|---|---|
| AMENDMENT | | CLAIMS REMAINING AFTER AMENDMENT | | HIGHEST NUMBER PREVIOUSLY PAID FOR | PRESENT EXTRA | | RATE ($) | ADDITIONAL FEE ($) |
| | Total<br>(37 CFR 1.16(i)) | * | Minus | ** | = | | x $0 = | |
| | Independent<br>(37 CFR 1.16(h)) | * | Minus | *** | = | | x $0 = | |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | |
| | | | | | | | TOTAL ADD'L FEE | |

| | |
|---|---|
| * If the entry in column 1 is less than the entry in column 2, write "0" in column 3. | LIE |
| ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". | /VICTOR BARLOW/ |
| *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". | |
| The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1. | |

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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# NOTICE OF ALLOWANCE AND FEE(S) DUE

27148 7590 11/17/2021

POLSINELLI PC
PO Box 140310
KANSAS CITY, MO 64114-0310

| EXAMINER | |
|---|---|
| DAVIS, BRIAN J | |
| ART UNIT | PAPER NUMBER |
| 1612 | |

DATE MAILED: 11/17/2021

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 16/641,985 | 02/25/2020 | Steven C. Quay | 109559-669805 | 7650 |

TITLE OF INVENTION: METHODS FOR MAKING AND USING ENDOXIFEN

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | SMALL | $600 | $0.00 | $0.00 | $600 | 02/17/2022 |

**THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.**

**THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.**

**HOW TO REPLY TO THIS NOTICE:**

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

**IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.**





Intas Exhibit 1002
Page 531 of 598
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## PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

27148 7590 11/17/2021

POLSINELLI PC
PO Box 140310
KANSAS CITY, MO 64114-0310

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

**Certificate of Mailing or Transmission**

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

| (Typed or printed name) |
|---|
| (Signature) |
| (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 16/641,985 | 02/25/2020 | Steven C. Quay | 109559-669805 | 7650 |

TITLE OF INVENTION: METHODS FOR MAKING AND USING ENDOXIFEN

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | SMALL | $600 | $0.00 | $0.00 | $600 | 02/17/2022 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| DAVIS, BRIAN J | 1612 | 514-651000 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1_____
2_____
3_____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required) ❑Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____



**Intas Exhibit 1002**
**Page 532 of 598**
**IPR2025-00799**

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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 11/17/2021

POLSINELLI PC
PO Box 140310
KANSAS CITY, MO 64114-0310

| EXAMINER | |
|---|---|
| DAVIS, BRIAN J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1612 | |

DATE MAILED: 11/17/2021

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

## OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

## Privacy Act Statement

**The Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

| Notice of Allowability | 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--*

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to inventor's AF amendment (10/27/2021).
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ 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.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), 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.**

4. ☐ 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)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   **Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

| /BRIAN J DAVIS/<br>Primary Examiner, Art Unit 1612 | 11/4/2021 |
|---|---|

Continuation of 3. The allowed claim(s) is/are: 1,5-9,32-35,38-43,46,47,49,52,158 [renumbered 1-21]

## 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.

### *112 Rejections Withdrawn*

The rejection of claims 43, 46, 47, 49 and 52 under 35 USC 112(a) or 35 USC 112 (pre-AIA), first paragraph, outlined in the previous Office Action, has been overcome by inventor's amendment. The amendment narrows the scope of the independent claim (claim 43) such that the claim set is now enabled.

### *Allowable Subject Matter*

Claims 1, 5-9, 32-35, 38-43, 46, 47, 49, 52 and 158 are allowed.

As was stated in the 9/7/2021 Office Action, the key to instant claims 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$^{th}$ 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.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

***Conclusion***

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 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 published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BRIAN J DAVIS/
Primary Examiner, Art Unit 1612
11/4/2021

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 16/641,985 | Quay et al. |
| | Examiner | Art Unit |
| | BRIAN J DAVIS | 1612 |

| CPC - Searched* | | |
|---|---|---|
| **Symbol** | **Date** | **Examiner** |
| C07C 217/18 (EAST, cursory, 10/2021 to date) | 11/04/2021 | /BJD/ |

| CPC Combination Sets - Searched* | | |
|---|---|---|
| **Symbol** | **Date** | **Examiner** |
| | | |

| US Classification - Searched* | | | |
|---|---|---|---|
| **Class** | **Subclass** | **Date** | **Examiner** |
| | | | |

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

| Search Notes | | |
|---|---|---|
| **Search Notes** | **Date** | **Examiner** |
| Global Dossier | 11/04/2021 | /BJD/ |
| Inventor name searches in PE2E | 11/04/2021 | /BJD/ |

| Interference Search | | | |
|---|---|---|---|
| **US Class/CPC Symbol** | **US Subclass/CPC Group** | **Date** | **Examiner** |
| C07C | 217/18 (EAST, 10/2021 to date) | 11/04/2021 | /BJD/ |

| /BRIAN J DAVIS/<br>Primary Examiner, Art Unit 1612 | 11/04/2021 |
|---|---|



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| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 16/641,985 | Quay et al. |
| | Examiner | Art Unit |
| | BRIAN J DAVIS | 1612 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

**CLAIMS**

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 08/31/2021 | 10/22/2021 | 11/04/2021 | | | | | | |
| 1 | 1 | ✓ | = | = | | | | | | |
| | 2 | - | - | - | | | | | | |
| | 3 | - | - | - | | | | | | |
| | 4 | ✓ | - | - | | | | | | |
| 2 | 5 | ✓ | = | = | | | | | | |
| 3 | 6 | ✓ | = | = | | | | | | |
| 4 | 7 | ✓ | = | = | | | | | | |
| 5 | 8 | ✓ | = | = | | | | | | |
| 6 | 9 | ✓ | = | = | | | | | | |
| | 10 | - | - | - | | | | | | |
| | 11 | - | - | - | | | | | | |
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| | 29 | - | - | - | | | | | | |
| | 30 | - | - | - | | | | | | |
| | 31 | - | - | - | | | | | | |
| 7 | 32 | ✓ | = | = | | | | | | |
| 8 | 33 | ✓ | = | = | | | | | | |
| 9 | 34 | ✓ | = | = | | | | | | |
| 10 | 35 | ✓ | = | = | | | | | | |
| | 36 | - | - | - | | | | | | |
| | 37 | - | - | - | | | | | | |
| 11 | 38 | ✓ | = | = | | | | | | |
| 12 | 39 | ✓ | = | = | | | | | | |
| 13 | 40 | ✓ | = | = | | | | | | |
| 14 | 41 | ✓ | = | = | | | | | | |
| 15 | 42 | ✓ | = | = | | | | | | |



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Page 541 of 598
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| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 16/641,985 | Quay et al. |
| | Examiner | Art Unit |
| | BRIAN J DAVIS | 1612 |

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 08/31/2021 | 10/22/2021 | 11/04/2021 | | | | | | |
| 16 | 43 | ✓ | ✓ | = | | | | | | |
| | 44 | ✓ | - | - | | | | | | |
| | 45 | - | - | - | | | | | | |
| 17 | 46 | ✓ | ✓ | = | | | | | | |
| 18 | 47 | ✓ | ✓ | = | | | | | | |
| | 48 | - | - | - | | | | | | |
| 19 | 49 | ✓ | ✓ | = | | | | | | |
| | 50 | - | - | - | | | | | | |
| | 51 | - | - | - | | | | | | |
| 20 | 52 | ✓ | ✓ | = | | | | | | |
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| | 82 | - | - | - | | | | | | |
| | 83 | - | - | - | | | | | | |
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| | 93 | - | - | - | | | | | | |
| | 94 | - | - | - | | | | | | |



Intas Exhibit 1002
Page 542 of 598
IPR2025-00799

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 16/641,985 | Quay et al. |
| | **Examiner** | **Art Unit** |
| | BRIAN J DAVIS | 1612 |

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 08/31/2021 | 10/22/2021 | 11/04/2021 | | | | | | |
| | 95 | - | - | - | | | | | | |
| | 96 | - | - | - | | | | | | |
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| | 139 | - | - | - | | | | | | |
| | 140 | - | - | - | | | | | | |
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| | 143 | - | - | - | | | | | | |
| | 144 | - | - | - | | | | | | |
| | 145 | - | - | - | | | | | | |
| | 146 | - | - | - | | | | | | |



**Intas Exhibit 1002**
**Page 543 of 598**
**IPR2025-00799**

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 16/641,985 | Quay et al. |
| | **Examiner** | **Art Unit** |
| | BRIAN J DAVIS | 1612 |

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 08/31/2021 | 10/22/2021 | 11/04/2021 | | | | | | |
| | 147 | - | - | - | | | | | | |
| | 148 | - | - | - | | | | | | |
| | 149 | - | - | - | | | | | | |
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| | 153 | - | - | - | | | | | | |
| | 154 | - | - | - | | | | | | |
| | 155 | - | - | - | | | | | | |
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| | 157 | - | - | - | | | | | | |
| 21 | 158 | | = | = | | | | | | |



**Intas Exhibit 1002**
**Page 544 of 598**
**IPR2025-00799**

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 16/641,985 | Quay et al. |
| | Examiner | Art Unit |
| | BRIAN J DAVIS | 1612 |

| CPC | | | | | | | |
|---|---|---|---|---|---|---|---|
| Symbol | | | | | | Type | Version |
| C07C | / | 217 | / | 18 | | F | 2013-01-01 |
| C07C | / | 213 | / | 10 | | I | 2013-01-01 |
| A61K | / | 9 | / | 0053 | | A | 2013-01-01 |
| A61K | / | 45 | / | 06 | | A | 2013-01-01 |
| C07B | / | 2200 | / | 13 | | A | 2013-01-01 |

| CPC Combination Sets | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Symbol | | | | | Type | Set | Ranking | Version |
| | / | | / | | | | | |

| NONE | | Total Claims Allowed: | |
|---|---|---|---|
| (Assistant Examiner) | (Date) | 21 | |
| /BRIAN J DAVIS/<br>Primary Examiner, Art Unit 1612 | 04 November 2021 | O.G. Print Claim(s) | O.G. Print Figure |
| (Primary Examiner) | (Date) | 1 | -- |

U.S. Patent and Trademark Office — Part of Paper No.: 20211104



Intas Exhibit 1002
Page 545 of 598
IPR2025-00799

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 16/641,985 | Quay et al. |
| | **Examiner** | **Art Unit** |
| | BRIAN J DAVIS | 1612 |

| INTERNATIONAL CLASSIFICATION | | | | |
|---|---|---|---|---|
| **CLAIMED** | | | | |
| C07C217/18 | / | 217 | / | 18 |
| C07C213/10 | / | 213 | / | 10 |

| NON-CLAIMED | | | | |
|---|---|---|---|---|
| A61K9/00 | / | 9 | / | 00 |
| A61K45/06 | / | 45 | / | 06 |

| US ORIGINAL CLASSIFICATION | |
|---|---|
| **CLASS** | **SUBCLASS** |
| | |

| CROSS REFERENCES(S) | | | | | | |
|---|---|---|---|---|---|---|
| **CLASS** | **SUBCLASS (ONE SUBCLASS PER BLOCK)** | | | | | |
| | | | | | | |

| NONE | | **Total Claims Allowed:** | |
|---|---|---|---|
| (Assistant Examiner) | (Date) | 21 | |
| /BRIAN J DAVIS/<br>Primary Examiner, Art Unit 1612 | 04 November 2021 | O.G. Print Claim(s) | O.G. Print Figure |
| (Primary Examiner) | (Date) | 1 | -- |

U.S. Patent and Trademark Office — Part of Paper No.: 20211104



**Intas Exhibit 1002**
**Page 546 of 598**
**IPR2025-00799**

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 16/641,985 | Quay et al. |
| | Examiner | Art Unit |
| | BRIAN J DAVIS | 1612 |

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

**CLAIMS**

| Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | | 21 | 14 | 41 | | 61 | | 81 | | 101 | | 121 | | 141 |
| | 2 | | 22 | 15 | 42 | | 62 | | 82 | | 102 | | 122 | | 142 |
| | 3 | | 23 | 16 | 43 | | 63 | | 83 | | 103 | | 123 | | 143 |
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| 2 | 5 | | 25 | | 45 | | 65 | | 85 | | 105 | | 125 | | 145 |
| 3 | 6 | | 26 | 17 | 46 | | 66 | | 86 | | 106 | | 126 | | 146 |
| 4 | 7 | | 27 | 18 | 47 | | 67 | | 87 | | 107 | | 127 | | 147 |
| 5 | 8 | | 28 | | 48 | | 68 | | 88 | | 108 | | 128 | | 148 |
| 6 | 9 | | 29 | 19 | 49 | | 69 | | 89 | | 109 | | 129 | | 149 |
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| | 11 | | 31 | | 51 | | 71 | | 91 | | 111 | | 131 | | 151 |
| | 12 | 7 | 32 | 20 | 52 | | 72 | | 92 | | 112 | | 132 | | 152 |
| | 13 | 8 | 33 | | 53 | | 73 | | 93 | | 113 | | 133 | | 153 |
| | 14 | 9 | 34 | | 54 | | 74 | | 94 | | 114 | | 134 | | 154 |
| | 15 | 10 | 35 | | 55 | | 75 | | 95 | | 115 | | 135 | | 155 |
| | 16 | | 36 | | 56 | | 76 | | 96 | | 116 | | 136 | | 156 |
| | 17 | | 37 | | 57 | | 77 | | 97 | | 117 | | 137 | | 157 |
| | 18 | 11 | 38 | | 58 | | 78 | | 98 | | 118 | | 138 | 21 | 158 |
| | 19 | 12 | 39 | | 59 | | 79 | | 99 | | 119 | | 139 | | |
| | 20 | 13 | 40 | | 60 | | 80 | | 100 | | 120 | | 140 | | |

| NONE | | Total Claims Allowed: | |
|---|---|---|---|
| (Assistant Examiner) | (Date) | 21 | |
| /BRIAN J DAVIS/<br>Primary Examiner, Art Unit 1612 | 04 November 2021 | O.G. Print Claim(s) | O.G. Print Figure |
| (Primary Examiner) | (Date) | 1 | -- |

U.S. Patent and Trademark Office — Part of Paper No.: 20211104



**Intas Exhibit 1002**
**Page 547 of 598**
**IPR2025-00799**

**EAST Search History**

**EAST Search History (Prior Art)**

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | Time Stamp |
|---|---|---|---|---|---|---|
| L1 | 82 | C07C217/18.cpc. | USPAT | OR | ON | 2021/11/04 11:40 |

**EAST Search History (Interference)**

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | Time Stamp |
|---|---|---|---|---|---|---|
| L2 | 74 | C07C217/18.cpc. | US-PGPUB | OR | ON | 2021/11/04 11:40 |

11/4/2021 11:41:46 AM
C:\Users\bdavis\Documents\EAST\Workspaces\~auto.07062018.040755.wsp

OK TO ENTER: /B.J.D/

11/04/2021

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on October 27, 2021.

POLSINELLI PC

By: /Megan Thornton/

Attorney Docket No.: 109559-669805

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re Application of: Steven C. Quay et al. | Confirmation No. 7650 |
| Application No.: 16/641,985 | Examiner: BRIAN J DAVIS |
| Filed: February 25, 2020 | Art Unit: 1612 |
| For: METHODS FOR MAKING AND USING ENDOXIFEN | AMENDMENT |
| Customer No. 27148 | |

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

Commissioner:

In response to the Office Action mailed October 26, 2021, please enter the following amendments and remarks.

**Amendments to the Claims** are reflected in the listing of claims which begins on page 2 of this paper.

**Remarks** begin on page 7 of this paper.



80490007.1

# Bibliographic Data

Application No: 16/641,985

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☑ No ☐ Met After Allowance

Verified and Acknowledged: /BRIAN J DAVIS/ (Examiner's Signature) | (Initials)

Title: METHODS FOR MAKING AND USING ENDOXIFEN

| FILING or 371(c) DATE | CLASS | GROUP ART UNIT | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 02/25/2020 | 514 | 1612 | 109559-669805 |
| RULE | | | |

**APPLICANTS**

ATOSSA THERAPEUTICS, INC., Seattle, WA, UNITED STATES

**INVENTORS**

Steven C. Quay, Seattle, WA, UNITED STATES

YaoLin Sun, Kaohsiung City, TAIWAN

LungHu Wang, Kaohsiung City, TAIWAN

ChangJung Wu, Kaohsiung City, TAIWAN

ChuanDer Huang, Tainan City, TAIWAN

**CONTINUING DATA**

This application is a 371 of PCT/US18/50272 09/10/2018

PCT/US18/50272 has PRO of 62693885 07/03/2018

PCT/US18/50272 has PRO of 62624787 01/31/2018

PCT/US18/50272 has PRO of 62556884 09/11/2017

PCT/US18/50272 has PRO of 62556799 09/11/2017

**FOREIGN APPLICATIONS**

**IF REQUIRED, FOREIGN LICENSE GRANTED****

03/20/2020

** SMALL ENTITY **

**STATE OR COUNTRY**

UNITED STATES

**ADDRESS**

POLSINELLI PC

PO Box 140310

KANSAS CITY, MO 64114-0310

UNITED STATES

**FILING FEE RECEIVED**

$600

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on January 4, 2022.

POLSINELLI PC

By: /Hillary Pratt/

Attorney Docket No.: 109559-669805

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re Application of: | Confirmation No. 7650 |
| Steven C. Quay et al. | |
| Application No.: 16/641,985 | Examiner: BRIAN J. DAVIS |
| Filed: February 25, 2020 | Art Unit: 1612 |
| For: METHODS FOR MAKING AND USING ENDOXIFEN | **AMENDMENT AFTER ALLOWANCE UNDER 37 C.F.R. § 1.312** |
| Customer No. 27148 | |

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

Commissioner:

Prior to issuance of the patent, Applicant respectfully requests entry of this amendment under 37 C.F.R. 1.312 for the above-captioned patent application.

**Amendments to the Specification** begin on page 2.

**Remarks** begin on page 3.



**Intas Exhibit 1002**
**Page 552 of 598**
**IPR2025-00799**

**Amendments to the Specification:**

Please replace paragraph **[0001]** of the Specification with the following amended paragraph:

**CROSS-REFERENCE**

**[0001]** This application is a U.S. National Phase Application under 35 U.S.C. § 371 of International Application No. PCT/US2018/050272, filed September 10, 2018, which claims the benefit of U.S. Provisional Application No. 62/556,799, filed September 11, 2017; U.S. Provisional Application No. 62/556,884, filed September 11, 2017; U.S. Provisional Application No. 62/624,787, filed January 31, 2018; and U.S. Provisional Application No. 62/693,885, filed July 3, 2018, each incorporated herein by reference in ~~its entirety~~ their entireties.

## REMARKS

In this Amendment, Applicant amends the Specification to update a typographical error in the cross-reference paragraph. No new matter has been added.

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: January 4, 2022

/Lisa G Lippert/

Lisa Lippert, Ph.D.
Registration No. 78,332

POLSINELLI PC
900 W. 48th Place, Suite 900
Kansas City, MO 64112-1895
Tel: 816-753-1000
Fax 816-753-1536

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 44666516 |
| **Application Number:** | 16641985 |
| **International Application Number:** | |
| **Confirmation Number:** | 7650 |
| **Title of Invention:** | METHODS FOR MAKING AND USING ENDOXIFEN |
| **First Named Inventor/Applicant Name:** | Steven C. Quay |
| **Customer Number:** | 27148 |
| **Filer:** | Lisa Gail Lippert/Hillary Pratt |
| **Filer Authorized By:** | Lisa Gail Lippert |
| **Attorney Docket Number:** | 109559-669805 |
| **Receipt Date:** | 04-JAN-2022 |
| **Filing Date:** | 25-FEB-2020 |
| **Time Stamp:** | 17:16:32 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

| | |
|---|---|
| Submitted with Payment | no |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | | 109559-669805_312_Amendment.pdf | 115664<br>7e6ca30ef69561041c47f4ed4d45920f633c45c8 | yes | 3 |

| | Multipart Description/PDF files in .zip description | | |
|---|---|---|---|
| | **Document Description** | **Start** | **End** |
| | Amendment after Notice of Allowance (Rule 312) | 1 | 1 |
| | Specification | 2 | 2 |
| | Applicant Arguments/Remarks Made in an Amendment | 3 | 3 |
| **Warnings:** | | | |
| **Information:** | | | |
| | **Total Files Size (in bytes):** | 115664 | |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**

**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**

**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**

**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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 01/13/2022

POLSINELLI PC
PO Box 140310
KANSAS CITY, MO 64114-0310

| EXAMINER |
|---|
| DAVIS, BRIAN J |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1612 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 01/13/2022 | 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
uspt@polsinelli.com

| Response to Rule 312 Communication | Application No. | Applicant(s) | |
|---|---|---|---|
| | 16/641,985 | Quay et al. | |
| | Examiner | Art Unit | AIA (FITF) Status |
| | BRIAN J DAVIS | 1612 | Yes |

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

1. ☑ The amendment filed on 04 January 2022 under 37 CFR 1.312 has been considered, and has been:
   a) ☑ entered.
   b) ☐ entered as directed to matters of form not affecting the scope of the invention.
   c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
      Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.
   d) ☐ disapproved. See explanation below.
   e) ☐ entered in part. See explanation below.

| /BRIAN J DAVIS/<br>Primary Examiner, Art Unit 1612 | 1/8/2022 |
|---|---|

OK TO ENTER: /B.J.D/

01/08/2022

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on January 4, 2022.

POLSINELLI PC

By: /Hillary Pratt/

Attorney Docket No.: 109559-669805

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re Application of: | Confirmation No. 7650 |
| Steven C. Quay et al. | |
| Application No.: 16/641,985 | Examiner: BRIAN J. DAVIS |
| Filed: February 25, 2020 | Art Unit: 1612 |
| For: METHODS FOR MAKING AND USING ENDOXIFEN | **AMENDMENT AFTER ALLOWANCE UNDER 37 C.F.R. § 1.312** |
| Customer No. 27148 | |

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

Commissioner:

Prior to issuance of the patent, Applicant respectfully requests entry of this amendment under 37 C.F.R. 1.312 for the above-captioned patent application.

**Amendments to the Specification** begin on page 2.

**Remarks** begin on page 3.

## PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

27148 7590 11/17/2021

POLSINELLI PC
PO Box 140310
KANSAS CITY, MO 64114-0310

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

**Certificate of Mailing or Transmission**

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

| | |
|---|---|
| Hillary Pratt | (Typed or printed name) |
| /Hillary Pratt/ | (Signature) |
| January 20, 2022 | (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 16/641,985 | 02/25/2020 | Steven C. Quay | 109559-669805 | 7650 |

TITLE OF INVENTION: METHODS FOR MAKING AND USING ENDOXIFEN

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | SMALL | $600 | $0.00 | $0.00 | $600 | 02/17/2022 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| DAVIS, BRIAN J | 1612 | 514-651000 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Polsinelli PC
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Atossa Therapeutics, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Seattle, WA

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ☒ Corporation or other private group entity ❑ Government

4a. Fees submitted: ☒ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 50-1662

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Lisa G Lippert/ Date January 20, 2022

Typed or printed name Lisa G. Lippert Registration No. 78332



**Intas Exhibit 1002**
**Page 560 of 598**
**IPR2025-00799**

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 16641985 |
| **Filing Date:** | 25-Feb-2020 |
| **Title of Invention:** | METHODS FOR MAKING AND USING ENDOXIFEN |
| **First Named Inventor/Applicant Name:** | Steven C. Quay |
| **Filer:** | Lisa Gail Lippert/Hillary Pratt |
| **Attorney Docket Number:** | 109559-669805 |

Filed as Small Entity

**Filing Fees for U.S. National Stage under 35 USC 371**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| UTILITY APPL ISSUE FEE | 2501 | 1 | 600 | 600 |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Extension-of-Time:** | | | | |
| **Miscellaneous:** | | | | |
| | | | **Total in USD ($)** | **600** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 44791087 |
| **Application Number:** | 16641985 |
| **International Application Number:** | |
| **Confirmation Number:** | 7650 |
| **Title of Invention:** | METHODS FOR MAKING AND USING ENDOXIFEN |
| **First Named Inventor/Applicant Name:** | Steven C. Quay |
| **Customer Number:** | 27148 |
| **Filer:** | Lisa Gail Lippert/Hillary Pratt |
| **Filer Authorized By:** | Lisa Gail Lippert |
| **Attorney Docket Number:** | 109559-669805 |
| **Receipt Date:** | 20-JAN-2022 |
| **Filing Date:** | 25-FEB-2020 |
| **Time Stamp:** | 18:13:30 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | DA |
| Payment was successfully received in RAM | $600 |
| RAM confirmation Number | E20221JI14054931 |
| Deposit Account | 501662 |
| Authorized User | Hillary Pratt |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:<br>37 CFR 1.17 (Patent application and reexamination processing fees)<br>37 CFR 1.19 (Document supply fees) | |

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

37 CFR 1.492 (National application filing, search, and examination fees)

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Application Data Sheet | 109559-669805_Marked_ADS.pdf | 488538<br>8ad2916b8bd006598992e26e2d6706806f07c450 | no | 10 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| This is not an USPTO supplied ADS fillable form | | | | | |
| 2 | Request for Corrected Filing Receipt | 109559-669805_Marked_FR.pdf | 221168<br>4e5f05ab572a1b2e3c7ff837509e6803f23fd791 | no | 4 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Request for Corrected Filing Receipt | 109559-669805_Request.pdf | 110123<br>decd7917360e818e6128af0835393a50f5afcedd | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Issue Fee Payment (PTO-85B) | 109559-669805_Issue_Transittal.pdf | 120413<br>622fe4477ccb0556af58f502a50b74d82e7b38b8 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | Fee Worksheet (SB06) | fee-info.pdf | 38005<br>b5f3df038ff9fa64fd52cea89307876b5cb8e690 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 978247 | | |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**

**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**

**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**

**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

PTO/AIA/14 (02-18)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 109559-669805 |
|---|---|---|
| | Application Number | 16/641,985 |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

## Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

## Inventor Information:

**Inventor 1** Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | Steven | C. | Quay | |

**Residence Information (Select One)** ◉ US Residency ○ Non US Residency ○ Active US Military Service

| City | Seattle | State/Province | WA | Country of Residence | US |
|---|---|---|---|---|---|

**Mailing Address of Inventor:**

| | |
|---|---|
| Address 1 | 107 Spring Street |
| Address 2 | |

| City | Seattle | State/Province | WA |
|---|---|---|---|
| Postal Code | 98104 | Country | US |

**Inventor 2** Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | ~~YaoLin~~ Yao-Lin | | Sun | |

**Residence Information (Select One)** ○ US Residency ◉ Non US Residency ○ Active US Military Service

| City | ~~Kaohsiung City~~ Tainan City | Country of Residence | TW |
|---|---|---|---|

**Mailing Address of Inventor:**

| | |
|---|---|
| Address 1 | ~~13F., No. 339-12, Sec. 2, Guangfu Rd.~~ 4F No.30, Ln. 31, Sec. 1, Huandong Rd. |
| Address 2 | ~~Fengshan Dist.~~ Xinshi Dist. |

| City | ~~Kaohsiung City~~ Tainan City | State/Province | |
|---|---|---|---|
| Postal Code | ~~830~~ 741 | Country | TW |

**Inventor 3** Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | LungHu | | Wang | |

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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 109559-669805 |
|---|---|---|
| | Application Number | 16/641,985 |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

**Residence Information (Select One)** ○ US Residency ◉ Non US Residency ○ Active US Military Service

| City | Kaohsiung City | Country of Residence [i] | TW |
|---|---|---|---|

**Mailing Address of Inventor:**

| | |
|---|---|
| **Address 1** | ~~No. 102-2, Beishan Ln.~~ 4F No.30, Ln. 31, Sec. 1, Huandong Rd. |
| **Address 2** | ~~Qijin Dist.~~ Xinshi Dist. |

| City | ~~Kaohsiung City~~ Tainan City | State/Province | |
|---|---|---|---|
| **Postal Code** | ~~805~~ 741 | **Country** [i] | TW |

**Inventor 4** Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | ChangJung | | Wu | |

**Residence Information (Select One)** ○ US Residency ◉ Non US Residency ○ Active US Military Service

| City | Kaohsiung City | Country of Residence [i] | TW |
|---|---|---|---|

**Mailing Address of Inventor:**

| | |
|---|---|
| **Address 1** | ~~No. 28, Ln. 150, Youchang St.~~ 4F No.30, Ln. 31, Sec. 1, Huandong Rd. |
| **Address 2** | ~~Nanzi Dist.~~ Xinshi Dist. |

| City | ~~Kaohsiung City~~ Tainan City | State/Province | |
|---|---|---|---|
| **Postal Code** | ~~811~~ 741 | **Country** [i] | TW |

**Inventor 5** Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | ChuanDer | | Huang | |

**Residence Information (Select One)** ○ US Residency ◉ Non US Residency ○ Active US Military Service

| City | Tainan City | Country of Residence [i] | TW |
|---|---|---|---|

**Mailing Address of Inventor:**

| | |
|---|---|
| **Address 1** | ~~No. 21, Aly. 11, Ln. 176, Sec. 1 Bei'an Rd.~~ 4F No.30, Ln. 31, Sec. 1, Huandong Rd. |
| **Address 2** | ~~North Dist.~~ Xinshi Dist. |

| City | Tainan City | State/Province | |
|---|---|---|---|
| **Postal Code** | ~~704~~ 741 | **Country** [i] | TW |

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 109559-669805 |
|---|---|---|
| | Application Number | 16/641,985 |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

## Correspondence Information:

**Enter either Customer Number or complete the Correspondence Information section below.**
**For further information see 37 CFR 1.33(a).**

☐ **An Address is being provided for the correspondence Information of this application.**

| | | | |
|---|---|---|---|
| **Customer Number** | 27148 | | |
| **Email Address** | Patentdocketing@polsinelli.com | Add Email | Remove Email |

## Application Information:

| | | | |
|---|---|---|---|
| **Title of the Invention** | METHODS FOR MAKING AND USING ENDOXIFEN | | |
| **Attorney Docket Number** | 109559-669805 | **Small Entity Status Claimed** | ☒ |
| **Application Type** | Nonprovisional | | |
| **Subject Matter** | Utility | | |
| **Total Number of Drawing Sheets (if any)** | 13 | **Suggested Figure for Publication (if any)** | 1 |

## Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

| Application number of the previously filed application | Filing date (YYYY-MM-DD) | Intellectual Property Authority or Country |
|---|---|---|
| | | |

## Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

## Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 109559-669805 |
|---|---|---|
| | Application Number | 16/641,985 |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

| Please Select One: | ◉ Customer Number | ○ US Patent Practitioner | ○ Limited Recognition (37 CFR 11.9) |
|---|---|---|---|
| Customer Number | 27148 | | |

## Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

| Prior Application Status | Pending | | Remove |
|---|---|---|---|
| Application Number | Continuity Type | Prior Application Number | Filing or 371(c) Date (YYYY-MM-DD) |
| 16/641,985 | a 371 of international | PCT/US2018/050272 | 2018-09-10 |
| Prior Application Status | Expired | | Remove |
| Application Number | Continuity Type | Prior Application Number | Filing or 371(c) Date (YYYY-MM-DD) |
| PCT/US2018/050272 | Claims benefit of provisional | 62/556799 | 2017-09-11 |
| Prior Application Status | Expired | | Remove |
| Application Number | Continuity Type | Prior Application Number | Filing or 371(c) Date (YYYY-MM-DD) |
| PCT/US2018/050272 | Claims benefit of provisional | 62/556884 | 2017-09-11 |
| Prior Application Status | Expired | | Remove |
| Application Number | Continuity Type | Prior Application Number | Filing or 371(c) Date (YYYY-MM-DD) |
| PCT/US2018/050272 | Claims benefit of provisional | 62/624787 | 2018-01-31 |
| Prior Application Status | Expired | | Remove |
| Application Number | Continuity Type | Prior Application Number | Filing or 371(c) Date (YYYY-MM-DD) |
| PCT/US2018/050272 | Claims benefit of provisional | 62/693885 | 2018-07-03 |

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

## Foreign Priority Information:

PTO/AIA/14 (02-18)
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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 109559-669805 |
|---|---|---|
| | Application Number | 16/641,985 |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

| Application Number | Country[i] | Filing Date (YYYY-MM-DD) | Access Code[i] (if applicable) |
|---|---|---|---|
| | | | |

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

## Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 109559-669805 |
|---|---|---|
| | Application Number | 16/641,985 |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

## Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

**NOTE**: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

**1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)**

**A. Priority Document Exchange (PDX)** - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

**B. Search Results from U.S. Application to EPO** - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

**2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)**

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

**NOTE:** Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 109559-669805 |
|---|---|---|
| | Application Number | 16/641,985 |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

## Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

**Applicant 1**

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

| | | |
|---|---|---|
| ◉ Assignee | ○ Legal Representative under 35 U.S.C. 117 | ○ Joint Inventor |
| ○ Person to whom the inventor is obligated to assign. | ○ Person who shows sufficient proprietary interest | |

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

| Organization Name | ATOSSA THERAPEUTICS, INC. | | |
|---|---|---|---|
| **Mailing Address Information For Applicant:** | | | |
| **Address 1** | 107 Spring Street | | |
| Address 2 | | | |
| **City** | Seattle | **State/Province** | WA |
| **Country** | US | Postal Code | 98104 |
| Phone Number | | Fax Number | |
| Email Address | | | |

Additional Applicant Data may be generated within this form by selecting the Add button.

## Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

| **Application Data Sheet 37 CFR 1.76** | Attorney Docket Number | 109559-669805 |
|---|---|---|
| | Application Number | 16/641,985 |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

**Assignee 1**

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

| Prefix | **Given Name** | Middle Name | **Family Name** | Suffix |
|---|---|---|---|---|
| | | | | |

**Mailing Address Information For Assignee including Non-Applicant Assignee:**

| | | | |
|---|---|---|---|
| **Address 1** | | | |
| Address 2 | | | |
| **City** | | **State/Province** | |
| **Country** i | | Postal Code | |
| Phone Number | | Fax Number | |
| Email Address | | | |

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

## Signature:

**NOTE:** This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

| **Signature** | /Lisa G Lippert/ | | | Date (YYYY-MM-DD) | 2022-01-20 |
|---|---|---|---|---|---|
| First Name | Lisa G. | Last Name | Lippert, Ph.D. | Registration Number | 78332 |

Additional Signature may be generated within this form by selecting the Add button.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

| **Application Data Sheet 37 CFR 1.76** | Attorney Docket Number | 109559-669805 |
|---|---|---|
| | Application Number | 16/641,985 |
| Title of Invention | METHODS FOR MAKING AND USING ENDOXIFEN | |

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

# Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on January 20, 2022

POLSINELLI PC

By: /Hillary Pratt/

Attorney Docket No.: 109559-669805

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re Application of: | Confirmation No. 7650 |
| Steven C. Quay et al. | |
| Application No.: 16/641,985 | Examiner: BRIAN J. DAVIS |
| Filed: February 25, 2020 | Art Unit: 1612 |
| For: METHODS FOR MAKING AND USING ENDOXIFEN | REQUEST FOR CORRECTED FILING RECEIPT |
| Customer No. 27148 | |

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

Commissioner:

Attached is a copy of the official Filing Receipt received from the United States Patent and Trademark Office in the above-referenced application for which issuance of a Corrected Filing Receipt is respectfully requested.

This Request for Corrected Filing Receipt is being made to correct the inventor's first name and to update the inventor's city of residence as follows:

from

~~**YaoLin Sun, Kaohsiung City, TAIWAN;**~~

to

**Yao-Lin Sun, Tainan City, TAIWAN;**



81647371.1

**Intas Exhibit 1002**
**Page 576 of 598**
**IPR2025-00799**

The Commissioner is hereby authorized to charge any additional fees associated with this paper or during the pendency of this application, or credit any overpayment, to Deposit Account No. 50-1662.

Respectfully submitted,

Dated: January 20, 2022

/Lisa G Lippert/

Lisa G. Lippert, Ph.D.
Registration No. 78,332

POLSINELLI PC
900 W. 48th Place, Suite 900
Kansas City, MO 64112-1895
Tel: 816-753-1000
Fax 816-753-1536

UNITED STATES PATENT AND TRADEMARK OFFICE

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

| APPLICATION NUMBER | FILING or 371(c) DATE | GRP ART UNIT | FIL FEE REC'D | ATTY.DOCKET.NO | TOT CLAIMS | IND CLAIMS |
|---|---|---|---|---|---|---|
| 16/641,985 | 02/25/2020 | 1629 | 750 | 38602-758.831 | 23 | 3 |

**CONFIRMATION NO. 7650**

**UPDATED FILING RECEIPT**

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

OC000000119159305

Date Mailed: 08/14/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

**Please verify the accuracy of the data presented on this receipt.** If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

**Inventor(s)**

Steven C. Quay, Seattle, WA;
~~YaoLin Sun, Kaohsiung City, TAIWAN;~~ Yao-Lin Sun, Tainan City, TAIWAN;
LungHu Wang, Kaohsiung City, TAIWAN;
ChangJung Wu, Kaohsiung City, TAIWAN;
ChuanDer Huang, Tainan City, TAIWAN;

**Applicant(s)**

ATOSSA THERAPEUTICS, INC., Seattle, WA;

**Power of Attorney:** None

**Domestic Priority data as claimed by applicant**

This application is a 371 of PCT/US18/50272 09/10/2018
which claims benefit of 62/556,799 09/11/2017
and claims benefit of 62/556,884 09/11/2017
and claims benefit of 62/624,787 01/31/2018
and claims benefit of 62/693,885 07/03/2018

**Foreign Applications** for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
*Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.*

**Permission to Access Application via Priority Document Exchange:** Yes

**Permission to Access Search Results:** Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

**If Required, Foreign Filing License Granted:** 03/20/2020

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/641,985**

**Projected Publication Date:** Not Applicable

**Non-Publication Request:** No

**Early Publication Request:** No

**** SMALL ENTITY ****

**Title**

METHODS FOR MAKING AND USING ENDOXIFEN

**Preliminary Class**

514

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:** No

## PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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## Title 35, United States Code, Section 184

## Title 37, Code of Federal Regulations, 5.11 & 5.15

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**NOT GRANTED**

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

---

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# United States Patent and Trademark Office

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Document Code:WFEE

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Sale Accounting Date:01/24/2022

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www.uspto.gov

| APPLICATION NUMBER | FILING or 371(c) DATE | GRP ART UNIT | FIL FEE REC'D | ATTY.DOCKET.NO | TOT CLAIMS | IND CLAIMS |
|---|---|---|---|---|---|---|
| 16/641,985 | 02/25/2020 | 1612 | 750 | 109559-669805 | 23 | 3 |

**CONFIRMATION NO. 7650**

**UPDATED FILING RECEIPT**

27148
POLSINELLI PC
PO Box 140310
KANSAS CITY, MO 64114-0310

OC000000131322624

Date Mailed: 01/25/2022

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

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**Inventor(s)**

Steven C. Quay, Seattle, WA;
Yao-Lin Sun, Tainan City, TAIWAN;
LungHu Wang, Kaohsiung City, TAIWAN;
ChangJung Wu, Kaohsiung City, TAIWAN;
ChuanDer Huang, Tainan City, TAIWAN;

**Applicant(s)**

ATOSSA THERAPEUTICS, INC., Seattle, WA;

**Power of Attorney:** The patent practitioners associated with Customer Number 27148

**Domestic Priority data as claimed by applicant**

This application is a 371 of PCT/US18/50272 09/10/2018
which claims benefit of 62/556,799 09/11/2017
and claims benefit of 62/556,884 09/11/2017
and claims benefit of 62/624,787 01/31/2018
and claims benefit of 62/693,885 07/03/2018

**Foreign Applications** for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
*Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.*

**Permission to Access Application via Priority Document Exchange:** Yes

**Permission to Access Search Results:** Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

**Projected Publication Date:** Not Applicable
**Non-Publication Request:** No
**Early Publication Request:** No
**** SMALL ENTITY ****
**Title**

METHODS FOR MAKING AND USING ENDOXIFEN

**Preliminary Class**

514

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:** No

## PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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## Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

**NOT GRANTED**

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---

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UNITED STATES PATENT AND TRADEMARK OFFICE

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

| APPLICATION NUMBER | FILING OR 371(C) DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO./TITLE |
|---|---|---|---|
| 16/641,985 | 02/25/2020 | Steven C. Quay | 109559-669805 |

**CONFIRMATION NO. 7650**

27148
POLSINELLI PC
PO Box 140310
KANSAS CITY, MO 64114-0310

**37 CFR 1.48(f)**
**ACKNOWLEDGEMENT LETTER**

*OC000000131322626*

Date Mailed: 01/25/2022

## NOTICE OF ACCEPTANCE OF REQUEST UNDER 37 CFR 1.48(f)

This is in response to the applicant's request under 37 CFR 1.48(f) submitted on 01/20/2022.

The request under 37 CFR 1.48(f) to correct the inventorship, to correct or update the name of an inventor, or to correct the order of names of joint inventors is accepted.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/byemane/

UNITED STATES PATENT AND TRADEMARK OFFICE

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

| APPLICATION NO. | ISSUE DATE | PATENT NO. | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 16/641,985 | 03/01/2022 | 11261151 | 109559-669805 | 7650 |

27148 7590 02/09/2022

POLSINELLI PC
PO Box 140310
KANSAS CITY, MO 64114-0310

# ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 68 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

INVENTOR(s) (Please see PAIR WEB site http://pair.uspto.gov for additional inventors):

Steven C. Quay, Seattle, WA;
Yao-Lin Sun, Tainan City, TAIWAN;
LungHu Wang, Kaohsiung City, TAIWAN;
ChangJung Wu, Kaohsiung City, TAIWAN;
ChuanDer Huang, Tainan City, TAIWAN;

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

ATOSSA THERAPEUTICS, INC., Seattle, WA;

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**Attorney Docket No.: 109559-669805**
**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Inventor: | Steven C. Quay et al. | Group Art Unit: | 1612 |
| Serial Number: | 16/641,985 | Examiner: | DAVIS, BRIAN J |
| Filing or 371 (c) Date: | February 25, 2020 | **CONFIRMATION NO:** | **7650** |
| Patent No.: | 11,261,151 | CUST. NO.: | 27148 |
| Issue Date: | March 1, 2022 | | |
| Title: | METHODS FOR MAKING AND USING ENDOXIFEN | | |

**DUTY UNDER 37 C.F.R. § 1.705**

**FILED ELECTRONICALLY ON APRIL 21, 2022**

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Dear Commissioner:

Pursuant to 37 C.F.R. § 1.705, in compliance with the practitioner's duty of candor and good faith, the Patentee believes that the Office's determination of patent term adjustment (PTA) indicated on the patent is greater than what the Patentee believes is appropriate. The PTA is believed to be 55 days instead of the 68 days of total PTA granted by the Office. Accordingly, please place this statement in the file without comment.

This statement is filed within two months of the issue date of the above-referenced patent and thus no fees are believed to be due. However, 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.

Respectfully submitted,

Dated: April 21, 2022

/Lisa G Lippert/
Lisa G. Lippert, Ph.D.
Registration No. 78,332

POLSINELLI PC
900 W. 48th Place, Suite 900
Kansas City, MO 64112-1895



82988307.1

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 45533309 |
| **Application Number:** | 16641985 |
| **International Application Number:** | |
| **Confirmation Number:** | 7650 |
| **Title of Invention:** | METHODS FOR MAKING AND USING ENDOXIFEN |
| **First Named Inventor/Applicant Name:** | Steven C. Quay |
| **Customer Number:** | 27148 |
| **Filer:** | Lisa Gail Lippert/Hillary Pratt |
| **Filer Authorized By:** | Lisa Gail Lippert |
| **Attorney Docket Number:** | 109559-669805 |
| **Receipt Date:** | 21-APR-2022 |
| **Filing Date:** | 25-FEB-2020 |
| **Time Stamp:** | 18:24:34 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

| | |
|---|---|
| Submitted with Payment | no |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Miscellaneous Incoming Letter | 109559-669805_Statement_37 CFR1705_good_faith.pdf | 106167<br>7cd94a290e44fadf1f8e04864fe5bd325a38c642 | no | 1 |
| **Warnings:** | | | | | |

| Information: | |
|---|---|
| Total Files Size (in bytes): | 106167 |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**
**National Stage of an International Application under 35 U.S.C. 371**
**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**
**New International Application Filed with the USPTO as a Receiving Office**
**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

PTO/AIA/80 (07-17)
Approved for use through 03/31/2021. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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# POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

[X] Practitioners associated with Customer Number: 187495

**OR**

[ ] Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

| Name | Registration Number |
|---|---|
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| Name | Registration Number |
|---|---|
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As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

[X] The address associated with Customer Number: 187495

**OR**

[ ]

| Firm or individual name | | |
|---|---|---|
| Address | | |
| City | State | Zip |
| Country | | |
| Telephone | Email | |

Assignee name and address: Atossa Therapeutics, Inc.
107 Spring Street
Seattle, Washington 98104

**A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.**

**SIGNATURE of Assignee of Record**

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee.

| Signature | Date 4/25/22 |
|---|---|
| Name Kyle Guse | Telephone |
| Title Chief Financial Officer and General Counsel | |

This collection of information is required by 37 CFR 1.31, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public, which is to update (and by the USPTO to process) the file of a patent or reexamination proceeding. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 18 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 45842006 |
| **Application Number:** | 16641985 |
| **International Application Number:** | |
| **Confirmation Number:** | 7650 |
| **Title of Invention:** | METHODS FOR MAKING AND USING ENDOXIFEN |
| **First Named Inventor/Applicant Name:** | Steven C. Quay |
| **Customer Number:** | 27148 |
| **Filer:** | Lisa Gail Lippert/Hillary Pratt |
| **Filer Authorized By:** | Lisa Gail Lippert |
| **Attorney Docket Number:** | 109559-669805 |
| **Receipt Date:** | 31-MAY-2022 |
| **Filing Date:** | 25-FEB-2020 |
| **Time Stamp:** | 20:34:02 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

| | |
|---|---|
| Submitted with Payment | no |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Assignee showing of ownership per 37 CFR 3.73 | 438558-758041_373c.pdf | 129363<br>96e5c8aaffc8e8e850543bc2f8356178a8aeffe6 | no | 2 |

**Warnings:**

| Information: | | | | | |
|---|---|---|---|---|---|
| 2 | Power of Attorney | Atossa-General_POA.pdf | 120191<br>7973268480d6c697846ee71cfa55599a90dc37b | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | | **Total Files Size (in bytes):** | 249554 | |

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**New Applications Under 35 U.S.C. 111**

**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**

**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**

**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

PTO/AIA/96 (08-12)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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# STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: ATOSSA THERAPEUTICS, INC.

Application No./Patent No.: 11,261,151 Filed/Issue Date: March 1, 2022

Titled: METHODS FOR MAKING AND USING ENDOXIFEN

ATOSSA THERAPEUTICS, INC., a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

B. ☑ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Yaolin SUN, Lunghu WANG, Changjung WU, Chuander HUANG To: KRISAN BIOTECH CO., LTD.

   The document was recorded in the United States Patent and Trademark Office at
   Reel 058198, Frame 0680, or for which a copy thereof is attached.

2. From: Steven C. QUAY To: ATOSSA THERAPEUTICS, INC.

   The document was recorded in the United States Patent and Trademark Office at
   Reel 058198, Frame 0968, or for which a copy thereof is attached.



This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

PTO/AIA/96 (08-12)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

## STATEMENT UNDER 37 CFR 3.73(c)

3. From: Yaolin SUN, Lunghu WANG, Changjung WU To: KRISAN BIOTECH CO., LTD.

The document was recorded in the United States Patent and Trademark Office at
Reel 058198, Frame 0901, or for which a copy thereof is attached.

4. From: KIRSAN BIOTECH CO., LTD. To: ATOSSA THERAPEUTICS, INC.

The document was recorded in the United States Patent and Trademark Office at
Reel 058199, Frame 0053, or for which a copy thereof is attached.

5. From: KRISAN BIOTECH CO., LTD. To: ATOSSA THERAPEUTICS, INC.

The document was recorded in the United States Patent and Trademark Office at
Reel 058539, Frame 0071, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☑ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

| | |
|---|---|
| /Lisa G Lippert/ | May 31, 2022 |
| Signature | Date |
| Lisa Lippert, Ph.D. | 78,332 |
| Printed or Typed Name | Title or Registration Number |

UNITED STATES PATENT AND TRADEMARK OFFICE

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

| APPLICATION NUMBER | FILING OR 371(C) DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO./TITLE |
|---|---|---|---|
| 16/641,985 | 02/25/2020 | Steven C. Quay | 109559-669805 |

**CONFIRMATION NO. 7650**

27148
POLSINELLI PC (Main Customer Number)
PO Box 140310
KANSAS CITY, MO 64114-0310

**POWER OF ATTORNEY NOTICE**

*OC00000135321308*

Date Mailed: 07/22/2022

## NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/31/2022.

- The Power of Attorney to you in this application has been revoked by the applicant. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/zabraha/

UNITED STATES PATENT AND TRADEMARK OFFICE

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

| APPLICATION NUMBER | FILING OR 371(C) DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO./TITLE |
|---|---|---|---|
| 16/641,985 | 02/25/2020 | Steven C. Quay | 109559-669805 |

**CONFIRMATION NO. 7650**

187495
DLA Piper LLP
701 Fifth Avenue
Suite 6900
Seattle, WA 98104

**POA ACCEPTANCE LETTER**

*OC000000135321317*

Date Mailed: 07/22/2022

## NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/31/2022.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/zabraha/