# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 13984559 |
| **Filing Date:** | 20-Mar-2014 |
| **Title of Invention:** | Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds |
| **First Named Inventor/Applicant Name:** | Jo Ann Wilson |
| **Filer:** | Heid Marie Berven/Allison McKenna |
| **Attorney Docket Number:** | 224990/10-039C-US/343999 |

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:** | | | | |

EXELIXIS 2009
Azurity v. Exelixis
IPR2025-00210
PART 1 OF 2

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| Extension - 3 months with $0 paid | 2253 | 1 | 700 | 700 |
| **Miscellaneous:** | | | | |
| Submission- Information Disclosure Stmt | 2806 | 1 | 90 | 90 |
| | | **Total in USD ($)** | | **790** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 21830320 |
| **Application Number:** | 13984559 |
| **International Application Number:** | |
| **Confirmation Number:** | 6725 |
| **Title of Invention:** | Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds |
| **First Named Inventor/Applicant Name:** | Jo Ann Wilson |
| **Customer Number:** | 91684 |
| **Filer:** | Heid Marie Berven/Allison McKenna |
| **Filer Authorized By:** | Heid Marie Berven |
| **Attorney Docket Number:** | 224990/10-039C-US/343999 |
| **Receipt Date:** | 20-MAR-2015 |
| **Filing Date:** | 20-MAR-2014 |
| **Time Stamp:** | 11:26:17 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $790 |
| RAM confirmation Number | 8784 |
| Deposit Account | 503145 |
| 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 | | 2015-03-20_EX10-039C-US_Response_to_Office_Action.pdf | 3158487<br>1c292551aeb922a7cc76f1a55a901a46504f1d2c | yes | 20 |

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

| Document Description | Start | End |
|---|---|---|
| Miscellaneous Incoming Letter | 1 | 1 |
| Amendment/Req. Reconsideration-After Non-Final Reject | 2 | 2 |
| Claims | 3 | 11 |
| Applicant Arguments/Remarks Made in an Amendment | 12 | 15 |
| Information Disclosure Statement (IDS) Form (SB08) | 16 | 18 |
| Extension of Time | 19 | 19 |
| Transmittal Letter | 20 | 20 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 2 | Foreign Reference | WO2011017639.PDF | 3224373<br>2e74b8029f16ca45869b1805710f3d6bfccc62c4 | no | 61 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 3 | Foreign Reference | WO2012009722.PDF | 1668309<br>e66877cd229674737c2aaff29b8e3b2c89fa3a84 | no | 40 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 4 | Foreign Reference | WO2005030140_Part1.pdf | 9027234<br>55e4cef4dc5d252682f9ecce7559a1b6f8112b3e | no | 214 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 5 | Foreign Reference | WO2005030140_Part2.pdf | 9163841<br>ecdfbf2ab105a906d050394eb75555ad66516a97 | no | 214 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 6 | Fee Worksheet (SB06) | fee-info.pdf | 32705<br>0bb4f895d9feb96caf689cfea83a7cdab2ffc35a | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | | **Total Files Size (in bytes):** | 26274949 | |

**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.**

HONIGMAN

Honigman Miller Schwartz and Cohn LLP
Attorneys and Counselors

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*VIA EFS*

March 20, 2015

Mail Stop Amendments
Commissioner for Patents
United States Patent and Trademark Office
P. O. Box 1450
Alexandria, VA 22313

***Re:*** ***Application No.: 13/984,559***
***Inventor: Jo Ann Wilson***
***Filing Date: March 20, 2014***
***Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds***
***Attorney Docket No.: 224990/10-039C-US/343999***

Dear Sir or Madam:

Enclosed for filing please find the following documents:

1. This Cover Letter to the Commissioner;
2. Response to Non-Final Office Action dated October 8, 2014;
3. Information Disclosure Statement;
4. Foreign Patent References (5);
5. Petition for Extension of Time (PTO/SB/22); and
6. Certificate of Transmission under 37 C.F.R. § 1.8(a).

The total fee for this response, including the extension of time fee and the fee for the Information Disclosure Statement, is $790. It is believed that no additional fees are required for this reply other than as provided above. However, if there are any additional charges or credits in relation to this response, please apply them to Deposit Account No. 503145, referencing Attorney Docket Number 224990/10-039C-US/343999.

Very truly yours,

HONIGMAN MILLER SCHWARTZ AND COHN LLP

Heidi M. Berven, Ph.D.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. 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 displays a valid OMB control number.

| PATENT APPLICATION FEE DETERMINATION RECORD<br>Substitute for Form PTO-875 | Application or Docket Number<br>13/984,559 | Filing Date<br>03/20/2014 | ☐ To be Mailed |
|---|---|---|---|

**ENTITY**: ☐ LARGE ☒ SMALL ☐ MICRO

## APPLICATION AS FILED – PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | RATE ($) | FEE ($) |
|---|---|---|---|---|
| ☐ BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | |
| ☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | |
| ☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | minus 20 = | * | X $ = | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | minus 3 = | * | X $ = | |
| ☐ 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 **03/20/2015**

| | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|
| Total (37 CFR 1.16(i)) | * 25 | Minus | ** 34 | = 0 | X $40 = | 0 |
| Independent (37 CFR 1.16(h)) | * 4 | Minus | ***15 | = 0 | X $210 = | 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) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|
| Total (37 CFR 1.16(i)) | * | Minus | ** | = | X $ = | |
| Independent (37 CFR 1.16(h)) | * | Minus | *** | = | X $ = | |
| ☐ 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.

** 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 number found in the appropriate box in column 1.

LIE
/SHARON HARRIS/

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.**

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 13/984,559 | 03/20/2014 | Jo Ann Wilson | 224990/10-039C-US/343999 | 6725 |

91684 7590 10/08/2014

JONATHAN P. O'BRIEN, PH.D.
HONIGMAN MILLER SCHWARTZ AND COHN LLP
350 EAST MICHIGAN AVENUE, SUITE 300
Kalamazoo, MI 49007-3800

| EXAMINER | |
|---|---|
| ROZOF, TIMOTHY R | |
| ART UNIT | PAPER NUMBER |
| 1625 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 10/08/2014 | PAPER |

**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.

| Office Action Summary | Application No. 13/984,559 | Applicant(s) WILSON, JO ANN | |
|---|---|---|---|
| | Examiner TIMOTHY R. ROZOF | Art Unit 1625 | AIA (First Inventor to File) Status No |

*-- 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 *July 31, 2014*.

☐ 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) *1-10, 12-16,19, 20, 23, and 28-39* is/are pending in the application.

5a) Of the above claim(s) *1-10 and 12-15* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *16,19,20,23 and 28-39* 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 _____ 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 _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

## DETAILED ACTION

This is a response to Applicant's communication filed on July 31, 2014. Application No. 13/984,559 is a 371 of PCT/US12/24591, filed February 10, 2012, which claims the benefit of U.S. Provisional Applications Nos.: 61/441,520, February 10, 2011; and 61/441,527, filed February 10, 2011. In a preliminary amendment filed March 20, 2014, Applicant cancelled claims 11, 17, 18, 21, 22, and 24-27. In an amendment filed July 31, 2014, Applicant added new claims 35-39. Claims 1-10, 12-16, 19, 20, 23, and 28-39 are pending.

### *Election/Restrictions*

Applicant's election without traverse of the invention of Group III in the reply filed on July 31, 2014, is acknowledged. Claims 1-10 and 12-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 31, 2014.

Claims 16, 19, 20, 23, and 28-29 are examined below.

### *Claim Rejections - 35 USC § 102(b)*

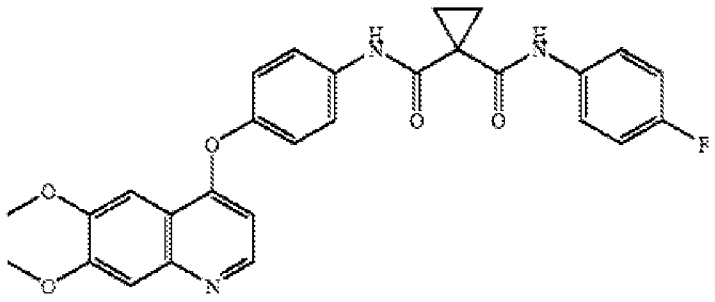
The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 16, 19, 20, 23, and 28-29 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Bannen et al., US2007/0054928 A1. Bannen et al. discloses the following compounds as well as pharmaceutical compositions of the compound:

12 N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide



(Bannen et al., Specification, para. [0165], Table 2, p. 105, Compound No. 12. See also Id., para. [0166], p. 129, for the pharmaceutical compositions of the compounds disclosed therein. Specifically, see Id. para. [0297]-[01310], p. 144-145, for the components the pharmaceutical compositions including the above compound.) This compound anticipates Compounds IA or IB. The compounds of the present invention appear to be drawn to a compound free of other impurities. Inherent in the compounds disclosed in the prior art is that the compounds are free of impurities. The prior art discloses that the compounds are pharmaceutical grade compounds which are free of impurities. See Id. para. [0297], p. 144, which states that administration of the compounds of the invention or their pharmaceutically acceptable salts, in *pure form* or in an appropriate pharmaceutical compositions, can be carried out via any of the accepted modes of administration or agents for serving similar utilities.

***Claim Rejections - 35 USC § 103(a)***

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

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16, 19, 20, 23, and 28-29 are rejected under pre-AIA 35 U.S.C. 102(b) as anticipated by or, in the alternative, under pre-AIA 35 U.S.C. 103(a) as obvious over Bannen et al., US2007/0054928 A1. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) 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.

As shown above, Bannen et al. discloses Compounds IA and IB of the present invention. (Bannen et al., Specification, para. [0165], Table 2, p. 105, Compound No. 12. See also Id., para. [0166], p. 129, for the pharmaceutical compositions of the compounds disclosed therein. Specifically, see Id. para. [0297]-[01310], p. 144-145, for the components of the pharmaceutical compositions of the compounds above.) To the extent that the prior art does not disclose the ranges, concentrations and conditions of

claims 19, 20, 23, and 28-39, these considerations have been obvious to the ordinary artisan as a matter of routine optimization.

In this case, the differences in reaction conditions will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such reaction conditions are critical.

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

(MPEP 2144.05.) Applicants have not provided evidence whether the claimed ranges, concentrations and conditions, etc., are critical to the claimed invention. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to

adjust the ranges, concentrations and conditions of the known elements to those of the instant invention to yield the best results as a matter of routine optimization.

***Claim Rejections - 35 USC § 112, Second Paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> 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 16, 19, 20, 23, and 28-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. In this case, the claims improperly refer to "Compound IA or IB," which are disclosed elsewhere in the specification, to give meaning to the compounds in the claims. See *Ex Parte Fressola* 27 USPQ2d 1608, for the proposition that:

> "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 in utility applications [1] that define the invention entirely by reference to the specification and/or drawings, so-called "omnibus" or "formal" claims, while perhaps once accepted in American patent practice, are properly rejected under Section 112 Para. 2 as failing to particularly point out and distinctly claim the invention. See MPEP Section 706.03(h) (5th ed., rev. 14, Nov. 1992); Landis, Mechanics of Patent Claim Drafting, Section 2 (1974). This analysis is limited to claims in utility applications. Plant patent claims are defined "in formal terms to the plant shown and described." Claims in design patents are recited in formal terms to the ornamental design "as shown" or, where there is a properly included special description of the design, the ornamental design "as shown and described." MPEP Section 1503.01…….The general rule is that the claims should be self-contained; that is, they should not expressly rely upon the description or drawing to give them meaning. . . . The terms "substantially as described" and the like, once much used in claims (GLASCOCK 1943 Section 5640) are now rarely seen. The Office disregards them in interpreting claims. . . . Claims consisting only in a reference to the disclosure, as "The features of novelty herein disclosed," are not allowed except in design cases……A claim which refers to the specification defeats the purpose of a claim."

The specification should not be referenced when the compounds of the claim(s) can be clearly described in the claim by either name or structural representation.

Similarly claims 19 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The claims improperly refer to "the N-2 form" and "the N-1 form," which are disclosed elsewhere in the specification, to give meaning to the forms in the claims. The specification should not be referenced when the forms of the compounds can be clearly described in the claim by either name or structural representation.

### *Conclusion*

No claims are allowed.

### *Contact Information*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY R. ROZOF whose telephone number is (571)270-5992. The examiner can normally be reached on Monday thru Friday, 9:00 am to 5:00 pm ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. 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 http://pair-direct.uspto.gov. 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.

/TIMOTHY R ROZOF/
Examiner, Art Unit 1625

| Notice of References Cited | Application/Control No. 13/984,559 | Applicant(s)/Patent Under Reexamination WILSON, JO ANN | |
|---|---|---|---|
| | Examiner TIMOTHY R. ROZOF | Art Unit 1625 | Page 1 of 1 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | Classification |
|---|---|---|---|---|---|
| * | A | US-2007/0054928 | 03-2007 | Bannen et al. | 514/266.2 |
| | B | US- | | | |
| | C | US- | | | |
| | D | US- | | | |
| | E | US- | | | |
| | F | US- | | | |
| | G | US- | | | |
| | H | US- | | | |
| | I | US- | | | |
| | J | US- | | | |
| | K | US- | | | |
| | L | US- | | | |
| | M | US- | | | |

**FOREIGN PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Country | Name | Classification |
|---|---|---|---|---|---|---|
| | N | | | | | |
| | O | | | | | |
| | P | | | | | |
| | Q | | | | | |
| | R | | | | | |
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| | T | | | | | |

**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
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| | X | |

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**EAST Search History**

**EAST Search History (Prior Art)**

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | Time Stamp |
|---|---|---|---|---|---|---|
| L1 | 1868 | 546/153 | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | ON | 2014/10/04 13:11 |
| L2 | 6107 | ((546/153) or (514/312)).CCLS. | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | OFF | 2014/10/04 13:12 |
| L3 | 4920 | l2 and @ad<="20110210" | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | ON | 2014/10/04 13:12 |
| L4 | 476 | l3 and (protein near3 kinase) | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | ON | 2014/10/04 13:14 |
| L5 | 88 | l4 and ((c$met) or (Ret)) | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | ON | 2014/10/04 13:14 |
| L6 | 2 | ("20070054928").PN. | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | OFF | 2014/10/04 13:14 |

**EAST Search History (Interference)**

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| L7 | 1 | ((546/153) or (514/312)).CCLS. | UPAD | OR | OFF | 2014/10/04 13:43 |

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**CONFIRMATION NO. 6725**

| SERIAL NUMBER | FILING or 371(c) DATE | CLASS | GROUP ART UNIT | ATTORNEY DOCKET NO. |
|---|---|---|---|---|
| 13/984,559 | 03/20/2014<br>RULE | 514 | 1625 | 224990/10-039C-US/343999 |

**APPLICANTS**

**INVENTORS**

Jo Ann Wilson, San Francisco, CA;

**** CONTINUING DATA ***************************

This application is a 371 of PCT/US12/24591 02/10/2012
which claims benefit of 61/441,520 02/10/2011
and claims benefit of 61/441,527 02/10/2011

**** FOREIGN APPLICATIONS ***************************

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| Foreign Priority claimed ☐ Yes ☑ No<br>35 USC 119(a-d) conditions met ☐ Yes ☐ No<br>Verified and Acknowledged /TIMOTHY R ROZOF/ Examiner's Signature | ☐ Met after Allowance<br>TRR Initials | STATE OR COUNTRY | SHEETS DRAWINGS | TOTAL CLAIMS | INDEPENDENT CLAIMS |
|---|---|---|---|---|---|
| | | CA | 0 | 25 | 6 |

**ADDRESS**

JONATHAN P. O'BRIEN, PH.D.
HONIGMAN MILLER SCHWARTZ AND COHN LLP
350 EAST MICHIGAN AVENUE, SUITE 300
Kalamazoo, MI 49007-3800
UNITED STATES

**TITLE**

Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

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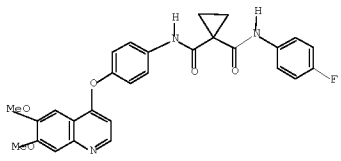
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=>
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L1 STRUCTURE UPLOADED

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L1 HAS NO ANSWERS
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FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
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PROJECTED ANSWERS: 0 TO 0

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L3 19 SEA SSS FUL L1

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L4 171 L3

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L3 19 SEA FILE=REGISTRY SSS FUL L1

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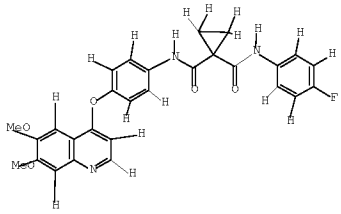
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L1 HAS NO ANSWERS
L1 STR



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SAMPLE SCREEN SEARCH COMPLETED - 20 TO ITERATE

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PROJECTED ITERATIONS: 132 TO 668
PROJECTED ANSWERS: 0 TO 0

L2 0 SEA SSS SAM L1

=> s l1 sss full
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FULL SCREEN SEARCH COMPLETED - 395 TO ITERATE

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SEARCH TIME: 00.00.01

L3 7 SEA SSS FUL L1

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L4 170 L3

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ACCESSION NUMBER: 2014:1563739 CAPLUS full-text
TITLE: Method for the prognosis and treatment of cancer metastasis
INVENTOR(S): Gomis, Roger; Planet, Evarist; Pavlovic, Milica; Arnal, Anna; Tarragona, Maria
PATENT ASSIGNEE(S): Fundacio Privada Institut de Recerca Biomedica, Spain; Fundacio Privada Institucio Catalana de Recerca i

Estudis Avancats
SOURCE: PCT Int. Appl., 97pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

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|---|---|---|---|---|
| WO 2014140933 | A2 | 20140918 | WO 2014-IB1253 | 20140314 |

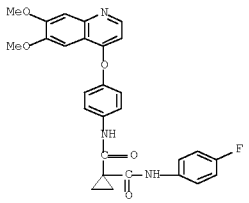
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2013-61801718 P 20130315

AB The invention relates to a method for the prognosis of bone metastasis in cancer which comprises using a probe to determine if a gene of interest is amplified in a primary tumor sample. Likewise, the invention also relates to a method for determining the tendency to develop bone metastasis with respect to metastasis in other organs, which comprise using a probe to determine the expression level of a gene of interest, or the amplification or translocation of a gene of interest. The invention also relates to a method for predicting early bone metastasis in a subject suffering cancer. The invention also relates to a c-MAF inhibitor as therapeutic agent for use in the treatment of cancer metastasis. The invention relates to kits for predicting bone metastasis and predicting the clin. outcome of a subject suffering from bone metastasis. Finally, the invention relates to a method for typing of a subject suffering cancer and for classifying a subject from cancer into a cohort.

IT INDEXING IN PROGRESS
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for prognosis and treatment of cancer metastasis)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L4 ANSWER 2 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:1476801 CAPLUS Full-text
DOCUMENT NUMBER: 161:446646
TITLE: Preparation of pyridine compounds as protein tyrosine kinase inhibitors for treatment of proliferative diseases
INVENTOR(S): Xi, Ning; Wang, Ruyong; Wang, Liang
PATENT ASSIGNEE(S): Sunshine Lake Pharma Co., Ltd., Peop. Rep. China; Jiatuo Sciences Company
SOURCE: Faming Zhuanli Shenqing, 118pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

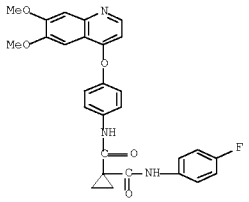
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| CN 104016979 | A | 20140903 | CN 2013-10597520 | 20131122 |
| PRIORITY APPLN. INFO.: | | | CN 2012-10480698 A | 20121123 |
| | | | CN 2013-10116667 A | 20130403 |

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention provides novel substituted pyridinyl compds. of general formula I, pharmaceutical acceptable salts and formulations thereof useful in modulating protein tyrosine kinase activity, and in modulating cellular activities such as proliferation, differentiation, apoptosis, migration and invasion. For I, each of R1, R2, R3, R4, R5 and R6 is independently H, D or F; X is C6-C10 aryl or 5-10 membered heteroaryl that are optionally substituted; and Y is an (un)substituted bicyclic heterocyclyl. The invention also provides pharmaceutically acceptable compns. comprising such compds. and methods of using the compns. in the treatment of hyperproliferative disorders in mammals, especially humans. Example compound II was prepared in a 6-step reaction that culminated in coupling of intermediates III and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-ol. Example compds. of the invention were also tested in ALK and c-Met kinase inhibition assays. Pharmacokinetic profiles were also examined in rats, as was compound stability in human and rat liver microsomes.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(codrug; preparation of pyridine compds. as protein tyrosine kinase inhibitors for treatment of proliferative diseases)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L4 ANSWER 3 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:1425621 CAPLUS Full-text
DOCUMENT NUMBER: 161:400645
TITLE: Treatment of cancer using an oncolytic virus and a receptor tyrosine kinase inhibitor
INVENTOR(S): Conner, Joe
PATENT ASSIGNEE(S): Virttu Biologics Limited, UK
SOURCE: PCT Int. Appl., 310pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2014128487 | A1 | 20140828 | WO 2014-GB50522 | 20140221 |

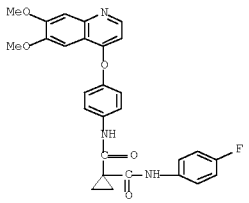
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: GB 2013-3184 A 20130222

AB A method of treating cancer is disclosed, the method comprising simultaneous or sequential administration of an oncolytic virus and a receptor tyrosine kinase (RTK) inhibitor.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of cancer using an oncolytic virus and a receptor tyrosine kinase inhibitor)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:1390694 CAPLUS Full-text
DOCUMENT NUMBER: 161:375913
TITLE: Preparation of pyrazolopyridine compounds as protein kinase modulators useful for treatment of hyperproliferative disorders
INVENTOR(S): Xi, Ning
PATENT ASSIGNEE(S): Sunshine Lake Pharma Co., Ltd., Peop. Rep. China; Calitor Sciences, LLC
SOURCE: U.S. Pat. Appl. Publ., 41pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

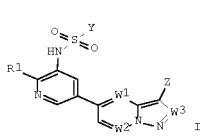
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|

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|---|---|---|---|---|---|
| US 20140234254 | A1 | 20140821 | US 2014-14181670 | 20140215 |
| WO 2014130375 | A1 | 20140828 | WO 2014-US16643 | 20140215 |

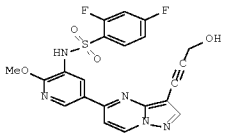
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW

PRIORITY APPLN. INFO.: US 2013-61767721 P 20130221
OTHER SOURCE(S): MARPAT 161:375913
GI



I

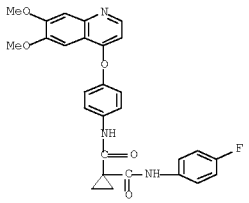


II

AB The invention provides heteroarom. derivs. and pharmaceutically acceptable salts and formulations thereof useful in modulating the protein kinase activity, especially phosphatidylinositol 3-kinases (PI3K) and mammalian target of rapamycin (mTOR), and in modulating inter- and/or intra-cellular signaling activities such as proliferation, differentiation, apoptosis, migration and invasion. The invention also provides pharmaceutically acceptable compns. comprising such compds. and methods of using the compns. in the treatment of hyperproliferative disorders in mammals, especially humans. Compds. of formula I [wherein W1, W2, and W3 are independently N or CRc; Z is D, CN, N3, etc.; Y is C1-6 alkyl, C3-6 cycloalkyl, C3-C6 heterocyclyl, etc.; R1 is H, Cl, C3-6 cycloalkyl, etc.; each Rc is independently H, D, F, etc.] or stereoisomers, geometric isomers, tautomers, N-oxides, solvates, metabolites, prodrugs, or pharmaceutically acceptable salts thereof are claimed and exemplified. Example compound II was prepared in seven steps (procedure given). Candidate compds. of I were assayed for their stability in liver microsomes, their oral and i.v. bioavailability, and inhibitory activity against PI3K and mTOR kinase (data given).

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(codrug; preparation of pyrazolopyridine compds. as protein kinase modulators useful for treatment of hyperproliferative disorders)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L4 ANSWER 5 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:1389525 CAPLUS Full-text
DOCUMENT NUMBER: 161:379820
TITLE: Efflux inhibitor compositions containing effect transporter protein inhibitors
INVENTOR(S): Bunt, Antonius Martinus Gustave; Tellingen, Olaf Van
PATENT ASSIGNEE(S): Izumi Biosciences LLC, USA; The Netherlands Cancer Institute
SOURCE: U.S. Pat. Appl. Publ., 33pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

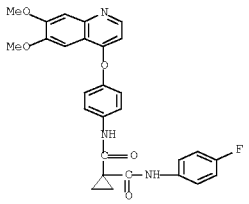
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 20140235631 | A1 | 20140821 | US 2013-13952476 | 20130726 |

PRIORITY APPLN. INFO.: US 2013-61767689 P 20130221
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The present invention relates to efflux inhibitor compns. and methods of using these agents for treating conditions where the activity of efflux transporter proteins (e.g., Breast Cancer Resistance Protein (BCRP) and P-Glycoprotein (P-GP)) inhibit effective delivery of a therapeutic agent to a target tissue (e.g., brain, spinal cord, nerves, cerebrospinal fluid, testis, eyeballs, retina, inner ear, placenta, mammary gland, liver, biliary tract, kidney, intestines, lung, adrenal cortex, endometrium, hematopoietic cells, and/or stem cells). E.g., elacridar nanoparticles were prepared

IT 849217-68-1, Cabozantinib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(kinase inhibitor; efflux inhibitor pharmaceuticals containing effect transporter protein inhibitors)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L4 ANSWER 6 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:1348855 CAPLUS Full-text
DOCUMENT NUMBER: 161:346659
TITLE: Drug selection for non-small cell lung cancer therapy
INVENTOR(S): Singh, Sharat; Kim, Phillip
PATENT ASSIGNEE(S): Nestec S.A., Switz.
SOURCE: PCT Int. Appl., 77pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2014122582 | A1 | 20140814 | WO 2014-IB58790 | 20140204 |

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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2013-61761105 P 20130205

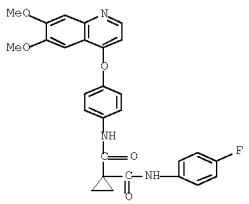
AB The invention provides methods for therapy selection for a patient with non-small cell lung cancer (NSCLC) based on detecting, quantifying, and comparing the activity of particular signal transduction pathways, and components thereof, which can be represented as the patient's analyte index (e.g., EGFR/cMET index) and can be used to determine whether the patient is likely to respond to a particular therapy such as EGFR inhibitor therapy alone, cMET inhibitor therapy alone, or a combination thereof. The EGFR inhibitor is selected from the group consisting of cetuximab, panitumumab, matuzumab, nimotuzumab, Erbl vaccine, erlotinib, gefitinib, CL-387785 and a combination thereof, wherein the c-MET inhibitor is selected from the group consisting of ARQ197, XL184, GSK1363089/XL880, MP470, MGCD265, SGX523, PF04217903, JNJ38877605, INCB28060, AMG-458, E7050, MK-2461, BMS-777607 and a combination thereof. The invention also provides methods for determining drug resistance in non-small cell lung cancer (NSCLC) patients receiving above mentioned therapy.

IT 1140909-48-3, XL184
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug selection for non-small cell lung cancer therapy)

RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

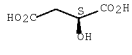
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:1339983 CAPLUS Full-text
DOCUMENT NUMBER: 161:329247
TITLE: Improved treatment for adenoid cystic carcinoma comprising growth factor receptor kinase and MET kinase inhibitors
INVENTOR(S): Stenman, Goeran; Andersson, Mattias
PATENT ASSIGNEE(S): Swed.
SOURCE: PCT Int. Appl., 116pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2014123476 | A1 | 20140814 | WO 2014-SE50140 | 20140204 |

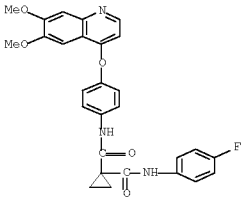
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2013-61849920 P 20130205

AB The present application relates to inhibitors of epidermal growth factor receptor (EGFR) kinase, MET kinase, insulin receptor (IR) kinase and insulin-like growth factor 1 (IGF1R) kinase for use in the treatment of neoplastic disease such as adenoid cystic carcinoma (ACC) and dermal cylindroma characterized by MYB activation. In an optional embodiment, the kinase inhibitor inhibits the MET kinase and the EGFR kinase and/or the IGF1R/IR kinase. In an optional embodiment, the kinase inhibitor is BMS-754807. In an optional embodiment, the IGF1R/IR kinase inhibitor is selected from a group consisting of linsitinib and BMS-754807. In an optional embodiment, the EGFR kinase inhibitor is selected from a group consisting of gefitinib, erlotinib, BMS-690514 and cetuximab. In an optional embodiment, the MET kinase inhibitor is selected from a group consisting of crizotinib, BMS-907351, BMS-777607 and BMS-754807.

IT 849217-68-1, BMS 907351
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(BMS 907351; improved treatment for adenoid cystic carcinoma comprising growth factor receptor kinase and MET kinase inhibitors)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

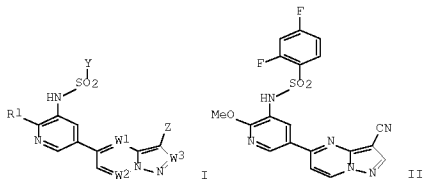


REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:1274352 CAPLUS Full-text
DOCUMENT NUMBER: 161:361023
TITLE: Preparation of aryl-heterocyclic compounds for treatment of hyperproliferative disorders
INVENTOR(S): Xi, Ning
PATENT ASSIGNEE(S): Sunshine Lake Pharma Co., Ltd., Peop. Rep. China; Jiatuo Sciences Company
SOURCE: Faming Zhuanli Shenqing, 59pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| CN 103965199 | A | 20140806 | CN 2014-10041929 | 20140128 |
| PRIORITY APPLN. INFO.: | | | CN 2013-10040391 A | 20130202 |
| | | | CN 2013-10117077 A | 20130404 |

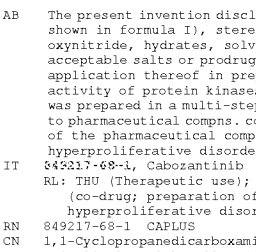
OTHER SOURCE(S): MARPAT 161:361023
GI



AB The present invention discloses aryl-heterocyclic compd. (with structure as shown in formula I), stereo isomers, geometrical isomers, tautomers, oxynitride, hydrates, solvates, metabolic products, pharmaceutically acceptable salts or prodrugs, pharmaceutical compns. containing thereof and application thereof in preparing agents for inhibiting or regulating the activity of protein kinases in biol. specimens. For example, compound II was prepared in a multi-step synthesis. The present invention also relates to pharmaceutical compns. containing the inventive compound, and application of the pharmaceutical compns. for treating mammal, particular human hyperproliferative disorders.

IT 849217-68-1, Cabozantinib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(co-drug; preparation of aryl-heterocyclic compds. for treatment of hyperproliferative disorders)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

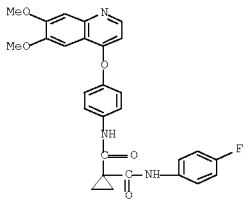


L4 ANSWER 9 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:1270460 CAPLUS Full-text
DOCUMENT NUMBER: 161:351479
TITLE: Degradation kinetics study of cabozantinib by a novel stability-indicating LC method and identification of its major degradation products by LC/TOF-MS and LC-MS/MS
AUTHOR(S): Wu, Chunyong; Xu, Xue; Feng, Chao; Shi, Yuanyuan; Liu, Wenyuan; Zhu, Xiaoyun; Zhang, Junying
CORPORATE SOURCE: Key Laboratory of Drug Quality Control and Pharmacovigilance, Ministry of Education, China Pharmaceutical University, Nanjing, 210009, Peop. Rep. China
SOURCE: Journal of Pharmaceutical and Biomedical Analysis (2014), 98, 356-363
CODEN: JPBADA; ISSN: 0731-7085
DIGITAL OBJECT ID: 10.1016/j.jpba.2014.06.008
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB The chem. stability of cabozantinib (CBZ) was investigated using a novel stability-indicating LC method. Forced degradation of CBZ was carried out under acidic, basic, thermal, oxidative and photolytic stress conditions. Hydrolysis and oxidation were the primary pathways for this compound and three major unknown degradation products were characterized by LC/TOF-MS and LC-MS/MS. The major oxidative degradation product was isolated by preparative LC and identified by UV, HRMS and NMR techniques to be N-{4-[(N-oxide-6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)- cyclopropane-1,1-dicarboxamide. The developed method was validated as per ICH guidelines and then successfully applied to investigate the degradation kinetics of CBZ. Degradation of CBZ followed first-order kinetics under all exptl. conditions. A V-shaped pH-rate profile over the pH range 2-10 was observed with maximum stability at pH 6. The effect of temperature on the rate of CBZ degradation was characterized using the Arrhenius equation. The activation energy for hydrolysis was 57.31 kJ mol-1 in alkaline solution

IT 849217-68-1, Cabozantinib 1140909-48-3, Cabozantinib (S)-Malate
RL: AMX (Analytical matrix); PEP (Physical, engineering or chemical process); PRP (Properties); ANST (Analytical study); PROC (Process)
(degradation kinetics study of cabozantinib by novel stability-indicating LC method and identification of major degradation products by LC/TOF-MS and LC-MS/MS)

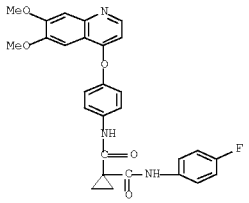
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

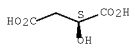
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

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|---|---|---|---|---|
| US 20140205681 | A1 | 20140724 | US 2014-14160018 | 20140121 |
| US 20140220159 | A1 | 20140807 | US 2014-14160001 | 20140121 |

PRIORITY APPLN. INFO.: US 2013-61754574 P 20130119
US 2013-61874190 P 20130905

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 161:269288

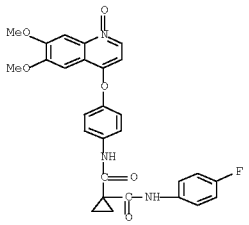
AB The present invention relates to peptidomimetics for reactivating p53. Methods of using the peptidomimetics are also disclosed. One aspect of the present invention relates to a peptidomimetic, where the peptidomimetic mimics a helix having the formula X1-X2-X2-X3-X2-X2-X1-X4, wherein each X1 is any neg. charged residue, each X2 is any hydrophobic residue, X3 is any pos.-charged residue, and X4 is any polar residue. Addnl., the peptidomimetic may contain one or more bridges linking the side chains of its component amino acids. Another aspect of the present invention relates to a method of treating or preventing in a subject a disorder mediated by interaction of E6 with CREB-binding protein and/or p300, the method comprising administering to the subject a peptidomimetic of the present invention under conditions effective to treat or prevent the disorder. Another aspect of the present invention relates to a method of inducing apoptosis and decreasing survival and/or proliferation of a cell, the method comprising contacting the cell with a peptidomimetic. In this study, the authors took a novel approach and functionally reactivated p53 in Human papillomaviruses (HPV)-pos. head and neck squamous cell carcinoma (HNSCC) by blocking the interaction between E6 and p300. Ectopic expression of the CH1 domain of p300 squelched E6 to disrupt E6-p300 association resulting in an increase in p53 acetylation, accumulation, and activity. CH1 domain inhibitors reactivated p53 and dramatically potentiated the efficacy of cisplatinum in HPV-pos. HNSCC. Taken together, the authors work revealed a novel druggable approach to reactivate p53 in HPV-pos. HNSCC that is expected to translate to other HPV-pos. carcinomas.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptidomimetics for p53 reactivation by inhibiting interaction of E6 with CREB-binding protein and/or p300 to treat HPV-associated cancer and combination with other agents)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

IT 1621681-63-7
RL: ANT (Analyte); FMU (Formation, unclassified); PRP (Properties); ANST (Analytical study); FORM (Formation, nonpreparative)
(degradation kinetics study of cabozantinib by novel stability-indicating LC method and identification of major degradation products by LC/TOF-MS and LC-MS/MS)

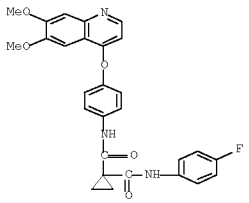
RN 1621681-63-7 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N-[4-[(6,7-dimethoxy-1-oxido-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:1205266 CAPLUS Full-text
DOCUMENT NUMBER: 161:269288
TITLE: Hydrogen-bond surrogate peptides and peptidomimetics for p53 reactivation by inhibiting interaction of E6 with CREB-binding protein and/or p300 to treat HPV-associated cancer
INVENTOR(S): Arora, Paramjit S.; Pan, Quintin; Mapp, Anna
PATENT ASSIGNEE(S): New York University, USA; The Ohio State University Research Foundation; University of Michigan
SOURCE: PCT Int. Appl., 98pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2014113792 | A1 | 20140724 | WO 2014-US12331 | 20140121 |



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:1202788 CAPLUS Full-text
DOCUMENT NUMBER: 161:269285
TITLE: Oligooxopiperazines for p53 reactivation by inhibiting interaction of E6 with CREB-binding protein and/or p300 to treat HPV-associated cancer
INVENTOR(S): Arora, Paramjit S.; Pan, Quintin; Mapp, Anna
PATENT ASSIGNEE(S): New York University, USA; The Ohio State University Research Foundation; The Regents of the University of Michigan
SOURCE: PCT Int. Appl., 95pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2014113794 | A2 | 20140724 | WO 2014-US12337 | 20140121 |
| WO 2014113794 | A3 | 20140912 | | |

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

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|---|---|---|---|---|
| US 20140205655 | A1 | 20140724 | US 2014-14160037 | 20140121 |

PRIORITY APPLN. INFO.: US 2013-61754575 P 20130119
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

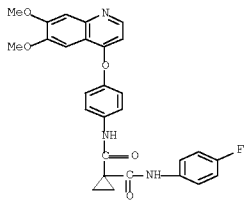
OTHER SOURCE(S): MARPAT 161:269285

AB The present invention relates to oligooxopiperazines for reactivating p53. Methods of using the oligooxopiperazines are also disclosed. A first aspect of the present invention relates to a method of treating or preventing in a subject a disorder mediated by interaction of E6 with CREB-binding protein and/or p300, the method comprising administering to the subject an oligooxopiperazine that substantially mimics helix αB of the C-terminal transactivation domain of Hypoxia-Inducible Factor Iα under conditions effective to treat or prevent the disorder. A second aspect of the present invention relates to a method of inducing apoptosis or decreasing survival and/or proliferation of a cell, the method comprising contacting the cell with an oligooxopiperazine. In this study, the authors took a novel approach and functionally reactivated p53 in Human papillomaviruses (HPV)-pos. head and neck squamous cell carcinoma (HNSCC) by blocking the interaction between E6 and p300. Ectopic expression of the CH1 domain of p300 squelched E6 to disrupt E6-p300 association resulting in an increase in p53 acetylation, accumulation, and activity. CH1 domain inhibitors reactivated p53 and dramatically potentiated the efficacy of cisplatinum in HPV-pos. HNSCC. Taken together, the authors work revealed a novel druggable approach to reactivate p53 in HPV-pos. HNSCC that is expected to translate to other HPV-pos. carcinomas. HMD: helix αB of C-terminal transactivation domain, of HIF-1α, mimics.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oligooxopiperazines for p53 reactivation by inhibiting interaction of E6 with CREB-binding protein and/or p300 to treat HPV-associated cancer and combination with other agents)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L4 ANSWER 12 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2014:1160177 CAPLUS Full-text

DOCUMENT NUMBER: 161:239766

TITLE: Androgen receptor modulator for treatment of prostate cancer and other conditions

INVENTOR(S): Chen, Isan; Hager, Jeffrey H.; Maneval, Edna Chow; Herbert, Mark R.; Smith, Nicholas D.

PATENT ASSIGNEE(S): Aragon Pharmaceuticals, Inc., USA

SOURCE: U.S. Pat. Appl. Publ., 46pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 20140199236 | A1 | 20140717 | US 2014-14151106 | 20140109 |
| WO 2014113260 | A1 | 20140724 | WO 2014-US10777 | 20140109 |

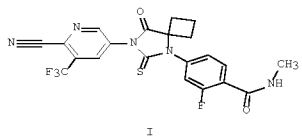
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2013-61752842 P 20130115

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

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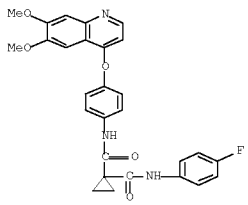
I

AB The invention discloses the androgen receptor modulator I for the treatment of prostate cancer in combination with other therapeutic options and for the treatment of diseases or conditions that are amenable to treatment with the androgen receptor modulator, as well as pharmaceutical compns. and medicaments that include I.

IT 849217-68-1, Cabozantinib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(androgen receptor modulator for treatment of prostate cancer and other conditions)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L4 ANSWER 13 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2014:1154296 CAPLUS Full-text

DOCUMENT NUMBER: 161:209516

TITLE: Predictive biomarker and method for combination therapy of EGFR and c-MET inhibitors in non-small cell lung cancer with wild type EGFR

INVENTOR(S): Lee, Mun Ja; Kim, Hyeon Jeong; Kang, Han Na

PATENT ASSIGNEE(S): JEUK Co., Ltd., S. Korea

SOURCE: Repub. Korea, 20pp.
CODEN: KRXXFC

DOCUMENT TYPE: Patent

LANGUAGE: Korean

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| KR 1418970 | B1 | 20140711 | KR 2013-29977 | 20130320 |

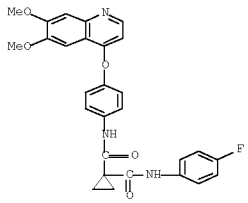
PRIORITY APPLN. INFO.: KR 2013-29977 20130320

AB The title method comprises the steps of: detg. the p53 genotypes of patients, separating out the patients having cooperation tumor effect probability of combination therapy according to EGFR and c-MET inhibitors. Therefore, the condition of p53 can be used as predicative factor for combination therapy of EGFR and c-MET inhibitors.

IT 849217-68-1, Cabozantinib, co-use with EGFR inhibitors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(c-MET inhibitor; predictive biomarker and method for combination therapy of EGFR and c-MET inhibitors in non-small cell lung cancer with wild type EGFR)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L4 ANSWER 14 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2014:1064742 CAPLUS Full-text

DOCUMENT NUMBER: 161:455975

TITLE: A targeted next-generation sequencing assay detects a high frequency of therapeutically targetable alterations in primary and metastatic breast cancers: implications for clinical practice

AUTHOR(S): Vasan, Neil; Yelensky, Roman; Wang, Kai; Moulder, Stacy; Dzimitrowicz, Hannah; Avritscher, Rony; Wang, Bauang; Wu, Yun; Cronin, Maureen T.; Palmer, Gary; Symmans, W. Fraser; Miller, Vincent A.; Stephens, Phiup; Pusztai, Lajos

CORPORATE SOURCE: Yale University School of Medicine, Connecticut, New Haven, USA

SOURCE: Oncologist (2014), 19(5), 453-458
CODEN: OCOLF6; ISSN: 1083-7159

DIGITAL OBJECT ID: 10.1634/theoncologist.2013-0377

PUBLISHER: AlphaMed Press

DOCUMENT TYPE: Journal

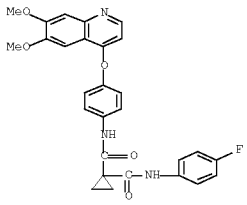
LANGUAGE: English

AB Background. The aim of this study was to assess the frequency of potentially actionable genomic alterations in breast cancer that could be targeted with approved agents or investigational drugs in clin. trials using a next-generation sequencing-based genomic profiling assay performed in a Clin. Laboratory Improvement Amendments-certified and College of American Pathologists-accredited com. laboratory Methods. Fifty-one breast cancers were analyzed, including primary tumor biopsies of 33 stage I-II and 18 stage IV cancers (13 soft tissue, 3 liver, and 2 bone metastases). We assessed 3,230 exons in 182 cancer-related genes and 37 introns in 14 genes often rearranged in cancer for base substitutions, indels, copy number alterations, and gene fusions. The average median sequencing depth was 1,154×. Results. We observed 158 genomic alterations in 55 genes in 48 of 51 (94%) tumors (mean 3.1, range 0-9). The average number of potentially therapeutically relevant alterations was similar in primary (1.6, range 0-4) and in heavily pretreated metastatic cancers (2.0, range 0-4) (p = .24). The most common actionable alterations were in PIK3CA (n = 9, phosphatidylinositol 3-kinase [PI3K]/mammalian target of rapamycin [mTOR] inhibitors), NF1 (n = 7, PI3K/mTOR/mitogen-activated protein kinase inhibitors), v-akt murine thymoma viral oncogene homolog 1-3 (n = 7,

PI3K/mTOR/AKT inhibitors), BRCA1/2 (n = 6, poly[ADP-ribose] polymerase inhibitors), and CCND1,2 and CCNE (n = 8)/cycline dependent kinase (CDK)6 (n = 1) (CDK4/6 inhibitors), KIT (n = 1, imatinib/sunitinib), ALK (n = 1, crizotinib), FGFR1,2 (n = 5, fibroblast growth factor receptor inhibitors), and EGFR (n = 2, epidermal growth factor receptor inhibitors). Our sequencing assay also correctly identified all six cases with HER2 (ERBB2) amplification by fluorescence in situ hybridization when tumor content was adequate. In addition, two known activating HER2 mutations were identified, both in unamplified cases. Conclusion. Overall, 84% of cancers harbored at least one genomic alteration linked to potential treatment options. Systematic evaluation of the predictive value of these genomic alterations is critically important for further progress in this field.

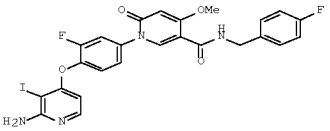
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeted next-generation sequencing assay detects a high frequency of therapeutically targetable alterations in primary and metastatic breast cancers and its implications for clin. practice)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:1049484 CAPLUS Full-text
DOCUMENT NUMBER: 161:246290
TITLE: Design, synthesis and evaluation of highly selective pyridone-based class II MET inhibitors
AUTHOR(S): She, Nengfang; Zhuo, Linsheng; Jiang, Wen; Zhu, Xiaolei; Wang, Jia; Ming, Zhihui; Zhao, Xinge; Cong, Xin; Huang, Wei
CORPORATE SOURCE: Key Laboratory of Pesticide and Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan, 430079, Peop. Rep. China
SOURCE: Bioorganic & Medicinal Chemistry Letters (2014), 24(15), 3351-3355
CODEN: BMCLE8; ISSN: 0960-894X
DIGITAL OBJECT ID: 10.1016/j.bmcl.2014.05.097
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
GI

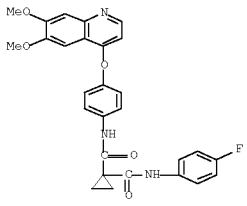


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AB The high incidence of MET oncogene activation in human malignancies has prompted researchers to develop MET inhibitors. As part of our efforts to developing effective and safe therapeutic agents against MET-dependent tumors, a pyridone-based class II MET inhibitor, namely, 1-(4-((2-amino-3-iodopyridin-4-yl)-oxy)-3-fluorophenyl)-N-(4-fluorobenzyl)- 4-methoxy-6-oxo-1,6-dihydropyridine-3-carboxamide (3s, I), was identified. Knowledge of the binding mode of class II MET inhibitors led to the design of new inhibitors that utilize 2-pyridone to conformationally restrain key pharmacophoric groups within the mol. Integrated mol. docking and SAR studies resulted in the discovery of a novel class of pyridone MET inhibitors with high potency (IC50 of 0.005 μM) and efficient selectivity (>5000 fold) to VEGFR-2, c-Kit and RET kinases.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(docking and kinase selectivity study; design, synthesis and evaluation of highly selective pyridone-based class II MET inhibitors)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



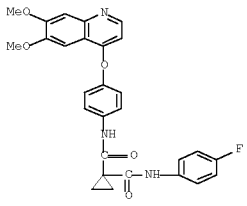
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:1006107 CAPLUS Full-text
DOCUMENT NUMBER: 161:238658
TITLE: Advanced thyroid cancers: new era of treatment
AUTHOR(S): Mohammed, Amrallah A.; El-Shentenawy, Ayman
CORPORATE SOURCE: Oncology Center, King Abdullah Medical City-Holy Capital, Makkah, 21995, Saudi Arabia
SOURCE: Medical Oncology (New York, NY, United States) (2014), 31(7), 1-8
CODEN: MONCEZ; ISSN: 1357-0560
DIGITAL OBJECT ID: 10.1007/s12032-014-0049-x
PUBLISHER: Springer
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English

AB A review. Since chemotherapy has been shown to be unsuccessful in case of advanced thyroid carcinomas, the research for new therapies is fundamental. Clin. trials of many tyrosine kinase inhibitors as well as anti-angiogenic inhibitors suggest that patients with thyroid cancer could have an advantage with new target therapy. Recently, Food and Drug Administration approved two targeted therapies, vandetanib and cabozantinib for the treatment of metastatic thyroid carcinomas with acceptable outcome. We summarized the results and the toxic effects associated with these treatments reported in clin. trials. Future trials should aim at combinations of targeted agents with or without other treatment modalities to obtain a more effective result in thyroid carcinoma treatment.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new era of treatment for advanced thyroid cancer)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:969861 CAPLUS Full-text
DOCUMENT NUMBER: 161:455940
TITLE: Role of salvage targeted therapy in differentiated thyroid cancer patients who failed first-line sorafenib
AUTHOR(S): Dadu, Ramona; Devine, Catherine; Hernandez, Mike; Waguespack, Steven G.; Busaidy, Naifa L.; Hu, Mimi I.; Jimenez, Camilo; Habra, Mouhammad A.; Sellin, Rena V.; Ying, Anita K.; Cote, Gilbert J.; Sherman, Steven I.; Cabanillas, Maria E.
CORPORATE SOURCE: Departments of Endocrine Neoplasia and Hormonal Disorders, Baylor College of Medicine, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Journal of Clinical Endocrinology and Metabolism (2014), 99(6), 2086-2094
CODEN: JCEMAZ; ISSN: 0021-972X
DIGITAL OBJECT ID: 10.1210/jc.2013-3588
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

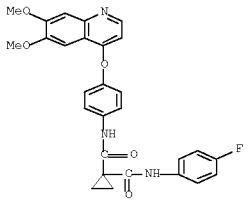
AB Context: Sorafenib, a tyrosine kinase inhibitor, is a common first-line therapy for advanced differentiated thyroid cancer (DTC). However, responses are not durable and drug toxicity remains a problem. Objective: The objective of the study was to determine the efficacy of salvage therapy after first-line sorafenib failure. Design: This was a retrospective review at M. D. Anderson Cancer Center from Jan. 2005 to May 2013. Patients: The study included patients with metastatic DTC who received salvage therapy after their initial sorafenib failure (group 2). Patients who received first-line sorafenib only (group 1) were evaluated for comparison of overall survival (OS). Outcome Measures: Progression-free survival, best response, and median OS were measured. Results: Sixty-four patients with metastatic, radioactive iodine refractory DTC were included; 35 were in group 1 and 25 were in group 2, and the groups were well balanced. Median OS of all 64 patients receiving first line sorafenib was 37 mo; median OS was significantly longer with salvage therapy compared with sorafenib alone (58

vs 28 mo, P = .013). In group 2, 17 patients were evaluable for best response, although two patients had toxicity with sorafenib, which was discontinued before restaging. Best responses with first-line sorafenib were partial response in 2 of 15 (13%), stable disease in 10 of 15 (67%), and progressive disease in 3 of 15 (20%) patients. With salvage therapy, partial responses were seen in 7 of 17 (41%) and stable disease in 10 of 17 (59%) patients. Median progression-free survival was 7.4 mo with first-line sorafenib and 11.4 mo with salvage therapy. Salvage therapy included sunitinib (n = 4), pazopanib (n = 3), cabozantinib (n = 4), lenvatinib (n = 3), and vemurafenib (n = 3). Conclusions: Other targeted agents are effective salvage treatments after sorafenib failure, despite similar mechanisms of action, and should be offered to patients who are able to receive salvage therapy.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(salvage targeted treatment with sunitinib, pazopanib, cabozantinib, lenvatinib and vemurafenib was effective in treatment of patient with metastatic differentiated thyroid cancer who failed first-line sorafenib therapy)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2014:951549 CAPLUS Full-text

DOCUMENT NUMBER: 161:86164

TITLE: Preparation of pyridine compounds as protein tyrosine kinase inhibitors for treatment of proliferative diseases

INVENTOR(S): Xi, Ning; Wang, Ruyong; Wang, Liang

PATENT ASSIGNEE(S): Calitor Sciences, LLC, USA; Sunshine Lake Pharma Co., Ltd.

SOURCE: PCT Int. Appl., 158pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2014089324 | A1 | 20140612 | WO 2013-US73367 | 20131205 |

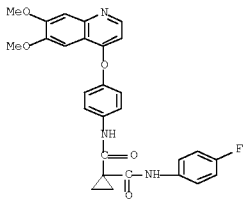
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2012-61734897 P 20121207

OTHER SOURCE(S): MARPAT 161:94410

AB The present invention provides novel substituted alkynyl compds., pharmaceutical acceptable salts and formulations thereof useful in modulating the protein tyrosine kinase activity, and in modulating cellular activities such as proliferation, differentiation, apoptosis, migration and invasion. The invention also provides pharmaceutically acceptable compns.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 19 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2014:951212 CAPLUS Full-text

DOCUMENT NUMBER: 161:94410

TITLE: Alkynyl compounds and methods of use

INVENTOR(S): Xi, Ning; Li, Xiaobo; Zhou, Shiqing

PATENT ASSIGNEE(S): Calitor Sciences, LLC, USA; Sunshine Lake Pharma Co., Ltd.

SOURCE: PCT Int. Appl., 86pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2014089280 | A1 | 20140612 | WO 2013-US73286 | 20131205 |

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2012-61734903 P 20121207
US 2013-61880184 P 20130920

OTHER SOURCE(S): MARPAT 161:86164

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention provides novel substituted pyridinyl compds. of general formula I, pharmaceutical acceptable salts and formulations thereof useful in modulating protein tyrosine kinase activity, and in modulating cellular activities such as proliferation, differentiation, apoptosis, migration and invasion. For I, each of R1, R2, R3, R4, R5 and R6 is independently H, D or F; X is C6-C10 aryl or 5-10 membered heteroaryl that are optionally substituted; and Y is an (un)substituted bicyclic heterocyclyl. The invention also provides pharmaceutically acceptable compns. comprising such compds. and methods of using the compns. in the treatment of hyperproliferative disorders in mammals, especially humans. Example compound II was prepared in a 6-step reaction that culminated in coupling of intermediates III and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-ol. Example compds. of the invention were tested in ALK and c-Met kinase inhibition assays. Pharmacokinetic profiles were also examined in rats, as was compound stability in human and rat liver microsomes.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(codrug; preparation of pyridine compds. as protein tyrosine kinase inhibitors for treatment of proliferative diseases)

RN 849217-68-1 CAPLUS

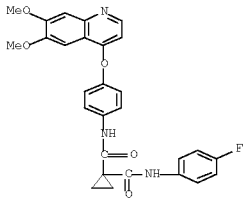
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

comprising such compds. and methods of using the compns. in the treatment of hyperproliferative disorders in mammals, especially humans.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(alkynyl compds. and methods of use)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 20 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2014:943695 CAPLUS Full-text

DOCUMENT NUMBER: 161:196584

TITLE: Adverse events of targeted therapies

AUTHOR(S): Klastersky, Jean A.

CORPORATE SOURCE: Institut Jules Bordet, Centre des Tumeurs de l'Universite Libre de Bruxelles, Brussels, Belg.

SOURCE: Current Opinion in Oncology (2014), 26(4), 395-402
CODEN: CUOOE8; ISSN: 1040-8746

DIGITAL OBJECT ID: 10.1097/CCO.0000000000000096

PUBLISHER: Lippincott Williams & Wilkins

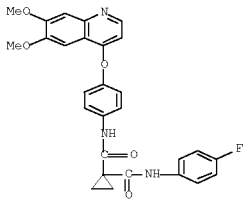
DOCUMENT TYPE: Journal; General Review; (online computer file)

LANGUAGE: English

AB Purpose of review: There is currently an explosion in the no. of so-called targeted therapies. As new indications for these agents multiply, there is also an increase of new and less new side-effects. Recent findings: Given this rapidly evolving field, any literature on that topic is rapidly obsolete and needs re-evaluation. Summary: Targeted therapies are associated with a wide spectrum of adverse events, which cannot always be easily separated from the complications linked to cancer, its therapy, and comorbidities. A high awareness of these events might improve the patient's quality of life and contribute to the recognition of new syndromes.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adverse events of targeted therapies)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



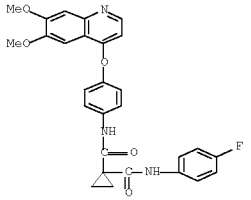
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 21 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:926742 CAPLUS Full-text
DOCUMENT NUMBER: 161:316322
TITLE: Cabozantinib Suppresses Tumor Growth and Metastasis in Hepatocellular Carcinoma by a Dual Blockade of VEGFR2 and MET
AUTHOR(S): Xiang, Qingfeng; Chen, Weiqiang; Ren, Meng; Wang, Jingnan; Zhang, Hongwu; Deng, David Y. B.; Zhang, Lei; Shang, Changzhen; Chen, Yajin
CORPORATE SOURCE: Departments of Hepatopancreatobiliary Surgery, Sun Yat-sen University, Guangzhou, Peop. Rep. China
SOURCE: Clinical Cancer Research (2014), 20(11), 2959-2970
CODEN: CCREF4; ISSN: 1078-0432
DIGITAL OBJECT ID: 10.1158/1078-0432.CCR-13-2620
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB MET signaling was suggested a potential role in hepatocellular carcinoma (HCC) and associated with prometastasis during antiangiogenesis therapy. We investigated the potential association between MET expression and therapeutic response to sorafenib in patients with HCC. Antitumor effects of cabozantinib, a dual inhibitor of MET and VEGFR2, were examined in cultured HCC cells as well as in vivo models. Total MET and phosphorylated MET (p-MET) were measured in 29 resected HCC specimens, and correlated with response to sorafenib as postoperative adjuvant therapy. In the second set of expts. using cultured HCC cells, and mouse xenograft and metastatic models, effects of cabozantinib were examined High level of p-MET in resected HCC specimens was associated with resistance to adjuvant sorafenib therapy. In cultured HCC cells that expressed p-MET, cabozantinib inhibited the activity of MET and its downstream effectors, leading to G1-phase arrest. Cabozantinib inhibited tumor growth in p-MET-pos. and p-MET-neg. HCC by decreasing angiogenesis, inhibiting proliferation, and promoting apoptosis, but it exhibited more profound efficacy in p-MET-pos. HCC xenografts. Cabozantinib blocked the hepatocyte growth factor (HGF)-stimulated MET pathway and inhibited the migration and invasion of the HCC cells. Notably, cabozantinib reduced the number of metastatic lesions in the lung and liver in the exptl. metastatic mouse model. Patients with HCC with high level of p-MET are associated with resistance to adjuvant sorafenib treatment. The dual blockade of VEGFR2 and MET by cabozantinib has significant antitumor activities in HCC, and the activation of MET in HCC may be a promising efficacy-predicting biomarker. Clin Cancer Res; 20(11); 2959-70. ©2014 AACR.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cabozantinib suppresses tumor growth and metastasis in hepatocellular carcinoma by dual blockade of VEGFR2 and MET)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

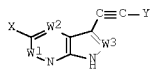


OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

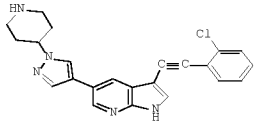
L4 ANSWER 22 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:923002 CAPLUS Full-text
DOCUMENT NUMBER: 161:99226
TITLE: Heterocyclic alkynyl compound, and its use and application as cell proliferation inhibitor and for regulating the activity of protein kinases
INVENTOR(S): Xi, Ning; Li, Xiaobo; Zhou, Shiqing
PATENT ASSIGNEE(S): HEC Pharm Co., Ltd., Peop. Rep. China; Jiatuo Sciences Company
SOURCE: Faming Zhuanli Shenqing, 64pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| CN 103833753 | A | 20140604 | CN 2013-10590780 | 20131121 |
| PRIORITY APPLN. INFO.: | | | CN 2012-10477798 A | 20121122 |
| | | | CN 2013-10116694 A | 20130403 |

OTHER SOURCE(S): MARPAT 161:99226
GI



I

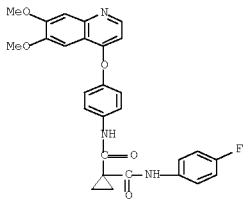


II

AB The present invention provides new substituted alkynyl compds. with the formula of I [W1-4 independently = N or CRc, wherein Rc = H, D, F, Cl, Br, etc.; X = Ph, pyridinyl, pyrrolyl, pyrazolyl, etc.; Y = (un)substituted aryl or heteroaryl], pharmaceutically acceptable salts thereof, pharmaceutical formulation thereof, and their use in regulating the activity of protein kinases and regulating the signal response in cells or between cells. Thus, e.g., II was prepared in a multi-step synthesis. Compds. of the invention were tested for their stability and Alk, c-Met kinase inhibitory activity, e.g., II showed IC50 value of 58 nM against Alkaline The present invention also relates to pharmaceutical compns. comprising a compound of the present invention, and using the pharmaceutical composition for treating a mammal, particularly to human hyperproliferative disorders.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(codrug; heterocyclic alkynyl compound, and its use and application as cell proliferation inhibitor and for regulating the activity of protein kinases)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L4 ANSWER 23 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:913474 CAPLUS Full-text
DOCUMENT NUMBER: 161:46548
TITLE: Cabozantinib capsule composition and its production method
INVENTOR(S): Wang, Luanqiu; Wang, Xinyao
PATENT ASSIGNEE(S): Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 11pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

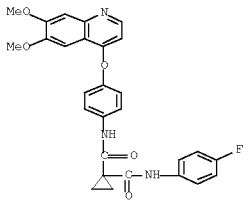
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| CN 103830203 | A | 20140604 | CN 2014-10078549 | 20140305 |
| PRIORITY APPLN. INFO.: | | | CN 2014-10078549 | 20140305 |

AB The invention provides a cabozantinib capsule compn. and its prodn. method. The cabozantinib capsule composition is composed of cabozantinib 10-60wt%, carrier 15-70 wt%, organic solvent 10-30wt%, surfactant 0.5-3.0wt%, micronized silica gel 1.0-3.0wt% and starch 5.0-20wt%. The carrier comprises one or more of glycerol monostearate, polyethylene glycol 6000, cetyl alc. and octyl alc. The organic solvent comprises one or more of ethanol, methanol and acetone. The surfactant comprises one or more of sodium dodecyl sulfate, Tween 80 and lecithin. The production method includes adding carrier into organic solvent, heating to 60℃, adding cabozantinib and surfactant, vacuum drying at 40℃, comminution by gas stream to obtain powder with grain size of 1-8 μm, adding micronized silica gel and starch, mixing, and packaging in. The produced cabozantinib capsule preparation has good oral absorption, high dissoln. rate, high bioavailability, and can remarkably inhibit the growth of tumor volume The invention has simple preparation process, low cost, and applicability for com. process.

IT 849217-68-1, Cabozantinib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for producing cabozantinib capsule composition)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-

quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

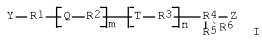


L4 ANSWER 24 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:873778 CAPLUS Full-text
DOCUMENT NUMBER: 161:77594
TITLE: Hydrophilic linkers and their uses for conjugation of drugs to cell binding molecules
INVENTOR(S): Zhao, R. Yongxin
PATENT ASSIGNEE(S): Hangzhou Dac Biotech Co., Ltd., Peop. Rep. China
SOURCE: PCT Int. Appl., 102pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

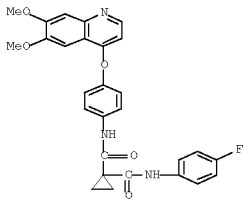
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2014080251 | A1 | 20140530 | WO 2012-IB56700 | 20121124 |

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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: WO 2012-IB56700 20121124
GI



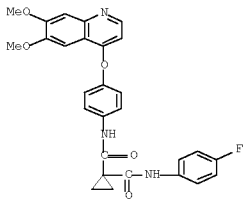
AB Prepn. of cell binding agent-drug conjugates comprising hydrophilic linker of formula (I), wherein:Y represents a functional group that enables reaction with a cell-binding agent; Q and T are either -P(=O)(OM)-, or -S(O)-;m and n are integer from 0 to 5, but not 0 at the same time; In addition, when m = I, n = 0, Q is not -P(=O)(OM)-; or when n = I, m = 0, T is not -P(=O)(OM)-;Z represents a functional group that enables linkage of a cytotoxic drug via a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, amine (secondary, tertiary, or quartary), imine, cycloheteroalkyane, heteroarom., alkoxime or amide bond; R1, R2, R3, R4, R5 and R6, are the same or different and are H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or 1-6 carbon atoms of esters, ether, amide, or polyethyleneoxy unit of formula (OCH2CH2)p, wherein p is an integer from 0 to about 1000, or combination thereof and methods of using such linkers and conjugates in pharmaceutical dosage forms for combination therapy of cancer, autoimmune and infectious diseases are provided.
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(hydrophilic linkers and their uses in preparation of cell binding agent-drug conjugates useful in combination therapy of cancer, autoimmune and infectious diseases)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 25 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:814874 CAPLUS Full-text

TITLE: Aerodigestive Fistula Formation as a Rare Side Effect of Antiangiogenic Tyrosine Kinase Inhibitor Therapy for Thyroid Cancer
AUTHOR(S): Blevins, Dean P.; Dadu, Ramona; Hu, Mimi; Baik, Christina; Balachandran, Diwakar; Ross, William; Gunn, Brandon; Cabanillas, Maria E.
CORPORATE SOURCE: Department of Internal Medicine, University of Texas Health Science Center at Houston, Houston, TX, USA
SOURCE: Thyroid (2014), 24(5), 918-922
CODEN: THYRER; ISSN: 1050-7256
DIGITAL OBJECT ID: 10.1089/thy.2012.0598
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Background: In the past decade, targeted therapy with antiangiogenic drugs has become standard of care for most types of metastatic, progressive thyroid cancer. While these drugs were thought initially to be less toxic than traditional chemotherapy, they can have rare but serious and fatal toxicities. Once such toxicity that has been reported in other tumor types is upper airway fistula formation, which can be life-threatening. Summary: Here, we describe three patients treated with antiangiogenic tyrosine kinase inhibitors at two academic institutions who developed aerodigestive fistula. All three patients had risk factors for fistula formation, which included external beam radiation and/or large tumor with invasion of the tracheal wall. Conclusions: Fistula formation is a known but rare side effect of antiangiogenic tyrosine kinase inhibitors. Knowledge of the risk factors that may predispose thyroid cancer patients to this serious adverse event is vital prior to prescribing antiangiogenics. Particular caution should be observed when using these drugs in patients undergoing radiation therapy or surgery, or in patients whose tumor is invading vital structures of the neck, as they may be at higher risk of developing this rare complication. In these patients, antiangiogenic tyrosine kinase inhibitors should be used cautiously, patients should be aware of the risk, and physicians should monitor patients for symptoms of fistula.
IT 849217-68-1, Cabozantinib
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aerodigestive fistula formation as a rare side effect of antiangiogenic tyrosine kinase inhibitor therapy for thyroid cancer)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



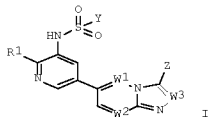
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 26 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:794981 CAPLUS Full-text
DOCUMENT NUMBER: 160:740120
TITLE: Preparation of heteroaromatic compounds as protein kinase modulators for treatment of hyperproliferative disorders
INVENTOR(S): Xi, Ning
PATENT ASSIGNEE(S): Sunshine Lake Pharma Co., Ltd., Peop. Rep. China; Calitor Sciences, LLC
SOURCE: U.S. Pat. Appl. Publ., 57pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

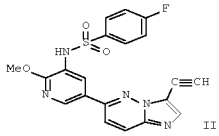
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 20140134133 | A1 | 20140515 | US 2013-14076256 | 20131110 |
| WO 2014078211 | A1 | 20140522 | WO 2013-US69366 | 20131110 |

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2012-61726139 P 20121114
OTHER SOURCE(S): MARPAT 160:740120
GI



I



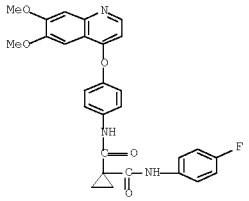
II

AB The invention provides heteroarom. derivs. and pharmaceutically acceptable salts and formulations thereof useful in modulating the protein kinase activity, especially phosphatidylinositol 3-kinases (PI3K) and mTOR kinase, and in modulating inter- and/or intra-cellular signaling activities such as proliferation, differentiation, apoptosis, migration and invasion. The invention also provides pharmaceutically acceptable compns. comprising such compds. and methods of using the compns. in the treatment of hyperproliferative disorders in mammals, especially humans. Compds. of formula I [wherein W1, W2, and W3 are independently N or CRc; Z is D CN, N3, etc.; Y is C1-C6 alkyl, C3-C6 cycloalkyl, C3-C6 heterocyclyl, etc.; R1 is H, Cl, C3-C6 cycloalkyl, etc.; each Rc is independently H, D, F, etc.] or stereoisomers, geometric isomers, tautomers, N-oxides, solvates, metabolites, prodrugs, or pharmaceutically acceptable salts thereof are claimed and exemplified. For example, II was prepared in five steps (procedure given). Candidate compds. of I were assayed for their stability in liver microsomes, their oral and i.v. bioavailability, and inhibitory activity against PI3K and mTOR kinase (data given).

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(codrug; preparation of heteroarom. compds. as protein kinase modulators for
treatment of hyperproliferative disorders)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L4 ANSWER 27 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2014:718961 CAPLUS Full-text
DOCUMENT NUMBER: 160:630742
TITLE: Replication-competent retroviral vectors for gene therapy using mini-promoters
INVENTOR(S): Gruber, Harry E.; Jolly, Douglas J.; Lin, Amy H.; Logg, Christopher R.; Kasahara, Noriyuki
PATENT ASSIGNEE(S): Tocagen Inc., USA
SOURCE: PCT Int. Appl., 89pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2014066700 | A1 | 20140501 | WO 2013-US66709 | 20131024 |

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2012-61718610 P 20121025

AB Compact replicating retroviral vectors using a minimal promoter to express a therapeutic gene with a size of 0.9-1.9 kb are described. An internal ribosome entry sequence may be used for polycistronic expression cassettes. The vectors do not use the prior art SCP1, Ad, or CMV core promoters. Development and optimization of vectors is described.

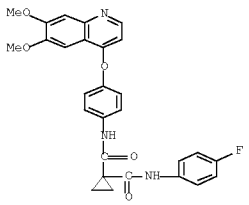
IT 1140909-48-3, XL-184
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in cancer therapy with retroviral gene therapy vectors; retroviral vectors for gene therapy using mini-promoters)

RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

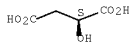
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 28 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2014:711027 CAPLUS Full-text
DOCUMENT NUMBER: 160:643049
TITLE: Cabozantinib dispersible tablet and preparation method thereof
INVENTOR(S): Peng, Zongyu; Li, Ran; Zheng, Feibo
PATENT ASSIGNEE(S): Qingdao Cancer Hospital, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 11pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| CN 103751140 | A | 20140430 | CN 2014-10017920 | 20140115 |

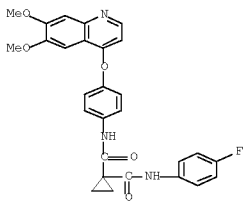
PRIORITY APPLN. INFO.: CN 2014-10017920 20140115

AB The invention discloses Cabozantinib dispersible tablet and prepn. method and application thereof. The inventive Cabozantinib dispersible tablet consists of the following component according to weight percentage: Cabozantinib 10-60%, filler 10-40%, disintegrant 10-50%, acidulant 10-50%, binder 0.1-10%, and lubricant and glidant 0.1-20%. Compared with the common tablet, the inventive dispersible tablet contains no surfactant, its solubility, dispersivity, and disintegrability are good, and it can be completely disintegrated within 1 min. The prepared Cabozantinib dispersible tablet has high dissoln. rate, high bioavailability, rapid distribution in vivo, stable quality, and good taste. The preparation method is simple, and suitable for industrial production

IT 849217-68-1, Cabozantinib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cabozantinib dispersible tablet)

RN 849217-68-1 CAPLUS

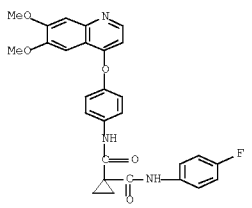
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



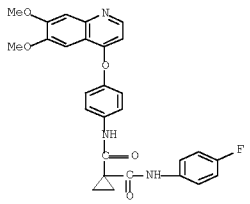
L4 ANSWER 29 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2014:679549 CAPLUS Full-text
DOCUMENT NUMBER: 161:30896
TITLE: Cabozantinib: a new molecular targeted antitumor drug
AUTHOR(S): Zhang, Xiu-ying; Liu, Yao; Bai, Qiu-jiang; Wang, Nan
CORPORATE SOURCE: Department of Pharmacy, Kailuan General Hospital, Tangshan, Hebei Province, 063000, Peop. Rep. China
SOURCE: Yiyao Daobao (2013), 32(11), 1468-1470
CODEN: YDIAAL; ISSN: 1004-0781
DIGITAL OBJECT ID: 10.3870/yydb.2013.11.021
PUBLISHER: Yiyao Daobao Zazhishe
DOCUMENT TYPE: Journal; General Review

LANGUAGE: Chinese
AB A review. Cabozantinib, a new mol. targeted antitumor drug, was introduced with several subsections as follow: action mechanisms, pharmacokinetics, adverse reactions, drug interactions, clin. trials, and conclusions.
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cabozantinib: a new mol. targeted antitumor drug)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L4 ANSWER 30 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:653844 CAPLUS Full-text
DOCUMENT NUMBER: 161:257408
TITLE: Preclinical Evaluation of Imaging Biomarkers for Prostate Cancer Bone Metastasis and Response to Cabozantinib
AUTHOR(S): Graham, Timothy J.; Box, Gary; Tunariu, Nina; Crespo, Mateus; Spinks, Terry J.; Miranda, Susana; Attard, Gerhardt; de Bono, Johann; Eccles, Suzanne A.; Davies, Faith E.; Robinson, Simon P.
CORPORATE SOURCE: Division of Radiotherapy and Imaging, Institute of Cancer Research and Royal Marsden NHS Trust, Surrey, SM2 5NG, UK
SOURCE: Journal of the National Cancer Institute (2014), 106(4), ???
CODEN: JNCIEQ; ISSN: 0027-8874
DIGITAL OBJECT ID: 10.1093/jnci/dju033
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Background Prostate cancer is incurable once it has metastasized to the bone. Appropriate preclin. models are lacking. The therapeutic efficacy of the multikinase inhibitor cabozantinib was assessed in an orthotopic xenograft model of castration-resistant prostate cancer (CRPC) bone metastasis using noninvasive, multimodality functional imaging. Methods NOD/SCID mice were injected intratibially with luciferase-expressing ERG (v-ets avian erythroblastosis virus E26 oncogene homolog) rearranged VCaP human prostate carcinoma cells. The response of VCaP xenografts (n = 7 per group) to cabozantinib was investigated using bioluminescence imaging and anatomical and diffusion weighted magnetic resonance imaging. This enabled quantitation of tumor volume and apparent diffusion coefficient (ADC). Bone uptake of technetium-methylene diphosphonate (99mTc-MDP) was assessed by single-photon emission computed tomog. Ex vivo micro computed tomog. was used to quantify bone volume and correlated with appropriate histopathol. Statistical significance was determined using the two-sided Mann-Whitney test or Wilcoxon signed rank test. Results VCaP xenografts were predominantly osteosclerotic with some osteolytic activity. Fluorescent in situ hybridization anal. confirmed retention of ERG oncogene rearrangements. Cabozantinib induced a statistically significant 52% reduction in tumor luminance (P = .02) and stasis in tumor volume after 15 days of treatment. Tumor ADC statistically significantly increased with cabozantinib and was associated with extensive necrosis (after 10 days, mean tumor ADC ± SD = 556±43×10-6 mm2/s vs pretreatment ADC = 485±43×10-6 mm2/s; P = .02 ). Tumor-associated uptake of 99mTc-MDP was statistically significantly reduced after 3 days of treatment (P = .02), sustained over 15 days treatment, and associated with a statistically significant (P = .048) reduction in bone growth on the tibial cortex, yet a highly statistically significant (P = .001) increase in trabecular bone volume Conclusions The intratibial VCaP model faithfully emulates clin. disease. Cabozantinib exerts potent effects on both tumor and tumor-induced bone matrix remodeling, and quantitation of ADC provides a clin. translatable imaging biomarker for early, sensitive assessment of treatment response in CRPC bone metastasis.
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(noninvasive, multimodality functional imaging was effective in imaging biomarkers in response to cabozantinib in xenografted mouse model of human bone metastatic castration-resistant prostate cancer)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

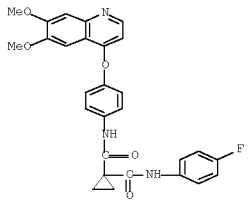


OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L4 ANSWER 31 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:628215 CAPLUS Full-text
DOCUMENT NUMBER: 160:542029
TITLE: Method for the diagnosis, prognosis and treatment of prostate cancer metastasis
INVENTOR(S): Gomis, Roger; Jean-Mairet, Joel
PATENT ASSIGNEE(S): Inbiomotion S.L., Spain
SOURCE: PCT Int. Appl., 140pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2014057357 | A2 | 20140417 | WO 2013-IB2866 | 20131009 |
| WO 2014057357 | A3 | 20140530 | | |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM | | | | |
| US 20140105918 | A1 | 20140417 | US 2013-14050262 | 20131009 |

PRIORITY APPLN. INFO.: US 2012-61713318 P 20121012
AB The present invention relates to a method for the diagnosis or the prognosis of metastasis in prostate cancer which comprises determining if the c-MAF gene is amplified in a primary tumor sample. Likewise, the invention also relates to a method for the diagnosis or the prognosis of metastasis in prostate cancer, as well as to a method for determining the tendency to develop bone metastasis with respect to metastasis in other organs, which, comprise determining the c-MAF expression level. Finally, the invention relates to the use of a c-MAF inhibitor as therapeutic target for treating the prostate cancer.
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(c-MAF gene for diagnosis, prognosis and treatment of prostate cancer metastasis)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L4 ANSWER 32 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:581585 CAPLUS Full-text
DOCUMENT NUMBER: 160:555604
TITLE: Phage display derived peptides highly specific against Mdm2/Mdm4 and methods for treating cancer
INVENTOR(S): Joseph, Thomas Leonard; Verma, Chandra Shekhar; Lane, David Phillip; Brown, Christopher John
PATENT ASSIGNEE(S): Agency for Science, Technology and Research, Singapore
SOURCE: PCT Int. Appl., 61pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2014055039 | A1 | 20140410 | WO 2013-SG428 | 20131001 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM | | | | |

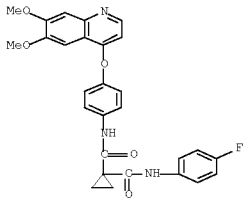
PRIORITY APPLN. INFO.: SG 2012-7302 A 20121001
OTHER SOURCE(S): MARPAT 160:555604
AB By using a phage display derived peptide as an initial template, compds. have been developed that are highly specific against Mdm2/Mdm4. These compds. exhibit greater potency in p53 activation and protein-protein interaction assays than a compound derived from the p53 wild-type sequence. Unlike nutlin, a small mol. inhibitor of Mdm2/Mdm4, the phage derived compds. can arrest cells resistant to p53 induced apoptosis over a wide concentration

range without cellular toxicity, suggesting they are highly suitable for cyclo-therapy. In one embodiment, there is disclosed the peptide comprising or consisting o f the amino acid sequence of SEQ ID NO 1 (TSFXaaiEYWXaa3LLXaai), wherein Xaa3 can be N or A and wherein in case Xaa3 is N, Xaai is not A and/or Xaa2 is not S. In one embodiment, Xaa3 can be any type of amino acid other than A and wherein in case Xaa3 is N, Xaaj is not A and/or Xaa2 is not S. Those peptides have been shown to inhibit the p53:Mdm2 interactions with a nanomolar affinity.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(XL184; phage display derived peptides highly specific against Mdm2/Mdm4 and methods for treating cancer)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 33 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2014:565947 CAPLUS Full-text

DOCUMENT NUMBER: 161:208503

TITLE: First-, second-, third-line therapy for mRCC: benchmarks for trial design from the IMDC

AUTHOR(S): Ko, J. J.; Choueiri, T. K.; Rini, B. I.; Lee, J.-L.; Kroeger, N.; Srinivas, S.; Harshman, L. C.; Knox, J. J.; Bjarnason, G. A.; MacKenzie, M. J.; Wood, L.; Vaishampayan, U. N.; Agarwal, N.; Pal, S. K.; Tan, M.-H.; Rha, S. Y.; Yuasa, T.; Donskov, F.; Bamias, A.; Heng, D. Y. C.

CORPORATE SOURCE: Tom Baker Cancer Center, University of Calgary, Calgary, AB, Can.

SOURCE: British Journal of Cancer (2014), 110(8), 1917-1922
CODEN: BJCAAI; ISSN: 0007-0920

DIGITAL OBJECT ID: 10.1038/bjc.2014.25

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal; (online computer file)

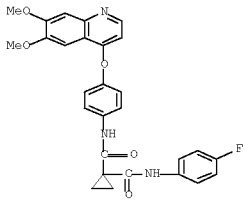
LANGUAGE: English

AB Background: Limited data exist on outcomes for metastatic renal cell carcinoma (mRCC) patients treated with multiple lines of therapy. Benchmarks for survival are required for patient counselling and clin. trial design. Methods: Outcomes of mRCC patients from the International mRCC Database Consortium database treated with 1, 2, or 3+ lines of targeted therapy (TT) were compared by proportional hazards regression. Overall survival (OS) and progression-free survival (PFS) were calculated using different population inclusion criteria. Results: In total, 2705 patients were treated with TT of which 57% received only first-line TT, 27% received two lines of TT, and 16% received 3+ lines of TT. Overall survival of patients who received 1, 2, or 3+ lines of TT were 14.9, 21.0, and 39.2 mo, resp., from first-line TT (P<0.0001). On multivariable anal., 2 lines and 3+ lines of therapy were each associated with better OS (HR=0.738 and 0.626, P<0.0001). Survival outcomes for the subgroups were as follows: for all patients, OS 20.9 mo and PFS 7.2 mo; for those similar to eligible patients in the first-line ADAPT trial, OS 14.7 mo and PFS 5.6 mo; for those similar to patients in first-line TIVO-1 trial, OS 24.8 mo and PFS 8.2 mo; for those similar to patients in second-line INTORSECT trial, OS 13.0 mo and PFS 3.9 mo; and for those similar to patients in the third-line GOLD trial, OS 18.0 mo and PFS 4.4 mo. Conclusions: Patients who are able to receive more lines of TT live longer. Survival benchmarks provide context and perspective when interpreting and designing clin. trials.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(first-, second-, third-line therapy for metastatic renal cell carcinoma)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 34 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2014:542996 CAPLUS Full-text

DOCUMENT NUMBER: 161:267984

TITLE: Bone-targeted therapies in metastatic castration-resistant prostate cancer: evolving paradigms

AUTHOR(S): El-Amm, Joelle; Freeman, Ashley; Patel, Nihar; Aragon-Ching, Jeanny B.

CORPORATE SOURCE: Division of Hematology/Oncology, Department of Medicine, George Washington University Medical Center, Washington, DC, 20037, USA

SOURCE: Prostate Cancer (2013) 210686/1-210686/11, 11 pp.
CODEN: PCRACU; ISSN: 2090-312X

DIGITAL OBJECT ID: 10.1155/2013/210686

PUBLISHER: Hindawi Publishing Corp.

DOCUMENT TYPE: Journal; General Review; (online computer file)

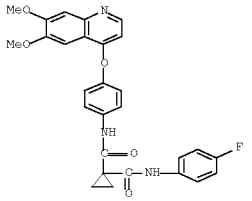
LANGUAGE: English

AB A review. Majority of patients with metastatic castrate resistant prostate cancer (mCRPC) develop bone metastases which results in significant morbidity and mortality as a result of skeletal-related events (SREs). Several bone-targeted agents are either in clin. use or in development for prevention of SREs. Bisphosphonates were the first class of drugs investigated for prevention of SREs and zoledronic acid is the only bisphosphonate that is FDA-approved for this indication. Another bone-targeted agent is denosumab which is a fully humanized monoclonal antibody that binds to the RANK-L thereby inhibiting RANK-L mediated bone resorption.While several radiopharmaceuticals were a approved for pain palliation in mCRPC including strontium and samarium, alpharadin is the first radiopharmaceutical to show significant overall survival benefit. Contemporary therapeutic options including enzalutamide and abiraterone have effects on pain palliation and SREs as well. Other novel bone-targeted agents are currently in development, including the receptor tyrosine kinase inhibitors cabozantinib and dasatinib. Emerging therapeutics in mCRPC has resulted in great strides in preventing one of the most significant sources of complications of bone metastases.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evolving paradigms of bone-targeted therapies in metastatic castration-resistant prostate cancer)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 35 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2014:479457 CAPLUS Full-text

DOCUMENT NUMBER: 160:515456

TITLE: Synthesis method of antitumor therapeutic drug of cabozantinib

INVENTOR(S): Cai, Jianping; Chen, Zengfei; Zhang, Lifeng; Fang, Ying

PATENT ASSIGNEE(S): Suzhou Moer Pharmaceutical Co., Ltd., Peop. Rep. China

SOURCE: Faming Zhuanli Shenqing, 9pp.
CODEN: CNXXEV

DOCUMENT TYPE: Patent

LANGUAGE: Chinese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| CN 103664778 | A | 20140326 | CN 2013-10631287 | 20131127 |

PRIORITY APPLN. INFO.: CN 2013-10631287 20131127

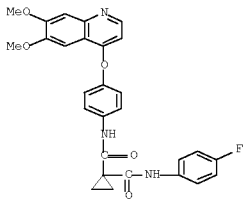
OTHER SOURCE(S): MARPAT 160:515456

AB The invention discloses a synthesis method of antitumor therapeutic drug of cabozantinib., comprising: using 4-(6, 7- dimethoxy quinoline -4- oxy)-phenylamine to react with 1-((4- fluorophenyl) carbamoyl) cyclopropyl acyl halide, an acid-binding agent in organic solvent at -5~20 ℃ for 0.5~2h to obtain cabozantinib; the inventive method uses cheap raw materials, has mild conditions, simple and convenient operation, stable process, good repeatability, high molar yield, low cost, so invention is an applicable method for com. production of cabozantinib. Cabozantinib was prepared via chlorination of 6,7-dimethoxyquinolin-4-ol; the resulting 4-chloro-6,7-dimethoxyquinoline underwent condensation with 4-aminophenol or 4-nitrophenol to give the corresponding ethers, which underwent redn and/or acylation with 1-[(4-fluorophenyl)carbamoyl]cyclopropylcarbonyl halides to give cabozantinib. The said 1-[(4-fluorophenyl)carbamoyl]cyclopropylcarbonyl halides were prepared via condensation of 1,1-cyclopropanedicarboxylic acid with p-fluoroaniline followed by halogenation. The inventive method uses cheap raw materials, has mild conditions, simple and convenient operation, stable process, good repeatability, high molar yield, low cost, so invention is an applicable method for com. production of cabozantinib.

IT 849217-68-1P, Cabozantinib
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of antitumor drug cabozantinib starting from (dimethoxy)quinolinol and cyclopropanedicarboxylic acid by using etherification and amidation as the key steps)

RN 849217-68-1 CAPLUS

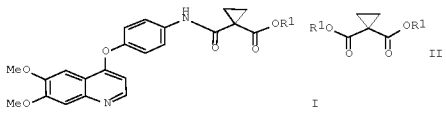
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L4 ANSWER 36 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:478399 CAPLUS Full-text
DOCUMENT NUMBER: 160:501685
TITLE: Process for the preparation of cabozantinib and its intermediate
INVENTOR(S): Shi, Xiangfei; Zhao, Rui; Meng, Qingyi; Zhang, Xiquan
PATENT ASSIGNEE(S): Chia Tai Tianqing Pharmaceutical Group Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 18pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| CN 103664776 | A | 20140326 | CN 2012-10374723 | 20120926 |
| PRIORITY APPLN. INFO.: | | | CN 2012-10374723 | 20120926 |

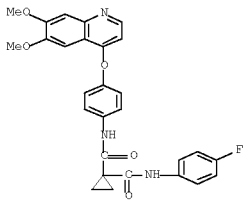
OTHER SOURCE(S): MARPAT 160:501685
GI



I II

AB The invention relates to process for the prepn. of cabozantinib and its intermediate of formula I from 1,1-cyclopropane dicarboxylic acid diester of formula II [R1 = C1-10 alkyl]. For example, cabozantinib was prepared by hydrolysis of compound II [R1 = Et] to afford 1-(ethoxycarbonyl)cyclopropanecarboxylic acid, which underwent amidation reaction with 4-aminophenol followed by arylation with 4-chloro-6,7-dimethoxyquinoline to afford compound I [R1 = Et], which underwent hydrolysis followed by amidation with 4-fluoroaniline to afford cabozantinib.

IT 849217-68-1, Cabozantinib
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for the preparation of cabozantinib and its intermediate)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

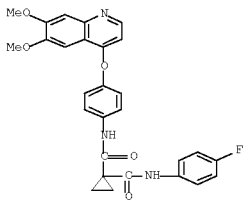


L4 ANSWER 37 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:448281 CAPLUS Full-text
DOCUMENT NUMBER: 160:480988
TITLE: Inhibition of viral infection-triggered asthma with c-kit inhibitor
INVENTOR(S): Umetsu, Dale T.; Chang, Ya-Jen; De Kruyff, Rosemarie Helena; Baumgarth, Nicole
PATENT ASSIGNEE(S): Children's Medical Center Corporation, USA
SOURCE: PCT Int. Appl., 128pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2014043442 | A1 | 20140320 | WO 2013-US59609 | 20130913 |
| W: | AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | |
| RW: | AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM | | | |
| PRIORITY APPLN. INFO.: | | | US 2012-61701296 P | 20120914 |

AB The invention provides methods, compns., and kits featuring a c-Kit kinase inhibitor for use in preventing or treating virus-induced respiratory pathol.

IT 849217-68-1, Cabozantinib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(c-kit inhibitors for treatment of viral infection-triggered asthma)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 38 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:443739 CAPLUS Full-text
DOCUMENT NUMBER: 160:485576
TITLE: Combination therapy for prevention or treatment of c-met or angiogenesis factor induced diseases
INVENTOR(S): Jeong, Yun Ju; Kim, Kyung Ah; Song, Yun Jeong; Lee, Ji Min; Lee, Hyo Seon; Choi, Jae Hyun; Lee, Saet Byoul
PATENT ASSIGNEE(S): Samsung Electronics Co., Ltd., S. Korea
SOURCE: Eur. Pat. Appl., 168pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 2708556 | A1 | 20140319 | EP 2013-184072 | 20130912 |
| R: | AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME | | | |
| KR 2014035266 | A | 20140321 | KR 2013-108913 | 20130911 |
| US 20140086926 | A1 | 20140327 | US 2013-14025403 | 20130912 |
| PRIORITY APPLN. INFO.: | | | KR 2012-101177 A | 20120912 |
| | | | KR 2013-108913 A | 20130911 |

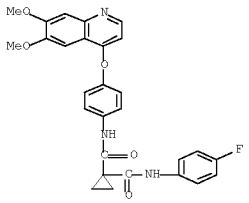
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The authors disclose combination therapy for prevention or treatment of c-Met-induced or angiogenesis factor-induced diseases. The therapy comprises the co-administration of an angiogenesis inhibitor and an anti-c-Met antibody. In one example, the metastatic potential (migration) of HUVEC cells is shown to be inhibited by the combined effects of an anti-c-Met antibody and an anti-VEGF antibody.

IT 1140909-48-3, XL 184
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in combination therapy with anti-MET receptor antibodies)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

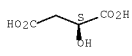
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

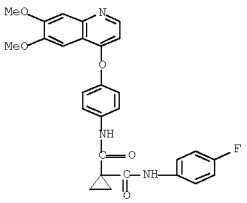


REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 39 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:410366 CAPLUS full-text
DOCUMENT NUMBER: 160:451706
TITLE: Inhibitors of Met, VEGFR and Ret for use in the treatment of lung adenocarcinoma
INVENTOR(S): Aftab, Dana T.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 80pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2014039971 | A1 | 20140313 | WO 2013-US58768 | 20130909 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM | | | | |
| US 20140121239 | A1 | 20140501 | US 2013-14021614 | 20130909 |

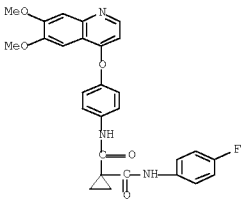
PRIORITY APPLN. INFO.: US 2012-61698143 P 20120907
OTHER SOURCE(S): CASREACT 160:451706; MARPAT 160:451706
AB This invention is directed to the treatment of cancer in a patient, particularly a patient with lung adenocarcinoma, and more particularly a patient with KIF5B-RET fusion-pos. non-small cell lung cancer, with an inhibitor of MET, VEGF, and RET.
IT 849217-68-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(inhibitors of Met, VEGFR and Ret for use in treatment of lung adenocarcinoma)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



IT 1140909-48-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(inhibitors of Met, VEGFR and Ret for use in treatment of lung adenocarcinoma)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

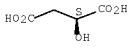
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

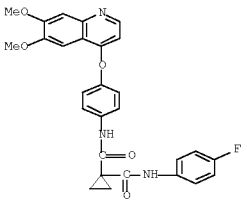
Absolute stereochemistry. Rotation (-).



IT 1365530-43-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors of Met, VEGFR and Ret for use in treatment of lung adenocarcinoma)
RN 1365530-43-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

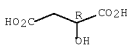
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 636-61-3
CMF C4 H6 O5

Absolute stereochemistry. Rotation (+).

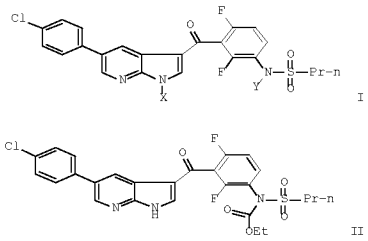


REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 40 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:327215 CAPLUS full-text
DOCUMENT NUMBER: 160:370140
TITLE: Preparation of substituted azaindole prodrugs, salts, pharmaceutical compositions thereof and methods of use in treating cancer and other proliferative disorders
INVENTOR(S): Xi, Ning; Wang, Tingjin; Tang, Yin; Sun, Mingming; Wang, Qian
PATENT ASSIGNEE(S): Sunshine Lake Pharma Co., Ltd., Peop. Rep. China; Calitor Sciences, LLC
SOURCE: U.S. Pat. Appl. Publ., 53pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 20140056849 | A1 | 20140227 | US 2013-13975371 | 20130826 |
| WO 2014035846 | A2 | 20140306 | WO 2013-US56548 | 20130826 |
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| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM | | | | |

PRIORITY APPLN. INFO.: US 2012-61693335 P 20120827
OTHER SOURCE(S): MARPAT 160:370140
GI



I



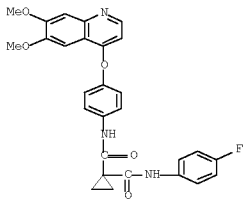
II

AB The present invention provides substituted azaindole prodrugs of vemurafenib, methods of making said prodrugs, pharmaceutical compns. of said prodrugs and methods of using said prodrugs and pharmaceutical compns. thereof to treat or prevent diseases or disorders such as cancer. The prodrugs have general formula I, wherein each of X and Y is independently H, -C(:O)R3, -C(:O)OR4, -C(R1R2)OC(:O)R3, -C(R1R2)OC(:O)OR4 or -C(R1R2)OP(:O)(OR4)(OR4a), with the proviso that when Y is H, X is not -C(:O)CH3 or H; each R1 and R2 is independently H, D, C1-6alkyl, etc.; each R3 is independently H, D, C1-10alkyl, etc.; and each R4 and R4a is independently H, C1-10alkyl, C3-8cycloalkyl, etc. Example compound II was prepared by reacting vemurafenib with Et chloroformate. Various prodrugs of the invention were studied for their stability in liver microsomes, their oral and i.v. bioavailability, and their antitumor properties.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(codrug; preparation of substituted azaindole prodrugs., salts, pharmaceutical compns. thereof and methods of use in treating cancer and other proliferative disorders)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L4 ANSWER 41 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2014:211024 CAPLUS Full-text

DOCUMENT NUMBER: 161:316285

TITLE: Cabozantinib Inhibits Prostate Cancer Growth and Prevents Tumor-Induced Bone Lesions

AUTHOR(S): Dai, Jinlu; Zhang, Honglai; Karatsinides, Andreas; Keller, Jill M.; Kozloff, Kenneth M.; Aftab, Dana T.; Schimmoller, Frauke; Keller, Evan T.

CORPORATE SOURCE: Departments of Urology and Orthopaedic Surgery, University of Michigan, Ann Arbor, MI, USA

SOURCE: Clinical Cancer Research (2014), 20(3), 617-630
CODEN: CCREF4; ISSN: 1078-0432

DIGITAL OBJECT ID: 10.1158/1078-0432.CCR-13-0839

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

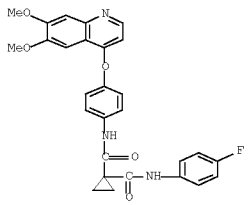
LANGUAGE: English

AB Purpose: Cabozantinib, an orally available multityrosine kinase inhibitor with activity against mesenchymal epithelial transition factor (MET) and VEGF receptor 2 (VEGFR2), induces resolution of bone scan lesions in men with castration-resistant prostate cancer bone metastases. The purpose of this study was to determine whether cabozantinib elicited a direct antitumor effect, an indirect effect through modulating bone, or both. Exptl. Design: Using human prostate cancer xenograft studies in mice, we determined the impact of cabozantinib on tumor growth in soft tissue and bone. In vitro studies with cabozantinib were performed using (i) prostate cancer cell lines to evaluate its impact on cell growth, invasive ability, and MET and (ii) osteoblast cell lines to evaluate its impact on viability and differentiation and VEGFR2. Results: Cabozantinib inhibited progression of multiple prostate cancer cell lines (Ace-1, C4-2B, and LuCaP 35) in bone metastatic and soft tissue murine models of prostate cancer, except for PC-3 prostate cancer cells in which it inhibited only s.c. growth. Cabozantinib directly inhibited prostate cancer cell viability and induced apoptosis in vitro and in vivo and inhibited cell invasion in vitro. Cabozantinib had a dose-dependent biphasic effect on osteoblast activity and inhibitory effect on osteoclast production in vitro that was reflected in vivo. It blocked MET and VEGFR2 phosphorylation in prostate cancer cells and osteoblast-like cells, resp. Conclusion: These data indicate that cabozantinib has direct antitumor activity, and that its ability to modulate osteoblast activity may contribute to its antitumor efficacy. Clin Cancer Res; 20(3); 617-30. ©2013 AACR.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cabozantinib inhibits prostate cancer growth and prevents tumor-induced bone lesions)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 42 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2014:211001 CAPLUS Full-text

DOCUMENT NUMBER: 161:316087

TITLE: Cabozantinib and Prostate Cancer: Inhibiting Seed and Disrupting Soil?

AUTHOR(S): Lee, Richard J.; Smith, Matthew R.

CORPORATE SOURCE: Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA

SOURCE: Clinical Cancer Research (2014), 20(3), 525-527
CODEN: CCREF4; ISSN: 1078-0432

DIGITAL OBJECT ID: 10.1158/1078-0432.CCR-13-2636

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal; General Review

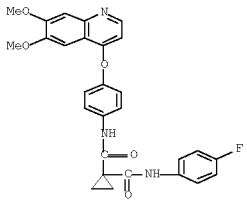
LANGUAGE: English

AB A review. Treatment with cabozantinib, an inhibitor of MET and VEGFR2 signaling, has demonstrated clin. benefit in early trials in men with metastatic prostate cancer. Preclin. evidence suggests that cabozantinib can kill cancer cell seeds while disrupting angiogenesis and stromal cells in the metastatic soil.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of cabozantinib in treatment of prostate cancer)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 43 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2014:175942 CAPLUS Full-text

DOCUMENT NUMBER: 160:310859

TITLE: Preparation of substituted pyrazolone compounds as protein tyrosine kinase modulators useful in treatment of proliferative diseases

INVENTOR(S): Xi, Ning; Wu, Yanjun; Liao, Min; Feng, Yanming

PATENT ASSIGNEE(S): Calitor Sciences, LLC, USA; Sunshine Lake Pharma Co., Ltd.

SOURCE: PCT Int. Appl., 106pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

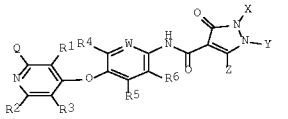
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

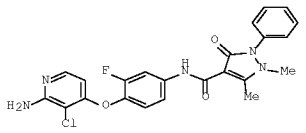
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2014022117 | A1 | 20140206 | WO 2013-US51175 | 20130719 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM | | | | |

PRIORITY APPLN. INFO.: US 2012-61676944 P 20120728
US 2012-61679416 P 20120803
OTHER SOURCE(S): CASREACT 160:310859; MARPAT 160:310859
GI



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II

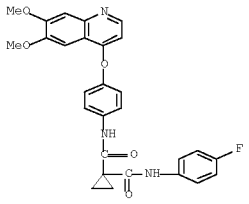
AB The invention provides substituted pyrazolone compds.of formula I, stereoisomers, geometric isomers, tautomers, oxynitrides, hydrates, solvates, metabolites, pharmaceutically acceptable salts or prodrugs thereof, and pharmaceutical preparation for regulating the activity of protein kinases and adjusting the signal response in the cell or between cells. The invention also relates to pharmaceutical compns. comprising the compds. and a method for treating hyperproliferative disorder of mammal, particularly human using the compns. Compds. of formula I [wherein Q is H, NH2 and derivative, OH and derivs., -NHCOR, etc.; W is (un)substituted CH or N; X, Y, and Z are independently H, D, C1-6 alkyl, C3-8 cycloalkyl-C1-4 alkylene, etc.; R1-R6 are independently H, D, F, Cl, Br, CN, etc.; R is H, C1-6 alkyl, C3-8 cycloalkyl-C1-4 alkylene, C3-7 heterocycloalkyl, etc.] and their stereoisomers, geometric isomers, tautomers, oxynitrides, hydrates, solvates, metabolites, pharmaceutically acceptable salts or prodrugs thereof, are claimed and exemplified. For example, II was prepared in a multistep process (procedure given). I were evaluated for stability in liver microsomes and pharmacokinetic properties in mice, rats, dogs, and monkeys (data given). Binding of I to receptor tyrosine kinases was determined using KINOMEscan where II exhibited binding constant (Kd) values of 23 nM for KDR tyrosine kinase and 4.4 nM for c-Met tyrosine kinase.

IT 849217-68-1

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(codrug; preparation of substituted pyrazolone compds. useful as protein tyrosine kinase modulators for treatment of proliferative disorders)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

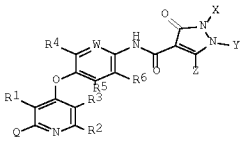


L4 ANSWER 44 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:175941 CAPLUS Full-text
DOCUMENT NUMBER: 160:310858
TITLE: Preparation of substituted pyrazolone compounds as protein tyrosine kinase modulators for treatment of proliferative disease
INVENTOR(S): Xi, Ning; Wu, Yanjun; Liao, Min; Feng, Yanming
PATENT ASSIGNEE(S): Calitor Sciences, LLC, USA; Sunshine Lake Pharma Co., Ltd.
SOURCE: PCT Int. Appl., 110pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

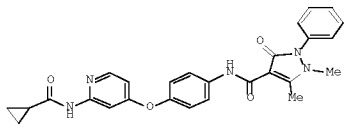
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 2014022116 | A2 | 20140206 | WO 2013-US51174 | 20130719 |
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| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM | | | | |

PRIORITY APPLN. INFO.: US 2012-61676944 P 20120728
US 2012-61679416 P 20120803
OTHER SOURCE(S): MARPAT 160:310858

GI



I



II

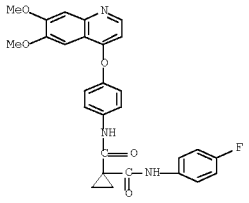
AB The invention provides substituted pyrazolone compds.of formula I, stereoisomers, geometric isomers, tautomers, oxynitrides, hydrates, solvates, metabolites, pharmaceutically acceptable salts or prodrugs thereof, and pharmaceutical preparation for regulating the activity of protein kinases and adjusting the signal response in the cell or between cells. The invention also relates to pharmaceutical compns. comprising the compds. and a method for treating hyperproliferative disorder of mammal, particularly human using the compns. Compds. of formula I [wherein Q is D, NH2 and derivs., -NHCOR, etc.; W is (un)substituted CH or N; each X, Y, and Z is independently H, D, C1-6 alkyl, C3-8 cycloalkyl, etc.; each R1-R6 is independently H, D, F, Cl, Br, CN, etc.; R is D, C3-8 cycloalkyl, -C1-4 alkylene -C6-10 aryl, etc.] and their stereoisomers, geometric isomers, tautomers, oxynitrides, hydrates, solvates, metabolites, pharmaceutically acceptable salts or prodrugs thereof, are claimed and exemplified. For example, II was prepared in a multistep process (procedure given). Candidate compds. of I were evaluated for stability in liver microsomes and pharmacokinetic properties in mice, rats, dogs, and monkeys (data given). Binding of I to receptor tyrosine kinases was determined using KINOMEscan where II exhibited binding constant (Kd) values of 2.9 nM for KDR tyrosine kinase and 0.21 nM for c-Met tyrosine kinase.

IT 849217-68-1, Cabozantinib

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(codrug; preparation of substituted pyrazolone compds. useful as protein tyrosine kinase modulators for treatment of proliferative disorders)

RN 849217-68-1 CAPLUS

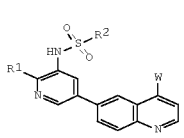
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



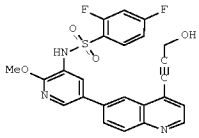
L4 ANSWER 45 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:173876 CAPLUS Full-text
DOCUMENT NUMBER: 160:294980
TITLE: Preparation of N-[3-(quinolin-6-yl)pyridin-5-yl] benzenesulfonamides as PI3 kinase modulators
INVENTOR(S): Xi, Ning; Li, Zhuo; Wang, Tingjin; Wu, Zuping; Wen, Qiuling
PATENT ASSIGNEE(S): Calitor Sciences, LLC, USA; Sunshine Lake Pharma Co., Ltd.
SOURCE: PCT Int. Appl., 88pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2014022128 | A1 | 20140206 | WO 2013-US51405 | 20130719 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM | | | | |

PRIORITY APPLN. INFO.: US 2012-61676966 P 20120729
OTHER SOURCE(S): CASREACT 160:294980; MARPAT 160:294980
GI



I



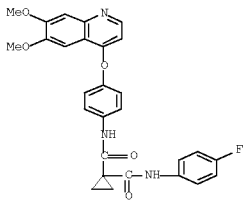
II

AB This invention relates to the field of lipid kinases and modulators thereof. In particular, the invention relates to compds. I [W = D, CN, N3, (un)substituted C5-12 spirobicyclyl or C=CX; X = H, D, alkyl, cycloalkyl, etc.; R1 = H, D, Cl, alkyl, etc.; R2 = alkyl, cycloalkyl, aryl, etc.] as modulators of phosphatidylinositol 3-kinases (PI3 kinases or PBKs) signaling pathways, and methods of their use. Twenty-nine compds. I were prepared and disclosed. E.g., a multi-step synthesis of II, starting from 5-bromo-2-chloro-3-nitropyridine, was described. Exemplified compds. I exhibited potent activities in the PI3Kα(h) and mTOR(h) assays (data given for representative compds. I). The invention also provides pharmaceutically acceptable compns. comprising compds. I and methods of using the compns. in modulating of PI3K signaling pathways and their related disorders in mammals, especially humans.

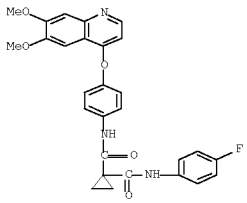
IT 849217-68-1, Cabozantinib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of N-[3-(quinolin-6-yl)pyridin-5-yl] benzenesulfonamides as PI3 kinase modulators)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



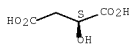
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 47 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:146206 CAPLUS Full-text
DOCUMENT NUMBER: 160:225648
TITLE: Efflux inhibitor compositions and methods of treatment using the same
INVENTOR(S): Bunt, Antonius Martinus Gustave; Van Tellingen, Olaf
PATENT ASSIGNEE(S): Neth.
SOURCE: PCT Int. Appl., 74pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2014018932 | A2 | 20140130 | WO 2013-US52402 | 20130726 |
| WO 2014018932 | A3 | 20140320 | | |

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA,

(1 CITINGS)

L4 ANSWER 46 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:151402 CAPLUS Full-text
DOCUMENT NUMBER: 160:242457
TITLE: In-frame fusion of genes CEP55 and RET associated with diffuse-type gastric cancer and their use in drug discovery and cancer therapy
INVENTOR(S): Shibata, Tatsuhiro; Hosoda, Fumie
PATENT ASSIGNEE(S): National Cancer Center, Japan
SOURCE: PCT Int. Appl., 53pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2014017491 | A1 | 20140130 | WO 2013-JP69929 | 20130723 |

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: JP 2012-165694 A 20120726

AB Through transcriptome an in-frame fusion of 2 genes (CEP55 and RET) of human chromosome 10 was found in patients with diffuse-type gastric cancer. The fused genes can be used for evaluation of the effectiveness of an antitumor agent such as RET tyrosine kinase inhibitors. Antibody to CEP55 or RET protein is also claimed.

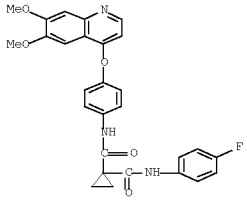
IT 1140909-48-3, XL184
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(RET tyrosine kinase inhibitors; in-frame fusion of genes CEP55 and RET associated with diffuse-type gastric cancer and their use in drug discovery and cancer therapy)

RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

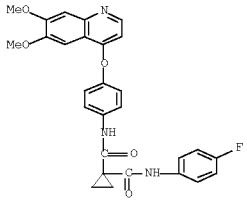
CM 1

CRN 849217-68-1
CMF C28 H24 F N3 O5



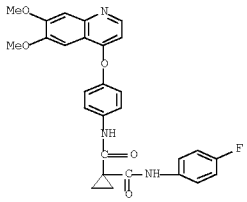
L4 ANSWER 48 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:127915 CAPLUS Full-text
DOCUMENT NUMBER: 160:362955
TITLE: Novel tyrosine kinase inhibitors for renal cell carcinoma
AUTHOR(S): Dorff, Tanya B.; Pal, Sumanta K.; Quinn, David I.
CORPORATE SOURCE: Department of Medicine, USC Norris Comprehensive Cancer Center, USC Keck School of Medicine, Los Angeles, CA, 90033, USA
SOURCE: Expert Review of Clinical Pharmacology (2014), 7(1), 67-73
CODEN: ERCPAG; ISSN: 1751-2433
DIGITAL OBJECT ID: 10.1586/17512433.2014.862496

PUBLISHER: Informa Healthcare
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
AB A review. Although targeted therapy against VEGF and mTOR have revolutionized the treatment of advanced renal cell carcinoma (RCC), addnl. agents are required due to toxicity and resistance to currently available drugs. Some next-generation tyrosine kinase inhibitors have focused on VEGF, narrowing the spectrum of receptors which are inhibited and enhancing binding affinity. However, targeting novel receptors with tyrosine kinase inhibition of addnl. receptor targets has also emerged as an important future therapeutic strategy for RCC, both clear cell and variant histol. New pathways being targeted include FGF, angiopoietin and MET. In this review, we highlight five novel tyrosine kinase inhibitors in development for RCC: tivozanib; dovitinib; regorafenib; cabozantinib; and tivantinib.
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel tyrosine kinase inhibitors for renal cell carcinoma)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



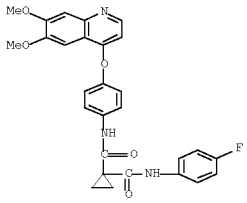
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 49 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2014:93138 CAPLUS Full-text
DOCUMENT NUMBER: 160:289739
TITLE: c-MET kinase inhibitors: a patent review (2011 - 2013)
AUTHOR(S): Zhu, Kongkai; Kong, Xiangqian; Zhao, Dan; Liang, Zhongjie; Luo, Cheng
CORPORATE SOURCE: Center for Systems Biology, Soochow University, Jiangsu, 215006, Peop. Rep. China
SOURCE: Expert Opinion on Therapeutic Patents (2014), 24(2), 217-230
CODEN: EOTPEG; ISSN: 1354-3776
DIGITAL OBJECT ID: 10.1517/13543776.2014.864279
PUBLISHER: Informa Healthcare
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
AB A review. Introduction: The receptor tyrosine kinase c-MET displays aberrant activation in the malignant phenotype of various tumors, and thus, has drawn considerable attention as drug target for cancer therapy. Many c-MET inhibitors are now under clin. investment, and one of them - Cabozantinib - has been approved by US FDA in 2012 for the treatment of medullary thyroid cancer, which further proved the feasibility of c-MET inhibition method in cancer therapy. Areas covered: This article briefly outlines the role of c-MET in oncogenesis and provides a broad overview of the assays used to characterize new inhibitors. Then, a series of representative small-mol. inhibitors of c-MET, especially from the published patent literature from 2011 to 2013, are recorded. Herein, the challenges in the kinase inhibitor design, such as the inhibitor selectivity and resistance mutations, are also discussed. Expert opinion: Up to now, at least 17 inhibitors of c-MET are under clin. evaluation, and several agents exhibit encouraging results. Thus, inhibiting c-MET signaling has major therapeutic value in cancer therapy. Focus on the selectivity of both types of inhibitors, with potent selectivity or multi-targets, have demonstrated antitumor efficacy. The network pharmacol. and clin. trials integrated would provide powerful tools to further evaluate the superiority of both inhibitors in continued efficacy and toxicity.
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(application of c-MET kinase inhibitors for the treatment of medullary thyroid cancer)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

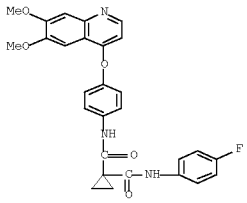


REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 50 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:2007812 CAPLUS Full-text
DOCUMENT NUMBER: 160:380536
TITLE: Newly approved antitumor drugs by FDA in 2012
AUTHOR(S): Yang, Minglun
CORPORATE SOURCE: Department of Pharmacy, Linqu County People's Hospital, Linqu, Shandong Province, 262600, Peop. Rep. China
SOURCE: Yaoxue Fuwu Yu Yanjiu (2013), 13(4), 304-306
CODEN: YFYYAH; ISSN: 1671-2838
DIGITAL OBJECT ID: 10.5428/pcar20130420
PUBLISHER: Yaoxue Fuwu Yu Yanjiu Zazhishe
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Chinese
AB A review. Newly approved antitumor drugs by FDA in 2012 were introduced.
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(newly approved antitumor drugs by FDA in 2012)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L4 ANSWER 51 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:2006727 CAPLUS Full-text
DOCUMENT NUMBER: 160:380516
TITLE: Pharmacological and clinical studies of cabozantinib
AUTHOR(S): Zheng, Xi-yuan; Jiang, Han-jie; Pu, Xiao-ping
CORPORATE SOURCE: Department of Molecular and Cellular Pharmacology, School of Pharmaceutical Sciences, Peking University, Beijing, 100191, Peop. Rep. China
SOURCE: Zhongguo Xinyao Zazhi (2013), 22(17), 1990-1993
CODEN: ZXZHA6; ISSN: 1003-3734
PUBLISHER: Zhongguo Xinyao Zazhi Youxian Gongsi
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Chinese
AB A review. Cabozantinib, a new drug for medullary thyroid cancer treatment, is a potent inhibitor of MET, RET, and vascular endothelial factor receptor 2 (VEGFR2) as well as other tyrosine kinases that have been implicated in tumor development and progression. The mechanism, pharmacokinetics, drug interaction, clin. evaluation, and safety of cabozantinib were reviewed.
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. and clin. studies of cabozantinib)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



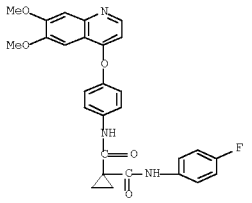
L4 ANSWER 52 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:1965166 CAPLUS Full-text
DOCUMENT NUMBER: 160:155703
TITLE: Metastatic castration-resistant prostate cancer reveals intrapatient similarity and interpatient heterogeneity of therapeutic kinase targets
AUTHOR(S): Drake, Justin M.; Graham, Nicholas A.; Lee, John K.; Stoyanova, Tanya; Faltermeier, Claire M.; Sud, Sudha; Titz, Bjorn; Huang, Jiaoti; Pienta, Kenneth J.; Graeber, Thomas G.; Witte, Owen N.
CORPORATE SOURCE: Department of Microbiology, Immunology, and Molecular Genetics, David Geffen School of Medicine, University of California, Los Angeles, CA, 90095, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2013), 110(49), E4762-E4769, SE4762/1-SE4762/23
CODEN: PNASA6; ISSN: 0027-8424
DIGITAL OBJECT ID: 10.1073/pnas.1319948110
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB In prostate cancer, multiple metastases from the same patient share similar copy number, mutational status, erythroblast transformation specific (ETS) rearrangements, and methylation patterns supporting their clonal origins. Whether actionable targets such as tyrosine kinases are also similarly expressed and activated in anatomically distinct metastatic lesions of the same patient is not known. We evaluated active kinases using phosphotyrosine peptide enrichment and quant. mass spectrometry to identify druggable targets in metastatic castration-resistant prostate cancer obtained at rapid autopsy. We identified distinct phosphopeptide patterns in metastatic tissues compared with treatment-naive primary prostate tissue and prostate cancer cell line-derived xenografts. Evaluation of metastatic castration-resistant prostate cancer samples for tyrosine phosphorylation

and upstream kinase targets revealed SRC, epidermal growth factor receptor (EGFR), rearranged during transfection (RET), anaplastic lymphoma kinase (ALK), and MAPK1/3 and other activities while exhibiting intrapatient similarity and interpatient heterogeneity. Phosphoproteomic analyses and identification of kinase activation states in metastatic castration-resistant prostate cancer patients have allowed for the prioritization of kinases for further clin. evaluation.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphokinase profiling for drug targets of metastatic castration-resistant prostate cancer reveals intrapatient similarity and interpatient heterogeneity)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

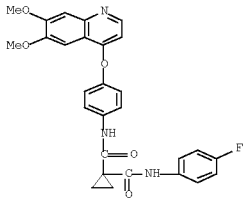
L4 ANSWER 53 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:1898455 CAPLUS Full-text
DOCUMENT NUMBER: 160:555100
TITLE: In Vitro and In Vivo Activity of Cabozantinib (XL184), an Inhibitor of RET, MET, and VEGFR2, in a Model of Medullary Thyroid Cancer
AUTHOR(S): Bentzien, Frauke; Zuzow, Marcus; Heald, Nathan; Gibson, Anna; Shi, Yongchang; Goon, Leanne; Yu, Peiwen; Engst, Stefan; Zhang, Wentao; Huang, Donghui; Zhao, Lora; Vysotskaia, Valentina; Chu, Felix; Bautista, Rajana; Cancilla, Belinda; Lamb, Peter; Joly, Alison H.; Yakes, F. Michael
CORPORATE SOURCE: ., Exelixis, Inc., South San Francisco, CA, USA
SOURCE: Thyroid (2013), 23(12), 1569-1577
CODEN: THYRER; ISSN: 1050-7256
DIGITAL OBJECT ID: 10.1089/thy.2013.0137
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB Background: A limited no. of approved therapeutic options are available to metastatic medullary thyroid cancer (MTC) patients, and the response to conventional chemotherapy and/or radiotherapy strategies is inadequate. Sporadic and inherited mutations in the tyrosine kinase RET result in oncogenic activation that is associated with the pathogenesis of MTC. Cabozantinib is a potent inhibitor of MET, RET, and vascular endothelial factor receptor 2 (VEGFR2), as well as other tyrosine kinases that have been implicated in tumor development and progression. The object of this study was to determine the in vitro biochem. and cellular inhibitory profile of cabozantinib against RET, and in vivo antitumor efficacy using a xenograft model of MTC.Methods: Cabozantinib was evaluated in biochem. and cell-based assays that determined the potency of the compound against wild type and activating mutant forms of RET. Addnl., the pharmacodynamic modulation of RET and MET and in vivo antitumor activity of cabozantinib was examined in a MTC tumor model following subchronic oral administration.Results: In biochem. assays, cabozantinib inhibited multiple forms of oncogenic RET kinase activity, including M918T and Y791F mutants. Addnl., it inhibited proliferation of TT tumor cells that harbor a C634W activating mutation of RET that is most often associated with MEN2A and familial MTC. In these same cells grown as xenograft tumors in nude mice, oral administration of cabozantinib resulted in dose-dependent tumor growth inhibition that correlated with a reduction in circulating plasma calcitonin levels. Moreover, immunohistochem. analyses of tumors revealed that cabozantinib reduced levels of phosphorylated MET and RET, and decreased tumor cellularity, proliferation, and vascularization.Conclusions: Cabozantinib is a potent inhibitor of RET and prevalent mutationally activated forms of RET known to be associated with MTC, and effectively inhibits the growth of a MTC tumor cell model in vitro and in vivo.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of in vitro and in vivo antitumor efficacy of cabozantinib in preclin. model of medullary thyroid cancer)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 54 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:1873443 CAPLUS Full-text
DOCUMENT NUMBER: 160:50465
TITLE: Substituted quinoline compounds and use as Antitumor agents
INVENTOR(S): Xi, Ning; Wang, Tingjin; Zeng, Shan; Sun, Mingming; Wang, Kunrui
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 80pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2013180949 | A1 | 20131205 | WO 2013-US41036 | 20130515 |

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

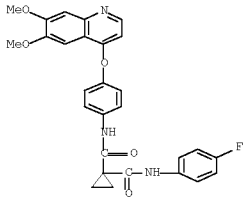
PRIORITY APPLN. INFO.: US 2012-61652210 P 20120527
OTHER SOURCE(S): CASREACT 160:50465; MARPAT 160:50465

AB The present invention provides novel substituted quinoline compds., pharmaceutical acceptable salts and formulations thereof useful in modulating the protein tyrosine kinase activity, and in modulating cellular activities such as proliferation, differentiation, apoptosis, migration and invasion. The invention also provides pharmaceutically acceptable compns. comprising such compds. and methods of using the compns. in the treatment of hyperproliferative disorders in mammals, especially humans.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(substituted quinoline compds. and methods of use)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

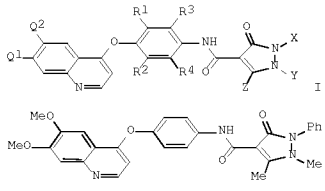


REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 55 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:1866363 CAPLUS Full-text
DOCUMENT NUMBER: 160:33885
TITLE: Substituted quinoline compound useful in treatment of hyperproliferative diseases and its preparation
INVENTOR(S): Xi, Ning; Wang, Tingjin; Zeng, Shan; Sun, Mingming; Wang, Kunrui
PATENT ASSIGNEE(S): HEC Pharm Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 57pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| CN 103420986 | A | 20131204 | CN 2013-10179608 | 20130515 |
| PRIORITY APPLN. INFO.: | | | CN 2012-10154478 A | 20120518 |
| | | | CN 2013-10118880 A | 20130403 |

OTHER SOURCE(S): CASREACT 160:33885; MARPAT 160:33885
GI



I



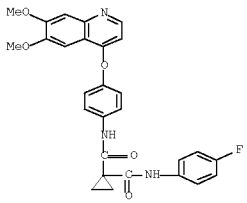
II

AB The invention relates to substituted quinoline compds. of formula I as protein kinase regulator useful in treatment of proliferative diseases and their preparation Compound I, wherein R1, R2, R3, and R4 are independently H, D, F, Cl, or Br; Q1 and Q2 are independently H, D, C1-6 alkyl, etc.; X and Z are independently H, D, Cl-6 alkyl, etc.; Y is H, D, C2-6 alkynyl, etc.; their stereoisomers, N-oxides, solvates, pharmaceutically acceptable salts, are claimed. Compound II was prepared by multi-step procedure (procedure given). The present invention also relates to the pharmaceutical compns. containing the inventive compds., and method of application of the pharmaceutical composition for treatment of a mammal, especially hyperproliferative disease.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of substituted quinoline compound useful in treatment of hyperproliferative diseases)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L4 ANSWER 56 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 57 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2013:1837363 CAPLUS Full-text

DOCUMENT NUMBER: 160:28188

TITLE: Substituted alkynyl pyridine compounds and methods of use

INVENTOR(S): Xi, Ning; Yin, Lihua; Li, Xiaobo; Yu, Na; Wu, Yanjun

PATENT ASSIGNEE(S): Sunshine Lake Pharma Co., Ltd., Peop. Rep. China

SOURCE: PCT Int. Appl., 83pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2013177092 | A1 | 20131128 | WO 2013-US41918 | 20130521 |

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2012-61650513 P 20120523

OTHER SOURCE(S): CASREACT 160:28188; MARPAT 160:28188

AB The present invention provides novel substituted alkynyl pyridine compds., pharmaceutical acceptable salts and formulations thereof useful in modulating the protein tyrosine kinase activity, and in modulating cellular activities such as proliferation, differentiation, apoptosis, migration and invasion. The invention also provides pharmaceutically acceptable compns. comprising such compds. and methods of using the compns. in the treatment of hyperproliferative disorders in mammals, especially humans.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(substituted alkynyl pyridine compds. and methods of use)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

ACCESSION NUMBER: 2013:1864045 CAPLUS Full-text

DOCUMENT NUMBER: 161:30833

TITLE: An update on clinical trials of targeted therapies in thyroid cancer

AUTHOR(S): Haraldsdottir, Sigurdis; Shah, Manisha H.

CORPORATE SOURCE: The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA

SOURCE: Current Opinion in Oncology (2014), 26(1), 36-44
CODEN: COONOE8; ISSN: 1040-8746

DIGITAL OBJECT ID: 10.1097/CCO.0000000000000029

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal; General Review; (online computer file)

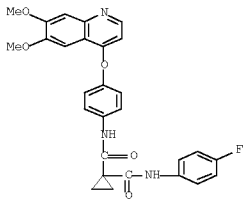
LANGUAGE: English

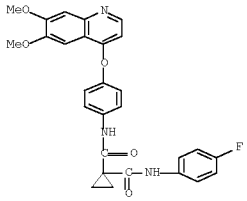
AB Purpose of review: Several new targeted therapies with multikinase inhibitors targeting vascular endothelial growth factor (VEGF), rearranged during transfection and v-raf murine sarcoma viral oncogene homolog B1 pathways have been tested in clin. trials for radioiodine-refractory differentiated thyroid cancer (DTC) and medullary thyroid cancer (MTC) in the past 10 years. Recent findings: Results of the first phase III trial of VEGF-targeted therapy (sorafenib) in DTC were presented in June 2013, and two phase III trials with VEGF and rearranged during transfection-targeted therapies (vandetanib and cabozantinib) in MTC have led to approval by US Food and Drug Administration in the past 2 years. Whereas such therapies increase median progression-free survival compared to placebo, there is no therapy proven to improve overall survival yet. Significant potential adverse event risks associated with such therapies need to be recognized. Dissemination of knowledge about targeted therapies is critical for various medical specialists as patient care for thyroid cancers is best delivered in a multidisciplinary setting. Summary: Successful development of targeted systemic therapies in DTC and MTC in the past 5 years is incredibly exciting in the field and patients with advanced DTC/MTC now have new standard-of-care therapy options.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(update on clin. trials of targeted therapies in thyroid cancer)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)





REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 58 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2013:1836624 CAPLUS Full-text

DOCUMENT NUMBER: 160:28252

TITLE: Compounds and methods of use thereof for treating neurodegenerative disorders

INVENTOR(S): Zack, Donald J.; Welsbie, Derek Stuart; Yang, Zhiyong

PATENT ASSIGNEE(S): The Johns Hopkins University, USA

SOURCE: PCT Int. Appl., 106pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

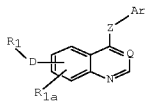
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2013177367 | A2 | 20131128 | WO 2013-US42367 | 20130523 |

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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2012-61650613 P 20120523
US 2012-61680931 P 20120808

GI



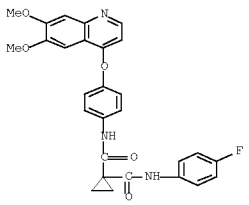
I

AB In some embodiments, the presently disclosed subject matter provides a method for treating or preventing a neurodegenerative disease, disorder, or condition in a subject in need thereof, the method comprising administering to the subject a 15 therapeutically effective amount of a compound of Formula I (wherein D is selected from the group consisting of O, S(O)0-2, and NR1b; R1a is selected from the group consisting of H, substituted or unsubstituted alkyl, halogen, OR1b, NO2, NR1bR1c; wherein: R1b and R1c are each independently selected from the group consisting of H or substituted or unsubstituted alkyl, aryl, etc.; R1 is H, substituted alkyl, aryl, etc.; Q is CR2a or N wherein R2a is H, alkyl or cyano; Z is O, NR1b and S(O)0-2; and Ar is substituted aryl or substituted heteroaryl), or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, thereby treating or preventing the neurodegenerative disease, disorder, or condition.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compds. and methods of use thereof for treating neurodegenerative disorders in relation to use of other agents and diagnosis)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L4 ANSWER 59 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2013:1823382 CAPLUS Full-text

DOCUMENT NUMBER: 161:178446

TITLE: Ocular adverse events of molecularly targeted agents approved in solid tumours: A systematic review

AUTHOR(S): Huillard, Olivier; Bakalian, Silvin; Levy, Christine; Desjardins, Laurence; Lumbroso-Le Rouic, Livia; Pop, Simona; Sablin, Marie-Paule; Le Tourneau, Christophe

CORPORATE SOURCE: Department of Medical Oncology, Clinical Trial Unit, Institut Curie, Paris, Fr.

SOURCE: European Journal of Cancer (2014), 50(3), 638-648
CODEN: EJCAEL; ISSN: 0959-8049

DIGITAL OBJECT ID: 10.1016/j.ejca.2013.10.016

PUBLISHER: Elsevier Ltd.

DOCUMENT TYPE: Journal; (online computer file)

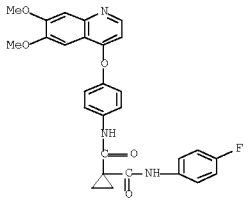
LANGUAGE: English

AB When using molecularly targeted agents (MTAs), oncologists and patients face new and sometimes unexpected toxicities. Though ocular adverse events (OAEs) are not uncommon with chemotherapy, they are rarely severe or dose limiting. Ocular toxicity profile may differ with MTAs, indeed severe and dose limiting toxicities have been described with targeted therapies currently under investigation. Our study aimed to review OAEs experienced with MTAs approved in solid tumors. This review revealed that many OAEs, frequent and potentially severe, exist and concern most MTAs. The suggestion is prompt referral of patients with severe pain and/or visual impairment to the ophthalmologist since these symptoms can be associated with potentially severe OAE and need ophthalmic assessment. Oncologists must be aware of such events and their potential severity for better treatment and better diagnosis in daily practice as well as in clin. trials.

IT 849217-68-1, Cabozantinib
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ocular adverse events of molecularly targeted agents approved in solid tumors)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 60 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2013:1802363 CAPLUS Full-text

DOCUMENT NUMBER: 160:509021

TITLE: Multivoxel 1H MR spectroscopy is superior to contrast-enhanced MRI for response assessment after anti-angiogenic treatment of orthotopic human glioma xenografts and provides handles for metabolic targeting

AUTHOR(S): Hamans, Bob; Navis, Anna Catharina; Wright, Alan; Wesseling, Pieter; Heerschap, Arend; Leenders, William

CORPORATE SOURCE: Department of Radiology, Radboud University Nijmegen Medical Centre, Nijmegen, Neth.

SOURCE: Neuro-Oncology (Cary, NC, United States) (2013), 15(12), 1615-1624
CODEN: NEURJR; ISSN: 1522-8517

DIGITAL OBJECT ID: 10.1093/neuonc/not129

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal; (online computer file)

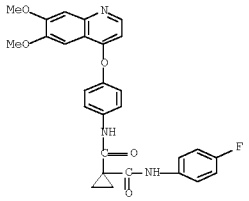
LANGUAGE: English

AB Background Anti-angiogenic treatment of glioblastoma characteristically results in therapy resistance and tumor progression via diffuse infiltration. Monitoring tumor progression in these patients is thwarted because therapy results in tumor invisibility in contrast-enhanced (CE) MRI. To address this problem, we examined whether tumor progression could be monitored by metabolic mapping using 1H MR spectroscopic imaging (MRSI). Methods We treated groups of BALB/c nu/nu mice carrying different orthotopic diffuse-infiltrative glioblastoma xenografts with bevacizumab (anti-vascular endothelial growth factor [VEGF] antibody, n = 13), cabozantinib (combined VEGF receptor 2/c-Met tyrosine kinase inhibitor, n = 11), or placebo (n = 15) and compared CE-MRI with MRS-derived metabolic maps before, during, and after treatment. Metabolic maps and CE-MRIs were subsequently correlated to histol. and immunohistochem. Results In vivo imaging of choline/n-acetyl aspartate ratios via multivoxel MRS is better able to evaluate response to therapy than CE-MRI. Lactate imaging revealed that diffuse infiltrative areas in glioblastoma xenografts did not present with excessive glycolysis. In contrast, glycolysis was observed in hypoxic areas in angiogenesis-dependent compact regions of glioma only, especially after anti-angiogenic treatment. Conclusion Our data present MRSI as a powerful and feasible approach that is superior to CE-MRI and may provide handles for optimizing treatment of glioma. Furthermore, we show that glycolysis is more prominent in hypoxic areas than in areas of diffuse infiltrative growth. The Warburg hypothesis of persisting glycolysis in tumors under normoxic conditions may thus not be valid for diffuse glioma.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(metabolic mapping via multivoxel magnetic resonance spectroscopy imaging than contrast-enhanced MRI showed better tumor progression after antiangiogenic Avastin and Exelixis treatment in mouse xenografted with human glioma cell)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 61 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2013:1792084 CAPLUS Full-text

DOCUMENT NUMBER: 159:737215

TITLE: Cabozantinib in progressive medullary thyroid cancer

AUTHOR(S): Elisei, Rossella; Schlumberger, Martin J.; Mueller, Stefan P.; Schoffski, Patrick; Brose, Marcia S.; Shah, Manisha H.; Licitra, Lisa; Jarzab, Barbara; Medvedev, Viktor; Kreissl, Michael C.; Niederle, Bruno; Cohen, Ezra E. W.; Wirth, Lori J.; Ali, Haythem; Hessel, Colin; Yaron, Yifah; Ball, Douglas; Nelkin, Barry; Sherman, Steven I.

CORPORATE SOURCE: University of Pisa, Pisa, Italy

SOURCE: Journal of Clinical Oncology (2013), 31(29), 3639-3646
CODEN: JCONDN; ISSN: 0732-183X

DIGITAL OBJECT ID: 10.1200/JCO.2012.48.4659

PUBLISHER: American Society of Clinical Oncology

DOCUMENT TYPE: Journal

LANGUAGE: English

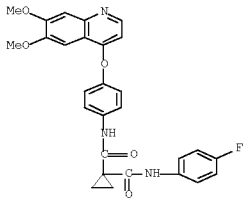
AB Purpose: Cabozantinib, a tyrosine kinase inhibitor (TKI) of hepatocyte growth factor receptor (MET), vascular endothelial growth factor receptor 2, and rearranged during transfection (RET), demonstrated clin. activity in patients with medullary thyroid cancer (MTC) in phase I. Patients and Methods: We conducted a double-blind, phase III trial comparing cabozantinib with placebo in 330 patients with documented radiog. progression of metastatic MTC. Patients were randomly assigned (2:1) to cabozantinib (140 mg per day) or placebo. The primary end point was progression-free survival (PFS). Addnl. outcome measures included tumor response rate, overall survival, and safety. Results: The estimated median PFS was 11.2 mo for cabozantinib vs. 4.0 mo for placebo (hazard ratio, 0.28; 95% CI, 0.19 to 0.40; P < .001). Prolonged PFS with cabozantinib was observed across all subgroups including by age, prior TKI treatment, and RET mutation status (hereditary or sporadic). Response rate was 28% for cabozantinib and 0% for placebo; responses were seen regardless of RET mutation status. Kaplan-Meier ests. of patients alive and progression-free at 1 yr are 47.3% for cabozantinib and 7.2% for placebo. Common cabozantinib-associated adverse events included

diarrhea, palmar-plantar erythrodysesthesia, decreased weight and appetite, nausea, and fatigue and resulted in dose redns. in 79% and holds in 65% of patients. Adverse events led to treatment discontinuation in 16% of cabozantinib-treated patients and in 8% of placebo-treated patients. Conclusion: Cabozantinib (140 mg per day) achieved a statistically significant improvement of PFS in patients with progressive metastatic MTC and represents an important new treatment option for patients with this rare disease. This dose of cabozantinib was associated with significant but manageable toxicity.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cabozantinib in progressive medullary thyroid cancer)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 21 THERE ARE 21 CAPLUS RECORDS THAT CITE THIS RECORD (21 CITINGS)

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 62 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2013:1772555 CAPLUS Full-text

DOCUMENT NUMBER: 159:738209

TITLE: Methods for determining nucleotide sequence

INVENTOR(S): Iafrate, Anthony John; Le, Long Phi; Zheng, Zongli

PATENT ASSIGNEE(S): The General Hospital Corporation, USA

SOURCE: PCT Int. Appl., 69pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2013169339 | A1 | 20131114 | WO 2013-US30201 | 20130311 |

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

| | | | | |
|---|---|---|---|---|
| US 20130303461 | A1 | 20131114 | US 2013-13793564 | 20130311 |
| PRIORITY APPLN. INFO.: | | | US 2012-61645364 P | 20120510 |
| | | | US 2012-61679302 P | 20120803 |

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The technol. described herein is directed to methods of detg. oligonucleotide sequences, e.g. by enriching target sequences prior to sequencing the sequences. The invention provides the sequences of the DNA primers used for sequencing anal. The target sequence may be genomic DNA, RNA or cDNA with or without gene rearrangement.

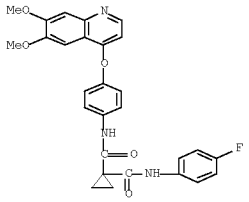
IT 1140909-48-3, XL184
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for determining nucleotide sequence)

RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

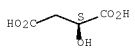
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 63 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2013:1771791 CAPLUS Full-text

DOCUMENT NUMBER: 159:742705

TITLE: Substituted alkynyl pyridine compounds as protein kinase regulator useful in treatment various diseases and their preparation

INVENTOR(S): Xi, Ning; Yin, Lihua; Li, Xiaobo; Yu, Na; Wu, Yanjun

PATENT ASSIGNEE(S): HEC Pharm Co., Ltd., Peop. Rep. China

SOURCE: Faming Zhuanli Shenqing, 65pp.
CODEN: CNXXEV

DOCUMENT TYPE: Patent

LANGUAGE: Chinese

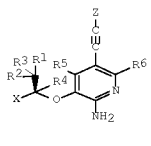
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

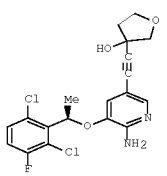
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| CN 103387535 | A | 20131113 | CN 2013-10173770 | 20130510 |
| PRIORITY APPLN. INFO.: | | | CN 2012-10141993 A | 20120510 |
| | | | CN 2013-10116652 A | 20130403 |

OTHER SOURCE(S): CASREACT 159:742705; MARPAT 159:742705

GI



I



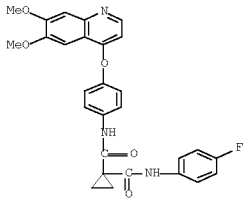
II

AB The invention relates to substituted alkynyl pyridine compds. of formula I as protein kinase regulator useful in treatment of various diseases and their preparation Compds. I, wherein R1, R2, R3, R4, R5 and R6 are independently H, D or F; X is C6-10 aryl or heteroaryl containing 5-10 atoms; Z is C1-6 alkyl, C3-6 cycloalkyl, C3-6 heterocyclic radical, etc.; their stereoisomers, solvates, N-oxidants, pharmaceutically acceptable salts, are claimed. Compound II was prepared by multi-step procedure (procedure given). The invention compds. were evaluated for their ALK(h) kinase activity. From assay, it was determined that II exhibited the IC50 value of 52 nM against ALK(h).

IT 849217-68-1, Cabozantinib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of substituted alkynyl pyridine compds. as protein kinase regulator useful in treatment of various diseases)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L4 ANSWER 64 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2013:1746648 CAPLUS Full-text

DOCUMENT NUMBER: 160:200751

TITLE: Cabozantinib: a novel agent with a dual mechanism of action for castration-resistant prostate carcinoma

AUTHOR(S): Pinto, Alvaro

CORPORATE SOURCE: Medical Oncology Department, University Hospital La Paz-IdiPAZ, Madrid, Spain

SOURCE: Cancer Chemotherapy and Pharmacology (2014), 73(2), 219-222
CODEN: CCPHDZ; ISSN: 0344-5704

DIGITAL OBJECT ID: 10.1007/s00280-013-2343-2

PUBLISHER: Springer

DOCUMENT TYPE: Journal; General Review; (online computer file)

LANGUAGE: English

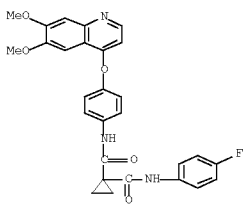
AB A review. The landscape of castration-resistant prostate carcinoma has changed completely in the last few years, with the approval of four new agents with proven benefit in overall survival. Abiraterone, cabazitaxel, enzalutamide and radium-223 dichloride have been added to the armamentarium of available agents for the treatment of these patients. We still lack information about which agent works best in an individual patient and how to optimally use them in a sequential strategy. Cabozantinib, a targeted agent against MET and vascular endothelial growth factor receptor-2, has shown promising results and could become the first targeted therapy to be

approved for castration-resistant prostate carcinoma. This paper reviews the clin. development of cabozantinib in prostate cancer and future research possibilities for this drug.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cabozantinib, a novel agent with a dual mechanism of action for castration-resistant prostate carcinoma)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 65 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:1734775 CAPLUS Full-text
DOCUMENT NUMBER: 159:691817
TITLE: A dual MET-VEGF modulator for treating osteolytic bone metastases
INVENTOR(S): Aftab, Dana T.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 44pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2013166296 | A1 | 20131107 | WO 2013-US39284 | 20130502 |

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

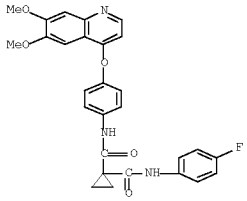
PRIORITY APPLN. INFO.: US 2012-61641837 P 20120502
OTHER SOURCE(S): CASREACT 159:691817; MARPAT 159:691817

AB This invention is directed to the treatment of cancer, particularly castration-resistant prostate cancer and osteolytic bone metastases, with a dual inhibitor of MET and VEGF.

IT 849217-68-1
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(dual MET-VEGF modulator for treating osteolytic bone metastases)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



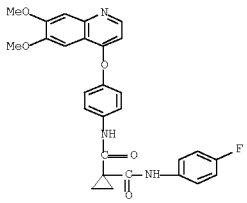
IT 1140909-48-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(dual MET-VEGF modulator for treating osteolytic bone metastases)

RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

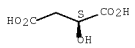
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



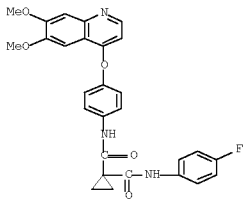
IT 1365530-43-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dual MET-VEGF modulator for treating osteolytic bone metastases)

RN 1365530-43-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

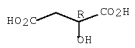
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 636-61-3
CMF C4 H6 O5

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

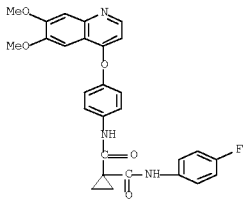
L4 ANSWER 66 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:1717033 CAPLUS Full-text
DOCUMENT NUMBER: 160:363229
TITLE: Cabozantinib inhibits growth of androgen-sensitive and castration-resistant prostate cancer and affects bone remodeling
AUTHOR(S): Nguyen, Holly M.; Ruppender, Nazanin; Zhang, Xiaotun; Brown, Lisha G.; Gross, Ted S.; Morrissey, Colm; Gulati, Roman; Vessella, Robert L.; Schimmoller, Frauke; Aftab, Dana T.; Corey, Eva
CORPORATE SOURCE: Department of Urology, University of Washington, Seattle, WA, USA
SOURCE: PLoS One (2013), 8(10), e78881
CODEN: POLNCL; ISSN: 1932-6203
DIGITAL OBJECT ID: 10.1371/journal.pone.0078881
PUBLISHER: Public Library of Science
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB Cabozantinib is an inhibitor of multiple receptor tyrosine kinases, including MET and VEGFR2. In a phase II clin. trial in advanced prostate cancer (PCa), cabozantinib treatment improved bone scans in 68% of evaluable patients. Our studies aimed to determine the expression of cabozantinib targets during PCa progression and to evaluate its efficacy in

hormone-sensitive and castration-resistant PCa in preclin. models while delineating its effects on tumor and bone. Using immunohistochem. and tissue microarrays containing normal prostate, primary PCa, and soft tissue and bone metastases, our data show that levels of MET, P-MET, and VEGFR2 are increasing during PCa progression. Our data also show that the expression of cabozantinib targets are particularly pronounced in bone metastases. To evaluate cabozantinib efficacy on PCa growth in the bone environment and in soft tissues we used androgen-sensitive LuCaP 23.1 and castration-resistant C4-2B PCa tumors. In vivo, cabozantinib inhibited the growth of PCa in bone as well as growth of s.c. tumors. Furthermore, cabozantinib treatment attenuated the bone response to the tumor and resulted in increased normal bone volume In summary, the expression pattern of cabozantinib targets in primary and castration-resistant metastatic PCa, and its efficacy in two different models of PCa suggest that this agent has a strong potential for the effective treatment of PCa at different stages of the disease.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(MET, VEGFR2, RET expressions were found higher while cabozantinib by inhibiting these targets, it safely, effectively inhibited tumor growth, improved bone remodeling in human androgen-sensitive, metastatic CRPC tumor xenografted mouse)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 67 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:1698309 CAPLUS Full-text
DOCUMENT NUMBER: 159:662217
TITLE: Detection of RET fusions in cancer
INVENTOR(S): Doebele, Robert; Garcia, Marileila Varella; Le, Anh T.; Xu, Liangguo
PATENT ASSIGNEE(S): University of Colorado, USA
SOURCE: PCT Int. Appl., 52pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

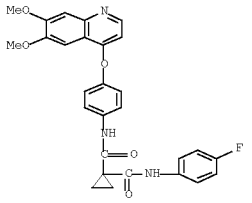
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2013163428 | A1 | 20131031 | WO 2013-US38215 | 20130425 |

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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2012-61638452 P 20120425
AB Disclosed are methods and assay systems for the identification of chromosomal rearrangements involving the RET kinase gene in cellular samples. Further described are methods for identifying cancer patients who are predicted to respond, or not respond to the therapeutic administration of a chemotherapeutic regimen including one or more kinase inhibitor(s), to treat cancer in the patient.

IT 849217-68-1, Cabozantinib
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(detection of RET fusions in cancer)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

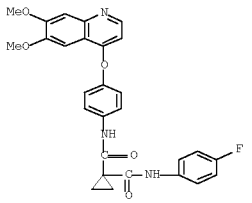


REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 68 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:1679191 CAPLUS Full-text
DOCUMENT NUMBER: 160:82446
TITLE: Commentary on "Cabozantinib in patients with advanced prostate cancer: results of a phase II randomized discontinuation trial." Smith DC, Smith MR, Sweeney C, Elfiky AA, Logothetis C, Corn PG, Vogelzang NJ, Small EJ, Harzstark AL, Gordon MS, Vaishampayan UN, Haas NB, Spira AI, Lara PN Jr, Lin CC, Srinivas S, Sella A, SchoffskiSchoeffski P, Scheffold C, Weitzman AL, Hussain M, University of Michigan, Ann Arbor, MI
AUTHOR(S): Trump, Donald L.
CORPORATE SOURCE: Neth.
SOURCE: Urologic Oncology: Seminars and Original Investigations (2013), 31(8), 1848
CODEN: UOSOAA; ISSN: 1078-1439
DIGITAL OBJECT ID: 10.1016/j.urolonc.2013.07.012
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
AB A review. Cabozantinib (XL184) is an orally bioavailable tyrosine kinase inhibitor with activity against MET and vascular endothelial growth factor receptor 2. We evaluated the activity of cabozantinib in patients with castration-resistant prostate cancer (CRPC) in a phase II randomized discontinuation trial with an expansion cohort. Patients received 100 mg of cabozantinib daily. Those with stable disease per RECIST at 12 wk were randomly assigned to cabozantinib or placebo. Primary end points were objective response rate at 12 wk and progression-free survival (PFS) after random assignment. One hundred seventy-one men with CRPC were enrolled. Random assignment was halted early based on the observed activity of cabozantinib. Seventy-two percent of patients had regression in soft tissue lesions, whereas 68% of evaluable patients had improvement on bone scan, including complete resolution in 12%. The objective response rate at 12 wk was 5%, with stable disease in 75% of patients. Thirty-one patients with stable disease at week 12 were randomly assigned. Median PFS was 23.9 wk (95% CI, 10.7 to 62.4 wk) with cabozantinib and 5.9 wk (95% CI, 5.4 to 6.6 wk) with placebo (hazard ratio, 0.12; P<.001). Serum total alkaline phosphatase and plasma cross-linked C-terminal telopeptide of type I collagen were reduced by≥50% in 57% of evaluable patients. On retrospective review, bone pain improved in 67% of evaluable patients, with a decrease in narcotic use in 56%. The most common grade 3 adverse events were fatigue (16%), hypertension (12%), and hand-foot syndrome (8%). Cabozantinib has clin. activity in men with CRPC, including reduction of soft tissue lesions, improvement in PFS, resolution of bone scans, and redns. in bone turnover markers, pain, and narcotic use.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cabozantinib in patients with advanced prostate cancer)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L4 ANSWER 69 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:1655693 CAPLUS Full-text
DOCUMENT NUMBER: 159:632725
TITLE: Menainv and cancer invasion and metastasis diagnosis and antitumor screening
INVENTOR(S): Gertler, Frank B.; Hughes-Alford, Shannon K.; Lauffenburger, Douglas A.; Neil, Jason; White, Forest; Condeelis, John S.; Oudin, Madeleine J.
PATENT ASSIGNEE(S): Massachusetts Institute of Technology, USA; Albert Einstein College of Medicine of Yeshiva University
SOURCE: PCT Int. Appl., 63pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2013158485 | A1 | 20131024 | WO 2013-US36336 | 20130412 |

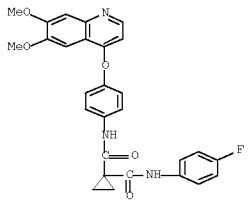
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2012-61625985 P 20120418
US 2013-61778767 P 20130313
AB Methods and compns. are provided for diagnosing or inhibiting invasion or metastasis of a cancer in a subject based on MenaINV. A method is provided of identifying an agent as an inhibitor of sarcoma or carcinoma cell invasion

or as an inhibitor of metastasis of a carcinoma or sarcoma, comprising contacting a preparation comprising a growth factor receptor and a protein tyrosine phosphatase 1b (PTP1b) in the presence of an amount of MenaINV and an amount of Mena and quantifying the association of the growth factor receptor and PTP1b in the presence of the agent and in the absence of the agent. An agent that increases the association of growth factor receptor and PTP1b in the presence of the agent as compared to in the absence of the agent is identified as an inhibitor of sarcoma or carcinoma cell invasion or of metastasis, and an agent that does not increase, or decreases, the association of growth factor receptor and PTP1b in the presence of the agent as compared to in the absence of the agent is not identified as an inhibitor of sarcoma or carcinoma cell invasion or metastasis. A further method is provided of identifying an agent as an inhibitor of sarcoma or carcinoma cell invasion or of metastasis of a carcinoma or sarcoma, the method comprising contacting a preparation comprising an amount of MenaINV, an amount of Mena, and a protein, wherein the protein is phosphorylated, with the agent and PTP1b and quantifying phosphorylation of the protein at the site or sites. A decrease in phosphorylation in (a) the presence of the agent and PTP1b as compared to (b) in the absence of the agent and presence of PTP1b identifies the agent as an inhibitor of sarcoma or carcinoma cell invasion or metastasis, and wherein an increase in, or no change in, phosphorylation in (i) the presence of the agent and PTP1b as compared to (ii) in the absence of the agent and presence of PTP1b does not identify the agent as an inhibitor of sarcoma or carcinoma cell invasion or metastasis.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Menainv and cancer invasion and metastasis diagnosis and antitumor screening)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 70 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:1629334 CAPLUS Full-text
DOCUMENT NUMBER: 159:602931
TITLE: Method for the prognosis and treatment of cancer metastasis
INVENTOR(S): Arnal, Anna; Tarragona, Maria; Pavlovic, Milica; Planet, Evarist; Gomis, Roger
PATENT ASSIGNEE(S): Inbiomotion S.L., Spain
SOURCE: PCT Int. Appl., 150pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

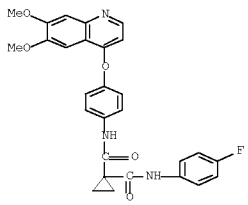
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2013153458 | A2 | 20131017 | WO 2013-IB1204 | 20130315 |
| WO 2013153458 | A3 | 20140227 | | |
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| EP 2650682 | A1 | 20131016 | EP 2012-382139 | 20120409 |
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PRIORITY APPLN. INFO.:
EP 2012-382139 A 20120409
US 2012-61621949 P 20120409
US 2012-61724807 P 20121109
US 2012-61732175 P 20121130

AB The present invention relates to a method for the prognosis of bone metastasis in triple neg. (including basal-like) breast cancer or, alternatively, ER+ breast cancer (including luminal A and β) which comprises determining if the c-MAF gene is amplified in a primary tumor sample. Likewise, the invention also relates to a method for determining the tendency to develop bone metastasis with respect to metastasis in other organs, which comprise determining the c-MAF gene expression level, amplification or translocation. The invention also relates to a method for predicting early bone metastasis in a subject suffering breast cancer. The invention also relates to a c-MAF inhibitor as therapeutic agent for use in the treatment of triple neg. (including basal-like) breast cancer metastasis or, alternatively, ER+ breast cancer (including luminal A and B) metastasis. The invention relates to kits for predicting bone metastasis and predicting the clin. outcome of a subject suffering from bone metastasis. Finally, the invention relates to a method for typing of a subject suffering breast cancer and for classifying a subject from breast cancer into a cohort.

IT 849217-68-1, Cabozantinib
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for the prognosis and treatment of cancer metastasis)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

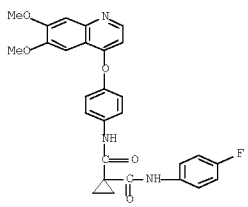


L4 ANSWER 71 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:1622779 CAPLUS Full-text
DOCUMENT NUMBER: 160:260019
TITLE: Novel Modeling of Cancer Cell Signaling Pathways Enables Systematic Drug Repositioning for Distinct Breast Cancer Metastases
AUTHOR(S): Zhao, Hong; Jin, Guangxu; Cui, Kemi; Ren, Ding; Liu, Timothy; Chen, Peikai; Wong, Solomon; Li, Fuhai; Fan, Yubo; Rodriguez, Angel; Chang, Jenny; Wong, Stephen T. C.
CORPORATE SOURCE: Department of Systems Medicine and Bioengineering; NCI Center for Modeling Cancer Development, The Methodist Hospital Research Institute, Weill Cornell Medical College; Methodist Cancer Center, The Methodist Hospital, Dan L. Duncan Cancer Center, Baylor College of Medicine, Houston, TX, USA
SOURCE: Cancer Research (2013), 73(20), 6149-6163
CODEN: CNREA8; ISSN: 0008-5472
DIGITAL OBJECT ID: 10.1158/0008-5472.CAN-12-4617
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new type of signaling network element, called cancer signaling bridges (CSB), has been shown to have the potential for systematic and fast-tracked drug repositioning. On the basis of CSBs, we developed a computational model to derive specific downstream signaling pathways that reveal previously unknown target-disease connections and new mechanisms for specific cancer subtypes. The model enables us to reposition drugs based on available patient gene expression data. We applied this model to repurpose known or shelved drugs for brain, lung, and bone metastases of breast cancer with the hypothesis that cancer subtypes have their own specific signaling mechanisms. To test the hypothesis, we addressed specific CSBs for each metastasis that satisfy (i) CSB proteins are activated by the maximal number of enriched signaling pathways specific to a given metastasis, and (ii) CSB proteins are involved in the most differential expressed coding genes specific to each breast cancer metastasis. The identified signaling networks for the three types of breast cancer metastases contain 31, 15, and 18 proteins and are used to reposition 15, 9, and 2 drug candidates for the brain, lung, and bone metastases. We conducted both in vitro and in vivo preclin. expts. as well as anal. on patient tumor specimens to evaluate the targets and repositioned drugs. Of special note, we found that the Food and Drug Administration-approved drugs, sunitinib and dasatinib, prohibit brain metastases derived from breast cancer, addressing one particularly challenging aspect of this disease.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel developed cancer signaling bridges-based computational model enabled systematic drug repositioning for brain, lung and bone metastasis in human breast cancer cell and in xenografted mouse model)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 72 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:1619978 CAPLUS Full-text
DOCUMENT NUMBER: 159:634400
TITLE: Method for the prognosis and treatment of cancer metastasis
INVENTOR(S): Gomis Cabre, Roger; Planet, Evarist; Pavlovic, M. Milica
PATENT ASSIGNEE(S): Fundacio Privada Institut de Recerca Biomedica, Spain; Fundacio Privada Institucio Catalana de Recerca i Estudis Avancats
SOURCE: Eur. Pat. Appl., 51pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

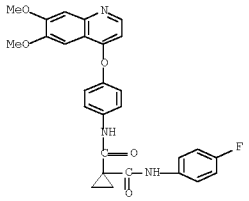
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 2650682 | A1 | 20131016 | EP 2012-382139 | 20120409 |
| R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME | | | | |
| WO 2013153458 | A2 | 20131017 | WO 2013-IB1204 | 20130315 |
| WO 2013153458 | A3 | 20140227 | | |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM | | | | |
| PRIORITY APPLN. INFO.: | | | EP 2012-382139 | A 20120409 |
| | | | US 2012-61621949 | P 20120409 |
| | | | US 2012-61724807 | P 20121109 |
| | | | US 2012-61732175 | P 20121130 |

AB The present invention relates to a method for the prognosis of bone metastasis in triple neg. (including basal-like) breast cancer which comprises determining if the c-MAF gene is amplified in a primary tumor sample. Likewise, the invention also relates to a method for determining the tendency to develop bone metastasis with respect to metastasis in other organs, which comprise determining the c-MAF gene expression level. The invention also relates to a method for predicting early bone metastasis in a subject suffering breast cancer. The invention also relates to a c-MAF inhibitor as therapeutic agent for use in the treatment of triple neg. (including basal-like) breast cancer metastasis. The invention relates to kits for predicting bone metastasis and predicting the clin. outcome of a subject suffering from bone metastasis. Finally, the invention relates to a method for typing of a subject suffering breast cancer and for classifying a subject from breast cancer into a cohort.

IT 849217-68-1, CAbozantinib
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for the prognosis and treatment of cancer metastasis)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 73 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:1549396 CAPLUS Full-text
DOCUMENT NUMBER: 159:577130
TITLE: Preparation of spirobicyclyl substituted pyrazolyl pyridinamine compounds as tyrosine kinase inhibitors for treating hyperproliferative disorders
INVENTOR(S): Xi, Ning; Li, Minxiong; Zhou, Xuan; Wu, Yanjun
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 90pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2013148537 | A1 | 20131003 | WO 2013-US33633 | 20130325 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM | | | | |
| PRIORITY APPLN. INFO.: | | | US 2012-61617626 | P 20120329 |
| OTHER SOURCE(S): | CASREACT 159:577130; MARPAT 159:577130 | | | |

GI

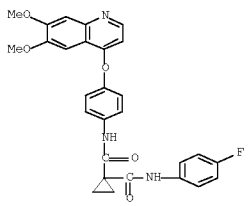
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention provides spirobicyclic compds. of general formula I (wherein R1-R6 are independently H, D, or F; each X and Y is independently (un)substituted C6-10aryl or (un)substituted 5-10 membered heteroaryl; Z is (un)substituted C5-12spirobicyclyl or (un)substituted -(C1-4alkylene)-(C5-12spirobicyclyl)-, with provisos), pharmaceutical acceptable salts and formulations thereof useful in modulating protein tyrosine kinase activity, and in modulating cellular activities such as proliferation, differentiation, apoptosis, migration and invasion. The invention also provides pharmaceutically acceptable compns. comprising such compds. and methods of using the compns. in the treatment of hyperproliferative disorders in mammals, especially humans. Synthetic procedures for preparing I are exemplified. For example, II was prepared in a 12-step synthesis that culminated in reaction of intermediates III and IV. II inhibited ALK kinase and c-Met kinase with IC50 values of 15 and 9 nM, resp.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(codrug; preparation of spirobicyclyl substituted pyrazolyl pyridinamine compds. as tyrosine kinase inhibitors for treating hyperproliferative disorders)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 74 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:1459937 CAPLUS Full-text
DOCUMENT NUMBER: 159:472093
TITLE: Preparation of substituted pyrazolylpyridinamine compounds as protein tyrosine kinase modulators for treatment of hyperproliferative disorders
INVENTOR(S): Xi, Ning; Wang, Tingjin; Yi, Lei
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 141pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2013138210 | A1 | 20130919 | WO 2013-US30096 | 20130311 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM | | | | |
| PRIORITY APPLN. INFO.: | | | US 2012-61610473 | P 20120314 |
| | | | US 2012-61617626 | P 20120329 |
| OTHER SOURCE(S): | CASREACT 159:472093; MARPAT 159:472093 | | | |

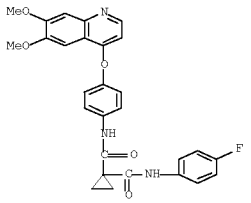
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention provides substituted pyrazolylpyridinamine compds. of formula I as protein tyrosine kinase modulators capable of regulating cellular activities such as proliferation, differentiation, apoptosis, migration and invasion for use in the treatment of hyperproliferative disorders. Compds. of formula I [wherein each R1, R2, R3, R4, R5, and R6 are independently H, D, or F; Z is substituted C3-7 heterocyclyl, substituted (C1-4 alkylene)-(C3-7 heterocyclyl), (un)substituted C5-12 fused bicyclyl, etc.;] stereoisomers, geometric isomers, tautomers, N-oxides, solvates, metabolites, or pharmaceutically acceptable salts or prodrugs thereof are claimed and prepared For example, II was prepared by the reaction of 4-iodo-1-(4-((tetrahydro-2H-pyran-2-yl)oxy)tetrahydrofuran-3-yl)-1H-pyrazole with III followed by removal of the tetrahydro-2H-pyran and deprotection of the amine group to afford II in 80% yield. Pharmacodynamic and pharmacokinetic assays were performed on II. II inhibited ALK kinase and c-Met kinase with IC50 of 5 nM and 4 nM resp., demonstrated 82% inhibition of glioblastoma tumor growth when dosed orally at 60 mg/kg to mice, and exhibited a half-life of 35.37 min in human microsomes.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(codrug; preparation of substituted pyrazolylpyridinamine compds. as protein tyrosine kinase modulators for treatment of hyperproliferative disorders)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

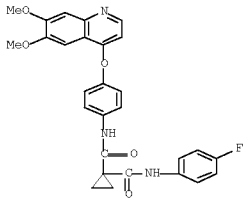


REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 75 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:1270627 CAPLUS Full-text
DOCUMENT NUMBER: 159:384885
TITLE: Epithelial membrane protein 2 (EMP2) regulates angiogenesis in cancer cells through induction of VEGF
INVENTOR(S): Wadehra, Madhuri; Braun, Jonathan; Gordon, Lynn K.
PATENT ASSIGNEE(S): University of California, USA; United States Dept. of Veterans Affairs
SOURCE: PCT Int. Appl., 84pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

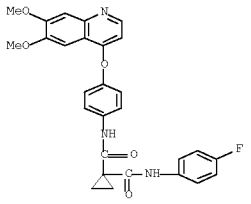
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2013119693 | A1 | 20130815 | WO 2013-US24968 | 20130206 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM | | | | |
| CA 2863986 | A1 | 20130815 | CA 2013-2863986 | 20130206 |
| AU 2013203424 | A1 | 20130822 | AU 2013-203424 | 20130206 |
| PRIORITY APPLN. INFO.: | | | US 2012-61595617 P | 20120206 |
| | | | WO 2013-US24968 W | 20130206 |

AB The authors disclose the targeting of epithelial membrane protein 2 (EMP2) for the treatment and prevention of endometrial cancer. In one example, EMP2 expression directly correlated with VEGF protein levels as well as with secreted protein expression by endometrial adenocarcinoma cells. Ribozyme-mediated reduction of EMP2 resulted in undetectable levels of VEGF.
IT 849217-68-1, Cabozantinib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in combination with anti-EMP2 antibodies for treatment of uterine cancer)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 76 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:1255893 CAPLUS Full-text
DOCUMENT NUMBER: 159:660795
TITLE: Ponatinib is a potent inhibitor of wild-type and drug-resistant gatekeeper mutant RET kinase
AUTHOR(S): Mologni, Luca; Redaelli, Sara; Morandi, Andrea; Plaza-Menacho, Ivan; Gambacorti-Passerini, Carlo
CORPORATE SOURCE: Dept. of Health Sciences, University of Milano-Bicoccavia Cadore, Monza, 20900, Italy
SOURCE: Molecular and Cellular Endocrinology (2013), 377(1-2), 1-6
CODEN: MCEND6; ISSN: 0303-7207
DIGITAL OBJECT ID: 10.1016/j.mce.2013.06.025
PUBLISHER: Elsevier Ireland Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB RET kinase is aberrantly activated in thyroid cancers and in rare cases of lung and colon cancer, and has been validated as a mol. target in these tumors. Vandetanib was recently approved for the treatment of medullary thyroid cancer. However, vandetanib is ineffective in vitro against RET mutants carrying bulky aminoacids at position 804, the gatekeeper residue, similarly to drug-resistant BCR-ABL mutants in chronic myeloid leukemia. Ponatinib is a multi-target kinase inhibitor that was recently approved for treatment-refractory Philadelphia-pos. leukemia. We show here potent inhibition of oncogenic RET by ponatinib, including the drug-insensitive V804M/L mutants. Ponatinib inhibited the growth of RET+ and BCR-ABL+ cells with similar potency, while not affecting RET-neg. cells. Both in biochem. and in cellular assays ponatinib compared favorably with known RET inhibitors, such as vandetanib, cabozantinib, sorafenib, sunitinib and motesanib, used as reference compds. We suggest that ponatinib should be considered for the treatment of RET+ tumors, in particular those expressing vandetanib-resistant V804M/L mutations.
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(multi-target tyrosine kinase inhibitor ponatinib exposure inhibited both wild-type and drug-resistant gatekeeper mutant RET kinase activity and inhibited growth of RET+ and BCR-ABL+ human cancer but not RET-cancer or normal cell)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

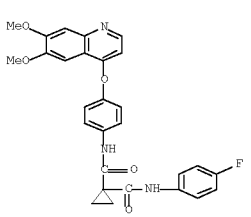


OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 77 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:1254595 CAPLUS Full-text
DOCUMENT NUMBER: 159:353569
TITLE: Combination therapy comprising selective VEGFR-2 inhibitors and MEK inhibitors
PATENT ASSIGNEE(S): Max-Planck-Gesellschaft zur Foerderung der Wissenschaften e.V., Germany
SOURCE: Eur. Pat. Appl., 106pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 2626066 | A1 | 20130814 | EP 2012-154880 | 20120210 |
| R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME | | | | |
| PRIORITY APPLN. INFO.: | | | EP 2012-154880 | 20120210 |

AB The present invention relates to a combination therapy comprising selective inhibitors of vascular endothelial growth factor receptor-2 (VEGFR-2) tyrosine kinase and inhibitors of MAP kinase kinase (MEK). Accordingly, a pharmaceutical composition is provided that comprises a selective inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2) tyrosine kinase or a pharmaceutically acceptable salt, solvate and/or hydrate thereof, and an inhibitor or a pharmaceutically acceptable salt, solvate and/or hydrate thereof, for use in medicine, especially in the treatment of cancer, like lung cancer, such as non-small cell lung cancer, lung adenocarcinoma or small cell lung cancer. Also a method for identifying patients that are particularly susceptible to such a combination therapy is subject of the present invention. The method comprises the evaluation of the expression level of VEGFR-2 and/or VEGF. An increase in said expression level indicates susceptibility to the combination therapy.
IT 849217-68-1, Cabozantinib
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy comprising selective VEGFR-2 inhibitors and MEK inhibitors)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 78 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:1227139 CAPLUS Full-text
DOCUMENT NUMBER: 159:329544

TITLE: Methods for predicting tumor response to targeted therapies with signal transduction pathway inhibitors using biomarkers
INVENTOR(S): Cohen, Jonathan M.; Derrien-Colemyn, Alexandrine Josephe; Gillespie, John Williams; Park, Soon Sik
PATENT ASSIGNEE(S): 20/20 Gene Systems, Inc., USA
SOURCE: PCT Int. Appl., 146pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

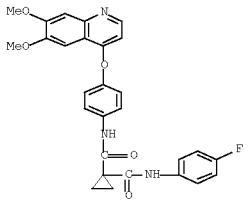
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2013116735 | A1 | 20130808 | WO 2013-US24456 | 20130201 |

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.:

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| US 2012-61593688 | P | 20120201 |
| US 2012-61654400 | P | 20120601 |
| US 2012-61660305 | P | 20120615 |
| US 2012-660692P | P | 20120616 |
| US 2012-61665943 | P | 20120629 |
| US 2012-61699760 | P | 20120911 |
| US 2012-61699874 | P | 20120912 |

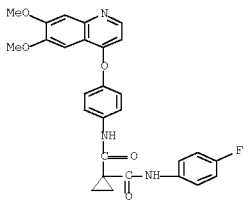
AB A method for identifying cancer patients that are likely to be responders or non-responders to a signal transduction pathway inhibitor is described. The present invention is directed to methods and tests that help predict the likelihood that a tumor will respond to a targeted therapy so that those cancer patients most likely to benefit can receive that drug in a timely manner and those patients unlikely to benefit from a particular drug can instead be prescribed alternative therapies. The test comprises a panel of two or more biomarkers that are part of a signal transduction pathway. The biomarkers included in the panel, in combination, express differently in tumors that respond the drug from those that do not respond. The drugs to which these tests predict response may be designed or determined to target the signal transduction pathway of which the biomarker panel is associated Examples of such drugs are those that target angiogenesis pathways like VEGF or cellular growth pathways like mTOR. Alternatively, the drugs might target something other than the pathway with which the biomarkers are associated but activation of that pathway might otherwise limit or defeat the effectiveness of that drug. Examples of such drugs are those that block cellular receptors but for which activation of downstream signaling pathways nevertheless maintains cellular growth.
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for predicting tumor response to targeted therapies with signal transduction pathway inhibitors using biomarkers)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 79 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:1191423 CAPLUS Full-text
DOCUMENT NUMBER: 159:508181
TITLE: Cabozantinib (XL184) for the treatment of locally advanced or metastatic progressive medullary thyroid cancer
AUTHOR(S): Viola, David; Cappagli, Virginia; Elisei, Rossella
CORPORATE SOURCE: Endocrinology Unit, Department of Clinical & Experimental Medicine, WHO Collaborating Center for the Study & Treatment of Thyroid Diseases & other Endocrine & Metabolic Disorders, University of Pisa, Via Paradisa 2, Pisa, 56124, Italy
SOURCE: Future Oncology (2013), 9(8), 1083-1092
CODEN: FOUNBN; ISSN: 1479-6694
DIGITAL OBJECT ID: 10.2217/fon.13.128
PUBLISHER: Future Medicine Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English

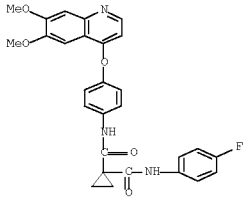
AB A review. Cabozantinib (XL184) is an oral multiple receptor tyrosine kinase inhibitor manufactured by Exelixis Inc., CA, USA. It mainly inhibits three tyrosine kinase receptors: MET, VEGFR2 and RET. In both preclin. and clin. studies it has been shown to inhibit tumor angiogenesis, invasiveness and metastases. The most frequent side effects are fatigue, diarrhea, decreased appetite, nausea, weight loss and palmar-plantar erythrodysesthesia. A Phase III clin. trial (EXAM study) of XL184 vs. placebo in advanced and progressive medullary thyroid cancer showed a 28 vs. 0% overall response rate and a progression-free survival of 11.2 vs. 4.0 mo (hazard ratio: 0.28; 95% CI: 0.19-0.40; p < 0.0001) in patients treated with cabozantinib and placebo, resp. The drug has been approved by the US FDA for the treatment of advanced/progressive metastatic medullary thyroid cancer in the USA. The EMA is now evaluating its approval in Europe.
IT 849217-68-1, Cabozantinib
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cabozantinib for treatment of locally advanced or metastatic progressive medullary thyroid cancer)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 80 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:1087476 CAPLUS Full-text
DOCUMENT NUMBER: 159:649618
TITLE: The novel c-Met inhibitor cabozantinib overcomes gemcitabine resistance and stem cell signaling in pancreatic cancer
AUTHOR(S): Hage, C.; Rausch, V.; Giese, N.; Giese, T.; Schoensiegel, F.; Labsch, S.; Nwaeburu, C.; Mattern, J.; Gladkich, J.; Herr, I.
CORPORATE SOURCE: Department of Experimental Medicine, Molecular OncoSurgery Group, University of Heidelberg and German Cancer Research Center, Heidelberg, Germany
SOURCE: Cell Death & Disease (2013), 4(May), e627
CODEN: CDDEA4; ISSN: 2041-4889
DIGITAL OBJECT ID: 10.1038/cddis.2013.158
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB Pancreatic ductal adenocarcinoma (PDA) is one of the most lethal malignancies. Cancer stem cells (CSCs), which are not targeted by current therapies, may be the reason for pronounced therapy resistance. A new treatment option in phase II trials is cabozantinib that inhibits the pancreatic CSC surface marker and tyrosine kinase receptor c-Met. The purpose of this study was to evaluate the effect of cabozantinib to stem-like features and therapy resistance. Established PDA cell lines, a gemcitabine-resistant subclone, non-malignant pancreatic ductal cells and primary spheroidal cultures from patient tumors were analyzed by MTT-assay, flow cytometry, colony and spheroid formation assays, western blotting, qRT-PCR, antibody protein array, immunohistochem. and morphol. features. Cabozantinib inhibited viability and spheroid formation and induced apoptosis in malignant cells with minor effects in non-malignant cells. After long-term cabozantinib treatment, PDA cells had altered anti- and pro-apoptotic signaling, but still responded to cabozantinib, as apoptosis only slightly decreased and viability only slightly increased suggesting a low resistance-inducing potential of cabozantinib. In parallel, c-Met expression and the pluripotency transcription factor SOX2 were downregulated, which might counteract development of full therapy resistance in long-term treated subclones. In single-treatment studies, cabozantinib increased efficacy of gemcitabine. Most importantly, cabozantinib strongly induced apoptosis and reduced viability in PDA cell lines, which are completely resistant toward gemcitabine. In primary, CSC-enriched spheroidal cultures cabozantinib downregulated CSC markers SOX2, c-Met and CD133 and induced apoptosis. These findings suggest that the clin. use of cabozantinib may be more effective than current chemotherapeutics.
IT 849217-68-1
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel c-mesenchymal-epithelial transition factor inhibitor cabozantinib overcomes gemcitabine resistance and stem cell signaling in pancreatic cancer)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

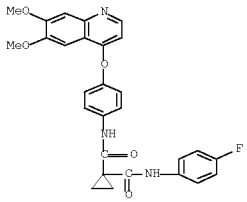
L4 ANSWER 81 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:948019 CAPLUS Full-text
DOCUMENT NUMBER: 159:312293

TITLE: Drug monographs: cabozantanib and omacetaxine
AUTHOR(S): Solimando, Dominic A., Jr.; Ho, Kristin V.; Waddell, J. Aubrey
CORPORATE SOURCE: Walter Reed National Military Medical Center, Bethesda, MD, USA
SOURCE: Hospital Pharmacy (2013), 48(5), 373-377
CODEN: HOPHAZ; ISSN: 0018-5787
DIGITAL OBJECT ID: 10.1310/hpj4805-373
PUBLISHER: Thomas Land Publishers, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The complexity of cancer chemotherapy requires pharmacists be familiar with the complicated regimens and highly toxic agents used. This column reviews various issues related to preparation, dispensing, and administration of antineoplastic therapy, and the agents, both com. available and investigational, used to treat malignant diseases. Questions or suggestions for topics should be addressed to Dominic A. Solimando, Jr, President, Oncol. Pharmacy Services, Inc, 4201 Wilson Blvd #110-545, Arlington, VA 22203, e-mail: OncRxSvc@aol.com; or J. Aubrey Waddell, Professor, University of Tennessee College of Pharmacy; Oncol. Pharmacist, Pharmacy Department, Blount Memorial Hospital, 907 E. Lamar Alexander Parkway, Maryville, TN 37804, e-mail: waddfour@charter.net.

IT 849217-68-1, Cabozantinib
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug monographs of cabozantinib and omacetaxine)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 82 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:909480 CAPLUS Full-text
DOCUMENT NUMBER: 159:736844
TITLE: Prostate cancer progression after androgen deprivation therapy: mechanisms of castrate resistance and novel therapeutic approaches
AUTHOR(S): Karantanos, T.; Corn, P. G.; Thompson, T. C.
CORPORATE SOURCE: Department of Genitourinary Medical Oncology-Research, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
SOURCE: Oncogene (2013), 32(49), 5501-5511
CODEN: ONCNES; ISSN: 0950-9232
DIGITAL OBJECT ID: 10.1038/onc.2013.206
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English

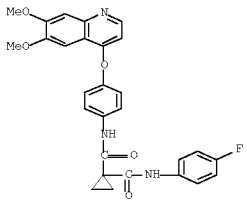
AB A review. Prostate cancer is the second-leading cause of cancer-related mortality in men in Western societies. Androgen receptor (AR) signaling is a critical survival pathway for prostate cancer cells, and androgen-deprivation therapy (ADT) remains the principal treatment for patients with locally advanced and metastatic disease. Although a majority of patients initially respond to ADT, most will eventually develop castrate resistance, defined as disease progression despite serum testosterone levels of <20 ng/dL. The recent discovery that AR signaling persists during systemic castration via intratumoral production of androgens led to the development of novel anti-androgen therapies including abiraterone acetate and enzalutamide. Although these agents effectively palliate symptoms and prolong life, metastatic castration-resistant prostate cancer remains incurable. An increased understanding of the mechanisms that underlie the pathogenesis of castrate resistance is therefore needed to develop novel therapeutic approaches for this disease. The aim of this review is to summarize the current literature on the biol. and treatment of castrate-resistant prostate cancer.

IT 1140909-48-3, XL184
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Cabozantinib; prostate cancer progression after androgen deprivation therapy in relation to mechanisms of castrate resistance and novel therapeutic approaches)

RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

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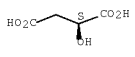
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



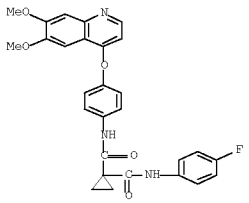
OS.CITING REF COUNT: 12 THERE ARE 12 CAPLUS RECORDS THAT CITE THIS RECORD (12 CITINGS)
REFERENCE COUNT: 158 THERE ARE 158 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 83 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:907853 CAPLUS Full-text
DOCUMENT NUMBER: 160:94029
TITLE: Response to Cabozantinib in Patients with RET Fusion-Positive Lung Adenocarcinomas
AUTHOR(S): Drilon, Alexander; Wang, Lu; Hasanovic, Adnan; Suehara, Yoshiyuki; Lipson, Doron; Stephens, Phil; Ross, Jeffrey; Miller, Vincent; Ginsberg, Michelle; Zakowski, Maureen F.; Kris, Mark G.; Ladanyi, Marc; Rizvi, Naiyer
CORPORATE SOURCE: Department of Medicine Thoracic Oncology Service, Lenox Hill Hospital, New York, NY, USA
SOURCE: Cancer Discovery (2013), 3(6), 630-635
CODEN: CDAIB2; ISSN: 2159-8274
DIGITAL OBJECT ID: 10.1158/2159-8290.CD-13-0035
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The discovery of RET fusions in lung cancers has uncovered a new therapeutic target for patients whose tumors harbor these changes. In an unselected population of non-small cell lung carcinomas (NSCLCs), RET fusions are present in 1%to2% of cases. This incidence increases substantially, however, in never-smokers with lung adenocarcinomas that lack other known driver oncogenes. Although preclin. data provide exptl. support for the use of RET inhibitors in the treatment of RET fusion-pos. tumors, clin. data on response are lacking. We report preliminary data for the first three patients treated with the RET inhibitor cabozantinib on a prospective phase II trial for patients with RET fusion-pos. NSCLCs (NCT01639508). Confirmed partial responses were observed in 2 patients, including one harboring a novel TRIM33-RET fusion. A third patient with a KIF5B-RET fusion has had prolonged stable disease approaching 8 mo (31 wk). All three patients remain progression-free on treatment.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(response to cabozantinib in patients with RET fusion-pos. lung adenocarcinomas)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 23 THERE ARE 23 CAPLUS RECORDS THAT CITE THIS RECORD (23 CITINGS)
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 84 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:884114 CAPLUS Full-text
DOCUMENT NUMBER: 161:430953
TITLE: Tumour angiogenesis: an elusive target in castration-resistant prostate cancer
AUTHOR(S): Galsky, Matthew D.; Oh, William K.
CORPORATE SOURCE: The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, 10029, USA
SOURCE: Lancet Oncology (2013), 14(8), 681-682
CODEN: LOANBN; ISSN: 1470-2045
DIGITAL OBJECT ID: 10.1016/S1470-2045(13)70239-0
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal; (online computer file)

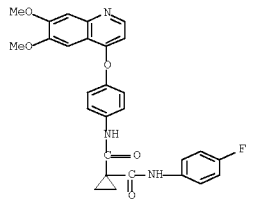
LANGUAGE: English

AB In this article, tumor angiogenesis an attractive target in castration-resistant prostate cancer is studied. Indeed, impressive single-agent activity has been reported with cabozantinib, a small mol. inhibitor of the tyrosine kinases MET and VEGFR2. The author reports on randomly allocated 1050 patients with castration-resistant prostate cancer to treatment with docetaxel plus prednisone with or without bevacizumab-the median overall survival for patients receiving bevacizumab was 22.6 mo compared with 21.5 mo for patients treated with placebo (hazard ratio 0.91, 95% CI 0.78-1.05; stratified log-rank p=0.181).

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(study on tumor angiogenesis as elusive target in castration-resistant prostate cancer)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 85 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2013:882495 CAPLUS Full-text

DOCUMENT NUMBER: 159:68803

TITLE: Targeting microRNA's miR-409-5p, miR-379 and miR-154* to treat prostate cancer bone metastasis and drug resistant lung cancer

INVENTOR(S): Chung, Leland W. K.; Josson, Sajni; Gururajan, Murali; Jain, Anjali

PATENT ASSIGNEE(S): Cedars-Sinai Medical Center, USA

SOURCE: PCT Int. Appl., 79pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

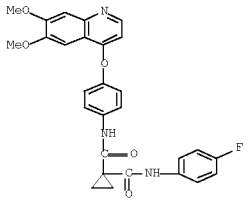
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 2013082499 | A1 | 20130606 | WO 2012-US67403 | 20121130 |
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| AU 2012345666 | A1 | 20140619 | AU 2012-345666 | 20121130 |
| CN 104080461 | A | 20141001 | CN 2012-80067969 | 20121130 |
| PRIORITY APPLN. INFO.: | | | US 2011-61565226 P | 20111130 |
| | | | WO 2012-US67403 W | 20121130 |

AB The present invention describes methods of treating cancer, cancer metastasis, and drug resistant cancers using miRNA inhibitors; for example, inhibitors of miR-409-5p. Also described are methods of using the miRNA as biomarkers; for example, to predict responsiveness to a cancer drug, to detect a disease state of cancer.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeting microRNA's to treat prostate cancer bone metastasis and drug resistant lung cancer and combination with other treatments and use of microRNA's as biomarkers)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 86 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2013:873882 CAPLUS Full-text

DOCUMENT NUMBER: 159:100783

TITLE: Medical combination containing hepatocyte growth factor receptor inhibitor and Bcl-2 inhibitor for treating cancer

INVENTOR(S): Zhao, Lei; Wang, Limei

PATENT ASSIGNEE(S): Beijing Tianhe Ruitong Technology Development Co., Ltd., Peop. Rep. China

SOURCE: Faming Zhuanli Shenqing, 25pp.
CODEN: CNXXEV

DOCUMENT TYPE: Patent

LANGUAGE: Chinese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

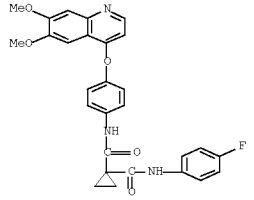
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| CN 103127510 | A | 20130605 | CN 2011-10389330 | 20111130 |
| PRIORITY APPLN. INFO.: | | | CN 2011-10389330 | 20111130 |

AB The title medical combination comprises a hepatocyte growth factor receptor (cMet) inhibitor and a Bcl-2 inhibitor. The medical combination can be used for preparing a drug for treating colon cancer, liver cancer, lung cancer, renal cancer, gastric cancer, brain tumor, sarcoma, neurospongioma, pancreas cancer, ovarian cancer or prostatic cancer. The medical combination has the advantages of good synergistic effects, high effects, low administration dosage and low side effects.

IT 849217-68-1
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(medical combination containing hepatocyte growth factor receptor inhibitor and Bcl-2 inhibitor for treating cancer)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L4 ANSWER 87 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2013:869127 CAPLUS Full-text

DOCUMENT NUMBER: 159:436784

TITLE: A Dose-Ranging Study of Cabozantinib in Men with Castration-Resistant Prostate Cancer and Bone Metastases

AUTHOR(S): Lee, Richard J.; Saylor, Philip J.; Dror Michaelson, M.; Michael Rothenberg, S.; Smas, Malgorzata E.; Miyamoto, David T.; Gurski, Carol A.; Xie, Wanling; Maheswaran, Shyamala; Haber, Daniel A.; Goldin, Jonathan G.; Smith, Matthew R.

CORPORATE SOURCE: Massachusetts General Hospital Cancer Center, Boston, MA, USA

SOURCE: Clinical Cancer Research (2013), 19(11), 3088-3094
CODEN: CCREF4; ISSN: 1078-0432

DIGITAL OBJECT ID: 10.1158/1078-0432.CCR-13-0319

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

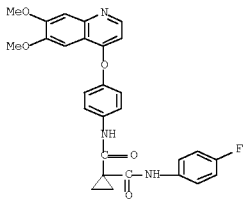
LANGUAGE: English

AB Background: Cabozantinib is an oral MET/VEGFR2 inhibitor. A recent phase II study of cabozantinib (100 mg daily) showed improved bone scans in subjects with metastatic castration-resistant prostate cancer (mCRPC), but adverse events (AE) caused frequent dose redns. This study was designed to determine the efficacy and tolerability of cabozantinib at lower starting doses. Exptl. Design: An adaptive design was used to determine the lowest active daily dose among 60, 40, and 20 mg. The primary endpoint was week 6 bone scan response, defined as ≥30% decrease in bone scan lesion area. The secondary endpoint was change in circulating tumor cells (CTC). Results: Among 11 evaluable subjects enrolled at 40 mg, there were 9 partial responses (PR), 1 complete response, and 1 stable disease (SD). Of 10 subjects subsequently enrolled at 20 mg, there were 1 PR, 5 SDs, and 4 with progressive disease. Among 13 subjects enrolled on the 40 mg expansion cohort, there were 6 PRs and 7 SDs. No subjects required dose reduction or treatment interruption at 6 or 12 wk; 3 subjects at dose level 0 discontinued due to AEs by 12 wk. At 40 mg, median treatment duration was 27 wk. 58% of subjects with ≥5 CTCs/7.5mL at baseline converted to <5. Conclusions: Cabozantinib 40 mg daily was associated with a high rate of bone scan response. Cabozantinib 40 mg daily was associated with better tolerability than previously reported for cabozantinib 100 mg daily. These observations informed the design of phase III studies of cabozantinib in mCRPC. Clin Cancer Res; 19(11); 3088-94. ©2013 AACR.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dose-ranging study of cabozantinib in men with castration-resistant prostate cancer and bone metastases)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

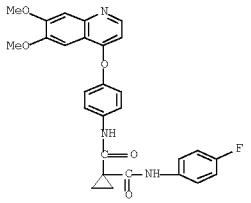


OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 88 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:847461 CAPLUS Full-text
DOCUMENT NUMBER: 159:357745
TITLE: The antiangiogenic ceiling in hepatocellular carcinoma: does it exist and has it been reached?
AUTHOR(S): Abou-Alfa, Ghassan K.; Venook, Alan P.
CORPORATE SOURCE: Section of Gastrointestinal Oncology, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
SOURCE: Lancet Oncology (2013), 14(7), e283-e288
CODEN: LOANBN; ISSN: 1470-2045
DIGITAL OBJECT ID: 10.1016/S1470-2045(13)70161-X
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English

AB A review. The recommendation of sorafenib as std. of care in advanced hepatocellular carcinoma has lent support to the increased use of antiangiogenic therapies. However, in three phase 3 randomised trials that compared other antiangiogenics with sorafenib, results did not show superiority or non-inferiority of the new therapies. The 10-mo median overall survival shown in these studies for patients given sorafenib might be a ceiling for single-agent antiangiogenic therapy. Strategies to increase survival time include combination therapies that pair antiangiogenic treatment with biol. therapy or chemotherapy. The combination of sorafenib and erlotinib was not superior to sorafenib alone, which suggests no pos. interaction between antiangiogenics and tyrosine kinase inhibitors in the treatment of advanced hepatocellular carcinoma. A combination of sorafenib and doxorubicin is being assessed in a randomised phase 3 trial. Differences in patient outcome with sorafenib because of disease cause and the ethnic origin of patients suggest that sorafenib's multitarget capacity, including RAF kinase inhibition, might be important. MET inhibitors cabozantinib and tivantinib are drugs that might also bypass the so-called antiangiogenic ceiling and have led to selective treatment of patients that overexpress MET with these drugs. Although this intense period of research activity has not yet resulted in significant improvements in survival for patients with advanced hepatocellular carcinoma, we are certainly closer to a customised treatment, which should increase the antiangiogenic survival ceiling.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(MET inhibitors cabozantinib and tivantinib may be useful in treatment of patient with hepatocellular carcinoma)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 89 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:761990 CAPLUS Full-text
DOCUMENT NUMBER: 158:704608
TITLE: Method of quantifying cancer treatment
INVENTOR(S): Holland, Jaymes
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 50pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2013070903 | A1 | 20130516 | WO 2012-US64134 | 20121108 |

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK,

SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

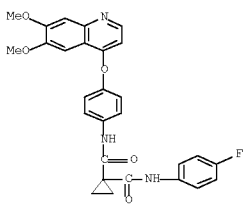
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|---|---|---|---|---|
| CA 2854664 | A1 | 20130516 | CA 2012-2854664 | 20121108 |
| AU 2012335750 | A1 | 20140605 | AU 2012-335750 | 20121108 |
| AR 88813 | A1 | 20140710 | AR 2012-104223 | 20121108 |
| CN 104039226 | A | 20140910 | CN 2012-80066413 | 20121108 |
| EP 2775921 | A1 | 20140917 | EP 2012-795939 | 20121108 |

R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME

PRIORITY APPLN. INFO.: US 2011-61557362 P 20111108
WO 2012-US64134 W 20121108
OTHER SOURCE(S): CASREACT 158:704608

AB This invention is directed to a method for quantifying cancer treatment response in patients with bone metastases using computer aided bone scan assessment, comprising: (a) obtaining a bone scan image; (b) normalizing the obtained bone scan image to identify normalized bone scan lesions; and (c) quant. assessing the normalized bone scan lesions using bone scan lesion area, bone scan intensity, or bone scan lesion count.

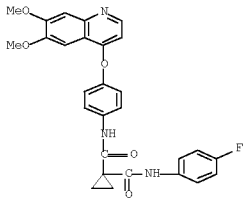
IT 849217-68-1
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(quantifying cancer treatment)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



IT 1140909-48-3
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(quantifying cancer treatment)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

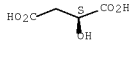
CRN 849217-68-1
CMF C28 H24 F N3 O5



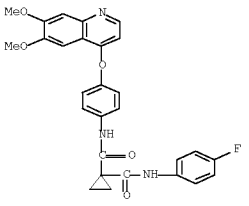
CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(quantifying cancer treatment)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

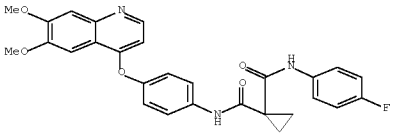


REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 90 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:761969 CAPLUS Full-text
DOCUMENT NUMBER: 158:704607
TITLE: Dual inhibitor of Met and VEGF for treating cancer
INVENTOR(S): Aftab, Dana T.; Schimmoller, Frauke
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 56pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2013070890 | A1 | 20130516 | WO 2012-US64116 | 20121108 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM | | | | |
| CA 2854336 | A1 | 20130516 | CA 2012-2854336 | 20121108 |
| AU 2012335737 | A1 | 20140605 | AU 2012-335737 | 20121108 |
| IL 232421 | A | 20140630 | IL 2012-232421 | 20121108 |
| KR 2014088610 | A | 20140710 | KR 2014-7015127 | 20121108 |
| EP 2776033 | A1 | 20140917 | EP 2012-787328 | 20121108 |
| R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME | | | | |

PRIORITY APPLN. INFO.: US 2011-61557358 P 20111108
WO 2012-US64116 W 20121108
OTHER SOURCE(S): CASREACT 158:704607; MARPAT 158:704607
GI

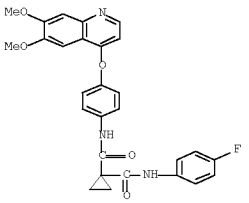


AB This invention is directed to the treatment of cancer, particularly castration-resistant prostate cancer and bone metastases, with a dual inhibitor of MET and VEGF.

IT 849217-68-1

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(dual inhibitor of Met and VEGF for treating cancer)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



IT 1140909-48-3

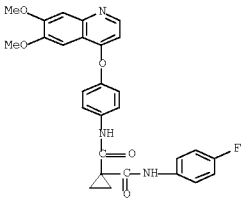
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(dual inhibitor of Met and VEGF for treating cancer)

RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with

N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

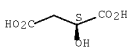
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

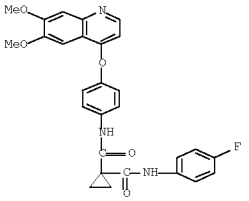
Absolute stereochemistry. Rotation (-).



IT 849217-68-1, Cabozantinib 1365530-43-3

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dual inhibitor of Met and VEGF for treating cancer)

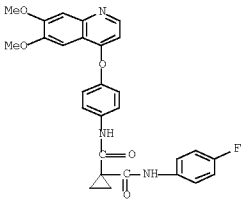
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



RN 1365530-43-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

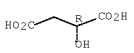
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 636-61-3
CMF C4 H6 O5

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 91 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:729332 CAPLUS Full-text
DOCUMENT NUMBER: 158:676742
TITLE: Fusion proteins with a C-terminal domain of the gene ret receptor and their use in cancer diagnosis
INVENTOR(S): Ju, Young-Seok; Seo, Jeong-Sun; Kim, Kun-Hee
PATENT ASSIGNEE(S): Macrogen Inc., S. Korea
SOURCE: U.S. Pat. Appl. Publ., 61pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 20130116280 | A1 | 20130509 | US 2012-13663565 | 20121030 |
| WO 2013066047 | A1 | 20130510 | WO 2012-KR9056 | 20121031 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
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| KR 2014092846 | A | 20140724 | KR 2014-7013826 | 20121031 |
| EP 2773673 | A1 | 20140910 | EP 2012-845116 | 20121031 |
| R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR | | | | |

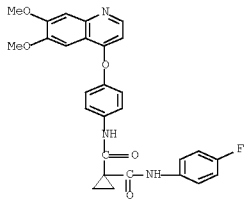
PRIORITY APPLN. INFO.: US 2011-61553483 P 20111031
US 2012-13663565 A 20121030
WO 2012-KR9056 W 20121031

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB A fusion protein including N-terminal domain of a fusion partner at N-terminal and C-terminal domain of RET protein at C-terminal and the gene encoding are identified as diagnostic markers for cancers, especially lung cancers. The somatic mutation forming the chimeric gene was identified in a poorly differentiated lung adenocarcinoma. The adenocarcinoma did not show any of the most common lung cancer-associated mutations, but several discordant reads, indicating transposition events, were identified. Expression of the chimeric KIF5B-RET gene in NIH-3T3 resulted in a neoplastic phenotype. Growth of these cells could be inhibited by the ret kinase inhibitor cabozantinib.

IT 849217-68-1
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as inhibitor of ret receptor fusion protein in cancer therapy; fusion proteins with C-terminal domain of gene ret receptor and their use in cancer diagnosis)

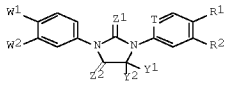
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L4 ANSWER 92 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:728614 CAPLUS Full-text
DOCUMENT NUMBER: 158:672026
TITLE: Methods using heteroaryl compounds for treatment of disorders involving androgen-, estrogen- and progesterone-receptors
INVENTOR(S): Protter, Andrew A.; Hung, David T.; Chakravarty, Sarvajit; Bernales, Sebastian
PATENT ASSIGNEE(S): Medivation Technologies, Inc., USA
SOURCE: PCT Int. Appl., 69pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2013067131 | A1 | 20130510 | WO 2012-US62980 | 20121101 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, | | | | |

SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM
PRIORITY APPLN. INFO.: US 2011-61554919 P 20111102
OTHER SOURCE(S): MARPAT 158:672026
GI

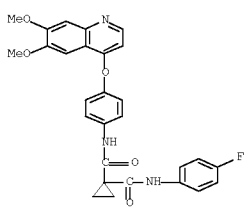


I

AB The disclosure describes compds. of formula I [W1 = CN, NO2, SO2R4; W2 = alkyl, alkenyl, alkynyl, halo; Z1 = S, O; Z2 = S, O, NR4; R4 = independently H, alkyl, aryl; Y1, Y2 = independently H, alkyl, alkenyl, aryl, arylalkyl, heterocyclic etc.; R1 = alkyl, cycloalkyl, heterocyclic etc.; R2 = independently H, halo, CN, alkyl etc.], or pharmaceutically acceptable salts thereof, useful for treating disorders involving androgen, estrogen, and/or progesterone receptors. In another embodiment of the invention the disorder is selected from the group consisting of neurodegenerative disorders, cancer, polyglutamate disease, rheumatoid arthritis, systemic hyperandrogenism, seborrhea, hirsutism, precocious puberty, polycystic ovary syndrome, acne, alopecia, benign prostatic hyperplasia, intrauterine fibroids, endometriosis, glaucoma, meningiomas, Kennedy's disease (KD) or X-linked spinal and bulbar muscular atrophy.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods using heteroaryl compds. for treatment of disorders involving androgen-, estrogen- and progesterone-receptors)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 93 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:725439 CAPLUS Full-text
DOCUMENT NUMBER: 158:676739
TITLE: Fusion proteins with a C-terminal domain of the gene ret receptor and their use in cancer diagnosis
INVENTOR(S): Ju, Young-Seok; Seo, Jeong-Sun; Kim, Eun-Hee
PATENT ASSIGNEE(S): Macrogen Inc., S. Korea
SOURCE: PCT Int. Appl., 67pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2013066047 | A1 | 20130510 | WO 2012-KR9056 | 20121031 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM | | | | |
| US 20130116280 | A1 | 20130509 | US 2012-13663565 | 20121030 |
| KR 2014092846 | A | 20140724 | KR 2014-7013826 | 20121031 |
| EP 2773673 | A1 | 20140910 | EP 2012-845116 | 20121031 |
| R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR | | | | |

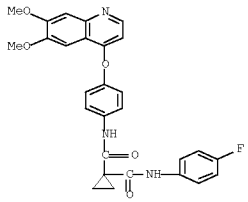
PRIORITY APPLN. INFO.: US 2011-61553483 P 20111031
US 2012-13663565 A 20121030
WO 2012-KR9056 W 20121031

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB A fusion protein including N-terminal domain of a fusion partner at N-terminal and C-terminal domain of RET protein at C-terminal and the gene encoding are identified as diagnostic markers for cancers, especially lung cancers. The somatic mutation forming the chimeric gene was identified in a poorly differentiated lung adenocarcinoma. The adenocarcinoma did not show any of the most common lung cancer-associated mutations, but several discordant reads, indicating transposition events, were identified. Expression of the chimeric KIF5B-RET gene in NIH-3T3 resulted in a neoplastic phenotype. Growth of these cells could be inhibited by the ret kinase inhibitor cabozantinib.

IT 849217-68-1
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as inhibitor of ret receptor fusion protein in cancer therapy; fusion proteins with C-terminal domain of gene ret receptor and their use in

cancer diagnosis)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

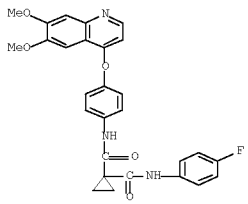


OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 94 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:684015 CAPLUS Full-text
DOCUMENT NUMBER: 158:649640
TITLE: Free prostate specific antigen (PSA) antibodies as diagnostics, prognostics and therapeutics for prostate cancer
INVENTOR(S): Sawyers, Charles; Ulmert, David; Lewis, Jason; Evans, Michael; Lija, Hans
PATENT ASSIGNEE(S): Memorial Sloan-Kettering Cancer Center, USA
SOURCE: PCT Int. Appl., 103pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2013063312 | A1 | 20130502 | WO 2012-US61982 | 20121025 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM | | | | |
| CA 2853705 | A1 | 20130502 | CA 2012-2853705 | 20121025 |
| AU 2012328679 | A1 | 20140612 | AU 2012-328679 | 20121025 |
| EP 2771688 | A1 | 20140903 | EP 2012-844178 | 20121025 |
| R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR | | | | |
| CN 104040341 | A | 20140910 | CN 2012-80063852 | 20121025 |
| PRIORITY APPLN. INFO.: | | | US 2011-61551195 P | 20111025 |
| | | | WO 2012-US61982 W | 20121025 |

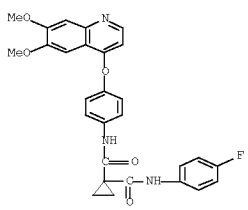
AB The authors disclose the use of antibodies to free prostate-specific antigen (fPSA) in the diagnosis, prognosis, and therapeutic monitoring of prostate cancer. In one example, tumor localization of labeled anti-fPSA antibody is shown to be reduced by the antiandrogen MDV3100.
IT 849217-68-1, Cabozantinib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antibodies to free PSA antigen therapy monitoring of)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 95 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:647172 CAPLUS Full-text
DOCUMENT NUMBER: 159:188392
TITLE: Emerging targeted therapies for castration-resistant prostate cancer
AUTHOR(S): Adamo, Vincenzo; Noto, Laura; Franchina, Tindara; Chiofalo, Giuseppe; Picciotto, Maria; Toscano, Giuseppe; Caristi, Nicola
CORPORATE SOURCE: Integrated Therapies in Oncology Unit, Department of Human Pathology, University of Messina, Messina, 98125, Italy
SOURCE: Frontiers in Cancer Endocrinology (2012), 3(May), 73
CODEN: FCERD9

DIGITAL OBJECT ID: 10.3389/fendo.2012.00073
PUBLISHER: Frontiers Media S.A.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
AB A review. Until recently, few therapeutic options were available for patients with castration-resistant prostate cancer (CRPC). Since 2010, four new mols. with a demonstrated benefit (sipuleucel-T, cabazitaxel, abiraterone and denosumab) have been approved in this setting and to-date several other agents are under investigation in clin. trials. The purpose of this review is to present an update of targeted therapies for CRPC. Presented data are obtained from literature and congress reports updated until Dec. 2011. Targeted therapies in advanced phases of clin. development include novel androgen signaling inhibitors, inhibitors of alternative signaling pathways, anti-angiogenic agents, inhibitors that target the bone microenvironment and immunotherapeutic agents. Radium-223 and MDV3100 demonstrated a survival advantage in phase III trials and the road for their introduction in clin. practice is rapidly ongoing. Results are also awaited for phase III studies currently underway or planned with new drugs given as monotherapy (TAK-700, cabozantinib, tasquinimod, PROSTVAC-VF, ipilimumab) or in combination with docetaxel (custirsen, aflibercept, dasatinib, zibotentan). The optimal timing, combination and sequencing of emerging therapies remain unknown and require further investigation. Addnl., the identification of novel markers of response and resistance to these therapies may better individualize treatment for patients with CRPC.
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(emerging targeted therapies for castration-resistance prostate cancer)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

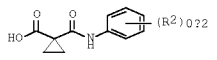


OS.CITING REF COUNT: 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)
REFERENCE COUNT: 98 THERE ARE 98 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

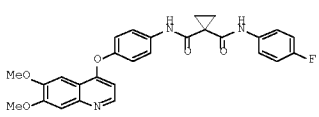
L4 ANSWER 96 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:644308 CAPLUS Full-text
DOCUMENT NUMBER: 158:620790
TITLE: Process for preparing quinoline derivatives
INVENTOR(S): Wilson, Jo Ann; Naganathan, Sriram; Pfeiffer, Matthew; Andersen, Neil G.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 47pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2013059788 | A1 | 20130425 | WO 2012-US61320 | 20121022 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM | | | | |
| CA 2852771 | A1 | 20130425 | CA 2012-2852771 | 20121022 |
| AU 2012325768 | A1 | 20140522 | AU 2012-325768 | 20121022 |
| IL 232139 | A | 20140528 | IL 2012-232139 | 20121022 |
| AR 88483 | A1 | 20140611 | AR 2012-103944 | 20121022 |
| KR 2014088874 | A | 20140711 | KR 2014-7012435 | 20121022 |
| EP 2768796 | A1 | 20140827 | EP 2012-783763 | 20121022 |
| R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME | | | | |
| US 20140256938 | A1 | 20140911 | US 2014-14353251 | 20140421 |
| PRIORITY APPLN. INFO.: | | | US 2011-61549312 P | 20111020 |
| | | | WO 2012-US61320 W | 20121022 |
| OTHER SOURCE(S): | | | CASREACT 158:620790; MARPAT 158:620790 | |

GI



I



II

AB The invention is directed to processes for prepg. compds. of formula I (R2 is H, F, Cl and Br) by activation of 1,1-cyclopropanedicarboxylic acid with thionyl chloride followed by amidation with substituted aniline derivative Example compound II L-malate was prepared by chlorination of 6,7-dimethoxyquinolin-4-ol followed by etherification of 4-chloro-6,7-dimethoxyquinoline with 4-aminophenol; the resulting 4-(6,7-dimethoxyquinolin-4-yloxy)phenylamine underwent acylation with 1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl chloride to give compound II, which underwent addition of L-malic acid to give the desired product.

IT 1140909-48-3P

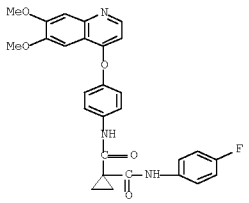
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(process for preparing quinoline derivs.)

RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

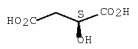
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

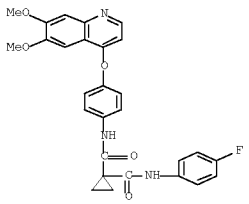


IT 849217-68-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing quinoline derivs.)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 97 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2013:564369 CAPLUS Full-text

DOCUMENT NUMBER: 159:419448

TITLE: Lessons learned and questions unanswered from use of multitargeted kinase inhibitors in medullary thyroid cancer

AUTHOR(S): Sherman, Steven I.

CORPORATE SOURCE: Department of Endocrine Neoplasia and Hormonal Disorders, University of Texas M.D. Anderson Cancer Center, Houston, TX, 77030, USA

SOURCE: Oral Oncology (2013), 49(7), 707-710
CODEN: EJCCER; ISSN: 1368-8375

DIGITAL OBJECT ID: 10.1016/j.oraloncology.2013.03.442

PUBLISHER: Elsevier Ltd.

DOCUMENT TYPE: Journal; General Review; (online computer file)

LANGUAGE: English

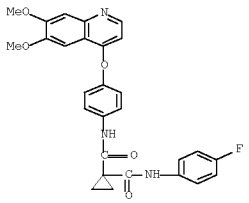
AB To review studies of novel multitargeted kinase inhibitors studied in patients with medullary thyroid cancer (MTC). Search of relevant refs. in PubMed and Google Scholar on "chemotherapy" and "medullary thyroid cancer". Multitargeted kinase inhibitors have revolutionized the role of chemotherapy for progressive MTC, providing for the first time tolerable therapeutic options that can improve outcomes in patients with progressive disease. Drugs thought to inhibit the RET kinase have advanced the furthest for this disease, but these agents also target the VEGF receptor along with other kinases that may be relevant to both beneficial and adverse effects. Vandetanib improved progression-free survival from 19.3 to 30.5 mo compared with placebo in patients with metastatic disease, whereas cabozantinib improved progression-free survival from 4.0 mo to 11.2 mo in a population with more aggressive disease. However, "cure" remains elusive, adverse events frequent, and exactly how such "targeted" agents actually function within MTC remains unclear. New approaches to clin. trial design and the preclin. development of targeted agents may be required to optimize the combination of maximum efficacy with minimal toxicity for patients with metastatic MTC.

IT 849217-68-1, Cabozantinib

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of multitargeted kinase inhibitors in medullary thyroid cancer)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 98 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2013:522453 CAPLUS Full-text

DOCUMENT NUMBER: 159:125821

TITLE: Emerging therapies in metastatic castration-sensitive and castration-resistant prostate cancer

AUTHOR(S): MacVicar, Gary R.; Hussain, Maha H.

CORPORATE SOURCE: Division of Hematology/Oncology, Department of Internal Medicine, Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

SOURCE: Current Opinion in Oncology (2013), 25(3), 252-260
CODEN: CUOOE8; ISSN: 1040-8746

DIGITAL OBJECT ID: 10.1097/CCO.0b013e32835ff161

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal; General Review; (online computer file)

LANGUAGE: English

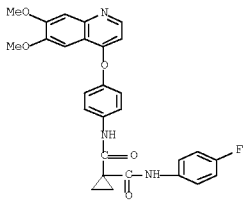
AB Purpose of review: Therapeutic options for men with metastatic prostate cancer are expanding. Here we discuss the scientific progress in this disease that led to approval of several agents in the last decade and highlight ongoing clin. investigation. Recent findings: In androgen-sensitive disease, trials are evaluating the role of intermittent androgen-deprivation therapy, early chemotherapy, and novel targeted and hormonal therapies. For chemotherapy-naive, metastatic castration-resistant prostate cancer (mCRPC), abiraterone is effective. Trials with addnl. agents targeting androgen receptor (AR) signaling, such as TAK-700 and enzalutamide, are ongoing. Other agents in development target the endothelin pathway, angiogenesis, AR chaperones, and immune mechanisms. Docetaxel with prednisone remains the standard first-line chemotherapeutic regimen as trials incorporating novel agents with docetaxel have been neg. Postdocetaxel, enzalutamide improves survival. Early results with cabozantinib are encouraging, and phase III studies are ongoing. Denosumab and radium-223 reduce the risk of skeletal-related events (SREs), but only radium-223 improves survival. Summary: Progress in understanding the disease biol. and mechanisms of castration resistance led to significant therapeutic advancements, particularly in the setting of mCRPC in which

several phase III trials, each incorporating agents with different mechanisms of action, have improved survival. As a result, new options exist, and the standard of care has changed significantly. Further advances are anticipated.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(emerging therapies in metastatic castration-sensitive and castration-resistant prostate cancer)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 99 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2013:522113 CAPLUS Full-text

DOCUMENT NUMBER: 159:125816

TITLE: From Bevacizumab to Tasquinimod: Angiogenesis as a Therapeutic Target in Prostate Cancer

AUTHOR(S): Schweizer, Michael T.; Carducci, Michael A.

CORPORATE SOURCE: Prostate Cancer Research Program, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins, Baltimore, MD, USA

SOURCE: Cancer Journal (Philadelphia, PA, United States) (2013), 19(1), 99-106
CODEN: CAJOCB; ISSN: 1528-9117

DIGITAL OBJECT ID: 10.1097/PPO.0b013e31827e0b86

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal; General Review; (online computer file)

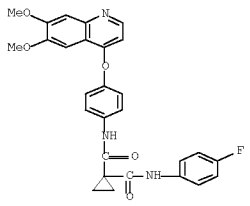
LANGUAGE: English

AB A review. It was first posited in the 1970s that angiogenesis may prove to be a useful target for anticancer therapies. Since then, a number of agents have been developed and tested across a range of tumor types; however, to date, there have unfortunately been more failures than successes. Prostate cancer (PCa) is no exception in this regard, and despite a strong preclin. rationale for targeting angiogenesis in men with PCa, there has yet to be an antiangiogenic therapy proven to prolong survival in this group of patients. Drugs have been developed to target a host of angiogenesis mediators. These include vascular endothelial growth factor (VEGF), the VEGF receptors, antiangiogenic factors (e.g., thrombospondin-1), and downstream mediators of angiogenesis (e.g., hypoxia-inducible factor-1α and MET). At present, there are 2 drugs being tested in the phase III setting for men with PCa: cabozantinib and tasquinimod. Cabozantinib, a dual VEGF receptor-2/MET inhibitor, has shown dramatic beneficial effects on radiog. evident bone metastases and pain in the phase II setting. There are currently 2 large phase III trials underway to further investigate cabozantinib's role in treating men with PCa. Both trials randomize subjects to cabozantinib vs. mitoxantrone: one is designed to evaluate overall survival, and the other, pain response durability. The other drug, tasquinimod, has a somewhat poorly understood mechanism of action. It is thought to exert an antiangiogenic effect through the inhibition of myeloid-derived suppressor cells, key to the support of an angiogenic environment, and down-regulation of hypoxia-inducible factor-1α. A phase II trial randomizing men to tasquinimod vs. placebo revealed a median progression-free survival advantage in the exptl. arm (7.6 vs. 3.3 mo with placebo; P = 0.0042). Based on these encouraging phase II results, a randomized, double-blind, placebo-controlled trial in men with metastatic castration-resistant PCa was launched. That trial is powered for a primary endpoint of progression-free survival and is expected to enroll 1200 men.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(angiogenesis as therapeutic target in prostate cancer and the role of various angiogenesis targeting drugs including bevacizumab and tasquinimod)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 100 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2013:522110 CAPLUS Full-text

DOCUMENT NUMBER: 159:125815

TITLE: Targeting MET and Vascular Endothelial Growth Factor Receptor Signaling in Castration-Resistant Prostate Cancer

AUTHOR(S): Lee, Richard J.; Smith, Matthew R.

CORPORATE SOURCE: Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA

SOURCE: Cancer Journal (Philadelphia, PA, United States) (2013), 19(1), 90-98
CODEN: CAJOCB; ISSN: 1528-9117

DIGITAL OBJECT ID: 10.1097/PPO.0b013e318281e280

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal; General Review; (online computer file)

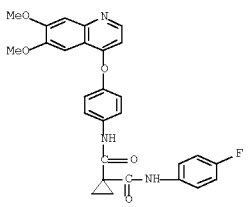
LANGUAGE: English

AB A review. Effective management of bone metastases in men with castration-resistant prostate cancer (CRPC) remains an important unmet medical need. MET and vascular endothelial growth factor receptor (VEGFR) are rational targets for intervention in CRPC. Clin. trials involving agents that inhibit one but not both pathways have reported modest activity and no improvement in overall survival. Cabozantinib is an oral multitargeted tyrosine kinase inhibitor that inhibits both MET and VEGFR-2. A phase II randomized discontinuation study involving subjects with CRPC demonstrated that cabozantinib therapy is associated with improvement in bone scans, bone turnover markers, and pain response, but with significant adverse events leading to dose reduction and treatment discontinuation. Lower doses of cabozantinib retain high levels of activity with less toxicity. Ongoing phase III clin. trials will define the role of cabozantinib in CRPC. We summarize the rationale for targeting MET and VEGFR pathways in CRPC and the clin. data available to date.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeting MET and vascular endothelial growth factor receptor signaling in castration-resistant prostate cancer)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 101 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2013:470327 CAPLUS Full-text

DOCUMENT NUMBER: 158:493976

TITLE: Combinations comprising c-Met antagonists and B-raf antagonists for treatment of cancer

INVENTOR(S): Wilson, Timothy R.; Koeppen, Hartmut; Merchant, Mark; Settleman, Jeffrey

PATENT ASSIGNEE(S): Genentech, Inc., USA; F. Hoffmann-La Roche AG

SOURCE: PCT Int. Appl., 148pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2013043715 | A1 | 20130328 | WO 2012-US56106 | 20120919 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
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| CA 2846630 | A1 | 20130328 | CA 2012-2846630 | 20120919 |
| US 20130078252 | A1 | 20130328 | US 2012-13622878 | 20120919 |
| AU 2012312515 | A1 | 20140313 | AU 2012-312515 | 20120919 |
| IL 231056 | A | 20140331 | IL 2012-231056 | 20120919 |
| KR 2014064971 | A | 20140528 | KR 2014-7010162 | 20120919 |
| CN 103930111 | A | 20140716 | CN 2012-80055708 | 20120919 |
| EP 2758055 | A1 | 20140730 | EP 2012-768982 | 20120919 |
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| MX 2014002990 | A | 20140521 | MX 2014-2990 | 20140313 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 2011-61536436 | P | 20110919 |
| US 2011-61551328 | P | 20111025 |
| US 2012-61598783 | P | 20120214 |
| US 2012-61641139 | P | 20120501 |
| WO 2012-US56106 | W | 20120919 |

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

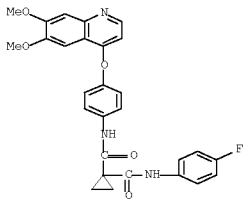
AB The invention provides combination therapies for treating a pathol. condition, such as cancer, wherein a c-met antagonist (e.g. crizotinib, tivantinib, anti-HGF antibody, onartuzumab) is combined with a B-raf

antagonist (e.g. vemurafenib), thereby providing significant antitumor activity. C-met expression was inversely correlated with sensitivity to vemurafenib treatment. In one aspect, provided are methods for treating a cancer patient who has increased likelihood of developing resistance to B-raf antagonist comprising administering an effective amount (in combination) of B-raf antagonist and c-met antagonist. In addition, patients with B-raf mutant melanoma who had higher levels of circulating hepatocyte growth factor (HGF) showed substantially reduced progression free survival and overall survival when treated with B-raf antagonist, relative to patients with lower circulating HGF levels treated with B-raf antagonist.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combinations comprising c-Met antagonists and B-raf antagonists for treatment of cancer)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 102 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2013:466384 CAPLUS Full-text

DOCUMENT NUMBER: 158:494085

TITLE: Method for treating osteoporosis

INVENTOR(S): Aftab, Dana T.; Clary, Douglas

PATENT ASSIGNEE(S): Exelixis, Inc., USA

SOURCE: PCT Int. Appl., 73pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2013043840 | A1 | 20130328 | WO 2012-US56281 | 20120920 |

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

| | | | | |
|---|---|---|---|---|
| CA 2848512 | A1 | 20130328 | CA 2012-2848512 | 20120920 |
| AU 2012312364 | A1 | 20140410 | AU 2012-312364 | 20120920 |
| IL 231495 | A | 20140430 | IL 2012-231495 | 20120920 |
| KR 2014069133 | A | 20140609 | KR 2014-7009534 | 20120920 |
| CN 103957915 | A | 20140730 | CN 2012-80051094 | 20120920 |
| EP 2758057 | A1 | 20140730 | EP 2012-770368 | 20120920 |

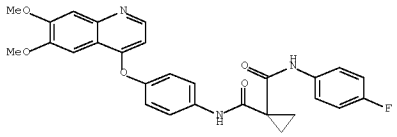
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| | | | | |
|---|---|---|---|---|
| AR 87995 | A1 | 20140430 | AR 2012-103501 | 20120921 |
| US 20140228401 | A1 | 20140814 | US 2014-14346570 | 20140321 |

PRIORITY APPLN. INFO.: US 2011-61538039 P 20110922
WO 2012-US56281 W 20120920

OTHER SOURCE(S): CASREACT 158:494085; MARPAT 158:494085

GI



AB This invention is directed to the treatment of osteoporosis using N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

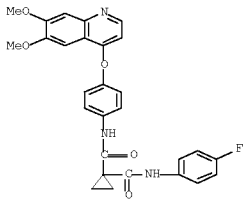
IT 1140909-48-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(method for treating osteoporosis)

RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

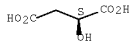
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



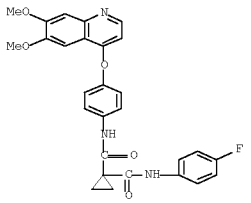
IT 1365530-43-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for treating osteoporosis)

RN 1365530-43-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

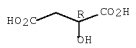
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 636-61-3
CMF C4 H6 O5

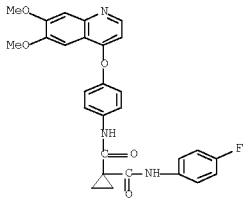
Absolute stereochemistry. Rotation (+).



IT 849217-68-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(method for treating osteoporosis)

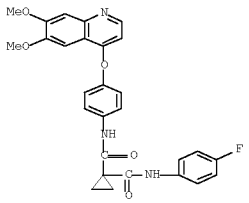
RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 103 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:417299 CAPLUS Full-text
DOCUMENT NUMBER: 159:86304
TITLE: Pharmacokinetic evaluation of
AUTHOR(S): Karras, Spyridon; Pontikides, Nikolaos; Krassas, Gerasimos E.
CORPORATE SOURCE: Department of Endocrinology, Diabetes and Metabolism, Panagia General Hospital, Thessaloniki, Greece
SOURCE: Expert Opinion on Drug Metabolism & Toxicology (2013), 9(4), 507-515
CODEN: EODMAP; ISSN: 1742-5255
DIGITAL OBJECT ID: 10.1517/17425255.2013.780028
PUBLISHER: Informa Healthcare
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
AB A review. Introduction: Conventional treatment modalities for thyroid cancer lead to complete remission in only one-third of patients with distant metastases. On the other hand, medullary thyroid cancer (MTC) and anaplastic thyroid cancer (ATC), although rare, are responsible for a significant percentage of thyroid cancer-related deaths. New treatments are needed to treat such patientsAreas covered: The aim of this review is to provide the latest information on , a new tyrosine kinase inhibitor (TKI) that is currently used mainly as a treatment of MTC. The authors collated data that were retrieved from a PubMed literature search.Expert opinion: CBZ targets multiple cell-signaling pathways involved in the mol. pathogenesis of thyroid cancer. These are namely VEGF receptor-2, hepatocyte growth factor receptor and rearranged during transfection receptor. Furthermore, it is a drug which may be used in cases where conventional therapies (mainly for MTC) are proved ineffective or have shown poor results with a good outcome. CBZ may also be administered alone or in combination with other drugs of the same family.
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(understanding pharmacokinetics of cabozantinib may be useful in treatment of patient with medullary thyroid cancer)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

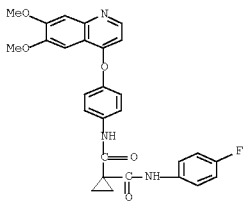


OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 104 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:414621 CAPLUS Full-text
DOCUMENT NUMBER: 159:53852
TITLE: Effects of dual targeting of tumor cells and stroma in human glioblastoma xenografts with a tyrosine kinase inhibitor against c-MET and VEGFR2
AUTHOR(S): Navis, Anna C.; Bourgonje, Annika; Wesseling, Pieter; Wright, Alan; Hendriks, Wiljan; Verrijp, Kiek; van der Laak, Jeroen A. W. M.; Heerschap, Arend; Leenders, William P. J.
CORPORATE SOURCE: Department of Pathology, Radboud University Nijmegen Medical Centre, Nijmegen, Neth.
SOURCE: PLoS One (2013), 8(3), e58262
CODEN: POLNCL; ISSN: 1932-6203
DIGITAL OBJECT ID: 10.1371/journal.pone.0058262
PUBLISHER: Public Library of Science
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Anti-angiogenic treatment of glioblastoma with Vascular Endothelial Growth Factor (VEGF)- or VEGF Receptor 2 (VEGFR2) inhibitors normalizes tumor vessels, resulting in a profound radiol. response and improved quality of life. This approach however does not halt tumor progression by diffuse infiltration, as this phenotype is less angiogenesis dependent. Combined inhibition of angiogenesis and diffuse infiltrative growth would therefore be a more effective treatment approach in these tumors. The HGF/c-MET axis is important in both angiogenesis and cell migration in several tumor types including glioma. We therefore analyzed the effects of the c-MET- and VEGFR2 tyrosine kinase inhibitor cabozantinib (XL184, Exelixis) on c-MET pos. orthotopic E98 glioblastoma xenografts, which routinely present with angiogenesis-dependent areas of tumor growth, as well as diffuse infiltrative growth. In in vitro cultures of E98 cells, cabozantinib effectively inhibited c-MET phosphorylation, concomitant with inhibitory effects on AKT and ERK1/2 phosphorylation, and cell proliferation and migration. VEGFR2 activation in endothelial cells was also effectively inhibited in vitro. Treatment of BALB/c nu/nu mice carrying orthotopic E98 xenografts resulted in a significant increase in overall survival. Cabozantinib effectively inhibited angiogenesis, resulting in increased hypoxia in angiogenesis-dependent tumor areas, and induced vessel normalization. Yet, tumors ultimately escaped cabozantinib therapy by diffuse infiltrative outgrowth via vessel co-option. Of importance, in contrast to the results from in vitro expts., in vivo blockade of c-MET activation was incomplete, possibly due to multiple factors including restoration of the blood-brain barrier resulting from cabozantinib-induced VEGFR2 inhibition. In conclusion, cabozantinib is a promising therapy for c-MET pos. glioma, but improving delivery of the drug to the tumor and/or the surrounding tissue may be needed for full activity.
IT 1140909-48-3, XL184
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of dual targeting of tumor cells and stroma in human glioblastoma xenografts with tyrosine kinase inhibitor against c-MET and VEGFR2)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

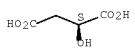
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CMF C28 H24 F N3 O5



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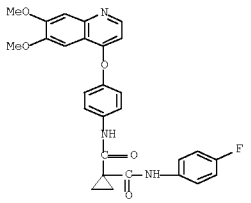
CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



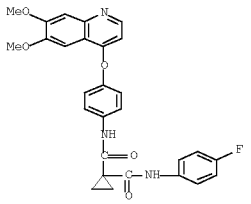
OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 105 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:378985 CAPLUS Full-text
DOCUMENT NUMBER: 159:193339
TITLE: Cellular signaling pathway alterations and potential targeted therapies for medullary thyroid carcinoma
AUTHOR(S): Giunti, Serena; Antonelli, Alessandro; Amorosi, Andrea; Santarpia, Libero
CORPORATE SOURCE: Department of Pathology, Centro Oncologico Fiorentino, Sesto Fiorentino, 50019, Italy
SOURCE: International Journal of Endocrinology (2013) 803171, 16 pp.
CODEN: IJENIG; ISSN: 1687-8345
DIGITAL OBJECT ID: 10.1155/2013/803171
PUBLISHER: Hindawi Publishing Corp.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
AB A review. Parafollicular C-cell-derived medullary thyroid cancer (MTC) comprises 3% to 4% of all thyroid cancers. While cytotoxic treatments have been shown to have limited efficacy, targeted mol. therapies that inhibit rearranged during transfection (RET) and other tyrosine kinase receptors that are mainly involved in angiogenesis have shown great promise in the treatment of metastatic or locally advanced MTC. Multi-tyrosine kinase inhibitors such as vandetanib, which is already approved for the treatment of progressive MTC, and cabozantinib have shown distinct advantages with regard to rates of disease response and control. However, these types of tyrosine kinase inhibitor compds. are able to concurrently block several types of targets, which limits the understanding of RET as a specific target. Moreover, important resistances to tyrosine kinase inhibitors can occur, which limit the long-term efficacy of these treatments. Deregulated cellular signaling pathways and genetic alterations in MTC, particularly the activationof the RAS/mammalian target of rapamycin (mTOR) cascades and RET crosstalk signaling, are now emerging as novel and potentially promising therapeutic treatments for aggressive MTC.
IT 849217-68-1, Cabozantinib
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cellular signaling pathway alterations and potential targeted therapies for medullary thyroid carcinoma)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 115 THERE ARE 115 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 106 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:377358 CAPLUS Full-text
DOCUMENT NUMBER: 159:86211
TITLE: Cabozantinib as a Novel Therapy for Renal Cell Carcinoma
AUTHOR(S): Vaishampayan, Ulka
CORPORATE SOURCE: Wayne State University, Detroit, MI, 48201, USA
SOURCE: Current Oncology Reports (2013), 15(2), 76-82
CODEN: CORUAT; ISSN: 1534-6269
DIGITAL OBJECT ID: 10.1007/s11912-012-0289-x
PUBLISHER: Springer
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
AB A review. Cabozantinib/XL184 (Exelexis, Inc.) has demonstrated remarkable responses in kidney cancer. Preclin. results revealed VEGF, KIT and MET inhibition in a variety of solid tumors such as thyroid, ovarian, renal, lung, liver and prostate cancers. A phase II trial demonstrated efficacy in renal cancer with a 28 % objective response rate, stable disease rate of 62 % and median progression free survival of 14.7 mo. Predominant toxicities of fatigue and diarrhea were noted. Dramatic responses in bone metastases (three of four patients) make the agent especially valuable for palliation in a disease, where presence of bone metastases is a predictor of worse survival. Cabozantinib is an emerging novel agent with promising activity in advanced kidney cancer. Randomized trials are planned in comparison with standard VEGF inhibitor therapy. Defining the role of MET overexpression would help patient selection and enrich and enhance the future evaluation of this targeted novel agent.
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cabozantinib as novel therapy may be useful for treatment of patient with renal cell carcinoma)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

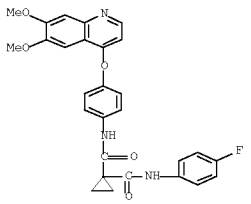


OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 107 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:359822 CAPLUS full-text
DOCUMENT NUMBER: 159:33929
TITLE: Treatment directed to signalling molecules in patients with advanced differentiated thyroid cancer
AUTHOR(S): Saez, Jose M. G.
CORPORATE SOURCE: Endocrinology and Nutrition Service, L'Hospitalet of Llobregat, Spanish Biomedical Research Centre in Diabetes and Associated Metabolic Disorders (CIBERDEM), University Hospital of Bellvitge, Barcelona, Spain
SOURCE: Anti-Cancer Agents in Medicinal Chemistry (2013), 13(3), 483-495
CODEN: AAMCE4; ISSN: 1871-5206
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Mutation detection in samples from thyroid cancer with the addition of BRAF mutation, and also the detection of RAS, RET/PTC, and PAX8/PPARγ mutations, may also contribute to cancer diagnosis. On the other hand, the MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase signaling pathway) and PI3K/Akt (lipid kinase phoshoinositid-3-kinase signaling pathway) play an important role in the transmission of cell signals. The genes, coding the signaling cascade proteins (RET, RAS, BRAF, PI3K, PTEN, AKT), are mutated or aberrantly expressed in thyroid cancer derived from follicular thyroid cells. Genetic and epigenetic alternations, concerning MAPK/ERK and PI3K/Akt signaling pathways, contribute to their activation and interaction as a consequence of malignant follicular cell transformation. The understanding of this mol. mechanism provides access to novel mol. prognostic and therapeutic strategies for inhibiting the oncogenic activity of the signaling pathways. This ability to investigate tumor biol. allows for the selection of different drugs. Nowadays the most relevant are treatments directed to tyrosine kinase receptors that bind for a wide variety of ligands and are frequently mutated and induce a constitutive activation such that a chimerical protein expression takes place in follicular cells in the domain of RET, as well as in other receptors. Many mols. such as: motesanib, sorafenib, vandetanib, sunitinib, XL-184, imatinib, axitinib, pazopanib, lenvatinib, combretastatin, gefitinib, cetuximab, bortezomib and thiazoldonedione have been developed. Some of them also can act in receptors of vascular endothelial growth factor and epidermal growth factor receptors. Information obtained through cytol. or biopsy samples permits the study of complex metabolic or genetic pathways, thus providing researchers with a high throughput tool for elucidating changes in the global expression patterns seen in tumor cells and allowing for different therapeutic strategies in thyroid cancer which take into account the predominant altered pathways observed in these samples.
IT 1140909-48-3, XL-184
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment directed to signaling mols. in patients with advanced differentiated thyroid cancer)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

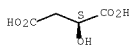
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 121 THERE ARE 121 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

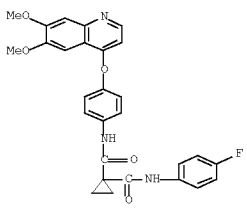
L4 ANSWER 108 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:260769 CAPLUS Full-text
DOCUMENT NUMBER: 158:690611
TITLE: Cabozantinib in patients with advanced prostate cancer: results of a phase II randomized discontinuation trial
AUTHOR(S): Smith, David C.; Smith, Matthew R.; Sweeney, Christopher; Elfiky, Aymen A.; Logothetis, Christopher; Corn, Paul G.; Vogelzang, Nicholas J.; Small, Eric J.; Harzstark, Andrea L.; Gordon, Michael S.; Vaishampayan, Ulka N.; Haas, Naomi B.; Spira, Alexander I.; Lara, Primo N., Jr.; Lin, Chia-Chi; Srinivas, Sandy; Sella, Avishay; Schoffski, Patrick; Scheffold, Christian; Weitzman, Aaron L.; Hussain, Maha
CORPORATE SOURCE: University of Michigan, Ann Arbor, USA
SOURCE: Journal of Clinical Oncology (2013), 31(4), 412-419
CODEN: JCONDN; ISSN: 0732-183X
DIGITAL OBJECT ID: 10.1200/JCO.2012.45.0494
PUBLISHER: American Society of Clinical Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Purpose: Cabozantinib (XL 184) is an orally bioavailable tyrosine kinase inhibitor with activity against MET and vascular endothelial growth factor receptor 2. We evaluated the activity of cabozantinib in patients with castration-resistant prostate cancer (CRPC) in a phase II randomized discontinuation trial with an expansion cohort. Patients and Methods: Patients received 100 mg of cabozantinib daily. Those with stable disease per RECIST at 12 wk were randomly assigned to cabozantinib or placebo. Primary end points were objective response rate at 12 wk and progression-free survival (PFS) after random assignment. Results: One hundred seventy-one men with CRPC were enrolled. Random assignment was halted early based on the observed activity of cabozantinib. Seventy-two percent of patients had regression in soft tissue lesions, whereas 68% of evaluable patients had improvement on bone scan, including complete resolution in 12%. The objective response rate at 12 wk was 5%, with stable disease in 75% of patients. Thirty-one patients with stable disease at week 12 were randomly assigned. Median PFS was 23.9 wk (95% CI, 10.7 to 62.4 wk) with cabozantinib and 5.9 wk (95% CI, 5.4 to 6.6 wk) with placebo (hazard ratio, 0.12; P < .001). Serum total alkaline phosphatase and plasma cross-linked C-terminal telopeptide of type I collagen were reduced by ≥ 50% in 57% of evaluable patients. On retrospective review, bone pain improved in 67% of evaluable patients, with a decrease in narcotic use in 56%. The most common grade 3 adverse events were fatigue (16%), hypertension (12%), and hand-foot syndrome (8%). Conclusion: Cabozantinib has clin. activity in men with CRPC, including reduction of soft tissue lesions, improvement in PFS,

resolution of bone scans, and redns. in bone turnover markers, pain, and narcotic use.

IT 849217-68-1, Cabozantinib
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cabozantinib improved progression-free survival, reduced soft tissue lesions, bone turnover markers, pain and narcotic use in patient with castration-resistant prostate cancer)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 68 THERE ARE 68 CAPLUS RECORDS THAT CITE THIS RECORD (68 CITINGS)

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 109 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2013:260767 CAPLUS Full-text

DOCUMENT NUMBER: 160:42366

TITLE: Cabozantinib in prostate cancer: the beginning of a precision paradigm?

AUTHOR(S): Goodin, Susan; DiPaola, Robert S.

CORPORATE SOURCE: The Cancer Institute of New Jersey, University of Medicine and Dentistry of New Jersey Robert Wood Johnson Medical School, New Brunswick, NJ, USA

SOURCE: Journal of Clinical Oncology (2013), 31(4), 401-403
CODEN: JCONDN; ISSN: 0732-183X

DIGITAL OBJECT ID: 10.1200/JCO.2012.46.6185

PUBLISHER: American Society of Clinical Oncology

DOCUMENT TYPE: Journal; General Review

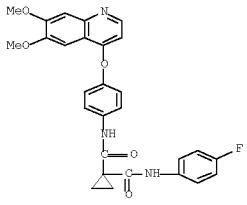
LANGUAGE: English

AB A review. The research of Smith et al. (2013) entitled, 'Cabozantinib in patients with advanced prostate cancer: Results of a phase II randomized discontinuation trial' is reviewed with commentary and refs. The authors presented data on a novel orally bioavailable tyrosine kinase inhibitor (TKI), cabozantinib, with activity against multiple targets including mesenchymal-epithelial transition factor (MET), also known as hepatocyte growth factor receptor, and the vascular endothelial growth factor receptor 2 (VEGFR2). They reported a reduction in uptake on bone scan with improvement in 68% of men (79 of 116) with bone metastasis and complete resolution in 14 patients.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cabozantinib in prostate cancer)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 110 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2013:187940 CAPLUS Full-text

DOCUMENT NUMBER: 159:33573

TITLE: Profile of cabozantinib and its potential in the treatment of advanced medullary thyroid cancer

AUTHOR(S): Hart, Christopher D.; De Boer, Richard H.

CORPORATE SOURCE: Department of Oncology, Royal Melbourne Hospital, Parkville, Victoria, 3050, Australia

SOURCE: OncoTargets and Therapy (2013), 6, 1-7
CODEN: OTNHAZ; ISSN: 1178-6930

DIGITAL OBJECT ID: 10.2147/OTT.S27671

PUBLISHER: Dove Medical Press Ltd.

DOCUMENT TYPE: Journal; General Review; (online computer file)

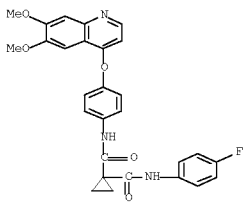
LANGUAGE: English

AB A review. Medullary thyroid cancer is an uncommon malignancy for which until recently little effective treatment existed. It is often characterized by mutation and overexpression of the receptor tyrosine kinases RET (rearranged during transfection), VEGFR2 (vascular endothelial growth factor receptor 2) and MET (mesenchymal-epithelial transition factor), which make attractive targets for drug development. Cabozantinib is an orally bioavailable tyrosine kinase inhibitor which blocks MET, VEGRF2 and RET, and has shown considerable activity in medullary thyroid cancer in a Phase III trial, including in heavily pretreated patients. Its novel combination of vascular endothelial growth factor and MET inhibition is believed to address the MET escape pathway, which is thought to be the cause of nonsustained tumor responses resulting from inhibition of vascular endothelial growth factor alone.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(profile of cabozantinib and potential in treatment of advanced medullary thyroid cancer)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 111 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2012:1893113 CAPLUS Full-text

DOCUMENT NUMBER: 158:123654

TITLE: Methods of treating cancer using a chemotherapeutic agent with an agent that blocks the activity of hepatocyte growth factor or its cognate receptor c-MET.

INVENTOR(S): Golub, Todd; Straussman, Ravid

PATENT ASSIGNEE(S): The Broad Institute, Inc., USA; Dana-Farber Cancer Institute, Inc.

SOURCE: PCT Int. Appl., 104pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2012178038 | A1 | 20121227 | WO 2012-US43788 | 20120622 |

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

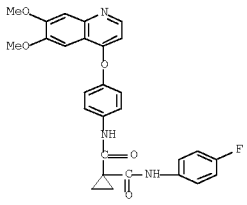
PRIORITY APPLN. INFO.: US 2011-61501091 P1 20110624

AB The invention provides methods of treating cancer by preventing or reducing chemoresistance in a tumor by administering a chemotherapeutic agent together with another agent that blocks the activity of hepatocyte growth factor or its cognate receptor c-MET.

IT 849217-68-1, Cabozantinib 1140909-48-3, XL184
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cancer treatment using a chemotherapeutic agent with an agent that blocks the activity of HGF or its cognate receptor c-MET)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

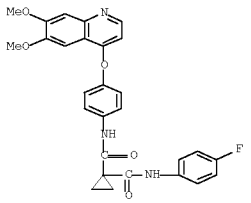


RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

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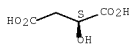
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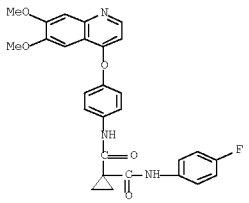
CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



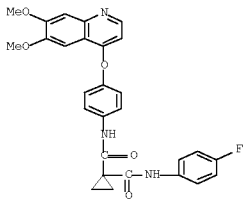
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 112 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:1845709 CAPLUS Full-text
DOCUMENT NUMBER: 158:644003
TITLE: New agents in metastatic prostate cancer
AUTHOR(S): Choudhury, Atish D.; Kantoff, Philip W.
CORPORATE SOURCE: Dana-Farber Cancer Institute, Boston, MA, USA
SOURCE: Journal of the National Comprehensive Cancer Network (2012), 10(11), 1403-1409
CODEN: JNCCA4; ISSN: 1540-1405
PUBLISHER: Harborside Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Discoveries of mol. mechanisms and therapeutic targets in metastatic castration-resistant prostate cancer (CRPC) have led to significant advancements in the development of effective agents in this setting, with diverse mechanisms of action. Within the past 2 years, 5 agents have been approved for the treatment of patients with metastatic CRPC (cabazitaxel, abiraterone, sipuleucel-T, denosumab, and enzalutamide), and another (Alpharadin) has shown overall survival benefit in a phase III trial. This article summarizes the phase III data showing clin. benefit from these agents, highlights other promising therapies in phase III studies as single agents (PROSTVAC-VF, ipilimumab, cabozantinib), discusses important unanswered questions regarding these therapies, and provides a schema for their use based on current regulatory approval and how this is likely to evolve as data from ongoing studies are reported. Although curative interventions in metastatic CRPC still do not exist, the hope is that optimization of therapeutic strategies can reduce the morbidity and mortality associated with this disease.
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new agents in metastatic prostate cancer)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 113 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:1765841 CAPLUS Full-text
DOCUMENT NUMBER: 158:670189
TITLE: Cabozantinib for the Treatment of Advanced Medullary Thyroid Cancer
AUTHOR(S): Nagilla, Madhavi; Brown, Rebecca L.; Cohen, Ezra E. W.
CORPORATE SOURCE: Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of Chicago, Chicago, IL, 60645, USA
SOURCE: Advances in Therapy (2012), 29(11), 925-934
CODEN: ADTHE7; ISSN: 0741-238X
DIGITAL OBJECT ID: 10.1007/s12325-012-0060-6
PUBLISHER: Springer Healthcare Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
AB A review. Introduction Patients with advanced medullary thyroid cancer (MTC) have poor prognoses and limited treatment options. Improved knowledge about mol. aberrations associated with MTC and the availability of novel targeted tyrosine kinase inhibitors (TKIs) have led to new potential treatment modalities. Cabozantinib is an oral multitargeted TKI with activity against multiple receptors including RET, vascular endothelial growth factor receptor type 2 (VEGFR2), and MET that has been evaluated in MTC in the preclin. and clin. arenas. Methods This article reviews unmet clin. needs in advanced MTC. The authors consider novel agents that have been studied in MTC, with a focus on the investigational agent cabozantinib. Up-to-date clin. data of cabozantinib in MTC are discussed. Results Recent clin. evaluation suggests that cabozantinib is the first agent to prolong progression-free survival in patients with progressive MTC. These findings indicate that cabozantinib may be an effective therapy in advanced MTC. No improvement in overall survival has been demonstrated but data are not mature. Conclusion Cabozantinib may be an effective treatment option for patients with advanced MTC and is worthy of further evaluation.
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cabozantinib for the treatment of advanced medullary thyroid cancer)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

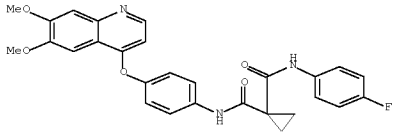


OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 114 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:1630842 CAPLUS Full-text
DOCUMENT NUMBER: 157:699601
TITLE: Method of treating cancer and bone cancer pain
INVENTOR(S): Schwab, Gisela; Aftab, Dana T.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 52pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2012151326 | A1 | 20121108 | WO 2012-US36191 | 20120502 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM | | | | |
| CA 2834778 | A1 | 20121108 | CA 2012-2834778 | 20120502 |
| AR 86242 | A1 | 20131127 | AR 2012-101544 | 20120502 |
| AU 2012250759 | A1 | 20131128 | AU 2012-250759 | 20120502 |
| IL 229094 | A | 20131231 | IL 2012-229094 | 20120502 |
| KR 2014025496 | A | 20140304 | KR 2013-7031635 | 20120502 |
| EP 2704717 | A1 | 20140312 | EP 2012-720754 | 20120502 |
| R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME | | | | |
| CN 103717221 | A | 20140409 | CN 2012-80026424 | 20120502 |
| JP 2014513129 | T | 20140529 | JP 2014-509417 | 20120502 |
| MX 2013012695 | A | 20140327 | MX 2013-12695 | 20131030 |
| ZA 2013008206 | A | 20140730 | ZA 2013-8206 | 20131101 |
| IN 2013KN03259 | A | 20140221 | IN 2013-KN3259 | 20131105 |
| US 20140179736 | A1 | 20140626 | US 2014-14115236 | 20140228 |

PRIORITY APPLN. INFO.: US 2011-61481682 P 20110502
US 2011-61557366 P 20111108
WO 2012-US36191 W 20120502
OTHER SOURCE(S): CASREACT 157:699601; MARPAT 157:699601
GI



AB This invention is directed to the treatment of cancer, particularly lung cancer, breast cancer, melanoma, renal cell carcinoma, thyroid cancer that has metastasized to the bone. The invention is also directed to a method for treating bone cancer pain in an individual in need of such treatment

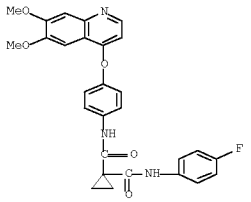
comprising administering to the individual an effective amount of a compound of Formula I.

IT 849217-68-1

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(method of treating cancer and bone cancer pain)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



IT 1140909-48-3

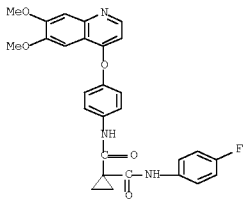
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(method of treating cancer and bone cancer pain)

RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

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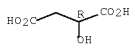
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 636-61-3
CMF C4 H6 O5

Absolute stereochemistry. Rotation (+).



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 115 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2012:1563334 CAPLUS Full-text

DOCUMENT NUMBER: 158:492390

TITLE: New developments in castrate-resistant prostate cancer

AUTHOR(S): Shore, N.; Mason, M.; de Reijke, Th. M.

CORPORATE SOURCE: Carolina Urologic Research Center, Atlantic Urology Clinics, Myrtle Beach, SC, USA

SOURCE: BJU International (2012), 109(Suppl. 6), 22-32
CODEN: BJINFO; ISSN: 1464-4096

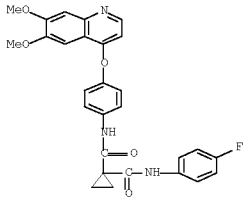
DIGITAL OBJECT ID: 10.1111/j.1464-410X.2012.11217.x

PUBLISHER: Wiley-Blackwell

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

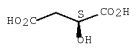
AB A review. Castrate-resistant prostate cancer (CRPC) occurs when disease progresses in the presence of castrate levels of androgens and remains sensitive to further hormonal manipulation. For many years the treatment of CRPC was limited to the use of docetaxel for metastatic disease. However, this has recently changed with the approval of several new agents. Sipuleucel-T, an immunotherapeutic vaccine, is now available in the US for patients with non-metastatic CRPC and abiraterone, an oral enzyme inhibitor of androgen biosynthesis, as well as cabazitaxel, a cytotoxic



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



IT 1365530-43-3

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of treating cancer and bone cancer pain)

RN 1365530-43-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

CRN 849217-68-1
CMF C28 H24 F N3 O5

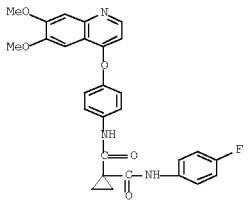
chemotherapeutic, have been approved for the treatment of metastatic CRPC. Also, denosumab, a s.c. antibody, is now an option for the treatment of patients with CRPC with bone metastases, in addition to zoledronic acid, an i.v. bisphosphonate. Further treatment advances for metastatic CRPC therapeutics are in late stage phase III development. These include therapies affecting the androgen receptor (MDV3100) as well as addnl. immune-based therapeutics, PROSTVAC and ipilimumab. A broad range of agents is also emerging under the term targeted therapies. The endothelin-A receptor antagonist zibotentan, the tyrosine kinase inhibitors dasatinib, sorafenib and cabozantinib, the anti-angiogenic agent aflibercept, and the clusterin inhibitor custirsen, are all currently being tested for efficacy in metastatic CRPC. The mechanism of action of these and other promising agents are discussed alongside current therapeutic options and their potential place in the treatment landscape for CRPC is considered.

IT 849217-68-1, Cabozantinib

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new developments in castrate-resistant prostate cancer)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 98 THERE ARE 98 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 116 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2012:1483426 CAPLUS Full-text

DOCUMENT NUMBER: 157:573884

TITLE: Methods for predicting and improving the survival of gastric cancer patients

INVENTOR(S): Kim, Phillip; Singh, Sharat

PATENT ASSIGNEE(S): Nestec SA, Switz.

SOURCE: PCT Int. Appl., 147pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 2012138785 | A1 | 20121011 | WO 2012-US32206 | 20120404 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| CA 2831468 | A1 | 20121011 | CA 2012-2831468 | 20120404 |
| AU 2012240242 | A1 | 20131010 | AU 2012-240242 | 20120404 |
| IL 228579 | A | 20131128 | IL 2012-228579 | 20120404 |
| EP 2694972 | A1 | 20140212 | EP 2012-716858 | 20120404 |
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| KR 2014020318 | A | 20140218 | KR 2013-7029113 | 20120404 |
| CN 103597354 | A | 20140219 | CN 2012-80027365 | 20120404 |
| JP 2014517259 | T | 20140717 | JP 2014-503964 | 20120404 |
| US 20140099300 | A1 | 20140410 | US 2013-14044792 | 20131002 |

| | | | |
|---|---|---|---|
| PRIORITY APPLN. INFO.: | US 2011-61471678 | P | 20110404 |
| | US 2012-61590787 | P | 20120125 |
| | WO 2012-US32206 | W | 20120404 |

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The present invention provides assays and methods for predicting the post-operative survival of a subject having an early stage gastric cancer after tumor surgery. The present invention also provides methods for treating a subject having an early stage gastric cancer by administering a combination therapy tailored to the signal transduction biomarkers that are activated in the cancer. In particular embodiments, the methods of the invention rely on the detection of the activation state or level of a specific combination of signal transducer analytes in a cancer cell obtained from the subject. Thus, the methods of the invention are particularly useful for predicting the survival or prognosis of a subject having an early stage gastric cancer and for guiding both pre- and post-operative treatment decisions by identifying subjects who would benefit from combination therapy as opposed to monotherapy.

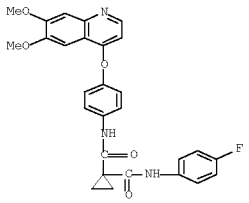
IT 1140909-48-3, XL184
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cMET and HER as markers and drug targets for predicting survival of a subject having type I or II gastric cancer after tumor surgery)

RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

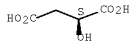
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 117 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

| | |
|---|---|
| ACCESSION NUMBER: | 2012:1450760 CAPLUS Full-text |
| DOCUMENT NUMBER: | 157:567006 |
| TITLE: | Method of treating cancer |
| INVENTOR(S): | Aftab, Dana T.; Schimmoller, Frauke |
| PATENT ASSIGNEE(S): | Exelixis, Inc., USA |
| SOURCE: | U.S. Pat. Appl. Publ., 17pp. CODEN: USXXCO |
| DOCUMENT TYPE: | Patent |
| LANGUAGE: | English |
| FAMILY ACC. NUM. COUNT: | 1 |

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 20120252840 | A1 | 20121004 | US 2012-13438964 | 20120404 |

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ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

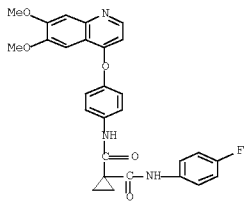
OTHER SOURCE(S): CASREACT 157:567006

AB This invention is directed to the treatment of cancer, particularly ocular melanoma, with a dual inhibitor of MET and VEGF such as Compound 1.

IT 849217-68-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(method of treating cancer)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



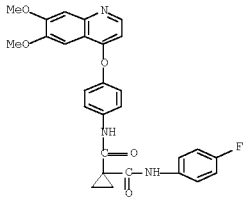
IT 1140909-48-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(method of treating cancer)

RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

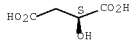
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



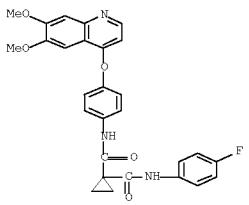
IT 1365530-43-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of treating cancer)

RN 1365530-43-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

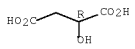
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 636-61-3
CMF C4 H6 O5

Absolute stereochemistry. Rotation (+).



L4 ANSWER 118 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:1270117 CAPLUS Full-text
DOCUMENT NUMBER: 157:438359
TITLE: Preparation of substituted quinoline compounds as protein tyrosine kinase modulators
INVENTOR(S): Xi, Ning
PATENT ASSIGNEE(S): Xi, Dr. Ning, USA
SOURCE: U.S. Pat. Appl. Publ., 39pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 20120219522 | A1 | 20120830 | US 2012-13400586 | 20120221 |
| CA 2820709 | A1 | 20120907 | CA 2012-2820709 | 20120221 |
| WO 2012118632 | A1 | 20120907 | WO 2012-US25834 | 20120221 |

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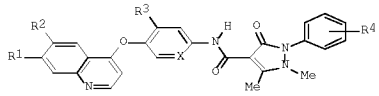
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| KR 2013095806 | A | 20130828 | KR 2013-7015842 | 20120221 |
| EP 2680886 | A1 | 20140108 | EP 2012-752321 | 20120221 |

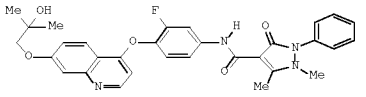
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR

| | | | | |
|---|---|---|---|---|
| JP 2014506925 | T | 20140320 | JP 2013-556713 | 20120221 |
| ZA 2013003793 | A | 20140730 | ZA 2013-3793 | 20120221 |
| MX 2013007278 | A | 20130913 | MX 2013-7278 | 20130621 |

PRIORITY APPLN. INFO.: US 2011-61447104 P 20110228
WO 2012-US25834 W 20120221
OTHER SOURCE(S): CASREACT 157:438359; MARPAT 157:438359
GI

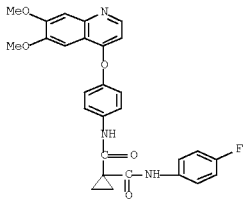


I



II

AB The present invention provides novel substituted quinoline compds. I [R1, R2 = H, alkoxy, hydroxyalkoxy; R3 = H, F; R4 = H, F, Cl, Br, I, etc.; X = CH or N, wherein at least one of R1 and R2 = hydroxyalkoxy], pharmaceutical acceptable salts and formulations thereof useful in modulating the protein tyrosine kinase activity, and in modulating cellular activities such as proliferation, differentiation, apoptosis, migration and invasion. Syntheses of exemplified compds. I were described. E.g., a multi-step synthesis of the pyrazolecarboxamide II, starting from 3-benzyloxybenzenamine, was provided. Exemplified compds. I were tested for their efficacy as inhibitors of receptor tyrosine kinases such as c-Met, VEGFR and Axl, and as antitumor agents (data given). The invention also provides pharmaceutically acceptable compns. comprising compds. I and methods of using the compns. in the treatment of hyperproliferative disorders in mammals, especially humans.
IT 849217-68-1, Cabozantinib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(co-drug; preparation of substituted quinoline compds. as protein tyrosine
kinase modulators)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L4 ANSWER 119 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:1269771 CAPLUS Full-text
DOCUMENT NUMBER: 157:431629
TITLE: Methods for detecting cancer and/or determining response to therapeutic agent, and numerous circulating markers (including proteins, nucleic acids and vesicles) used in said methods
INVENTOR(S): Spetzler, David; Holterman, Daniel A.; Pawlowski, Traci; Tasinato, Andrea
PATENT ASSIGNEE(S): Caris Life Sciences Luxembourg Holdings, S.A.R.L., Luxembourg
SOURCE: PCT Int. Appl., 695pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 13
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2012115885 | A1 | 20120830 | WO 2012-US25741 | 20120217 |

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

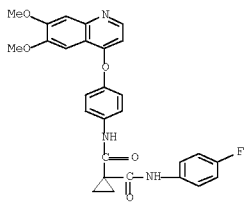
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| CA 2827894 | A1 | 20120830 | CA 2012-2827894 | 20120217 |
| AU 2012220872 | A1 | 20130912 | AU 2012-220872 | 20120217 |
| CN 103492590 | A | 20140101 | CN 2012-80019718 | 20120217 |
| EP 2678448 | A1 | 20140101 | EP 2012-749642 | 20120217 |

R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR

| | | | | |
|---|---|---|---|---|
| JP 2014507160 | T | 20140327 | JP 2013-555467 | 20120217 |
| US 20140141986 | A1 | 20140522 | US 2014-14001016 | 20140207 |

PRIORITY APPLN. INFO.: US 2011-61445273 P 20110222
US 2011-61446313 P 20110224
US 2011-61471417 P 20110404
US 2011-61501680 P 20110627
US 2011-61523763 P 20110815
WO 2012-US25741 W 20120217

AB The invention provides methods for detecting cancer, for detg. whether a cancer is responding to treatment, and /or for determining whether a cancer is likely to respond to treatment that involve detecting of circulating biomarkers. The invention relates that said circulating biomarkers can includie nucleic acids, proteins, vesicles and/or microRNAs. The invention also relates that said biol. samples used in the disclosed methods include isolated extracellular microvesicle populations. The invention also provides kits comprising all reagents used in the disclosed methods. In the examples, the invention disclosed that specific biomarkers are elevated in specific types of cancer, which can used in diagnosis and in determining treatments.
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for detecting cancer and/or determining response to therapeutic agent, and numerous circulating markers (including proteins, nucleic acids and vesicles) used in said methods)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

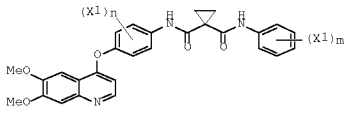


OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

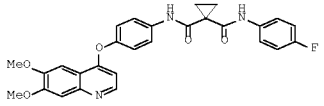
L4 ANSWER 120 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:1201570 CAPLUS Full-text
DOCUMENT NUMBER: 157:382704
TITLE: Processes for preparing quinoline compounds and pharmaceutical compositions containing such compounds
INVENTOR(S): Wilson, Jo Ann
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 49pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2012109510 | A1 | 20120816 | WO 2012-US24591 | 20120210 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| CA 2826751 | A1 | 20120816 | CA 2012-2826751 | 20120210 |
| AU 2012214322 | A1 | 20130829 | AU 2012-214322 | 20120210 |
| AR 85155 | A1 | 20130911 | AR 2012-100446 | 20120210 |
| IL 227848 | A | 20130930 | IL 2012-227848 | 20120210 |
| CN 103459373 | A | 20131218 | CN 2012-80017723 | 20120210 |
| EP 2673262 | A1 | 20131218 | EP 2012-704492 | 20120210 |
| R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME | | | | |
| JP 2014505109 | T | 20140227 | JP 2013-553580 | 20120210 |
| KR 2014044782 | A | 20140415 | KR 2013-7023174 | 20120210 |
| MX 2013009116 | A | 20140131 | MX 2013-9116 | 20130807 |
| ZA 2013006072 | A | 20140430 | ZA 2013-6072 | 20130813 |
| IN 2013KN02666 | A | 20140103 | IN 2013-KN2666 | 20130903 |
| US 20140200242 | A1 | 20140717 | US 2014-13984559 | 20140320 |

PRIORITY APPLN. INFO.: US 2011-61441520 P 20110210
US 2011-61441527 P 20110210
WO 2012-US24591 W 20120210
OTHER SOURCE(S): CASREACT 157:382704; MARPAT 157:382704
GI

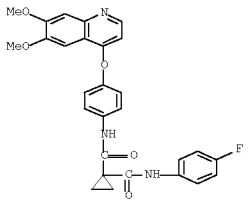


I



II

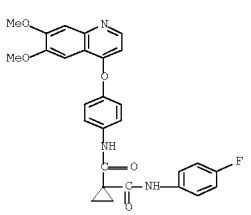
AB The invention is directed to processes for prepg. quinoline compds. of formula I wherein X1 is H, Br, Cl and F; X2 is H, Br, Cl and F; n is 1-2 and m is 1-2; and pharmaceutically acceptable salts thereof. Example compound II L-malate was prepared by chlorination of 6,7-dimethoxyquinolin-4-ol followed by etherification of 4-chloro-6,7-dimethoxyquinoline with 4-aminophenol; the resulting 4-(6,7-dimethoxyquinolin-4-yloxy)phenylamine underwent acylation with 1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl chloride to give compound II, which underwent addition of L-malic acid to give the desired product.
IT 849217-68-1P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



IT 1140909-48-3P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

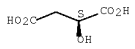
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

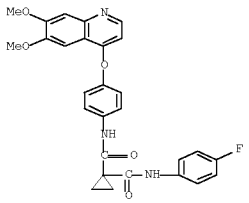


OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 121 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:1051547 CAPLUS Full-text
DOCUMENT NUMBER: 157:218520
TITLE: Molecular diagnostic methods for predicting brain metastasis of breast cancer
INVENTOR(S): Wong, Stephen T. C.; Zhao, Hong
PATENT ASSIGNEE(S): The Methodist Hospital Research Institute, USA
SOURCE: U.S. Pat. Appl. Publ., 53pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 20120184560 | A1 | 20120719 | US 2011-13245706 | 20110926 |

PRIORITY APPLN. INFO.: US 2010-61386186 P 20100924
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB Disclosed are mol. diagnostic compns. and methods for predicting brain metastasis of breast cancer, as well as methods for drug repositioning to identify existing and new therapeutics for use in developing individualized, patient-specific treatment regimens for improving diagnoses and patient outcomes in individuals at risk for brain metastasis of breast cancer.
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mol. diagnostic methods for predicting brain metastasis of breast cancer)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L4 ANSWER 122 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:1042874 CAPLUS Full-text
DOCUMENT NUMBER: 157:221701
TITLE: Bcl-2-like protein 11 (BIM) SRM/MRM assay
INVENTOR(S): Krizman, David B.; Hembrough, Todd; Thyparambil, Sheeno; Liao, Wei-Li
PATENT ASSIGNEE(S): Expression Pathology, Inc., USA
SOURCE: PCT Int. Appl., 28pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2012097276 | A2 | 20120719 | WO 2012-US21283 | 20120113 |
| WO 2012097276 | A3 | 20121129 | | |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| CA 2824752 | A1 | 20120719 | CA 2012-2824752 | 20120113 |
| AU 2012205337 | A1 | 20130801 | AU 2012-205337 | 20120113 |
| IL 227471 | A | 20130829 | IL 2012-227471 | 20120113 |
| EP 2663863 | A2 | 20131120 | EP 2012-734572 | 20120113 |
| R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME | | | | |
| CN 103384828 | A | 20131106 | CN 2011-80068269 | 20111221 |
| KR 2014002711 | A | 20140108 | KR 2013-7019356 | 20111221 |
| JP 2014503821 | T | 20140213 | JP 2013-546392 | 20111221 |
| US 20140024548 | A1 | 20140123 | US 2013-13923316 | 20130620 |
| MX 2013007429 | A | 20140131 | MX 2013-7429 | 20130621 |

PRIORITY APPLN. INFO.: US 2010-61426948 P 20101223
US 2011-61438904 P 20110202
WO 2011-US66624 W 20111221

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

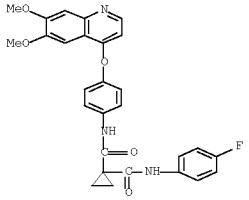
AB The present invention provides methods for selecting a suitable anticancer drug therapy, and for identifying and predicting response, for the treatment of a malignant cancer involving aberrant c-Met signaling. The present invention also provides methods for monitoring the status of a malignant cancer involving aberrant c-Met signaling and monitoring how a patient with the malignant cancer is responding to anticancer drug therapy. Information on the expression and/or activation states of components of signal transduction pathways (e.g., HER3 and/or c-Met signal transduction pathway components) derived from practice of the present invention can be used for malignant cancer diagnosis, prognosis, and in the design of cancer treatments for malignancies involving aberrant c-Met signaling. Certain embodiments comprise administering a cMet inhibitor alone or a cMet inhibitor in combination with a pathway-directed therapy based upon the differences between the expression and/or activation levels of cMet protein and/or HER3 protein in the sample compared to the control protein and/or control sample.

IT [redacted], XL 184
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug selection for therapy for malignancies involving aberrant c-Met signaling using antibody-based arrays)

RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

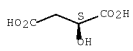
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 124 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:706472 CAPLUS Full-text
DOCUMENT NUMBER: 156:628365

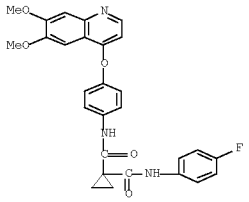
RS, SE, SI, SK, SM, TR

| | | | | |
|---|---|---|---|---|
| JP 2014505251 | T | 20140227 | JP 2013-549580 | 20120113 |
| US 20130302334 | A1 | 20131114 | US 2013-13942574 | 20130715 |
| PRIORITY APPLN. INFO.: | | | US 2011-61432462 P | 20110113 |
| | | | WO 2012-US21283 W | 20120113 |

AB Specific peptides, and derived ionization characteristics of those peptides, from the Bcl-2-like protein 11 (BIM) are provided that are particularly advantageous for quantifying the BIM protein directly in biol. samples that have been fixed in formalin by the method of Selected Reaction Monitoring (SRM) mass spectrometry, or what can also be termed as Multiple Reaction Monitoring (MRM). Such biol. samples are chemical preserved and fixed where the biol. sample is selected from tissues and cells treated with formaldehyde containing agents/fixatives including formalin-fixed tissue/cells, formalin- fixed/paraffin embedded (FFPE) tissue/cells, FFPE tissue blocks and cells from those blocks, and tissue culture cells that have been formalin fixed and or paraffin embedded. A protein sample is prepared from the biol. sample using the Liquid Tissue reagents and protocol, and the BIM protein is quantitated in the Liquid Tissue sample by the method of SRM/MRM mass spectrometry by quantitating in the protein sample at least one or more of the peptides described. These peptides can be quantitated if they reside in a modified or an unmodified form. An example of a modified form of a BIM peptide is phosphorylation of a tyrosine, threonine, serine, and/or other amino acid residues within the peptide sequence. Samples were prepared with Liquid Tissue and digested with trypsin. Three peptides from BIM were found to be suitable for SRM/MRM assay.

IT [redacted], Cabozantinib
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(determination of cancer resistance to; BIM protein determination by determining BIM peptides by SRM/MRM mass spectrometry)

RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L4 ANSWER 123 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:924299 CAPLUS Full-text
DOCUMENT NUMBER: 157:122897

TITLE: Cancer cell-derived receptor activator of the NF-KB ligand drives bone and soft tissue metastases
INVENTOR(S): Chu, Gina C. Y.; Chung, Leland W. K.; Zhau, Haiyen E.; Wang, Ruoxiang
PATENT ASSIGNEE(S): Cedars-Sinai Medical Center, USA
SOURCE: PCT Int. Appl., 143pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2012064967 | A2 | 20120518 | WO 2011-US60204 | 20111110 |
| WO 2012064967 | A3 | 20120705 | | |

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

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|---|---|---|---|---|
| US 20130263297 | A1 | 20131003 | US 2013-13889135 | 20130507 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 2010-61412360 | P | 20101110 |
| US 2011-61442679 | P | 20110214 |
| WO 2011-US60204 | A2 | 20111110 |
| US 2012-61718626 | P | 20121025 |

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The present invention relates to metastases. More specifically, the invention relates to compns. and methods for the inhibition of metastases of cancer cells, such as prostate cancer cells, to bones and soft tissue. The present invention also relates to the treatment of cancer, including but not limited to prostate cancer. Also provided are animal models for studying cancer metastasis; particularly, prostate cancer metastasis.

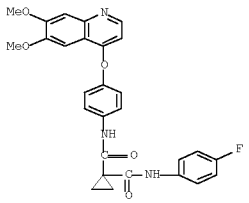
IT 1140909-48-3, XL 184
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cancer cell-derived receptor activator of the NF-KB ligand drives bone and soft tissue metastases)

RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

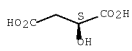
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L4 ANSWER 125 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

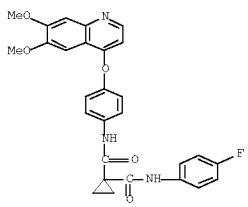
ACCESSION NUMBER: 2012:560657 CAPLUS Full-text
DOCUMENT NUMBER: 158:122090
TITLE: Recent advances in the molecular pathogenesis and targeted therapies of medullary thyroid carcinoma
AUTHOR(S): Almeida, Madson Q.; Hoff, Ana O.
CORPORATE SOURCE: Instituto do Cancer da Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, Brazil
SOURCE: Current Opinion in Oncology (2012), 24(3), 229-234
CODEN: CUOOE8; ISSN: 1040-8746
DIGITAL OBJECT ID: 10.1097/CCO.0b013e328351c71a
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB Purpose of review: This review will focus on the recent advances in mol. pathogenesis and targeted therapies for medullary thyroid carcinoma (MTC). Unlike hereditary MTC in which rearranged during transfection (RET) mutations are the most important precipitating events, in sporadic MTC the genetic or mol. biomarkers are yet to be established. Recent findings: Targeted mol. therapies that inhibit RET and other tyrosine kinase receptors involved in angiogenesis have shown great promise in the treatment of metastatic or locally advanced MTC and are under investigation. In addition, the recent findings of H-RAS mutations in 56% of RET-neg. sporadic MTC and the activation of the mammalian target of rapamycin (mTOR) intracellular signaling pathway in hereditary MTC suggests that addnl. or alternative genetic events are important for MTC pathogenesis. Summary: Recently, vandetanib (ZD6474), an inhibitor of vascular endothelial growth factor receptor (VEGFR) 2 and VEGFR 3, RET, and epidermal growth factor receptor (EGFR), was approved for the treatment of adults with symptomatic or progressive MTC. Significant advantages for vandetanib over placebo were seen in terms of response rate, disease control rate, and biochem. response in a phase III study. Furthermore, cabozantinib (XL184), an inhibitor of VEGFR 1 and VEGFR 2, hepatocyte growth factor receptor (MET), and RET, was associated with partial response and stable disease in 29 and 41%, resp.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vandetanib and cabozantinib was effective in treatment of patient with medullary thyroid carcinoma)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 126 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

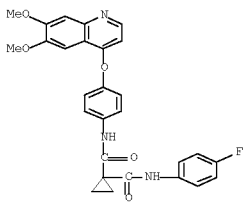
ACCESSION NUMBER: 2012:508891 CAPLUS Full-text
DOCUMENT NUMBER: 158:93453
TITLE: Novel Molecular Targets for the Therapy of Castration-Resistant Prostate Cancer
AUTHOR(S): Agarwal, Neeraj; Sonpavde, Guru; Sternberg, Cora N.
CORPORATE SOURCE: Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA
SOURCE: European Urology (2012), 61(5), 950-960
CODEN: EUURAV; ISSN: 0302-2838
DIGITAL OBJECT ID: 10.1016/j.eururo.2011.12.028
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English

AB A review. Improved understanding of mechanisms underlying metastatic castration-resistant prostate cancer (mCRPC) progression has led to the recognition of multiple mol. targets and advances in the therapeutic landscape. The addition of abiraterone acetate, sipuleucel-T, cabazitaxel, and denosumab to the therapeutic armamentarium and the impending addition of MDV-3100 and radium-223 underscore the importance of androgen pathway inhibition, immunotherapy, tubulin antagonism, and pathophysiol. of bone metastasis. Review the next generation of mol. targets in mCRPC. Medline databases were searched for >100 original articles published as of Oct. 18, 2011, with the search terms metastatic castration-resistant prostate cancer, targeted therapy, biol. agents, and immunotherapy. Proceedings from the last 5 yr of conferences of the American Society of Clin. Oncol., American Urol. Association, European Society of Medical Oncol., and the European Association of Urol. were also searched. We included novel and promising drugs that have reached clin. trial evaluation. The major findings were addressed in an evidence-based fashion. Prospective trials and important preclin. data were analyzed.mCRPC is a disease with multiple mol. drivers. Mol. pathways being targeted in ongoing phase 3 trials are androgen signaling (MDV3100, TAK700), immunoregulatory pathways (ipilimumab, Prostvac-VF-TRICOM), Src (dasatinib), Met (cabozantinib), clusterin (custirsen), and angiogenesis (aflibercept, tasquinimod). The strides made in identifying multiple other novel mol. targets offer potential opportunities for further improving outcomes.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(knowledge on novel mol. targets like Met signaling pathway using drugs like cabozantinib could be more beneficial in patient with metastatic castration-resistant prostate cancer)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 18 THERE ARE 18 CAPLUS RECORDS THAT CITE THIS RECORD (18 CITINGS)
REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

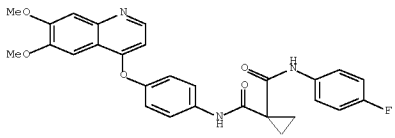
L4 ANSWER 127 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2012:495814 CAPLUS Full-text
DOCUMENT NUMBER: 156:469436
TITLE: Dual inhibitors of Met and VEGF for the treatment of castration- resistant prostate cancer and osteoblastic bone metastases
INVENTOR(S): Smith, David; Hussain, Maha
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 47pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2012044572 | A1 | 20120405 | WO 2011-US53233 | 20110926 |
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| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| CA 2812750 | A1 | 20120405 | CA 2011-2812750 | 20110926 |
| AU 2011307304 | A1 | 20130502 | AU 2011-307304 | 20110926 |
| IL 225507 | A | 20130530 | IL 2011-225507 | 20110926 |
| EP 2621481 | A1 | 20130807 | EP 2011-764655 | 20110926 |
| R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME | | | | |
| JP 2013537916 | T | 20131007 | JP 2013-530386 | 20110926 |
| CN 103402505 | A | 20131120 | CN 2011-80056580 | 20110926 |
| KR 2014025304 | A | 20140304 | KR 2013-7010372 | 20110926 |
| MX 2013003594 | A | 20130801 | MX 2013-3594 | 20130327 |
| ZA 2013002422 | A | 20131223 | ZA 2013-2422 | 20130404 |
| IN 2013KN00998 | A | 20130906 | IN 2013-KN998 | 20130409 |
| US 20140057943 | A1 | 20140227 | US 2013-13876290 | 20131105 |

PRIORITY APPLN. INFO.:
US 2010-61386959 P 20100927
US 2011-61481671 P 20110502
WO 2011-US53233 W 20110926

OTHER SOURCE(S): CASREACT 156:469436; MARPAT 156:469436
GI

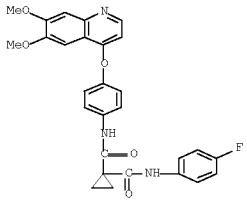


AB This invention is directed to the treatment of cancer, particularly castration-resistant prostate cancer and osteoblastic bone metastases, with a dual inhibitor of MET and VEGF.

IT 849217-68-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(dual inhibitors of Met and VEGF for treatment of castration resistant prostate cancer and osteoblastic bone metastases)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



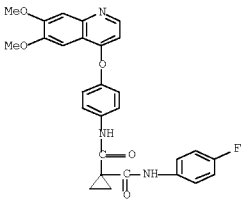
IT 1140909-48-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(dual inhibitors of Met and VEGF for treatment of castration resistant prostate cancer and osteoblastic bone metastases)

RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

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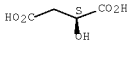
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



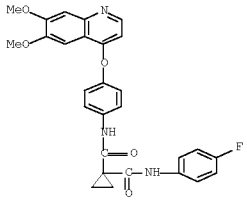
IT 1365530-43-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dual inhibitors of Met and VEGF for treatment of castration resistant prostate cancer and osteoblastic bone metastases)

RN 1365530-43-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

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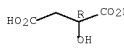
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 636-61-3
CMF C4 H6 O5

Absolute stereochemistry. Rotation (+).



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 128 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:495788 CAPLUS Full-text
DOCUMENT NUMBER: 156:469435
TITLE: Dual inhibitors of Met and VEGF for the treatment of castration resistant prostate cancer and osteoblastic bone metastases
INVENTOR(S): Smith, David; Hussain, Maha
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 70pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2012044577 | A1 | 20120405 | WO 2011-US53245 | 20110926 |
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KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

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| CA 2812744 | A1 | 20120405 | CA 2011-2812744 | | 20110926 |
| AU 2011307309 | A1 | 20130502 | AU 2011-307309 | | 20110926 |
| EP 2621483 | A1 | 20130807 | EP 2011-764657 | | 20110926 |
| R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR | | | | | |
| JP 2013537918 | T | 20131007 | JP 2013-530392 | | 20110926 |
| CN 103391773 | A | 20131113 | CN 2011-80056999 | | 20110926 |
| US 20140057908 | A1 | 20140227 | US 2013-13876306 | | 20131108 |
| PRIORITY APPLN. INFO.: | | | US 2010-61386971 | P | 20100927 |
| | | | US 2010-61386983 | P | 20100927 |
| | | | US 2010-61386993 | P | 20100927 |
| | | | WO 2011-US53245 | W | 20110926 |

OTHER SOURCE(S): CASREACT 156:469435; MARPAT 156:469435

AB This invention discloses compds. directed at the treatment of cancer, particularly castration- resistant prostate cancer and osteoblastic bone metastases, with a dual inhibitor of MET and VEGF.

IT 1140909-48-3P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(dual inhibitors of Met and VEGF for treatment of castration resistant prostate cancer and osteoblastic bone metastases)

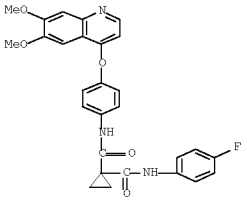
RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

CRN 849217-68-1

CMF C28 H24 F N3 O5

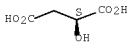


CM 2

CRN 97-67-6

CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



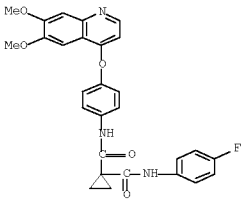
IT 849217-68-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(dual inhibitors of Met and VEGF for treatment of castration resistant prostate cancer and osteoblastic bone metastases)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 129 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2012:425741 CAPLUS Full-text

DOCUMENT NUMBER: 156:412018

TITLE: Methods of using C-met modulators as Anticancer agents

INVENTOR(S): Bannen, Lynne Canne; Chan, Diva Sze-Ming; Forsyth, Timothy Patrick; Khoury, Richard George; Leahy, James William; Mac, Morrison B.; Mann, Larry W.; Nuss, John M.; Parks, Jason Jevious; Wang, Yong; Xu, Wei; Simeone, Diane

PATENT ASSIGNEE(S): Exelixis, Inc., USA

SOURCE: U.S. Pat. Appl. Publ., 25pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

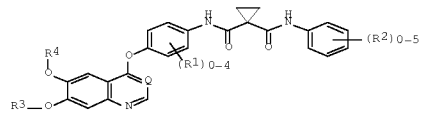
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| US 20120070368 | A1 | 20120322 | US 2011-13087094 | | 20110414 |
| PRIORITY APPLN. INFO.: | | | US 2010-61325095 | P | 20100416 |

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 156:412018; MARPAT 156:412018

GI



I

AB Disclosed are methods of treating cancer by administering a compd. of Formula I (wherein R1, R2 = independently, halo; R3, R4 = independently, (C1-C6)-alkyl; Q = CH, N) in combination with gemcitabine (GEM).

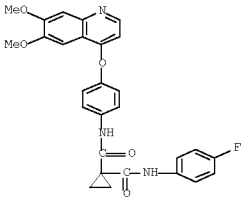
IT 849217-68-1P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(c-met modulators as antitumor agents)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



IT 1365530-43-3P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(c-met modulators as antitumor agents)

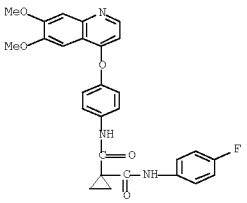
RN 1365530-43-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

CRN 849217-68-1

CMF C28 H24 F N3 O5

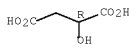


CM 2

CRN 636-61-3

CMF C4 H6 O5

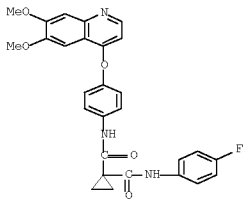
Absolute stereochemistry. Rotation (+).



L4 ANSWER 130 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:373163 CAPLUS Full-text
DOCUMENT NUMBER: 157:622817
TITLE: Multi-targeted tyrosine kinase inhibitors in clinical development: focus on XL-184 (cabozantinib)
AUTHOR(S): Bowles, D. W.; Kessler, E. R.; Jimeno, A.
CORPORATE SOURCE: Division of Medical Oncology, University of Colorado Denver, Aurora, CO, USA
SOURCE: Drugs of Today (2011), 47(11), 857-868
CODEN: MDACAP; ISSN: 1699-3993
DIGITAL OBJECT ID: 10.1358/dot.2011.47.11.1688487
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. XL-184 (cabozantinib) is a novel, small-mol., multi-targeted receptor tyrosine kinase inhibitor with particular activity against hepatocyte growth factor receptor (tyrosine-protein kinase Met), vascular endothelial growth factor receptor 2 (VEGFR-2) and proto-oncogene tyrosine-protein kinase receptor Ret. There is ample evidence of Met, VEGFR-2 and Ret signaling in several tumor types. Preclin. data suggest that XL-184 has activity in tumors derived from both epithelial and mesenchymal origins. Phase I and II clin. studies support significant antitumor activity, particularly in medullary thyroid cancer and cancers metastatic to the bone. This review will evaluate XL-184's preclin. pharmacol., pharmacokinetics, drug interactions and clin. activity in phase I through phase III studies.
IT 1140909-48-3, XL184
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(focus on XL-184 (cabozantinib) is a novel multi-targeted tyrosine kinase inhibitors in clin. development)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

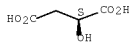
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

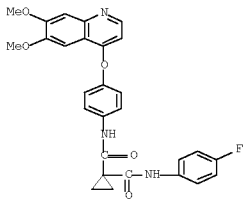


OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT: 85 THERE ARE 85 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 131 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:345887 CAPLUS Full-text
DOCUMENT NUMBER: 156:388076
TITLE: C-met biomarker in treatment efficacy and prognosis
INVENTOR(S): Patel, Premal; Peterson, Amy C.; Yauch, Robert L.; Zha, Jiping
PATENT ASSIGNEE(S): Genentech, Inc., USA
SOURCE: PCT Int. Appl., 134pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2012031027 | A1 | 20120308 | WO 2011-US50069 | 20110831 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, | | | | |
| MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| CA 2808236 | A1 | 20120308 | CA 2011-2808236 | 20110831 |
| US 20120089541 | A1 | 20120412 | US 2011-13223173 | 20110831 |
| AU 2011295919 | A1 | 20130307 | AU 2011-295919 | 20110831 |
| IL 224962 | A | 20130430 | IL 2011-224962 | 20110831 |
| EP 2612151 | A1 | 20130710 | EP 2011-754597 | 20110831 |
| R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME | | | | |
| CN 103221825 | A | 20130724 | CN 2011-80051781 | 20110831 |
| KR 2013103734 | A | 20130924 | KR 2013-7008025 | 20110831 |
| JP 2013537966 | T | 20131007 | JP 2013-526209 | 20110831 |
| ZA 2013001175 | A | 20140430 | ZA 2013-1175 | 20110831 |
| MX 2013002084 | A | 20130509 | MX 2013-2084 | 20130221 |
| AU 2013202759 | A1 | 20130502 | AU 2013-202759 | 20130406 |
| US 20140037625 | A1 | 20140206 | US 2013-14046867 | 20131004 |
| PRIORITY APPLN. INFO.: | | | US 2010-61378911 P | 20100831 |
| | | | US 2010-61389922 P | 20101005 |
| | | | US 2010-61390995 P | 20101007 |
| | | | US 2010-61420703 P | 20101207 |
| | | | US 2011-61487527 P | 20110518 |
| | | | US 2011-61492338 P | 20110601 |
| | | | US 2011-61503489 P | 20110630 |
| | | | AU 2011-295919 A3 | 20110831 |
| | | | US 2011-13223173 B1 | 20110831 |
| | | | WO 2011-US50069 W | 20110831 |

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB The authors disclose the use of c-met as a biomarker for patient selection and patient prognosis in cancer. In a clin. trial, combination treatment with MetMAb (onartuzumab) and erlotinib provided a clin. meaningful benefit to patients with non-small cell lung cancer (NSCLC) that expressed high levels of c-met biomarker. The results showed that the efficacy, as evaluated by progression free survival (PFS) and overall survival (OS), was pos. especially when compared to PFS and OS data for erlotinib treatment alone. The addition of MetMAb to erlotinib nearly doubled the progression free and overall survival in patients with NSCLC that expressed high levels of c-met biomarker. The clin. trial data also showed that treatment with MetMAb in combination with erlotinib increased the risk of progression and death in patients with NSCLC that expressed low levels of c-met biomarker.
IT 849217-68-1, Cabozantinib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Met receptor as biomarker for combination therapy efficacy and cancer prognosis)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

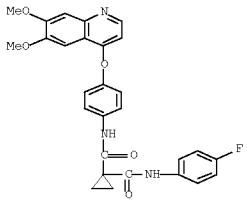
L4 ANSWER 132 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:340365 CAPLUS Full-text
DOCUMENT NUMBER: 156:380310
TITLE: Synergistic drug combination for the treatment of cancer
INVENTOR(S): Gusenbauer, Simone; Ullrich, Axel
PATENT ASSIGNEE(S): Max-Planck-Gesellschaft zur Foerderung der Wissenschaften e.V., Germany
SOURCE: Eur. Pat. Appl., 111pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 2425830 | A1 | 20120307 | EP 2010-75382 | 20100903 |
| R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BA, ME, RS | | | | |
| PRIORITY APPLN. INFO.: | | | EP 2010-75382 | 20100903 |

AB The invention relates to synergistic drug combinations and the use of said drug combinations for the treatment of proliferative diseases such as cancer. Combination of drugs include e.g. chlorethamine, cyclophosphamide, trofosfamide, daunorubicin, doxorubicin, mitomycin C.
IT 1140909-48-3, XL184
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic drug combination for treatment of cancer)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

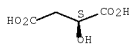
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



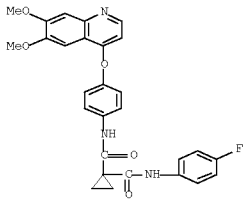
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 133 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:265414 CAPLUS Full-text
DOCUMENT NUMBER: 156:357951
TITLE: Circulating biomarkers for disease
INVENTOR(S): Spetzler, David; Holterman, Daniel; Pawlowski, Traci; Kuslich, Christine
PATENT ASSIGNEE(S): Caris Life Sciences Luxembourg Holdings, Luxembourg
SOURCE: PCT Int. Appl., 639pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 13
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2012024543 | A1 | 20120223 | WO 2011-US48327 | 20110818 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| CA 2808417 | A1 | 20120223 | CA 2011-2808417 | 20110818 |
| AU 2011291599 | A1 | 20130307 | AU 2011-291599 | 20110818 |
| EP 2606353 | A1 | 20130626 | EP 2011-818814 | 20110818 |
| R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR | | | | |
| JP 2013540995 | T | 20131107 | JP 2013-526012 | 20110818 |
| US 20140148350 | A1 | 20140529 | US 2013-13817383 | 20130520 |
| PRIORITY APPLN. INFO.: | | | US 2010-61374951 | P 20100818 |
| | | | US 2010-61379670 | P 20100902 |
| | | | US 2010-61381305 | P 20100909 |
| | | | US 2010-61383305 | P 20100915 |
| | | | US 2010-61391504 | P 20101008 |
| | | | US 2010-61393823 | P 20101015 |
| | | | US 2010-61411890 | P 20101109 |
| | | | US 2010-61413377 | P 20101112 |
| | | | US 2010-61414870 | P 20101117 |
| | | | US 2010-61416560 | P 20101123 |
| | | | US 2010-61421851 | P 20101210 |
| | | | US 2010-61423557 | P 20101215 |
| | | | US 2010-61428196 | P 20101229 |
| | | | US 2011-61471417 | P 20110404 |
| | | | WO 2011-US48327 | W 20110818 |

AB Biomarkers can be assessed for diagnostic, therapy-related or prognostic methods to identify phenotypes, such as a condition or disease, or the stage or progression of a disease. Circulating biomarkers from a bodily fluid can be used in profiling of physiol. states or determining phenotypes. These include nucleic acids, protein, and circulating structures such as vesicles. Biomarkers can be used for theranostic purposes to select candidate treatment regimens for diseases, conditions, disease stages, and stages of a condition, and can also be used to determine treatment efficacy. The biomarkers can be circulating biomarkers, including vesicles and microRNA. Various anti-DLL4 antibodies were tethered to beads and used to capture vesicles in blood samples from subjects with breast cancer, colorectal cancer or normal subjects. The bead captured vesicles were detected with fluorescently-labeled antibodies against the tetraspanins CD9, CD63, and CD81. The median fluorescence intensity of the captured and labeled vesicles was measured using laser detection. There were noticeable differences both among normals and breast cancer plasma as well as between the avs. of normals and cancer patients.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological activity); USES (Uses)
(DLL4, vesicle, and microRNA circulating biomarkers for disease diagnosis, therapy, prognosis, or theranostics)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

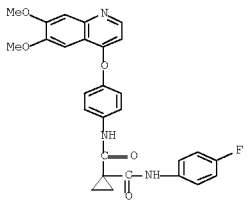


OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 134 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:155432 CAPLUS Full-text
DOCUMENT NUMBER: 157:565304
TITLE: Drug development to overcome resistance to EGFR inhibitors in lung and colorectal cancer
AUTHOR(S): Dienstmann, Rodrigo; De Dosso, Sara; Felip, Enriqueta; Tabernero, Josep
CORPORATE SOURCE: Medical Oncology Department, Vall d'Hebron University Hospital, Universitat Autonoma de Barcelona, Barcelona, 08035, Spain
SOURCE: Molecular Oncology (2012), 6(1), 15-26
CODEN: MOONC3; ISSN: 1574-7891
DIGITAL OBJECT ID: 10.1016/j.molonc.2011.11.009
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English

AB A review. Epidermal growth factor receptor (EGFR) is a validated target in different human malignancies. EGFR tyrosine kinase inhibitors (TKIs) are known to contribute considerably to the extension of progression-free survival in EGFR-mutant non-small cell lung cancer and monoclonal antibodies (mAbs) targeting EGFR have also improved the efficacy outcomes in KRAS wild-type colorectal cancer. Nevertheless, a significant percentage of lung and colorectal cancer patients do not respond to anti-EGFR agents and secondary resistance after initial benefit is a challenging reality faced by clinicians. Extensive preclin. work on the potential mechanisms of resistance to EGFR inhibitors in different disease settings has guided the development of second-generation irreversible EGFR TKIs, more efficient anti-EGFR mAbs, and combination strategies with agents targeting other receptors and downstream effectors. In order to elucidate the role of the multiple therapeutic strategies under investigation to overcome EGFR inhibitors-resistance, rational drug development based on stringent preclin. data, biomarker validation and proper selection of patients in the ongoing clin. trials are of paramount importance. Preliminary results of clin. trials evaluating these approaches will be discussed in this manuscript, with emphasis on TKIs in lung cancer and mAbs in advanced colorectal cancer.

IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug development to overcome resistance to EGFR inhibitors in lung and colorectal cancer)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT: 83 THERE ARE 83 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 135 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:99813 CAPLUS Full-text
DOCUMENT NUMBER: 157:249246
TITLE: HGF/c-MET targeted therapeutics: novel strategies for cancer medicine
AUTHOR(S): Yap, Timothy A.; Sandhu, Shahneen K.; Alam, Salma M.; de Bono, Johann S.
CORPORATE SOURCE: The Royal Marsden NHS Foundation Trust, Sutton, Surrey, SM2 5PT, UK
SOURCE: Current Drug Targets (2011), 12(14), 2045-2058
CODEN: CDTUAU; ISSN: 1389-4501
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The hepatocyte growth factor/mesenchymal-epithelial transition factor (HGF/c-MET) receptor tyrosine kinase (RTK) pathway plays a pleotropic role in cell proliferation, migration, invasion, angiogenesis and survival. Although it has critical physiol. functions in embryonic development and

tissue repair, this signaling cascade is frequently deregulated in a wide range of tumors. Aberrant HGF/c-MET signaling, driven by various mechanisms, including constitutive activation and over-expression, has multifunctional effects in oncogenesis and is implicated in the acquisition of an aggressive phenotype with metastatic potential. The central role of c-MET activity in cancer progression, as well as disparities between quiescent HGF/c-MET signaling in normal tissue and overexpression in tumor may provide a degree of tumor selectivity for therapeutic intervention, making HGF or c-MET inhibition an attractive proposition in oncol. This review focuses on the underlying oncogenic role of aberrant HGF/c-MET signaling in malignant progression, as well as recent preclin. and clin. data on the different strategies employed in inhibiting HGF/c-MET function.

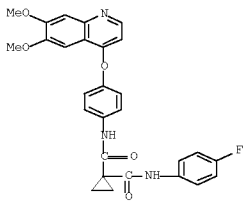
IT 1140909-48-3, XL 184
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapies targeting hepatocyte growth factor/mesenchymal-epithelial transition factor signaling involved in cell proliferation, migration, invasion, angiogenesis and survival may be useful for treatment of patient with cancer)

RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

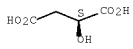
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)
REFERENCE COUNT: 134 THERE ARE 134 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 136 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:94602 CAPLUS Full-text
DOCUMENT NUMBER: 156:167648
TITLE: Administration of hypoxia activated prodrugs and antiangiogenic agents for the treatment of cancer
INVENTOR(S): Hart, Charles; Curd, John; Kroll, Stewart; Sun, Jessica
PATENT ASSIGNEE(S): Threshold Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 36pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2012009288 | A2 | 20120119 | WO 2011-US43594 | 20110711 |
| WO 2012009288 | A9 | 20120419 | | |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| CA 2803675 | A1 | 20120119 | CA 2011-2803675 | 20110711 |
| KR 2013045341 | A | 20130503 | KR 2013-7002206 | 20110711 |
| EP 2593139 | A2 | 20130522 | EP 2011-807356 | 20110711 |
| R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR | | | | |
| JP 2013531038 | T | 20130801 | JP 2013-519747 | 20110711 |
| MX 2012014428 | A | 20130305 | MX 2012-14428 | 20121210 |
| ZA 2013000692 | A | 20130925 | ZA 2013-692 | 20130125 |
| US 20140010805 | A1 | 20140109 | US 2013-13809135 | 20130724 |

| PRIORITY APPLN. INFO.: | | | |
|---|---|---|---|
| | US 2010-61363610 | P | 20100712 |
| | US 2011-61470412 | P | 20110331 |
| | US 2011-61470812 | P | 20110401 |

WO 2011-US43594 W 20110711

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB Administration of a hypoxia activated prodrug in combination with an antiangiogenic agent is useful for treating cancer. Hypoxia activated prodrug is selected from the group consisting of TH-281, TH-302, and TH-308. The antiangiogenic agent is selected from the group consisting of an anti-VEGF antibody, a VEGF-trap, an anti-VEGFR antibody, a VEGFR inhibitor, thalidomide etc.

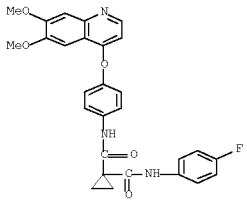
IT 1140909-48-3, XL-184
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(administration of hypoxia activated prodrugs and antiangiogenic agents for treatment of cancer)

RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

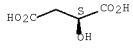
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

L4 ANSWER 137 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:90800 CAPLUS Full-text
DOCUMENT NUMBER: 156:186804
TITLE: C-met modulator pharmaceutical compositions comprising N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide
INVENTOR(S): Wilson, Jo Ann
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 40pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2012009722 | A1 | 20120119 | WO 2011-US44378 | 20110718 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| CA 2805645 | A1 | 20120119 | CA 2011-2805645 | 20110718 |
| AR 82252 | A1 | 20121121 | AR 2011-102584 | 20110718 |
| AU 2011278950 | A1 | 20130307 | AU 2011-278950 | 20110718 |
| IL 224189 | A | 20130324 | IL 2011-224189 | 20110718 |
| EP 2593090 | A1 | 20130522 | EP 2011-740764 | 20110718 |
| R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME | | | | |
| CN 103221035 | A | 20130724 | CN 2011-80044602 | 20110718 |
| JP 2013531045 | T | 20130801 | JP 2013-519870 | 20110718 |
| KR 2013137586 | A | 20131217 | KR 2013-7003043 | 20110718 |
| IN 2013KN00112 | A | 20130705 | IN 2013-KN112 | 20130114 |
| MX 2013000567 | A | 20130501 | MX 2013-567 | 20130115 |
| ZA 2013000458 | A | 20130925 | ZA 2013-458 | 20130117 |
| US 20130337015 | A1 | 20131219 | US 2013-13810537 | 20130826 |

| PRIORITY APPLN. INFO.: | | | |
|---|---|---|---|
| | US 2010-61365253 | P | 20100716 |
| | US 2010-61370843 | P | 20100805 |
| | WO 2011-US44378 | W | 20110718 |

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

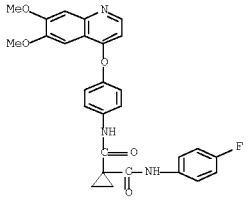
OTHER SOURCE(S): CASREACT 156:186804

AB Pharmaceutical compns. and unit dosage forms comprising N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (I) are disclosed. Thus, 6,7-dimethoxyquinolin-4-ol was converted to 4-chloro-6.7-dimethoxyquinoline followed by reaction with 4-aminphenol to give 4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylamine. This was further

allowed to react with 1-(4-fluorophenylcarbamoyl)cyclopropanecarbonyl chloride to give I. A tablet composition comprised 31.68% along with excipients such as microcryst. cellulose 38.85, lactose, HPC, and Croscarmellose sodium.

IT 849217-68-1 1140909-48-3, Cabozantinib S-malate
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(C-met modulator pharmaceutical compns. comprising dimethoxyquinolinyloxyphenyl(fluorophenyl)cyclopropanedicarboxamide)

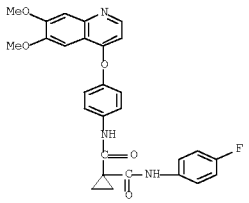
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

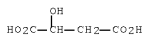


RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

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CRN 849217-68-1
CMF C28 H24 F N3 O5

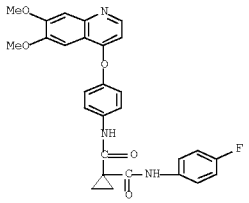




RN 1235470-38-8 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:?) (CA INDEX NAME)

CM 1

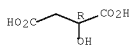
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 636-61-3
CMF C4 H6 O5

Absolute stereochemistry. Rotation (+).



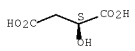
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 138 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:10093 CAPLUS full-text
DOCUMENT NUMBER: 157:152076
TITLE: In the clinic: ongoing clinical trials evaluating

CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

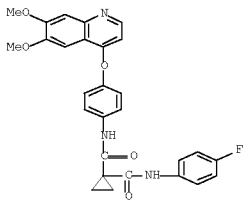


IT 1235470-36-6 1235670-38-8
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C-met modulator pharmaceutical compns. comprising dimethoxyquinolinyloxyphenyl(fluorophenyl)cyclopropanedicarboxamide)

RN 1235470-36-6 CAPLUS
CN Butanedioic acid, 2-hydroxy-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:?) (CA INDEX NAME)

CM 1

CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 6915-15-7
CMF C4 H6 O5

c-MET-inhibiting drugs
AUTHOR(S): Sharma, Neelesh; Adjei, Alex A.
CORPORATE SOURCE: Department of Medicine, Roswell Park Cancer Institute, Buffalo, NY, USA
SOURCE: Therapeutic Advances in Medical Oncology (2011), 3(Suppl. 1), S37-S50
CODEN: TAMOB8; ISSN: 1758-8340
DIGITAL OBJECT ID: 10.1177/1758834011423403
PUBLISHER: Sage Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

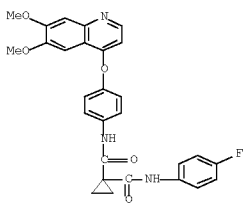
AB A review. The c-MET (mesenchymal-epithelial transition factor) pathway is dysregulated in many human cancers and promotes tumor growth, invasion and dissemination. The c-MET receptor tyrosine kinase can be activated via gene mutation, gene amplification, protein overexpression and/or a Ligand-dependent autocrine/paracrine loop. Abnormalities in c-MET signaling have been reported to correlate with poor clin. outcomes and drug resistance in patients with cancer. Significant progress has been made in advancement of c-MET pathway inhibitors through to clin. trials. A robust pipeline of high-quality inhibitors targeting different aspects of c-MET activation is currently being explored in phase I, II and III clin. trials across multiple tumor types. Preliminary data demonstrate promising clin. activity with these agents, along with an acceptable toxicity profile. In this manuscript, the pharmacol. profile of drugs targeting the c-MET pathway and available data from ongoing clin. trials of these drugs are discussed.

IT 1140909-48-3, X1184
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ongoing clin. trials evaluating mesenchymal-epithelial transition factor-inhibiting drugs)

RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

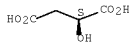
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

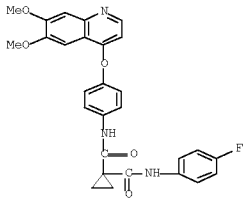
CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 139 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2011:1586879 CAPLUS Full-text
DOCUMENT NUMBER: 156:655505
TITLE: Cabozantinib (XL184), a Novel MET and VEGFR2 Inhibitor, Simultaneously Suppresses Metastasis, Angiogenesis, and Tumor Growth
AUTHOR(S): Yakes, F. Michael; Chen, Jason; Tan, Jenny; Yamaguchi, Kyoko; Shi, Yongchang; Yu, Peiwen; Qian, Fawn; Chu, Felix; Bentzien, Frauke; Cancilla, Belinda; Orf, Jessica; You, Andrew; Laird, A. Douglas; Engst, Stefan; Lee, Lillian; Lesch, Justin; Chou, Yu-Chien; Joly, Alison H.
CORPORATE SOURCE: Exelixis, Inc., South San Francisco, CA, 94083, USA
SOURCE: Molecular Cancer Therapeutics (2011), 10(12), 2298-2308
CODEN: MCTOCF; ISSN: 1535-7163
DIGITAL OBJECT ID: 10.1158/1535-7163.MCT-11-0264
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The signaling pathway of the receptor tyrosine kinase MET and its ligand hepatocyte growth factor (HGF) is important for cell growth, survival, and motility and is functionally linked to the signaling pathway of VEGF, which is widely recognized as a key effector in angiogenesis and cancer progression. Dysregulation of the MET/VEGF axis is found in a number of human malignancies and has been associated with tumorigenesis. Cabozantinib (XL184) is a small-mol. kinase inhibitor with potent activity toward MET and VEGF receptor 2 (VEGFR2), as well as a number of other receptor tyrosine kinases that have also been implicated in tumor pathobiol., including RET, KIT, AXL, and FLT3. Treatment with cabozantinib inhibited MET and VEGFR2 phosphorylation in vitro and in tumor models in vivo and led to significant redns. in cell invasion in vitro. In mouse models, cabozantinib dramatically altered tumor pathol., resulting in decreased tumor and endothelial cell proliferation coupled with increased apoptosis and dose-dependent inhibition of tumor growth in breast, lung, and glioma tumor models. Importantly, treatment with cabozantinib did not increase lung tumor burden in an exptl. model of metastasis, which has been observed with inhibitors of VEGF signaling that do not target MET. Collectively, these data suggest that cabozantinib is a promising agent for inhibiting tumor angiogenesis and metastasis in cancers with dysregulated MET and VEGFR signaling. Mol Cancer Ther; 10(12); 2298-308.
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cabozantinib inhibited proliferation of human, mouse and rat cancer cell and suppressed metastasis, angiogenesis, tumor growth via inhibiting MET and VEGFR2 protein phosphorylation in mouse and rat xenografted with cancer)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 114 THERE ARE 114 CAPLUS RECORDS THAT CITE THIS RECORD (114 CITINGS)
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 140 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2011:1503311 CAPLUS Full-text
DOCUMENT NUMBER: 155:694113
TITLE: Replication-competent retroviral vectors carrying expression cassettes for cytosine deaminase variants
INVENTOR(S): Gruber, Harry E.; Jolly, Douglas J.; Perez, Omar D.; Logg, Christopher R.
PATENT ASSIGNEE(S): Tocagen Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 207pp., Cont.-in-part of Appl. No. PCT/US2009/058512.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

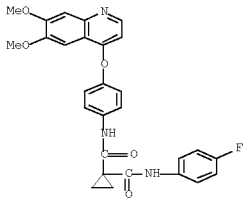
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| US 20110287020 | A1 | 20111124 | US 2011-13072704 | 20110326 |
| US 8829173 | B2 | 20140909 | | |
| WO 2010036986 | A2 | 20100401 | WO 2009-US58512 | 20090926 |
| WO 2010036986 | A3 | 20100701 | | |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA | | | | |
| WO 2011126864 | A2 | 20111013 | WO 2011-US30402 | 20110329 |
| WO 2011126864 | A3 | 20120419 | | |
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| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| EP 2547353 | A2 | 20130123 | EP 2011-766479 | 20110329 |
| R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR | | | | |
| JP 2013523754 | T | 20130617 | JP 2013-502771 | 20110329 |
| US 20130130986 | A1 | 20130523 | US 2013-13638490 | 20130116 |
| AU 2013205006 | A1 | 20130516 | AU 2013-205006 | 20130413 |

PRIORITY APPLN. INFO.:
US 2008-61100666 P 20080926
US 2008-61120618 P 20081208
US 2009-61186823 P 20090613
WO 2009-US58512 A2 20090926
US 2010-61318728 P 20100329
AU 2009-303690 A3 20090926
WO 2011-US30402 W 20110329

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB Methods of delivering cytosine deaminase variants for prodrug activation using retroviral expression vectors are described. The vector includes the viral gag, pol, and env genes with the cytosine deaminase gene being coexpressed using an internal ribosome entry site. Vectors were derived from the prior art pACE-GFPemd vector. The envelope protein of the virus is amphotropic and excess viral sequences outside the long terminal repeats were removed. The resulting vector was named pACE-emdGFP. The vector was stable in storage and replicated efficiently in mammalian cells and could be used to deliver a range of therapeutic genes. The Saccharomyces cerevisiae cytosine deaminase gene was modified to give a codon usage suitable for mammalian cells and to improve thermostability of the enzyme. Use of these vectors results in high intracellular copy nos. for the therapeutic gene and these cells can be superinfected by the vector.
IT 1140909-48-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in cancer therapy with retroviral gene therapy vectors; replication-competent retroviral vectors carrying expression cassettes for cytosine deaminase variants)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

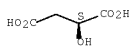
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



L4 ANSWER 141 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2011:1304241 CAPLUS Full-text
DOCUMENT NUMBER: 155:559702
TITLE: Detection of circulating mRNA, microRNA, protein and vesicle markers in disease diagnosis and selection of therapies
INVENTOR(S): Kuslich, Christine; Poste, George; Klass, Michael;

Spetzler, David; Pawlowski, Traci
PATENT ASSIGNEE(S): Caris Life Sciences Luxembourg Holdings, Luxembourg
SOURCE: PCT Int. Appl., 584pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 13
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 2011127219 | A1 | 20111013 | WO 2011-US31479 | 20110406 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| CA 2795776 | A1 | 20111013 | CA 2011-2795776 | 20110406 |
| AU 2011237669 | A1 | 20121101 | AU 2011-237669 | 20110406 |
| IL 222232 | A | 20121129 | IL 2011-222232 | 20110406 |
| EP 2556172 | A1 | 20130213 | EP 2011-766687 | 20110406 |
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| CN 103025890 | A | 20130403 | CN 2011-80027541 | 20110406 |
| KR 2013043104 | A | 20130429 | KR 2012-7028831 | 20110406 |
| JP 2013526852 | T | 20130627 | JP 2013-503934 | 20110406 |
| US 20140162888 | A1 | 20140612 | US 2013-13639756 | 20130424 |

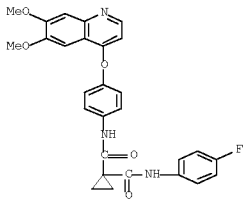
PRIORITY APPLN. INFO.:

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| US 2010-61321392 | P | 20100406 |
| US 2010-61321407 | P | 20100406 |
| US 2010-61322690 | P | 20100409 |
| US 2010-61332174 | P | 20100506 |
| US 2010-61334547 | P | 20100513 |
| US 2010-61348214 | P | 20100525 |
| US 2010-61348685 | P | 20100526 |
| US 2010-61354125 | P | 20100611 |
| US 2010-61355387 | P | 20100616 |
| US 2010-61356974 | P | 20100621 |
| US 2010-61357517 | P | 20100622 |
| US 2010-61362674 | P | 20100708 |
| US 2010-61364785 | P | 20100715 |
| US 2010-61370088 | P | 20100802 |
| US 2010-61379670 | P | 20100902 |
| US 2010-61381305 | P | 20100909 |
| US 2010-61383305 | P | 20100915 |
| US 2010-61391504 | P | 20101008 |
| US 2010-61393823 | P | 20101015 |
| US 2010-61411890 | P | 20101109 |
| US 2010-61413377 | P | 20101112 |
| US 2010-61416560 | P | 20101123 |

WO 2011-US31479 W 20110406
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB Biomarkers can be assessed for diagnostic, therapy-related or prognostic methods to identify phenotypes, such as a condition or disease, or the stage or progression of a disease. Circulating biomarkers from a bodily fluid can be used in profiling of physiol. states or determining phenotypes. These include nucleic acids, protein, and circulating structures such as vesicles. Biomarkers can be used for theranostic purposes to select candidate treatment regimens for diseases, conditions, disease stages, and stages of a condition, and can also be used to determine treatment efficacy. The biomarkers can be circulating biomarkers, including microvesicles and their protein content and microRNAs.
IT 1140909-48-3, XL184
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(selection for cancer therapy; detection of circulating mRNA, microRNA, protein and vesicle markers in disease diagnosis)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

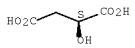
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

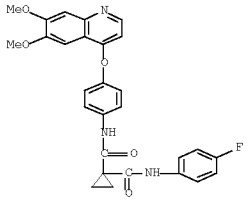


OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 142 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2011:1016190 CAPLUS Full-text
DOCUMENT NUMBER: 156:353197
TITLE: Biologically targeted therapies for thyroid cancers
AUTHOR(S): Sherman, Steven I.
CORPORATE SOURCE: Department of Endocrine Neoplasia and Hormonal Disorders Division of Internal Medicine, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA
SOURCE: Thyroid Cancer (2011), 329-349. Editor(s): Carpi, Angelo; Mechanick, Jeffrey I. CRC Press: Boca Raton, Fla.
CODEN: 69OKVM; ISBN: 978-1-4398-6221-6
DIGITAL OBJECT ID: 10.1201/b10945-21
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review. Systemic chemotherapies for advanced or metastatic thyroid carcinomas have been of only limited effectiveness. For patients with differentiated thyroid epithelial or medullary thyroid carcinomas unresponsive to conventional treatments, novel therapies are needed to improve disease outcomes. Multiple novel therapies primarily targeting angiogenesis have entered clin. trials for metastatic thyroid carcinoma. Partial response rates up to 30% have been reported in single agent studies, but prolonged disease stabilization is more commonly seen. The most successful agents target the vascular endothelial growth factor receptors, with potential targets including the mutant kinases associated with papillary and medullary oncogenesis. Two drugs approved for other malignancies, sorafenib and sunitinib, have had promising preliminary results reported, and are being used selectively for patients who do not qualify for clin. trials. Addnl. agents targeting tumor vasculature, nuclear receptors, epigenetic abnormalities, and the immune response to neoplasia have also been investigated. Randomized trials for several agents are under way that may lead to eventual drug approval for thyroid cancer. Treatment for patients with metastatic or advanced thyroid carcinoma now emphasizes clin. trial opportunities for novel agents with considerable promise. Alternative options now exist for use of these mol. targeted therapies, especially tyrosine kinase inhibitors, which are well tolerated and may prove worthy of regulatory approval for this disease.
IT 1140909-48-3, XL 184
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biol. targeted therapies for thyroid cancer)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

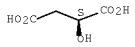
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 128 THERE ARE 128 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 143 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2011:991678 CAPLUS Full-text
DOCUMENT NUMBER: 156:440657
TITLE: Activity of XL184 (cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer
AUTHOR(S): Kurzrock, Razelle; Sherman, Steven I.; Ball, Douglas W.; Forastiere, Arlene A.; Cohen, Roger B.; Mehra, Ranee; Pfister, David G.; Cohen, Ezra E. W.; Janisch, Linda; Nauling, Forlisa; Hong, David S.; Ng, Chaan S.; Ye, Lei; Gagel, Robert F.; Frye, John; Muller, Thomas; Ratain, Mark J.; Salgia, Ravi
CORPORATE SOURCE: The University of Texas MD Anderson Cancer Center, Houston, USA
SOURCE: Journal of Clinical Oncology (2011), 29(19), 2660-2666
CODEN: JCONDN; ISSN: 0732-183X
DIGITAL OBJECT ID: 10.1200/JCO.2010.32.4145
PUBLISHER: American Society of Clinical Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Purpose: XL184 (cabozantinib) is a potent inhibitor of MET, vascular endothelial growth factor receptor 2 (VEGFR2), and RET, with robust antiangiogenic, antitumor, and anti-invasive effects in preclin. models. Early observations of clin. benefit in a phase I study of cabozantinib, which included patients with medullary thyroid cancer (MTC), led to expansion of an MTC-enriched cohort, which is the focus of this article. Patients and Methods: A phase I dose-escalation study of oral cabozantinib was conducted in patients with advanced solid tumors. Primary end points included evaluation of safety, pharmacokinetics, and maximum-tolerated dose (MTD) determination Addnl. end points included RECIST (Response Evaluation Criteria in Solid Tumors) response, pharmacodynamics, RET mutational status, and biomarker analyses. Results: Eighty-five patients were enrolled, including 37 with MTC. The MTD was 175 mg daily. Dose-limiting toxicities were grade 3 palmar plantar erythrodysesthesia (PPE), mucositis, and AST, ALT, and lipase elevations and grade 2 mucositis that resulted in dose interruption and reduction Ten (29%) of 35 patients with MTC with measurable disease had a confirmed partial response. Overall, 18 patients experienced tumor shrinkage of 30% or more, including 17 (49%) of 35 patients with MTC with measurable disease. Addnl., 15 (41%) of 37 patients with MTC had stable disease (SD) for at least 6 mo, resulting in SD for 6 mo or longer or confirmed partial response in 68% of patients with MTC. Conclusion: Cabozantinib has an acceptable safety profile and is active in MTC. Cabozantinib may provide clin. benefit by simultaneously targeting multiple pathways of importance in MTC, including MET, VEGFR2, and RET. A global phase III pivotal study in MTC is ongoing (ClinicalTrials.gov number NCT00215605).

IT 1140909-48-3

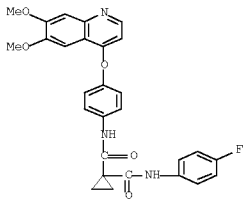
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(activity of cabozantinib, an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer)

RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

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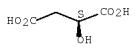
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 145 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2011:724271 CAPLUS Full-text

DOCUMENT NUMBER: 155:290943

TITLE: The effects of four different tyrosine kinase inhibitors on medullary and papillary thyroid cancer cells

AUTHOR(S): Verbeek, Hans H. G.; Alves, Maria M.; de Groot, Jan-Willem B.; Osinga, Jan; Plukker, John T. M.; Links, Thera P.; Hofstra, Robert M. W.

CORPORATE SOURCE: Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, 9700 RB, Neth.

SOURCE: Journal of Clinical Endocrinology and Metabolism (2011), 96(6), E991-E995
CODEN: JCEMAZ; ISSN: 0021-972X

DIGITAL OBJECT ID: 10.1210/jc.2010-2381

PUBLISHER: Endocrine Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Medullary and papillary thyroid carcinoma (MTC and PTC) are 2 types of thyroid cancer that can originate from activating mutations or rearrangements in the RET gene. Therapeutic options are limited in recurrent disease, but because RET is a tyrosine kinase (TK) receptor involved in cellular growth and proliferation, treatment with a TK inhibitor might be promising. Several TK inhibitors were tested in clin. trials, but it is unknown which inhibitor is most effective and whether there is any specificity for particular RET mutations. We aimed to compare the effect of 4 TK inhibitors (axitinib, sunitinib, vandetanib, and XL184) on cell proliferation, RET expression and autophosphorylation, and ERK activation in cell lines expressing a MEN2A (MTC-TT), a MEN2B (MZ-CRC-1) mutation, and a RET/PTC (TPC-1) rearrangement. The 3 cell lines were cultured and treated with the 4 TK inhibitors. Effects on cell proliferation and RET and ERK expression and activation were determined XL184 and vandetanib most effectively inhibited cell proliferation, RET autophosphorylation in combination with a reduction of RET expression, and ERK phosphorylation in MTC-TT and MZ-CRC-1, resp. TPC-1 cells showed a decrease in RET autophosphorylation after treatment with XL184, but no effect was observed on ERK activation. There is indeed specificity for different RET mutations, with XL184 being the most potent inhibitor in MEN2A and PTC and vandetanib the most effective in MEN2B in vitro. No TK inhibitor was superior for all the cell lines tested, indicating that mutation-specific therapies could be beneficial in treating MTC and PTC.

IT 1140909-48-3, XL184

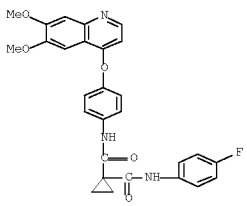
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Tyr kinase inhibitors effect on medullary and papillary thyroid cancer related to RET mutation, rearrangement, and ERK)

RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

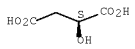
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CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 98 THERE ARE 98 CAPLUS RECORDS THAT CITE THIS RECORD (98 CITINGS)

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 144 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2011:945715 CAPLUS Full-text

DOCUMENT NUMBER: 156:301829

TITLE: Current status of molecularly targeted drugs for the treatment of advanced thyroid cancer

AUTHOR(S): Takami, Hiroshi E.

CORPORATE SOURCE: Department of Surgery, Teikyo University School of Medicine, Tokyo, 173-8605, Japan

SOURCE: Endocrine Journal (Kyoto, Japan) (2011), 58(3), 151-153
CODEN: ENJOEO; ISSN: 0918-8959

DIGITAL OBJECT ID: 10.1507/endocrj.K11E-076

PUBLISHER: Japan Endocrine Society

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. The prognosis of almost all thyroid cancers is good, but some patients have indications for these molecularly targeted drugs. Some of these drugs, i.e., vandetanib, XL-184, sorafenib, motesanib, axitinib, and pazopanib, are clearly useful clin.

IT 1140909-48-3, XL-184

RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(current status of molecularly targeted drugs for the treatment of advanced thyroid cancer)

RN 1140909-48-3 CAPLUS

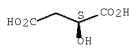
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

CRN 849217-68-1
CMF C28 H24 F N3 O5

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 24 THERE ARE 24 CAPLUS RECORDS THAT CITE THIS RECORD (24 CITINGS)
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

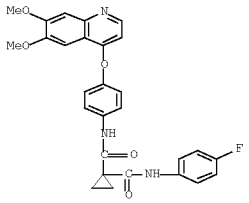
L4 ANSWER 146 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2011:461207 CAPLUS Full-text
DOCUMENT NUMBER: 156:46100
TITLE: Novel agents and new therapeutics in castration-resistant prostate cancer
AUTHOR(S): Wu, Yichao; Rosenberg, Jonathan E.; Taplin, Mary-Ellen
CORPORATE SOURCE: Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA
SOURCE: Current Opinion in Oncology (2011), 23(3), 290-296
CODEN: CUOOE8; ISSN: 1040-8746
DIGITAL OBJECT ID: 10.1097/CCO.0b013e3283449400
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB Purpose of review: This review highlights recent therapeutic advances in systemic therapies for prostate cancer (PCa). Recent findings: Progress in PCa therapeutics has been made during the past year with the approval of a vaccine therapy, second-line chemotherapy, and reported survival advantage for a CYP (17,20) lyase inhibitor in castration-resistant prostate cancer (CRPC). This report will summarize the recently reported and expected data for PCa trials including an evaluation of intermittent vs. continuous androgen deprivation therapy. Denosumab is shown to support bone mineral d. in hormonal sensitive PCa patients. Targeting of androgen-dependent pathways in CRPC postchemotherapy has been shown to improve survival with the lyase inhibitor abiraterone, and lead to prostate-specific antigen and objective responses with an androgen receptor antagonist (MDV3100). However, the addition of bevacizumab to docetaxel/prednisone in treating metastatic CRPC failed to provide a survival benefit. Cabazitaxel in metastatic CRPC postdocetaxel did demonstrate a survival benefit. Provenge, an autologous dendritic cell-based vaccine, demonstrated a reduction in the risk of death in metastatic CRPC. Other immunotherapy agents, including Prostvac and ipilimumab are under investigation. We also discuss the receptor tyrosine kinase inhibitor XL184 and poly (ADP-ribose) polymerase inhibitors which are in early clin. trials. Summary: Recent advances in androgen targeting, chemotherapy, immunotherapy, and other targeted therapies have led to significant improvements in the care of CRPC patients.

IT 1140909-48-3, XL184
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel agents and new therapeutics in castration-resistant prostate cancer)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

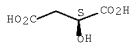
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

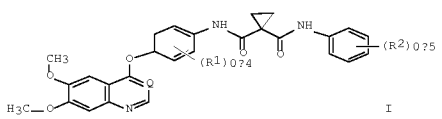


OS.CITING REF COUNT: 13 THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (13 CITINGS)
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 147 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2011:174316 CAPLUS Full-text
DOCUMENT NUMBER: 154:225400
TITLE: C-met modulators as antitumor agents
INVENTOR(S): Aftab, Dana T.; Mueller, Thomas; Weitzman, Aaron; Holland, Jaymes
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 61pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2011017639 | A1 | 20110210 | WO 2010-US44749 | 20100806 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| CA 2770100 | A1 | 20110210 | CA 2010-2770100 | 20100806 |
| AU 2010279234 | A1 | 20120301 | AU 2010-279234 | 20100806 |
| KR 2012059540 | A | 20120608 | KR 2012-7006111 | 20100806 |
| EP 2461810 | A1 | 20120613 | EP 2010-742985 | 20100806 |
| R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR | | | | |
| CN 102647985 | A | 20120822 | CN 2010-80045677 | 20100806 |
| JP 2013501731 | T | 20130117 | JP 2012-523982 | 20100806 |
| IL 217889 | A | 20130228 | IL 2010-217889 | 20100806 |
| NZ 598055 | A | 20140530 | NZ 2010-598055 | 20100806 |
| IN 2012MN00278 | A | 20120824 | IN 2012-MN278 | 20120203 |
| ZA 2012000842 | A | 20121128 | ZA 2012-842 | 20120203 |
| MX 2012001654 | A | 20120314 | MX 2012-1654 | 20120207 |
| US 20120282179 | A1 | 20121108 | US 2012-13389266 | 20120712 |
| PRIORITY APPLN. INFO.: | | | US 2009-61232382 P | 20090807 |
| | | | WO 2010-US44749 W | 20100806 |

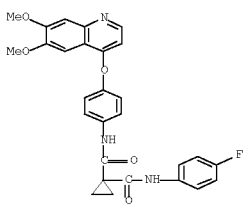
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 154:225400; MARPAT 154:225400
GI



I

AB Methods of treating cancer by administering a compd. of Formula I (wherein R1 = halo; R2 = halo; Q = CH, N; n = 0-4; m = 0-5) or a pharmaceutically acceptable salt or solvate thereof, in combination with other cancer treatments are described.

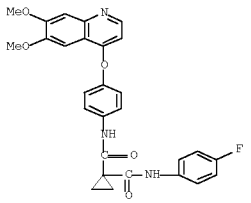
IT 849217-68-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(methods of using c-met modulators)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



IT 1140909-48-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(methods of using c-met modulators)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

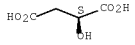
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



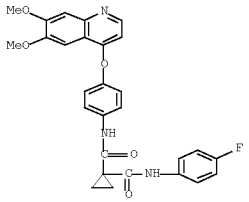
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 148 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2011:111410 CAPLUS Full-text
DOCUMENT NUMBER: 155:346258
TITLE: Antiangiogenic agents in the treatment of recurrent or newly diagnosed glioblastoma: analysis of single-agent and combined modality approaches
AUTHOR(S): Beal, Kathryn; Abrey, Lauren E.; Gutin, Philip H.
CORPORATE SOURCE: Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA
SOURCE: Radiation Oncology (2011), 6, 2
CODEN: ROANCM; ISSN: 1748-717X
URL: http://www.ro-journal.com/content/pdf/1748-717X-6-2.pdf

DIGITAL OBJECT ID: 10.1186/1748-717X-6-2
PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
AB A review. Surgical resection followed by radiotherapy and temozolomide in newly diagnosed glioblastoma can prolong survival, but it is not curative. For patients with disease progression after frontline therapy, there is no standard of care, although further surgery, chemotherapy, and radiotherapy may be used. Antiangiogenic therapies may be appropriate for treating glioblastomas because angiogenesis is critical to tumor growth. In a large, noncomparative phase II trial, bevacizumab was evaluated alone and with irinotecan in patients with recurrent glioblastoma; combination treatment was associated with an estimated 6-mo progression-free survival (PFS) rate of 50.3%, a median overall survival of 8.9 mo, and a response rate of 37.8%. Single-agent bevacizumab also exceeded the predetd. threshold of activity for salvage chemotherapy (6-mo PFS rate, 15%), achieving a 6-mo PFS rate of 42.6% (p<0.0001). On the basis of these results and those from another phase II trial, the US Food and Drug Administration granted accelerated approval of single-agent bevacizumab for the treatment of glioblastoma that has progressed following prior therapy. Potential antiangiogenic agents - such as cilengitide and XL184 - also show evidence of single-agent activity in recurrent glioblastoma. Moreover, the use of antiangiogenic agents with radiation at disease progression may improve the therapeutic ratio of single-modality approaches. Overall, these agents appear to be well tolerated, with adverse event profiles similar to those reported in studies of other solid tumors. Further research is needed to determine the role of antiangiogenic therapy in frontline treatment and to identify the optimal schedule and partnering agents for use in combination therapy.
IT 1140909-48-3, XL184
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiangiogenic agents in the treatment of recurrent or newly diagnosed glioblastoma)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

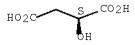
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 27 THERE ARE 27 CAPLUS RECORDS THAT CITE THIS RECORD (27 CITINGS)
REFERENCE COUNT: 115 THERE ARE 115 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 149 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2011:80577 CAPLUS Full-text
DOCUMENT NUMBER: 154:174225
TITLE: Drug selection for gastric cancer therapy using antibody-based arrays
INVENTOR(S): Singh, Sharat; Kim, Phillip; Liu, Xinjun; Ybarrondo, Belen
PATENT ASSIGNEE(S): Prometheus Laboratories Inc., USA
SOURCE: PCT Int. Appl., 189pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

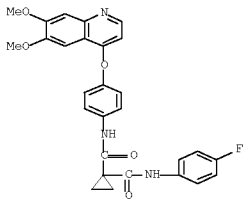
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2011008990 | A1 | 20110120 | WO 2010-US42182 | 20100715 |
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| RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| CA 2768013 | A1 | 20110120 | CA 2010-2768013 | 20100715 |
| AU 2010273319 | A1 | 20120223 | AU 2010-273319 | 20100715 |
| EP 2454598 | A1 | 20120523 | EP 2010-800567 | 20100715 |
| R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BA, ME, RS | | | | |
| JP 2012533738 | T | 20121227 | JP 2012-520794 | 20100715 |
| US 20110281748 | A1 | 20111117 | US 2011-13014674 | 20110126 |
| US 20130237436 | A9 | 20130912 | | |
| US 20120270745 | A1 | 20121025 | US 2012-13354257 | 20120119 |
| AU 2013202682 | A1 | 20130502 | AU 2013-202682 | 20130405 |

PRIORITY APPLN. INFO.:
US 2009-61225866 P 20090715
US 2009-61265218 P 20091130
US 2010-61325000 P 20100416
US 2006-61007527 P 20060921
US 2007-60913087 P 20070420
AU 2007-299774 A3 20070920
WO 2007-US79002 A1 20070920
US 2008-46381 A2 20080311
WO 2010-US42182 W 20100715
US 2011-13014674 A2 20110126
US 2011-61436945 P 20110127
US 2011-61467950 P 20110325

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB The present invention provides methods for selecting a suitable anticancer therapy, and for identifying and predicting response for the treatment of a gastric cancer. The present invention provides compns. and methods for detecting the status (e.g., expression and/or activation levels) of components of signal transduction pathways in tumor cells (e.g., gastric tumor cells). Information on the expression and/or activation states of components of signal transduction pathways (e.g., HER2 and/or c-Met signal transduction pathway components) derived from practice of the present invention can be used for gastric cancer diagnosis, prognosis, and in the design of gastric cancer treatments. The compns. and methods of the present invention advantageously provide accurate prediction, selection, and monitoring of cancer patients (e.g., gastric cancer patients) most likely to benefit from targeted therapy by performing pathway profiling on easily accessible tumor cells using multiplexed, antibody-based proximity assays.
IT 1140909-48-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug selection for gastric cancer therapy using antibody-based arrays for detecting the status of signal transduction pathways)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

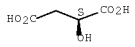
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

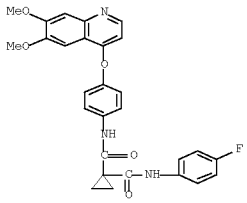


OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 150 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2010:1570396 CAPLUS Full-text
DOCUMENT NUMBER: 155:177406
TITLE: Targeting RET Receptor Tyrosine Kinase Activation in Cancer
AUTHOR(S): Phay, John E.; Shah, Manisha H.
CORPORATE SOURCE: Department of Surgery, Division of Surgical Oncology, Department of Internal Medicine, and Division of Medical Oncology, The Ohio State University, Columbus, OH, USA
SOURCE: Clinical Cancer Research (2010), 16(24), 5936-5941
CODEN: CCREF4; ISSN: 1078-0432
DIGITAL OBJECT ID: 10.1158/1078-0432.CCR-09-0786
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. After ligand binding induces dimerization, the RET receptor tyrosine kinase activates multiple signal transduction pathways. Constitutively activating mutations and chromosomal rearrangements are the primary oncogenic event in a significant number of medullary thyroid cancers (MTC) and papillary thyroid cancers (PTC), resp. When specific germline mutations in RET are identified early, prophylactic thyroidectomy can be timed to remove at-risk tissue in patients with multiple endocrine neoplasia 2 (MEN2) syndromes who would otherwise develop MTC. Conventional therapy for progressive metastatic MTC is limited. Small-mol. tyrosine kinase inhibitors can target multiple kinases at nanomolar concns., including RET, and have shown efficacy against a variety of malignancies. Initial clin. evidence suggests that several of these inhibitors, including sorafenib, vandetanib, motesanib, sunitinib, and XL-184, may have some benefit in treating progressive MTC. Although initial success seen in these trials seems to be modest, it represents a major breakthrough in the treatment of patients with widespread metastatic MTC. Clin Cancer Res; 16(24); 5936-41.
IT 1140909-48-3, XL-184,
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(role of RET receptor tyrosine kinase activation in cancer)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

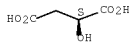
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

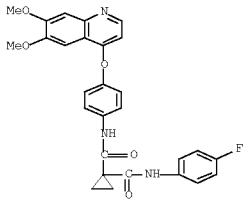


OS.CITING REF COUNT: 30 THERE ARE 30 CAPLUS RECORDS THAT CITE THIS RECORD (30 CITINGS)
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 151 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2010:1240526 CAPLUS Full-text
DOCUMENT NUMBER: 153:595314
TITLE: Tyrosine kinase inhibitors in thyroid cancer
AUTHOR(S): Illouz, Frederic
CORPORATE SOURCE: Service EDN, Centre de reference des pathologies de la receptivite hormonale, CHU d'Angers, Fr.
SOURCE: Correspondances en Metabolismes, Hormones, Diabetes et Nutrition (2010), 14(7), 210-214
CODEN: CMHDBH; ISSN: 2100-9619
PUBLISHER: Edimark SAS
DOCUMENT TYPE: Journal; General Review
LANGUAGE: French
AB A review.
IT 1140909-48-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitors in thyroid cancer therapy)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

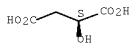
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

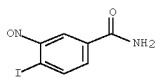


REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 152 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2010:1003327 CAPLUS Full-text
DOCUMENT NUMBER: 153:278035
TITLE: Treatment of lung cancer with a PARP inhibitor in combination with a growth factor inhibitor
INVENTOR(S): Sherman, Barry M.; Bradley, Charles; Ossovskaya, Valeria S.
PATENT ASSIGNEE(S): BiPar Sciences, Inc., USA
SOURCE: PCT Int. Appl., 118 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2010091140 | A1 | 20100812 | WO 2010-US23137 | 20100204 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| CA 2751397 | A1 | 20100812 | CA 2010-2751397 | 20100204 |
| AR 75239 | A1 | 20110316 | AR 2010-100305 | 20100204 |
| AU 2010210636 | A1 | 20110922 | AU 2010-210636 | 20100204 |
| KR 2011113648 | A | 20111017 | KR 2011-7020246 | 20100204 |
| EP 2393364 | A1 | 20111214 | EP 2010-739097 | 20100204 |
| R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, AL, BA, RS | | | | |
| CN 102307475 | A | 20120104 | CN 2010-80006536 | 20100204 |
| JP 2012516895 | T | 20120726 | JP 2011-549246 | 20100204 |
| IL 214366 | A | 20130131 | IL 2010-214366 | 20100204 |
| MX 2011008221 | A | 20110817 | MX 2011-8221 | 20110804 |
| IN 2011CN06195 | A | 20121012 | IN 2011-CN6195 | 20110829 |
| US 20120130144 | A1 | 20120524 | US 2011-13146865 | 20111222 |
| PRIORITY APPLN. INFO.: | | | US 2009-61149977 P | 20090204 |
| | | | WO 2010-US23137 W | 20100204 |

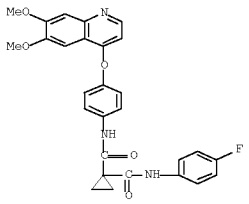
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 153:278035
GI



AB In one aspect, the present invention provides a method of treating lung cancer, comprising administering to a subject at least one PARP inhibitor in combination with at least one growth factor inhibitor. In another aspect, the present invention provides a method of treating non-small cell lung cancer comprising administering to a subject at least one PARP inhibitor in combination with at least one growth factor inhibitor.
IT 1140909-48-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of lung cancer with a PARP inhibitor in combination with a growth factor inhibitor)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

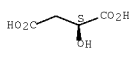
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

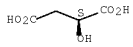


OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 154 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2010:928655 CAPLUS Full-text

CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

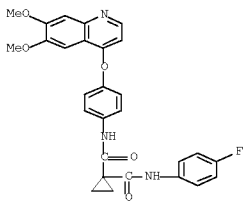


REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 153 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2010:944155 CAPLUS Full-text
DOCUMENT NUMBER: 155:230334
TITLE: Patients with advanced head and neck cancers have similar progression-free survival on phase I trials and their last food and drug administration-approved treatment
AUTHOR(S): Garrido-Laguna, Ignacio; Janku, Filip; Falchook, Gerald S.; Fu, Siqing; Hong, David S.; Naing, Aung; Aaron, Joanne; Wang, Xuemei; Kies, Merrill; Kurzrock, Razelle
CORPORATE SOURCE: Departments of Investigational Cancer Therapeutics (Phase I Clinical Trials Program), The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA
SOURCE: Clinical Cancer Research (2010), 16(15), 4031-4037
CODEN: CCREF4; ISSN: 1078-0432
DIGITAL OBJECT ID: 10.1158/1078-0432.CCR-10-0672
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Purpose: To compare clin. outcomes of metastatic head and neck cancer patients treated in phase I clin. trials with clin. outcomes of those patients who had their last Food and Drug Administration (FDA)-approved therapy in the setting of metastatic disease. Exptl. Design: We retrospectively reviewed the outcomes of 61 consecutive patients with head and neck tumors treated in 36 phase I trials at The University of Texas M.D. Anderson Cancer Center between July 2004 and Sept. 2009. Results: The most common histol. was head and neck squamous cell carcinoma (62%). Median age was 55 years (range, 26-80). Eastern Cooperative Oncol. Group performance status was 0 to 1 for 95% of patients. Fifty-nine patients had received FDA-approved drugs as the backbone of their last systemic therapy before inclusion in phase I trials (median, 2 systemic therapies). Progression-free survival (PFS) on phase I trials was not inferior to PFS on their last FDA-approved therapies (12 vs. 10.7 wk, log-rank P = 0.87). Fifty-three patients were evaluable for response by Response Evaluation Criteria in Solid Tumors criteria. Four (7%) had partial responses and 16 (26%) had stable disease for ≥4 mo. In univariate anal., number of metastatic sites, lactate dehydrogenase (LDH) levels at baseline, and Royal Marsden Hospital prognosis scores were significant predictors of survival. Only LDH was significant in multivariate anal. (hazard ratio, 6.35; P ≤ 0.0001). Conclusions: For patients with heavily pretreated advanced head and neck tumors, PFS on phase I trials is not inferior to PFS with their last FDA-approved therapy. The only significant predictor of survival in the multivariate anal. was baseline LDH.
IT 1140909-48-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(patients with advanced head and neck cancers have similar progression-free survival on phase I trials and their last food and drug administration-approved treatment)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

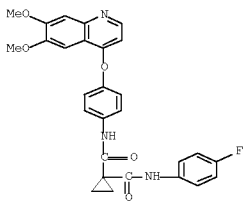


REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 155 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2010:925137 CAPLUS Full-text
DOCUMENT NUMBER: 154:425137
TITLE: XL-184, a MET, VEGFR-2 and RET kinase inhibitor for the treatment of thyroid cancer, glioblastoma multiforme and NSCLC
AUTHOR(S): Zhang, Ying; Guessous, Fadila; Kofman, Alex; Schiff, David; Abounader, Roger
CORPORATE SOURCE: Department of Microbiology, University of Virginia, Charlottesville, VA, 22903, USA
SOURCE: IDrugs (2010), 13(2), 112-121
CODEN: IDRUFN; ISSN: 2040-3410
URL: http://www.biomedcentral.com/content/pdf/cd-1071541.pdf
PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
AB A review. XL-184 (BMS-907351), under development by Exelixis Inc and Bristol-Myers Squibb Co, is a pan-tyrosine kinase inhibitor for the potential oral treatment of medullary thyroid cancer, glioblastoma multiforme and NSCLC. The prinicipal targets of XL-184 are MET, VEGFR-2 and RET, but the drug is also reported to display inhibitory activity against KIT, FLT3 and TEK. Preclin. studies demonstrated that XL-184 potently inhibited multiple receptor tyrosine kinases in various cancer cell lines and animal xenograft models, and that the drug exhibited significant oral bioavailability and blood-brain barrier penetration. A phase I clin. trial in patients with advanced solid malignancies indicated that XL-184 accumulated dose-dependently in the plasma and had a long terminal half-life. A phase II trial in patients with progressive or recurrent glioblastoma revealed modest but promising median progression-free survival. Toxicity and side effects for the drug have generally been of low-to-moderate severity. At the time of publication, three addnl. trials of XL-184 were recruiting patients, including a phase I trial in combination with standard of care in patients with glioblastoma, a phase I/II trial in combination with erlotinib in patients with NSCLC, and a phase III trial in patients with medullary thyroid cancer.
IT 1140909-48-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(XL-184, a MET, VEGFR-2 and RET kinase inhibitor for the treatment of thyroid cancer, glioblastoma multiforme and NSCLC)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

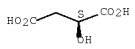
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 34 THERE ARE 34 CAPLUS RECORDS THAT CITE THIS RECORD (34 CITINGS)
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 155 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2010:912816 CAPLUS Full-text
DOCUMENT NUMBER: 153:204211
TITLE: Preparation of malate salts of N-[4-[[6,7-bis(methyloxy)quinolin-4-yl]oxy]phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and crystalline forms thereof for the treatment of cancer.
INVENTOR(S): St Clair Brown, Adrian; Lamb, Peter; Gallagher, William P.
PATENT ASSIGNEE(S): Exelixis, Inc., USA; Bristol-Meyers Squibb Company
SOURCE: PCT Int. Appl., 72pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2010083414 | A1 | 20100722 | WO 2010-US21194 | 20100115 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| CA 2758030 | A1 | 20100722 | CA 2010-2758030 | 20100115 |
| AR 75025 | A1 | 20110302 | AR 2010-100098 | 20100115 |
| AU 2010204619 | A1 | 20110901 | AU 2010-204619 | 20100115 |
| EP 2387563 | A1 | 20111123 | EP 2010-701175 | 20100115 |
| EP 2387563 | B1 | 20130306 | | |
| R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, AL, BA, RS | | | | |
| KR 2012013301 | A | 20120214 | KR 2011-7018924 | 20100115 |
| CN 102388024 | A | 20120321 | CN 2010-80012656 | 20100115 |
| JP 2012515220 | T | 20120705 | JP 2011-546390 | 20100115 |
| IL 214086 | A | 20130131 | IL 2010-214086 | 20100115 |
| PT 2387563 | E | 20130325 | PT 2010-701175 | 20100115 |
| ES 2402524 | T3 | 20130506 | ES 2010-701175 | 20100115 |
| NZ 594594 | A | 20131129 | NZ 2010-594594 | 20100115 |
| EA 19959 | B1 | 20140730 | EA 2011-70941 | 20100115 |
| ZA 2011005167 | A | 20120328 | ZA 2011-5167 | 20110713 |
| MX 2011007620 | A | 20111104 | MX 2011-7620 | 20110715 |
| IN 2011KN03402 | A | 20121102 | IN 2011-KN3402 | 20110811 |
| US 20120035212 | A1 | 20120209 | US 2011-13145054 | 20111020 |
| HK 1164305 | A1 | 20131108 | HK 2012-104893 | 20120518 |
| AU 2013203780 | A1 | 20130502 | AU 2013-203780 | 20130411 |

PRIORITY APPLN. INFO.: US 2009-61145421 P 20090116
AU 2010-204619 A3 20100115
WO 2010-US21194 W 20100115

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 153:204211

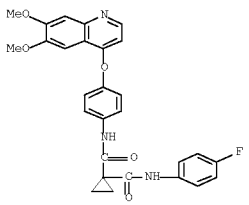
AB N-[4-[[6,7-bis(methyloxy)quinolin-4-yl]oxy]phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide malate salts were prepared Thus, 1-(4-fluorophenylcarbamoyl)cyclopropanecarboxylic acid (preparation given) was stirred with (COCl)2 in THF/DMF at ≤30° and the mixture was added to 4-(6,7-dimethoxyquinolin-4-yloxy)phenylamine (preparation given) and K2CO3 in THF/H2O followed by addition of H2O and stirring for 10 h to give N-[4-[[6,7-bis(methyloxy)quinolin-4-yl]oxy]phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. The latter in EtOH was treated with malic acid in H2O followed by addition of C, thiol silica, heating to 78°, and addition of H2O followed by filtration, addition of Me2CHOH, cooling, and filtration to give N-[4-[[6,7-bis(methyloxy)quinolin-4-yl]oxy]phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide malate.

IT 1235470-36-6
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of malate salts of bismethoxyquinolinyloxyphenylfluorophenylcyclopropanedicarboxamide and crystalline forms thereof for the treatment of cancer)

RN 1235470-36-6 CAPLUS
CN Butanedioic acid, 2-hydroxy-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:?) (CA INDEX NAME)

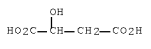
CM 1

CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 6915-15-7
CMF C4 H6 O5

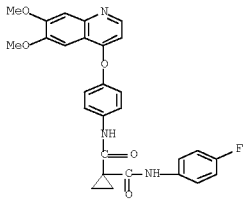


IT 1235470-37-7 1235470-38-8
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of malate salts of bismethoxyquinolinyloxyphenylfluorophenylcyclopropanedicarboxamide and crystalline forms thereof for the treatment of cancer)

RN 1235470-37-7 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:?) (CA INDEX NAME)

CM 1

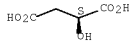
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

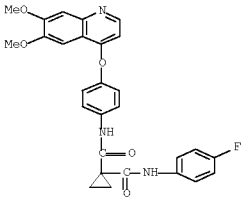
Absolute stereochemistry. Rotation (-).



RN 1235470-38-8 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:?) (CA INDEX NAME)

CM 1

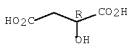
CRN 849217-68-1
CMF C28 H24 F N3 O5



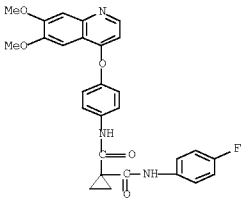
CM 2

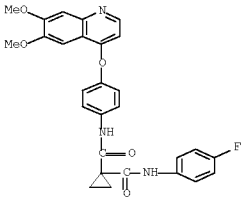
CRN 636-61-3
CMF C4 H6 O5

Absolute stereochemistry. Rotation (+).



IT 849217-68-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of malate salts of bismethoxyquinolinyloxyphenylfluorophenylcyclopropanedicarboxamide and crystalline forms thereof for the treatment of cancer)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

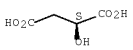




CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

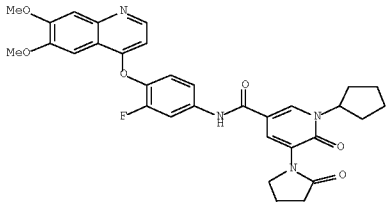


OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 157 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2010:439254 CAPLUS Full-text
DOCUMENT NUMBER: 152:422278
TITLE: Methods for the treatment of cancer
INVENTOR(S): Johns, Terrance
PATENT ASSIGNEE(S): Ludwig Institute for Cancer Research, USA
SOURCE: PCT Int. Appl., 139pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2010039248 | A1 | 20100408 | WO 2009-US5421 | 20090930 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| AU 2009300328 | A1 | 20100408 | AU 2009-300328 | 20090930 |
| CA 2738583 | A1 | 20100408 | CA 2009-2738583 | 20090930 |
| EP 2349328 | A1 | 20110803 | EP 2009-740207 | 20090930 |
| R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, AL, BA, RS | | | | |
| JP 2012504606 | T | 20120223 | JP 2011-530051 | 20090930 |
| MX 2011003363 | A | 20110427 | MX 2011-3363 | 20110329 |
| US 20110229469 | A1 | 20110922 | US 2011-13122106 | 20110613 |
| PRIORITY APPLN. INFO.: | | | US 2008-61101971 P | 20081001 |
| | | | WO 2009-US5421 W | 20090930 |

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 152:422278
GI



AB Methods for treating cancer with at least one HGF-Met inhibitor and at least one EGFR inhibitor are provided.
IT 1140909-48-3, XL 184
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for treatment of cancer)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

CRN 849217-68-1
CMF C28 H24 F N3 O5

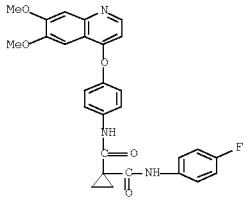
OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 156 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2010:726266 CAPLUS Full-text
DOCUMENT NUMBER: 153:633557
TITLE: Targeted therapy for thyroid cancer: an updated review of investigational agents
AUTHOR(S): Deshpande, Hari A.; Gettinger, Scott N.; Sosa, Julie A.
CORPORATE SOURCE: Yale Cancer Center, New Haven, CT, 06520, USA
SOURCE: Current Opinion in Investigational Drugs (BioMed Central) (2010), 11(6), 661-668
CODEN: COIDAZ; ISSN: 2040-3429
URL: http://www.biomedcentral.com/content/pdf/cd-1102161.pdf

PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
AB A review. The treatment of thyroid cancer is evolving. The mol. mechanisms of carcinogenesis for many thyroid cancers have been investigated, and have yielded targets for potential therapies. These targets include VEGFR in the treatment of all thyroid cancers, BRAF in the treatment of papillary thyroid cancer, and RET in the treatment of medullary thyroid cancer (MTC). Many promising drugs that target one or more of these proteins are currently being evaluated, including sorafenib and sunitinib, both of which are still under development for the treatment of thyroid cancer but which have been approved for use in other malignancies. In addition, compds. such as vandetanib (AstraZeneca plc) and XL-184 (Bristol-Myers Squibb Co/Exelixis Inc) have demonstrated activity in early-phase clin. trials of MTC and are being tested further in randomized trials.
IT 1140909-48-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(XL-184 targeting vascular endothelial growth factor receptor, RET and BRAF protein may be effective in patient with thyroid cancer)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

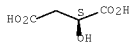
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 158 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2010:402977 CAPLUS Full-text
DOCUMENT NUMBER: 152:423197
TITLE: Recombinant replication-competent retroviral vectors expressing therapeutic products for treatment of proliferative disorders
INVENTOR(S): Gruber, Harry E.; Jolly, Douglas; Perez, Omar
PATENT ASSIGNEE(S): Tocagen Inc., USA
SOURCE: PCT Int. Appl., 194 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2010036986 | A2 | 20100401 | WO 2009-US58512 | 20090926 |
| WO 2010036986 | A3 | 20100701 | | |

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

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|---|---|---|---|---|
| EP 2344648 | A2 | 20110720 | EP 2009-816967 | 20090926 |
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| CN 102227503 | A | 20111026 | CN 2009-80147515 | 20090926 |
| JP 2012503987 | T | 20120216 | JP 2011-529292 | 20090926 |
| ZA 2011002115 | A | 20120725 | ZA 2011-2115 | 20090926 |
| US 20110287020 | A1 | 20111124 | US 2011-13072704 | 20110326 |
| US 8829173 | B2 | 20140909 | | |
| AU 2013205006 | A1 | 20130516 | AU 2013-205006 | 20130413 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 2008-61100666 | P | 20080926 |
| US 2008-61120618 | P | 20081208 |
| US 2009-61186823 | P | 20090613 |
| AU 2009-303690 | A3 | 20090926 |
| WO 2009-US58512 | W | 20090926 |
| US 2010-61318728 | P | 20100329 |

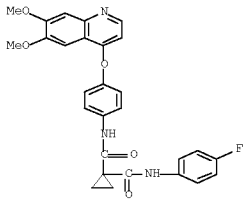
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB Recombinant replication-competent retroviral (RCR) vectors are provided comprising: a retroviral gag protein; a retroviral pol protein; a retroviral envelop, a retroviral polynucleotide comprising long terminal repeat (LTR) sequence at the 3' end of the retroviral polynucleotide sequence; a mammalian-suitable promoter sequence at the 5' end of the retroviral polynucleotide, a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous polynucleotide; and cis-acting sequences necessary for reverse transcription, packaging and integration in a target cell. The RCR maintains higher replication competency after 6 passages compared to a pACE vector. The heterologous polynucleotide may encode modified cytosine deaminase (thermostabilized and codon optimized), single-chain antibody to CTLA-4, microRNAs miR-128-1 and miR-128-2, γ-interferon, interleukin 2, or other therapeutic proteins of interest. The disclosure further relates to cells and vector expressing or comprising such modified CDs and methods of using such modified CDs in the treatment of disease and disorders, and in particular cell proliferative disorders such as cancer.

IT 1140909-48-3, XL 184
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination cancer therapy with; recombinant replication-competent retroviral vectors expressing therapeutic products for treatment of proliferative disorders)

RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1



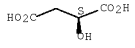
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



L4 ANSWER 159 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2010:55413 CAPLUS Full-text
DOCUMENT NUMBER: 152:163651
TITLE: Methods for diagnosis, prognosis and treatment
INVENTOR(S): Fantl, Wendy J.; Rosen, David B.; Cesano, Alessandra; Putta, Santosh K.; Nolan, Garry P.; Cohen, Aileen C.; Evenson, Erik
PATENT ASSIGNEE(S): Nodality, Inc., USA
SOURCE: PCT Int. Appl., 201pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2010006291 | A1 | 20100114 | WO 2009-US50295 | 20090710 |

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RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

| | | | | |
|---|---|---|---|---|
| EP 2304436 | A1 | 20110406 | EP 2009-790295 | 20090710 |
| R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, AL, BA, RS | | | | |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 2008-61079766 | P | 20080710 |
| US 2008-61085789 | P | 20080801 |
| US 2008-61104666 | P | 20081010 |
| US 2008-61120320 | P | 20081205 |
| WO 2009-US50295 | W | 20090710 |

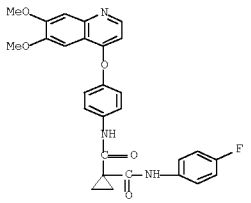
AB The present invention provides an approach for the detn. of the activation states of a plurality of proteins in single cells. This approach permits the rapid detection of heterogeneity in a complex cell population based on activation states, expression markers and other criteria, and the identification of cellular subsets that exhibit correlated changes in activation within the cell population. Moreover, this approach allows the correlation of cellular activities or properties. In addition, the use of modulators of cellular activation allows for characterization of pathways and cell populations. Several exemplary diseases that can be analyzed using the invention include AML, MDS, and MPN.

IT 1140909-48-3, XL 184
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hematopoietic cell flow cytometry anal. and pathway stimulation for diagnosing, prognosing, therapy and progression of acute leukemia, myelodysplastic syndrome and myeloproliferative syndrome)

RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

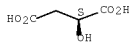
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

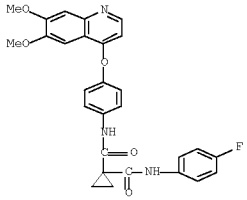


OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 160 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2009:1534585 CAPLUS Full-text
DOCUMENT NUMBER: 153:76060
TITLE: Antiangiogenic strategies for treatment of malignant gliomas
AUTHOR(S): Chi, Andrew S.; Norden, Andrew D.; Wen, Patrick Y.
CORPORATE SOURCE: Stephen E. and Catherine Pappas Center for Neuro-Oncology, Department of Neurology, Division of Hematology and Oncology, Dana-Farber/Harvard Cancer Center, Harvard Medical School, Massachusetts General Hospital Cancer Center, USA
SOURCE: Neurotherapeutics (2009), 6(3), 513-526
CODEN: NEURNV; ISSN: 1933-7213
DIGITAL OBJECT ID: 10.1016/j.nurt.2009.04.010
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Numerous antiangiogenic agents with diverse mechanisms of action are currently under investigation for the treatment of patients with glioblastoma (GBM), a diagnosis that continues to carry a poor prognosis despite maximal conventional therapy. Early clin. trials suggest that antiangiogenic drugs, which target the blood vessels of these highly angiogenic tumors, may have clin. benefit in GBM patients. Antiangiogenic agents have potent antiedema and steroid-sparing effects in patients, and emerging data suggest that these drugs may modestly improve progression-free survival. Although these early results are encouraging, several issues arise regarding the use and efficacy of these agents. Interpretation of the radiog. changes that occur after treatment with antiangiogenic agents presents a major challenge. Still lacking are reliable radiog. and biol. markers that can predict which patients will benefit from treatment and that accurately indicate response and progression during therapy. In addition, most patients treated with antiangiogenic drugs eventually progress, and the mechanisms by which tumors escape from therapy are only beginning to be understood. Larger prospective trials that incorporate correlative biomarker studies will be required to address these challenges. Here, we summarize the clin. experience with antiangiogenic therapy in patients with malignant gliomas (MG), review the major issues concerning the use and development of these agents, and discuss strategies that may build upon the initial gains observed with antiangiogenic agents.
IT 1140909-48-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiangiogenic agent XL 184 may show clin. utility in treatment of patient with malignant glioblastoma)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

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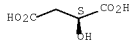
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CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

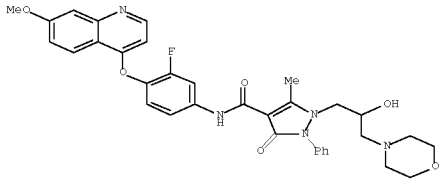


OS.CITING REF COUNT: 13 THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (13 CITINGS)
REFERENCE COUNT: 127 THERE ARE 127 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 161 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2009:1435911 CAPLUS Full-text
DOCUMENT NUMBER: 151:565112
TITLE: Combinations VEGF(R) inhibitors and hepatocyte growth factor (c-met) inhibitors for the treatment of cancer
INVENTOR(S): Burgess, Theresa L.; Coxon, Angela; Dussault, Isabelle; Kaplan-Lefko, Paula; Polverino, Anthony J.; Beaupre, Darrin
PATENT ASSIGNEE(S): Amgen Inc., USA
SOURCE: PCT Int. Appl., 83pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2009140549 | A1 | 20091119 | WO 2009-US44034 | 20090514 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| AU 2009246263 | A1 | 20091119 | AU 2009-246263 | 20090514 |
| AU 2009246263 | B2 | 20140821 | | |
| CA 2723617 | A1 | 20091119 | CA 2009-2723617 | 20090514 |
| EP 2288383 | A1 | 20110302 | EP 2009-747630 | 20090514 |
| R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, RS | | | | |
| JP 2011520908 | T | 20110721 | JP 2011-509721 | 20090514 |
| MX 2010012290 | A | 20110221 | MX 2010-12290 | 20101110 |
| US 20110104161 | A1 | 20110505 | US 2011-992359 | 20110111 |
| US 20140243339 | A1 | 20140828 | US 2014-14194431 | 20140228 |

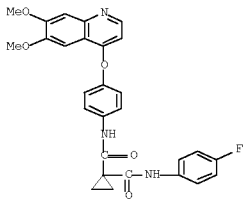
PRIORITY APPLN. INFO.: US 2008-61127753 P 20080514
WO 2009-US44034 W 20090514
US 2011-992359 B3 20110111
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 151:565112
GI



AB This invention is in the field of pharmaceutical agents and specifically relates to compds., compns., uses and methods for treating cancer, by combining VEGF(R) inhibitors and inhibitors of HGF/SF:c-Met. E.g., enhanced activity was observed when AMG 706 (Motesanib) was combined with Amgen Compound 3 [N-[4-[4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamido)-2-fluorophenoxy]pyridin-2-yl]morpholine-4-carboxamide] compared to either single agent alone when tested on human gastric adenocarcinoma cancer cells.
IT 1140909-48-3, XL 184
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combinations VEGF(R) inhibitors and hepatocyte growth factor inhibitors for cancer treatment)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

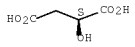
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

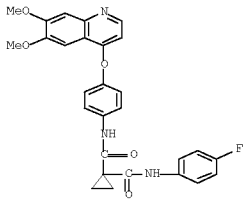


OS.CITING REF COUNT: 12 THERE ARE 12 CAPLUS RECORDS THAT CITE THIS RECORD (15 CITINGS)
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 162 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2009:1001773 CAPLUS Full-text
DOCUMENT NUMBER: 152:349858
TITLE: Novel treatment of medullary thyroid cancer
AUTHOR(S): Sugawara, Masahiro; Geffner, David L.; Martinez, Dorothy; Hershman, Jerome M.
CORPORATE SOURCE: aEndocrinology and Diabetes Division, Veterans Affairs Greater Los Angeles Medical Center, Department of Medicine, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA
SOURCE: Current Opinion in Endocrinology, Diabetes and Obesity (2009), 16(5), 367-372
CODEN: COEDFK; ISSN: 1752-296X
DIGITAL OBJECT ID: 10.1097/MED.0b013e3283304f0c
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB Purpose of review: Metastatic medullary thyroid cancer (MTC) is an incurable disease once metastasis becomes unresectable. Many therapeutic drugs and methods have been tried to circumvent this difficulty. We review currently published treatments and hope for future developments of more effective treatment methods. Recent findings: Motesanib, vandetanib, axitinib (tyrosine kinase inhibitors), and XL184 (multikinase inhibitor) have been shown to achieve partial response or stable disease state of metastatic MTC. Sunitinib and sorafenib, currently available tyrosine kinase inhibitors, can also be tried for patients with MTC. However, these medications are not curative and do not improve survival rate. Only carcinoembryonic antigen-I-iodine-based radioimmunotherapy improved survival of a subset of patients with a very aggressive type of MTC. Drugs currently available for possible use of MTC treatment include bortezomib (proteasome inhibitor), valproic acid (histone deacetylase inhibitor), capecitabine (5-fluorouracil prodrug), and indomethacin (NSAID), although clin. studies have yet to be done. Cardiac natriuretic hormones and an extract of the plant Cautleya gracilis are new agents to be studied for MTC. Summary: Kinase inhibitors are the first drugs showing some efficacy in MTC. To improve survival, unconventional drugs or other therapies with or without kinase inhibitors need to be considered.
IT 1140909-48-3, XL 184
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(multikinase inhibitors like XL184 was effective in patient with metastatic thyroid cancer)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

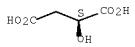
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

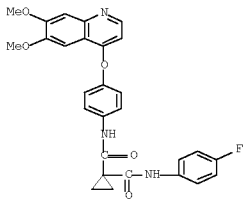


OS.CITING REF COUNT: 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 163 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2009:378374 CAPLUS Full-text
DOCUMENT NUMBER: 153:495871
TITLE: EGFR agonist: irreversible EGFR-TKI and c-Met inhibitors combination
AUTHOR(S): Yadoya, Takehito; Takahashi, Toshiaki; Yamamoto, Nobuyuki
CORPORATE SOURCE: Dep. of Respiratory Diseases, Shizuoka Cancer Center, Shizuoka, Japan
SOURCE: Mebio Oncology (2009), 6(1), 23-31
CODEN: MOENAJ; ISSN: 1349-2179
PUBLISHER: Mejikarubyusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review discussing (1) resistant mechanism to reversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), (2) irreversible EGFR-TKIs HKI-272, BIBW-2992, PF-299804 and CI-1033 and (3) c-Met inhibitors AMG-102, XL-184, XL-880 and ARQ-197.
IT 1140909-48-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(epidermal growth factor receptor agonist and the combination of irreversible EGFR-TKI and c-Met inhibitors)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

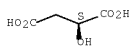
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



L4 ANSWER 164 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2009:239386 CAPLUS Full-text
DOCUMENT NUMBER: 150:275539
TITLE: Methods for diagnosis, prognosis and methods of treatment
INVENTOR(S): Fantl, Wendy J.; Putta, Santosh K.; Perez, Omar D.; Francis-Lang, Helen L.; Cohen, Aileen C.
PATENT ASSIGNEE(S): Nodality, Inc., USA
SOURCE: PCT Int. Appl., 109pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2009025847 | A2 | 20090226 | WO 2008-US9975 | 20080821 |
| WO 2009025847 | A3 | 20090611 | | |

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ,

TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

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|---|---|---|---|---|
| AU 2008289442 | A1 | 20090226 | AU 2008-289442 | 20080821 |
| CA 2696402 | A1 | 20090226 | CA 2008-2696402 | 20080821 |
| US 20090098594 | A1 | 20090416 | US 2008-229476 | 20080821 |
| EP 2179037 | A2 | 20100428 | EP 2008-795509 | 20080821 |
| R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, MK, RS | | | | |
| CN 101802182 | A | 20100811 | CN 2008-80107737 | 20080821 |
| JP 2010536371 | T | 20101202 | JP 2010-521884 | 20080821 |
| IN 2010DN01966 | A | 20100820 | IN 2010-DN1966 | 20100319 |
| US 20120309029 | A1 | 20121206 | US 2012-13493857 | 20120611 |

PRIORITY APPLN. INFO.: US 2007-60957160 P 20070821
US 2008-61048920 P 20080429
US 2008-229476 A1 20080821
WO 2008-US9975 W 20080821

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB This invention is directed to methods and compns. for diagnosis, prognosis and for determining methods of treatment. The physiol. status of cells present in a sample (e.g. clin. sample) can be used in diagnosis or prognosis of a condition (e.g. chronic lymphocytic leukemia), in patient selection for therapy, to monitor treatment and to modify or optimize therapeutic regimens. The physiol. status of a cell can be determined by comparing the intracellular status of one or more activation elements (e.g. the phosphorylation status of a signaling mol.) in a cell (e.g. a cancer cell) to that of another cell (e.g. a normal cell). The physiol. status of a cell can be further classified by adding one or more modulators (e.g. an inhibitor or activator) to the cell in question. In some embodiments, the invention is directed to methods of determining a phenotypic profile of a population of cells.

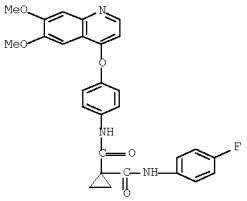
IT 1140909-48-3, XL 184
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(methods for diagnosis, prognosis and treatment of diseases)

RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

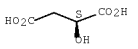
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)

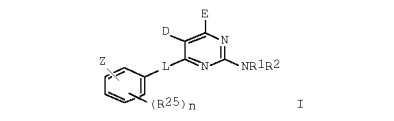
L4 ANSWER 165 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2009:140345 CAPLUS Full-text
DOCUMENT NUMBER: 150:214411
TITLE: Pyrimidine derivatives as JAK-2 inhibitors in combination with other agents and their preparation and use in the treatment of diseases
INVENTOR(S): Lamb, Peter
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 854pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2009017838 | A2 | 20090205 | WO 2008-US9360 | 20080731 |
| WO 2009017838 | A3 | 20090702 | | |

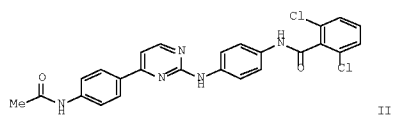
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ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

PRIORITY APPLN. INFO.: US 2007-60962776 P 20070801
OTHER SOURCE(S): CASREACT 150:214411; MARPAT 150:214411
GI



I



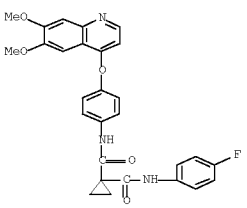
II

AB A method of treating a disease in a mammal, comprising administering to the mammal a therapeutically effective amount of a JAK-2 compound of formula I, or a pharmaceutical composition comprising a therapeutically effective amount of the JAK-2 compound of formula I and a pharmaceutically acceptable carrier, in combination with an active agent selected from of a Raf inhibitor, an EGFR inhibitor, a VEGFR inhibitor, a ErbB2 inhibitor, a BCR-Abl, inhibitor, a Flt3 inhibitor, a Src inhibitor, a c Kit inhibitor, an Akt inhibitor, a Ret inhibitor, an IFG1R inhibitor, an m-Tor inhibitor, a PI3K inhibitor, a PI3Kalpha inhibitor, wherein the mammal is in need of the treatment. Compds. of formula I wherein D and E are independently H, halo, CF3, heterocycloalkyl and alkyl; D and E taken together to form a 5- to 7-membered heteroaryl, and 5- to 7-membered heterocycloalkyl; L is a bond, O and NH; Z is alkoxy, cycloalkyl, and (un)substituted heteroaryl; Z and R25 taken together for form a 5- to 6-membered heterocycloalkyl, 5- to 6-membered heteroaryl, 5- to 6-membered cycloalkyl, etc.; each R25 is independently alkyl, alkenyl, lower alkyl, halo, haloalkyl, haloalkoxy, amino, etc.; R1 is H; R2 is (un)substituted aryl, (un)substituted heteroaryl, alkyl, etc.; n is 0 - 4; and pharmaceutically acceptable salts thereof, are claimed. Example compound II was prepared by acylation of 2-(4-aminophenylamino)-5-(4-acetylaminophenyl)pyrimidine with 2,6-dichlorobenzoyl chloride. All the invention compds. were evaluated for their JAK-2 inhibitory activity (some data given).

IT 849217-68-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of pyrimidine derivs. as JAK-2 inhibitors in combination with other agents useful in treatment of diseases)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)

L4 ANSWER 166 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2008:1282443 CAPLUS Full-text
DOCUMENT NUMBER: 149:486836
TITLE: Methods for treating cancer resistant to ErbB therapeutics
INVENTOR(S): Janne, Pasi A.; Engelman, Jeffrey; Cantley, Lewis C.
PATENT ASSIGNEE(S): Dana Farber Cancer Institute, USA; Beth Israel Deaconess Medical Center; Massachusetts General Hospital
SOURCE: PCT Int. Appl., 96pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2008127710 | A2 | 20081023 | WO 2008-US4804 | 20080411 |
| WO 2008127710 | A3 | 20081204 | | |

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PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

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| AU 2008239594 | A1 | 20081023 | AU 2008-239594 | 20080411 |
| AU 2008239594 | B2 | 20131024 | | |
| CA 2683559 | A1 | 20081023 | CA 2008-2683559 | 20080411 |
| EP 2076289 | A2 | 20090708 | EP 2008-742861 | 20080411 |
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| JP 2010523680 | T | 20100715 | JP 2010-503084 | 20080411 |
| US 20120225870 | A1 | 20120906 | US 2010-450826 | 20100318 |
| US 8715665 | B2 | 20140506 | | |
| AU 2013203111 | A1 | 20130502 | AU 2013-203111 | 20130409 |
| US 20140296100 | A1 | 20141002 | US 2014-14256418 | 20140418 |
| JP 2014141530 | A | 20140807 | JP 2014-97474 | 20140509 |

PRIORITY APPLN. INFO.:
US 2007-60923384 P 20070413
AU 2008-239594 A3 20080411
JP 2010-503084 A3 20080411
WO 2008-US4804 W 20080411
US 2010-450826 A1 20100318

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB Provided herein are methods for treating cancer that is resistant to treatment with an anti- ErbB therapeutic agent and which is associated with an activating MET gene mutation or a MET gene amplification. The methods involve administering to a subject a combination of an anti- ErbB therapeutic and an anti-MET therapeutic. Also provided are methods for reducing ErbB mediated signaling or PI3 kinase mediated signaling in a cancer cell.

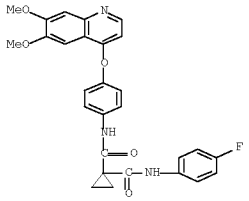
IT 1140909-68-3, XL 184
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for treating cancer resistant to ErbB therapeutics using combination of anti-Met receptor agent and anti-ErbB receptor agent in relation to activation mutation or gene amplification)

RN 1140909-68-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

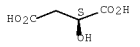
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L4 ANSWER 167 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2008:771167 CAPLUS Full-text
DOCUMENT NUMBER: 149:104583
TITLE: N-Acylazetidine derivatives as MEK inhibitors and their preparation, pharmaceutical compositions and use in the treatment of cancer
INVENTOR(S): Lamb, Peter
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 534pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2008076415 | A1 | 20080626 | WO 2007-US25751 | 20071214 |

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PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

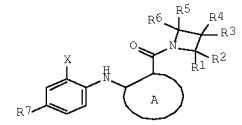
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| AU 2007334402 | A1 | 20080626 | AU 2007-334402 | 20071214 |
| AU 2007334402 | B2 | 20140213 | | |
| CA 2671982 | A1 | 20080626 | CA 2007-2671982 | 20071214 |
| US 20080166359 | A1 | 20080710 | US 2007-2340 | 20071214 |
| US 7999006 | B2 | 20110816 | | |
| EP 2101759 | A1 | 20090923 | EP 2007-853418 | 20071214 |
| R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS | | | | |
| JP 2010513288 | T | 20100430 | JP 2009-541420 | 20071214 |
| JP 5311673 | B2 | 20131009 | | |
| CN 101605540 | A | 20091216 | CN 2007-80051355 | 20090814 |
| AU 2013204026 | A1 | 20130516 | AU 2013-204026 | 20130411 |
| JP 2013151569 | A | 20130808 | JP 2013-102016 | 20130514 |

PRIORITY APPLN. INFO.:
US 2006-60875412 P 20061214
AU 2007-334402 A3 20071214
JP 2009-541420 A3 20071214
WO 2007-US25751 W 20071214

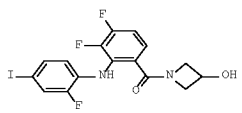
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 149:104583; MARPAT 149:104583

GI



I



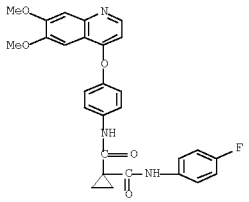
II

AB The invention provides methods of treating cancer by administering a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, in combination with other cancer treatments. Compds. of formula I wherein ring A is (un)substituted (hetero)arylene; X is (halo)alkyl, halo and haloalkoxy; R1, R2, R3, R4, R5 and R6 are independently H, halo, NO2, NH2 and derivs., OH and derivs., NHSO2H and derivs., CN, SH and derivs., etc.; R7 is H, halo and alkyl; and their pharmaceutically acceptable salts and solvates thereof are claimed. Example compound II was prepared by amidation of 3,4-difluoro-2-[(2-fluoro-4- iodophenyl)amino]benzoic acid with azetidin-3-ol hydrochloride. All the invention compds. were evaluated for their MEK inhibitory activity (some data given).

IT 849217-68-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of N-acylazetidine derivs. as MEK inhibitors useful in the mono- and combination therapy of cancer)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

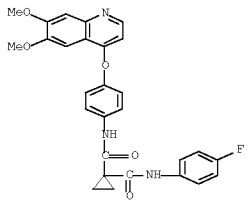
L4 ANSWER 168 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2008:699999 CAPLUS Full-text
DOCUMENT NUMBER: 149:30417
TITLE: Antibodies and inhibitory nucleic acids for targeing HIF-1α and for diagnosing/treating tumor or metastasis
INVENTOR(S): Huang, L. Eric
PATENT ASSIGNEE(S): University of Utah Research Foundation, USA
SOURCE: PCT Int. Appl., 157pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|

WO 2008070616 A2 20080612 WO 2007-US86264 20071203
WO 2008070616 A3 20090430
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US 20100074897 A1 20100325 US 2009-517132 20090710
PRIORITY APPLN. INFO.: US 2006-60868188 P 20061201
WO 2007-US86264 W 20071203
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB Disclosed are compns. and methods related to HIF-1α (hypoxia-inducible factor 1α). The compns. and methods comprise use of HIF-1α inhibitors for reducing tumor growth or metastatic tumor growth. The HIF-1α inhibitor is an antibody (including monoclonal, human and humanized antibody), small mol., siRNA, shRNA, or antisense polynucleotide.
IT 1140909-48-3, XL 184
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antibodies and inhibitory nucleic acids for targeing HIF-1α and for diagnosing/treating tumor or metastasis)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

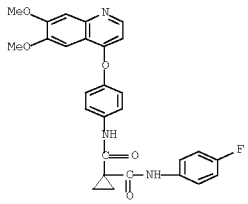
CRN 849217-68-1
CMF C28 H24 F N3 O5



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ES 2411505 T3 20130705 ES 2006-820476 20061212
CN 103341168 A 20131009 CN 2013-10251494 20061212
AR 58359 A1 20080130 AR 2006-105550 20061215
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AU 2011201326 A1 20110414 AU 2011-201326 20110323
AU 2011201326 B2 20120112
AU 2012202120 A1 20120503 AU 2012-202120 20120412
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AU 2006-324477 A3 20061212
CN 2006-80052740 A3 20061212
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JP 2008-545075 A3 20061212
WO 2006-GB4611 W 20061212
US 2008-97384 B1 20080613
US 2010-890101 A1 20100924
AU 2011-201326 A3 20110323
US 2012-13472862 A1 20120516
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB The invention relates to agents which possess anti-angiogenic activity and are accordingly useful in methods of treatment of disease states associated with angiogenesis in the animal or human body. More specifically the invention concerns a combination of a monoclonal antibody against human angiopoietin 2 (anti-Ang-2) and an antagonist of the biol. activity of VEGF-A, and/or KDR receptor, and/or FLT1, and uses of such antagonists. The nucleotide sequences and the encoded amino acid sequences of anti-Ang-2 monoclonal antibodies are disclosed.
IT 1140909-48-3, XL 184
RL: PAC (Pharmacological activity); BIOL (Biological study)
(combination of anti-angiopoietin 2 human monoclonal antibody and of VEGF-A, KDR and/or FLT1 antagonist for treating cancer)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

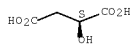
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

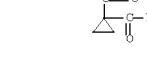
L4 ANSWER 169 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2007:671771 CAPLUS Full-text
DOCUMENT NUMBER: 147:93969
TITLE: Combination of anti-angiopoietin 2 human monoclonal antibody and of VEGF-A, KDR and/or FLT1 antagonist for treating cancer
INVENTOR(S): Brown, Jeffrey Lester; Emery, Stephen Charles; Blakey, David Charles
PATENT ASSIGNEE(S): AstraZeneca AB, Swed.; AstraZeneca UK Limited
SOURCE: PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 2007068895 | A1 | 20070621 | WO 2006-GB4611 | 20061212 |
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| AU 2006324477 | A1 | 20070621 | AU 2006-324477 | 20061212 |
| CA 2633211 | A1 | 20070621 | CA 2006-2633211 | 20061212 |
| KR 2008073766 | A | 20080811 | KR 2008-7015745 | 20061212 |
| KR 1371773 | B1 | 20140307 | | |
| EP 1962903 | A1 | 20080903 | EP 2006-820476 | 20061212 |
| EP 1962903 | B1 | 20130313 | | |
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CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

L4 ANSWER 170 OF 170 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2005:300201 CAPLUS Full-text
DOCUMENT NUMBER: 142:373856
TITLE: Preparation of quinolines and quinazolines as inhibitors of c-Met and other tyrosine kinases and therapeutic uses against proliferative diseases
INVENTOR(S): Bannen, Lynne Canne; Chan, Diva Sze-ming; Chen, Jeff; Dalrymple, Lisa Esther; Forsyth, Timothy Patrick; Huynh, Tai Phat; Jammalamadaka, Vasu; Khoury, Richard George; Leahy, James William; Mac, Morrison B.; Mann, Grace; Mann, Larry W.; Nuss, John M.; Parks, Jason Jevious; Takeuchi, Craig Stacy; Wang, Yong; Xu, Wei
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 428 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 2005030140 | A2 | 20050407 | WO 2004-US31523 | 20040924 |
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| ES 2369652 | T3 | 20111202 | ES 2010-160518 | 20040924 |
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| US 20070054928 | A1 | 20070308 | US 2006-586751 | 20061026 |
| US 20070225307 | A1 | 20070927 | US 2007-753462 | 20070524 |
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| US 20070244116 | A1 | 20071018 | US 2007-753503 | 20070524 |
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| US 20090105299 | A1 | 20090423 | US 2007-753514 | 20070524 |
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| HK 1143068 | A1 | 20120518 | HK 2010-109531 | 20101006 |
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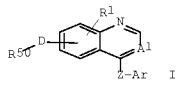
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| AU 2004-275842 | A3 | 20040924 |
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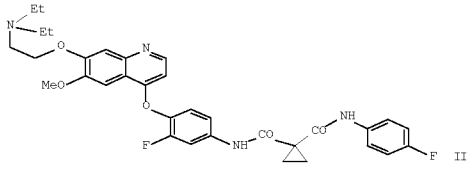
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 142:373856; MARPAT 142:373856

GI



I



II

AB The present invention provides compds. (shown as I; variables defined below; e.g. N-[4-[[7-[[2-(diethylamino)ethyl]oxy]-6-(methyloxy)quinolin-4-yl]oxy]-3-fluorophenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (shown as II)) for modulating protein kinase enzymic activity for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration and chemoinvasion. More specifically, the invention provides quinazolines and quinolines which inhibit, regulate and/or modulate kinase receptors, particularly c-Met, KDR, c-Kit, flt-3 and flt-4, signal transduction pathways related to the changes in cellular activities as mentioned above, compns. which contain these compds., and methods of using them to treat kinase-dependent diseases and conditions. The present invention also provides methods for making compds. as mentioned above, and compns. which contain these compds. For I: R1 = H, halogen, OR3, NO2, NH2, NR3R4, and (un)substituted lower alkyl; A1 = :N-, :C(H)-, and :C(CN)-; Z = -S(O)0-2-, -O-, and -NR5-; Ar is aryl or heteroaryl; D = -O-, -S(O)0-2-, and -NR15-; R50 = R3 or bicyclic radical; addnl. details are given in the claims. Methods of preparation are claimed and .apprx.80 example prepns. of I and intermediates are included. For example, II was prepared (34 %) from 2-(diethylamino)ethanol and cyclopropane-1,1-dicarboxylic acid N-[3-fluoro-4-[(7-hydroxy-6-methoxyquinolin-4-yl)oxy]phenyl]amide N-(4-fluorophenyl)amide, which was prepared (89 %) by deprotection of cyclopropane-1,1-dicarboxylic acid N-[4-[(7-benzyloxy-6-methoxyquinolin-4-yl)oxy]-3-fluorophenyl]amide N-(4-fluorophenyl)amide, which was prepared (48 %) from trifluoromethanesulfonic acid 7-benzyloxy-6-methoxyquinolin-4-yl ester and cyclopropane-1,1-dicarboxylic acid N-(3-fluoro-4-hydroxyphenyl)amide N-(4-fluorophenyl)amide, which was prepared (85 %) by deprotection of cyclopropane-1,1-dicarboxylic acid N-(4-benzyloxy-3-fluorophenyl)amide N-(4-fluorophenyl)amide, which was prepared (98 %) from (4-benzyloxy-3-fluorophenyl)amine and 1-(4-fluorophenylcarbamoyl)cyclopropanecarboxylic acid; addnl. details are given in the examples.

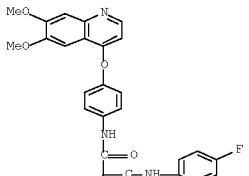
IT 849217-68-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of quinolines and quinazolines as inhibitors of c-Met and other tyrosine kinases and therapeutic uses against proliferative diseases)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 42 THERE ARE 42 CAPLUS RECORDS THAT CITE THIS RECORD (51 CITINGS)

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FILE 'REGISTRY' ENTERED AT 12:58:42 ON 04 OCT 2014

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Connecting via Winsock to STN at pto-stn on port 23



Welcome to STN International!  Enter x:X

LOGINID:SSPTATRR1625

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * * *   Welcome to STN International   * * * * * * * * * * *

 NEWS  1  JAN 29  Instructor-led and on-demand STN training options available
                  from CAS
 NEWS  2  MAY 27  Get the Latest Version of STN Express, Version 8.5.2.1,
                  Available May 2014
 NEWS  3  JAN 09  Updated Enzyme Nomenclature Improves Access to Biological
                  Information in CAS REGISTRY
 NEWS  4  JAN 09  DEFULL - German (Deutschland, DE) Patents Full-text Database
                  New on STN
 NEWS  5  JAN 09  Chinese Dissertations Added to CAplus
 NEWS  6  JAN 27  STN on the Web Now Compatible with Microsoft Windows 8.1 and
                  current Versions of Internet Explorer and Google Chrome
 NEWS  7  JAN 27  Annual MEDLINE Reload on STN Introduces New Searching
                  Capabilities and the Updated 2014 MeSH Thesaurus
 NEWS  8  FEB 03  DWPI: Latest Manual Code Revision goes live
 NEWS  9  FEB 03  DWPI: New coverage of Singapore PCT-transfers and grants
 NEWS 10  FEB 24  INFULL and DEFULL databases Now Available via STN Viewer
 NEWS 11  MAR 28  New STN Platform Enhancements Available, Increase Efficiency
                  of Search Workflow.
 NEWS 12  APR 25  New Format Adopted for Taiwanese Granted Patent Numbers
                  in CAS Databases and INPADOC.
 NEWS 13  MAY 2   New STN Global Value Pricing Empowers You to Maximize the
                  Value of STN
 NEWS 14  MAY 9   STN AnaVist, Version 2.1, Improves Operating System
                  Compatibility and Performance
 NEWS 15  MAY 19  Availability of Digital Object Identifiers (DOIs) Enhanced in
                  STN Databases
 NEWS 16  MAY 20  New Cluster NPS available for all Databases with the Numeric
                  Property Search feature
 NEWS 17  MAY 29  CAS REGISTRY BLAST Upgrade Improves Search Capabilities and
                  Results Ranking
 NEWS 18  JUN 10  Additional Experimental Spectra Now Available in CAS REGISTRY
                  on STN
 NEWS 19  JUN 10  MEDLINE on STN Now Updated Daily
 NEWS 20  AUG 18  Latest Version of Emtree Introduces 811 New Terms
 NEWS 21  JUL 1   CHEMCATS (Chemical Catalogs Online) on STN Enhanced with New
                  Search and Display Fields and More Frequent Updates
 NEWS 22  JUL 24  Batch search results for DGENE, USGENE and PCTGEN now
                  available for 30 days
 NEWS 23  JUL 28  Latest release of new STN now available, expands global
                  patent coverage and enhances search capabilities
 NEWS 24  SEP 4   KRFULL: New Full-text Database for Korean Patent
                  Publications Now Available on new STN
 NEWS 25  SEP 12  Surge in US Patent Publications in Coming Weeks
 NEWS 26  OCT 1   Cooperative Patent Classification (CPC) Combination Set Data
                  Now Available in CAplus, INPADOCDB and USPAT Databases

 NEWS EXPRESS 27 MAY 2014 CURRENT WINDOWS VERSION IS V8.5.2.1,
              AND CURRENT DISCOVER FILE IS DATED 29 SEPTEMBER 2014.

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FILE LAST UPDATED: 2 Oct 2014 (20141002/ED)
HIGHEST GRANTED PATENT NUMBER: US8850611
HIGHEST APPLICATION PUBLICATION NUMBER: US20140298555
CA INDEXING IS CURRENT THROUGH 28 Sep 2014 (20140928/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 2 Oct 2014 (20141002/PD)
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HIGHEST GRANTED PATENT NUMBER: US8850611
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=> s US2014-0200242/pn
L1            1 US2014-0200242/PN
                (US20140200242/PN)

=> d ind

L1   ANSWER 1 OF 1  USPATFULL on STN


=> d ind

L1   ANSWER 1 OF 1  USPATFULL on STN


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L2            1 US2014-0200242/PN
                (US20140200242/PN)

=> d ind

L2   ANSWER 1 OF 1  USPATFULL on STN


=> log y


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     FILE 'USPATFULL' ENTERED AT 13:09:13 ON 04 OCT 2014
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                D IND
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FULL ESTIMATED COST                                     6.30       8.19

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | |
| | Filing Date | 2012-02-10 |
| | First Named Inventor | Jo Ann Wilson |
| | Art Unit | TBD |
| | Examiner Name | TBD |
| | Attorney Docket Number | 224990/10-039C-US/343999 |

**U.S.PATENTS**

| 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 |
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|---|---|---|---|---|---|---|---|---|
| | 1 | 2010/083414 | WO | | 2010-07-22 | Exelixis, Inc. | | ☐ |

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| INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | |
| | Filing Date | 2012-02-10 |
| | First Named Inventor | Jo Ann Wilson |
| | Art Unit | TBD |
| | Examiner Name | TBD |
| | Attorney Docket Number | 224990/10-039C-US/343999 |

| | | | |
|---|---|---|---|
| | 1 | International Search Report for PCT/US2012/024591 mailed May 25, 2012 | ☐ |

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**EXAMINER SIGNATURE**

| Examiner Signature | /Timothy Rozof/ | Date Considered | 10/04/2014 |
|---|---|---|---|

*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.GOVor 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.



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| INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | |
| | Filing Date | 2012-02-10 |
| | First Named Inventor | Jo Ann Wilson |
| | Art Unit | TBD |
| | Examiner Name | TBD |
| | Attorney Docket Number | 224990/10-039C-US/343999 |

**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 | | Date (YYYY-MM-DD) | 2013-08-09 |
| Name/Print | Heidi M. Berven | Registration Number | 48951 |

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.**



ALL REFERENCES CONSIDERED EXCEPT WHERE LINE THROUGH. /T.R./

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13984559 | WILSON, JO ANN |
| | Examiner | Art Unit |
| | TIMOTHY R ROZOF | 1625 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 04/23/2014 | 10/04/2014 | | | | | | | |
| | 1 | ÷ | N | | | | | | | |
| | 2 | ÷ | N | | | | | | | |
| | 3 | ÷ | N | | | | | | | |
| | 4 | ÷ | N | | | | | | | |
| | 5 | ÷ | N | | | | | | | |
| | 6 | ÷ | N | | | | | | | |
| | 7 | ÷ | N | | | | | | | |
| | 8 | ÷ | N | | | | | | | |
| | 9 | ÷ | N | | | | | | | |
| | 10 | ÷ | N | | | | | | | |
| | 11 | - | - | | | | | | | |
| | 12 | ÷ | N | | | | | | | |
| | 13 | ÷ | N | | | | | | | |
| | 14 | ÷ | N | | | | | | | |
| | 15 | ÷ | N | | | | | | | |
| | 16 | ÷ | ✓ | | | | | | | |
| | 17 | - | - | | | | | | | |
| | 18 | - | | | | | | | | |
| | 19 | ÷ | ✓ | | | | | | | |
| | 20 | ÷ | ✓ | | | | | | | |
| | 21 | - | - | | | | | | | |
| | 22 | - | - | | | | | | | |
| | 23 | ÷ | ✓ | | | | | | | |
| | 24 | - | - | | | | | | | |
| | 25 | - | - | | | | | | | |
| | 26 | - | - | | | | | | | |
| | 27 | - | - | | | | | | | |
| | 28 | ÷ | ✓ | | | | | | | |
| | 29 | ÷ | ✓ | | | | | | | |
| | 30 | ÷ | ✓ | | | | | | | |
| | 31 | ÷ | ✓ | | | | | | | |
| | 32 | ÷ | ✓ | | | | | | | |
| | 33 | ÷ | ✓ | | | | | | | |
| | 34 | ÷ | ✓ | | | | | | | |
| | 35 | | ✓ | | | | | | | |
| | 36 | | ✓ | | | | | | | |

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13984559 | WILSON, JO ANN |
| | Examiner | Art Unit |
| | TIMOTHY R ROZOF | 1625 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 04/23/2014 | 10/04/2014 | | | | | | | |
| | 37 | | ✓ | | | | | | | |
| | 38 | | ✓ | | | | | | | |
| | 39 | | ✓ | | | | | | | |

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13984559 | WILSON, JO ANN |
| | Examiner | Art Unit |
| | TIMOTHY R ROZOF | 1625 |

| CPC- SEARCHED | | |
|---|---|---|
| Symbol | Date | Examiner |
| | | |

| CPC COMBINATION SETS - SEARCHED | | |
|---|---|---|
| Symbol | Date | Examiner |
| | | |

| US CLASSIFICATION SEARCHED | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| | | | |

| SEARCH NOTES | | |
|---|---|---|
| Search Notes | Date | Examiner |
| Class, inventor, STN and EAST search | 10/4/2014 | TRR |

| INTERFERENCE SEARCH | | | |
|---|---|---|---|
| US Class/ CPC Symbol | US Subclass / CPC Group | Date | Examiner |
| | | | |

| /TIMOTHY R ROZOF/<br>Examiner.Art Unit 1625 | |
|---|---|

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

Inventor(s): Jo Ann Wilson, et al.
Application No.: 13/984,559
Filing Date: March 20, 2014

Group Art Unit: 1625
Examiner: Timothy R. Rozof
Attorney Docket No.: 224990/10-039C-US/343999

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

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

**RESPONSE TO RESTRICTION REQUIREMENT DATED MAY 1, 2014**

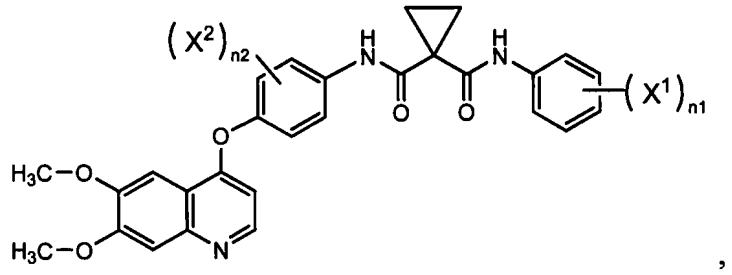
This communication is in response to the Requirement for Restriction/ Election dated May 1, 2014.

Amendments begin on page 2.

Remarks begin on page 10.

## Amendments to the Claims

1. (Withdrawn) A process for preparing a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is H, Br, Cl, or F;

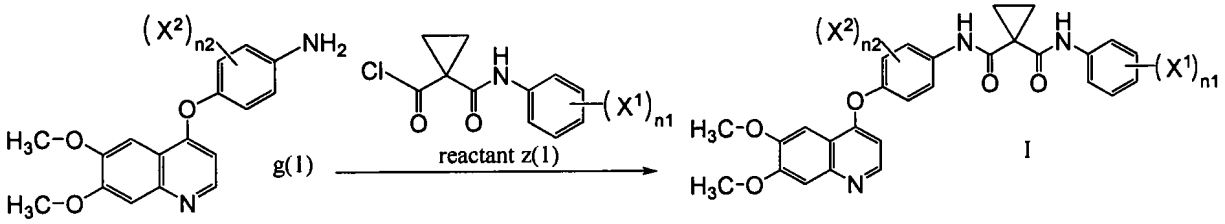
$X^2$ is H, Br, Cl, or F;

n1 is 1-2; and

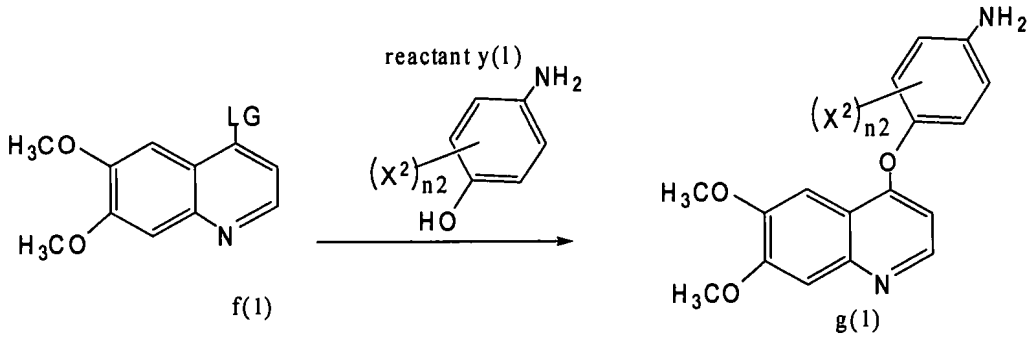
n2 is 1-2;

the process comprising:

contacting the compound of formula g(1) with reactant z(1) to yield the compound of formula I:

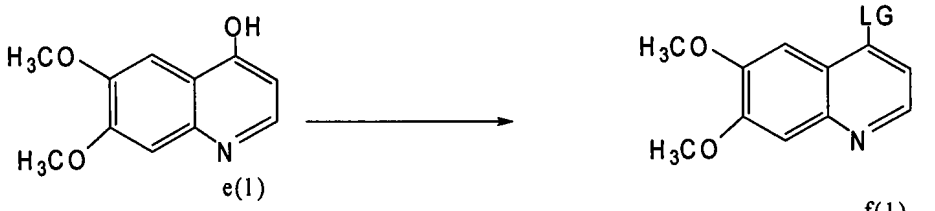



2. (Withdrawn) The process according to claim 1, wherein the compound of formula g(1) is made by reacting a compound of formula f(1) with reactant y(1) to yield the compound of formula g(1):




wherein LG represents a leaving group, and each $X^2$ and n2 are as defined in claim 1.

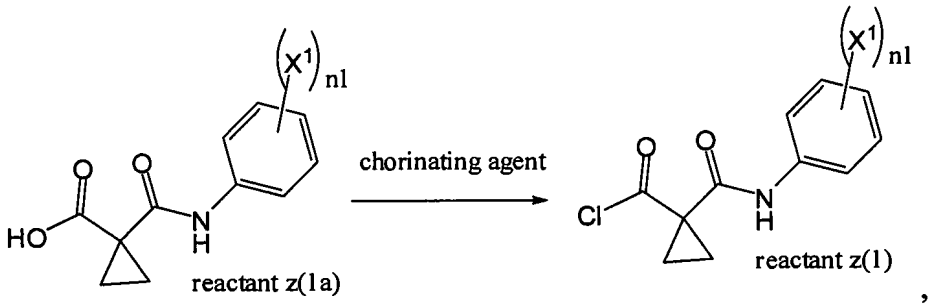
3. (Withdrawn) The process according to claim 2, wherein the compound of formula f(1) is made by converting compound e(1) to the compound of formula f(1):




e(1) f(1),

wherein LG represents a leaving group.

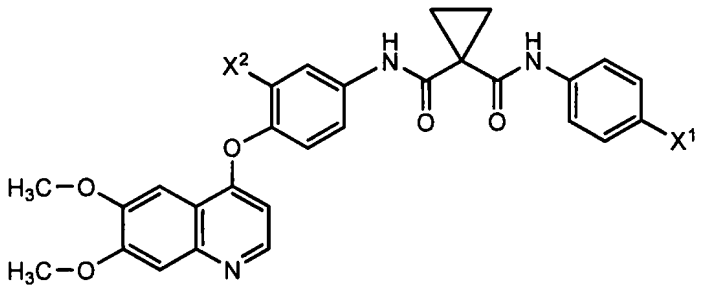
4. (Withdrawn) The process according to claim 1, wherein reactant z(1) is made by reacting reactant z(1a) with a chlorinating agent to yield reactant z(1):




reactant z(1a) reactant z(1),

wherein $X^1$ is Br, Cl, or F; and n1 is 1-2.

5. (Withdrawn) The process according to claim 1, wherein the compound of formula I is compound IA[[-1]]:



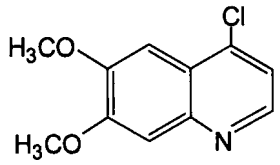

IA

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is H, Cl, Br, or F; and

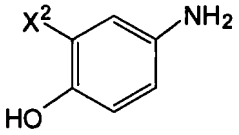
$X^2$ is H, Cl, Br, or F.

6. (Withdrawn) The process according to claim 5, wherein the compound of formula f(1) is compound f(2):




f(2) ;

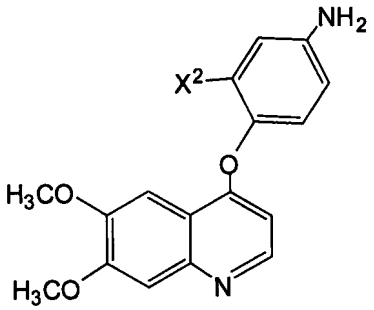
reactant y(1) is reactant (y)(2):




reactant (y)(2) ,

wherein $X^2$ is hydrogen or fluoro; and

the compound of formula g(1) is of formula g(2):




g(2) .

7. (Withdrawn) The process according to claim 6, wherein the reaction employs a non-nucleophilic base.

8. (Withdrawn) The process according to claim 7, wherein the non-nucleophilic base is an alkali metal alkoxide; and the reaction is carried out in a polar solvent.

9. (Withdrawn) The process according to claim 8, wherein the alkali metal alkoxide is sodium tert-butoxide, and the polar solvent is DMA.

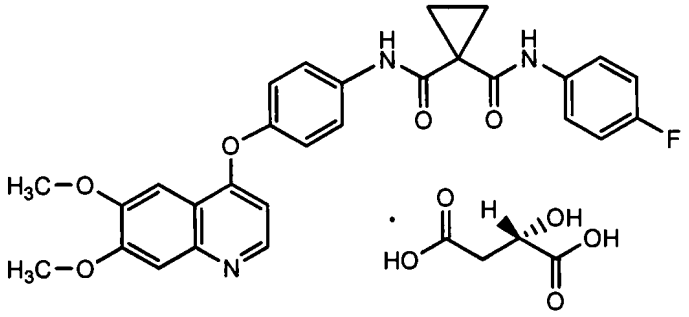
10. (Withdrawn) The process according to claim 8, wherein the alkali metal alkoxide is sodium tert-pentoxide, and the polar solvent is DMA.

11. Cancelled.

12. (Withdrawn) The process according to claim 1, wherein the reaction is carried out in the presence of an inorganic base.

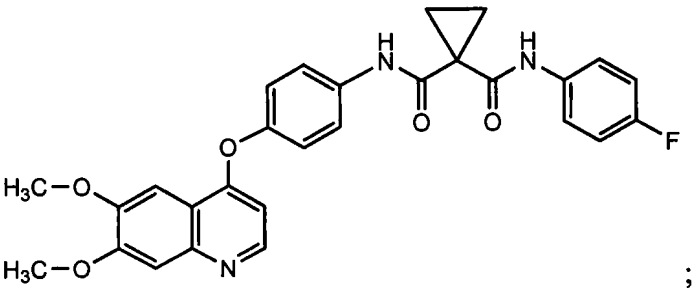
13. (Withdrawn) The process according to claim 12, wherein the inorganic base is $K_2CO_3$, and the solvent employed in this reaction is a combination of THF and $H_2O$.

14. (Withdrawn) A process for preparing compound IB:



IB

with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol from compound IA:



;

IA

comprising:

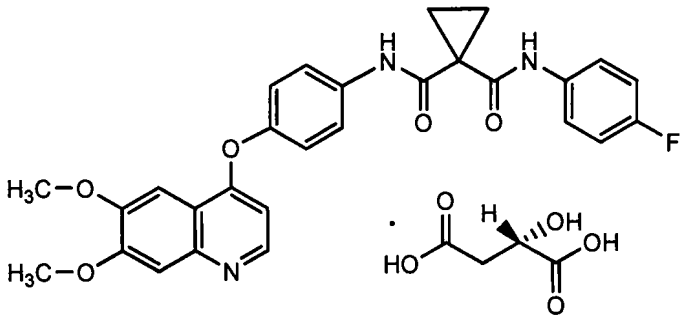
(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) vacuum distilling the mixture successively; and

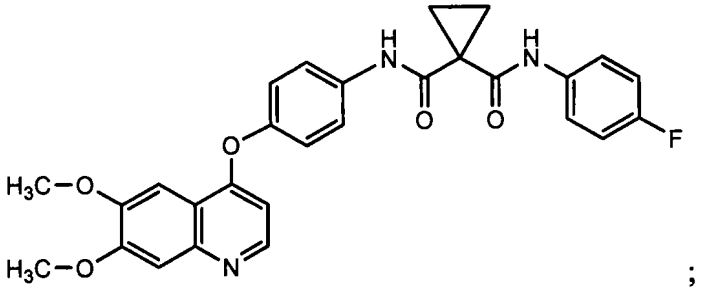
(d) isolating the compound of IB by filtration;.

15. (Withdrawn) The process of claim 14 for preparing compound IB:



IB

with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol from compound IA:



;

IA

comprising:

(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) seeding the mixture with the compound of IB;

(d) vacuum distilling the mixture; and

(e) isolating the compound of IB by filtration.

16. (Original) Compound IA or IB admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

17. Cancelled.

18. Cancelled.

19. (Original) Compound IB in the N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

20. (Original) Compound IB as a mixture of the N-1 form and N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

21. Cancelled.

22. Cancelled.

23. (Currently Amended) A pharmaceutical composition selected from the group consisting of Table 2A, 3, 4, 5, and ~~or~~ 6.

**Table 2A**

| **Ingredient** | **% w/w** |
|---|---|
| Compound IB (10 % drug load as Compound IA) | 12.67 |
| MCC | 51.52 |
| Lactose | 25.76 |
| Hydroxypropyl cellulose | 3.0 |
| Croscarmellose Sodium | 6.0 |
| Colloidal Silicon Dioxide | 0.3 |
| Magnesium Stearate | 0.75 |
| **Total** | **100** |

**Table 3**

| Ingredient | mg/unit dose |
|---|---|
| Compound IB (10 % drug load as Compound IA) | 25 |
| Silicified Microcrystalline Cellulose | 196.75 |
| Croscarmellose sodium | 12.5 |
| Sodium starch glycolate | 12.5 |
| Fumed Silica | 0.75 |
| Stearic acid | 2.5 |
| **Total Fill Weight** | 250 |

**Table 4**

| Ingredient | mg/unit dose |
|---|---|
| Compound IB (50 % drug load as Compound IA) | 100 |
| Silicified Microcrystalline Cellulose | 75.40 |
| Croscarmellose sodium | 10.00 |
| Sodium Starch Glycolate | 10.00 |
| Fumed silica | 0.6 |
| Stearic Acid | 4.0 |
| **Total Fill Weight** | 200 |

**Table 5**

| | mg/unit dose |
|---|---|
| **Ingredient** | **50mg** |
| Compound IB (10 % drug load as Compound IA) | 63.35 |
| Microcrystalline Cellulose | 95.39 |
| Croscarmellose sodium | 9.05 |
| Sodium starch glycolate | 9.05 |
| Fumed Silica | 0.54 |
| Stearic acid | 3.62 |
| **Total Fill Weight** | 181.00 |

**Table 6**

| | **mg/unit dose** |
|---|---|
| **Ingredient** | **60mg** |
| Compound IB | 73.95 |
| Microcrystalline Cellulose | 114.36 |
| Croscarmellose sodium | 10.85 |
| Sodium starch glycolate | 10.85 |
| Fumed Silica | 0.65 |
| Stearic acid | 4.34 |
| **Total Fill Weight** | 217.00 |

24-27. Cancelled.

28. (Previously Presented) The pharmaceutical composition of claim 23 admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

29. (Previously Presented) The pharmaceutical composition of claim 23 admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

30. (Previously Presented) The pharmaceutical composition of claim 23 admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

31. (Previously Presented) The pharmaceutical composition of claim 23 admixed with 15 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

32. (Previously Presented) The pharmaceutical composition of claim 23 admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

33. (Previously Presented) The pharmaceutical composition of claim 23 admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

34. (Previously Presented) The pharmaceutical composition of claim 23 admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

35. (New) A pharmaceutical composition comprising Compound IB; microcrystalline cellulose; croscarmellose sodium; sodium starch glycolate; fumed silica; and stearic acid.

36. (New) The pharmaceutical composition of claim 35, which is capsule composition.

37. (New) The pharmaceutical composition of claim 36, comprising 25 mg or 100 mg of Compound 1B.

38. (New) The pharmaceutical composition of claim 37 comprising 25 mg Compound IB, wherein formation of 6,7-dimethoxy-quinoline-4-ol is limited to 50 ppm over 9 months at temperatures of 25, 30, or 40 °C and relative humidities of 60 or 75 percent.

39. (New) The pharmaceutical composition of claim 37 comprising 100 mg Compound IB, wherein formation of 6,7-dimethoxy-quinoline-4-ol is limited to 50 ppm over 6 months at temperatures of 25, 30, or 40 °C and relative humidities of 60 or 75 percent.

## REMARKS

**Claim Status**

Claims 35-39 are new. Support for claims 35-37 is available in the specification as filed at page 23, paragraphs 104-109 and paragraph 111, as well as Tables 3 and 4. Support for claims 38-39 is available in the specification as filed at pages 35-36, paragraphs 161-163, as well as the accompanying tables. Thus, the new claims introduce no new matter.

Claims 11, 17-18, 21-22, and 24-27 are cancelled.

Claims 1-10 and 12-15 are withdrawn.

Claims 16 and 19-20 are original.

Claims 28-34 are previously presented.

Claim 23 is currently amended for clarity. No new matter has been added to currently amended claim 23.

Thus, claims 1-10, 12-16, 19-20, 23, and 28-34 are currently pending.

By amending the claims, Applicant does not concede that the available patent coverage would not extend as far as the original claim. Rather, Applicant reserves the right to file continuation applications to pursue the breadth of the claims as filed. Further, by the present amendments, it does not follow that the amended claims have become so perfect in their description that no one could devise an equivalent. After amendment, as before, limitations in the ability to describe the present invention in language in the patent claims naturally prevent Applicant from capturing every nuance of the invention or describing with complete precision the range of its novelty or every possible equivalent. See, *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 62 USPQ2d 1705 (2002). Accordingly, the foregoing amendments are made specifically in the interest of expediting prosecution and there is no intention of surrendering any range of equivalents to which Applicant would otherwise be entitled, and the Applicant seeks the timely allowance of the amended claims.

**Requirement for Election**

Pursuant to 37 C.F.R. 1.499, the Examiner requires the Applicant to elect a single invention from the following groups to which the claims must be restricted. The Examiner has listed the following groups:

- Group I, claims 1-10, 12, and 13, drawn to a process for preparing a compound of formula I. If this group is elected, a further election of a single disclosed species of formula I compound is required.
- Group II, claims 14-15, drawn to a process for preparing a compound of formula IB.
- Group III, claims 16, 19, 20, 23, and 28-34, drawn to compounds IA or IB and pharmaceutical compositions thereof. If this group is elected, a further election of a single disclosed species of formula IA or IB compound is required.

In response, the Applicant elects Group III, claims 16, 19, 20, 23, and 28-34, drawn to compounds IA or IB and pharmaceutical compositions thereof. The election is made without traverse. To complete the requirement, the Applicant further elects formula IB as the single disclosed specie.

## OTHER C-MET INHIBITOR CASES

The Applicant wishes to make the Examiner aware of the Applicant's other applications related to c-Met inhibitors and their use in the treatment of cancer. For the Examiner's convenience, the Applicant is providing a list of the Applicant's applications directed to the treatment of cancer using c-Met inhibitors. The Applicant understands the Examiner has electronic access to these applications and to the Office Actions that have issued in these applications, and has therefore not included copies with this Response. The Applicant will gladly provide the applications and Office Actions to the Examiner, however, upon request.

| Application No. | Filing or 371 Date | Patent No. | Examiner | Status |
|---|---|---|---|---|
| 10/573,336 | 09/18/2006 | | Koontz, Tammy J | Abandoned |
| 11/571,140 | 12/21/2006 | 7,977,345 | Moore, Susanna | Issued |
| 11/586,751 | 10/26/2006 | | Ward, Paul V. | Pending |
| 11/753,462 | 05/24/2007 | 8,178,532 | Ward, Paul V | Issued |
| 11/753,503 | 05/24/2007 | 8,476,298 | Ward, Paul V | Issued |
| 11/753,514 | 05/24/2007 | 8,067,436 | Bernhardt, Emily A | Issued |
| 12/393,806 | 02/26/2009 | 7,579,473 | Seaman, D Margaret M | Issued |
| 12/911,442 | 10/25/2010 | | Ward, Paul, V. | Pending |
| 13/087,094 | 04/14/2011 | | Chickos, Sarah, J. | Pending |
| 13/129,183 | 05/13/2011 | | Seaman, D Margaret M | Pending |

| Application No. | Filing or 371 Date | Patent No. | Examiner | Status |
|---|---|---|---|---|
| 13/132,650 | 06/03/2011 | | Seaman, D Margaret M | Pending |
| 13/145,054 | 10/20/2011 | | Carter, Kendra D | Pending |
| 13/249,815 | 09/30/2011 | 8,497,284 | Bernhardt, Emily A | Pending |
| 13/384,451 | 07/12/2012 | | Anderson, Rebecca L | Pending |
| 13/389,266 | 07/12/2012 | | Perreira, Melissa Jean | Pending |
| 13/427,093 | 03/22/2012 | | Ward, Paul V | Pending |
| 13/438,964 | 04/04/2012 | | Brown-Pettigrew, Angela C | Pending |
| 13/634,275 | 09/12/2012 | | Anderson, Rebecca L | Pending |
| 13/810,537 | 01/16/2013 | | Soroush, Ali | Pending |
| 13/810,546 | 01/16/2013 | | Branson, Daniel L | Pending |
| 13/876,290 | 03/27/2013 | | Stone, Christopher R. | Pending |
| 13/876,318 | 03/27/2013 | | Claytor, Deirdre Renee | Pending |
| 13/876,306 | 03/27/2013 | | Andrew P. Lee | Pending |
| 13/888,592 | 05/07/2013 | | Paul V. Ward | Pending |
| 13/928,977 | 06/27/2013 | | Emily A. Bernhardt | Pending |
| 13/984,559 | 08/09/2013 | | Timothy R. Rozof | Pending |
| 14/021,614 | 09/09/2013 | | Matos Negron, Taina Del Mar | Pending |
| 14/115,236 | 11/01/2013 | | Not Yet Assigned | Pending |
| 14/166,545 | 01/28/2014 | | Not Yet Assigned | Pending |
| 14/346,570 | 03/21/2014 | | Not Yet Assigned | Pending |
| 14/353,251 | 04/21/2014 | | Not Yet Assigned | Pending |
| 14/356,927 | 05/08/2014 | | Not Yet Assigned | Pending |
| 14/356,938 | 05/08/2014 | | Not Yet Assigned | Pending |

## CONCLUSION

Applicant believes this reply is fully responsive to the Restriction Requirement dated May 1, 2014. Applicant reserves the right to file divisional applications or take such other appropriate action as deemed necessary to protect the subject matter restricted, canceled, or withdrawn from this application.

The total fee for this response, including the extension of time fee is $100. It is believed that no additional fees are required for this reply other than as provided above. However, if there are any additional charges or credits in relation to this response, please apply them to Deposit Account No. 503145, referencing Attorney Docket Number 224990/10-039C-US/343999.

Respectfully submitted,

Date: 31 July 2014

Heidi M. Berven, Ph.D., J.D.
Reg. No. 48,951
Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue, Suite 300
Kalamazoo, Michigan 49007
Telephone: (269) 337-7710
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PTO/AIA/22 (03-13)
Approved for use through 7/31/2016. 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.

# PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): 224990/10-039C-US/343999

Application Number: 13/984,559

Filed: March 20, 2014

For: Exelixis, Inc.

Art Unit: 1625

Examiner: Timothy R. Rozof

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

| | | Fee | Small Entity Fee | Micro Entity Fee | |
|---|---|---|---|---|---|
| ☑ | One month (37 CFR 1.17(a)(1)) | $200 | $100 | $50 | $ 100 |
| ☐ | Two months (37 CFR 1.17(a)(2)) | $600 | $300 | $150 | $ |
| ☐ | Three months (37 CFR 1.17(a)(3)) | $1,400 | $700 | $350 | $ |
| ☐ | Four months (37 CFR 1.17(a)(4)) | $2,200 | $1,100 | $550 | $ |
| ☐ | Five months (37 CFR 1.17(a)(5)) | $3,000 | $1,500 | $750 | $ |

☑ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 503145.

☑ Payment made via EFS-Web.

**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.**

I am the

☐ applicant.

☑ attorney or agent of record. Registration number 48951.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

| | |
|---|---|
| Signature | July 31, 2014 (Date) |
| Heidi M. Berven (Typed or printed name) | 269-337-7710 (Telephone Number) |

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.136(a). 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 6 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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | | |
|---|---|---|---|
| Inventors(s) | : Jo Ann Wilson | Art Unit | : 1625 |
| Serial No. | : 13/984,559 | Examiner | : Timothy R. Rozof |
| Filed | : March 20, 2014 | Docket No.: | 224990/10-039C-US/343999 |

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

**CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. §1.8(a)**

The undersigned hereby certifies that the following documents are being electronically filed in accordance with §1.6(a)(4), on the 31st day of July, 2014:

1. Cover Letter to the Commissioner;
2. Response to Restriction Requirement dated May 1, 2014;
3. Petition for Extension of Time (PTO/SB/22); and
4. Certificate of Transmission under 37 C.F.R. § 1.8(a).

Allison M. Kenna (for Heidi M. Berven, Ph.D., Reg. No.: 48,951)

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 13984559 |
| **Filing Date:** | 20-Mar-2014 |
| **Title of Invention:** | Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds |
| **First Named Inventor/Applicant Name:** | Jo Ann Wilson |
| **Filer:** | Heid Marie Berven/Allison McKenna |
| **Attorney Docket Number:** | 224990/10-039C-US/343999 |

Filed as Small Entity

## U.S. National Stage under 35 USC 371 Filing Fees

| 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:** | | | | |
| Extension - 1 month with $0 paid | 2251 | 1 | 100 | 100 |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Miscellaneous:** | | | | |
| | | | **Total in USD ($)** | **100** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 19738980 |
| **Application Number:** | 13984559 |
| **International Application Number:** | |
| **Confirmation Number:** | 6725 |
| **Title of Invention:** | Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds |
| **First Named Inventor/Applicant Name:** | Jo Ann Wilson |
| **Customer Number:** | 91684 |
| **Filer:** | Heid Marie Berven/Allison McKenna |
| **Filer Authorized By:** | Heid Marie Berven |
| **Attorney Docket Number:** | 224990/10-039C-US/343999 |
| **Receipt Date:** | 31-JUL-2014 |
| **Filing Date:** | 20-MAR-2014 |
| **Time Stamp:** | 12:57:27 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $100 |
| RAM confirmation Number | 10344 |
| Deposit Account | 503145 |
| Authorized User | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 1 | | 2014-07-31_EX10-039C-US_Response_to_Restriction_Requirement.pdf | 2377991<br>a16e68b641281214790453 9ed06abfe80e59f81f | yes | 17 |

| Multipart Description/PDF files in .zip description | | |
|---|---|---|
| **Document Description** | **Start** | **End** |
| Miscellaneous Incoming Letter | 1 | 1 |
| Response to Election / Restriction Filed | 2 | 2 |
| Claims | 3 | 11 |
| Response to Election / Restriction Filed | 12 | 15 |
| Extension of Time | 16 | 16 |
| Transmittal Letter | 17 | 17 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 2 | Fee Worksheet (SB06) | fee-info.pdf | 30355<br>1fd9cbb7ad4400c0381bfec67e50aea32c32cb0f | no | 2 |

**Warnings:**

**Information:**

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|---|---|
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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.**

HONIGMAN

Honigman Miller Schwartz and Cohn LLP
Attorneys and Counselors

Heidi M. Berven, Ph.D.

(269) 337-7710
Fax: (269) 337-7711
hberven@honigman.com

*VIA EFS*

July 31, 2014

Mail Stop Missing Parts
Commissioner for Patents
United States Patent and Trademark Office
P. O. Box 1450
Alexandria, VA 22313

***Re:*** ***Application No.: 13/984,559***
***Inventor: Jo Ann Wilson***
***Filing Date: March 20, 2014***
***Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds***
***Attorney Docket No.: 224990/10-039C-US/343999***

Dear Sir or Madam:

Enclosed for filing please find the following documents:

1. This Cover Letter to the Commissioner;
2. Response to Restriction Requirement dated May 1, 2014;
3. Petition for Extension of Time (PTO/SB/22); and
4. Certificate of Transmission under 37 C.F.R. § 1.8(a).

The total fee for this response, including the extension of time fee is $100. It is believed that no additional fees are required for this reply other than as provided above. However, if there are any additional charges or credits in relation to this response, please apply them to Deposit Account No. 503145, referencing Attorney Docket Number 224990/10-039C-US/343999.

Very truly yours,

HONIGMAN MILLER SCHWARTZ AND COHN LLP

Heidi M. Berven, Ph.D.

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 19738980 |
| **Application Number:** | 13984559 |
| **International Application Number:** | |
| **Confirmation Number:** | 6725 |
| **Title of Invention:** | Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds |
| **First Named Inventor/Applicant Name:** | Jo Ann Wilson |
| **Customer Number:** | 91684 |
| **Filer:** | Heid Marie Berven/Allison McKenna |
| **Filer Authorized By:** | Heid Marie Berven |
| **Attorney Docket Number:** | 224990/10-039C-US/343999 |
| **Receipt Date:** | 31-JUL-2014 |
| **Filing Date:** | 20-MAR-2014 |
| **Time Stamp:** | 12:57:27 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $100 |
| RAM confirmation Number | 10344 |
| Deposit Account | 503145 |
| Authorized User | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 1 | | 2014-07-31_EX10-039C-US_Response_to_Restriction_Requirement.pdf | 2377991<br>a16e68b641281214790453 9ed06abfe80e59f81f | yes | 17 |

| Multipart Description/PDF files in .zip description | | |
|---|---|---|
| **Document Description** | **Start** | **End** |
| Miscellaneous Incoming Letter | 1 | 1 |
| Response to Election / Restriction Filed | 2 | 2 |
| Claims | 3 | 11 |
| Response to Election / Restriction Filed | 12 | 15 |
| Extension of Time | 16 | 16 |
| Transmittal Letter | 17 | 17 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 2 | Fee Worksheet (SB06) | fee-info.pdf | 30355<br>1fd9cbb7ad4400c0381bfec67e50aea32c32cb0f | no | 2 |

**Warnings:**

**Information:**

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|---|---|
| **Total Files Size (in bytes):** | 2408346 |

**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/SB/06 (09-11)
Approved for use through 1/31/2014. 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 displays a valid OMB control number.

| PATENT APPLICATION FEE DETERMINATION RECORD<br>Substitute for Form PTO-875 | Application or Docket Number<br>13/984,559 | Filing Date<br>03/20/2014 | ☐ To be Mailed |
|---|---|---|---|

**ENTITY**: ☐ LARGE ☒ SMALL ☐ MICRO

## APPLICATION AS FILED – PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | RATE ($) | FEE ($) |
|---|---|---|---|---|
| ☐ BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | |
| ☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | |
| ☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | minus 20 = | * | X $ = | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | minus 3 = | * | X $ = | |
| ☐ 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 **07/31/2014**

| | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|
| Total (37 CFR 1.16(i)) | * 30 | Minus | ** 34 | = 0 | X $40 = | 0 |
| Independent (37 CFR 1.16(h)) | * 7 | Minus | ***15 | = 0 | X $210 = | 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) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|
| Total (37 CFR 1.16(i)) | * | Minus | ** | = | X $ = | |
| Independent (37 CFR 1.16(h)) | * | Minus | *** | = | X $ = | |
| ☐ 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.
** 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 number found in the appropriate box in column 1.

LIE
/POLIN ANG/

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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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www.uspto.gov

| APPLICATION NUMBER | FILING OR 371(C) DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO./TITLE |
|---|---|---|---|
| 13/984,559 | 03/20/2014 | Jo Ann Wilson | 224990/10-039C-US/343999 |

**CONFIRMATION NO. 6725**

91684
JONATHAN P. O'BRIEN, PH.D.
HONIGMAN MILLER SCHWARTZ AND COHN LLP
350 EAST MICHIGAN AVENUE, SUITE 300
Kalamazoo, MI 49007-3800

**PUBLICATION NOTICE**




**Title:**Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

**Publication No.**US-2014-0200242-A1
**Publication Date:**07/17/2014

## 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/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

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 http://pair.uspto.gov/. 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.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

# MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

| Application Number | Filing Date |
|---|---|
| 13984559 | |

Applicant(s) Jo Ann Wilson

* 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 |
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| 7 | | 1 | | 1 | | | 57 | | | | | | |
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| 13 | | 1 | | 1 | | | 63 | | | | | | |
| 14 | 1 | | 1 | | | | 64 | | | | | | |
| 15 | 1 | | | 1 | | | 65 | | | | | | |
| 16 | 1 | | 1 | | | | 66 | | | | | | |
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| 23 | 1 | | 1 | | | | 73 | | | | | | |
| 24 | 1 | | | | | | 74 | | | | | | |
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| 28 | | (1) | | 1 | | | 78 | | | | | | |
| 29 | | (1) | | 1 | | | 79 | | | | | | |
| 30 | | (1) | | 1 | | | 80 | | | | | | |
| 31 | | (1) | | 1 | | | 81 | | | | | | |
| 32 | | (1) | | 1 | | | 82 | | | | | | |
| 33 | | (1) | | 1 | | | 83 | | | | | | |
| 34 | | (1) | | 1 | | | 84 | | | | | | |
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| 50 | | | | | | | 100 | | | | | | |
| Total Indep | 15 | | 6 | | 0 | | | | | | | | |
| Total Depend | 19 | ↵ | 19 | ↵ | 0 | ↵ | | | | | | | |
| Total Claims | 34 | | 25 | | 0 | | | | | | | | |

UNITED STATES PATENT AND TRADEMARK OFFICE

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

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 13/984,559 | 03/20/2014 | Jo Ann Wilson | 224990/10-039C-US/343999 | 6725 |

91684 7590 05/01/2014

JONATHAN P. O'BRIEN, PH.D.
HONIGMAN MILLER SCHWARTZ AND COHN LLP
350 EAST MICHIGAN AVENUE, SUITE 300
Kalamazoo, MI 49007-3800

| EXAMINER | |
|---|---|
| ROZOF, TIMOTHY R | |
| ART UNIT | PAPER NUMBER |
| 1625 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 05/01/2014 | PAPER |

**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.

| Office Action Summary | Application No. 13/984,559 | Applicant(s) WILSON, JO ANN | |
|---|---|---|---|
| | Examiner TIMOTHY R. ROZOF | Art Unit 1625 | AIA (First Inventor to File) Status No |

*-- 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 2 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 *March 20, 2014*.

☐ 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) *1-10,12-16,19,20,23 and 28-34* 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) _____ is/are rejected.

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

9)☒ Claim(s) *1-10,12-16,19,20,23 and 28-34* 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 _____ 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 _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

## DETAILED ACTION

This is a response to Applicant's communication filed on March 20, 2014. Application No. 13/984,559 is a 371 of PCT/US12/24591, filed February 10, 2012, which claims the benefit of U.S. Provisional Applications Nos.: 61/441,520, February 10, 2011; and 61/441,527, filed February 10, 2011. In a preliminary amendment filed March 20, 2014, Applicant cancelled claims 11, 17, 18, 21, 22, and 24-27. Claims 1-10, 12-16, 19, 20, 23, and 28-34.

### *Election/Restrictions*

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claims 1-10, 12, and 13, drawn to a process for preparing a compound of formula I. If this group is elected, a further election of a single disclosed species of formula I compound is required.

Group II, claims 14-15, drawn to a process for preparing a compound of formula IB.

Group III, claims 16, 19, 20, 23, and 28-34, drawn to compounds IA or IB and pharmaceutical compositions thereof. If this group is elected, a further election of a single disclosed species of formula IA or IB compound is required.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because:

**PCT Rule 13.1** states that the international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention").

**PCT Rule 13.2** states that the unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features.

Annex B, **Part 1(a)**, indicates that the application should relate to only one invention, of if there is more than one invention, inclusion is permitted if they are so slinked to form a single general inventive concept.

Annex B **Part 1(b)**, indicates that "special technical features" means those technical features that as a whole define a contribution over the prior art.

Annex B **Part 1(c)**, further defines independent and dependent claims. Unity of invention only is concerned in relation to independent claims. Dependent claims are defined as a claim that contains all the features of another claim and is in the same category as the other claim. The category of a claim refers to the classification of claims according to subject matter e.g. product, process, use, apparatus, means, etc.

Annex B **Part 1(e)**, indicates that the permissible combinations of different categories of claims. **Part 1(e) I**, states that inclusion of an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product, and an independent claim for a use of the said product is permissible.

Annex B, **Part 1(f)**, indicates the "Markush practice" of alternatives in a single claim. **Part 1(f)I**, indicates the technical relationship and the same or corresponding special technical feature is considered to be met when (A) all alternatives have a common property or activity, and (B) a common structure is present or all alternatives belong to a recognized class of chemical compounds. Further defining (B), Annex B, **Part 1(f)(i-iii)**, the common structure must; a) occupy a large portion of their structure, or b) the common structure constitutes a structurally distinctive portion, or c) where the structures are equivalent and therefore a recognized class of chemical compounds, each member could be substituted for one another with the same intended result. That is, with a common or equivalent structure, there is an expectation relationship and the corresponding special technical feature result from a common (or equivalent) structure that is responsible for the common activity (or property). **Part 1(f) iv**, indicates that when all alternatives of a Markush grouping can be differently classified, it shall no, take alone, be considered justification for finding a lack of unity. **Part 1(f) v**, indicates that "[w]hen dealing with alternatives, if it can be shown that at least *one* Markush alternative is not novel over the prior art, the question of unity of invention shall be reconsidered by the examiner"

In the instant application, the related technical feature of Groups I-III is the compound of formula I disclosed in the specification. The related technical feature is known in the art and, therefore, does not constitute a *special* technical feature. See references cited in the International Search Report filed August 9, 2013

***Species Election***

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

*The compounds of formula I, IA, and IB.*

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The following claim(s) are generic: 1-10, 12-16, 19, 20, 23, and 28-34.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

As disclosed the unique species of compounds have mutually exclusive chemical characteristics and properties. In addition, the species are not obvious variants of each other based on the current record.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP

§ 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

### *Contact Information*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY R. ROZOF whose telephone number is (571) 270-5992. The examiner can normally be reached on Monday thru Friday, 8:00 am to 5:00 pm ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. 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 http://pair-direct.uspto.gov. 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.

/TIMOTHY R ROZOF/
Examiner, Art Unit 1625

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13984559 | WILSON, JO ANN |
| | Examiner | Art Unit |
| | TIMOTHY R ROZOF | 1625 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
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Address: COMMISSIONER FOR PATENTS
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www.uspto.gov

| U.S. APPLICATION NUMBER NO. | FIRST NAMED APPLICANT | ATTY. DOCKET NO. |
|---|---|---|
| 13/984,559 | Jo Ann Wilson | 224990/10-039C-US/343999 |

91684
JONATHAN P. O'BRIEN, PH.D.
HONIGMAN MILLER SCHWARTZ AND COHN LLP
350 EAST MICHIGAN AVENUE, SUITE 300
Kalamazoo, MI 49007-3800

| INTERNATIONAL APPLICATION NO. | |
|---|---|
| PCT/US12/24591 | |
| I.A. FILING DATE | PRIORITY DATE |
| 02/10/2012 | 02/10/2011 |

**CONFIRMATION NO. 6725**

**371 ACCEPTANCE LETTER**

*OC000000067504887*

Date Mailed: 04/10/2014

## 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 and the relevant dates are:

| 03/20/2014 | 03/20/2014 |
|---|---|
| DATE OF RECEIPT OF 35 U.S.C. 371(c)(1), (c)(2) and (c)(4) REQUIREMENTS | DATE OF COMPLETION OF ALL 35 U.S.C. 371 REQUIREMENTS |

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE " FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 (c)(1), (c)(2) and (c)(4) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *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).*

The following items have been received:

- Indication of Small Entity Status
- Copy of the International Application filed on 08/09/2013
- Copy of the International Search Report filed on 08/09/2013
- Preliminary Amendments filed on 08/09/2013
- Information Disclosure Statements filed on 08/09/2013
- Inventor's Oath or Declaration filed on 03/20/2014
- U.S. Basic National Fees filed on 08/09/2013
- Assignee Statement for PGPUB filed on 08/09/2013
- Priority Documents filed on 08/09/2013

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)

JOHN L ANDERSON

Telephone: (571) 272-0385

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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| APPLICATION NUMBER | FILING or 371(c) DATE | GRP ART UNIT | FIL FEE REC'D | ATTY.DOCKET.NO | TOT CLAIMS | IND CLAIMS |
|---|---|---|---|---|---|---|
| 13/984,559 | 03/20/2014 | | 3890 | 224990/10-039C-US/343999 | 25 | 6 |

**CONFIRMATION NO. 6725**

91684
JONATHAN P. O'BRIEN, PH.D.
HONIGMAN MILLER SCHWARTZ AND COHN LLP
350 EAST MICHIGAN AVENUE, SUITE 300
Kalamazoo, MI 49007-3800

**FILING RECEIPT**




Date Mailed: 04/10/2014

Receipt is acknowledged of this non-provisional 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 APPLICANT, 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 Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections 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**

**Inventor(s)**
Jo Ann Wilson, San Francisco, CA;

**Applicant(s)**
Jo Ann Wilson, San Francisco, CA;

**Assignment For Published Patent Application**
Exelixis, Inc., San Francisco, CA

**Power of Attorney:** The patent practitioners associated with Customer Number 91684

**Domestic Priority data as claimed by applicant**
This application is a 371 of PCT/US12/24591 02/10/2012
which claims benefit of 61/441,520 02/10/2011
and claims benefit of 61/441,527 02/10/2011

**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.*

**If Required, Foreign Filing License Granted:** 04/01/2014
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/984,559**
**Projected Publication Date:** 07/17/2014
**Non-Publication Request:** No
**Early Publication Request:** No
**** SMALL ENTITY ****

**Title**

Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

**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).

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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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## PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/984,559

### 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 | 140 | | N/A | |
| SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | 240 | | N/A | |
| EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | 360 | | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | 25 minus 20 = | * 5 | x 40 = | 200 | OR | | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | 6 minus 3 = | * 3 | x 210 = | 630 | | | |
| 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 | 1570 | | 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.

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

Inventor: Jo Ann Wilson
Application No.: 13/984,559
Filed: August 9, 2013

Art Unit: TBD
Examiner: TBD
Atty. Docket No.: 224990/10-039C-US/343999

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

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

**RESPONSE TO NOTIFICATION OF MISSING REQUIREMENTS MAILED AUGUST 20, 2013 AND PRELIMINARY AMENDMENT UNDER 37 CFR 1.115**

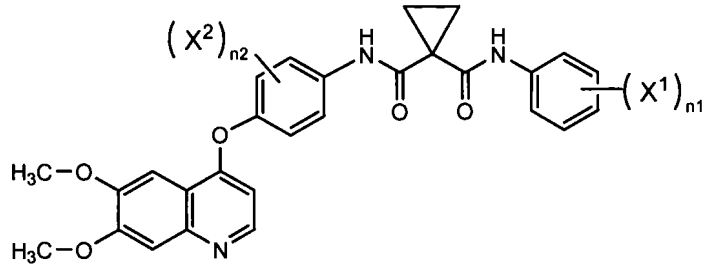
In response to the Notification of Missing Requirements, Applicant submits the following preliminary amendments along with the Combined Declaration and Power of Attorney.

Amendments to the claims begin on page 2.

Remarks begin on page 10.

## CLAIM AMENDMENTS

1. (Original) A process for preparing a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is H, Br, Cl, or F;

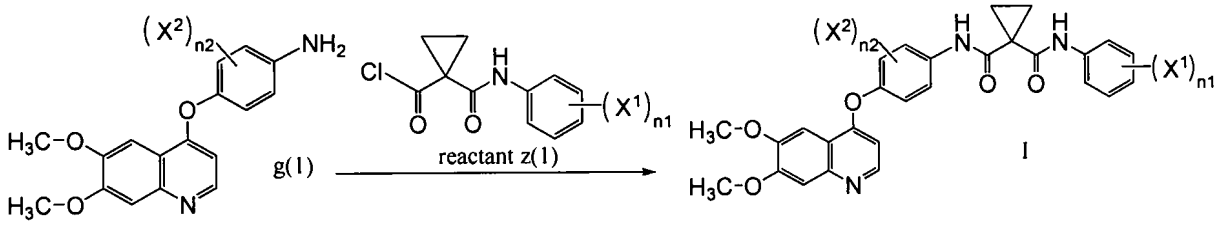
$X^2$ is H, Br, Cl, or F;

n1 is 1-2; and

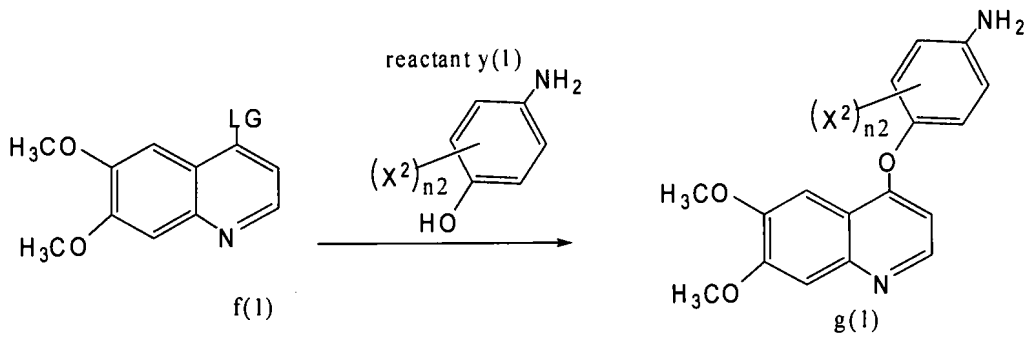
n2 is 1-2;

the process comprising:

contacting the compound of formula g(1) with reactant z(1) to yield the compound of formula I:

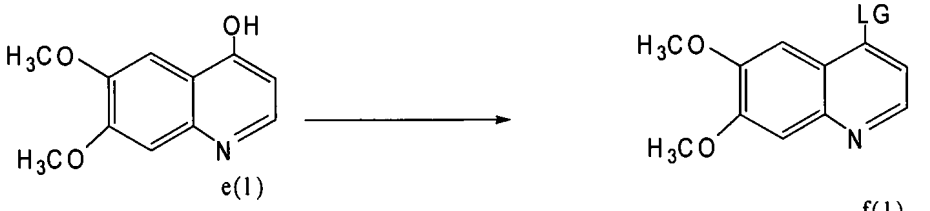



2. (Original) The process according to claim 1, wherein the compound of formula g(1) is made by reacting a compound of formula f(1) with reactant y(1) to yield the compound of formula g(1):



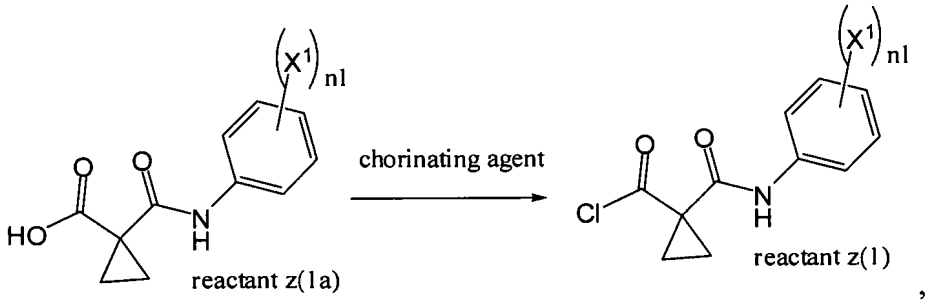
wherein LG represents a leaving group, and each $X^2$ and n2 are as defined in claim 1.

3. (Original) The process according to claim 2, wherein the compound of formula f(1) is made by converting compound e(1) to the compound of formula f(1):



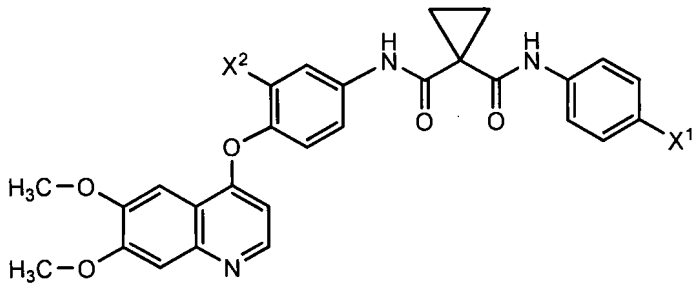

wherein LG represents a leaving group.

4. (Original) The process according to claim 1, wherein reactant z(1) is made by reacting reactant z(1a) with a chlorinating agent to yield reactant z(1):




wherein $X^1$ is Br, Cl, or F; and n1 is 1-2.

5. (Currently Amended) The process according to claim 1, wherein the compound of formula I is compound IA[[-1]]:



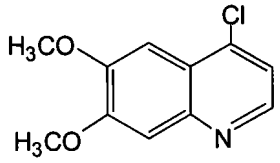

IA

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is H, Cl, Br, or F; and

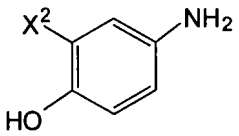
$X^2$ is H, Cl, Br, or F.

6. (Original) The process according to claim 5, wherein the compound of formula f(1) is compound f(2):




f(2) ;

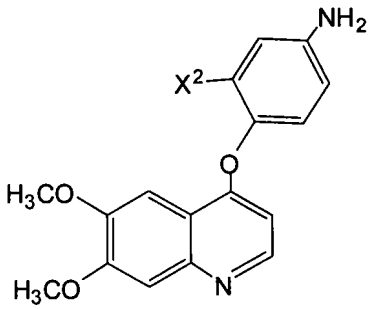
reactant y(1) is reactant (y)(2):




reactant (y)(2) ,

wherein $X^2$ is hydrogen or fluoro; and

the compound of formula g(1) is of formula g(2):




g(2) .

7. (Original) The process according to claim 6, wherein the reaction employs a non-nucleophilic base.

8. (Original) The process according to claim 7, wherein the non-nucleophilic base is an alkali metal alkoxide; and the reaction is carried out in a polar solvent.

9. (Original) The process according to claim 8, wherein the alkali metal alkoxide is sodium tert-butoxide, and the polar solvent is DMA.

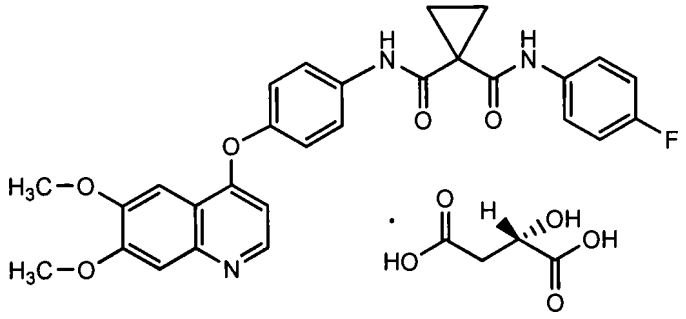
10. (Original) The process according to claim 8, wherein the alkali metal alkoxide is sodium tert-pentoxide, and the polar solvent is DMA.

11. Cancelled.

12. (Currently Amended) The process according to claim 1[[11]], wherein the reaction is carried out in the presence of an inorganic base.

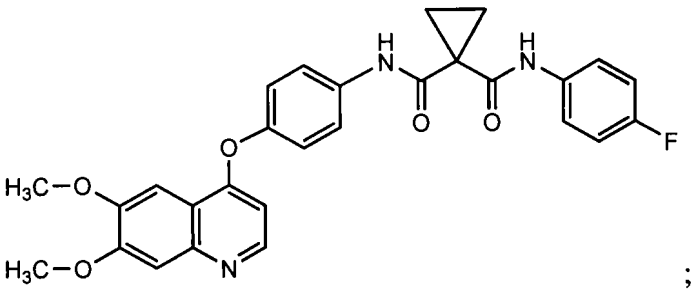
13. (Original) The process according to claim 12, wherein the inorganic base is $K_2CO_3$, and the solvent employed in this reaction is a combination of THF and $H_2O$.

14. (Currently Amended) A process for preparing compound IB:



IB

with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol from compound IA:



;

IA

comprising:

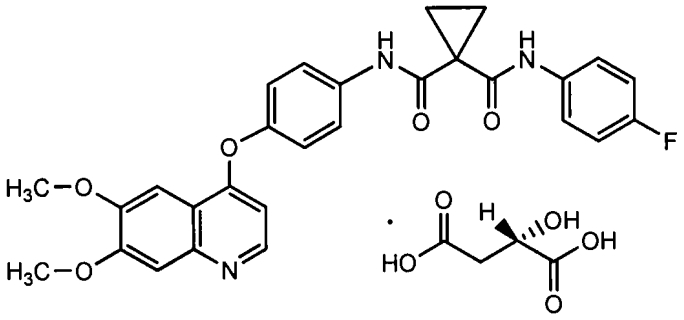
(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) vacuum distilling the mixture successively; and

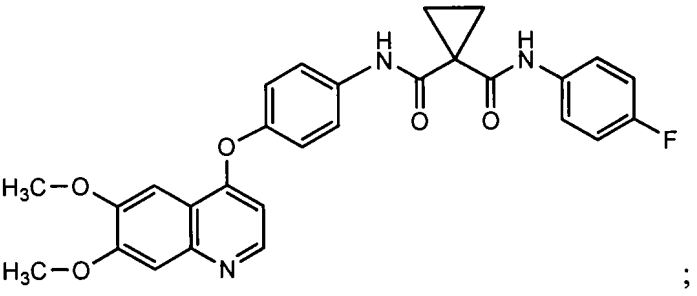
(d) isolating the compound of IB by filtration;.

15. (Currently Amended) The process of claim 14 for preparing compound IB:



IB

with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol from compound IA:



IA;

comprising:

(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) seeding the mixture with the compound of IB;

(d) vacuum distilling the mixture; and

(e) isolating the compound of IB by filtration.

16. (Original) Compound IA or IB admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

17. Cancelled.

18. Cancelled.

19. (Original) Compound IB in the N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

20. (Original) Compound IB as a mixture of the N-1 form and N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

21. Cancelled.

22. Cancelled.

23. (Currently Amended) A pharmaceutical composition selected from the group consisting of ~~according to~~ Table 2A, 3, 4,5, or 6 .

**Table 2A**

| **Ingredient** | **% w/w** |
|---|---|
| Compound IB (10 % drug load as Compound IA) | 12.67 |
| MCC | 51.52 |
| Lactose | 25.76 |
| Hydroxypropyl cellulose | 3.0 |
| Croscarmellose Sodium | 6.0 |
| Colloidal Silicon Dioxide | 0.3 |
| Magnesium Stearate | 0.75 |
| **Total** | **100** |

**Table 3**

| **Ingredient** | **mg/unit dose** |
|---|---|
| Compound IB (10 % drug | 25 |

| | |
|---|---|
| load as Compound IA) | |
| Silicified Microcrystalline Cellulose | 196.75 |
| Croscarmellose sodium | 12.5 |
| Sodium starch glycolate | 12.5 |
| Fumed Silica | 0.75 |
| Stearic acid | 2.5 |
| **Total Fill Weight** | 250 |

**Table 4**

| **Ingredient** | **mg/unit dose** |
|---|---|
| Compound IB (50 % drug load as Compound IA) | 100 |
| Silicified Microcrystalline Cellulose | 75.40 |
| Croscarmellose sodium | 10.00 |
| Sodium Starch Glycolate | 10.00 |
| Fumed silica | 0.6 |
| Stearic Acid | 4.0 |
| **Total Fill Weight** | 200 |

**Table 5**

| | **mg/unit dose** |
|---|---|
| **Ingredient** | **50mg** |
| Compound IB (10 % drug load as Compound IA) | 63.35 |
| Microcrystalline Cellulose | 95.39 |
| Croscarmellose sodium | 9.05 |
| Sodium starch glycolate | 9.05 |
| Fumed Silica | 0.54 |
| Stearic acid | 3.62 |
| **Total Fill Weight** | 181.00 |

**Table 6**

| | **mg/unit dose** |
|---|---|
| **Ingredient** | **60mg** |
| Compound IB | 73.95 |
| Microcrystalline Cellulose | 114.36 |
| Croscarmellose sodium | 10.85 |
| Sodium starch glycolate | 10.85 |
| Fumed Silica | 0.65 |

| | |
|---|---|
| Stearic acid | 4.34 |
| **Total Fill Weight** | 217.00 |

24-27. Cancelled.

28. (Currently Amended) The pharmaceutical composition of claim 23 ~~claims 20-27~~ admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

29. (Currently Amended) The pharmaceutical composition of claim 23 ~~claims 20-27~~ admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

30. (Currently Amended) The pharmaceutical composition of claim 23 ~~claims 20-27~~ admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

31. (Currently Amended) The pharmaceutical composition of claim 23 ~~claims 20-27~~ admixed with 15 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

32. (Currently Amended) The pharmaceutical composition of claim 23 ~~claims 20-27~~ admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

33. (Currently Amended) The pharmaceutical composition of claim 23 ~~claims 20-27~~admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

34. (Currently Amended) The pharmaceutical composition of claim 23 ~~claims 20-27~~ admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

## REMARKS

### Claim Status

Claims 1-10, 13-14, 16, 19-20 are original.

Claims 11, 17-18, 21-22, 24-27 are cancelled.

Claims 12, 15, 23, 28-34 are currently amended. The claims are supported by the previous claims and specification. No new matter has been added. Upon entry of the foregoing amendments, claims 1-10, 12-16, 19-20, 23, 28-34 are pending and in condition for examination, which action is respectfully requested.

### Notification of Missing Requirements

The U.S. Patent Office issued a Notification of Missing Requirements under 35 U.S.C. 371 in the United States Designated/Elected Office (DO/EO/US) on August 20, 2013. The Notice states that an executed oath or declaration and a supplemental fee are required.

Applicant submits the attached signed Declaration and Power of Attorney with additional surcharge fee in the amount of $70.00.

### OTHER C-MET INHIBITOR CASES

The Applicant wishes to make the Examiner aware of the Applicant's other applications related to c-Met inhibitors and their use in the treatment of cancer. For the Examiner's convenience, the Applicant is providing a list of the Applicant's applications directed to the treatment of cancer using c-Met inhibitors. The Applicant understands the Examiner has electronic access to these applications and to the Office Actions that have issued in these applications, and has therefore not included copies with this Response. The Applicant will gladly provide the applications and Office Actions to the Examiner, however, upon request.

| Application No. | Filing or 371 Date | Patent No. | Examiner | Status |
|---|---|---|---|---|
| 10/573,336 | 09/18/2006 | | Koontz, Tammy J | Abandoned |
| 11/571,140 | 12/21/2006 | 7,977,345 | Moore, Susanna | Issued |
| 11/586,751 | 10/26/2006 | | Ward, Paul V. | Pending |
| 11/753,462 | 05/24/2007 | 8,178,532 | Ward, Paul V | Issued |
| 11/753,503 | 05/24/2007 | 8,476,298 | Ward, Paul V | Issued |
| 11/753,514 | 05/24/2007 | 8,067,436 | Bernhardt, Emily A | Issued |
| 12/393,806 | 02/26/2009 | 7,579,473 | Seaman, D Margaret M | Issued |
| 12/911,442 | 10/25/2010 | | Ward, Paul, V. | Pending |

| | | | | |
|---|---|---|---|---|
| 13/087,094 | 04/14/2011 | | Chickos, Sarah, J. | Pending |
| 13/129,183 | 05/13/2011 | | Seaman, D Margaret M | Pending |
| 13/132,650 | 06/03/2011 | | Seaman, D Margaret M | Pending |
| 13/145,054 | 10/20/2011 | | Carter, Kendra D | Pending |
| 13/249,815 | 09/30/2011 | 8,497,284 | Bernhardt, Emily A | Issued |
| 13/384,451 | 07/12/2012 | 8,673,912 | Anderson, Rebecca L | Issued |
| 13/389,266 | 07/12/2012 | | Perreira, Melissa Jean | Pending |
| 13/427,093 | 03/22/2012 | | Ward, Paul V | Pending |
| 13/438,964 | 04/04/2012 | | Brown-Pettigrew, Angela C | Pending |
| 13/634,275 | 09/12/2012 | | Anderson, Rebecca L | Pending |
| 13/810,537 | 01/16/2013 | | Soroush, Ali | Pending |
| 13/810,546 | 01/16/2013 | | Branson, Daniel L | Pending |
| 13/876,290 | 03/27/2013 | | Stone, Christopher R | Pending |
| 13/876,318 | 03/27/2013 | | Claytor, Deirdre Renee | Pending |
| 13/876,306 | 03/27/2013 | | Andrew P. Lee | Pending |
| 13/888,592 | 05/07/2013 | | Ward, Paul V | Pending |
| 13/928,977 | 06/27/2013 | | Bernhardt, Emily A | Pending |
| 13/984,559 | 08/09/2013 | | Not Yet Assigned | Pending |
| 14/021,614 | 09/09/2013 | | Matos Negron, Taina Del Mar | Pending |
| 14/115,236 | 11/01/2013 | | Not Yet Assigned | Pending |
| 14/166,545 | 01/28/2014 | | Not Yet Assigned | Pending |

## PETITION FOR EXTENSION OF TIME

Applicant hereby petitions for a five-month extension of time under 37 CFR § 1.136 to respond to the Notification of Missing Requirements mailed August 20, 2013, regarding the above-referenced application. Please charge the $1500.00 five-month extension of time fee for a small entity to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C-US/343999.

## CONCLUSION

It is believed that a surcharge fee of $70.00 for a small entity is due for the late filing of a Declaration along with extension of time fees of $1500.00 for a small entity for a five-month extension of time. Please apply this charge of $1570.00 to Deposit Account No. 503145, referencing Attorney Docket Number 224990/10-039C-US/343999.

Respectfully submitted,

Date: March 20, 2014

Heidi M. Berven, Ph.D.
Reg. No. 48,951

Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue, Ste. 300
Kalamazoo, MI 49007-3800
Direct (269) 337-7710
Fax (269) 337-7711

# DECLARATION AND POWER OF ATTORNEY

We, the below named inventors, hereby declare that our citizenship, residency, and mailing address is as identified below next to our respective names; we have reviewed and understand the content of the specification, including the claims, of the attached specification; We believe that we are the original, first, and sole/joint inventors of the subject matter which is claimed therein and for which a patent is sought on the invention or discovery entitled:

Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

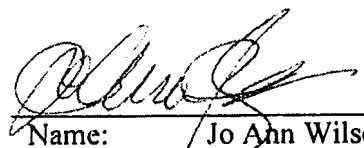
This application, United States Serial No. 13/984,559[1] is a United States National Phase filing of PCT/US2012/024591, filed February 10, 2012, which claims priority to U.S. Provisional Application No. 61/441,520, filed February 10, 2011, and 61/441,527, filed February 10, 2011, which are incorporated herein by reference.

We acknowledge our duty to disclose information of which we are aware that is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

We hereby appoint the practitioners associated with Customer No. 91684, as our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark office connected therewith.

Please recognize the address associated with Customer Number 91684 as the correspondence address for the above-identified application.

We further declare that all statements made herein of our own knowledge are true and that all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, Section 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



06 Sept. 2013

Name: Jo Ann Wilson Date:
Address: 74 Seward Street, San Francisco, CA 94114
Citizenship: US

1 We authorize and request Assignee to insert the filing date and/or application number of said application when known.

13006603.1

PTO/SB/22 (03-13)
Approved for use through 3/31/2013. 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.

# PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): 224990/10-039C-US/343999

Application Number: 13984559 | Filed: 08/09/2013

For: Exelixis, Inc.

Art Unit: NA | Examiner: NA

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

| | Fee | Small Entity Fee | Micro Entity Fee | |
|---|---|---|---|---|
| ☐ One month (37 CFR 1.17(a)(1)) | $200 | $100 | $50 | $ |
| ☐ Two months (37 CFR 1.17(a)(2)) | $600 | $300 | $150 | $ |
| ☐ Three months (37 CFR 1.17(a)(3)) | $1,400 | $700 | $350 | $ |
| ☐ Four months (37 CFR 1.17(a)(4)) | $2,200 | $1,100 | $550 | $ |
| ☑ Five months (37 CFR 1.17(a)(5)) | $3,000 | $1,500 | $750 | $ 1500 |

☑ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 503145.

☑ Payment made via EFS-Web.

**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.**

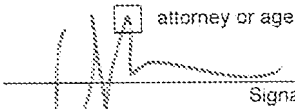
I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. 37 CFR 3.73(b) statement is enclosed (Form PTO/SB/96).

☑ attorney or agent of record. Registration number 48951.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.



Signature

March 20, 2014
Date

HEIDI M. BERVEN
Typed or printed name

269-337-7710
Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.136(a). 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 6 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.*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

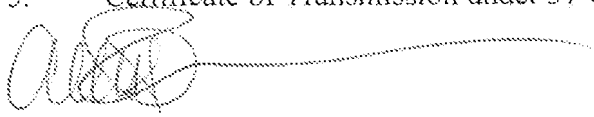
| | | | |
|---|---|---|---|
| Inventors(s) | : Jo Ann Wilson | Art Unit | : To Be Determined |
| Serial No. | : 13/984,559 | Examiner | : To Be Determined |
| Filed | : August 9, 2013 | Docket No.: | 224990/10-039C-US/343999 |

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

**CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. §1.8(a)**

The undersigned hereby certifies that the following documents are being electronically filed in accordance with §1.6(a)(4), on the 20th day of March, 2014:

1. Cover Letter to the Commissioner;
2. Response to the Notification of Missing Requirements mailed August 20, 2013;
3. Inventor's Signed Declaration and Power of Attorney;
4. Petition for Extension of Time (PTO/SB/22); and
5. Certificate of Transmission under 37 C.F.R. § 1.8(a).



Allison M°Kenna (for Heidi M. Berven, Ph.D., Reg. No.: 48,951)

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 13984559 |
| **Filing Date:** | |
| **Title of Invention:** | Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds |
| **First Named Inventor/Applicant Name:** | Jo Ann Wilson |
| **Filer:** | Heid Marie Berven/Allison McKenna |
| **Attorney Docket Number:** | 224990/10-039C-US/343999 |

Filed as Small Entity

## U.S. National Stage under 35 USC 371 Filing Fees

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| Oath/Decl > 30 Mos From 371 commencement | 2617 | 1 | 70 | 70 |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| Extension - 5 months with $0 paid | 2255 | 1 | 1500 | 1500 |
| **Miscellaneous:** | | | | |
| | | | **Total in USD ($)** | **1570** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 18537446 |
| **Application Number:** | 13984559 |
| **International Application Number:** | |
| **Confirmation Number:** | 6725 |
| **Title of Invention:** | Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds |
| **First Named Inventor/Applicant Name:** | Jo Ann Wilson |
| **Customer Number:** | 91684 |
| **Filer:** | Heid Marie Berven/Allison McKenna |
| **Filer Authorized By:** | Heid Marie Berven |
| **Attorney Docket Number:** | 224990/10-039C-US/343999 |
| **Receipt Date:** | 20-MAR-2014 |
| **Filing Date:** | |
| **Time Stamp:** | 15:25:55 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $1570 |
| RAM confirmation Number | 1713 |
| Deposit Account | 503145 |
| Authorized User | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 1 | | 2014-03-20_EX10-039C-US_Response_to_NTFMP.pdf | 2354175<br>8bfd8c7c4333fb3e2aa5f48b8eb5bdeb4c5b3745 | yes | 16 |

| Multipart Description/PDF files in .zip description | | |
|---|---|---|
| **Document Description** | **Start** | **End** |
| Miscellaneous Incoming Letter | 1 | 1 |
| Applicant Response to Pre-Exam Formalities Notice | 2 | 2 |
| Claims | 3 | 10 |
| Applicant Arguments/Remarks Made in an Amendment | 11 | 13 |
| Oath or Declaration filed | 14 | 14 |
| Extension of Time | 15 | 15 |
| Transmittal Letter | 16 | 16 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 2 | Fee Worksheet (SB06) | fee-info.pdf | 32264<br>bed76d7e67467c48a4ffefaba2e4a70a477042b8 | no | 2 |

**Warnings:**

**Information:**

| | |
|---|---|
| **Total Files Size (in bytes):** | 2386439 |

**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.**

HONIGMAN

Honigman Miller Schwartz and Cohn LLP
Attorneys and Counselors

Heidi M. Berven, Ph.D.

(269) 337-7710
Fax: (269) 337-7711
hberven@honigman.com

*VIA EFS*

March 20, 2014

Mail Stop Missing Parts
Commissioner for Patents
United States Patent and Trademark Office
P. O. Box 1450
Alexandria, VA 22313

***Re:*** ***Application No.: 13/984,559***
***Inventor: Jo Ann Wilson***
***Filing Date: August 9, 2013***
***Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds***
***Attorney Docket No.: 224990/10-039C-US/343999***

Dear Sir or Madam:

Enclosed for filing please find the following documents:

1. This Cover Letter to the Commissioner;
2. Response to the Notification of Missing Requirements mailed August 20, 2013;
3. Inventor's Signed Declaration and Power of Attorney;
4. Petition for Extension of Time (PTO/SB/22); and
5. Certificate of Transmission under 37 C.F.R. § 1.8(a).

It is believed that a surcharge fee of $70.00 for a small entity is due for the late filing of a Declaration along with extension of time fees of $1500.00 for a small entity for a five-month extension of time. Please apply this charge of $1570.00 to Deposit Account No. 503145, referencing Attorney Docket Number 224990/10-039C-US/343999.

Very truly yours,

HONIGMAN MILLER SCHWARTZ AND COHN LLP

Heidi M. Berven, Ph.D.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. 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 displays a valid OMB control number.

| PATENT APPLICATION FEE DETERMINATION RECORD<br>Substitute for Form PTO-875 | Application or Docket Number<br>13/984,559 | Filing Date<br>03/20/2014 | ☐ To be Mailed |
|---|---|---|---|

**ENTITY**: ☐ LARGE ☒ SMALL ☐ MICRO

## APPLICATION AS FILED – PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | RATE ($) | FEE ($) |
|---|---|---|---|---|
| ☐ BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | |
| ☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | |
| ☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | minus 20 = | * | X $ = | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | minus 3 = | * | X $ = | |
| ☐ 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

| 03/20/2014 | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|
| Total (37 CFR 1.16(i)) | * 25 | Minus | ** 25 | = 0 | X $40 = | 0 |
| Independent (37 CFR 1.16(h)) | * 6 | Minus | ***6 | = 0 | X $210 = | 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) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|
| Total (37 CFR 1.16(i)) | * | Minus | ** | = | X $ = | |
| Independent (37 CFR 1.16(h)) | * | Minus | *** | = | X $ = | |
| ☐ 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.

** 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 number found in the appropriate box in column 1.

LIE
/ADRIENE SELLMAN/

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.**

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

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

| U.S. APPLICATION NUMBER NO. | FIRST NAMED APPLICANT | ATTY. DOCKET NO. |
|---|---|---|
| 13/984,559 | Jo Ann Wilson | 224990/10-039C-US/343999 |

91684
JONATHAN P. O'BRIEN, PH.D.
HONIGMAN MILLER SCHWARTZ AND COHN LLP
350 EAST MICHIGAN AVENUE, SUITE 300
Kalamazoo, MI 49007-3800

| INTERNATIONAL APPLICATION NO. | |
|---|---|
| PCT/US12/24591 | |
| I.A. FILING DATE | PRIORITY DATE |
| 02/10/2012 | 02/10/2011 |

**CONFIRMATION NO. 6725**
**371 FORMALITIES LETTER**

*OC000000063346178*

Date Mailed: 08/20/2013

# NOTIFICATION OF MISSING REQUIREMENTS UNDER 35 U.S.C. 371 IN THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

The following items have been submitted by the applicant or the IB to the United States Patent and Trademark Office as a Designated Office (37 CFR 1.494):

- Indication of Small Entity Status
- Priority Document
- Copy of the International Application filed on 08/09/2013
- Copy of the International Search Report filed on 08/09/2013
- Preliminary Amendments filed on 08/09/2013
- Information Disclosure Statements filed on 08/09/2013
- Oath or Declaration filed on 08/09/2013
- U.S. Basic National Fees filed on 08/09/2013
- Assignee Statement for PGPUB filed on 08/09/2013
- Priority Documents filed on 08/09/2013

The applicant needs to satisfy supplemental fees problems indicated below.

The following items **MUST** be furnished within the period set forth below in order to complete the requirements for acceptance under 35 U.S.C. 371:

- Oath or declaration of the inventors, in compliance with 37 CFR 1.497(a) and (b), identifying the application by the International application number and international filing date. The current oath or declaration does not comply with 37 CFR 1.497(a) and (b) in that it:
  - is not executed in accordance with either 37 CFR 1.66 or 37 CFR 1.68.
- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.492(h) of $70 for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this letter.

SUMMARY OF FEES DUE:

Total additional fees required for this application is $**70** for a Small Entity:
- $**70** Surcharge.

**ALL OF THE ITEMS SET FORTH ABOVE MUST BE SUBMITTED WITHIN TWO (2) MONTHS FROM THE DATE OF THIS NOTICE OR BY 32 MONTHS FROM THE PRIORITY DATE FOR THE APPLICATION, WHICHEVER IS LATER. 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)

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.**

JOHN L ANDERSON

Telephone: (571) 272-0385

## PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/984,559

### 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 | 140 | | N/A | |
| SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | 240 | | N/A | |
| EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | 360 | | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | 34 minus 20 = | * 14 | x 40 = | 560 | OR | | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | 15 minus 3 = | * 12 | x 210 = | 2520 | | | |
| 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 | 3820 | | 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 |
|---|---|
| 13984559 | |

Applicant(s) Jo Ann Wilson

* May be used for additional claims or amendments

| CLAIMS | AS FILED | | AFTER FIRST AMENDMENT | | AFTER SECOND AMENDMENT | |
|---|---|---|---|---|---|---|
| | Indep | Depend | Indep | Depend | Indep | Depend |
| 1 | 1 | | | | | |
| 2 | | 1 | | | | |
| 3 | | 1 | | | | |
| 4 | | 1 | | | | |
| 5 | | 1 | | | | |
| 6 | | 1 | | | | |
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| 50 | | | | | | |
| Total Indep | 15 | | 0 | | 0 | |
| Total Depend | 19 | ↵ | 0 | ↵ | 0 | ↵ |
| Total Claims | 34 | | 0 | | 0 | |

| | * | | * | | * | |
|---|---|---|---|---|---|---|
| | Indep | Depend | Indep | Depend | Indep | Depend |
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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Inventors(s) | : Jo Ann Wilson | Art Unit | : To Be Determined |
| Serial No. | : To Be Determined | Examiner | : To Be Determined |
| Filed | : February 10, 2012 | Docket No.: | 224990/10-039C-US/343999 |

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

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

**PRELIMINARY AMENDMENT UNDER 37 CFR 1.115**

Prior to examination, please amend the application as indicated on the following pages.

Amendments to the Specification begin on page 2.

Remarks begin on page 3.

## AMENDMENTS TO THE SPECIFICATION

After the title at page 1, please replace paragraph [0001] with the following paragraph:

### CLEAN VERSION

### CROSS-REFERENCE TO RELATED APPLICATIONS

**[0001]** This application is a United States National Phase filing of PCT/US2012/024591, filed February 10, 2012, which claims priority to U.S. Provisional Application No. 61/441,520, filed February 10, 2011, and 61/441,527, filed February 10, 2011, which are incorporated herein by reference.

### MARKED-UP VERSION

### CROSS-REFERENCE TO RELATED APPLICATIONS

**[0001]** This application ~~claims the benefit of~~ is a United States National Phase filing of PCT/US2012/024591, filed February 10, 2012, which claims priority to U.S. Provisional Application No. 61/441,520, filed February 10, 2011, and 61/441,527, filed February 10, 2011, which are incorporated herein by reference.

## REMARKS

### Amendment to the Specification

Applicant has updated the Specification to recite the cross-reference and priority information, stating that this application is a United States National Phase filing of PCT/US2012/024591, filed February 10, 2012, which claims priority to U.S. Provisional Application No. 61/441,520, filed February 10, 2011, and 61/441,527, filed February 10, 2011, which are incorporated herein by reference.

### Information Disclosure Statement

Applicant notes that the filing of the enclosed Information Disclosure Statement shall not be construed to be an admission that the information cited in the statement qualifies as prior art under 35 U.S.C. § 102 or § 103, or is considered to be material to patentability as defined in § 1.56(b).

### Conclusion

Please charge the Basic National Fee of $140.00, Examination Fee of $360.00, and Search Fee of $300.00 to Deposit Account 503145, referencing Attorney Docket Number 224990/10-039C-US/343999. It is believed that no claim fees are currently due.

Respectfully submitted,

Date: August 9, 2013

Heidi M. Berven, Ph.D.
Reg. No. 48,951

Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue
Kalamazoo, MI 49007-3800
Direct (269) 337-7710
Fax (269) 337-7711

# DECLARATION AND POWER OF ATTORNEY

We, the below named inventors, hereby declare that our citizenship, residency, and mailing address is as identified below next to our respective names; we have reviewed and understand the content of the specification, including the claims, of the attached specification; We believe that we are the original, first, and sole/joint inventors of the subject matter which is claimed therein and for which a patent is sought on the invention or discovery entitled:

Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

This application, United States Serial No. _____[1] is a United States National Phase filing of PCT/US2012/024591, filed February 10, 2012, which claims priority to U.S. Provisional Application No. 61/441,520, filed February 10, 2011, and 61/441,527, filed February 10, 2011, which are incorporated herein by reference.

We acknowledge our duty to disclose information of which we are aware that is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

We hereby appoint the practitioners associated with Customer No. 91684, as our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark office connected therewith.

Please recognize the address associated with Customer Number 91684 as the correspondence address for the above-identified application.

We further declare that all statements made herein of our own knowledge are true and that all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, Section 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

_____ _____

Name: Jo Ann Wilson Date:
Address: 74 Seward Street, San Francisco, CA 94114
Citizenship: US

1 We authorize and request Assignee to insert the filing date and/or application number of said application when known.

13006603.1

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. 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 contains a valid OMB control number.

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**(Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | |
| Filing Date | 2012-02-10 |
| First Named Inventor | Jo Ann Wilson |
| Art Unit | TBD |
| Examiner Name | TBD |
| Attorney Docket Number | 224990/10-039C-US/343999 |

**U.S.PATENTS**

| 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 | | | | | |

If you wish to add additional U.S. Patent citation information please click the Add button.

**U.S.PATENT APPLICATION PUBLICATIONS**

| 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 | | | | | |

If you wish to add additional U.S. Published Application citation information please click the Add button.

**FOREIGN PATENT DOCUMENTS**

| 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 | 2010/083414 | WO | | 2010-07-22 | Exelixis, Inc. | | ☐ |

If you wish to add additional Foreign Patent Document citation information please click the Add button

**NON-PATENT LITERATURE DOCUMENTS**

| 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 | |
| | Filing Date | 2012-02-10 |
| | First Named Inventor | Jo Ann Wilson |
| | Art Unit | TBD |
| | Examiner Name | TBD |
| | Attorney Docket Number | 224990/10-039C-US/343999 |

| | | | |
|---|---|---|---|
| | 1 | International Search Report for PCT/US2012/024591 mailed May 25, 2012 | ☐ |

If you wish to add additional non-patent literature document citation information please click the Add button

**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.GOVor 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 | |
| | Filing Date | 2012-02-10 |
| | First Named Inventor | Jo Ann Wilson |
| | Art Unit | TBD |
| | Examiner Name | TBD |
| | Attorney Docket Number | 224990/10-039C-US/343999 |

**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 | | Date (YYYY-MM-DD) | 2013-08-09 |
|---|---|---|---|
| Name/Print | Heidi M. Berven | Registration Number | 48951 |

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.**

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

| | | | |
|---|---|---|---|
| Inventors(s) | : Jo Ann Wilson | Art Unit | : To Be Determined |
| Serial No. | : To Be Determined | Examiner | : To Be Determined |
| Filed | : February 10, 2012 | Docket No.: | 224990/10-039C-US/343999 |

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical

**CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. §1.8(a)**

The undersigned hereby certifies that the following documents are being electronically filed in accordance with §1.6(a)(4), on the 9th day of August, 2013:

1. Cover Letter to the Commissioner;
2. Application Data Sheet (PTO/SB/14);
3. Application as filed in the PCT;
4. Preliminary Amendment;
5. Declaration and Power of Attorney (unsigned);
6. Information Disclosure Statement (PTO/SB/08a);
7. Foreign Patent Documents;
8. Non-Patent Literature Documents; and
9. Certificate of Transmission under 37 C.F.R. § 1.8(a).

Lejla Duvnjak (for Heidi M. Berven, Ph.D., Reg. No.: 48,951)

13005742.1

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/024591

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D215/227 A61K31/47 A61P35/00
ADD.

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)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 2010/083414 A1 (EXELIXIS INC [US]; ST CLAIR BROWN ADRIAN [GB]; LAMB PETER [US]; GALLAG) 22 July 2010 (2010-07-22) cited in the application Scheme 1 on page24; claims;claim 11 ----- | 1-34 |

☐ 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 |
|---|---|
| 16 May 2012 | 25/05/2012 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Wolf, Claudia |

1

Form PCT/ISA/210 (second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/024591

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 2010083414 A1 | 22-07-2010 | AR 075025 A1 | 02-03-2011 |
| | | AU 2010204619 A1 | 01-09-2011 |
| | | CA 2758030 A1 | 22-07-2010 |
| | | CN 102388024 A | 21-03-2012 |
| | | EP 2387563 A1 | 23-11-2011 |
| | | KR 20120013301 A | 14-02-2012 |
| | | SG 173014 A1 | 29-08-2011 |
| | | TW 201036948 A | 16-10-2010 |
| | | US 2012035212 A1 | 09-02-2012 |
| | | WO 2010083414 A1 | 22-07-2010 |

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 July 2010 (22.07.2010)

PCT

(10) International Publication Number
WO 2010/083414 A1

(51) International Patent Classification:
*C07D 215/227* (2006.01) *A61P 35/00* (2006.01)
*A61K 31/47* (2006.01)

(21) International Application Number:
PCT/US2010/021194

(22) International Filing Date:
15 January 2010 (15.01.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/145,421 16 January 2009 (16.01.2009) US

(71) Applicants *(for all designated States except US)*: **EXELIXIS, INC.** [US/US]; P.O. Box 511, 249 East Grand Avenue, South San Francisco, CA 94080 (US). **BRISTOL-MEYERS SQUIBB COMPANY** [US/US]; P.O. Box 4000, Princeton, NJ 08543 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **ST CLAIR BROWN, Adrian** [GB/GB]; 67 Stour Green, Ely, Cambridgeshire CB6 2XJ (GB). **LAMB, Peter** [US/US]; 814 Mandana Blvd., Oakland, CA 94610 (US). **GALLAGHER, William, P.** [US/US]; P.O. Box 4000, Princeton, NJ 08543 (US).

(74) Agent: **BERVEN, Heidi M.**; Honigman Miller Schwartz and Cohn LLP, 350 East Michigan Avenue, Suite 300, Kalamazoo, MI 49007 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published**:

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

WO 2010/083414 A1

(54) Title: MALATE SALT OF N- (4- { [ 6, 7-BIS (METHYLOXY) QUINOLIN-4-YL] OXY}PHENYL-N' - (4 -FLUOROPHENYL) CYCLOPROPANE-1-DICARBOXAMIDE, AND CRYSTALLINE FORMS THEROF FOR THE TREATMENT OF CANCER

(57) Abstract: Disclosed are malate salts of N-(4-{ [6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)- N'-(4-fluorophenyl)cyclopropane-l,l-dicarboxamide, including a (L)-malate salt, a (D)- malate salt, a (DL) malate salt, and mixtures thereof; and crystalline and amorphous forms of the malate salts. Also disclosed are pharmaceutical compositions comprising at least one malate salts of N-(4-{ [6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)- cyclopropane-l,l-dicarboxamide; and methods of treating cancer comprising administering at least one malate salt of N-(4-{ [6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-ffuorophenyl)cyclopropane- 1, 1 -dicarboxamide.

MALATE SALT OF N-(4-{[6,7-BIS(METHYLOXY) QUINOLIN-4-YL]OXY}PHENYL-N'-(4-FLUOROPHENYL) CYCLOPROPANE-1,1-DICARBOXAMIDE, AND CRYSTALLINE FORMS THEROF FOR THE TREATMENT OF CANCER

## Cross-reference to Related Applications

**[0001]** This application claims priority to U.S. provisional application 61/145,421, filed January 16, 2009, which is incorporated herein by reference.

## Technical Field

**[0002]** This disclosure relates to malate salts of N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and to crystalline and amorphous forms of the malate salts of N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. The malate salts of N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide include one of (1) the (L)-malate salt, (2) the (D)-malate salt, (3) the (D,L)-malate salt, and (4) mixtures therof. The disclosure also relates to pharmaceutical compositions comprising at least one malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide.

**[0003]** The disclosure also relates to pharmaceutical compositions comprising a crystalline or an amorphous form of at least one malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide.

**[0004]** The disclosure also relates to methods of treating cancer comprising administering at least one malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

**[0005]** The disclosure further relates to methods of treating cancer comprising administering a crystalline or an amorphous form of at least one malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

## Background

**[0006]** Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. One mechanism that can be exploited in cancer treatment is the modulation of protein kinase activity because signal transduction through protein kinase activation is responsible for many of the

characteristics of tumor cells. Protein kinase signal transduction is of particular relevance in, for example, thyroid, gastric, head and neck, lung, breast, prostate, and colorectal cancers, as well as in the growth and proliferation of brain tumor cells.

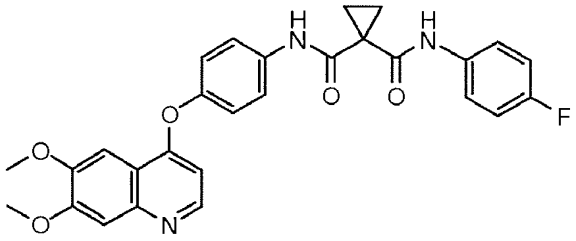
**[0007]** Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., DN&P 7(6): 334-339, 1994. Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases, including, for example, immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, protein kinases are attractive targets for small molecule drug discovery. Particularly attractive targets for small-molecule modulation with respect to antiangiogenic and antiproliferative activity include receptor type tyrosine kinases Ret, c-Met, and VEGFR2.

**[0008]** The kinase c-Met is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs) which include Met, Ron and Sea. The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenesis. Binding of HGF to c-Met induces activation of the receptor via autophosphorylation resulting in an increase of receptor dependent signaling, which promotes cell growth and invasion. Anti-HGF antibodies or HGF antagonists have been shown to inhibit tumor metastasis *in vivo* (See: Maulik et al Cytokine & Growth Factor Reviews 2002 13, 41-59). c-Met, VEGFR2 and/or Ret overexpression has been demonstrated on a wide variety of tumor types including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytic tumor (which includes glioblastoma,
giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components). The Ret protein is a transmembrane receptor with tyrosine kinase activity. Ret is mutated in most familial forms of medullary thyroid cancer. These mutations activate the kinase function of Ret and convert it into an oncogene product.

**[0009]** Inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc. Technol. 2001 6, 1005-1024).Kinase KDR (refers to kinase insert domain receptor tyrosine kinase) and flt-4 (fms-like tyrosine kinase-4) are both vascular endothelial growth factor (VEGF) receptors. Inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular

processes needed for tumor growth and survival (Matter A. Drug Disc. Technol. 2001 6, 1005-1024). EGF and VEGF receptors are desirable targets for small molecule inhibition.

**[0010]** Accordingly, small-molecule compounds that specifically inhibit, regulate and/or modulate the signal transduction of kinases, particularly including Ret, c-Met and VEGFR2 described above, are particularly desirable as a means to treat or prevent disease states associated with abnormal cell proliferation and angiogenesis. One such small-molecule is N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, which has the chemical structure:



WO 2005/030140 describes the synthesis of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (Example 12, 37, 38, and 48) and also discloses the therapeutic activity of this molecule to inhibit, regulate and/or modulate the signal transduction of kinases, (Assays, Table 4, entry 289). Example 48 is on paragraph [0353] in WO 2005/030140.

**[0011]** Besides therapeutic efficacy, the drug developer endeavors to provide a suitable form of the therapeutic agent that has properties relating to processing, manufacturing, storage stability, and/or usefulness as a drug. Accordingly, the discovery of a form that possesses some or all of these desired properties is vital to drug development.

**[0012]** Applicants have found a salt form of the drug N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide that has suitable properties for use in a pharmaceutical composition for the treatment of a proliferative disease such as cancer. The novel salt form of the invention exists in crystalline and amorphous forms

## Summary

**[0013]** This disclosure relates to malate salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as described herein, pharmaceutical compositions thereof as described herein, and uses thereof as described herein.

**[0014]** Another aspect relates to crystalline and amorphous forms of the malate salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as described herein, pharmaceutical compositions thereof as described herein, and uses thereof as described herein.

## Brief Description of the Figures

**[0015]** Figure 1 shows the experimental XRPD pattern for crystalline Compound (I), Form N-1 at 25 °C.

**[0016]** Figure 2 shows the solid state $^{13}C$ NMR spectrum of crystalline Compound (I), Form N-1.

**[0017]** Figure 3 shows the solid state $^{15}N$ NMR spectrum of crystalline Compound (I), Form N-1.

**[0018]** Figure 4 shows the solid state $^{19}F$ NMR spectrum of crystalline Compound (I), Form N-1.

**[0019]** Figure 5 shows the thermal gravimetric analysis (TGA) of crystalline Compound (I), Form N-1.

**[0020]** Figure 6 shows the differential scanning calorimetry (DSC) of crystalline Compound (I), Form N-1.

**[0021]** Figure 7 shows the moisture sorption of crystalline Compound (I), Form N-1.

**[0022]** Figure 8 shows the experimental XRPD pattern for crystalline Compound (I), Form N-2 at 25 °C.

**[0023]** Figure 9 shows the solid state $^{13}C$ NMR spectrum of crystalline Compound (I), Form N-2.

**[0024]** Figure 10 shows the solid state $^{15}N$ NMR spectrum of crystalline Compound (I), Form N-2.

**[0025]** Figure 11 shows the solid state $^{19}F$ NMR spectrum of crystalline Compound (I), Form N-2.

**[0026]** Figure 12 shows the thermal gravimetric analysis (TGA) of crystalline Compound (I), Form N-2.

**[0027]** Figure 13 shows the differential scanning calorimetry (DSC) of crystalline Compound (I), Form N-2.

**[0028]** Figure 14 shows the moisture sorption of crystalline Compound (I), Form N-2.

**[0029]** Figure 15 shows the experimental and simulated XRPD patterns for crystalline Compound (III), Form N-1 at room temperature.

**[0030]** Figure 16 shows the solid state $^{13}C$ NMR spectrum of crystalline Compound (III), Form N-1.

**[0031]** Figure 17 shows the solid state $^{15}N$ NMR spectrum of crystalline Compound (III), Form N-1.

**[0032]** Figure 18 shows the solid state $^{19}F$ NMR spectrum of crystalline Compound (III), Form N-1.

**[0033]** Figure 19 shows the thermal gravimetric analysis (TGA) of crystalline Compound (III), Form N-1.

**[0034]** Figure 20 shows the differential scanning calorimetry (DSC) of crystalline Compound (III), Form N-1.

**[0035]** Figure 21 shows the moisture sorption of crystalline Compound (III), Form N-1.

**[0036]** Figure 22 shows the XRPD pattern of amorphous Compound (I) at room temperature.

**[0037]** Figure 23 shows the solid state $^{13}C$ NMR spectrum of amorphous Compound (I).

**[0038]** Figure 24 shows the solid state $^{15}N$ NMR spectrum of amorphous Compound (I).

**[0039]** Figure 25 shows the solid state $^{19}F$ NMR spectrum of amorphous Compound (I).

**[0040]** Figure 26 shows the differential scanning calorimetry (DSC) of amorphous Compound (I).

**[0041]** Figure 27 shows the moisture sorption of amorphous Compound (I).

## Detailed Description

**[0042]** This disclosure relates to improvements of the physiochemical properties of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, whereby this compound may be suitable for drug development. Disclosed herein are malate salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. New solid state forms of those salts are also disclosed. The malate salts as well as their crystalline and amorphous forms disclosed herein each represent separate aspects of the disclosure. Although the malate salts and their solid state forms are described herein, the invention also relates to novel compositions containing the disclosed salts and solid state forms. Therapeutic uses of the salts and solid state forms described as well as therapeutic compositions containing them represent separate aspects of the disclosure. The techniques used to characterize the salts and their solid state forms are described in the examples below. These techniques, alone or in combination, may be used to characterize the salts and their solid state forms disclosed herein. The salts and their solid state forms may be also characterized by reference to the disclosed figures.

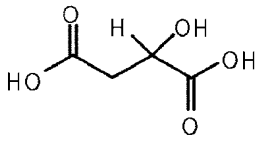
**[0043]** N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide was found to have an enzyme Ret $IC_{50}$ value of about 5.2 nM (nanomolar) and an enzyme c-Met $IC_{50}$ value of about 1.3 nM (nanomolar). The assay that was used to measure this c-Met activity is described in paragraph [0458] in WO2005-030140.

**[0044]** RET biochemical activity was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format as described in WO2005-030140. Kinase activity was measured as the percent ATP remaining following the kinase reaction. Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 2μM ATP, 1μM poly-EY and 15nM RET (baculovirus expressed human RET kinase domain M700-D1042 with a $(His)_6$ tag on the N-terminus) in a 20uL assay buffer (20mM Tris-HCL pH 7.5, 10mM $MgCl_2$, 0.01% Triton X-100, 1 mM DTT, 3mM $MnCl_2$). The mixture was incubated at ambient temperature for 2hours after which 20uL luciferase-luciferin mix was added and the chemiluminescent signal read using a Wallac Victor$^2$ reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5ug/mL oxalic acid (pH 7.8), 5 mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 μM AMP, 28 μg/mL luciferin and 40,000 units of light/mL luciferase.

Malate Salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

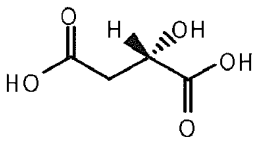
**[0045]** This disclosure relates to malate salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. These malate salts are a combination of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide with malic acid which forms a 1:1 malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

**[0046]** Malic acid has the following structure:



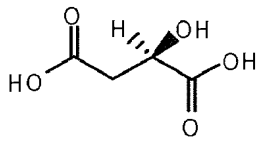

Due to its chiral carbon, two enantiomers of malic acid exist, (L)-malic acid and (D)-malic acid.

**[0047]** (L)-malic acid has the following structure:



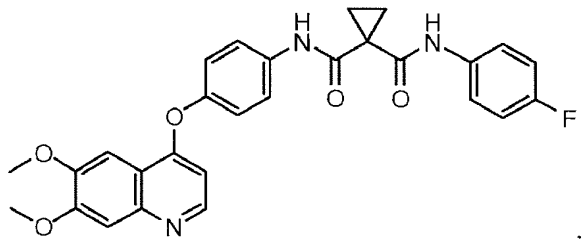
There are various names or designations for the (L)-malic acid that are known in the art. These include butanedioic acid, hydroxy-, (2S)- (9CI); butanedioic acid, hydroxy-, (S)-; malic acid, L- (8CI); malic acid, l- (3CI); (-)-(S)-malic acid; (-)-Hydroxysuccinic acid; (-)-(L)-malic acid; (-)-malic acid; (2S)-2-hydroxybutanedioic acid; (2S)-2-hydroxysuccinic acid; (S)-malic acid; apple acid; L-(-)-malic acid; (L)-malic acid; NSC 9232; S-(-)-malic acid; and S-2-hydroxybutanedioic acid.

**[0048]** (D) malic acid has the following structure:



There are various names or designations for the (D)-malic acid that are known in the art. These include butanedioic acid, 2-hydroxy-, (2R)-, butanedioic acid, hydroxy-, (2R)- (9CI); butanedioic acid, hydroxy-, (R)-; (+)-malic acid; (2R)-2-hydroxybutanedioic acid; (2R)-malic acid; (R)-(+)-malic acid; (R)-malic acid; D-(+)-2-hydroxysuccinic acid; D-(+)-malic acid; and D-malic acid.

**[0049]** As discussed above, the chemical structure of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is



There are no chiral carbons in its chemical structure. There are various names for N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide which are publicly known, and some of these various names or designations include 1,1-cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- and 1,1-cyclopropanedicarboxamide, N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)- (9CI).

**[0050]** N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide can be prepared according to any of several different methodologies, either on a gram scale (<1 kg) or a kilogram scale (>1 kg). A gram-scale method is set forth in WO 2005-030140, which describes the synthesis of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (Examples 25, 37, 38, and 48), which is hereby incorporated by reference. Alternatively, N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, including the active compound(s), can be prepared on a kilogram scale using the procedure set forth in Example 1 below.

**[0051]** This disclosure relate to malate salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide:

the (L)-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (Compound (I));

the (D)-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (Compound (II)); and

the (DL)-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (Compound (III)).

Each has improved properties over N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and its other salts. The names used herein to characterize a specific form, e.g. "N-2" etc., are not to be limited so as to exclude any other substance possessing similar or identical physical and chemical characteristics, but rather such names are used as mere identifiers that are to be interpreted in accordance with the characterization information presented herein.

**[0052]** The malate salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, and particularly Compound (I), have a preferred combination of pharmaceutical properties for development. Under the conditions of 25°C/60% relative humidity (RH) and 40 °C/60%RH, Compound (I) showed no change in assay, purity, moisture and dissolution. The DSC/TGA showed the Compound (I) to be stable up to 185°C. No solvent losses were observed. The uptake of water by the (L)-malate salt was reversible with a slight hysteresis. The amount of water taken up was calculated at about 0.60wt% at 90%RH. The (L)-malate salt was synthesized with good yield and purity >90% and had sufficient solubility for use in a pharmaceutical composition. The amount of water associated with this salt was calculated at about 0.5wt% by Karl Fischer analysis and correlates with TGA and GVS analysis. The (D)-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-

dicarboxamide) will have the same properties as the (L)-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide).

**[0053]** The Compound (I) salt itself, and separately its crystalline and amorphous forms, exhibit beneficial properties over the free base and the other salts of the N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. For example, the hydrochloride salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide exhibits undesirable moisture sensitivity, changing phase upon exposure to high humidity (75% humidity) and high temperature (40°C). The maleate salt had low solubility. The tartrate salt had low crystallinity and low solubility. The phosphate salt exhibited an 8% weight gain due to absorption of $H_2O$ – the highest among the salts tested.

**[0054]** The water solubility of the various salts was determined using 10 mg solids per mL water. The salts were prepared in a salt screen by reacting an acetone solution of the freebase with stock tetrahydrofuran (THF) solutions of a range of acids in about a 1:1 molar ratio. Table 1 below summarizes the water solubility and other data relating to the free base and each salt.

**Table 1**

| | Solubility (mg/ml) | |
|---|---|---|
| Free base | <<0.001 | very low solubility |
| Propionate | <<0.001 | no salt formation; mixture of free base and acid |
| Acetate | <<0.001 | no salt formation; mixture of free base and acid |
| Succinate | 0.010 | no salt formation; mixture of free base and acid |
| Benzoate | 0.005 | no salt formation; mixture of free base and acid |
| L-Lactate | 0.015 | Amorphous, salt |
| Pyrroglutamate | 0.44 | Amorphous, salt |
| Glycolate | 0.016 | Amorphous, salt |
| L-Ascorbate | 0.053 | low crystallinity |
| Sulfate | 0.004 | Crystalline salt, low solubility |
| Tosylate | 0.007 | Crystalline salt, low solubility |
| Malonate | 0.003 | Crystalline salt, low solubility |
| 2,5dihydroxybenzoate | <<0.001 | Crystalline Salt, low solubility |
| Fumarate | 0.008 | Crystalline Salt, low solubility |
| Citrate | 0.002 | Crystalline Salt, low solubility |
| Mesylate | 0.175 | Crystalline Salt; possible sulfonic acid formation when made with alcohol |
| Esylate | 0.194 | Crystalline Salt; possible sulfonic acid formation when made with alcohol |
| Benzenesulfonate | 0.039 | Crystalline Salt; possible sulfonic acid formation |

| | Solubility (mg/ml) | |
|---|---|---|
| | | when made with alcohol |
| Chloride | 0.070 | Crystalline but Hygroscopic; possible hydrate formation. Change in XRPD pattern upon exposure to humidity. |
| Maleate | 0.005 | Crystalline salt, possible hydrate formation; low solubility; different XRPD pattern observed upon scale up (possible polymorphism issue) |
| Phosphate | 0.026 | Crystalline but Hygroscopic. |
| L-Tartrate | 0.014 | Low degree of crystallinity; Hygroscopic. |
| (L)-Malate | 0.059 | Crystalline; non-Hygroscopic with no indication of hydrate formation. Suitable solubility, and chemical/physical stability. |

**[0055]** Another aspect of this disclosure relates to crystalline forms of Compound (I), which include the N-1 and/or the N-2 crystalline form of Compound (I) as described herein. Each of form of Compound (I) is a separate aspect of the disclosure. Similarly, another aspect of this disclosure relates to crystalline forms of Compound (II), which include the N-1 and/or the N-2 crystalline form of Compound (II) as described herein. Each of which is also a separate aspect of the disclosure. As is known in the art, the crystalline (D) malate salt will form the same crystalline form and have the same properties as crystalline Compound (I). See WO 2008/083319, which discusses the properties of crystalline enantiomers. Mixtures of the crystalline forms of Compounds (I) and (II) are another aspect of the disclosure.

**[0056]** The crystalline N-1 forms of Compounds (I) and (II) as described here may be characterized by at least one of the following:

(i) a solid state $^{13}C$ NMR spectrum with peaks at 18.1, 42.9, 44.5, 70.4, 123.2, 156.2, 170.8, 175.7, and 182.1 ppm, ± 0.2 ppm;

(ii) a solid state $^{13}C$ NMR spectrum substantially in accordance with the pattern shown in Figure 2;

(iii) an x-ray powder diffraction pattern (CuKα λ=1.5418Å) comprising four or more peaks selected from: 6.4, 9.0, 12.0, 12.8, 13.5, 16.9, 19.4, 21.5, 22.8, 25.1, and 27.6 °2θ ± 0.2 °2θ, wherein measurement of the crystalline form is at an ambient room temperature;

(iv) an x-ray powder diffraction (XRPD) spectrum substantially in accordance with the pattern shown in Figure 1;

(v) a solid state $^{15}N$ NMR spectrum with peaks at 118.6, 119.6, 120.7, 134.8, 167.1, 176.0, and 180 ppm, ±0.2 ppm; and/or

(vi) a solid state $^{15}N$ NMR spectrum substantially in accordance with the pattern shown in Figure 3.

**[0057]** Other solid state properties which may be used to characterize the crystalline N-1 forms of Compounds (I) and (II) are shown in the figures and discussed in the examples below. For crystalline Compound (I), the solid state phase and the degree of crystallinity remained unchanged after exposure to 75%RH at 40°C for 1 week.

**[0058]** The crystalline N-2 forms of Compounds (I) and (II) as described here may be characterized by at least one of the following:

(i) a solid state $^{13}C$ NMR spectrum with peaks at 23.0, 25.9, 38.0, 54.4, 56.11, 41.7, 69.7, 102.0, 122.5, 177.3, 179.3, 180.0, and 180.3, ± 0.2 ppm;

(ii) a solid state $^{13}C$ NMR spectrum substantially in accordance with the pattern shown in Figure 9;

(ii) an x-ray powder diffraction pattern (CuKα λ=1.5418Å) comprising four or more peaks selected from: 6.4, 9.1, 12.0, 12.8, 13.7, 17.1, 20.9, 21.9, 22.6, and 23.7 °2θ ± 0.2 °2θ, wherein measurement of the crystalline form is at an ambient room temperature;

(iv) an x-ray powder diffraction (XRPD) spectrum substantially in accordance with the pattern shown in Figure 8;

(v) a solid state $^{15}N$ NMR spectrum with peaks at 118.5, 120.8, 135.1, 167.3, and 180.1 ppm; and/or

(vi) a solid state $^{15}N$ NMR spectrum substantially in accordance with the pattern shown in Figure 10.

Other solid state properties which may be used to characterize the crystalline N-2 forms of Compounds (I) and (II) are shown in the figures and discussed in the examples below.

**[0059]** In another embodiment, the disclosure relates to a crystalline form of Compound (I), as described herein in any of the aspects and/or embodiments, is substantially pure N-1 form.

**[0060]** In another embodiment, the disclosure relates to a crystalline form of Compound (I), as described herein in any of the aspects and/or embodiments, is substantially pure N-2 form.

**[0061]** The disclosure also relates to amorphous forms of Compounds (I) and (II). The preparation and solid state properties and characteristics of the amorphous form of Compound (I) are described in the examples below. The amorphous forms of Compounds (I) and (II) represent another aspect of the disclosure.

**[0062]** One further aspect of the disclosure relates to mixtures of Compound (I) and Compound (II). The mixtures may have from greater than zero weight % to less than 100 weight % Compound (I) and from less than 100 weight % to greater zero weight % Compound (II), based on the total weight of Compound (I) and Compound (II). In other embodiments, the mixture comprises from about 1 to about 99 weight % Compound (I) and from about 99 to about 1 weight % Compound (II), based on the total weight of Compound (I) and Compound (II) in said mixture. In a further embodiment, the mixture comprises from about 90 weight % to less than 100 weight % Compound (I) and from greater than zero weight % to about 10 weight % Compound (II), based on the total weight of Compound (I) and Compound (II). Accordingly, the mixture may have 1-10% by weight of Compound (I); 11-20% by weight of Compound (I); 21-30% by weight of Compound (I); 31-40% by weight of Compound (I); 41-50% by weight of Compound (I); 51-60% by weight of Compound (I); 61-70% by weight of Compound (I); 71-80% by weight of Compound (I); 81-90% by weight of Compound (I); or 91-99% by weight of Compound (I) with the remaining weight percentage of malate salt being that of Compound (II).

**[0063]** Another aspect of this disclosure relates to crystalline forms of (DL)-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, Compound (III). The (DL)-malate salt is prepared from racemic malic acid. The crystalline N-1 form of Compound (III) as described here may be characterized by at least one of the following:

(i) a solid state $^{13}C$ NMR spectrum with four or more peaks selected from 20.8, 26.2, 44.8, 55.7, 70.7, 100.4, 101.0, 114.7, 115.2, 116.0, 119.7, 120.4, 121.6, 124.4, 136.9, 138.9, 141.1, 145.7, 150.3, 156.5, 157.6, 159.6, 165.2, 167.4, 171.2, 176.3, 182.1 ppm, ± 0.2 ppm;

(ii) a solid state $^{13}C$ NMR spectrum substantially in accordance with the pattern shown in Figure 16;

(iii) a powder x-ray diffraction pattern (CuKα λ=1.5418Å) comprising four or more 2θ values selected from: 12.8, 13.5, 16.9, 19.4, 21.5, 22.8, 25.1, and 27.6, ±0.2 °2θ, wherein measurement of the crystalline form is at temperature of room temperature;

(iv) an x-ray powder diffraction (XRPD) spectrum substantially in accordance with the pattern shown in Figure 15;

(v) a solid state $^{15}N$ NMR spectrum with peaks at 119.6, 134,7, and 175.5 ppm, ± 0.2 ppm; and/or

(vi) a solid state $^{15}N$ NMR spectrum substantially in accordance with the pattern shown in Figure 17.

Other solid state properties which may be used to characterize the crystalline N-1 form of Compound (III) are shown in the figures and discussed in the examples below. In one embodiment, the N-1 Form of Compound (III) is characterized by unit cell parameters approximately equal to the following:

Cell dimensions: a = 14.60 Å
b = 5.20 Å
c = 39.09 Å
α = 90.0°
β = 90.4°
γ = 90.0°

Space group: $P2_1/n$
Molecules of Compound (I)/unit cell: 4
Volume = 2969 $Å^3$
Density (calculated) = 1.422 $g/cm^3$

The unit cell parameters of Form N-1 of Compound (III) were measured at a temperature of approximately 25°C, *e.g.*, ambient or room temperature.

**[0064]** Each of the N-1 and N-2 crystalline forms of Compounds (I) and (II) and the crystalline form N-1 of Compound (III) have unique characteristics that can distinguish them one from another. These characteristics can be understood by comparing the physical properties of the solid state forms which are presented in the Examples below. For example, Table 2 lists characteristic XRPD peak positions (°2θ±0.2 °2θ) for crystalline Compound (III), Form N-1 and Forms N-1 and N-2 of crystalline Compound (I). Amorphous forms do not display reflection peaks in their XRPD patterns.

**Table 2**

**Characteristic diffraction peak positions (degrees 2θ±0.2 ) @ RT, based on pattern collected with a diffractometer (CuKα) with a spinning capillary.**

| Compound (I) Form N-1 | Compound (I) Form N-2 | Compound (III) Form N-1 |
|---|---|---|
| 6.4 | 6.4 | 6.4 |
| 9.0 | 9.1 | 9.1 |
| 12.0 | 12.0 | 12.1 |
| 12.8 | 12.8 | 12.8 |
| 13.5 | 13.7 | 13.6 |
| 16.9 | 17.1 | 17.1 |
| 19.4* | 20.9* | 19.3 |
| 21.5* | 21.9* | 21.4 |
| 22.8* | 22.6 | 22.8 |
| 25.1* | 23.7 | 25.1 |
| 27.6* | -- | 27.6 |

*unique reflections between Compound (I), Form N-1 and Compound (I), Form N-2.

The unique reflections between Forms N-1 and N-2 of crystalline Compound (II) are designated by an asterisk (*). As discussed above, Compound (II) is an enantiomer of Compound (I) and thus, Compound (II), Form N-1 will have the same characteristic reflection pattern and unique peaks as those listed in Table 2 for Compound (I), Form N-1. Likewise, Compound (II), Form N-2 will have the same characteristic reflection pattern and unique peaks as those listed in Table 2 for Compound (I), Form N-2. Compounds (I) and (II) are distinct from one another based on their absolute stereochemistry, *i.e.*, the (L)-malate salt versus the (D)-malate salt, respectively. Crystalline Compound (III), Form N-1, is distinct as the (D,L)-malate salt.

**[0065]** The characteristic peaks from the solid state NMR may also serve to distinguish the crystalline and amorphous forms disclosed herein. For example, Table 3 lists characteristic solid state $^{13}C$ NMR peaks for crystalline Compound (III), Form N-1; crystalline Compound (I), Forms N-1 and N-2, and the amorphous form of Compound (I).

**Table 3**

| **Solid State Carbon-13 NMR Resonances (ppm, ±0.2 ppm)** | | | |
|---|---|---|---|
| (I) Form N-1 | (I), Form N-2 | (III), Form N-1 | (I), Amorphous |
| 18.1 | 23.0 | 20.8 | 27.2 |
| 42.9 | 25.9 | 26.2 | 33.8 |
| 44.5 | 38.0 | 44.8 | 142.9 |
| 54.4 | 54.4 | 70.7 | -- |
| 56.1 | 56.1 | 114.7 | -- |
| 70.4 | 41.7 | 141.1 | -- |
| 123.2 | 69.7 | 145.7 | -- |
| 156.2 | 102.0 | 176.3 | -- |
| 170.8 | 122.5 | 182.1 | -- |
| 175.7 | 177.3 | -- | -- |
| 182.1 | 179.3 | -- | -- |
| -- | 180.0 | -- | -- |
| -- | 180.3 | -- | -- |

The solid state $^{19}F$ and $^{15}N$ NMR spectra, discussed below, provide data for similar comparison and characterization. As discussed above, being an enantiomer of Compound (I),

crystalline Forms N-1 and N-2 and the amorphous form of Compound (II) will have the same solid state NMR resonances, and unique peaks between them, as those listed in Table 3 for Forms N-1 and N-2 of crystalline Compound (I).

Pharmaceutical Compositions and Methods of Treatment

**[0066]** Another aspect of this disclosure relates to a pharmaceutical composition comprising at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, and a pharmaceutically acceptable excipient. The amount of Compound (I), Compound (II), Compound (III), or the combinations thereof in the pharmaceutical composition can be a therapeutically effective amount. Compound (I), Compound (II), or Compound (III) may individually be present in the pharmaceutical composition as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a solid or dispersion pharmaceutical composition comprising at least one of a therapeutically effective amount of a crystalline form of Compound (I), Compound (II), Compound (III), or combinations thereof, and a pharmaceutically acceptable excipient.

**[0067]** Another aspect of this disclosure relates to a method of treating cancer comprising administering to a subject in need thereof at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. The amount of Compound (I), Compound (II), or combinations thereof administered can be a therapeutically effective amount. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms, with crystalline Compound (I), Form N-1or N-2 being preferred. Accordingly another aspect of this disclosure relates to a method of treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, the method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above.

**[0068]** Another aspect of this disclosure relates to a method of treating cancer, as discussed above, where the cancer treated is stomach cancer, esophageal carcinoma, kidney cancer, liver cancer, ovarian carcinoma, cervical carcinoma, large bowel cancer, small bowel cancer, brain cancer (including astrocytic tumor, which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components), lung cancer

(including non-small cell lung cancer), bone cancer, prostate carcinoma, pancreatic carcinoma, skin cancer, bone cancer, lymphoma, solid tumors, Hodgkin's disease, non-Hodgkin's lymphoma or thyroid cancer thyroid cancer (including medullary thyroid cancer).

**[0069]** Tyrosine kinase inhibitors have also been used to treat non-small cell lung cancer (NSCLC). Gefitinib and erlotinib are angiogenesis inhibitors that target receptors of an epidermal growth factor called tyrosine kinase. Erlotinib and Gefitinib are currently being used for treating NSCLC. Another aspect of this disclosure relates to a method of treating non-small cell lung cancer (NSCLC) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, or a pharmaceutically acceptable salt thereof, optionally in combination with Erlotinib or Gefitinib. In another embodiment, the combination is with Erlotinib.

**[0070]** Another aspect of this disclosure relates to a method of treating non-small cell lung cancer (NSCLC) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of Erlotinib or Gefitinib in combination with at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a method of treating a method of treating non-small cell lung cancer (NSCLC) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of Erlotinib or Gefitinib in combination with at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above. In another embodiment, the combination administered in this method is Erlotinib with at least one of Compound (I), Compound (II), Compound (III), or combinations thereof.

**[0071]** Another aspect of this disclosure relates to a method of treating an astrocytic tumor (which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components in a subject) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

**[0072]** Another aspect of this disclosure relates to a method of treating an astrocytic tumor (which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components in a subject) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a method of treating an astrocytic tumor comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above.

**[0073]** Another aspect of this disclosure relates to a method of treating thyroid cancer (including medullary thyroid cancer) in a subject, the method comprising administering to the subject in need of the treatment N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, or a pharmaceutically acceptable salt thereof. The amount administered can be a therapeutically effective amount.

**[0074]** Another aspect of this disclosure relates to a method of treating thyroid cancer (including medullary thyroid cancer) in a subject, the method comprising administering to the subject in need of the treatment at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a method of treating thyroid cancer comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above.

**[0075]** Another aspect of this disclosure relates to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities. This

method administers, to a subject in need thereof, at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. The amount of Compound (I), Compound (II), or combinations thereof administered can be a therapeutically effective amount. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms.

**[0076]** Accordingly another aspect of this disclosure relates to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above. Another aspect of this disclosure relates to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities. This method administers, to a subject in need thereof, a crystalline form of Compound (I), Compound (II), or any combination of Compound (I) and (II). The amount of Compound (I), Compound (II), or any combination of Compound (I) and (II) administered can be a therapeutically effective amount.

**[0077]** Another aspect of this disclosure relates to a use of the N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to any of the above embodiments for the manufacture of a medicament for the treatment of a disease or disorder discussed above. When dissolved, a crystalline or amorphous form according to this disclosure loses its solid state structure, and is therefore referred to as a solution of, for example, Compound (I). At least one crystalline form disclosed herein may be used to prepare at least one liquid formulation in which at least one crystalline form according to the disclosure is dissolved and/or suspended.

**[0078]** A pharmaceutical composition such as discussed above may be any pharmaceutical form which contains active Compound (I), Compound (II) and/or Compound (III), including the solid state forms thereof (hereinafter referred to as active compound(s). The pharmaceutical composition may be, for example, a tablet, capsule, liquid suspension, injectable, topical, or transdermal. The pharmaceutical compositions generally contain about 1% to about 99% by weight of the active compound(s), or a crystalline form of the active compound(s), and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of active

compound, with the rest being suitable pharmaceutical excipients or other adjuvants, as discussed below.

**[0079]** A "therapeutically effective amount of the active compounds, or a crystalline or amorphous form of the active compound(s), according to this disclosure to inhibit, regulate and/or modulate the signal transduction of kinases (discussed here concerning the pharmaceutical compositions) refers to an amount sufficient to treat a patient suffering from any of a variety of cancers associated with abnormal cell proliferation and angiogenesis. A therapeutically effective amount according to this disclosure is an amount therapeutically useful for the treatment or prevention of the disease states and disorders discussed herein. Compounds (I), (II), and/or (III) (including their solid state forms), possess therapeutic activity to inhibit, regulate and/or modulate the signal transduction of kinases such as described in WO2005-030140. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide.

**[0080]** The actual amount required for treatment of any particular patient will depend upon a variety of factors including the disease state being treated and its severity; the specific pharmaceutical composition employed; the age, body weight, general health, sex and diet of the patient; the mode of administration; the time of administration; the route of administration; and the rate of excretion of the active compound(s), or a crystalline form of the active compound(s), according to this disclosure; the duration of the treatment; any drugs used in combination or coincidental with the specific compound employed; and other such factors well known in the medical arts. These factors are discussed in Goodman and Gilman's "The Pharmacological Basis of Therapeutics", Tenth Edition, A. Gilman, J.Hardman and L. Limbird, eds., McGraw-Hill Press, 155-173, 2001, which is incorporated herein by reference. The active compound(s) , or a crystalline form of active compound(s), according to this disclosure and pharmaceutical compositions comprising them, may be used in combination with anticancer or other agents that are generally administered to a patient being treated for cancer. They may also be co-formulated with one or more of such agents in a single pharmaceutical composition.

**[0081]** Depending on the type of pharmaceutical composition, the pharmaceutically acceptable carrier may be chosen from any one or a combination of carriers known in the art. The choice of the pharmaceutically acceptable carrier depends partly upon the desired method of administration to be used. For a pharmaceutical composition of this disclosure, that is, one of the active compound(s), or a crystalline form of the active compound(s), of this disclosure, a carrier should be chosen so as to substantially maintain the particular form of the active compound(s), whether it would be crystalline or not. In other words, the carrier should

not substantially alter the form the active compound(s) are. Nor should the carrier be otherwise incompatible with the form of the active compound(s), such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition.

**[0082]** The pharmaceutical compositions of this disclosure may be prepared by methods know in the pharmaceutical formulation art, for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). In a solid dosage forms Compound (I) is admixed with at least one pharmaceutically acceptable excipient such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alginates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

**[0083]** Pharmaceutically acceptable adjuvants known in the pharmaceutical formulation art may also be used in the pharmaceutical compositions of this disclosure. These include, but are not limited to, preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. If desired, a pharmaceutical composition of this disclosure may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, and antioxidants, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, and butylalted hydroxytoluene.

**[0084]** Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active

compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

**[0085]** Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

**[0086]** Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the active compound(s), or a crystalline form of the active compound(s), with, for example, suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

**[0087]** Because the active compound(s), or a crystalline form of the active compound(s), is maintained during their preparation, solid dosage forms are preferred for the pharmaceutical composition of this disclosure. Solid dosage forms for oral administration, which includes capsules, tablets, pills, powders, and granules, are particularly preferred. In such solid dosage forms, the active compound(s) mixed with at least one inert, pharmaceutically acceptable excipient (also known as a pharmaceutically acceptable carrier). Administration of the active compound(s), or a crystalline form of the active compound(s), in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. One preferable route of administration is oral administration, using a convenient dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

General Preparation Methods of Crystalline Forms

**[0088]** Crystalline forms may be prepared by a variety of methods including, but not limited to, for example, crystallization or recrystallization from a suitable solvent mixture; sublimation; growth from a melt; solid state transformation from another phase; crystallization from a supercritical fluid; and jet spraying. Techniques for crystallization or recrystallization of crystalline forms of a solvent mixture include, but are not limited to, for

example, evaporation of the solvent; decreasing the temperature of the solvent mixture; crystal seeding of a supersaturated solvent mixture of the compound and/or salt thereof; crystal seeding a supersaturated solvent mixture of the compound and/or a salt from thereof; freeze drying the solvent mixture; and adding antisolvents (countersolvents) to the solvent mixture. High throughput crystallization techniques may be employed to prepare crystalline forms including polymorphs.

**[0089]** Crystals of drugs, including polymorphs, methods of preparation, and characterization of drug crystals are discussed in *Solid-State Chemistry of Drugs*, S.R. Byrn, R.R. Pfeiffer, and J.G. Stowell, 2nd Edition, SSCI, West Lafayette, Indiana (1999).

**[0090]** In a crystallization technique in which solvent is employed, the solvent(s) are typically chosen based on one or more factors including, but not limited to, for example, solubility of the compound; crystallization technique utilized; and vapor pressure of the solvent. Combinations of solvents may be employed. For example, the compound may be solubilized in a first solvent to afford a solution to which antisolvent is then added to decrease the solubility of the Compound (I)n the solution and precipitate the formation of crystals. An antisolvent is a solvent in which a compound has low solubility.

**[0091]** In one method that can be used in preparing crystals, Compound (I), Compound (II) and/or Compound (III) can be suspended and/or stirred in a suitable solvent to afford a slurry, which may be heated to promote dissolution. The term "slurry", as used herein, means a saturated solution of the compound, wherein such solution may contain an additional amount of compound to afford a heterogeneous mixture of compound and solvent at a given temperature.

**[0092]** Seed crystals may be added to any crystallization mixture to promote crystallization. Seeding may be employed to control growth of a particular polymorph and/or to control the particle size distribution of the crystalline product. Accordingly, calculation of the amount of seeds needed depends on the size of the seed available and the desired size of an average product particle as described, for example, in Programmed Cooling Batch Crystallizers," J.W. Mullin and J. Nyvlt, Chemical Engineering Science, 1971, 26, 3690377. In general, seeds of small size are needed to effectively control the growth of crystals in the batch. Seeds of small size may be generated by sieving, milling, or micronizing large crystals, or by microcrystallizing a solution. In the milling or micronizing of crystals, care should be taken to avoid changing crystallinity from the desired crystalline form (i.e., changing to an amorphous or other polymorphic form).

**[0093]** A cooled crystallization mixture may be filtered under vacuum and the isolated solid product washed with a suitable solvent, such as, for example, cold recrystallization

solvent. After being washed, the product may be dried under a nitrogen purge to afford the desired crystalline form. The product may be analyzed by a suitable spectroscopic or analytical technique including, but not limited to, for example, differential scanning calorimetry (DSC); x-ray powder diffraction (XRPD); and thermogravimetric analysis (TGA) to assure the crystalline form of the compound has been formed. The resulting crystalline form may be produced in an amount greater than about 70 wt.% isolated yield, based on the weight of the compound originally employed in the crystallization procedure, and preferably greater than about 90 wt.% isolated yield. Optionally, the product may be delumped by being comilled or passed through mesh screen.

**[0094]** The features and advantages of this disclosure may be more readily understood by those of ordinary skill in the art upon reading the following detailed description. It is to be appreciated that certain features of the invention that are, for clarity reasons, described above and below in the context of separate embodiments, may also be combined to form a single embodiment. Conversely, various features of this disclosure that are, for brevity reasons, described in the context of a single embodiment, may also be combined so as to form sub-combinations thereof. The disclosure is further illustrated by the following examples, which are not to be construed as limiting the disclosure in scope or spirit to the specific procedures described in them.

**[0095]** The definitions set forth herein take precedence over definitions set forth in any patent, patent application, and/or patent application publication incorporated herein by reference. All measurements are subject to experimental error and are within the spirit of the invention.

**[0096]** As used herein, "amorphous" refers to a solid form of a molecule and/or ion that is not crystalline. An amorphous solid does not display a definitive X-ray diffraction pattern with sharp maxima.

**[0097]** As used herein, the term "substantially pure" means the crystalline form of Compound (I) referred to contains at least about 90wt.% based on the weight of such crystalline form. The term "at least about 90 wt.%," while not intending to limit the applicability of the doctrine of equivalents to the scope of the claims, includes, but is not limited to, for example, about 90, about 91, about 92, about 93, about 94, about 95, about 96, about 97, about 98, about 99 and about 100% wt. %, based on the weight of the crystalline form referred to. The remainder of the crystalline form of Compound (I) may comprise other Form(s) of Compound (I) and/or reaction impurities and/or processing impurities that arise, for example, when the crystalline form is prepared. The presence of reaction impurities and/or processing impurities may be determined by analytical techniques known in the art,

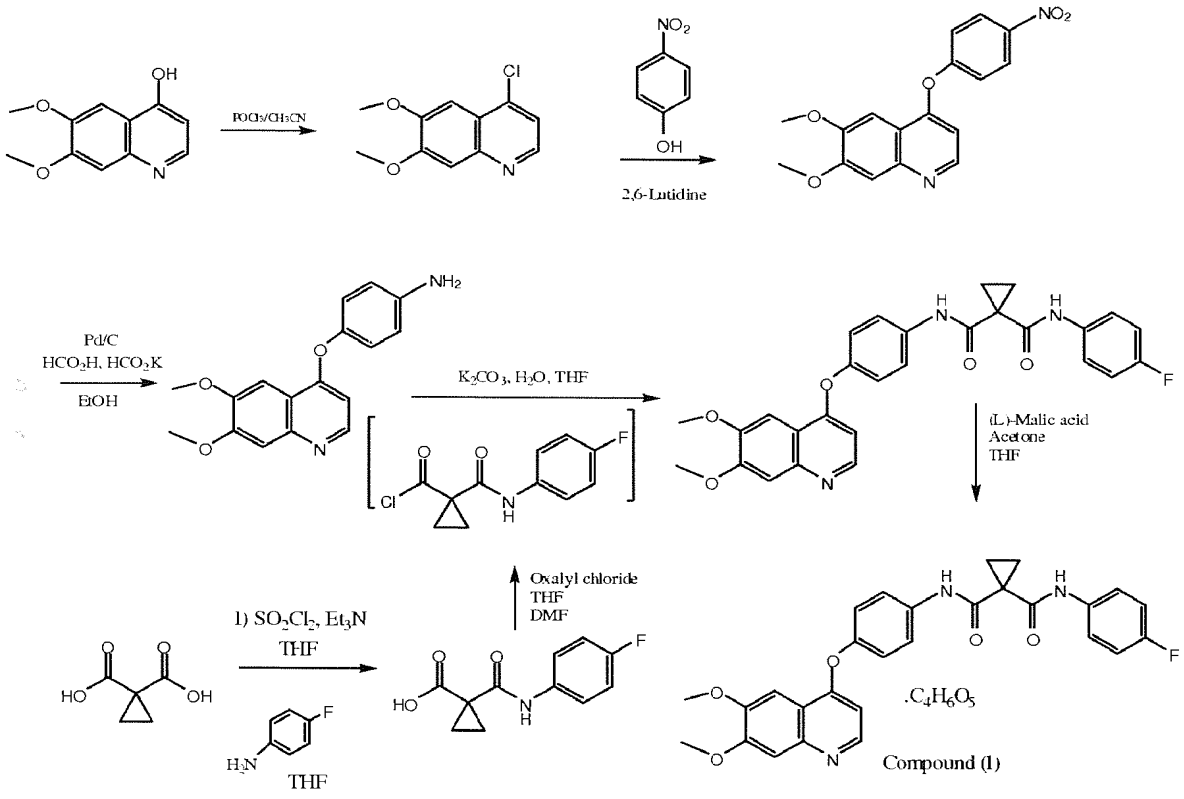
such as, for example, chromatography, nuclear magnetic resonance spectroscopy, mass spectroscopy, and/or infrared spectroscopy.

## PREPARATIVE EXAMPLES

**[0098] Example 1: Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof (Compound (I)).**

**[0099]** The synthetic route used for the preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Scheme 1:

**SCHEME 1**




**[00100]** The process shown in Scheme 1 is described in more detail below.

**[00101] 1.1 Preparation of 4–Chloro–6,7–dimethoxy–quinoline**

**[00102]** A reactor was charged sequentially with 6,7–dimethoxy–quinoline–4–ol (1 L, 10.0 kg) and acetonitrile (64.0 L). The resulting mixture was heated to approximately 65°C and phosphorus oxychloride ($POCl_3$, 50.0 kg) was added. After the addition of $POCl_3$, the

temperature of the reaction mixture was raised to approximately 80°C. The reaction was deemed complete (approximately 9.0 hours) when <2% of the starting material remained (in process high-performance liquid chromatography [HPLC] analysis). The reaction mixture was cooled to approximately 10°C and then quenched into a chilled solution of dichloromethane (DCM, 238.0 kg), 30% $NH_4OH$ (135.0 kg), and ice (440.0 kg). The resulting mixture was warmed to approximately 14°C, and phases were separated. The organic phase was washed with water (40.0 kg) and concentrated by vacuum distillation with the removal of solvent (approximately 190.0 kg). Methyl-t-butyl ether (MTBE, 50.0 kg) was added to the batch, and the mixture was cooled to approximately 10°C, during which time the product crystallized out. The solids were recovered by centrifugation, washed with n-heptane (20.0 kg), and dried at approximately 40°C to afford the title compound (8.0 kg).

**[00103] 1.2 Preparation of 6,7–Dimethyl–4–(4-nitro–phenoxy)–quinoline**

**[00104]** A reactor was sequentially charged with 4–chloro–6,7–dimethoxy–quinoline (8.0 kg), 4 nitrophenol (7.0 kg), 4 dimethylaminopyridine (0.9 kg), and 2,6 lutidine (40.0 kg). The reactor contents were heated to approximately 147°C. When the reaction was complete (<5% starting material remaining as determined by in process HPLC analysis, approximately 20 hours), the reactor contents were allowed to cool to approximately 25°C. Methanol (26.0 kg) was added, followed by potassium carbonate (3.0 kg) dissolved in water (50.0 kg). The reactor contents were stirred for approximately 2 hours. The resulting solid precipitate was filtered, washed with water (67.0 kg), and dried at 25°C for approximately 12 hours to afford the title compound (4.0 kg).

**[00105] 1.3 Preparation of 4–(6,7 –Dimethoxy–quinoline–4–yloxy)–phenylamine**

**[00106]** A solution containing potassium formate (5.0 kg), formic acid (3.0 kg), and water (16.0 kg) was added to a mixture of 6,7-dimethoxy–4–(4-nitro–phenoxy)–quinoline (4.0 kg), 10% palladium on carbon (50% water wet, 0.4 kg) in tetrahydrofuran (40.0 kg) that had been heated to approximately 60°C. The addition was carried out such that the temperature of the reaction mixture remained approximately 60°C. When the reaction was deemed complete as determined using in-process HPLC analysis (<2% starting material remaining, typically 1 5 hours), the reactor contents were filtered. The filtrate was concentrated by vacuum distillation at approximately 35°C to half of its original volume, which resulted in the precipitation of the product. The product was recovered by filtration, washed with water (12.0 kg), and dried under vacuum at approximately 50°C to afford the title compound (3.0 kg; 97% AUC).

**[00107] 1.4 Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid**

**[00108]** Triethylamine (8.0 kg) was added to a cooled (approximately 4°C) solution of commercially available cyclopropane–1,1–dicarboxylic acid (2 1, 10.0 kg) in THF (63.0 kg) at a rate such that the batch temperature did not exceed 10°C. The solution was stirred for approximately 30 minutes, and then thionyl chloride (9.0 kg) was added, keeping the batch temperature below 10°C. When the addition was complete, a solution of 4–fluoroaniline (9.0 kg) in THF (25.0 kg) was added at a rate such that the batch temperature did not exceed 10°C. The mixture was stirred for approximately 4 hours and then diluted with isopropyl acetate (87.0 kg). This solution was washed sequentially with aqueous sodium hydroxide (2.0 kg dissolved in 50.0 L of water), water (40.0 L), and aqueous sodium chloride (10.0 kg dissolved in 40.0 L of water). The organic solution was concentrated by vacuum distillation followed by the addition of heptane, which resulted in the precipitation of solid. The solid was recovered by centrifugation and then dried at approximately 35°C under vacuum to afford the title compound. (10.0 kg).

**[00109] 1.5 Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride**

**[00110]** Oxalyl chloride (1.0 kg) was added to a solution of 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (2.0 kg) in a mixture of THF (11 kg) and N, N-dimethylformamide (DMF; 0.02 kg) at a rate such that the batch temperature did not exceed 30°C. This solution was used in the next step without further processing.

**[00111] 1.6 Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide**

**[00112]** The solution from the previous step containing 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride was added to a mixture of 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (3.0 kg) and potassium carbonate (4.0 kg) in THF (27.0 kg) and water (13.0 kg) at a rate such that the batch temperature did not exceed 30°C. When the reaction was complete (in typically 10 minutes), water (74.0 kg) was added. The mixture was stirred at 15–30°C for approximately 10 hours, which resulted in the precipitation of the product. The product was recovered by filtration, washed with a premade solution of THF (11.0 kg) and water (24.0 kg), and dried at approximately 65°C under vacuum for approximately 12 hours to afford the title compound (free base, 5.0 kg). $^1$H NMR (400 MHz, $d_6$-DMSO): δ 10.2 (s, 1H), 10.05 (s, 1H), 8.4 (s, 1H), 7.8 (m, 2H), 7.65 (m, 2H), 7.5 (s, 1H), 7.35 (s, 1H), 7.25 (m, 2H), 7.15(m, 2H), 6.4 (s, 1H), 4.0 (d, 6H), 1.5 (s, 4H). LC/MS: M+H= 502.

**[00113] 1.7 Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L) malate salt (Compound (I))**

**[00114]** A solution of (L)-malic acid (2.0 kg) in water (2.0 kg) was added to a solution of Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide free base (1 5, 5.0 kg) in ethanol, maintaining a batch temperature of approximately 25°C. Carbon (0.5 kg) and thiol silica (0.1 kg) were then added, and the resulting mixture was heated to approximately 78°C, at which point water (6.0 kg) was added. The reaction mixture was then filtered, followed by the addition of isopropanol (38.0 kg), and was allowed to cool to approximately 25°C. The product was recovered by filtration and washed with isopropanol (20.0 kg) and dried at approximately 65°C to afford Compound (I) (5.0 kg).

**[00115] Example 2: Preparation of Crystalline Compound (I), Form N-1**

**[00116]** A solution was prepared by adding tetrahydrofuran (12 mL/g-bulk-LR (limiting reagent); 1.20 L) and N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (100 g; 1.00 equiv; 100.00 g) and (L)-malic acid (1.2 equiv (molar); 32.08 g) to a 1 L reactor. Water (0.5317 mL/g-bulk-LR; 53.17 mL) was added and the solution was heated to 60 °C and maintained at that temperature for one hour until the solids were fully dissolved. The solution was passed through a Polish Filter.

**[00117]** At 60 °C, acetonitrile (12 mL/g-bulk-LR; 1.20 L) was added over a period of 8 hours. The solution was held at 60 °C for 10 hours. The solution was then cooled to 20 °C and held for 1 hour. The solids were filtered and washed with acetonitrile (12 mL/g-bulk-LR; 1.20 L). The solids were dried at 60 °C (25 mm Hg) for 6 hours to afford Compound (I), Form N-1 (108 g; 0.85 equiv; 108.00 g; 85.22% yield) as a white crystalline solid.

**[00118] Example 3: Alternate Preparation of Crystalline Compound (I), Form N-1**

**[00119]** A solution was prepared with 190 mL tetrahydrofuran (110 mL), methyl isobutyl ketone, and 29 mL water. Next, 20 mL of this solution were transferred into an amber bottle, and then saturated by adding N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L)-malate until a thick slurry formed, and aging for at least 2 h with stirring at room temperature. The solids were removed by filtration through a Buchner funnel, rendering a clear saturated solution.

**[00120]** Separately, a powder blend was made with known amounts of two batches of Compound (I): (1) 300 mg of batch 1, which contained approximately 41% Compound (I), Form N-1 and 59% Compound (I), Form N-2 by Raman spectroscopy analysis, and (2) 200 mg of batch 2, which had a XPRD pattern similar to Compound (I), Form N-2.

**[00121]** The Compound (I), Form N-1 and Compound (I), Form N-2 powder blend was added into the saturated solution, and the slurry was aged under magnetic stirring at room temperature for 25 days. The slurry was then sampled and filtered through a Buchner funnel to obtain 162 mg of wet cake. The wet cake was dried in a vacuum oven at 45°C to afford 128 mg of crystalline Compound (I) in the N-1 form.

**[00122] Example 4: Preparation of Crystalline Compound (I), Form N-2**

**[00123] 4.1 Preparation of Crystalline Compound (I), Form N-2 Seed Crystals**

**[00124]** A solution was prepared by combining 20 ml of acetone and 300mg of freebase N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide in a 25ml screw capped vial. Next, 0.758ml of a 0.79M (L)-malic acid stock solution was added to the vial with magnetic stirring. The solution was then left stirring for 24hr at ambient temperature. The sample was then suction filtered with 0.45µm PTFE filter cartridge and dried *in vacuo* at ambient temperature overnight.

**[00125] 4.2 Preparation of Crystalline Compound (I), Form N-2.**

**[00126]** To a reactor were added N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (48 g; 1.00 equiv; 48.00 g) and tetrahydrofuran (16.5 mL/g-bulk-LR; 792.00 mL). The water content was adjusted to 1 wt% water. The solution was heated to 60°C. Once dissolved, the solution was passed through a polish filter to provide the first solution.

**[00127]** In a separate reactor, (L)-malic acid (1.2 equiv (molar); 15.40 g) was dissolved into methyl isobutyl ketone (10 mL/g-bulk-LR; 480.00 mL) and tetrahydrofuran (1 mL/g-bulk-LR; 48.00 mL). Next, 50 mL of the (L)-malic acid solution was added to the first solution at 50°C. Seed crystals were added (1%, 480 mg) and the malic acid solution was added at 50°C dropwise via an addition funnel (1.3 ml/min (3 h)). The slurry was held at 50°C for 18 h and then was cooled to 25°C over 30 min. The solids were filtered, and washed with 20% tetrahydrofuran/methyl isobutyl ketone (10V, 480 mL). The solids were dried under vacuum at 60 °C for 5 h to afford Compound (I) (55.7 g; 0.92 equiv; 55.70 g; 91.56% yield) as an off-white crystalline solid.

**[00128] Example 5: Preparation of Crystalline Compound (III), Form N-1**

**[00129]** A one ml aliquot (DL)-malic acid salt of N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, slurried in tetrahydrofuran (THF), was heated to 60 °C on a hot-plate in a half-dram vial. Next,

tetrahydrofuran was added drop-wise until an almost clear solution was obtained. The vial was capped, removed from the hot plate and equilibrated at ambient temperature without agitation. Crystallization was apparent after several hours and the solution was allowed to stand overnight to allow completion. Several droplets of the resulting slurry were placed on a glass slide for microscopic analysis. The crystalline material consisted of many elongated plates ranging up to 60 microns in the longest dimension.

**[00130] Alternate Preparation of Crystalline Compound (III), Form N-1**

**[00131]** To a reactor were added N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (15 g; 1.00 equiv; 15.00 g) and tetrahydrofuran (16.5 mL/g-bulk-LR; 792.00 mL). The water content was adjusted to 1 wt % water. The solution was heated to 60 °C. Once dissolved, the solution was passed through a polish filter to provide the first solution.

**[00132]** In a separate reactor, (DL)-malic acid (1.2 equiv (molar); 4.53 g) was dissolved into methyl isobutyl ketone (8 mL/g-bulk-LR; 120.00 mL) and tetrahydrofuran (1 mL/g-bulk-LR; 15.00 mL). Next, 20 mL of the solution was added to the first solution at 50 °C. The malic acid solution was added at 50 °C dropwise via an addition funnel (1.3 ml/min (3 h)). The slurry was held at 50 °C for 18 h and then was cooled to 25 °C over 30 min. The solids were filtered, and washed with 20 %THF/MIBK (10V, 150 mL). The solids were dried under vacuum at 60 °C for 5 h to afford Compound (III) (15.52 g; 86.68% yield) as an off-white solid.

**[00133] Example 6: Preparation of Amorphous Compound (I)**

**[00134]** A solution was prepared with 5 g of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L)-malate and 250 mL of a 1:1 (v:v) mixture of methanol and dichloromethane. The hazy solution was filtered through a 0.45 micron filter to yield a clear, yellowish solution. The solution was pumped through the spray dryer nozzle at a rate of 12.9 cc/min, and was atomized by nitrogen gas fed at a rate of 10.9 L/min. The temperature at the inlet of the cyclone was set to 65 °C to dry the wet droplets. Dry amorphous powder (1.5 g) was collected (yield = 30%).

## CHARACTERIZATION EXAMPLES

**[00135] I. NMR Spectra in Dimethyl Sulfoxide Solution**

**[00136] I.1 Compound (I), Form N-1**

**[00137]** $^1$H NMR (400 MHz, $d_6$-DMSO): δ 1.48 (s, 1 H), 2.42-2.48 (m, 1 H), 2.60-2.65 (m, 1 H), 3.93-3.96 (m, 6 H), 4.25-4.30 (dd, 1 H, $J$ = 5, 8 Hz), 6.44 (d, 1H, $J$ = 5 Hz, 1 H), 7.12-7.19 (m, 2 H), 7.22-7.26 (m, 2 H), 7.40 (s, 1 H), 7.51 (s, 1 H), 7.63-7.68 (m, 2 H), 7.76-7.80 (m, 2 H), 8.46-8.49 (m, 1 H), 10.08 (s, 1 H), 10.21 (s, 1 H).

**[00138]** $^{13}$C NMR($d_6$-DMSO): 15.36, 31.55, 55.64, 55.67, 66.91, 99.03, 102.95, 107.66, 114.89, 115.07, 115.11, 121.17, 122.11, 122.32, 122.39, 135.15, 136.41, 146.25, 148.7, 149.28,

149.38, 152.54, 157.03, 159.42, 160.02, 168.07, 171.83, 174.68.

**[00139] I.2 Compound (I), Form N-2**

**[00140]** $^1$H NMR (400 MHz, $d_6$-DMSO): δ 1.48 (s, 1 H), 2.42-2.48 (m, 1 H), 2.60-2.65 (m, 1 H), 3.93-3.96 (m, 6 H), 4.25-4.30 (dd, 1 H, $J$ = 5, 8 Hz), 6.44 (d, $J$ = 5 Hz, 1 H), 7.12-7.19 (m, 2 H), 7.22-7.26 (m, 2 H), 7.40 (s, 1 H), 7.51 (s, 1 H), 7.63-7.68 (m, 2 H), 7.76-7.80 (m, 2 H), 8.46-8.49 (m, 1 H), 10.08 (s, 1 H), 10.21 (s, 1 H).

**[00141]** $^{13}$C NMR($d_6$-DMSO): 15.36, 31.55, 55.64, 55.67, 66.91, 99.03, 102.95, 107.66, 114.89, 115.07, 115.11, 121.17, 122.11, 122.32, 122.39, 135.15, 136.41, 146.25, 148.7, 149.28, 149.38, 152.54, 157.03, 159.42, 160.02, 168.07, 171.83, 174.68.

**[00142] I.3 Compound (III), Form N-1**

**[00143]** $^1$H NMR (400 MHz, $d_6$-DMSO): δ 1.48 (s, 1 H), 2.42-2.48 (m, 1 H), 2.60-2.65 (m, 1 H), 3.93-3.96 (m, 6 H), 4.25-4.30 (dd, 1 H, $J$ = 5, 8 Hz), 6.44 (d, $J$ = 5 Hz, 1 H), 7.12-7.19 (m, 2 H), 7.22-7.26 (m, 2 H), 7.40 (s, 1 H), 7.51 (s, 1 H), 7.63-7.68 (m, 2 H), 7.76-7.80 (m, 2 H), 8.46-8.49 (m, 1 H), 10.08 (s, 1 H), 10.21 (s, 1 H).

**[00144]** $^{13}$C NMR($d_6$-DMSO): 15.36, 31.55, 55.64, 55.67, 66.91, 99.03, 102.95, 107.66, 114.89, 115.07, 115.11, 121.17, 122.11, 122.32, 122.39, 135.15, 136.41, 146.25, 148.7, 149.28, 149.38, 152.54, 157.03, 159.42, 160.02, 168.07, 171.83, 174.68.

**[00145] Characterization of Solid State Forms of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, malate**

**[00146] II. Powder X-Ray Diffraction (XRPD) Studies**

**[00147]** X-Ray Powder Diffraction (XRPD) patterns were collected on a Bruker AXS C2 GADDS diffractometer equipped with an automated XYZ stage, laser video microscope for auto-sample positioning and a HiStar 2-dimensional area detector. The radiation source used was copper (Cu Kα = 1.5406 Å), wherein the voltage was set at 40 kV and the current was set at 40 mA, X-ray optics consists of a single Göbel multilayer mirror coupled with a pinhole collimator of 0.3 mm. The beam divergence, *i.e.* the effective size of the X-ray beam on the

sample, was approximately 4 mm. A θ-θ continuous scan mode was employed with a sample - detector distance of 20 cm which gives an effective 2θ range of 3.2 °-29.8 °. Samples run under ambient conditions (from about 18 °C to about 25 °C) were prepared as flat plate specimens using powder as received without grinding. Approximately 1-2 mg of the sample was lightly pressed on a glass slide to obtain a flat surface. Typically the sample would be exposed to the X-ray beam for 120 seconds. Beam divergence (*i.e.*, effective size of X-ray spot, gives a value of approximately 4mm. Alternatively, the powder samples were placed in sealed glass capillaries of 1mm or less in diameter; the capillary was rotated during data collection at a sample-detector distance of 15 cm. Data were collected for $3 \leq 2\theta \leq 35°$ with a sample exposure time of at least 2000 seconds. The resulting two-dimensional diffraction arcs were integrated to create a traditional 1-dimensional XRPD pattern with a step size of 0.02 °2θ in the range of 3 to 35 °2θ ± 0.2 °2θ. The software used for data collection was GADDS for WNT 4.1.16 and the data were analyzed and presented using Diffrac Plus EVA v 9.0.0.2 or v 13.0.0.2.

**[00148] II.1 Compound (I), Form N-1**

**[00149]** Figure 1 shows the experimental XRPD pattern of crystalline Compound (I), Form N-1 acquired at room temperature (about 25 °C). A list of the peaks are shown in Table 2, above. The 2θ values at 19.4, 21.5, 22.8, 25.1, and 27.6 (± 0.2 °2θ) are useful for characterizing crystalline Compound (I), Form N-1. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-1.

**[00150] II.2 Compound (I), Form N-2**

**[00151]** Figure 8 shows the experimental XRPD pattern of crystalline Compound (I), Form N-2 acquired at room temperature (about 25 °C). A list of the peaks are shown in Table 2, above. The 2θ values at 20.9 and 21.9 (± 0.2 °2θ) are useful for characterizing crystalline Compound (I), Form N-2. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-2.

**[00152] II.3 Compound (III), Form N-1**

**[00153]** Figure 15 shows the experimental and the simulated XRPD pattern of crystalline Compound (III), Form N-1, acquired at 25°C using a spinning capillary sample. A list of the peaks are shown in Table 2, above. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (III), Form N-2.

**[00154] II.4 Amorphous Compound (I)**

**[00155]** Figure 22 shows the experimental XRPD pattern of amorphous Compound (I) acquired at room temperature (about 25°C). The spectra is characterized a broad peak and the absence of sharp peaks, which is consistent with an amorphous material.

**[00156] III. Single Crystal X-Ray Study for Compound (III), Form N-1**

**[00157]** Data were collected on a Bruker-Nonius CAD4 serial diffractometer. Unit cell parameters were obtained through least-squares analysis of the experimental diffractometer settings of 25 high-angle reflections. Intensities were measured using Cu Kα radiation (λ = 1.5418 Å) at a constant temperature with the θ-2θ variable scan technique and were corrected only for Lorentz-polarization factors. Background counts were collected at the extremes of the scan for half of the time of the scan. Alternately, single crystal data were collected on a Bruker-Nonius Kappa CCD 2000 system using Cu Kα radiation (λ = 1.5418 Å). Indexing and processing of the measured intensity data were carried out with the HKL2000 software package (Otwinowski, Z. & Minor, W. (1997) in *Macromolecular Crystallography,* eds. Carter, W.C. Jr & Sweet, R.M. (Academic, NY), Vol. 276, pp.307-326) in the Collect program suite (Collect Data collection and processing user interface: Collect: Data collection software, R. Hooft, Nonius B.V., 1998). Alternately, single crystal data were collected on a Bruker-AXS APEX2 CCD system using Cu Kα radiation (λ = 1.5418 Å). Indexing and processing of the measured intensity data were carried out with the APEX2 software package/program suite (APEX2 Data collection and processing user interface: APEX2 User Manual, v1.27). When indicated, crystals were cooled in the cold stream of an Oxford cryo system (Oxford Cryosystems Cryostream cooler: J. Cosier and A.M. Glazer, J. Appl. Cryst., 1986, 19, 105) during data collection.

**[00158]** The structures were solved by direct methods and refined on the basis of observed reflections using either the SDP software package (SDP, Structure Determination Package, Enraf-Nonius, Bohemia NY 11716. Scattering factors, including *f'* and *f''*, in the SDP software were taken from the" International Tables for Crystallography", Kynoch Press, Birmingham, England, 1974; Vol IV, Tables 2.2A and 2.3.1) with minor local modifications or the crystallographic packages MAXUS (maXus solution and refinement software suite: S. Mackay, C.J. Gilmore, C. Edwards, M. Tremayne, N. Stewart, K. Shankland. maXus: a computer program for the solution and refinement of crystal structures from diffraction data) or SHELXTL (APEX2 Data collection and processing user interface: APEX2 User Manual, v1.27).

**[00159]** The derived atomic parameters (coordinates and temperature factors) were refined through full matrix least-squares. The function minimized in the refinements was $\Sigma_w(|F_o| -$

$|F_c|)^2$. R is defined as $\Sigma \, ||F_o| - |F_c||/\Sigma \, |F_o|$ while $R_w = [\Sigma_w( |F_o| - |F_c|)^2/\Sigma_w \, |F_o|^2]^{1/2}$ where w is an appropriate weighting function based on errors in the observed intensities. Difference maps were examined at all stages of refinement. Hydrogens were introduced in idealized positions with isotropic temperature factors, but no hydrogen parameters were varied.

**[00160]** "Hybrid" simulated powder X-ray patterns were generated as described in the literature (Yin. S.; Scaringe, R. P.; DiMarco, J.; Galella, M. and Gougoutas, J. Z., *American Pharmaceutical Review*, 2003, 6,2, 80). The room temperature cell parameters were obtained by performing a cell refinement using the CellRefine.xls program. Input to the program includes the 2-theta position of *ca.* 10 reflections, obtained from the experimental room temperature powder pattern; the corresponding Miller indices, *hkl*, were assigned based on the single-crystal data collected at low temperature. A new (hybrid) XRPD was calculated (by either of the software programs, Alex or LatticeView) by inserting the molecular structure determined at low temperature into the room temperature cell obtained in the first step of the procedure. The molecules are inserted in a manner that retains the size and shape of the molecule and the position of the molecules with respect to the cell origin, but, allows intermolecular distances to expand with the cell.

**[00161]** A single crystal, measuring 40 x 30 x 10 microns, was selected from the slurry of crystals described in Example 5 for single crystal diffraction analysis. The selected crystal was affixed to a thin glass fiber with a small amount of a light grease, and mounted at room temperature on a Bruker ApexII single crystal diffractometer equipped with a rotating copper anode.

**[00162]** Crystalline Compound (III), From N-1 is characterized by unit cell parameters approximately equal to those reported in Table 4. The unit cell parameters were measured at a temperature of about 25°C.

**Table 4**

| |
|---|
| a = 14.60 Å |
| b = 5.20 Å |
| c = 39.09 Å |
| α = 90.0° |
| β = 90.4° |
| γ = 90.0° |
| Space group: $P2_1/n$ |
| Molecules of Compound (I)/unit cell: 4 |
| Volume = 2969 $Å^3$ |

**[00163]** Structure solution and refinement were routine in the monoclinic space group, $P2_1/n$, with four formula units in the unit cell. The structure contains cations of N-(4-{[6,7-

bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, protonated at the quinoline nitrogen atom, and singly ionized malic acid anions, in a 1:1 ratio. Further, the crystal contained a 1:1 ratio of (L)-malic acid ions to (D)-malic acid ions. Table 5

fractional atomic coordinates for Compound (III), Form N-1 calculated at a temperature of about 25°C.

**[00164]** Based on the single crystal X-ray data, crystalline Compound (III), Form N-1 may be characterized by a simulated powder x-ray diffraction (XRPD) pattern substantially in accordance with the simulated pattern shown in Figure 15 and/or by an observed XRPD pattern substantially in accordance with the experimental pattern shown in Figure 15.

**Table 5**

**Fractional Atomic Coordinates for Compound (III), Form N-1**

**Calculated at a Temperature of about 25°C**

| Atom | X | Y | Z | Atom | X | Y | Z |
|---|---|---|---|---|---|---|---|
| O1 | 0.30601 | -0.52166 | 0.22875 | C40 | 0.25712 | -0.35516 | 0.17574 |
| O2 | 0.29518 | 0.12504 | 0.09391 | C41 | 0.63543 | 0.13842 | 0.29041 |
| O3 | 0.19041 | -0.53232 | 0.18147 | C42 | 0.22703 | 0.46640 | 0.06306 |
| F5 | -0.07307 | 2.12170 | -0.08811 | C43 | 0.34559 | 1.01717 | -0.10021 |
| O6 | 0.18186 | 1.20500 | -0.03241 | C44 | 0.39312 | 1.20834 | -0.08137 |
| O7 | 0.57137 | 0.22739 | 0.23473 | C45 | 0.48224 | 0.32340 | 0.15059 |
| O8 | 0.58700 | -0.17911 | 0.24998 | O46 | 0.77400 | 0.04784 | 0.34652 |
| O9 | 0.41742 | 0.76377 | -0.04319 | C47 | 0.79349 | 0.09920 | 0.31966 |
| N10 | 0.28649 | 0.82210 | -0.01420 | H10 | 0.22646 | 0.91057 | -0.01479 |
| O11 | 0.87391 | 0.22086 | 0.31241 | H16 | 0.24790 | 1.42164 | -0.10317 |
| N12 | 0.46887 | 0.17029 | 0.17613 | H19 | -0.04176 | 1.82973 | -0.03893 |
| C13 | 0.29647 | 0.64886 | 0.01247 | H20 | 0.16347 | 1.73025 | -0.13083 |
| C14 | 0.31416 | 1.08187 | -0.06304 | H22 | 0.43179 | -0.17902 | 0.22447 |
| C15 | 0.33900 | -0.02207 | 0.14761 | H23 | 0.17093 | 0.73524 | 0.03244 |
| N16 | 0.20651 | 1.40640 | -0.08267 | H27 | 0.21953 | -0.24212 | 0.12962 |
| C17 | 0.40079 | -0.01723 | 0.17602 | H29 | 0.07954 | 1.50390 | -0.03492 |
| C18 | 0.29743 | 0.29956 | 0.06604 | H30 | 0.04671 | 2.05817 | -0.13354 |
| C19 | 0.00418 | 1.80556 | -0.05680 | H33 | 0.41851 | 0.16255 | 0.04395 |
| C20 | 0.11925 | 1.73626 | -0.11097 | H34 | 0.43433 | 0.41859 | 0.10106 |
| C21 | 0.22556 | 1.24019 | -0.05791 | H38 | 0.41440 | 0.45648 | -0.00227 |
| C22 | 0.39150 | -0.17467 | 0.20389 | H41 | 0.61062 | 0.02238 | 0.31086 |
| C23 | 0.22558 | 0.63870 | 0.03619 | H42 | 0.17752 | 0.45794 | 0.07911 |
| O24 | 0.62714 | 0.39565 | 0.29760 | H45 | 0.53033 | 0.44239 | 0.15049 |
| C25 | 0.34591 | 0.87438 | -0.03961 | H31a | 0.76754 | 0.12071 | 0.26693 |
| C26 | 0.36467 | -0.51389 | 0.25773 | H31b | 0.74726 | -0.15247 | 0.28137 |
| C27 | 0.26562 | -0.20277 | 0.14859 | H43a | 0.30237 | 1.06909 | -0.12187 |
| C28 | 0.35380 | 0.15272 | 0.12054 | H43b | 0.36868 | 0.85693 | -0.10836 |
| C29 | 0.07365 | 1.60604 | -0.05443 | H44a | 0.45563 | 1.18725 | -0.07495 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| C30 | 0.04897 | 1.92890 | -0.11212 | H44b | 0.38932 | 1.39942 | -0.08846 |
| C31 | 0.73841 | 0.04517 | 0.28641 | H26a | 0.35958 | -0.37184 | 0.27147 |
| C32 | 0.32089 | -0.35160 | 0.20385 | H26b | 0.42813 | -0.55605 | 0.25348 |
| C33 | 0.36641 | 0.29052 | 0.04302 | H26c | 0.34954 | -0.66814 | 0.27571 |
| C34 | 0.42458 | 0.32272 | 0.12143 | H35a | 0.08189 | -0.39941 | 0.15398 |
| C35 | 0.11723 | -0.54030 | 0.15742 | H35b | 0.06671 | -0.68838 | 0.16269 |
| C36 | 0.12933 | 1.59042 | -0.08228 | H35c | 0.13276 | -0.61095 | 0.13323 |
| C37 | -0.00344 | 1.93494 | -0.08547 | H11 | 0.88836 | 0.21926 | 0.28968 |
| C38 | 0.36439 | 0.47245 | 0.01586 | H12 | 0.50720 | 0.16494 | 0.19477 |
| C39 | 0.59040 | 0.05797 | 0.25625 | H24 | 0.61522 | 0.45898 | 0.27789 |

**[00165] IV. Solid State Nuclear Magnetic Resonance (SSNMR)**

**[00166]** All solid-state C-13 NMR measurements were made with a Bruker DSX-400, 400 MHz NMR spectrometer. High resolution spectra were obtained using high-power proton decoupling and the TPPM pulse sequence and ramp amplitude cross-polarization (RAMP-CP) with magic-angle spinning (MAS) at approximately 12 kHz (A.E. Bennett et al, *J. Chem. Phys.*,1995, 103, 6951),(G. Metz, X. Wu and S.O. Smith, *J. Magn. Reson. A*,. 1994, 110, 219-227). Approximately 70 mg of sample, packed into a canister-design zirconia rotor was used for each experiment. Chemical shifts (δ) were referenced to external adamantane with the high frequency resonance being set to 38.56 ppm (W.L. Earl and D.L. VanderHart, *J. Magn. Reson.*, 1982, 48, 35-54).

**[00167] IV.1 Compound (I), Form N-1**

**[00168]** The solid state $^{13}C$ NMR spectrum of crystalline Compound (I), Form N-1 is shown in Figure 2. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-1.

**[00169]** SS $^{13}C$ NMR Peaks: 18.1, 20.6, 26.0, 42.9, 44.5, 54.4, 55.4, 56.1, 70.4, 99.4, 100.1, 100.6, 114.4, 114.9, 115.8, 119.6, 120.1, 121.6, 123.2, 124.1, 136.4, 138.6, 140.6, 145.4, 150.1, 150.9, 156.2, 157.4, 159.4, 164.9, 167.1, 170.8, 175.7, and 182.1 ppm, ± 0.2 ppm.

**[00170]** Figure 3 shows the solid state $^{15}N$ NMR spectrum of crystalline Compound (I), Form N-1. The spectrum shows peaks at 118.6, 119.6, 120.7, 134.8, 167.1, 176.0, and 180 ppm, ± 0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-1.

**[00171]** Figure 4 shows the solid state $^{19}F$ NMR spectrum of crystalline Compound (I), Form N-1. The spectrum shows a peak at -121.6, -120.8, and -118.0 ppm, ± 0.2 ppm.

**[00172] IV.2 Compound (I), Form N-2**

**[00173]** The solid state $^{13}C$ NMR spectrum of crystalline Compound (I), Form N-2 is shown in Figure 9. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-2.

**[00174]** SS $^{13}C$ NMR Peaks: 20.5, 21.8, 23.0, 25.9, 26.4, 38.0, 41.7, 54.7, 55.8, 56.2, 56.6, 69.7, 99.4, 100.0, 100.4, 100.8, 102.3, 114.5, 115.5, 116.7, 119.0, 120.2, 121.1, 121.2, 122.1, 122.9, 124.5, 136.0, 137.3, 138.1, 138.9, 139.5, 140.2, 144.9, 145.7, 146.1, 150.7, 156.7, 157.7, 159.6, 159.7, 165.1, 167.0, 168.0, 171.5, 177.3, 179.3, 180.0, and 180.3 ppm, ± 0.2 ppm.

**[00175]** Figure 10 shows the solid state $^{15}N$ NMR spectrum of crystalline Compound (I), Form N-2. The spectrum shows peaks at 118.5, 120.8, 135.1, 167.3, and 180.1 ppm, ± 0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-2.

**[00176]** Figure 11 shows the solid state $^{19}F$ NMR spectrum of crystalline Compound (I), Form N-2. The spectrum shows peaks at -121.0 and -119.1 ppm, ± 0.2 ppm. Those peaks, individually or together, may be sufficient to characterize crystalline Compound (I), Form N-2.

**[00177] IV.3 Compound (III), Form N-1**

**[00178]** The solid state $^{13}C$ NMR spectrum of crystalline Compound (III), Form N-1 is shown in Figure 16. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (III), Form N-1.

**[00179]** SS $^{13}C$ NMR Peaks: 20.8, 26.2, 44.8, 55.7, 70.7, 100.4, 101.0, 114.7, 115.2, 116.0, 119.7, 120.4, 121.6, 124.4, 136.9, 138.9, 141.1, 145.7, 150.3, 156.5, 157.6, 159.6, 165.2, 167.4, 171.2, 176.3, and 182.1 ppm, ± 0.2 ppm.

**[00180]** Figure 17 shows the solid state $^{15}N$ NMR spectrum of crystalline Compound (III), Form N-1. The spectrum shows peaks at 119.6, 134.7, and 175.5 ppm, ± 0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (III), Form N-1.

**[00181]** Figure 18 shows the solid state $^{19}F$ NMR spectrum of crystalline Compound (III), Form N-1. The spectrum shows a peak at -120.5 ppm, ± 0.2 ppm.

**[00182] IV.4 Compound (I), Amorphous**

**[00183]** Figure 23 shows the solid state $^{13}C$ NMR spectrum of amorphous Compound (I). The entire list of peaks, or a subset thereof, may be sufficient to characterize amorphous Compound (I).

**[00184]** SS $^{13}C$ NMR Peaks (ppm): 12.2, 17.8, 20.3, 21.8, 27.2, 33.8, 41.7, 56.9, 69.9, 99.9, 102.2, 115.6, 122.2, 134.4, 137.8, 142.9, 149.1, 150.9, 157.3, 159.7, 167.0, 171.7, 173.1, 177.4, and 179.5 ppm, ± 0.2 ppm.

**[00185]** Figure 24 shows the solid state $^{15}N$ NMR spectrum of amorphous Compound (I). The spectrum shows peaks at 120.8, 131.8, 174.7, and 178.3 ppm, ± 0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize amorphous Compound (I).

**[00186]** Figure 25 shows the solid state $^{19}F$ NMR spectrum of amorphous Compound (I). The spectrum shows a peak at -118.9 ppm, ± 0.2 ppm.

**[00187] V. Thermal Characterization Measurements**

**[00188] Thermal Gravimetric Analysis (TGA)**

**[00189]** The TGA measurements were performed in a TA Instruments™ model Q500 or 2950, employing an open pan setup. The sample (about 10-30 mg) was placed in a platinum pan previously tared. The weight of the sample was measured accurately and recorded to a thousand of a milligram by the instrument. The furnace was purged with nitrogen gas at 100mL/min. Data were collected between room temperature and 300°C at 10°C/min heating rate.

**[00190] Differential Scanning Calorimetry (DSC) Analysis**

**[00191]** DSC measurements were performed in a TA Instruments™ model Q2000, Q1000 or 2920, employing an open pan setup. The sample (about 2-6 mg) was weighed in an aluminum pan and recorded accurately recorded to a hundredth of a milligram, and transferred to the DSC. The instrument was purged with nitrogen gas at 50mL/min. Data were collected between room temperature and 300°C at 10°C/min heating rate. The plot was made with the endothermic peaks pointing down.

**[00192] V.1 Compound (I), Form N-1**

**[00193]** Figure 5 shows the TGA thermogram for crystalline Compound (I), Form N-1, which shows a weight loss of approximately 0.4 weight % at a temperature of 170°C.

**[00194]** Figure 6 shows the DSC thermogram for crystalline Compound (I), Form N-1, which showed a melting point of approximately 187°C.

**[00195] V.2 Compound (I), Form N-2**

**[00196]** Figure 12 shows the TGA thermogram for crystalline Compound (I), Form N-2, which shows a weight loss of approximately 0.1 weight % at a temperature of 170°C.

**[00197]** Figure 13 shows the DSC thermogram for crystalline Compound (I), Form N-2, which showed a melting point of approximately 186°C.

**[00198] V.3 Compound (III), Form N-1**

**[00199]** Figure 19 shows the TGA thermogram for crystalline Compound (III), Form N-1, which shows a weight loss of approximately 0.2 weight % at a temperature of 170°C.

**[00200]** Figure 20 shows the DSC thermogram for crystalline Compound (III), Form N-1, which showed a melting point of approximately 186°C.

**[00201] V.2 Compound (I), Amorphous**

**[00202]** Figure 26 shows the DSC for crystalline Compound (I).

**[00203] VI. Moisture Vapor Isotherm Measurements**

**[00204]** Moisture sorption isotherms were collected in a VTI SGA-100 Symmetric Vapor Analyzer using approximately 10 mg of sample. The sample was dried at 60°C until the loss rate of 0.0005 wt %/min was obtained for 10 minutes. The sample was tested at 25°C and 3 or 4, 5, 15, 25, 35, 45, 50, 65, 75, 85, and 95% RH. Equilibration at each RH was reached when the rate of 0.0003 wt%/min for 35 minutes was achieved or a maximum of 600 minutes.

**[00205] VI.1 Compound (I), Form N-1**

**[00206]** Figure 7 shows the moisture vapor isotherm of crystalline Compound (I), Form N-1.

**[00207] VI.2 Compound (I), Form N-1**

**[00208]** Figure 14 shows the moisture vapor isotherm of crystalline Compound (I), Form N-2.

**[00209] VI.3 Compound (III), Form N-1**

**[00210]** Figure 21 shows the moisture vapor isotherm of crystalline Compound (III), Form N-1.

**[00211] VI.4 Compound (I), Amorphous**

**[00212]** Figure 27 shows the moisture vapor isotherm of amorphous Compound (I).

**[00213]** The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with

reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

## Claims

What is claimed is:

1. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt.

2. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 1, wherein said salt is the (DL)-malate salt.

3. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 1, wherein said salt is a (L)-malate salt or (D)-malate salt.

4. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 3, wherein said salt is the (L)-malate salt.

5. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 3, wherein said salt is the (D)-malate salt.

6. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to any one of claims 3 to 5, wherein said salt is crystalline.

7. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 6, wherein said salt is in crystalline Form N-1 and said Form N-1 is characterized by at least one of the following:
(i) a solid state $^{13}C$ NMR spectrum with four or more peaks selected from 18.1, 42.9, 44.5, 70.4, 123.2, 156.2, 170.8, 175.7, and 182.1, ± 0.2 ppm;
(ii) a powder x-ray diffraction pattern (CuKα λ=1.5418Å) comprising four or more 2θ values selected from: 12.8±0.2 °2θ, 13.5±0.2 °2θ, 16.9±0.2 °2θ, 19.4±0.2 °2θ, 21.5±0.2 °2θ, 22.8±0.2 °2θ, 25.1±0.2 °2θ, 27.6±0.2 °2θ, wherein measurement of the crystalline form is at room temperature; and/or

(iii) an x-ray powder diffraction (XRPD) pattern substantially in accordance with the pattern shown in Figure 1.

8. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 7, wherein said salt is least 90 weight % Form N-1, based on weight of said salt.

9. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 6, wherein said salt is in crystalline Form N-2 and said Form N-2 is characterized by at least one of the following:
(i) a solid state $^{13}C$ NMR spectrum with four or more peaks selected from 23.0, 25.9, 38.0, 41.7, 69.7, 102.0, 122.5, 177.3, 179.3, 180.0, and 180.3, ± 0.2 ppm;
(ii) a powder x-ray diffraction pattern (CuKα λ=1.5418Å) comprising 2θ values at 20.9±0.2 °2θ and 21.9±0.2 °2θ, and two or more 2θ values selected from: 6.4±0.2 °2θ, 9.1±0.2 °2θ, 12.0±0.2 °2θ, 12.8±0.2, 13.7±0.2, 17.1±0.2, 22.6±0.2, 23.7±0.2, wherein measurement of the crystalline form is at room temperature; and/or
(iii) an x-ray powder diffraction (XRPD) pattern substantially in accordance with the pattern shown in Figure 8.

10. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 9, wherein said salt is least 90 weight % Form N-2, based on weight of said salt.

11. A pharmaceutical composition comprising the N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to any one of claim 4-10; and a pharmaceutically acceptable excipient.

12. Use of the N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to any one of claims 3-10, for the manufacture of a medicament for the treatment of cancer.

13. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to any one of claims 3-10, for use in therapy in treating cancer.

14. The crystalline form of the (L)-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide according to any one of claims 6-10, for use as a medicament for treating thyroid cancer in a subject.

15. The crystalline form of the (L)-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide according to any one of claims 6-10, for use as a medicament for treating glioblastoma in a subject.

**Figure 1**

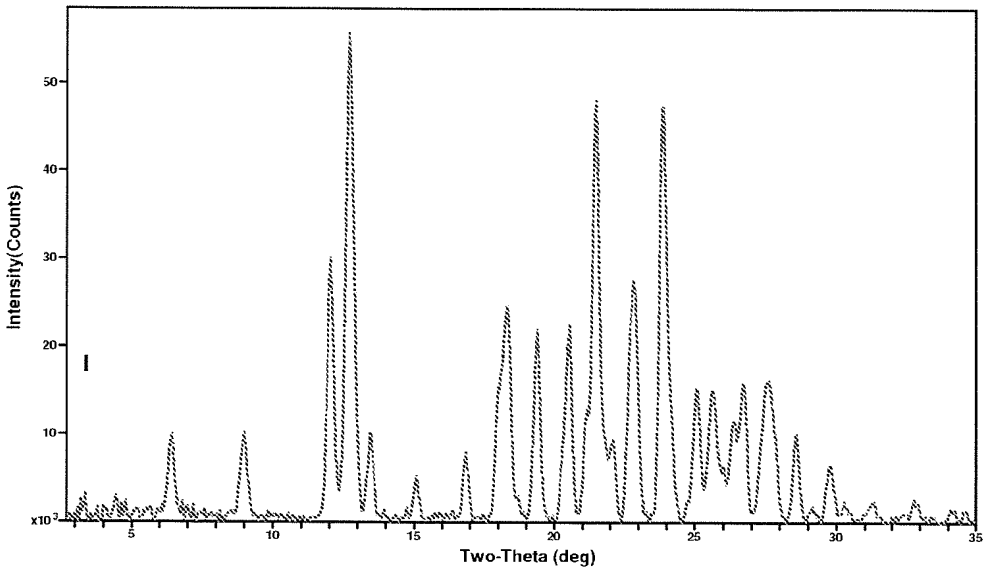

Intensity(Counts)
x10^3
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40
30
20
10
I
5
10
15
20
25
30
35
Two-Theta (deg)

**Figure 2**

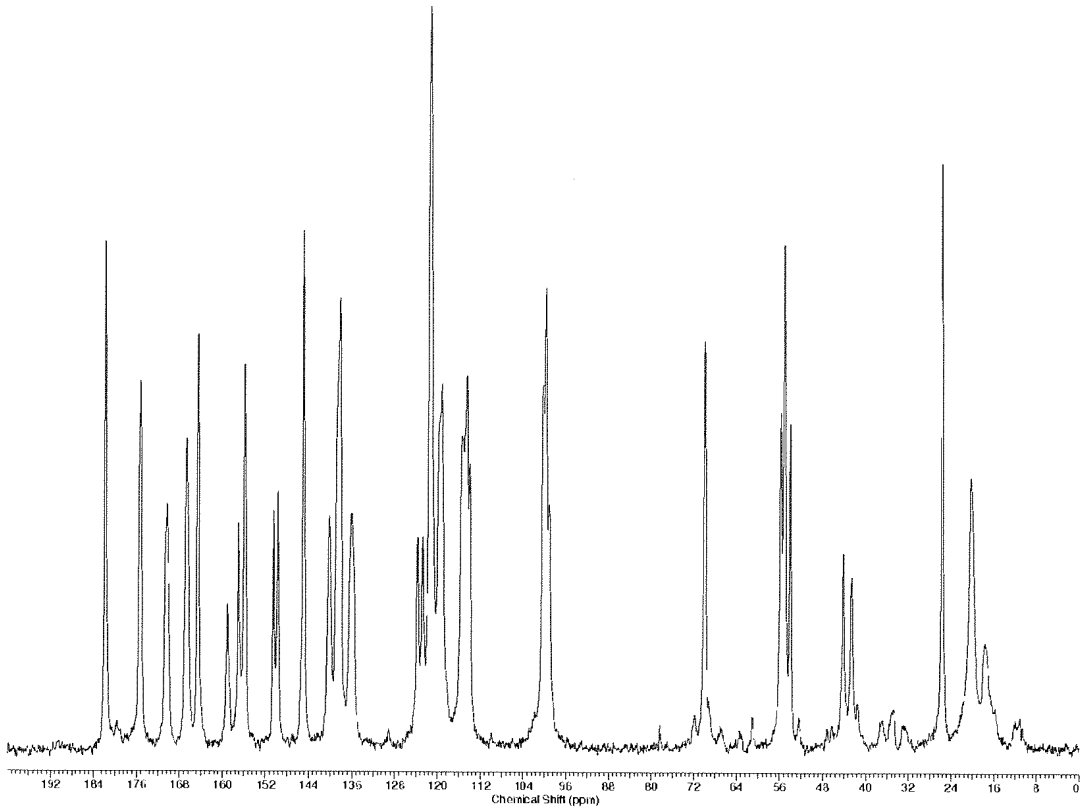

192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

**Figure 3**

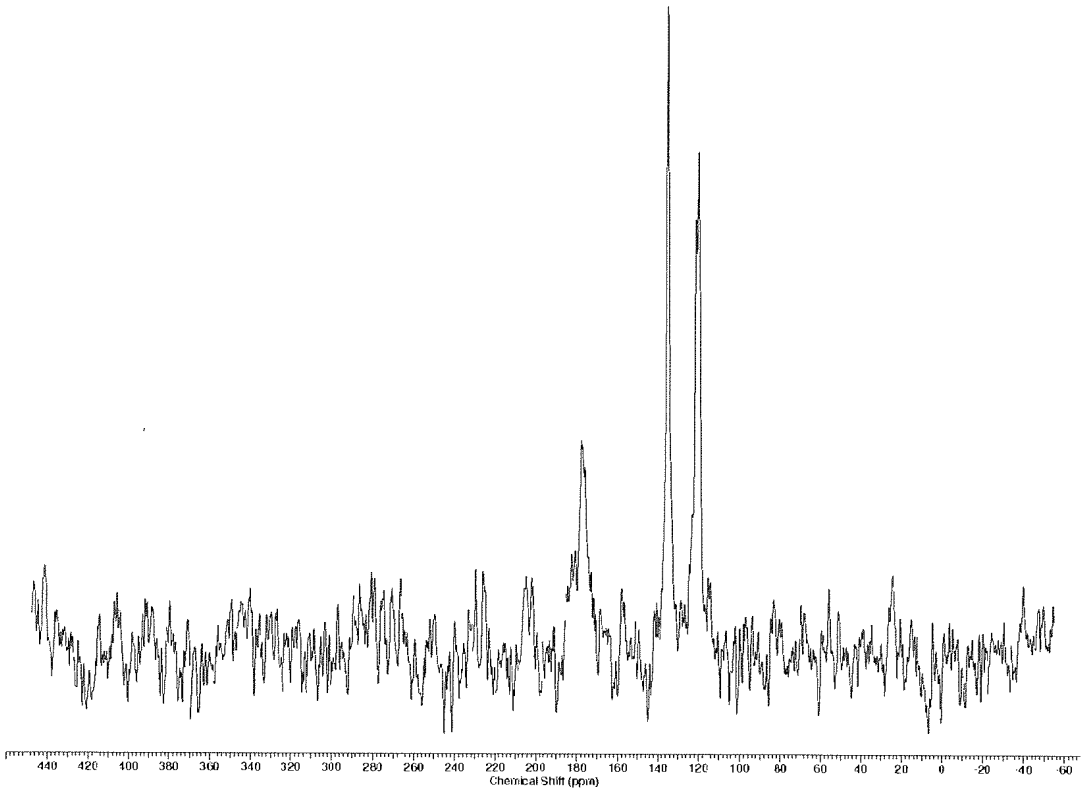

440 420 400 380 360 340 320 300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 -20 -40 -60
Chemical Shift (ppm)

**Figure 4**

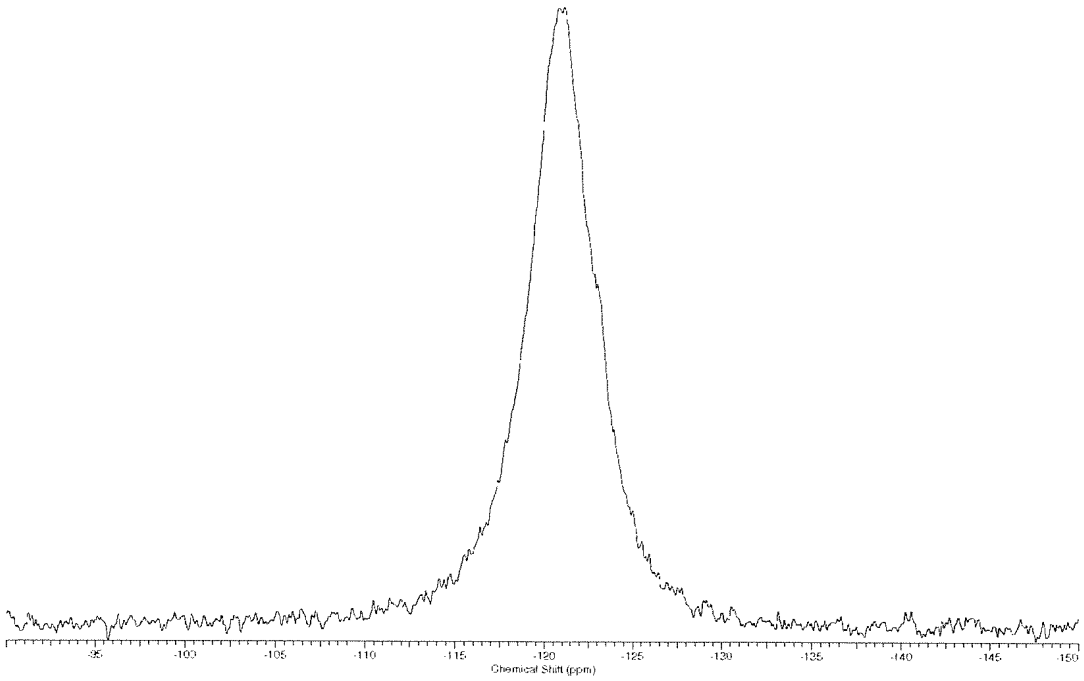

-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
Chemical Shift (ppm)

**Figure 5**

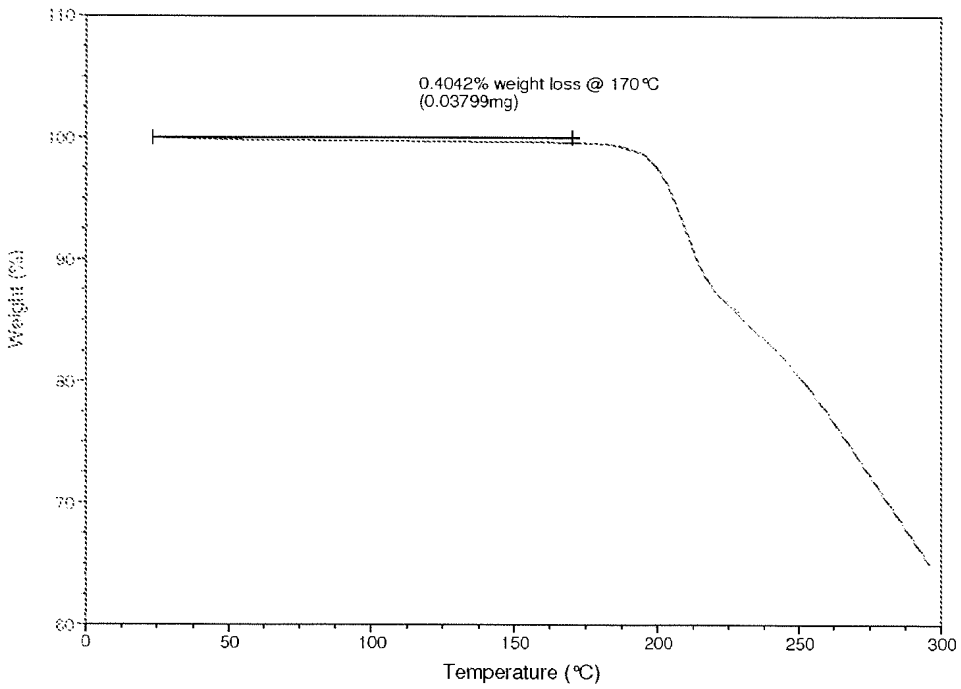

TGA
0.4042% weight loss @ 170°C
(0.03799mg)
Weight (%)
110
100
90
80
70
60
0
50
100
150
200
250
300
Temperature (°C)

**Figure 6**

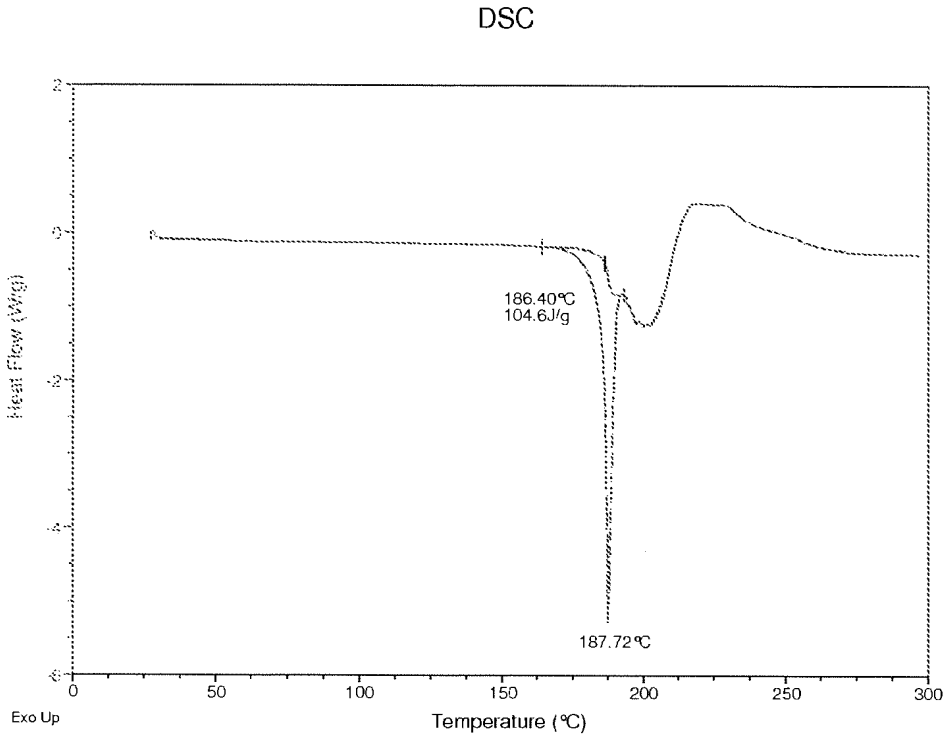
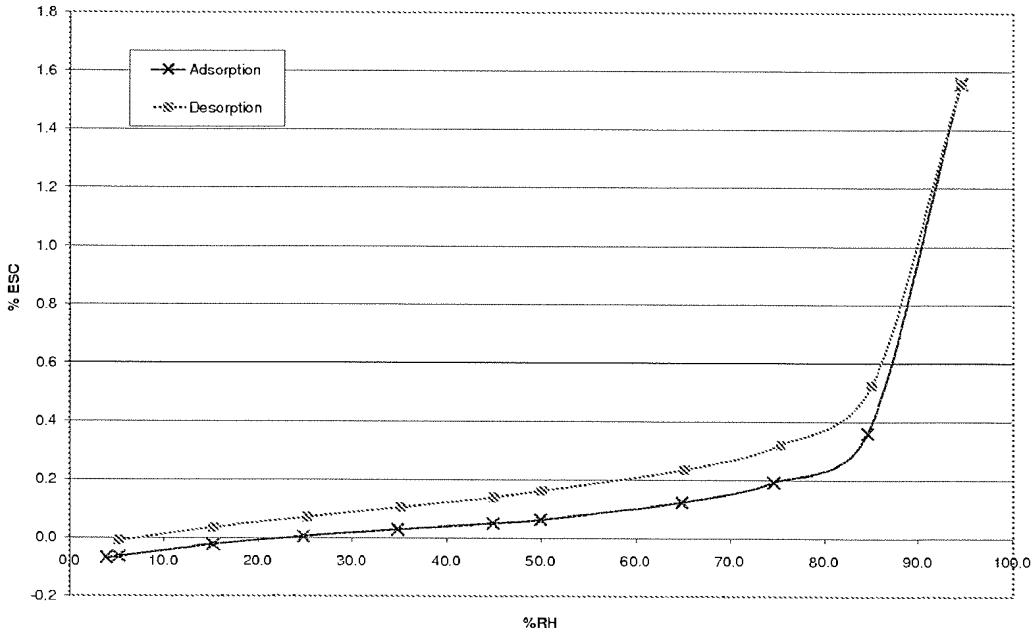

DSC
Heat Flow (W/g)
186.40℃
104.6J/g
187.72℃
0
50
100
150
200
250
300
Exo Up
Temperature (℃)

**Figure 7**




**Moisture Sorption of Compound (I), Form N-1**

**Figure 8**

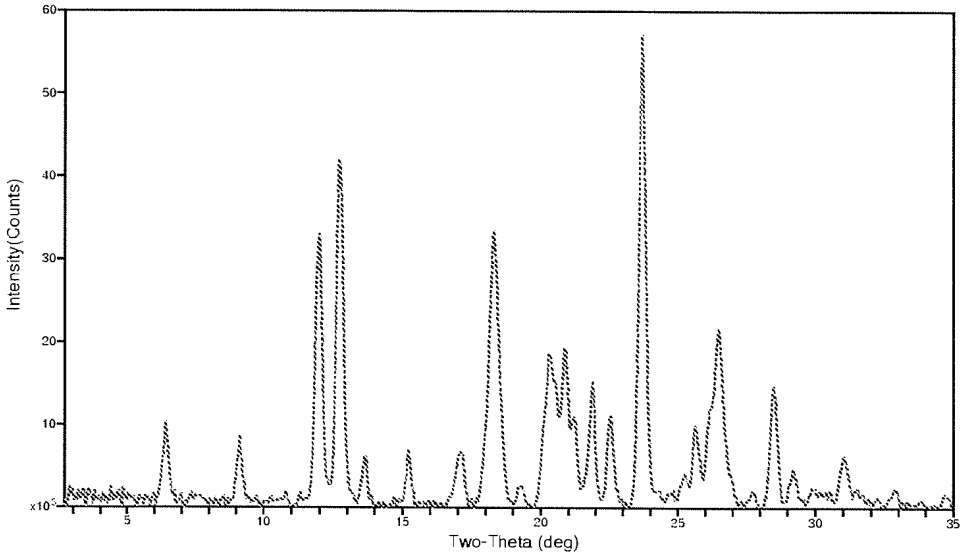

Intensity(Counts)
x10^3
60
50
40
30
20
10
5
10
15
20
25
30
35
Two-Theta (deg)

**Figure 9**

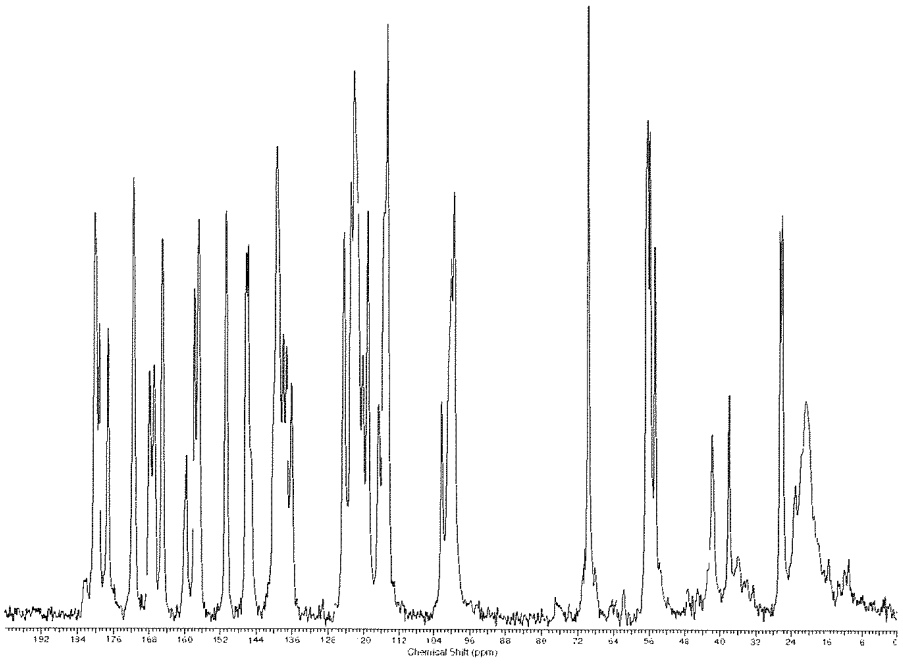

192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

**Figure 10**

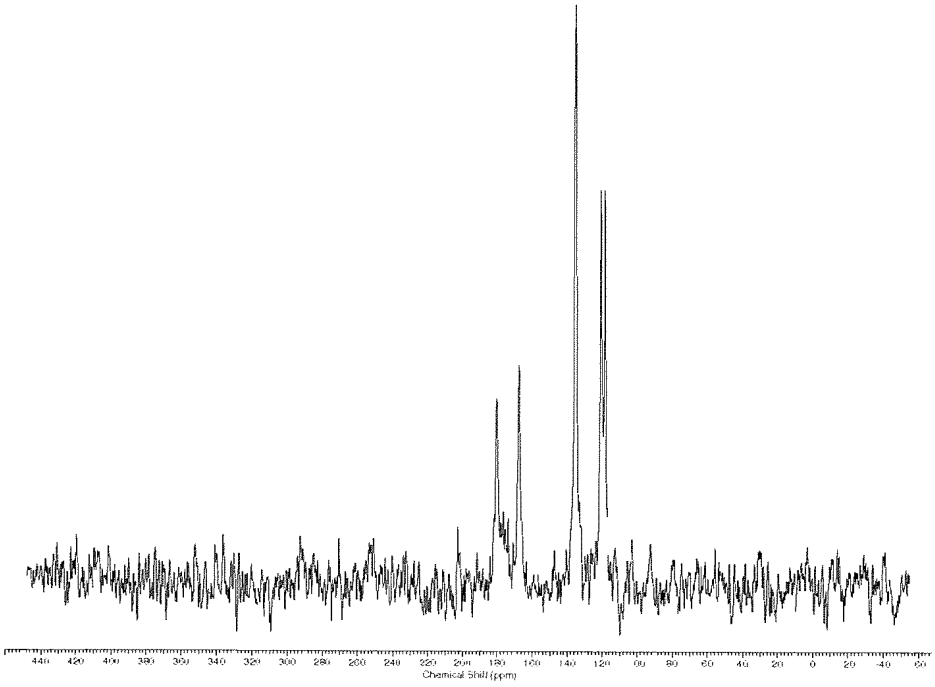

440 420 400 380 360 340 320 300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 -20 -40 -60
Chemical Shift (ppm)

**Figure 11**

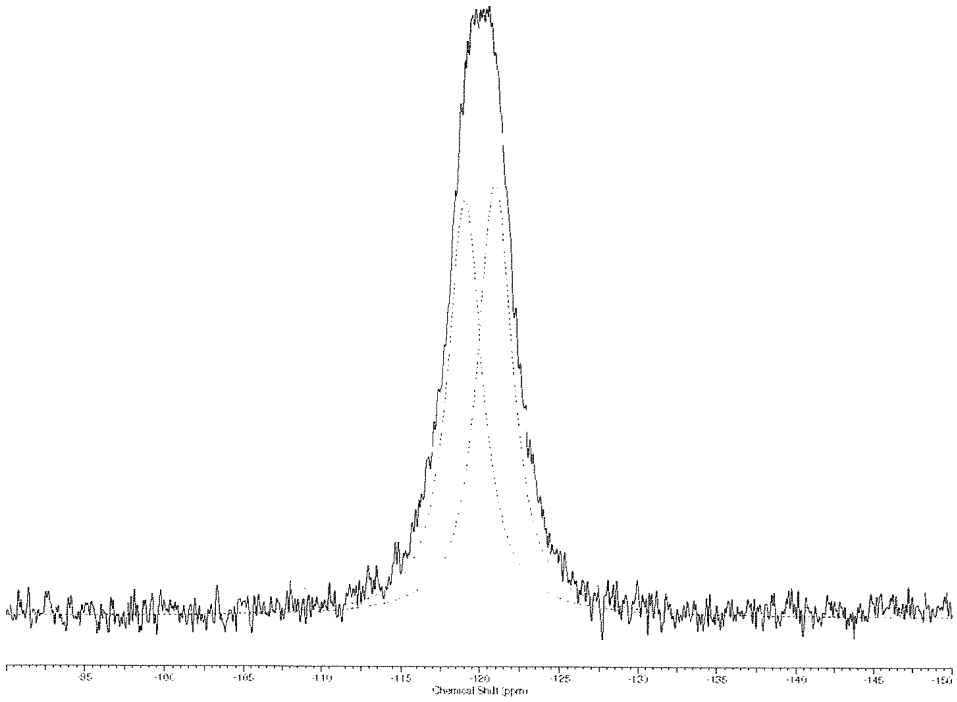

-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
Chemical Shift (ppm)

**Figure 12**

TGA

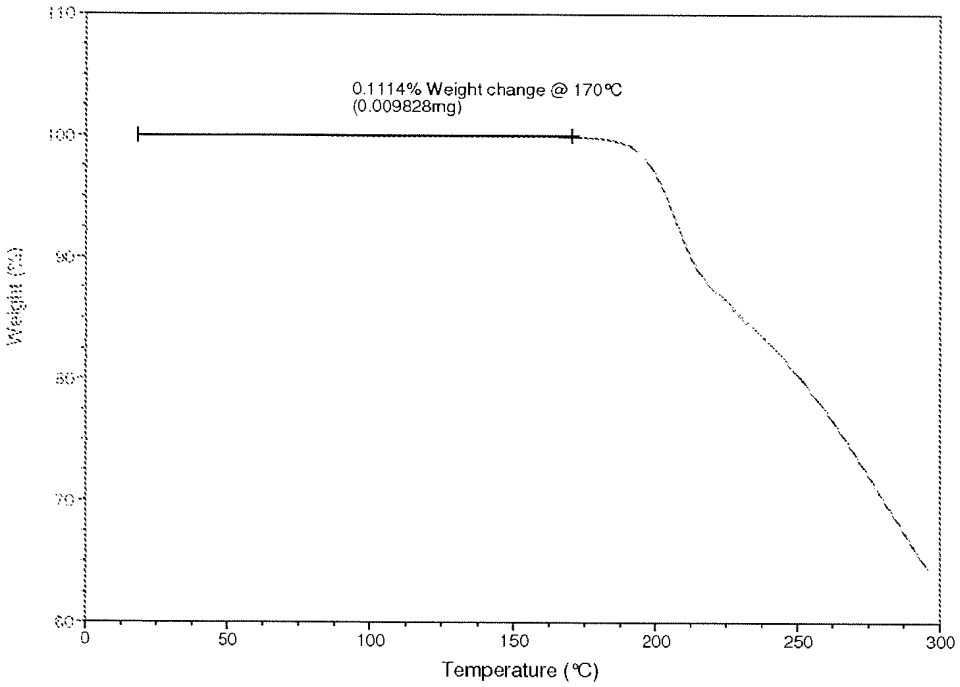


**Figure 13**

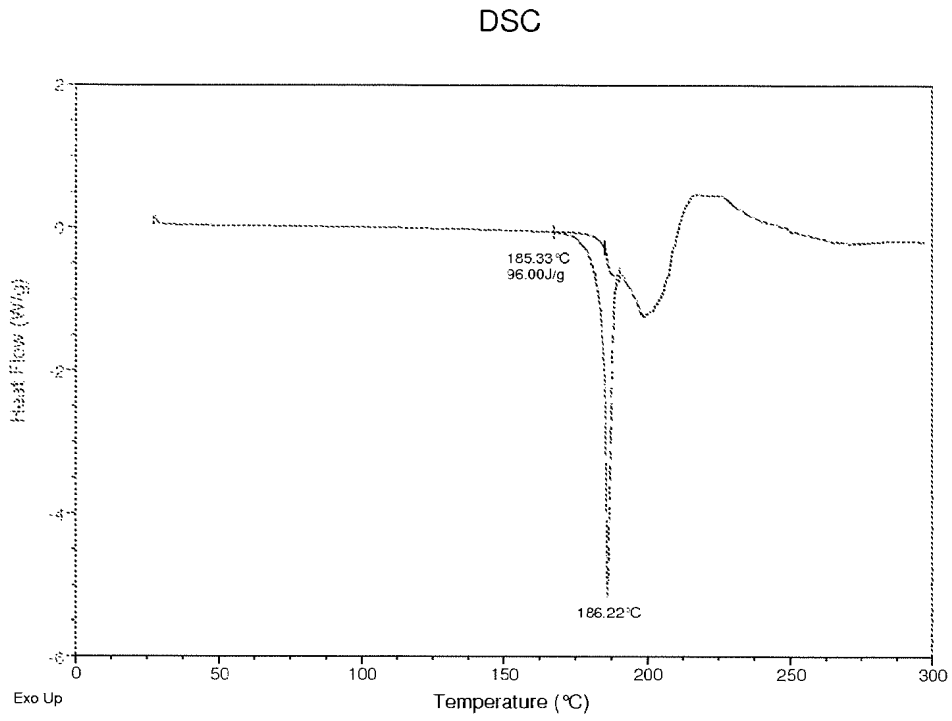

DSC
185.33°C
96.00J/g
186.22°C
Heat Flow (W/g)
Exo Up
Temperature (°C)
0
50
100
150
200
250
300

**Figure 14**

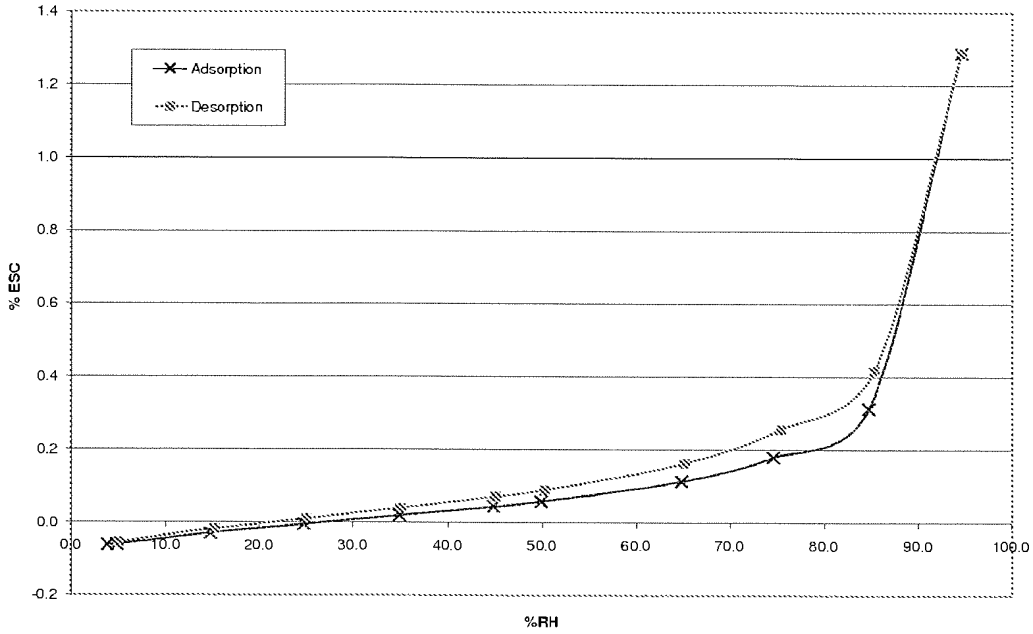

Adsorption
Desorption
% ESC
%RH
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0

**Figure 15**

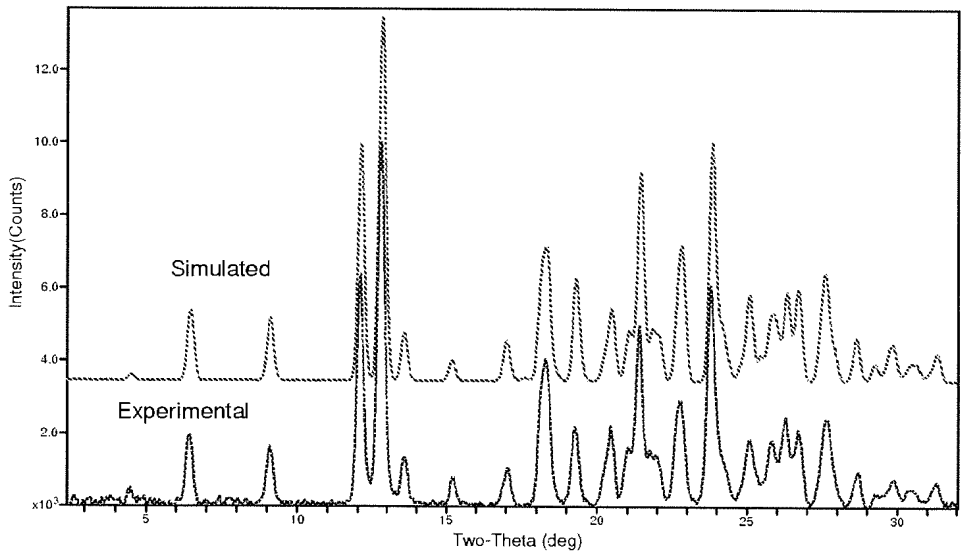

Intensity(Counts)
x10^3
12.0
10.0
8.0
6.0
4.0
2.0
Simulated
Experimental
5
10
15
20
25
30
Two-Theta (deg)

**Figure 16**

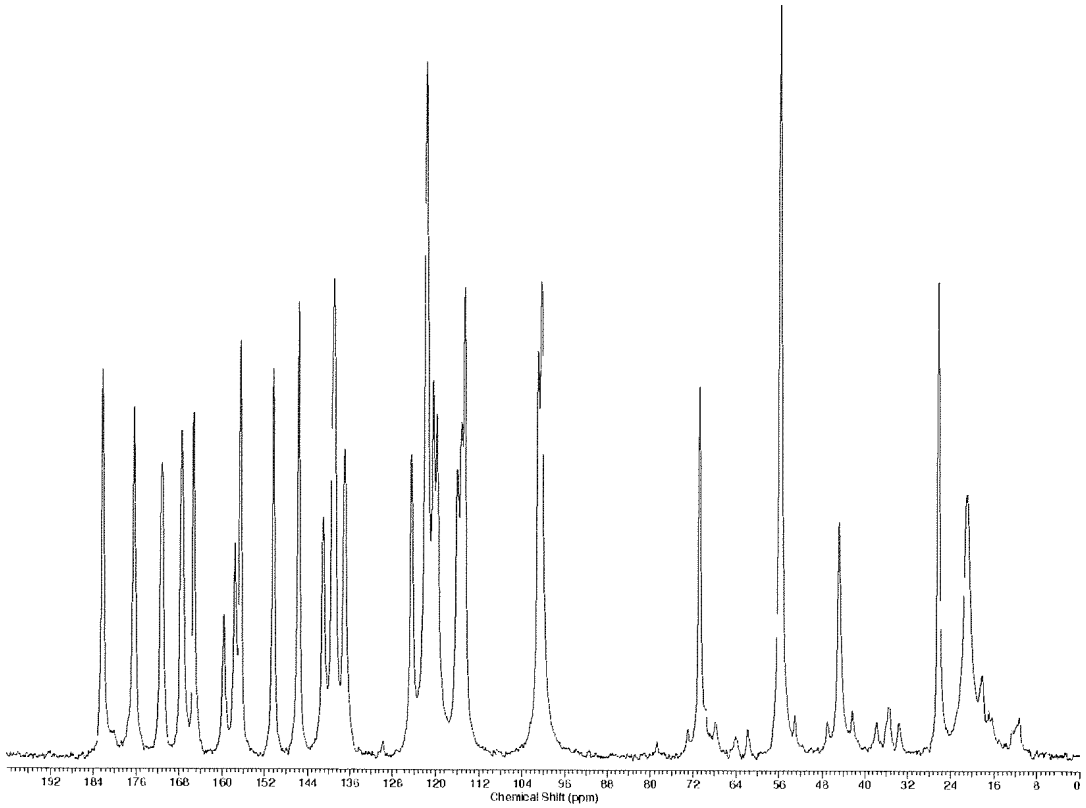

192 184 176 168 160 152 144 136 126 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

**Figure 17**

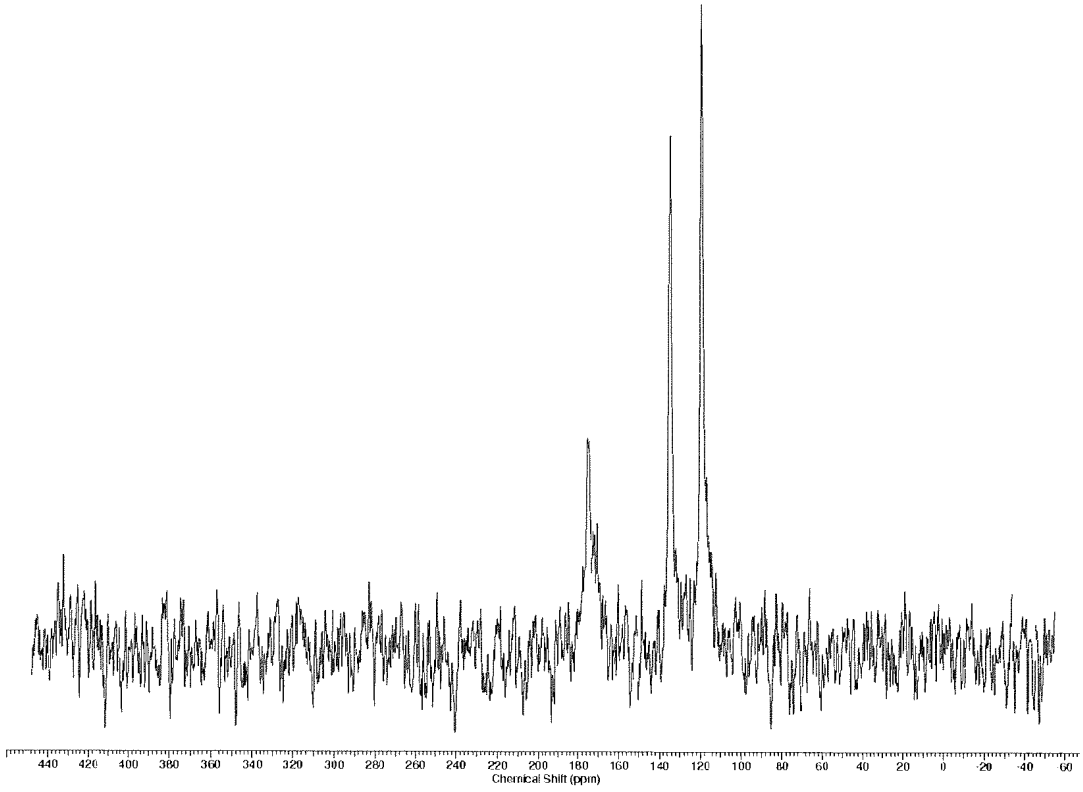

440 420 400 380 360 340 320 300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 -20 -40 -60
Chemical Shift (ppm)

**Figure 18**

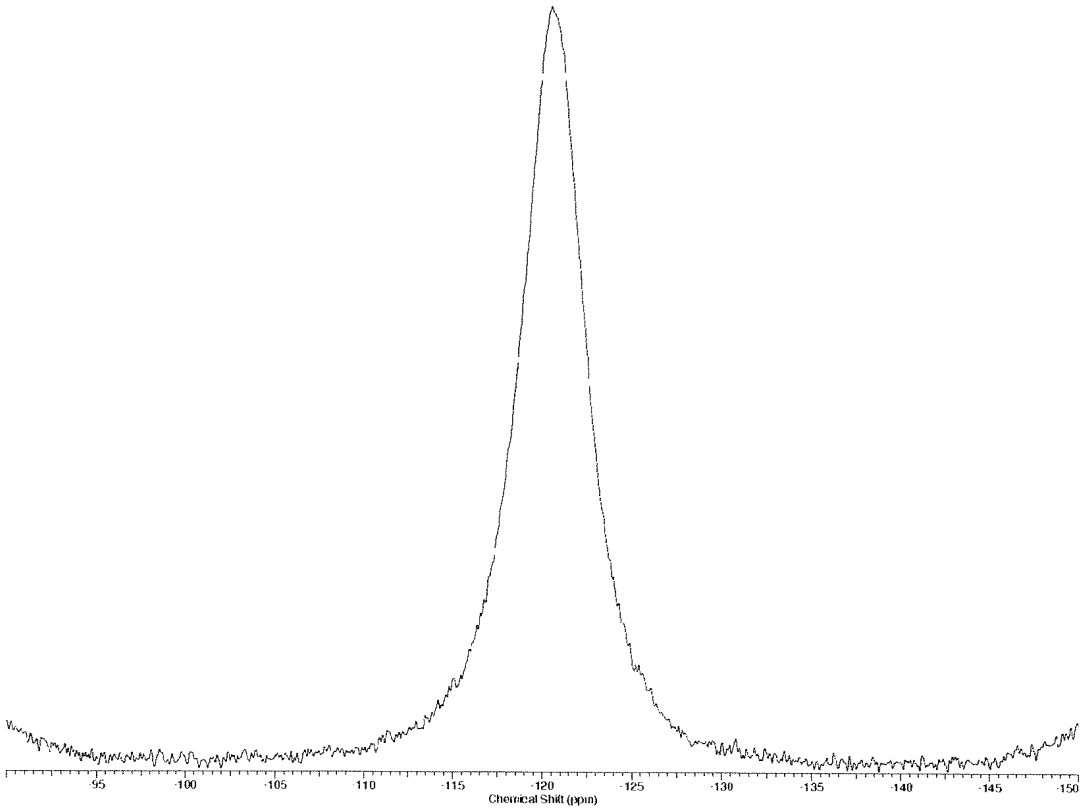

-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
Chemical Shift (ppm)

**Figure 19**

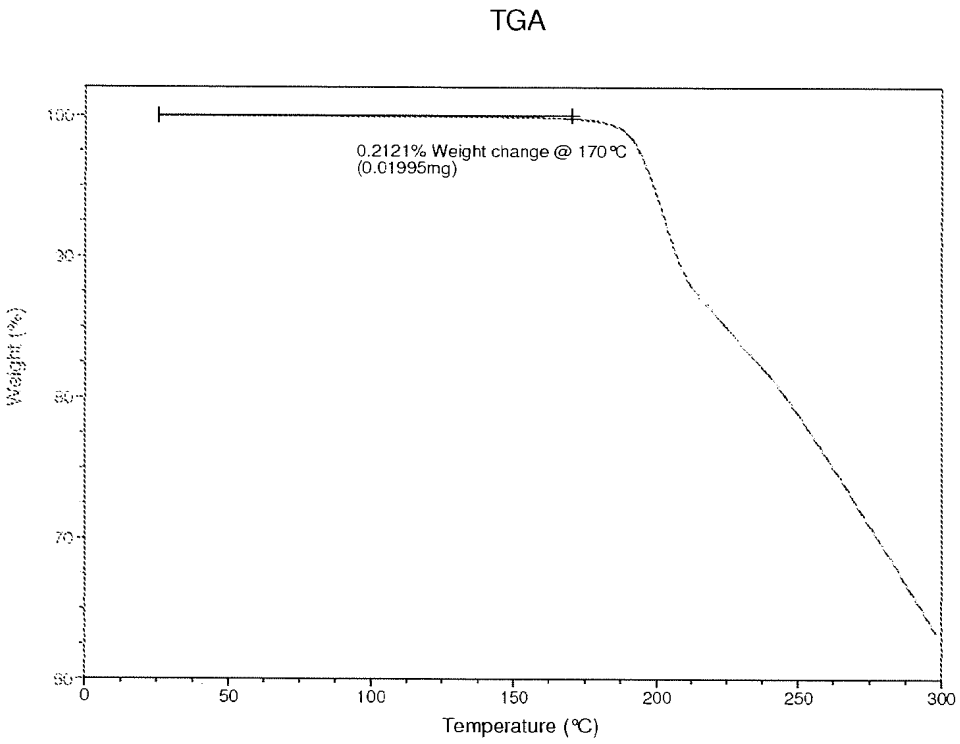

TGA
0.2121% Weight change @ 170°C
(0.01995mg)
Weight (%)
100
90
80
70
60
0
50
100
150
200
250
300
Temperature (°C)

**Figure 20**

DSC

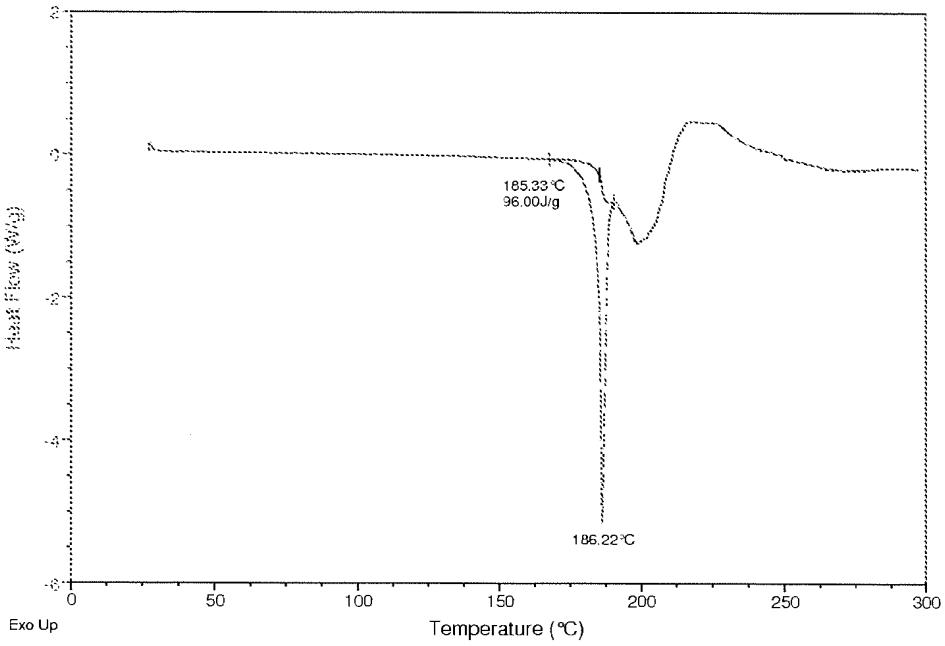


**Figure 21**

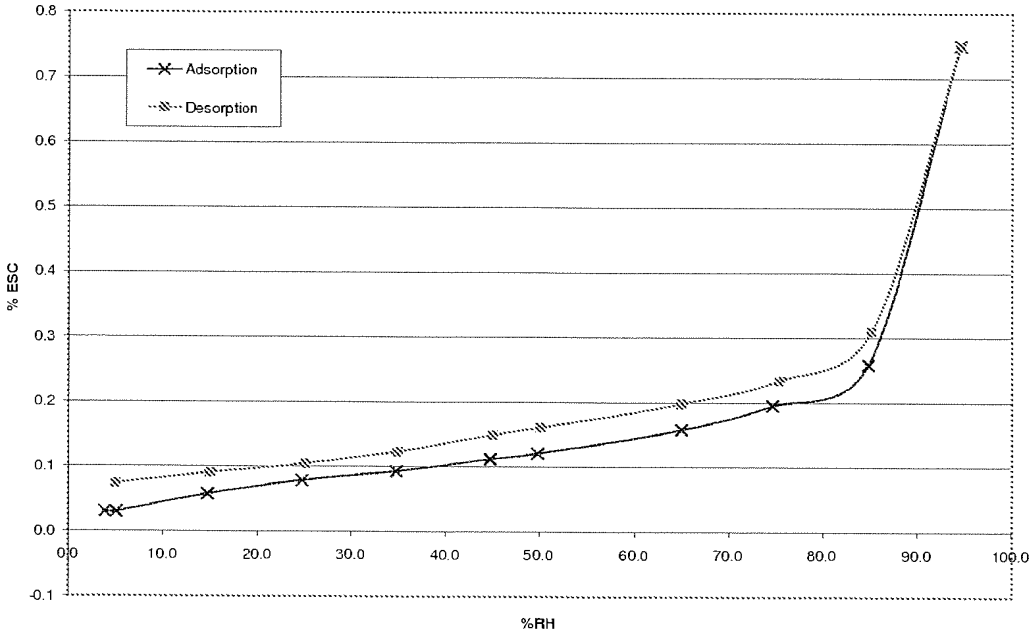

Adsorption
Desorption
% ESC
%RH
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0

**Figure 22**

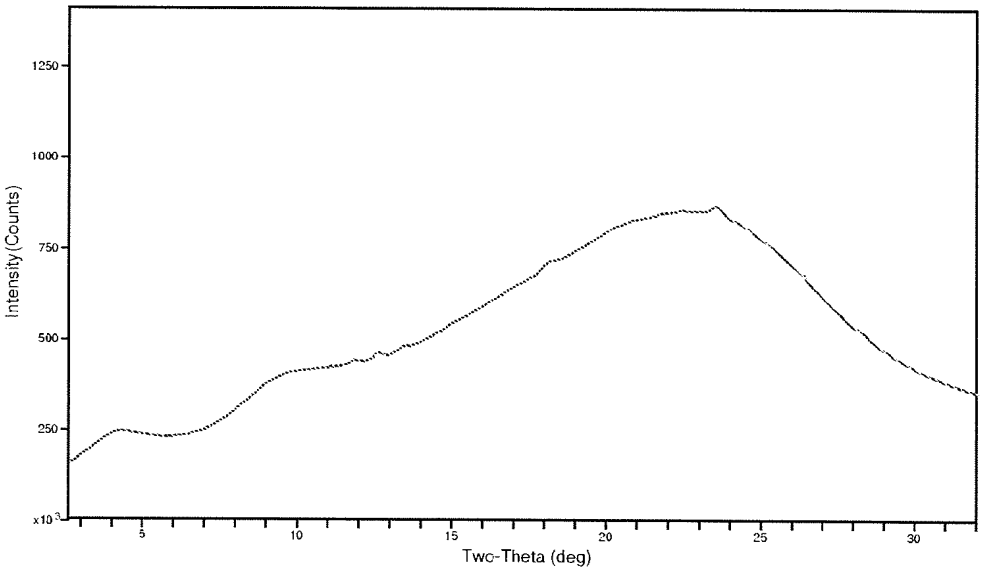

1250
1000
750
500
250
x10 3
Intensity (Counts)
5
10
15
20
25
30
Two-Theta (deg)

**Figure 23**

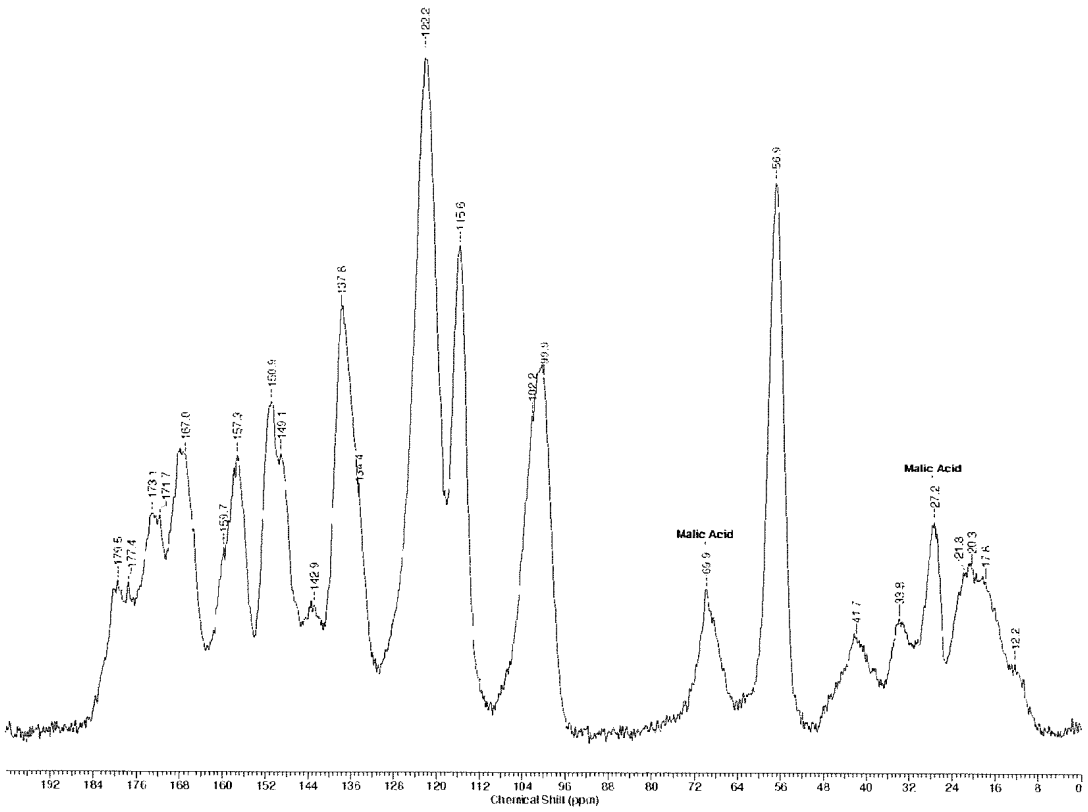


**Figure 24**

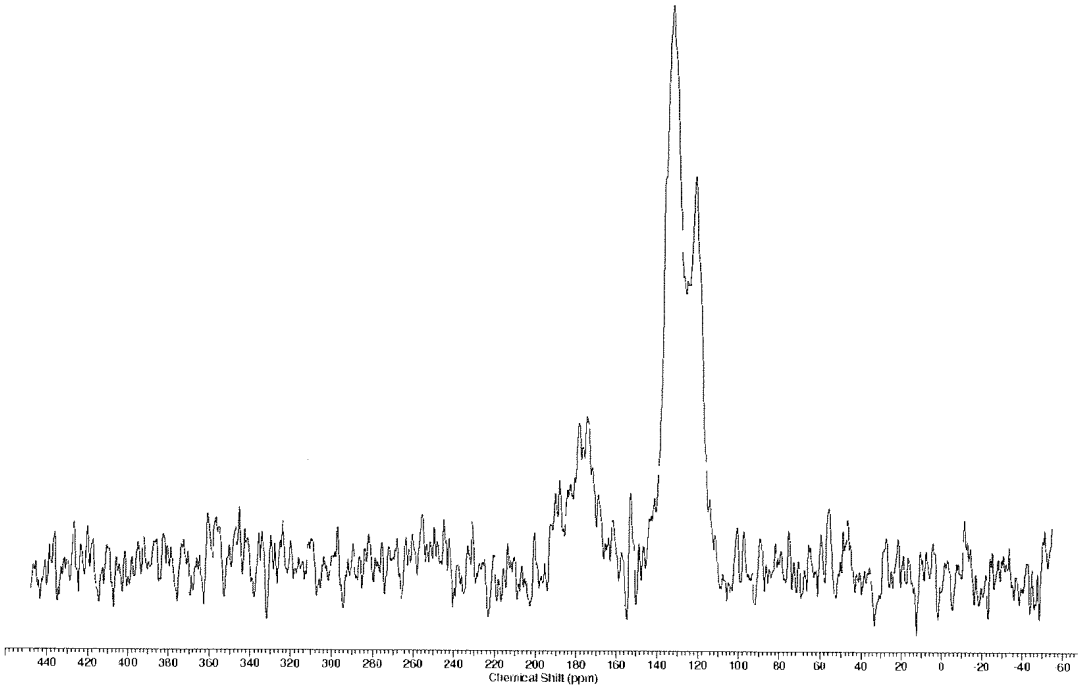

440 420 400 380 360 340 320 300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 -20 -40 -60
Chemical Shift (ppm)

**Figure 25**

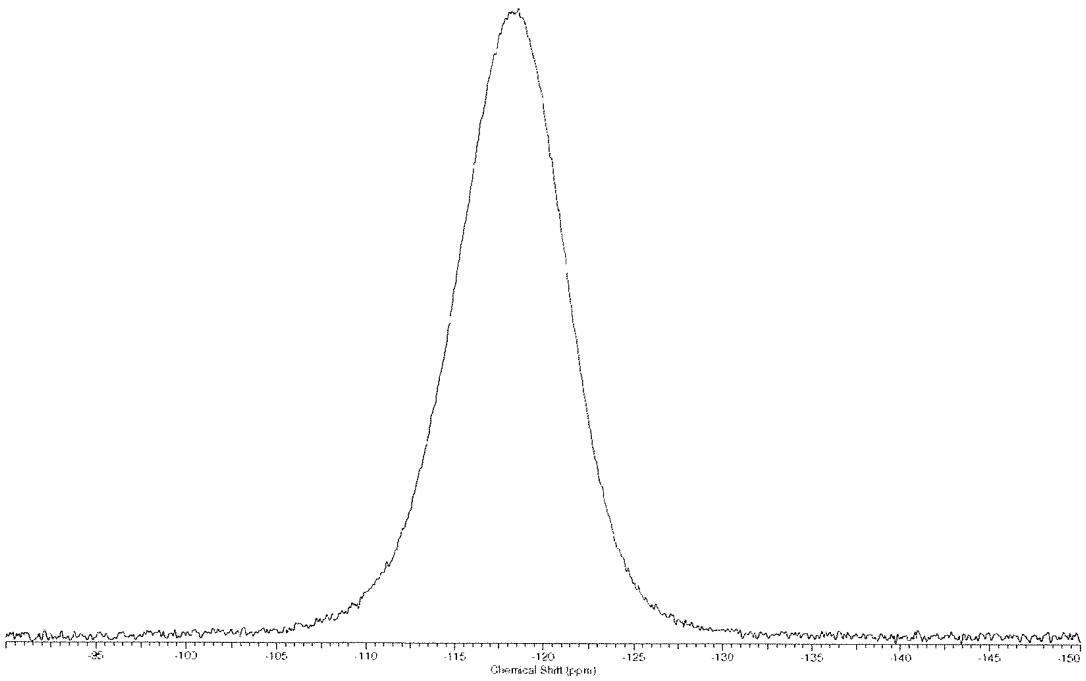

-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
Chemical Shift (ppm)

**Figure 26**

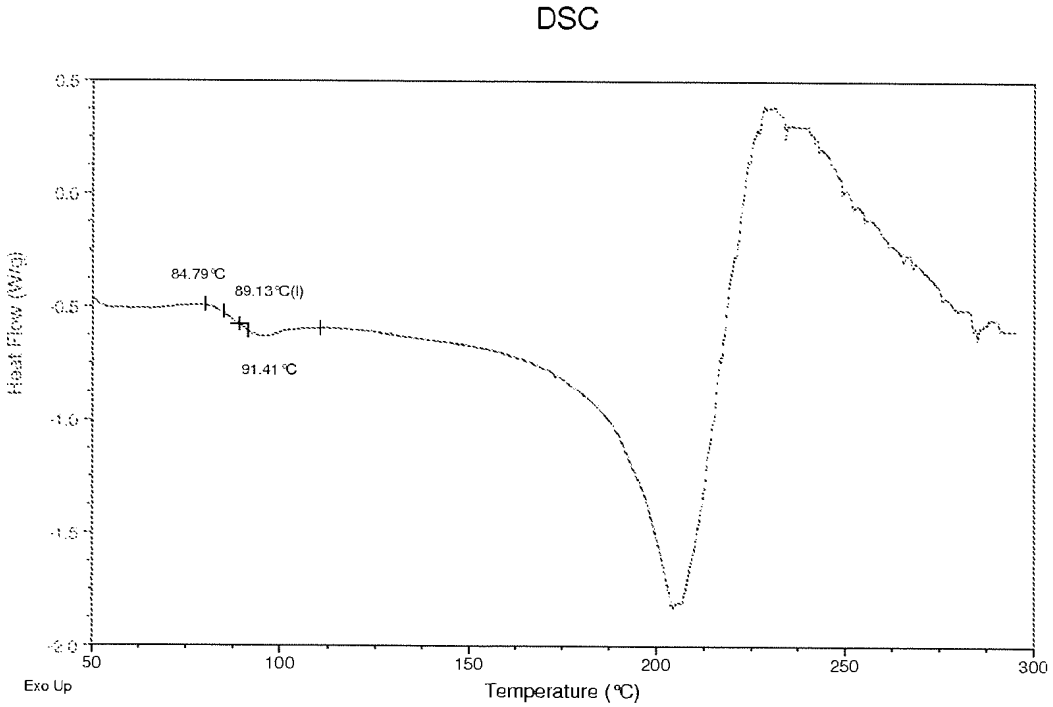
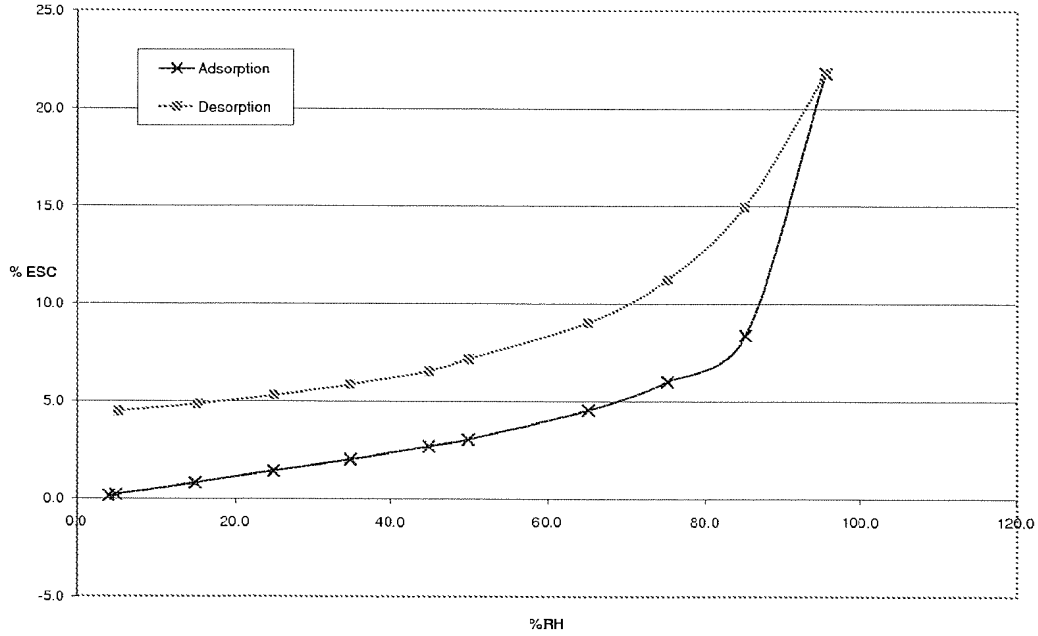

DSC
0.5
0.0
-0.5
-1.0
-1.5
-2.0
Heat Flow (W/g)
84.79°C
89.13°C(I)
91.41°C
50
100
150
200
250
300
Exo Up
Temperature (°C)

**Figure 27**




KALAMAZOO.46896.1

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/021194

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D215/227 A61K31/47 A61P35/00

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)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 2005/030140 A2 (EXELIXIS INC [US]; BANNEN LYNNE CANNE [US]; CHAN DIVA SZE-MING [US]; C) 7 April 2005 (2005-04-07) cited in the application page 212, paragraph 353 - page 213; example 48 claims 1-168 page 159, paragraph 236 | 1-15 |

☐ 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 document 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

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 17 March 2010 | 24/03/2010 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Marzi, Elena |

1

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/021194

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 2005030140 A2 | 07-04-2005 | AU 2004275842 A1 | 07-04-2005 |
| | | CA 2537812 A1 | 07-04-2005 |
| | | EP 1673085 A2 | 28-06-2006 |
| | | JP 2007506777 T | 22-03-2007 |
| | | US 2009170896 A1 | 02-07-2009 |
| | | US 2007054928 A1 | 08-03-2007 |
| | | US 2007225307 A1 | 27-09-2007 |
| | | US 2007244116 A1 | 18-10-2007 |
| | | US 2009105299 A1 | 23-04-2009 |

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CORRECTED VERSION

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(26) Publication Language: English

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(71) Applicants *(for all designated States except US)*: **EXELIXIS, INC.** [US/US]; P.O. Box 511, 249 East Grand Avenue, South San Francisco, CA 94080 (US). **BRISTOL-MEYERS SQUIBB COMPANY** [US/US]; P.O. Box 4000, Princeton, NJ 08543 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **ST CLAIR BROWN, Adrian** [GB/GB]; 67 Stour Green, Ely, Cambridgeshire CB6 2XJ (GB). **LAMB, Peter** [US/US]; 814 Mandana Blvd., Oakland, CA 94610 (US). **GALLAGHER, William, P.** [US/US]; P.O. Box 4000, Princeton, NJ 08543 (US).

(74) Agent: **BERVEN, Heidi M.**; Honigman Miller Schwartz and Cohn LLP, 350 East Michigan Avenue, Suite 300, Kalamazoo, MI 49007 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published**:

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(15) Information about Correction:
see Notice of 2 December 2010

(54) Title: MALATE SALT OF N- (4- { [ 6, 7-BIS (METHYLOXY) QUINOLIN-4-YL] OXY}PHENYL-N' - (4 -FLUOROPHENYL) CYCLOPROPANE-1,1-DICARBOXAMIDE, AND CRYSTALLINE FORMS THEROF FOR THE TREATMENT OF CANCER

(57) Abstract: Disclosed are malate salts of N-(4-{ [6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)- N'-(4-fluorophenyl)cyclopropane-l,l-dicarboxamide, including a (L)-malate salt, a (D)- malate salt, a (DL) malate salt, and mixtures thereof; and crystalline and amorphous forms of the malate salts. Also disclosed are pharmaceutical compositions comprising at least one malate salts of N-(4-{ [6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)- cyclopropane-1,l-dicarboxamide; and methods of treating cancer comprising administering at least one malate salt of N-(4-{ [6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-ffuorophenyl)cyclopropane- 1, 1 -dicarboxamide.

WO 2010/083414 A8

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(19) World Intellectual Property Organization
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PCT

(10) International Publication Number
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*A61K 31/47* (2006.01)

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PCT/US2010/021194

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(26) Publication Language: English

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(71) Applicants *(for all designated States except US)*: **EXELIXIS, INC.** [US/US]; P.O. Box 511, 249 East Grand Avenue, South San Francisco, CA 94080 (US). **BRISTOL-MEYERS SQUIBB COMPANY** [US/US]; P.O. Box 4000, Princeton, NJ 08543 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BROWN, Adrian, St. Clair** [GB/GB]; 67 Stour Green, Ely, Cambridgeshire CB6 2XJ (GB). **LAMB, Peter** [US/US]; 814 Mandana Blvd., Oakland, CA 94610 (US). **GALLAGHER, William, P.** [US/US]; P.O. Box 4000, Princeton, NJ 08543 (US).

(74) Agent: **BERVEN, Heidi, M.**; Honigman Miller Schwartz and Cohn LLP, 350 East Michigan Avenue, Suite 300, Kalamazoo, MI 49007 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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**Previous Correction**:
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(54) Title: MALATE SALT OF N- (4- { [ 6, 7-BIS (METHYLOXY) QUIN0LIN-4-YL] OXY}PHENYL)-N' - (4 -FLUOROPHENYL) CYCLOPROPANE-1,1-DICARBOXAMIDE, AND CRYSTALLINE FORMS THEROF FOR THE TREATMENT OF CANCER

(57) Abstract: Disclosed are malate salts of N-(4-{ [6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)- N'-(4-fluorophenyl)cyclopropane-l,l-dicarboxamide, including a (L)-malate salt, a (D)- malate salt, a (DL) malate salt, and mixtures thereof; and crystalline and amorphous forms of the malate salts. Also disclosed are pharmaceutical compositions comprising at least one malate salts of N-(4-{ [6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)- cyclopropane-l,l-dicarboxamide; and methods of treating cancer comprising administering at least one malate salt of N-(4-{ [6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-ffuorophenyl)cyclopropane- 1, 1 -dicarboxamide.

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61/441,520 10 February 2011 (10.02.2011) US
61/441,527 10 February 2011 (10.02.2011) US

(71) Applicant *(for all designated States except US)*: **EXELIXIS, INC.** [US/US]; 210 East Grand Avenue, South San Francisco, CA 94080 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **WILSON, Jo Ann** [US/US]; 74 Seward Street, San Francisco, CA 94114 (US).

(74) Agent: **BERVEN, Heidi, M.**; Honigman, Miller Schwart And Cohn, LLP, 350 East Michigan Avenue, Suite 300, Kalamazoo, MI 49007-3800 (US).

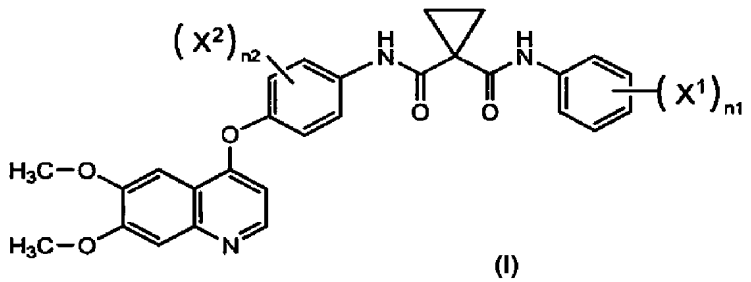
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published**:

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

(54) Title: PROCESSES FOR PREPARING QUINOLINE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH COMPOUNDS




(I)

(57) Abstract: The present invention is directed to processes for making and compositions containing quinolines such as formula I or pharmaceutically acceptable salts thereof wherein: X1 is H, Br, CI, or X2 is H, Br, CI, or n1 is 1-2; and n2 is 1-2.

WO 2012/109510 A1

# PROCESSES FOR PREPARING QUINOLINE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH COMPOUNDS

## CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 61/441,520, filed February 10, 2011, and 61/441,527, filed February 10, 2011, which are incorporated herein by reference

## FIELD OF THE INVENTION

[0002] This disclosure relates to processes for preparing compounds useful for modulating protein kinase enzymatic activity. More specifically, this disclosure relates to processes for preparing quinolines that are useful for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration, and chemo-invasion and to pharmaceutical compositions containing such compounds.

## BACKGROUND OF THE INVENTION

[0003] Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. One mechanism that can be exploited in cancer treatment is the modulation of protein kinase activity because signal transduction through protein kinase activation is responsible for many of the characteristics of tumor cells. Protein kinase signal transduction is of particular relevance in, for example, renal, gastric, head and neck, lung, breast, prostate, and colorectal cancers; hepatocellular carcinoma; as well as in the growth and proliferation of brain tumor cells.

[0004] Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., DN&P 7(6): 334-339, 1994. Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases, including, for example, immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, protein kinases are attractive targets for small molecule drug discovery. Particularly attractive targets for small-molecule modulation with respect to antiangiogenic

and antiproliferative activity include receptor type tyrosine kinases c-Met, KDR, c-Kit, Axl, flt-3, and flt-4.

**[0005]** The kinase c-Met is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs) which include Met, Ron, and Sea. The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenesis. Binding of HGF to c-Met induces activation of the receptor via autophosphorylation, resulting in an increase of receptor dependent signaling, which promotes cell growth and invasion. Anti-HGF antibodies or HGF antagonists have been shown to inhibit tumor metastasis *in vivo* (See: Maulik et al Cytokine & Growth Factor Reviews 2002 13, 41-59). c-Met overexpression has been demonstrated on a wide variety of tumor types including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytomas, and glioblastomas. Additionally, activating mutations in the kinase domain of c-Met have been identified in hereditary and sporadic renal papilloma and squamous cell carcinoma. (See, e.g., Maulik et al., Cytokine & growth Factor reviews 2002 13, 41-59; Longati et al., Curr Drug Targets 2001, 2, 41-55; Funakoshi et al., Clinica Chimica Acta 2003 1-23).

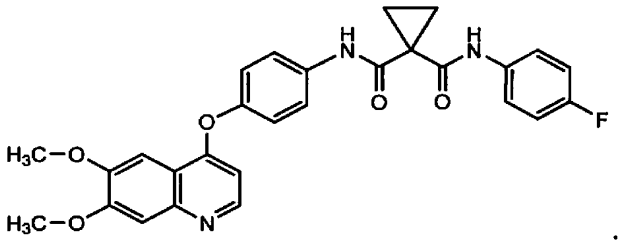
**[0006]** Inhibition of epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A., Drug Disc. Technol. 2001 6, 1005-1024). Kinase KDR (refers to kinase insert domain receptor tyrosine kinase) and flt-4 (fms-like tyrosine kinase-4) are both VEGF receptors. Inhibition of EGF, VEGF, and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc. Technol. 2001 6, 1005-1024). EGF and VEGF receptors are desirable targets for small molecule inhibition. All members of the VEGF family stimulate cellular responses by binding to tyrosine kinase receptors (the VEGFRs) on the cell surface, causing them to dimerize and become activated through transphosphorylation. The VEGF receptors have an extracellular portion with immunoglobulin-like domains, a single transmembrane spanning region, and an intracellular portion containing a split tyrosine-kinase domain. VEGF binds to VEGFR-1 and VEGFR-2. VEGFR-2 is known to mediate almost all of the known cellular responses to VEGF.

**[0007]** Kinase c-Kit (also called stem cell factor receptor or steel factor receptor) is a type 3 receptor tyrosine kinase (RTK) belonging to the platelet-derived growth factor receptor subfamily. Overexpression of c-Kit and c-Kit ligand has been described in variety of human

diseases, including human gastrointestinal stromal tumors, mastocytosis, germ cell tumors, acute myeloid leukemia (AML), NK lymphoma, small-cell lung cancer, neuroblastomas, gynecological tumors, and colon carcinoma. Moreover, elevated expression of c-Kit may also relate to the development of neoplasia associated with neurofibromatosis type 1 (NF-1), mesenchymal tumors GISTs, and mast cell disease, as well as other disorders associated with activated c-Kit.

**[0008]** Kinase Flt-3 (fms-like tyrosine kinase-3) is constitutively activated via mutation, either in the juxtamembrane region or in the activation loop of the kinase domain, in a large proportion of patients with AML (Reilly, Leuk. Lymphoma, 2003, 44: 1-7).

**[0009]** Small-molecule compounds that specifically inhibit, regulate, and/or modulate the signal transduction of kinases, such as c-Met, VEGFR2, KDR, c-Kit, Axl, flt-3, and flt-4 described above, are particularly desirable as a means to treat or prevent disease states associated with abnormal cell proliferation and angiogenesis. One such small-molecule is compound IA, which has the chemical structure:




IA

WO2005/030140 describes the synthesis of compound IA (Table 2, Compound 12, Example 48) and also discloses the therapeutic activity of this molecule to inhibit, regulate, and/or modulate the signal transduction of kinases (Assays, Table 4, entry 289), the entire contents of which is incorporated herein by reference.

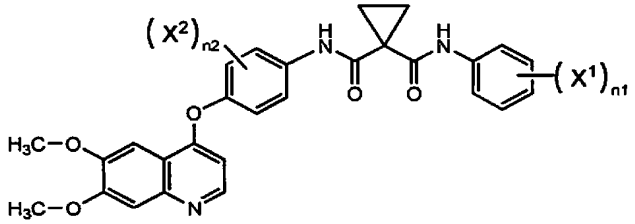
**[0010]** Although therapeutic efficacy is the primary concern for a therapeutic agent, the pharmaceutical composition can be equally important to its development. Generally, the drug developer endeavors to discover a pharmaceutical composition that possesses desirable properties, such as satisfactory water-solubility (including rate of dissolution), storage stability, hygroscopicity, and reproducibility, all of which can impact the processability, manufacture, and/or bioavailability of the drug.

**[0011]** Accordingly, there is a need for the discovery of new processes for making quinolines such as compound IA that minimize the formation of undesirable process contaminants or byproducts. There is also a need for new pharmaceutical compositions containing quinolines such as compound IA that are essentially free of process byproducts.

## SUMMARY OF THE INVENTION

**[0012]** These and other needs are met by the present disclosure, which is directed to processes for making and compositions containing quinolines or pharmaceutically acceptable salts thereof.

**[0013]** In one aspect, the disclosure relates to processes for preparing a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is H, Br, Cl, or F;

$X^2$ is H, Br, Cl, or F;

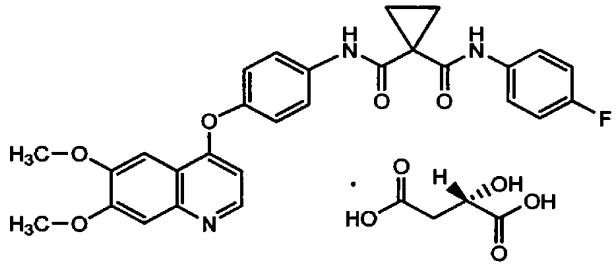
n1 is 1-2; and

n2 is 1-2.

**[0014]** Intermediates useful in preparing the above compounds are also disclosed.

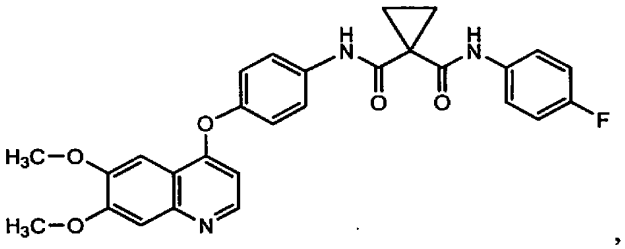
**[0015]** The compounds of formula I are useful as protein kinase modulators, and they inhibit various protein kinases including Ret and c-Met.

**[0016]** In another aspect, the disclosure provides a process for preparing compound IB:



IB

from compound IA:



IA,

comprising:

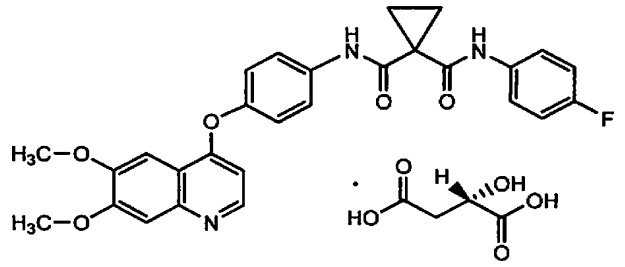
(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) vacuum distilling the mixture successively; and

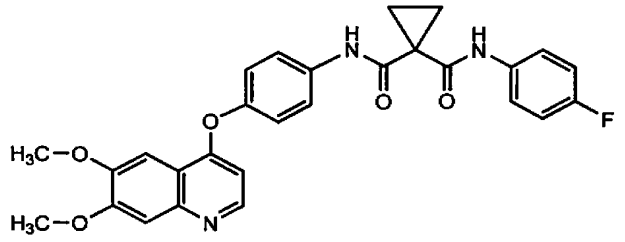
(d) isolating the compound of IB by filtration.

**[0017]** In another aspect, the disclosure provides a process for preparing compound IB:



IB

from compound IA:



IA,

comprising:

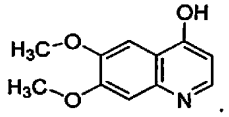
(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) seeding the mixture with compound IB;

(d) vacuum distilling the mixture; and

(e) isolating compound IB by filtration.

**[0018]** In another aspect, the disclosure provides compound I, IA, or IB admixed with less than 100 ppm 6,7-dimethoxy-quinoline-4-ol, the structure of which is 

.

**[0019]** In another aspect, the disclosure provides pharmaceutical compositions containing the compound of formula I, compound IA, or compound IB for oral administration.

**[0020]** In another aspect, the disclosure provides a pharmaceutical tablet composition according to Table 1.

**Table 1**

| Ingredient | % w/w |
|---|---|
| Compound I | 31.68 |
| Microcrystalline Cellulose (MCC) (Avicel PH102) | 38.85 |
| Lactose anhydrous 60 M | 19.42 |
| Hydroxypropyl Cellulose, EXF | 3.00 |
| Croscarmellose Sodium | 3.00 |
| **Total Intra-granular** | **95.95** |
| Silicon dioxide, Colloidal PWD | 0.30 |
| Croscarmellose Sodium | 3.00 |
| Magnesium Stearate | 0.75 |
| **Total** | **100.00** |

**[0021]** In another aspect, the disclosure provides a pharmaceutical tablet composition according to Table 2.

**Table 2**

| Ingredient | (% w/w) |
|---|---|
| Compound I | 25.0-33.3 |
| Microcrystalline Cellulose, NF | q.s |
| Hydroxypropyl Cellulose, NF | 3 |
| Poloxamer, NF | 0-3 |
| Croscarmellose Sodium, NF | 6.0 |
| Colloidal Silicon Dioxide, NF | 0.5 |
| Magnesium Stearate, NF | 0.5-1.0 |
| Total | 100 |

**[0022]** In another aspect, the disclosure provides a pharmaceutical tablet composition according to Table 2A.

**Table 2A**

| Ingredient | % w/w |
|---|---|
| Compound IB (10 % drug load as Compound IA) | 12.67 |
| MCC | 51.52 |
| Lactose | 25.76 |
| Hydroxypropyl cellulose | 3.0 |
| Croscarmellose Sodium | 6.0 |
| Colloidal Silicon Dioxide | 0.3 |
| Magnesium Stearate | 0.75 |
| **Total** | **100** |

**[0023]** In another aspect, the disclosure provides a pharmaceutical capsule composition according to Table 3.

**Table 3**

| Ingredient | mg/unit dose |
|---|---|
| Compound IB (10 % drug load as Compound IA) | 25 |
| Silicified Microcrystalline Cellulose | 196.75 |
| Croscarmellose sodium | 12.5 |
| Sodium starch glycolate | 12.5 |
| Fumed Silica | 0.75 |
| Stearic acid | 2.5 |
| **Total Fill Weight** | 250 |

**[0024]** In another aspect, the disclosure provides a pharmaceutical capsule composition according to Table 4.

**Table 4**

| Ingredient | mg/unit dose |
|---|---|
| Compound IB (50 % drug load as Compound IA) | 100 |
| Silicified Microcrystalline Cellulose | 75.40 |
| Croscarmellose sodium | 10.00 |
| Sodium Starch Glycolate | 10.00 |
| Fumed silica | 0.6 |
| Stearic Acid | 4.0 |
| **Total Fill Weight** | 200 |

**[0025]** In another aspect, the disclosure provides a pharmaceutical capsule composition according to Table 5, wherein the IB weight equivalents are provided.

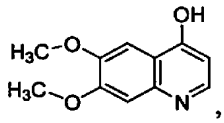
**Table 5**

| | mg/unit dose |
|---|---|
| **Ingredient** | **50mg** |
| Compound IB | 63.35 |
| Microcrystalline Cellulose | 95.39 |
| Croscarmellose sodium | 9.05 |
| Sodium starch glycolate | 9.05 |
| Fumed Silica | 0.54 |
| Stearic acid | 3.62 |
| **Total Fill Weight** | 181.00 |

**[0026]** In another aspect, the disclosure provides a pharmaceutical capsule composition according to Table 6, wherein the IB weight equivalents are provided.

**Table 6**

| | mg/unit dose |
|---|---|
| **Ingredient** | **60mg** |
| Compound IB | 73.95 |
| Microcrystalline Cellulose | 114.36 |
| Croscarmellose sodium | 10.85 |
| Sodium starch glycolate | 10.85 |
| Fumed Silica | 0.65 |
| Stearic acid | 4.34 |
| **Total Fill Weight** | 217.00 |

**[0027]** In another aspect, the invention is directed to a pharmaceutical composition comprising compound I, IA, or IB admixed with less than 100 ppm 6,7-dimethoxy-quinoline-4-ol, the structure of which is 

, and a pharmaceutically acceptable carrier.

**[0028]** There are many different aspects and embodiments of the disclosure described herein, and each aspect and each embodiment is non-limiting in regard to the scope of the disclosure. The terms "aspects" and "embodiments" are meant to be non-limiting regardless of where the terms "aspect" or "embodiment" appears in this specification. The transitional term "comprising," as used herein, which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements.

## DETAILED DESCRIPTION OF THE INVENTION

**Definitions**

**[0029]** As used herein, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise or they are expressly defined to mean something different.

**[0030]** The word "can" is used in a non-limiting sense and in contradistinction to the word "must." Thus, for example, in many aspects of the invention a certain element is described as "can" having a specified identity, which is meant to convey that the subject element is permitted to have that identity according to the invention but is not required to have it.

**[0031]** If a group "R" is depicted as "floating" on a ring system, then unless otherwise defined, the substituent(s) "R" can reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

**[0032]** When there are more than one such depicted "floating" groups, such as where there are two groups; then, unless otherwise defined, the "floating" groups can reside on any atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

**[0033]** "Pharmaceutically acceptable salts" include acid addition salts.

**[0034]** "Pharmaceutically acceptable acid addition salt" refers to those salts that retain the biological effectiveness of the free bases and that are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or mixtures thereof, as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like, or mixtures thereof.

**[0035]** "Essentially free" as used in the phrase "essentially free of process byproducts or contaminants," means that a compound or composition as disclosed here in is admixed with 200 parts per million (ppm) or less of such byproducts or contaminants.

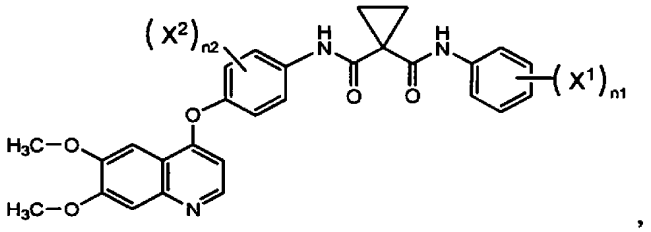
**[0036]** The disclosure is further illustrated by the following examples, which are not to be construed as limiting the disclosure in scope or spirit to the specific procedures described in them. Unless specified otherwise, the starting materials and various intermediates may be

obtained from commercial sources, prepared from commercially available organic compounds, or prepared using well-known synthetic processes.

**Processes**

**Aspect 1: Processes for Making Compounds of Formula I**

**[0037]** Aspect (1) of the invention relates to a process of preparing a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is H, Br, Cl, or F;

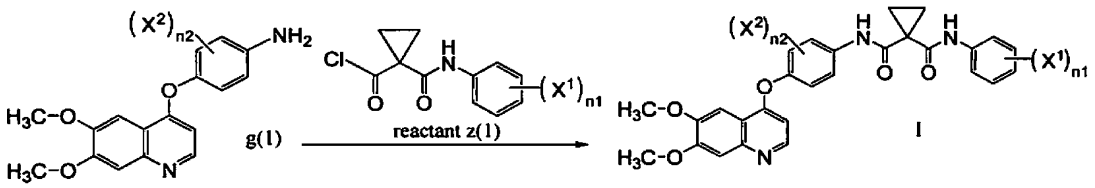
$X^2$ is H, Br, Cl, or F;

n1 is 1-2; and

n2 is 1-2;

the process comprising:

contacting the compound of formula g(1) with reactant z(1) to yield the compound of formula I:




**[0038]** The reaction is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions include using basic conditions. Non-limiting examples of basic conditions that can be used in Aspect (1) include the use of inorganic bases, such as aqueous KOH, NaOH, $K_2CO_3$, $Na_2CO_3$, $K_3PO_4$, $Na_3PO_4$, $K_2HPO_4$, $Na_2HPO_4$, and the like, or mixtures thereof. Other non-limiting examples of suitable reaction conditions include using suitable solvents. Non-limiting examples of suitable solvents that can be used include water miscible solvents, such as THF, acetone, ethanol, and the like, or mixtures thereof. Other non-limiting examples of suitable reaction conditions include using suitable temperatures. Suitable temperatures that may be used for the reaction include a

temperature at a range from about 10 °C to about 30 °C, or alternatively, at a range from about 15 °C to about 28 °C, or alternatively, at a range from about 20 °C to about 25 °C. The product formed by the reaction is in the free base form, and this free base form may be converted into a pharmaceutically acceptable salt thereof by processes known in the art. For example, the compound of formula I can be converted to the L-malate salt by the addition of L-malic acid and a suitable solvent.

**[0039]** Utilities of the compound of formula I are further described in WO 2005/030140 A2, which is incorporated herein by reference.

**Embodiments of Aspect (1) Part A**

**[0040]** In another embodiment of Aspect (1), $X^1$ is Cl or F.

**[0041]** In another embodiment of Aspect (1), $X^2$ is Cl or F.

**[0042]** In another embodiment of Aspect (1), $X^1$ is F.

**[0043]** In another embodiment of Aspect (1), $X^2$ is F.

**[0044]** In another embodiment of Aspect (1), $X^1$ is H.

**[0045]** In another embodiment of Aspect (1), $X^2$ is H.

**[0046]** In another embodiment of Aspect (1), n1 is 1.

**[0047]** In another embodiment of Aspect (1), n2 is 1.

**[0048]** In another embodiment of Aspect (1), n1 is 2.

**[0049]** In another embodiment of Aspect (1), n2 is 2.

**[0050]** All compounds of formula I for Aspect (1) disclosed above include any of the disclosed alternative embodiments in Part A for each of $X^1$, $X^2$, n1 or n2, in combination with any other of the disclosed alternative embodiments in Part A for each of $X^1$, $X^2$, n1, or n2, as well as a pharmaceutically acceptable salt of any such combination.

**Embodiments of Aspect (1) Part B**

**[0051]** In another embodiment of Aspect (1), n1 and n2 are each 1.

**[0052]** In another embodiment of Aspect (1), n1 and n2 are each 2.

**[0053]** In another embodiment of Aspect (1), n1 is 1; and n2 is 2.

**[0054]** In another embodiment of Aspect (1), n1 is 2 and n2 is 1.

**[0055]** In another embodiment of Aspect (1), $X^1$ is H; and $X^2$ is F.

**[0056]** In another embodiment of Aspect (1), $X^1$ is F; and $X^2$ is H.

**[0057]** In another embodiment of Aspect (1), $X^1$ and $X^2$ are each H.

**[0058]** In another embodiment of Aspect (1), $X^1$ and $X^2$ are each F.

[0059] In another embodiment of Aspect (1), $X^1$ is Cl; and $X^2$ is H.

[0060] In another embodiment of Aspect (1), $X^1$ is H; and $X^2$ is Cl.

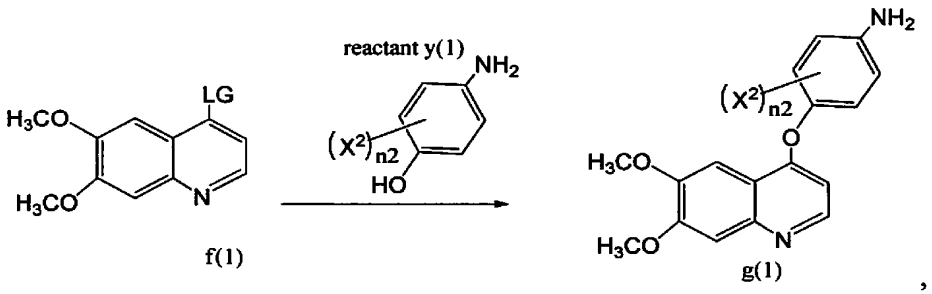
[0061] In another embodiment of Aspect (1), $X^1$ and $X^2$ are each Cl.

[0062] In another embodiment of Aspect (1), $X^1$ is Cl; and $X^2$ is F.

[0063] In another embodiment of Aspect (1), $X^1$ is F; and $X^2$ is Cl.

**Embodiments of Aspect (1) Part C**

[0064] In an embodiment of Aspect (1), the compound of formula g(1) can be made by reacting a compound of formula f(1) with reactant y(1) to yield the compound of g(1):




,

wherein LG represents a leaving group, and each of $X^2$, and n2 are as defined in Aspect (1), or as in any of the embodiments of Aspect (1) Part A. A non-limiting example of a leaving group includes a halo group such as Cl, Br, or F. Various compounds of reactant y(1) are commercially available, such as 2-fluoro-4-aminophenol and 4-aminophenol. Also, the skilled artisan would be able to make any variation of reactant y(1) using commercially available starting materials and by using known techniques to modify these commercially available starting materials to yield various compounds within the scope of reactant y(1).

[0065] The reaction in this embodiment is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions include using suitable solvents such as polar solvents. Non-limiting examples of polar solvents that can be used include tetrahydrofuran (THF), dimethylacetamide (DMA), dimethylsulfoxide (DMSO), dimethylformamide (DMF), ethyl acetate, N-methyl pyrrolidone (NMP), propylene carbonate, and the like, or mixtures thereof. In another embodiment, the polar solvent is dimethylacetamide (DMA). In another embodiment, the polar solvent is dimethylsulfoxide (DMSO). In another embodiment, the polar solvent is dimethylformamide (DMF). In another embodiment, the polar solvent is ethyl acetate. In another embodiment, the polar solvent is N-methyl pyrrolidone (NMP). In another embodiment, the polar solvent is propylene carbonate. In another embodiment, the solvent is a mixture of solvents, such as a mixture comprising THF and DMA.

**[0066]** The reactants f(1) and y(1) can be added together at a temperature ranging from about 10 °C to about 30 °C, or alternatively, from about 15 °C to about 28 °C, or alternatively, from about 20 °C to about 25 °C. The mixture is then heated to a temperature ranging from about 80 °C to about 125 °C, or alternatively, from about 95 °C to about 110 °C, or alternatively, from about 100 °C to about 105 °C, and the selected temperature is maintained until the reaction is complete.

**[0067]** Other non-limiting examples of suitable reaction conditions in this step of Aspect (1) include the use of a suitable base, such as a metal hydroxide or a non-nucleophilic base. Examples of metal hydroxides include sodium hydroxide or potassium hydroxide. Non-limiting examples of non-nucleophilic bases that can be used include lithium diisopropylamide, lithium tetramethylpiperidide, and alkali metal alkoxides such as sodium tert-butoxide, potassium tert-butoxide, sodium-pentoxide, and the like, or mixtures thereof. Preferably, the base is sodium tert-butoxide or sodium tert-pentoxide. In one embodiment, the base is sodium tert-pentoxide. Typically the sodium tert-pentoxide is commercially available as 35 weight percent solution of base in tetrahydrofuran, or as a 95 weight percent solid reagent. Preferably, the sodium tert-pentoxide is a 95 weight percent solid.

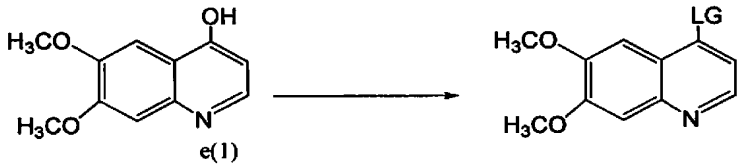
**[0068]** Typically, approximately 1.1 to 3.0 molar equivalents of base are used relative the moles of f(1) that are used. More preferably, 1.3 to 2.5 molar equivalents of base are used relative the moles of f(1) that are used. More preferably, 1.5 to 2.2 molar equivalents of base are used relative the moles of f(1) that are used. More preferably, 1.7 to 2.1 molar equivalents of base are used relative the moles of f(1) that are used.

**[0069]** Typically, the amount of molar equivalents of amino phenol that are used exceeds the molar equivalents of base that are used. In one embodiment, 1.1 to 2 molar equivalents of amino phenol are used relative to the molar equivalents of base that are used.

**[0070]** Once the reaction is substantially complete, the reaction mixture can be cooled to a temperature ranging from about 10 °C to about 25 °C. Precooled water can be charged at a rate to maintain a temperature that ranges from about 5 °C to about 35 °C. Alternatively, the precooled water can be charged at a rate to maintain a temperature that ranges from about 10 °C to about 25 °C. As a non-limiting example, the precooled water can be at a temperature ranging from about 0 °C to about 10 °C. As another non-limiting example, the precooled water can be at a temperature ranging from about 2 °C to about 7 °C. The precipitate can be collected by filtration under standard conditions and purified by standard purification techniques.

**Embodiments of Aspect (1) Part D**

**[0071]** In an embodiment of Aspect (1), the compound of formula f(1) can be made by converting a compound of formula e(1) to the compound of formula f(1):



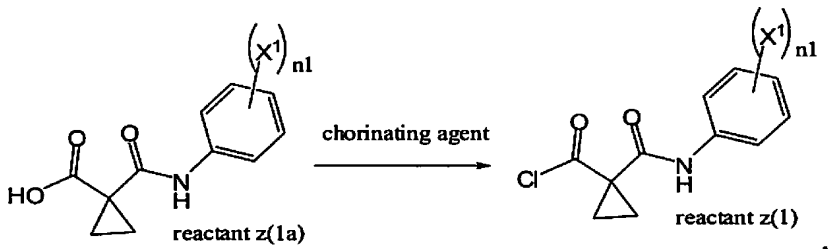

e(1) f(1),

wherein LG represents a leaving group. Non-limiting examples of leaving groups that can be used include halo groups (e.g., Cl, Br, or F) that can be added by halogenating agents. Non-limiting examples of halogenating agents that can be used include chlorinating agents, such as $SOCl_2$, $SO_2Cl_2$, $COCl_2$, $PCl_5$, $POCl_3$, and the like.

**[0072]** The reaction is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions in Part D of Aspect (1) include the use of suitable solvents. Non-limiting example of suitable solvents that can be used during the halogenation of the compound of formula e(1) include a polar, aprotic solvent, such as $CH_3CN$, DMF, and the like, or mixtures thereof. In other embodiments, the chlorination can be carried out using $POCl_3$ in acetonitrile, $COCl_2$ in DMF, or $SOCl_2$ in DMF. The addition of the chlorination agent is advantageously carried out at a temperature ranging from about 60 °C to about 90 °C. In another embodiment, the addition of the chlorination agent can be carried out at a temperature ranging from about 70 °C to about 85 °C. In another embodiment, the addition of the chlorination agent can be carried out at a temperature ranging from about 74 °C to about 80 °C. The product can then be collected by filtration and purified using standard techniques.

**Embodiments of Aspect (1) Part E**

**[0073]** In an embodiment of Aspect (1), reactant z(1) can be made by reacting reactant z(1a) with a chlorinating agent to yield reactant z(1):



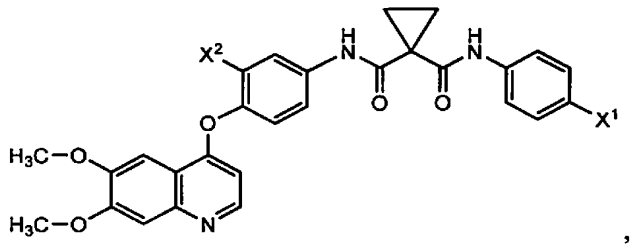

reactant z(1a) reactant z(1),

wherein $X^1$ is Br, Cl, or F; and n1 is 1-2. Compounds of reactant z(1a) can be made according to the process described in Example 25 of WO 2005/030140 A2, and the skilled artisan would be able to make any necessary substitutions using commercially available starting materials to come up with various compounds within the scope of reactant z(1a). Example 25 in WO 2005/030140 A2 is incorporated herein by reference.

**[0074]** The reaction is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions include using a chlorinating agent such as $POCl_3$, oxalyl chloride, and the like. In another embodiment, oxalyl chloride is used as a chlorinating agent. Non-limiting examples of suitable reaction conditions include carrying out the reaction at a temperature in the range from about 0 °C to about 25 °C, or alternatively at a temperature in the range from about 5 °C to about 20 °C. Other non-limiting examples of suitable reaction conditions include carrying out the reaction in a suitable solvent. Non-limiting examples of suitable solvents that can be used include polar aprotic solvents, such as halogenated hydrocarbons (e.g., dichloromethane and chloroform), ethers (e.g., $Et_2O$), dioxane, tetrahydrofuran (THF) containing catalytic DMF, and the like, or mixtures thereof. The resulting solution containing reactant z(1) can be used, without further processing, to make the compound of formula I.

**Other Embodiments of Aspect (1)**

**[0075]** In another embodiment of Aspect (1), the compound of formula I is a compound of formula IA-1:

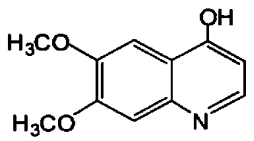



IA-1

or a pharmaceutically acceptable salt thereof, wherein:

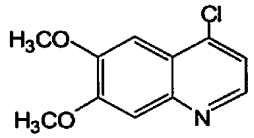
$X^1$ is H, Cl, Br, or F; and $X^2$ is H, Cl, Br, or F. Compound IA can be in the free base form or it can converted to a pharmaceutically acceptable salt thereof. Accordingly, compound IA can be converted to its L-malate salt by the addition of L-malic acid and a suitable solvent.

**[0076]** In another embodiment of Part D of Aspect (1), the compound of formula e(1) is compound e(2):



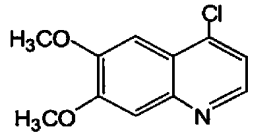

e(2) ;

and the compound of formula f(1) is compound f(2):



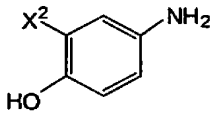

f(2) .

**[0077]** In another embodiment of Part C of Aspect (1), the compound of formula f(1) is compound f(2):




f(2) ;

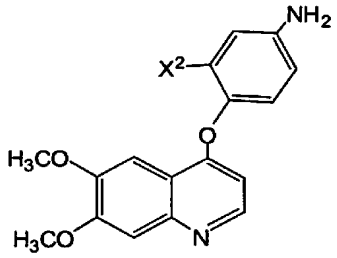
reactant y(1) is reactant (y)(2):




reactant (y)(2) ,

wherein $X^2$ is hydrogen or fluoro; and

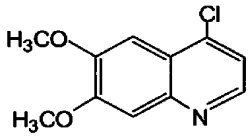
the compound of formula g(1) is of formula g(2):




g(2) .

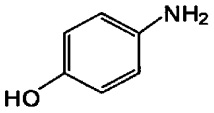
**[0078]** In a further embodiment, the reaction employs a non-nucleophilic base. In a further embodiment, the non-nucelophilic base is an alkali metal alkoxide; and the reaction is carried out in a polar solvent. In a further embodiment, the alkali metal alkoxide is sodium tert-butoxide, and the polar solvent is DMA.

**[0079]** In another embodiment of Part C of Aspect (1), the compound of formula f(1) is compound f(2):



f(2) ;

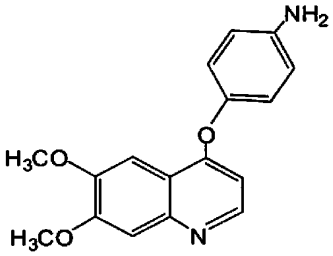
reactant y(1) is reactant (y)(3):



reactant (y)(3) ,

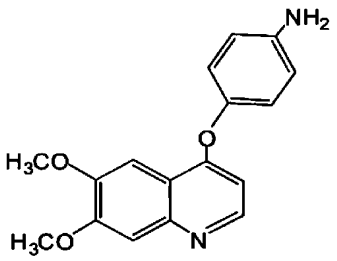
wherein $X^2$ is hydrogen or fluoro; and

the compound of formula g(1) is compound g(3):



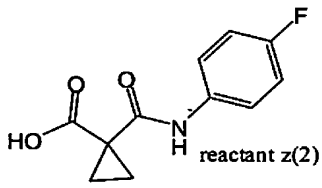
g(3) .

**[0080]** In another embodiment of Aspect (1) of this disclosure, the compound of formula g(1) is compound g(3):



g(3) ;

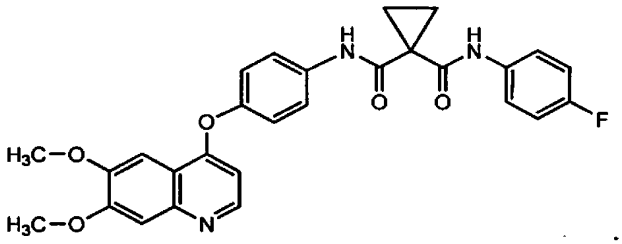
reactant z(1) is reactant (z)(2):




reactant z(2)

; and

the compound of formula I is compound IA:

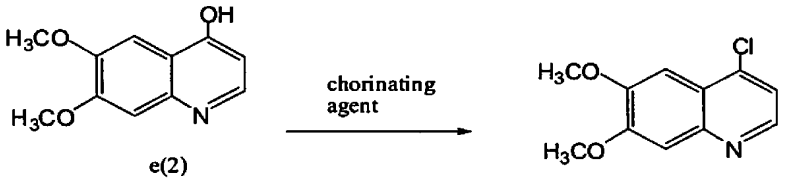



IA

**[0081]** In a further embodiment, the reaction is carried out in the presence of an inorganic base. In a further embodiment, the inorganic base is $K_2CO_3$, and the solvent employed in this reaction is a combination of THF and $H_2O$.

**[0082]** In another embodiment of Aspect (1) of this disclosure, $X^1$ and $X^2$ for each of formula g(1) and reactant z(1) are each selected from Cl or F. In another embodiment, $X^1$ and $X^2$ for each of formula g(2), and reactant z(1) are both F.

**[0083]** The compound of formula f(2),or a pharmaceutically acceptable salt thereof, can be made by converting the compound of formula e(2) to a compound of formula f(2) with a chlorinating agent in a suitable solvent:

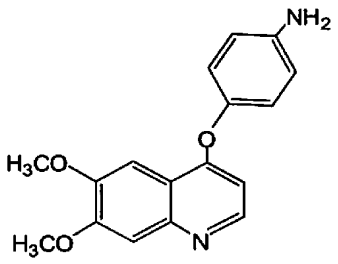



e(2) f(2)

The compound of formula f(2) can be in its free base form or converted to a pharmaceutically acceptable salt thereof. The reaction conditions that can be used in this aspect include any of the reaction conditions disclosed in Part E of Aspect (1).

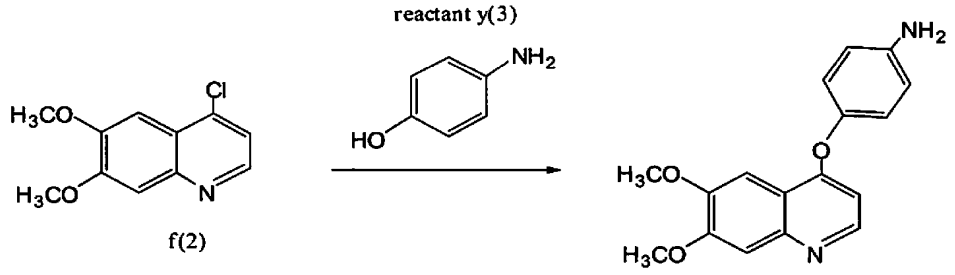
**Aspect 2: Processes for Making Compounds of Formula g(2)**

**[0084]** Aspect (2) of the disclosure relates to a process of preparing compound g(2):



g(2)

or a pharmaceutically acceptable salt thereof; the process comprising reacting compound f(2) with reactant y(3) under basic conditions (e.g., using 2,6-lutidine) in an appropriate solvent to yield compound g(3):



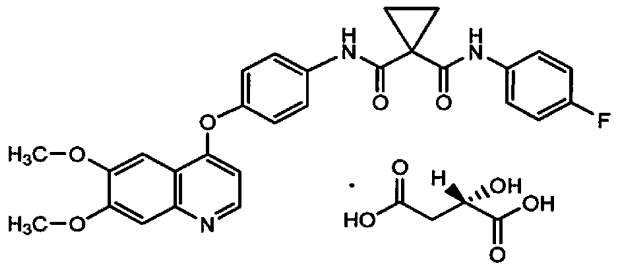

f(2) g(3)

The reaction conditions that can be used in this aspect include any of the reaction conditions disclosed in Part C of Aspect (1).

**[0085]** Alternative reaction conditions that can be used in this aspect include any of the reaction conditions disclosed in Parts C and D of Aspect (1).

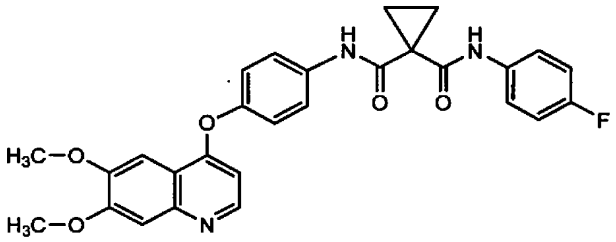
**Aspect 3: Processes for Making Compounds of IB**

**[0086]** As indicated above, in one aspect, the invention provides a process for preparing compound IB:



IB

from compound IA:



IA;

comprising:

(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) vacuum distilling the mixture successively; and

(d) isolating the compound of IB by filtration.

**[0087]** In one embodiment of this aspect, compound IA is admixed with a sufficient amount of L-malic acid in a methylethyl ketone (MEK)/water (1:1) mixture. Alternatively, L-malic acid is added as a solution in water to a mixture of compound IA in methyl ethyl ketone. Generally the amount of L-malic is greater than 1 molar equivalent relative to compound IA. The mixture of compound IA and L-malic acid in MEK/water is heated at about 40-70 °C, and preferably at about 50-60 °C, and more preferably at about 55-60 °C with agitation, such as by stirring or the like, for about 1 to about 5 hours. At the end of the heating, the mixture is optionally clarified by filtering to give a clear solution. The resulting clear solution is then vacuum distilled from 1 to about 5 times at 150 to 200 mm Hg and a maximum jacket temperature of 55 °C to provide the desired crystalline compound of IB.

**[0088]** In one embodiment, L-malic acid is charged as a solution in water to compound IA. Generally the amount of L-malic is greater than 1 molar equivalent relative to compound IA. The mixture of compound IA and L-malic acid in MEK/water is heated at about 40-70 °C, and preferably at about 50-60 °C, and more preferably at about 55-60 °C with agitation, such as by stirring or the like, for about 1 to about 5 hours. At the end of the heating, the mixture is optionally clarified by filtering to give a clear solution which is at a temperature of about 30-40 °C, and more preferably at a temperature of about 33-37 °C. This clear solution is optionally seeded to facilitate crystallization. After seeding, the resulting mixture is vacuum distilled as provided above.

**[0089]** In one embodiment, compound IB is in the N-1 form. In another embodiment, compound IB is in the N-2 form. In another embodiment, compound IB is a mixture of the N-1 form and the N-2 form. Processes for preparing the N-1 and N-2 forms of compound IB

are disclosed in WO 2010/083414 (PCT/US2010021194), the entire contents of which are incorporated herein by reference.

**[0090]** In another embodiment, the disclosure relates to compound IA or IB admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

**[0091]** In another embodiment, the disclosure relates to compound IA admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

**[0092]** In another embodiment, the disclosure relates to compound IB admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

**[0093]** In another embodiment, the disclosure relates to compound IB in the N-1 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

[0094] In another embodiment, the disclosure relates to compound IB in the N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

[0095] In another embodiment, the disclosure relates to compound IB as a mixture of the N-1 form and the N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

## Pharmaceutical Compositions

[0096] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound I, IA, or IB. Various carriers used in formulating pharmaceutically acceptable compositions and known techniques for their bulk preparation and subsequent production into unit dosage forms are employed to make the pharmaceutical compositions disclosed herein and are described in Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. D. B. Troy, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York. The amount of carriers and excipients used in a composition can be varied proportionally according to the amount of active ingredient used (that is, Compound I, IA or IB).

[0097] In one embodiment, the pharmaceutical composition is a tablet.

[0098] In another embodiment, the pharmaceutical composition is a capsule.

[0099] In another embodiment, the pharmaceutical composition comprises Compound IA.

[00100] In another embodiment, the pharmaceutical composition comprises Compound IB.

**[00101]** In another embodiment, the pharmaceutical composition comprises Compound IB. as the N-1 polymorph.

**[00102]** In another embodiment, the pharmaceutical composition comprises Compound IB as the N-2 polymorph.

**[00103]** In another embodiment, the pharmaceutical composition comprises Compound IB as a mixture of the N-1 form and the N-2 form.

**[00104]** In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; one or more fillers; one or more disintergrants; one or more glidants; and one or more lubricants.

**[00105]** In this embodiment, the filler comprises microcrystalline cellulose.

**[00106]** In this embodiment, the disintegrant comprises croscarmellose sodium.

**[00107]** In this embodiment, the disintegrant comprises croscarmellose sodium and sodium starch glycolate.

**[00108]** In this embodiment, the glidant comprises fumed silica.

**[00109]** In this embodiment, the lubricant comprises stearic acid.

**[00110]** In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; lactose; hydroxypropyl cellulose; croscarmellose sodium; colloidal silicon dioxide; and magnesium stearate.

**[00111]** In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; hydroxypropyl cellulose; a surfactant; croscarmellose sodium; colloidal silicon dioxide; and magnesium stearate.

**[00112]** In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; croscarmellose sodium; fumed silica; and stearic acid.

**[00113]** In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; anhydrous lactose; hydroxypropyl cellulose; croscarmellose sodium; silicon dioxide; and magnesium stearate.

**[00114]** In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; anhydrous lactose; hydroxypropyl cellulose; a surfactant; croscarmellose sodium; silicon dioxide; and magnesium stearate.

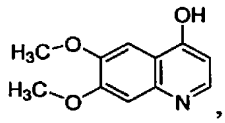
**[00115]** In another aspect, the disclosure provides a pharmaceutical composition according to Tables 1, 2, 2A, 3, 4, 5, and 6 as provided above. The compositions are prepared according to methods available to the skilled artisan. For example, the Tablet

formulations are prepared by combining, blending, and compacting the components of the tablet compositions. The capsule compositions are prepared by combining and blending the components and then placing the blend in a gelatin capsule.

**[00116]** For example, the 25 mg capsules (Table 3, 10 percent drug load formulation) are prepared as follows. The drug substance is delumped through a mill. The delumped drug substance is then co-screened with an equal volume Prosolv HD90. The excipients, except for stearic acid, are screened and charged to a blender along with the co-screened drug substance. The mixture is blended in a V-Blender. This process is repeated to manufacture a second sublot of unlubricated blend. The two sublots are then combined together in a V-blender and lubricated with stearic acid which has been co-screened with an equal volume of unlubricated blend. The final blend is then encapsulated into opaque, size 1 gelatin capsules using an automated capsule filling machine. The capsules are then weight sorted through an automatic weight sorter.

**[00117]** The 100-mg capsules (Table 4, 50% drug load formulation) are manufactured in two equal sublots of 5 kg of blend which are combined prior to lubricant blend The drug substance is delumped through a mill. The excipients, except for stearic acid, are screened and charged to the mixer along with the delumped drug substance. The mixture is blended with a high shear mixer. The process is repeated to manufacture a second sublot of unlubricated blend. The final blend is then encapsulated into Swedish oraopaque, size 1 gelatin capsules using an automated capsule filling machine. The capsuare then weight sorted through an automatic weight sorter.

**[00118]** The 50 and 60 mg capsules (Tables 5 and 6) are prepared in a similar fashion as the 25 and 100 mg capsules.

**[00119]** In another aspect, the disclosure relates to a pharmaceutical composition comprising a compound of Formula IA or IB and a pharmaceutically acceptable carrier admixed with less than 100 ppm of 6,7-dimethoxy-quinoline-4-ol. 6,7-dimethoxy-quinoline-4-ol, the structure of which is 

, can be used as reagent e(1) to make chloride f(1) and is a byproduct that may form during the synthesis of Compound IA or IB. Minimizing the concentration of contaminants or byproducts such as 6,7-dimethoxy-quinoline-4-ol in pharmaceutical compositions destined for human administration is desirable.

**[00120]** In one embodiment, the pharmaceutical composition as defined in any of the previous embodiments (for example, the pharmaceutical composition of Tables 1, 2, 2A, 3, 4, 5, and6) is admixed with 100 ppm 6,7-dimethoxy-quinoline-4-ol.

**[00121]** In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 50 ppm 6,7-dimethoxy-quinoline-4-ol.

**[00122]** In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 25 ppm 6,7-dimethoxy-quinoline-4-ol.

**[00123]** In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 15 ppm 6,7-dimethoxy-quinoline-4-ol.

**[00124]** In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 10 ppm 6,7-dimethoxy-quinoline-4-ol.

**[00125]** In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 5 ppm 6,7-dimethoxy-quinoline-4-ol.

**[00126]** In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 2.5 ppm 6,7-dimethoxy-quinoline-4-ol.

**[00127]** In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; one or more fillers; one or more disintergrants; one or more glidants; and one or more lubricants admixed with 100 ppm or less 6,7-dimethoxy-quinoline-4-ol.

**[00128]** In this embodiment, the filler comprises microcrystalline cellulose.

**[00129]** In this embodiment, the disintegrant comprises croscarmellose sodium.

**[00130]** In this embodiment, the disintegrant comprises croscarmellose sodium and sodium starch glycolate.

**[00131]** In this embodiment, the glidant comprises fumed silica.

**[00132]** In this embodiment, the lubricant comprises stearic acid.

**[00133]** In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; croscarmellose sodium; fumed silica; and stearic acid; admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment of this embodiment, the composition is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with

5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

**[00134]** In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; anhydrous lactose; hydroxypropyl cellulose; a surfactant; croscarmellose sodium; silicon dioxide; and magnesium stearate; admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment of this embodiment, the composition is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

**[00135]** In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; croscarmellose sodium; fumed silica; and stearic acid; ; admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment of this embodiment, the composition is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

## EXAMPLES

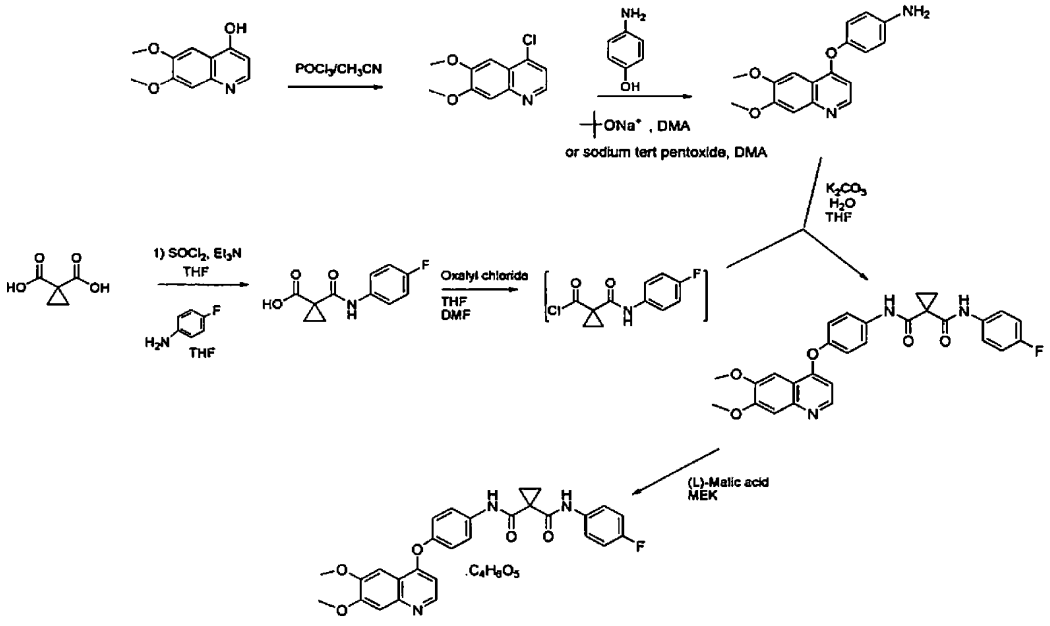
**[00136]** The invention is illustrated further by the following examples in Scheme 1 and the description thereof, which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the invention, as demonstrated by the following examples. Those skilled in the art will also recognize that it may be necessary to utilize different solvents or reagents to achieve some of the above transformations. Unless otherwise specified, all reagents and solvents are of standard commercial grade and are used without further purification. The

appropriate atmosphere to run the reaction under, for example, air, nitrogen, hydrogen, argon, and the like, will be apparent to those skilled in the art.

**Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof.**

**[00137]** A synthetic route that can be used for the preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Figure 1:

**Figure 1**




**Preparation of 4-Chloro-6,7-dimethoxy-quinoline**

**[00138]** A reactor was charged sequentially with 6,7-dimethoxy-quinoline-4-ol (47.0 kg) and acetonitrile (318.8 kg). The resulting mixture was heated to approximately 60 °C, and phosphorus oxychloride ($POCl_3$, 130.6 kg) was added. After the addition of $POCl_3$, the temperature of the reaction mixture was raised to approximately 77 °C. The reaction was deemed complete (approximately 13 hours) when less than 3% of the starting material remained (in-process high-performance liquid chromatography [HPLC] analysis). The reaction mixture was cooled to approximately 2 – 7 °C and then quenched into a chilled solution of dichloromethane (DCM, 482.8 kg), 26 % $NH_4OH$ (251.3 kg), and water (900 L). The resulting mixture was warmed to approximately 20 – 25 °C, and phases were separated.

The organic phase was filtered through a bed of AW hyflo super-cel NF (Celite; 5.4 kg) and the filter bed was washed with DCM (118.9 kg). The combined organic phase was washed with brine (282.9 kg) and mixed with water (120 L). The phases were separated and the organic phase was concentrated by vacuum distillation with the removal of solvent (approximately 95 L residual volume). DCM (686.5 kg) was charged to the reactor containing organic phase and concentrated by vacuum distillation with the removal of solvent (approximately 90 L residual volume). Methyl t-butyl ether (MTBE, 226.0 kg) was then charged and the temperature of the mixture was adjusted to -20 to -25 °C and held for 2.5 hours resulting in solid precipitate which was then filtered and washed with n-heptane (92.0 kg), and dried on a filter at approximately 25 °C under nitrogen to afford the title compound. (35.6 kg).

**Preparation of 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine**

**[00139]** 4-Aminophenol (24.4 kg) dissolved in N,N-dimethylacetamide (DMA, 184.3 kg) was charged to a reactor containing 4-chloro-6,7-dimethoxyquinoline (35.3 kg), sodium t-butoxide (21.4 kg) and DMA (167.2 kg) at 20-25 °C. This mixture was then heated to 100-105 °C for approximately 13 hours. After the reaction was deemed complete as determined using in-process HPLC analysis (<2% starting material remaining), the reactor contents were cooled at 15 to 20 °C and water (pre-cooled, 2 to 7 °C, 587 L) charged at a rate to maintain 15 to 30 °C temperature . The resulting solid precipitate was filtered, washed with a mixture of water (47 L) and DMA (89.1 kg) and finally with water (214 L). The filter cake was then dried at approximately 25 °C on filter to yield crude 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (59.4 kg wet, 41.6 kg dry calculated based on LOD). Crude 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine was refluxed (approximately 75 °C) in a mixture of tetrahydrofuran (THF, 211.4 kg) and DMA (108.8 kg) for approximately 1hour and then cooled to 0-5 °C and aged for approximately 1 h after which time the solid was filtered, washed with THF (147.6 kg) and dried on a filter under vacuum at approximately 25 °C to yield 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (34.0 kg).

**Alternative Preparation of 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine**

**[00140]** 4-chloro-6,7-dimethoxyquinoline (34.8 kg) and 4-aminophenol (30.8 kg) and sodium tert pentoxide (1.8 equivalents) 88.7 kg, 35 wt percent in THF) were charged to a reactor, followed by N,N-dimethylacetamide (DMA, 293.3 kg). This mixture was then heated to 105-115 °C for approximately 9 hours. After the reaction was deemed complete as

determined using in-process HPLC analysis (<2% starting material remaining), the reactor contents were cooled at 15 to 25 °C and water (315 kg) was added over a two hour period while maintaining the temperature between 20 and 30 °C. The reaction mixture was then agitated for an additional hour at 20 to 5 °C. The crude product was collected by filtration and washed with a mixture of 88 kg water and 82.1 kg DMA, followed by 175 kg water. The product was dried on a filter drier for 53 hours. The LOD showed less than 1% w/w.

**[00141]** In an alternative procedure, 1.6 equivalents of sodium tert-pentoxide were used and the reaction temperature was increased from 110-120 °C. In addition , the cool down temperature was increased to 35-40 °C and the starting temperature of the water addition was adjusted to 35-40 °C, with an allowed exotherm to 45 °C.

**Preparation of 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid**

**[00142]** Triethylamine (19.5 kg) was added to a cooled (approximately 5 C) solution of cyclopropane-1,1-dicarboxylic acid (24.7 kg) in THF (89.6 kg) at a rate such that the batch temperature did not exceed 5 °C. The solution was stirred for approximately 1.3 hours, and then thionyl chloride (23.1 kg) was added, keeping the batch temperature below 10 °C. When the addition was complete, the solution was stirred for approximately 4 h keeping temperature below 10 °C. A solution of 4–fluoroaniline (18.0 kg) in THF (33.1 kg) was then added at a rate such that the batch temperature did not exceed 10 °C. The mixture was stirred for approximately 10 hours after which the reaction was deemed complete. The reaction mixture was then diluted with isopropyl acetate (218.1 kg). This solution was washed sequentially with aqueous sodium hydroxide (10.4 kg, 50 % dissolved in 119 L of water) further diluted with water (415 L), then with water (100 L) and finally with aqueous sodium chloride (20.0 kg dissolved in 100 L of water). The organic solution was concentrated by vacuum distillation (100 L residual volume) below 40 °C followed by the addition of n-heptane (171.4 kg), which resulted in the precipitation of solid. The solid was recovered by filtration and washed with n-Heptane (102.4 kg) resulting in wet crude, 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (29.0 kg). The crude, 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid was dissolved in methanol (139.7 kg) at approximately 25 °C followed by the addition of water (320 L) resulting in slurry which was recovered by filtration, washed sequentially with water (20 L) and n-heptane (103.1 kg) and then dried on the filter at approximately 25 °C under nitrogen to afford the title compound (25.4 kg).

**Preparation of 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride**

**[00143]** Oxalyl chloride (12.6 kg) was added to a solution of 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (22.8 kg) in a mixture of THF (96.1 kg) and N, N-dimethylformamide (DMF; 0.23 kg) at a rate such that the batch temperature did not exceed 25 °C. This solution was used in the next step without further processing.

**Alternative Preparation of 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride**

**[00144]** A reactor was charged with 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (35 kg), 344 g DMF, and 175kg THF. The reaction mixture was adjusted to 12-17 °C and then to the reaction mixture was charged 19.9 kg of oxalyl chloride over a period of 1 hour. The reaction mixture was left stirring at 12-17 °C for 3 to 8 hours. This solution was used in the next step without further processing.

**Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (Compound IA)**

**[00145]** The solution from the previous step containing 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride was added to a mixture of compound 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (23.5 kg) and potassium carbonate (31.9 kg) in THF (245.7 kg) and water (116 L) at a rate such that the batch temperature did not exceed 30 °C. When the reaction was complete (in approximately 20 minutes), water (653 L) was added. The mixture was stirred at 20-25 °C for approximately 10 hours, which resulted in the precipitation of the product. The product was recovered by filtration, washed with a pre-made solution of THF (68.6 kg) and water (256 L), and dried first on a filter under nitrogen at approximately 25 °C and then at approximately 45 °C under vacuum to afford the title compound (41.0 kg, 38.1 kg, calculated based on LOD).

**Alternative Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide**

**[00146]** A reactor was charged with 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (35.7 kg, 1 equivalent), followed by 412.9 kg THF. To the reaction mixture was charged a solution of 48.3 $K_2CO_3$ in 169 kg water. The acid chloride solution of described in the Alternative Preparation of 1-(4–Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride above was transferred to the reactor containing 4-(6,7-dimethoxy-quinoline-4-yloxy)-

phenylamine while maintaining the temperature between 20-30 °C over a minimum of two hours. The reaction mixture was stirred at 20-25 °C for a minimum of three hours. The reaction temperature was then adjusted to 30-25 °C and the mixture was agitated. The agitation was stopped and the phases of the mixture were allowed to separate. The lower aqueous phase was removed and discarded. To the remaining upper organic phase was added 804 kg water. The reaction was left stirring at 15-25 °C for a minimum of 16 hours.

**[00147]** The product precipitated. The product was filtered and washed with a mixture of 179 kg water and 157.9 THF in two portions. The crude product was dried under a vacuum for at least two hours. The dried product was then taken up in 285.1 kg THF. The resulting suspension was transferred to reaction vessel and agitated until the suspension became a clear (dissolved) solution, which required heating to 30-35 °C for approximately 30 minutes. 456 kg water was then added to the solution, as well as 20 kg SDAG-1 ethanol (ethanol denatured with methanol over two hours. The mixture was agitated at 15-25 °C for at least 16 hours. The product was filtered and washed with a mixture of 143 kg water and 126.7 THF in two portions. The product was dried at a maximum temperature set point of 40 °C.

**[00148]** In an alternative procedure, the reaction temperature during acid chloride formation was adjusted to 10-15 °C. The recrystallization temperature was changed from 15-25 °C to 45-50 °C for 1 hour and then cooled to 15-25 °C over 2 hours.

**Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy- quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L) malate salt (Compound IB)**

**[00149]** Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (1-5; 13.3 kg), L-malic acid (4.96 kg), methyl ethyl ketone (MEK; 188.6 kg) and water (37.3 kg) were charged to a reactor and the mixture was heated to reflux (approximately 74 °C) for approximately 2 hours. The reactor temperature was reduced to 50 to 55 °C and the reactor contents were filtered. These sequential steps described above were repeated two more times starting with similar amounts of 1-5 (13.3 kg), L-Malic acid (4.96 kg), MEK (198.6 kg) and water (37.2 kg). The combined filtrate was azeotropically dried at atmospheric pressure using MEK (1133.2 kg) (approximate residual volume 711 L; KF $\leq$ 0.5 % w/w) at approximately 74 °C. The temperature of the reactor contents was reduced to 20 to 25 °C and held for approximately 4 hours resulting in solid precipitate which was filtered, washed with MEK (448 kg) and dried under vacuum at 50°C to afford the title compound (45.5 kg).

**Alternative Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L) malate salt**

**[00150]** Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (47.9 kg), L-malic acid (17.2), 658.2 kg methyl ethyl ketone, and 129.1 kg water (37.3 kg) were charged to a reactor and the mixture was heated 50-55 °C for approximately 1-3 hours, and then at 55-60 °C for an addition al 4-5 hours. The mixture was clarified by filtration through a 1 μm cartridge. The reactor temperature was adjusted to 20-25 °C and vacuum distilled with a vacuum at 150-200 mm Hg with a maximum jacket temperature of 55 °C to the volume range of 558-731 L.

**[00151]** The vacuum distillation was performed two more times with the charge of 380 kg and 380.2 kg methyl ethyl ketone, respectively. After the third distillation, the volume of the batch was adjusted to 18 v/w of Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide by charging 159.9 kg methyl ethyl ketone to give a total volume of 880L. An addition al vacuum distillation was carried out by adjusting 245.7 methyl ethyl ketone. The reaction mixture was left with moderate agitation at 20-25 °C for at least 24 hours. The product was filtered and washed with 415.1 kg methyl ethyl ketone in three portions. The product was dried under a vacuum with the jacket temperature set point at 45 °C.

**[00152]** In an alternative procedure, the order of addition was changed so that a solution of 17.7 kg L-malic acid dissolved in 129.9 kg water was added to Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (48.7 kg) in methyl ethyl ketone (673.3 kg).

**Preparation of Compound IB, Form N-1**

**[00153]** A solution was prepared by adding tetrahydrofuran (12 mL/g-bulk-LR (limiting reagent); 1.20 L) and N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (100 g; 1.00 equiv; 100.00 g) and (L)-malic acid (1.2 equiv (molar); 32.08 g) to a 1 L reactor. Water (0.5317 mL/g-bulk-LR; 53.17 mL) was added and the solution was heated to 60 °C and maintained at that temperature for one hour until the solids were fully dissolved. The solution was passed through a Polish Filter.

**[00154]** At 60 °C, acetonitrile (12 mL/g-bulk-LR; 1.20 L) was added over a period of 8 hours. The solution was held at 60 °C for 10 hours. The solution was then cooled to 20 °C and held for 1 hour. The solids were filtered and washed with acetonitrile (12 mL/g-bulk-LR;

1.20 L). The solids were dried at 60 °C (25 mm Hg) for 6 hours to afford compound (I), Form N-1 (108 g; 0.85 equivalent; 108.00 g; 85.22% yield) as a white crystalline solid.

**Alternate Preparation of Compound IB, Form N-1**

**[00155]** A solution was prepared with 190 mL tetrahydrofuran (110 mL), methyl isobutyl ketone, and 29 mL water. Next, 20 mL of this solution were transferred into an amber bottle, and then saturated by adding N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L)-malate until a thick slurry formed, and aging for at least 2 hours with stirring at room temperature. The solids were removed by filtration through a Buchner funnel, rendering a clear saturated solution.

**[00156]** Separately, a powder blend was made with known amounts of two batches of compound IB: (1) 300 mg of batch 1, which contained approximately 41% compound IB, Form N-1 and 59% compound IB, Form N-2 by Raman spectroscopy analysis, and (2) 200 mg of batch 2, which had a XPRD pattern similar to compound IB, Form N-2.

**[00157]** The compound IB, Form N-1 and compound (I), Form N-2 powder blend was added into the saturated solution, and the slurry was aged under magnetic stirring at room temperature for 25 days. The slurry was then sampled and filtered through a Buchner funnel to obtain 162 mg of wet cake. The wet cake was dried in a vacuum oven at 45 °C to afford 128 mg of crystalline compound IB in the N-1 form.

**Preparation of Crystalline Compound IB, Form N-2**

**Preparation of Crystalline Compound IB, Form N-2 Seed Crystals**

**[00158]** A solution was prepared by combining 20 ml of acetone and 300 mg of compound IA (N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide) in a 25ml screw capped vial. Next, 0.758ml of a 0.79M (L)-malic acid stock solution was added to the vial with magnetic stirring. The solution was then left stirring for 24 hours at ambient temperature. The sample was then suction filtered with 0.45μm PTFE filter cartridge and dried *in vacuo* at ambient temperature overnight.

**Preparation of Crystalline Compound IB, Form N-2.**

**[00159]** To a reactor were added N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (48 g; 1.00 equiv; 48.00 g) and tetrahydrofuran (16.5 mL/g-bulk-LR; 792.00 mL). The water content was adjusted to 1 wt% water. The solution was heated to 60 °C. Once dissolved, the solution was passed through a polish filter to provide the first solution.

**[00160]** In a separate reactor, (L)-malic acid (1.2 equiv (molar); 15.40 g) was dissolved into methyl isobutyl ketone (10 mL/g-bulk-LR; 480.00 mL) and tetrahydrofuran (1 mL/g-bulk-LR; 48.00 mL). Next, 50 mL of the (L)-malic acid solution was added to the first solution at 50 °C. Seed crystals were added (1%, 480 mg) and the malic acid solution was added at 50 °C dropwise via an addition funnel (1.3 ml/min over 3 hours). The slurry was held at 50 °C for 18 hours and then was cooled to 25 °C over 30 minutes. The solids were filtered, and washed with 20% tetrahydrofuran/methyl isobutyl ketone (10V, 480 mL). The solids were dried under vacuum at 60 °C for 5 hours to afford compound IB (55.7 g; 0.92 equivalent; 55.70 g; 91.56% yield) as an off-white crystalline solid.

**Stability Studies of Pharmaceutical Compositions**

**[00161]** The pharmaceutical capsule compositions of Tables 3 and 4 were prepared by mixing the ingredients according to processes known in the art.

**Table 3**

| **Ingredient** | **mg/unit dose** |
|---|---|
| Compound IB (10 % drug load as Compound IA) | 25 |
| Microcrystalline Cellulose | 196.75 |
| Croscarmellose sodium | 12.5 |
| Sodium starch glycolate | 12.5 |
| Fumed Silica | 0.75 |
| Stearic acid | 2.5 |
| **Total Fill Weight** | 250 |

**Table 4**

| **Ingredient** | **mg/unit dose** |
|---|---|
| Compound IB (50 % drug load as Compound IA) | 100 |
| Silicified Microcrystalline Cellulose | 75.40 |
| Croscarmellose sodium | 10.00 |
| Sodium Starch Glycolate | 10.00 |
| Fumed silica | 0.6 |
| Stearic Acid | 4.0 |
| **Total Fill Weight** | 200 |

**[00162]** The capsule compositions were subjected to stability studies to monitor the formation of 6,7-dimethoxy-quinoline-4-ol at various temperatures and relative humidities over time. The results are summarized in Tables 7A and 7B and Tables 8A and 8B.

**Table 7A: Stability of 25 Mg Capsules (Table 3)**

| | Conditions | Bottle A1 | Bottle A2 | Bottle A3 | Bottle A4 |
|---|---|---|---|---|---|
| | | PPM of 6,7-dimethoxy-quinoline-4-ol | | | |
| Initial T=0 | 25 °C/60% RH | 2 | 2 | 3 | 3 |
| 1 Month | 25 °C/60% RH | 3 | 4 | 5 | NA |
| | 30 °C/75% RH | 4 | 4 | NA | NA |
| | 40 °C/75% RH | 9 | 9 | 10 | NA |
| 3 Months | 25 °C/60% RH | 5 | 5 | 7 | NA |
| | 30 °C/75% RH | 7 | 6 | NA | NA |
| | 40 °C/75% RH | 22 | 23 | 24 | NA |
| 6 Months | 25 °C/60% RH | 6 | 6 | 7 | 7 (3M in blister) |
| | 30 °C/75% RH | 9 | 9 | NA | NA |
| | 40 °C/75% RH | 40 | 44 | 43 | 27 (3M in blister) |
| 9 Months | 25 °C/60% RH | 7 | 7 | 9 | 8 (6M in blister) |
| | 30 °C/75% RH | 13 | 12 | NA | NA |
| | 40 °C/75% RH | NA | NA | 68 | 60 (6M in blister) |

M=Months; NA=Not Applicable; RH= Relative Humidity; PPM= Parts per Million. A portion of Bottle A4 was repackaged in a blister pack after being stored in bottles for 3 months.

**Table 7B: Stability of 25 Mg Capsules (Table 3)**

| | Conditions | Bottle B1 | Bottle B | Bottle B3 | Bottle B4 |
|---|---|---|---|---|---|
| | | PPM of 6,7-dimethoxy-quinoline-4-ol | | | |
| Initial T=0 | 25 °C/60% RH | 3 | 1 | 2 | 2 |
| 1 Month | 25 °C/60% RH | <2 | <2 | <2 | NA |
| | 30 °C/75% RH | <2 | <2 | NA | NA |
| | 40 °C/75% RH | 2 | <2 | <2 | NA |
| 3 Months | 25 °C/60% RH | 2 | <2 | <2 | NA |
| | 30 °C/75% RH | 2 | <2 | NA | NA |
| | 40 °C/75% RH | 3 | <2 | <2 | NA |
| 6 Months | 25 °C/60% RH | <2 | <2 | <2 | <2 (3M in blister) |
| | 30 °C/75% RH | 2 | <2 | NA | NA |
| | 40 °C/75% RH | 4 | <2 | 3 | 3 (3M in blister) |
| 9 Months | 25 °C/60% RH | <2 | <2 | <2 | <2 (6M in blister) |
| | 30 °C/75% RH | 3 | <2 | NA | NA |
| | 40 °C/75% RH | NA | NA | 5 | 4 (6M in blister) |

A portion of Bottle B4 was repackaged in a blister pack after being stored in bottles for 3 months.

**Table 8A: Stability of 100 Mg Capsules (Table 4)**

| | Conditions | Bottle A1 | Blister A2 | Bottle A3 |
|---|---|---|---|---|
| | | PPM of 6,7-dimethoxy-quinoline-4-ol | | |
| Initial T=0 | 25 °C/60% RH | 4 | 4 | 6 |
| 1 Month | 25 °C/60% RH | 4 | 4 | 6 |
| | 30 °C/75% RH | 4 | NA | 6 |
| | 40 °C/75% RH | 6 | 6 | 9 |
| 3 Months | 25 °C/60% RH | 5 | 5 | 7 |
| | 30 °C/75% RH | 6 | NA | 7 |
| | 40 °C/75% RH | 10 | 10 | 12 |
| 6 Months | 25 °C/60% RH | 5 | 5 | |
| | 30 °C/75% RH | 6 | NA | |
| | 40 °C/75% RH | 11 | 17 | |

M=Months; NA=Not Applicable; RH= Relative Humidity; PPM= Parts per Million.

**Table 8B: Stability of 100 Mg Capsules (Table 4)**

| | Conditions | Bottle B1 | Blister B2 | Bottle B3 |
|---|---|---|---|---|
| | | PPM of 6,7-dimethoxy-quinoline-4-ol | | |
| Initial T=0 | 25 °C/60% RH | 1 | 1 | 2 |
| 1 Month | 25 °C/60% RH | <2 | <2 | <2 |
| | 30 °C/75% RH | <2 | <2 | 2 |
| | 40 °C/75% RH | <2 | <2 | 2 |
| 3 Months | 25 °C/60% RH | <2 | <2 | <2 |
| | 30 °C/75% RH | <2 | NA | <2 |
| | 40 °C/75% RH | <2 | <2 | 2 |
| 6 Months | 25 °C/60% RH | <2 | <2 | |
| | 30 °C/75% RH | <2 | NA | |
| | 40 °C/75% RH | 2 | 2 | |

M=Months; NA=Not Applicable; RH= Relative Humidity; PPM= Parts per Million.

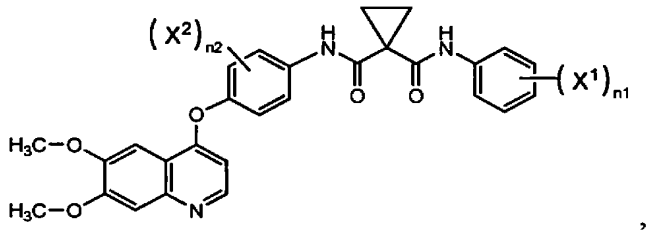
**[00163]** The results summarized in Tables 7A and 7B and 8A and 8B indicate that formation of 6,7-dimethoxy-quinoline-4-ol was minimized to 50 ppm or less over time in the capsule formulations.

**[00164]** The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that

changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled. All references cited herein are incorporated by reference in their entirety.

## CLAIMS

1. A process for preparing a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is H, Br, Cl, or F;

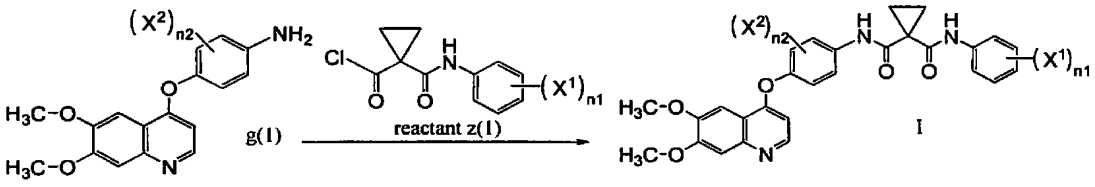
$X^2$ is H, Br, Cl, or F;

n1 is 1-2; and

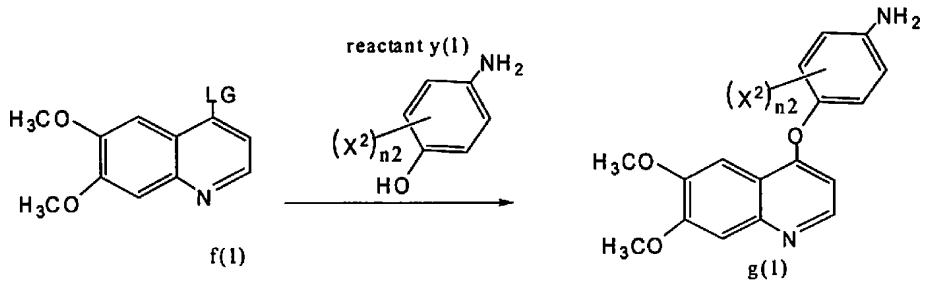
n2 is 1-2;

the process comprising:

contacting the compound of formula g(1) with reactant z(1) to yield the compound of formula I:

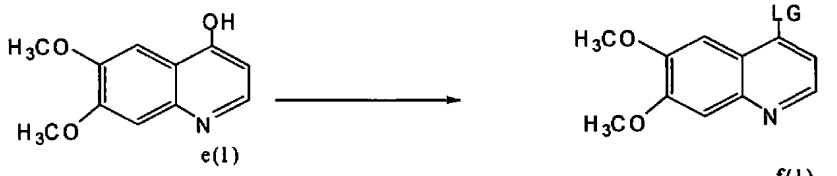



2. The process according to claim 1, wherein the compound of formula g(1) is made by reacting a compound of formula f(1) with reactant y(1) to yield the compound of formula g(1):



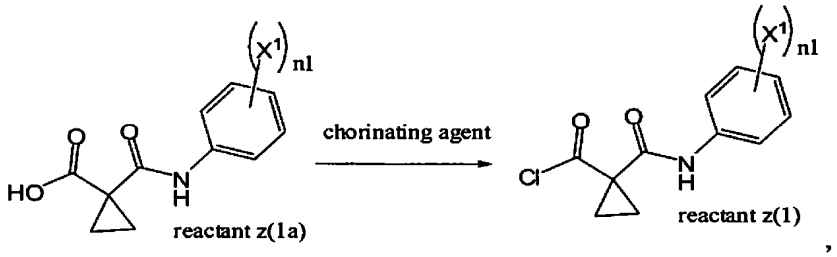

wherein LG represents a leaving group, and each $X^2$ and n2 are as defined in claim 1.

3. The process according to claim 2, wherein the compound of formula f(1) is made by converting compound e(1) to the compound of formula f(1):



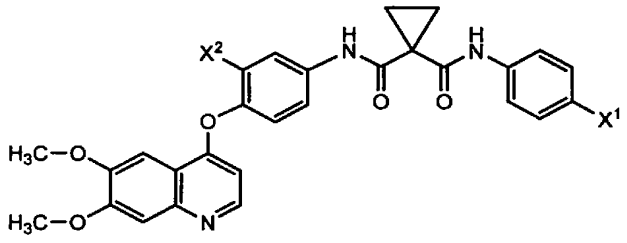

wherein LG represents a leaving group.

4. The process according to claim 1, wherein reactant z(1) is made by reacting reactant z(1a) with a chlorinating agent to yield reactant z(1):




wherein $X^1$ is Br, Cl, or F; and n1 is 1-2.

5. The process according to claim 1, wherein the compound of formula I is compound IA-1:



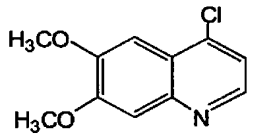

IA

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is H, Cl, Br, or F; and

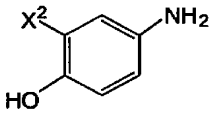
$X^2$ is H, Cl, Br, or F.

6. The process according to claim 5, wherein the compound of formula f(1) is compound f(2):



f(2) ;

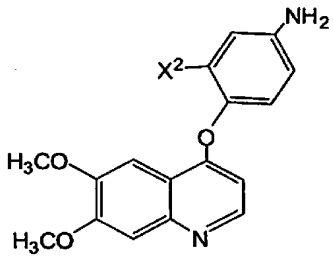
reactant y(1) is reactant (y)(2):



reactant (y)(2) ,

wherein $X^2$ is hydrogen or fluoro; and

the compound of formula g(1) is of formula g(2):



g(2) .

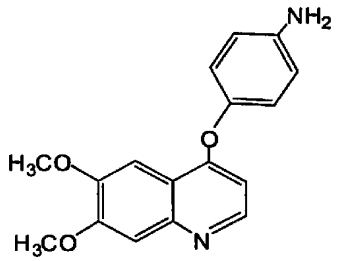
7. The process according to claim 6, wherein the reaction employs a non-nucleophilic base.

8. The process according to claim 7, wherein the non-nucleophilic base is an alkali metal alkoxide; and the reaction is carried out in a polar solvent.

9. The process according to claim 8, wherein the alkali metal alkoxide is sodium tert-butoxide, and the polar solvent is DMA.

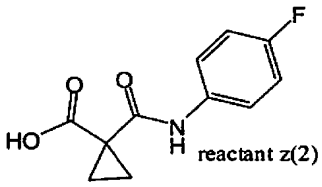
10. The process according to claim 8, wherein the alkali metal alkoxide is sodium tert-pentoxide, and the polar solvent is DMA.

11. The process according to claim 1, wherein the compound of formula g(1) is of compound g(3):



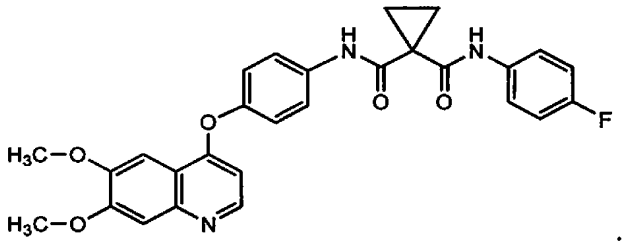
g(3) ;

reactant z(1) is reactant (z)(2):



reactant z(2) ; and

the compound of formula I is compound IA:

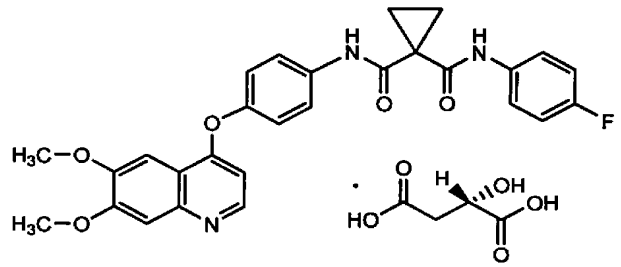


IA

12. The process according to claim 11, wherein the reaction is carried out in the presence of an inorganic base.

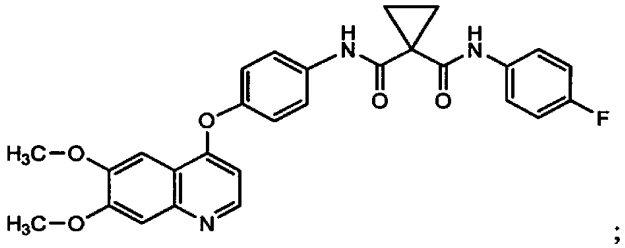
13. The process according to claim 12, wherein the inorganic base is $K_2CO_3$, and the solvent employed in this reaction is a combination of THF and $H_2O$.

14. A process for preparing compound IB:



IB

from compound IA:



;

IA

comprising:

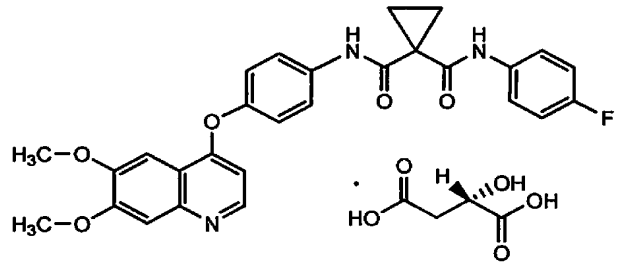
(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) vacuum distilling the mixture successively; and

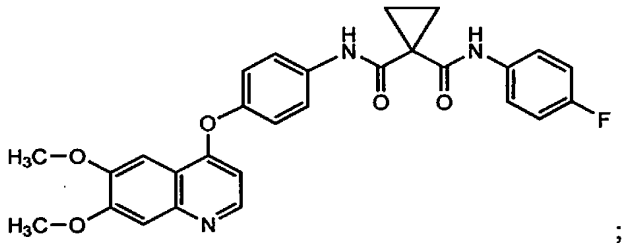
(d) isolating the compound of IB by filtration.

15. A process for preparing compound IB:



IB

from compound IA:



;

IA

comprising:

(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;
(b) cooling the mixture;
(c) seeding the mixture with the compound of IB;
(d) vacuum distilling the mixture; and
(e) isolating the compound of IB by filtration.

16. Compound IA or IB admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

17. Compound IB admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

18. Compound IB in the N-1 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

19. Compound IB in the N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

20. Compound IB as a mixture of the N-1 form and N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

21. A pharmaceutical composition according to Table 1.

**Table 1**

| Ingredient | % w/w |
|---|---|
| Compound I | 31.68 |
| Microcrystalline Cellulose (Avicel PH102) | 38.85 |
| Lactose anhydrous 60 M | 19.42 |
| Hydroxypropyl Cellulose, EXF | 3.00 |
| Croscarmellose Sodium | 3.00 |
| **Total Intra-granular** | **95.95** |
| Silicon dioxide, Colloidal PWD | 0.30 |
| Croscarmellose Sodium | 3.00 |
| Magnesium Stearate | 0.75 |
| **Total** | **100.00** |

22. A pharmaceutical composition according to Table 2.

**Table 2**

| Ingredient | (% w/w) |
|---|---|
| Compound I | 25.0-33.3 |
| Microcrystalline Cellulose, NF | q.s |
| Hydroxypropyl Cellulose, NF | 3 |
| Poloxamer, NF | 0-3 |
| Croscarmellose Sodium, NF | 6.0 |
| Colloidal Silicon Dioxide, NF | 0.5 |
| Magnesium Stearate, NF | 0.5-1.0 |
| Total | 100 |

23. A pharmaceutical composition according to Table 2A.

**Table 2A**

| **Ingredient** | **% w/w** |
|---|---|
| Compound IB (10 % drug load as Compound IA) | 12.67 |
| MCC | 51.52 |
| Lactose | 25.76 |
| Hydroxypropyl cellulose | 3.0 |
| Croscarmellose Sodium | 6.0 |
| Colloidal Silicon Dioxide | 0.3 |
| Magnesium Stearate | 0.75 |
| **Total** | **100** |

24. A pharmaceutical composition according to Table 3.

**Table 3**

| **Ingredient** | **mg/unit dose** |
|---|---|
| Compound IB (10 % drug load as Compound IA) | 25 |
| Silicified Microcrystalline Cellulose | 196.75 |
| Croscarmellose sodium | 12.5 |
| Sodium starch glycolate | 12.5 |
| Fumed Silica | 0.75 |
| Stearic acid | 2.5 |
| **Total Fill Weight** | 250 |

25. A pharmaceutical composition according to Table 4.

**Table 4**

| **Ingredient** | **mg/unit dose** |
|---|---|
| Compound IB (50 % drug load as Compound IA) | 100 |
| Silicified Microcrystalline Cellulose | 75.40 |
| Croscarmellose sodium | 10.00 |
| Sodium Starch Glycolate | 10.00 |
| Fumed silica | 0.6 |
| Stearic Acid | 4.0 |
| **Total Fill Weight** | 200 |

26. A pharmaceutical composition according to Table 5.

**Table 5**

| | **mg/unit dose** |
|---|---|
| **Ingredient** | **50mg** |
| Compound IB (10 % drug load as Compound IA) | 63.35 |
| Microcrystalline Cellulose | 95.39 |
| Croscarmellose sodium | 9.05 |
| Sodium starch glycolate | 9.05 |
| Fumed Silica | 0.54 |
| Stearic acid | 3.62 |
| **Total Fill Weight** | 181.00 |

27. A pharmaceutical composition according to Table 6.

**Table 6**

| | **mg/unit dose** |
|---|---|
| **Ingredient** | **60mg** |
| Compound IB | 73.95 |
| Microcrystalline Cellulose | 114.36 |
| Croscarmellose sodium | 10.85 |
| Sodium starch glycolate | 10.85 |
| Fumed Silica | 0.65 |
| Stearic acid | 4.34 |
| **Total Fill Weight** | 217.00 |

28. The pharmaceutical composition of claims 20-27 admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

29. The pharmaceutical composition of claims 20-27 admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

30. The pharmaceutical composition of claims 20-27 admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

31. The pharmaceutical composition of claims 20-27 admixed with 15 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

32. The pharmaceutical composition of claims 20-27 admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

33. The pharmaceutical composition of claims 20-27 admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

34. The pharmaceutical composition of claims 20-27 admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | |
| **Filing Date:** | |
| **Title of Invention:** | Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds |
| **First Named Inventor/Applicant Name:** | Jo Ann Wilson |
| **Filer:** | Heid Marie Berven/Lejla Duvnjak |
| **Attorney Docket Number:** | 224990/10-039C-US/343999 |

Filed as Small Entity

## U.S. National Stage under 35 USC 371 Filing Fees

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| Basic National Stage Fee | 2631 | 1 | 140 | 140 |
| Natl Stage Search Fee - Report provided | 2642 | 1 | 240 | 240 |
| Natl Stage Exam Fee - all other cases | 2633 | 1 | 360 | 360 |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |
| **Miscellaneous:** | | | | |
| | | | **Total in USD ($)** | **740** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 16545560 |
| **Application Number:** | 13984559 |
| **International Application Number:** | PCT/US12/24591 |
| **Confirmation Number:** | 6725 |
| **Title of Invention:** | Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds |
| **First Named Inventor/Applicant Name:** | Jo Ann Wilson |
| **Customer Number:** | 91684 |
| **Filer:** | Heid Marie Berven/Lejla Duvnjak |
| **Filer Authorized By:** | Heid Marie Berven |
| **Attorney Docket Number:** | 224990/10-039C-US/343999 |
| **Receipt Date:** | 09-AUG-2013 |
| **Filing Date:** | |
| **Time Stamp:** | 10:36:59 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $740 |
| RAM confirmation Number | 8317 |
| Deposit Account | 503145 |
| Authorized User | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 1 | | EX10-039C-US_Application_Filing_Documents.pdf | 994476<br>698c7e58dbb04b891a36ad85dd5fd340296cb695 | yes | 13 |

| | Multipart Description/PDF files in .zip description | | |
|---|---|---|---|
| | **Document Description** | **Start** | **End** |
| | Transmittal Letter | 1 | 2 |
| | Application Data Sheet | 3 | 5 |
| | Preliminary Amendment | 6 | 6 |
| | Specification | 7 | 7 |
| | Applicant Arguments/Remarks Made in an Amendment | 8 | 8 |
| | Oath or Declaration filed | 9 | 9 |
| | Information Disclosure Statement (IDS) Form (SB08) | 10 | 12 |
| | Transmittal Letter | 13 | 13 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 2 | Non Patent Literature | isr.pdf | 52703<br>3b85a225c4dafb1a3462accef9fc7d0ebb97009e | no | 2 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 3 | Foreign Reference | WO2010-083414.PDF | 1652633<br>04f165260ce54c53d8d6dc74afd555c3dac568f8 | no | 74 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 4 | | 10-039C-US_Application.pdf | 1727566<br>27b040e55ac61156f000e466394c910af1672949 | yes | 47 |

| | Multipart Description/PDF files in .zip description | | |
|---|---|---|---|
| | **Document Description** | **Start** | **End** |
| | Abstract | 1 | 1 |
| | Specification | 2 | 38 |

| | | | | | |
|---|---|---|---|---|---|
| | Claims | | 39 | 47 | |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | Fee Worksheet (SB06) | fee-info.pdf | 33197<br>b3273f8ae7606a9ad7e9718e35060f13cd79d7a6 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 4460575 | | |

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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.**

HONIGMAN

Honigman Miller Schwartz and Cohn LLP
Attorneys and Counselors

Heidi M. Berven, Ph.D.

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Fax: (269) 337-7711
hberven@honigman.com

*VIA EFS*

August 9, 2013

Commissioner for Patents
United States Patent and Trademark Office
P. O. Box 1450
Alexandria, VA 22313

***Re:*** ***Application No.: To Be Determined***
***Inventors: Jo Ann Wilson***
***Filing Date: February 10, 2012***
***Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds***
***Attorney Docket No.: 224990/10-039C-US/343999***

Dear Sir or Madam:

Enclosed for filing please find the following documents:

1. Cover letter to Commissioner;
2. Application Data Sheet (PTO/SB/14);
3. Application as filed in the PCT;
4. Preliminary Amendment;
5. Declaration and Power of Attorney (unsigned);
6. Information Disclosure Statement (PTO/SB/08a);
7. Foreign Patent Documents;
8. Non-Patent Literature Documents; and
9. Certificate of Transmission under 37 C.F.R. § 1.8(a).

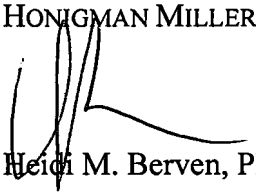
This application is a United States National Phase filing of PCT/US2012/024591, filed February 10, 2012, which claims priority to U.S. Provisional Application No. 61/441,520, filed February 10, 2011, and 61/441,527, filed February 10, 2011, which are incorporated herein by reference.

Applicants note that the filing of the enclosed Information Disclosure Statement shall not be construed to be an admission that the information cited in the statement qualifies as prior art under 35 U.S.C. § 102 or § 103, or is considered to be, material to patentability as defined in § 1.56(b).

It is believed that a fee of $800.00 is due for the filing, search, and examination fees. However, if there are any charges or credits, please apply them to Deposit Account No 503145, referencing Attorney Docket Number 224990/10-039C-US/343999.

Very truly yours,

HONIGMAN MILLER SCHWARTZ AND COHN LLP



Heidi M. Berven, Ph.D.

PTO/SB/14 (11-08)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 224990/10-039C-US/343999 |
|---|---|---|
| | Application Number | |
| Title of Invention | Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds | |

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.)

## Applicant Information:

**Applicant 1**

**Applicant Authority** ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | Jo Ann | | Wilson | |

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

| City | San Francisco | State/Province | CA | Country of Residence | US |
|---|---|---|---|---|---|

**Citizenship under 37 CFR 1.41(b)** US

**Mailing Address of Applicant:**

| Address 1 | 74 Seward Street |
|---|---|
| Address 2 | |

| City | San Francisco | State/Province | CA |
|---|---|---|---|
| Postal Code | 94114 | Country | US |

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

## 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 | 91684 | | |
|---|---|---|---|
| Email Address | patents@honigman.com | Add Email | Remove Email |

## Application Information:

| Title of the Invention | Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds | | |
|---|---|---|---|
| Attorney Docket Number | 224990/10-039C-US/343999 | Small Entity Status Claimed | ☒ |
| Application Type | Nonprovisional | | |
| Subject Matter | Utility | | |
| Suggested Class (if any) | | Sub Class (if any) | |
| Suggested Technology Center (if any) | | | |
| Total Number of Drawing Sheets (if any) | | Suggested Figure for Publication (if any) | |

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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 224990/10-039C-US/343999 |
|---|---|---|
| | Application Number | |
| Title of Invention | Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds | |

## 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). Enter either 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.

| Please Select One: | ◉ Customer Number | ○ US Patent Practitioner | ○ Limited Recognition (37 CFR 11.9) |
|---|---|---|---|
| Customer Number | 91684 | | |

## Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this 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(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

| Prior Application Status | Pending | | Remove |
|---|---|---|---|
| Application Number | Continuity Type | Prior Application Number | Filing Date (YYYY-MM-DD) |
| | a 371 of international | PCT/US2012/024591 | 2012-02-10 |
| Prior Application Status | Expired | | Remove |
| Application Number | Continuity Type | Prior Application Number | Filing Date (YYYY-MM-DD) |
| PCT/US2012/024591 | non provisional of | 61441520 | 2011-02-10 |
| Prior Application Status | Expired | | Remove |
| Application Number | Continuity Type | Prior Application Number | Filing Date (YYYY-MM-DD) |
| PCT/US2012/024591 | non provisional of | 61441527 | 2011-02-10 |

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

## Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. 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(a).

| | | | Remove |
|---|---|---|---|
| Application Number | Country[1] | Parent Filing Date (YYYY-MM-DD) | Priority Claimed |
| | | | ○ Yes ◉ No |

PTO/SB/14 (11-08)
Approved for use through 01/31/2014. OMB 0651-0032
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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 224990/10-039C-US/343999 |
|---|---|---|
| | Application Number | |
| Title of Invention | Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds | |

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## Assignee Information:

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

**Assignee 1**

If the Assignee is an Organization check here. [x]

| Organization Name | Exelixis, Inc. | | |
|---|---|---|---|
| **Mailing Address Information:** | | | |
| **Address 1** | 210 East Grand Ave. | | |
| Address 2 | | | |
| **City** | South San Francisco | **State/Province** | CA |
| **Country** | US | Postal Code | 94080 |
| Phone Number | | Fax Number | |
| Email Address | | | |

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

## Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.

| **Signature** | | | | Date (YYYY-MM-DD) | 2013-08-09 |
|---|---|---|---|---|---|
| First Name | Heidi | Last Name | Berven | Registration Number | 48951 |

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.**

448894

# THE UNITED STATES OF AMERICA

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UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

*February 17, 2012*

**THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.**

**APPLICATION NUMBER:** ***61/441,520***
**FILING DATE:** ***February 10, 2011***
**RELATED PCT APPLICATION NUMBER:** ***PCT/US12/24591***

**THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS** ***US61/441,520***

Certified by

David J. Kappos

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

HONIGMAN

Honigman Miller Schwartz and Cohn LLP
Attorneys and Counselors

Heidi M. Berven, Ph.D.

(269) 337-7710
Fax: (269) 337-7711
hberven@honigman.com

VIA EFS

February 10, 2011

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

***Re: Application No.: To Be Determined***
***Inventors: To Be Determined***
***Filing Date: February 10, 2011***
***Title: Methods of Preparing Quinoline Derivatives***
***Our Ref. No.: 224990/10-039P/308000***

Dear Sir:

The following documents are being electronically filed:

1. Cover Letter to the Commissioner for Patents;
2. Provisional Application for Patent Cover Sheet (PTO/SB/16);
3. Provisional Application; and
4. Certificate of Transmission under 37 C.F.R. §1.8(a).

It is believed that the filing fee required for this submission is $110. If there are any charges or credits regarding this filing, however, please apply them to Deposit Account 503145, referencing Attorney Docket 224990/10-039P/308000.

Very truly yours,

HONIGMAN MILLER SCHWARTZ AND COHN LLP

Heidi M. Berven, Ph.D.
Reg. No. 48,951

ACTIVE:8770131.1

Doc Code: **TR.PROV**
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)
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## Provisional Application for Patent Cover Sheet

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

### Inventor(s)

Inventor 1 — Remove

| Given Name | Middle Name | Family Name | City | State | Country i |
|---|---|---|---|---|---|
| - | | - | - | | |

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

| | |
|---|---|
| **Title of Invention** | Methods of Preparing Quinoline Derivatives |
| Attorney Docket Number (if applicable) | 224990/10-039P/308000 |

### Correspondence Address

Direct all correspondence to (select one):

| | |
|---|---|
| ◉ The address corresponding to Customer Number | ○ Firm or Individual Name |
| Customer Number | 91684 |

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

◉ No.

○ Yes, the name of the U.S. Government agency and the Government contract number are:

Doc Code: **TR.PROV**
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)

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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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## Entity Status

Applicant claims small entity status under 37 CFR 1.27

(●) Yes, applicant qualifies for small entity status under 37 CFR 1.27

( ) No

## 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 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 CFR1.14). 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.

## Signature

Please see 37 CFR 1.4(d) for the form of the signature.

| | | | | | |
|---|---|---|---|---|---|
| Signature | | | | Date (YYYY-MM-DD) | 2011-02-10 |
| First Name | Heidi | Last Name | Berven | Registration Number (If appropriate) | 48951 |

This collection of information is required by 37 CFR 1.51. 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 8 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, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **This form can only be used when in conjunction with EFS-Web. If this form is mailed to the USPTO, it may cause delays in handling the provisional application.**

| Electronic Acknowledgement Receipt | |
|---|---|
| **EFS ID:** | 9421334 |
| **Application Number:** | 61441520 |
| **International Application Number:** | |
| **Confirmation Number:** | 1613 |
| **Title of Invention:** | Methods of Preparing Quinoline Derivatives |
| **First Named Inventor/Applicant Name:** | . . |
| **Customer Number:** | 91684 |
| **Filer:** | Heid Marie Berven/Lejla Duvnjak |
| **Filer Authorized By:** | Heid Marie Berven |
| **Attorney Docket Number:** | 224990/10-039P/308000 |
| **Receipt Date:** | 10-FEB-2011 |
| **Filing Date:** | |
| **Time Stamp:** | 17:13:34 |
| **Application Type:** | Provisional |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $110 |
| RAM confirmation Number | 3828 |
| Deposit Account | 503145 |
| Authorized User | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 1 | | EX10-039P_Application.pdf | 2214712<br>6debd0cf1e7b0846c11c6922acc122f659741f965 | yes | 36 |

| Multipart Description/PDF files in .zip description | | |
|---|---|---|
| **Document Description** | **Start** | **End** |
| Transmittal of New Application | 1 | 1 |
| Provisional Cover Sheet (SB16) | 2 | 3 |
| Specification | 4 | 27 |
| Claims | 28 | 34 |
| Abstract | 35 | 35 |
| Miscellaneous Incoming Letter | 36 | 36 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 2 | Fee Worksheet (PTO-875) | fee-info.pdf | 29409<br>5476a7db1c087e5feddaa621efd1068bd28b5a97 | no | 2 |

**Warnings:**

**Information:**

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|---|---|
| **Total Files Size (in bytes):** | 2244121 |

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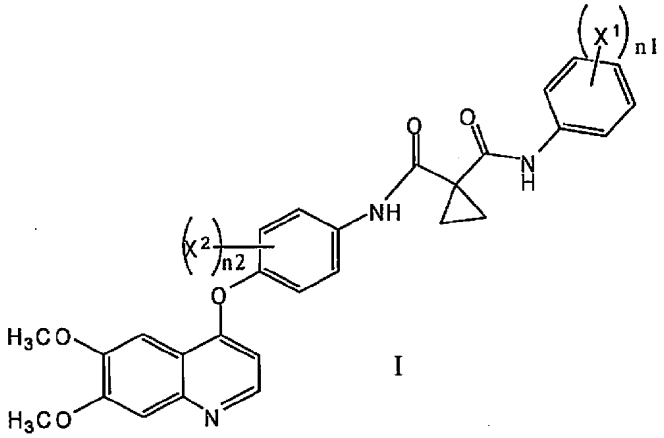
**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt 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.**

## ABSTRACT

Methods of preparing compounds of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is H, Br, Cl or F;

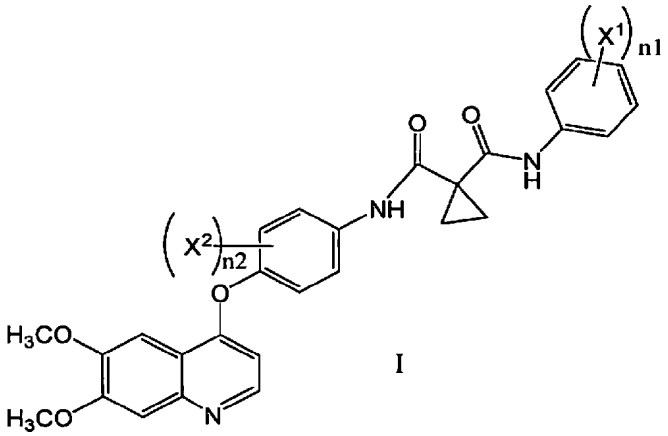
$X^2$ is H, Br, Cl or F;

n1 is 1-2; and

n2 is 1-2.

We Claim:

1. A method of preparing a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is H, Br, Cl or F;

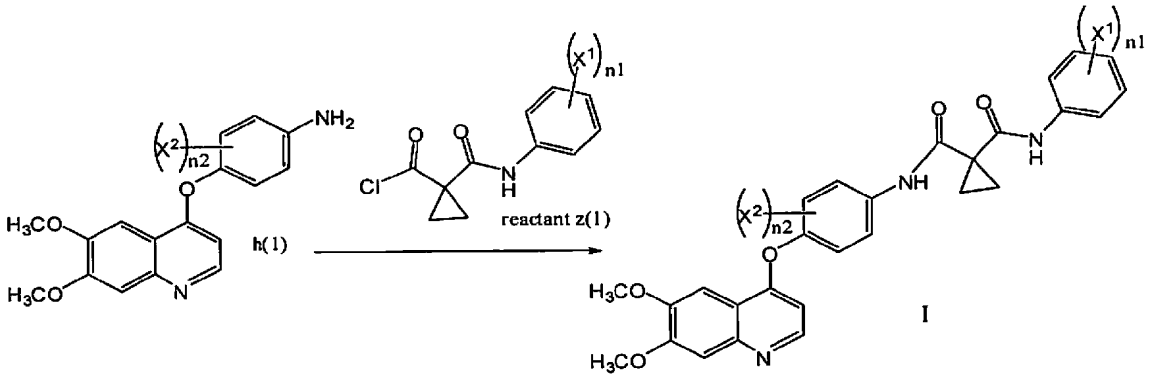
$X^2$ is H, Br, Cl or F;

n1 is 1-2; and

n2 is 1-2,

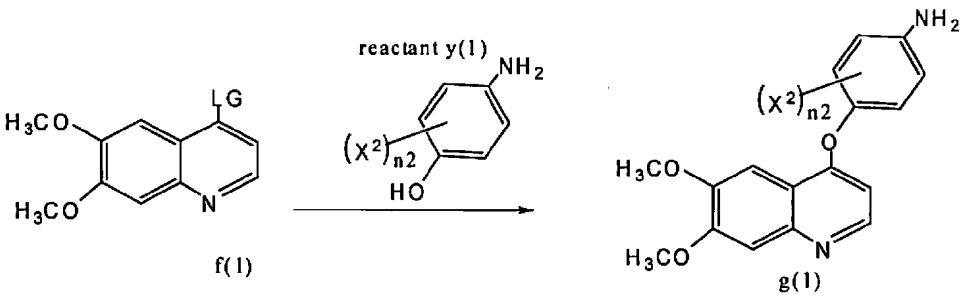
the method comprising:

contacting the compound of formula g(1) with reactant z(1) to yield the compound of formula I:



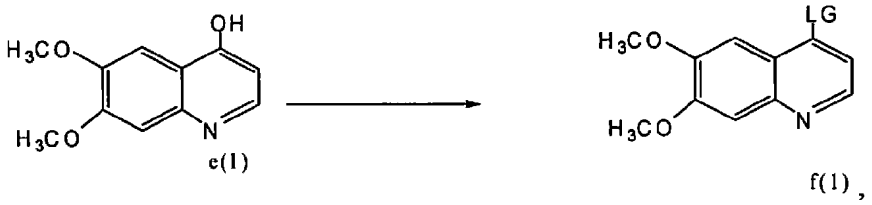

I

2. The method according to claim 1, wherein the compound of formula g(1) is made by reacting a compound of formula f(1) with reactant y(1) to yield the compound of formula g(1):



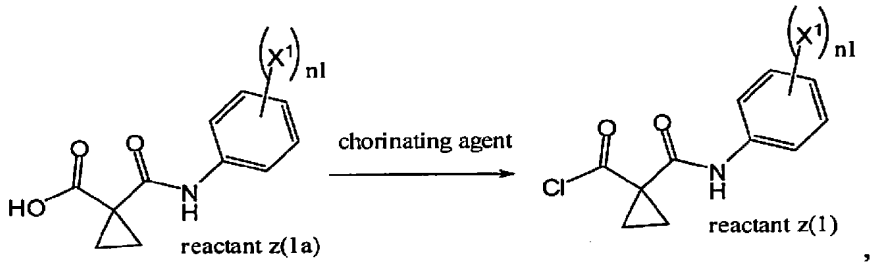

wherein LG represents a leaving group, and each $X^2$ and n2 are as defined in claim 1.

3. The method according to claim 2, wherein the compound of formula f(1) is made by converting a compound of formula e(1) to the compound of formula f(1):



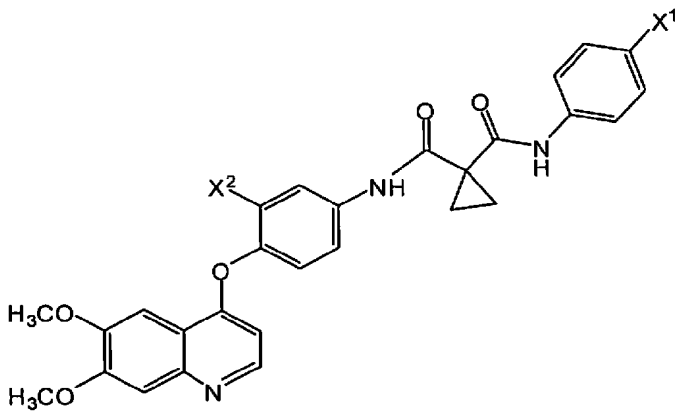

wherein LG represents a leaving group.

4. The method according to claim 1, wherein reactant z(1) is made by reacting reactant z(1a) with a chlorinating agent to yield reactant z(1):




wherein $X^1$ is Br, Cl or F; and n1 is 1-2.

5. The method according to claim 1, wherein the compound of formula I is of formula IA:



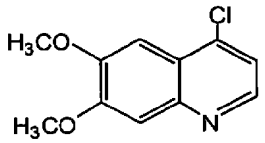
I(A)

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is H, Cl, Br or F; and

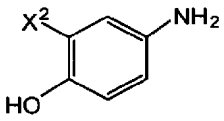
$X^2$ is H, Cl, Br or F.

6. The method according to claim 5, wherein the compound of formula f(1) is of formula f(2):



f(2) ;

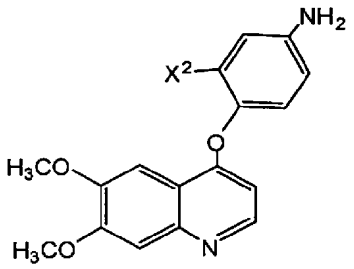
reactant y(1) is reactant (y)(2):



reactant (y)(2) ,

wherein $X^2$ is hydrogen or fluoro; and

the compound of formula g(1) is of formula g(2):




g(2) .

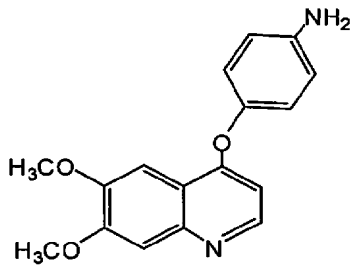
7. The method according to claim 6, wherein the reaction employs a non-nucleophilic base.

8. The method according to claim 7, wherein the non-nucleophilic base is an alkali metal alkoxide; and the reaction is carried out in a polar solvent.

9. The method according to claim 8, wherein the alkali metal alkoxide is sodium tert-butoxide, and the polar solvent is DMA.

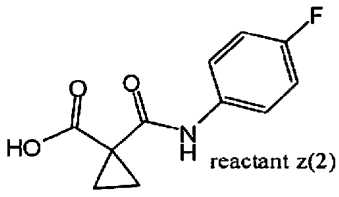
10. The method according to claim 8, wherein the alkali metal alkoxide is sodium tert-pentoxide, and the polar solvent is DMA.

11. The method according to claim 1, wherein the compound of formula g(1) is of formula g(3):




g(3) ;

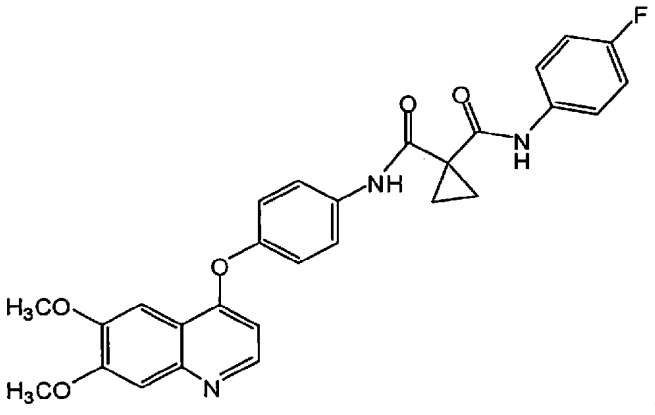
reactant z(1) is reactant (z)(2):




reactant z(2)

; and

the compound of formula I is of formula I(B):

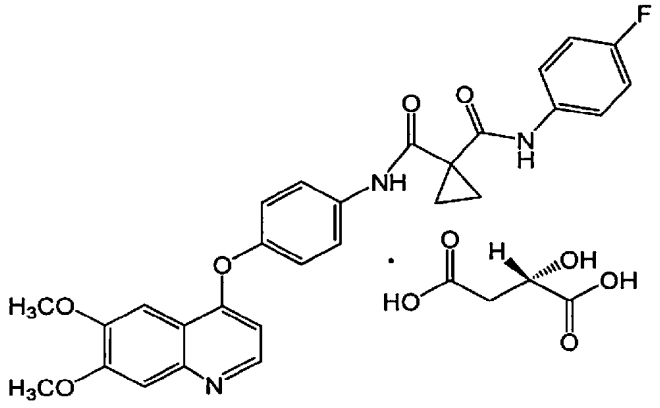



I(B)

12. The method according to claim 11, wherein the reaction is carried out in the presence of an inorganic base.

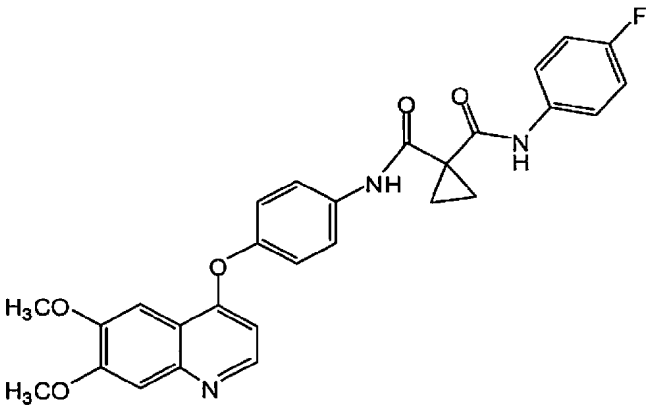
13. The method according to claim 12, wherein the inorganic base is $K_2CO_3$, and the solvent employed in this reaction is a combination of THF and $H_2O$.

14. A method for preparing a compound of formula IB




Formula IB

from a compound of formula IA



Formula IA

comprising:

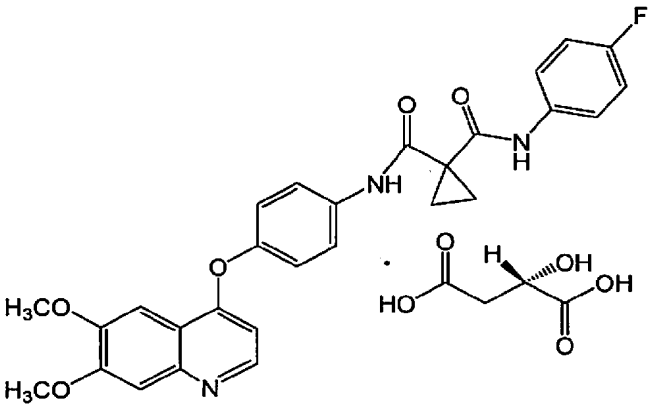
(a) heating and agitating a mixture comprising a compound of formula IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) vacuum distilling the mixture successively; and

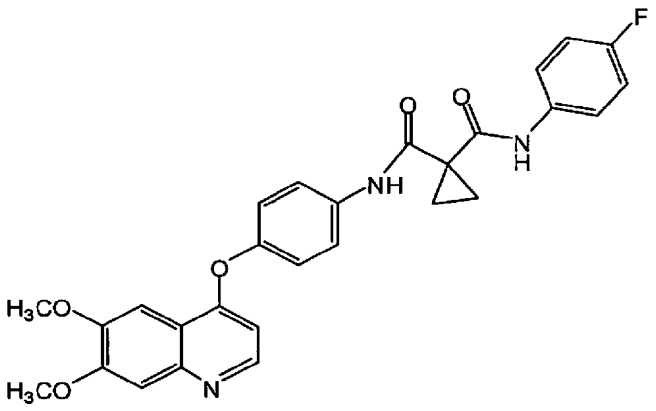
(d) isolating the compound of formula IB by filtration.

15. A method for preparing a compound of formula IB



Formula IB

from a compound of formula IA




Formula IA

comprising:

(a) heating and agitating a mixture comprising a compound of formula IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) seeding the mixture with the compound of formula IB;

(d) vacuum distilling the mixture; and

(d) isolating the compound of formula IB by filtration.

# METHODS OF PREPARING QUINOLINE DERIVATIVES

## BACKGROUND OF THE INVENTION

Field of the Invention

**[0001]** This disclosure relates to methods of preparing compounds useful for modulating protein kinase enzymatic activity. More specifically, this disclosure relates to methods of preparing compounds useful for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration and chemoinvasion.

Summary of the Related Art

**[0002]** Improvements in the specificity of agents used to treat cancer is of considerable interest because of the therapeutic benefits which would be realized if the side effects associated with the administration of these agents could be reduced. Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms.

**[0003]** Protein kinases are enzymes that catalyze the phosphorylation of proteins, in particular, hydroxy groups on tyrosine, serine and threonine residues of proteins. The consequences of this seemingly simple activity are staggering; cell differentiation and proliferation; *i.e.*, virtually all aspects of cell life in one-way or another depend on protein kinase activity. Furthermore, abnormal protein kinase activity has been related to a host of disorders, ranging from relatively non-life threatening diseases such as psoriasis to extremely virulent diseases such as glioblastoma (brain cancer).

**[0004]** Therapeutic use of kinase modulation can relate to oncological indications. For example, modulation of protein kinase activity for the treatment of cancer has been demonstrated successfully with the FDA approval of GleevecG) (imatinib mesylate, produced by Novartis Pharmaceutical Corporation of East Hanover, NJ) for the treatment of Chronic Myeloid Leukemia (CML) and gastrointestinal stroma cancers (GIST). Gleevec is a c-Kit and Abl kinase inhibitor.

**[0005]** Modulation (particularly inhibition) of cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc Technol 2001 6, 1005-1024), is an attractive goal for development of small-molecule drugs. Anti-angiogenic therapy represents a potentially important approach for the treatment of solid tumors and other diseases associated with dysregulated vascularization, including ischemic

coronary artery disease, diabetic retinopathy, psoriasis and rheumatoid arthritis. As well, cell antiproliferative agents are desirable to slow or stop the growth of tumors.

**[0006]** A target of interest for small-molecule modulation, with respect to antiangiogenic and antiproliferative activity is c-Met. The kinase, c-Met, is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs) which include Met, Ron and Sea. Expression of c-Met occurs in a wide variety of cell types including epithelial, endothelial and mesenchymal cells where activation of the receptor induces cell migration, invasion, proliferation and other biological activities associated with "invasive cell growth." As such, signal transduction through c-Met receptor activation is responsible for many of the characteristics of tumor cells.

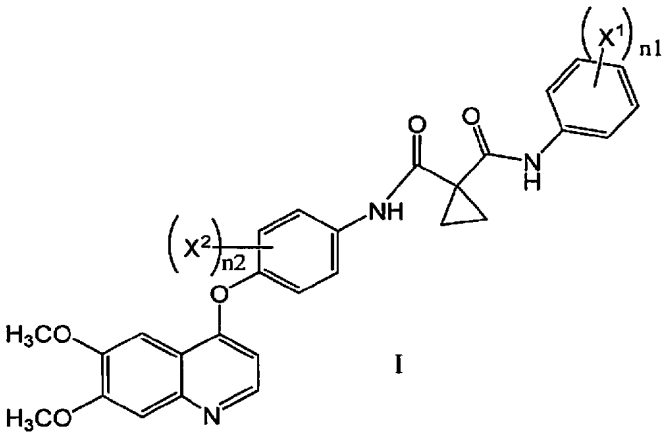
**[0007]** The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenesis, also known as "scatter factor" (SF). Binding of HGF to c-Met induces activation of the receptor via autophosphorylation resulting in an increase of receptor dependent signaling, which promotes cell growth and invasion. Anti-HGF antibodies or HGF antagonists have been shown to inhibit tumor metastasis *in vivo* (See: Maulik et al Cytokine & Growth Factor Reviews 2002 13, 41-59).

**[0008]** Tumor growth progression requires the recruitment of new blood vessels into the tumor from preexisting vessels as well as invasion, adhesion and proliferation of malignant cells. Accordingly, c-Met overexpression has been demonstrated on a wide variety of tumor types including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytomas, and glioblastomas. Additionally activating mutations in the kinase domain of c-Met have been identified in hereditary and sporadic renal papilloma and squamous cell carcinoma. (See: Maulik et al Cytokine & growth Factor reviews 2002 13, 41-59; Longati et al Curr Drug Targets 2001, 2, 41-55; Funakoshi et al Clinica Chimica Acta 2003 1-23). Thus modulation of c-Met is desirable as a means to treat cancer and cancer-related disease.

**[0009]** Accordingly, there is a need for new methods of making compounds that are protein kinase modulators.

## SUMMARY OF THE INVENTION

**[0010]** In one aspect, the disclosure relates to methods of preparing compounds of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is H, Br, Cl or F;

$X^2$ is H, Br, Cl or F;

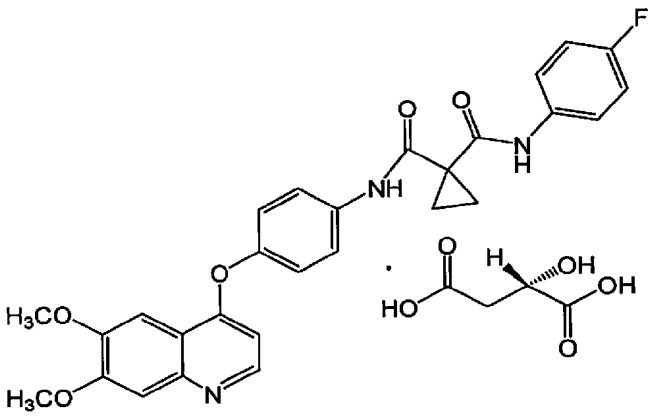
n1 is 1-2; and

n2 is 1-2,

**[0011]** Intermediates useful in preparing the above compounds are also disclosed.

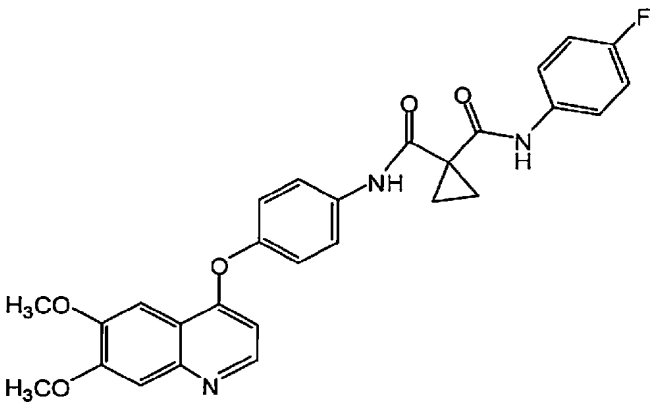
**[0012]** The compounds of formula I are useful as protein kinase modulators, and they inhibit various protein kinases including Ret and c-Met.

**[0013]** In another aspect, the invention provides a method for preparing a compound of formula IB



Formula IB

from a compound of formula IA



Formula IA

comprising:

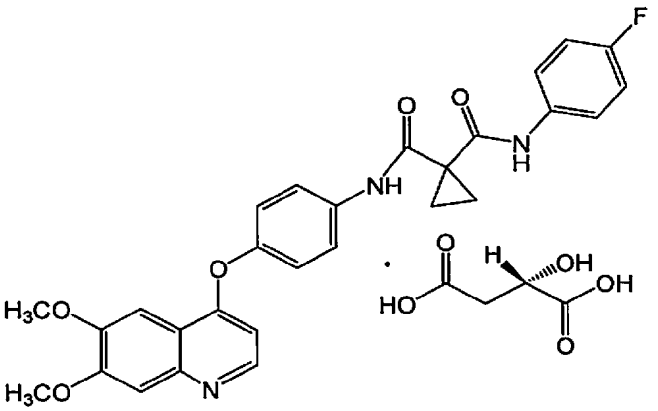
(a) heating and agitating a mixture comprising a compound of formula IA and L-malic acid, methylethyl ketone, and water; and

(b) cooling the mixture; and

(c) vacuum distilling the mixture successively; and

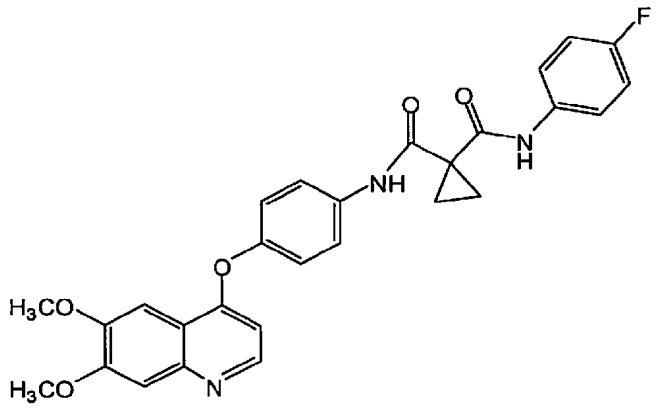
(d) isolating the compound of formula IB by filtration.

**[0014]** In another aspect, the invention provides a method for preparing a compound of formula IB



Formula IB

from a compound of formula IA




Formula IA

comprising:

(a) heating and agitating a mixture comprising a compound of formula IA and L-malic acid, methylethyl ketone, and water; and

(b) cooling the mixture;

(c) seeding the mixture with the compound of formula IB;

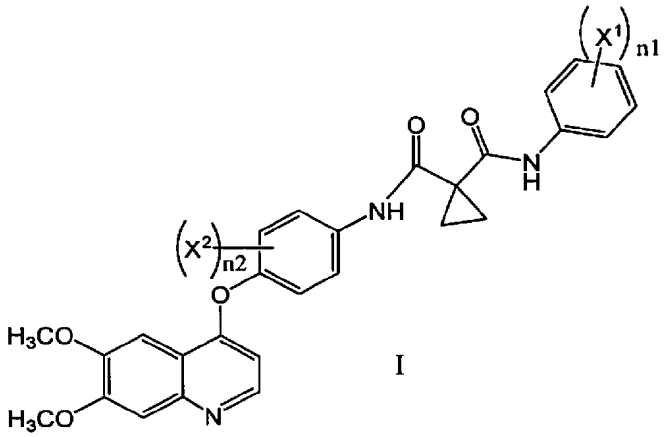
(d) vacuum distilling the mixture; and

(d) isolating the compound of formula IB by filtration.

**[0015]** There are many different aspects and embodiments of the disclosure described hereinbelow, and each aspect and each embodiment is non-limiting in regard to the scope of the disclosure. The terms "aspects" and "embodiments" are meant to be non-limiting regardless of where the terms "aspect" or "embodiment" appears in this specification. The transitional term "comprising" as used herein, which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements.

## DETAILED DESCRIPTION OF THE INVENTION

**[0016]** Aspect (1) of this disclosure relates to a method of preparing a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is H, Br, Cl or F;

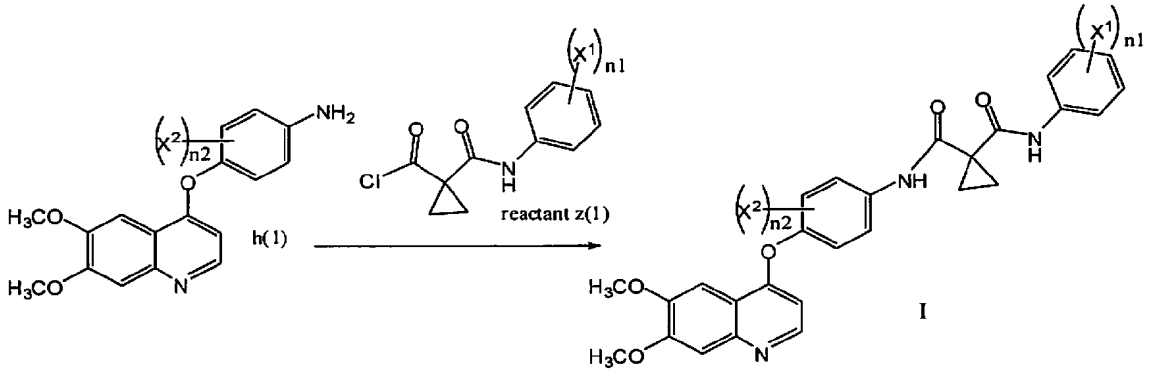
$X^2$ is H, Br, Cl or F;

n1 is 1-2; and

n2 is 1-2,

the method comprising:

contacting the compound of formula g(1) with reactant z(1) to yield the compound of Formula I:




I

**[0017]** The reaction in Aspect (1) of this disclosure is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions in Aspect (1) include using basic conditions. Non-limiting examples of basic conditions that can be used in Aspect (1) of this disclosure include the use of inorganic bases, such as aqueous KOH, NaOH, $K_2CO_3$, $Na_2CO_3$, $K_3PO_4$, $Na_3PO_4$, $K_2HPO_4$, $Na_2HPO_4$, and the like, or mixtures thereof. Other non-limiting examples of suitable reaction conditions in Aspect (1) include using suitable solvents. Non-limiting examples of suitable solvents that can be used in Aspect (1) of this disclosure include water miscible solvents, such as THF, acetone, ethanol,

and the like, or mixtures thereof. Other non-limiting examples of suitable reaction conditions in Aspect (1) include using suitable temperatures. Suitable temperatures that may be used for the reaction in Aspect (1) include a temperature at a range of from about 10°C to about 30°C, or alternatively, at a range of from about 15°C to about 28°C, or alternatively, at a range of from about 20°C to about 25°C. The product formed in Aspect (1) is in the free base form and this free base form may be converted into a pharmaceutically acceptable salt thereof, by methods known in the art. In one example, the compound of formula I can be converted to its bis-maleate salt by the addition of maleic acid and a suitable solvent. In another example, the compound of formula I can be converted to its bis-phosphate salt by the addition of phosphoric acid and a suitable solvent.

**[0018]** Utilities of the compound of Formula I are further described in WO 2005/030140 A2.

Embodiments of Aspect (1) (Part A)

**[0019]** In another embodiment of Aspect (1), $X^1$ is Cl or F.

**[0020]** In another embodiment of Aspect (1), $X^2$ is Cl or F.

**[0021]** In another embodiment of Aspect (1), $X^1$ is F.

**[0022]** In another embodiment of Aspect (1), $X^2$ is F.

**[0023]** In another embodiment of Aspect (1), $X^1$ is H.

**[0024]** In another embodiment of Aspect (1), $X^2$ is H.

**[0025]** In another embodiment of Aspect (1), n1 is 1.

**[0026]** In another embodiment of Aspect (1), n2 is 1.

**[0027]** In another embodiment of Aspect (1), n1 is 2.

**[0028]** In another embodiment of Aspect (1), n2 is 2.

**[0029]** All compounds of formula I for Aspect (1) disclosed above include any of the disclosed alternative embodiments in Part A for each of $X^1$, $X^2$, n1 or n2, in combination with any other of the disclosed alternative embodiments in Part A for each of $X^1$, $X^2$, n1, or n2, as well as a pharmaceutically acceptable salt of any such combination.

Embodiments of Aspect (1) Part B

**[0030]** In another embodiment of Aspect (1), n1 and n2 are each 1.

**[0031]** In another embodiment of Aspect (1), n1 and n2 are each 2.

**[0032]** In another embodiment of Aspect (1), n1 is 1; and n2 is 2.

**[0033]** In another embodiment of Aspect (1), n1 is 2 and n2 is 1.

**[0034]** In another embodiment of Aspect (1), $X^1$ is H; and $X^2$ is F.

**[0035]** In another embodiment of Aspect (1), $X^1$ is F; and $X^2$ is H.

**[0036]** In another embodiment of Aspect (1), $X^1$ and $X^2$ are each H.

**[0037]** In another embodiment of Aspect (1), $X^1$ and $X^2$ are each F.

**[0038]** In another embodiment of Aspect (1), $X^1$ is Cl; and $X^2$ is H.

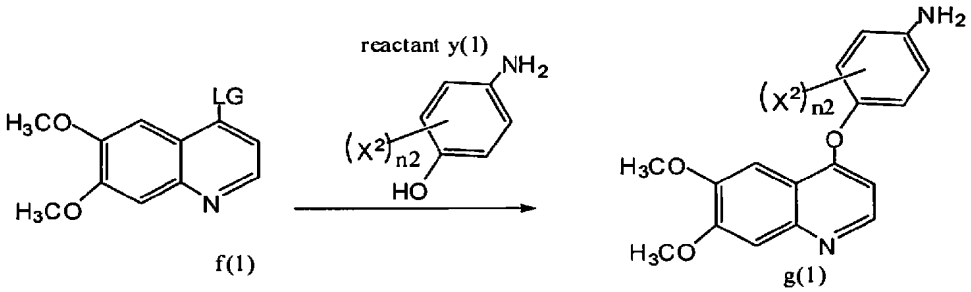
**[0039]** In another embodiment of Aspect (1), $X^1$ is H; and $X^2$ is Cl.

**[0040]** In another embodiment of Aspect (1), $X^1$ and $X^2$ are each Cl.

**[0041]** In another embodiment of Aspect (1), $X^1$ is Cl; and $X^2$ is F.

**[0042]** In another embodiment of Aspect (1), $X^1$ is F; and $X^2$ is Cl.

**[0043]** In embodiment (C) of Aspect (1), the compound of formula g(1) can be made by reacting a compound of formula f(1) with reactant y(1) to yield the compound of g(1):




wherein LG represents a leaving group, and each of $X^2$, and n2 are as defined in Aspect (1), or as in any of the embodiments of Aspect (1) (Part A), of this disclosure. A non-limiting example of a leaving group includes halo groups (such as Cl, Br or F). Various compounds of reactant y(1) are commercially available, such as 2-fluoro-4-aminophenol and 4-aminophenol. Also, the skilled artisan would be able to make any variation of reactant y(1) using commercially available starting materials and by using known techniques to modify these commercially available starting materials to come up with various compounds within the scope of reactant y(1).

**[0044]** The reaction in embodiment (C) of Aspect (1) of this disclosure is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions in embodiment (C) of Aspect (1) include using suitable solvents such as polar solvents. Non-limiting examples of polar solvents that can be used include tetrahydrofuran (THF), dimethylacetamide (DMA), dimethylsulfoxide (DMSO), dimethylformamide (DMF), ethyl acetate, N-methyl pyrrolidone (NMP), propylene carbonate, and the like, or mixtures thereof. In another embodiment, the polar solvent is dimethylacetamide (DMA). In another embodiment, the polar solvent is dimethylsulfoxide (DMSO). In another embodiment, the

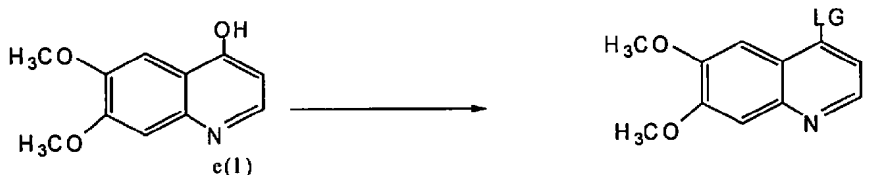
polar solvent is dimethylformamide (DMF). In another embodiment, the polar solvent is ethyl acetate. In another embodiment, the polar solvent is N-methyl pyrrolidone (NMP). In another embodiment, the polar solvent is propylene carbonate. In another embodiment, the solvent is a mixture of solvents, such as a mixture comprising THF and DMA.

**[0045]** In embodiment (C) of Aspect (1), the reactants f(1) and y(1) can be added together at a temperature ranging from about 10°C to about 30°C, or alternatively, from about 15°C to about 28°C, or alternatively, from about 20°C to about 25°C. The mixture is then heated to a temperature ranging from about 80°C to about 125°C, or alternatively, from about 95°C to about 110°C, or alternatively, from about 100°C to about 105°C, and the selected temperature is maintained until the reaction is complete.

**[0046]** Other non-limiting examples of suitable reaction conditions in this step of Aspect (1) include the use of a suitable base, such as non-nucleophilic base. Non-limiting examples of non-nucleophilic bases that can be used include lithium diisopropylamide, lithium tetramethylpiperidide and alkali metal alkoxides such as sodium tert-butoxide, potassium tert-butoxide, sodium-pentoxide, and the like, or mixtures thereof. Preferably, the base is sodium tert-butoxide or sodium tert-pentoxide or the like.

**[0047]** Once the reaction is substantially complete, the reaction mixture can be cooled to a temperature ranging from about 10°C to about 25°C. Precooled water can be charged at rate to maintain a temperature that ranges from about 5°C to about 35°C. Alternatively, the precooled water can be charged at rate to maintain a temperature that ranges from about 10°C to about 25°C. As a non-limiting example, the precooled water can be at a temperature ranging from about 0°C to about 10°C. As another non-limiting example, the precooled water can be at a temperature ranging from about 2°C to about 7°C. The precipitate can be collected by filtration under standard conditions and purified by standard purification techniques.

**[0048]** In embodiment (D) of Aspect (1), the compound of formula f(1) can be made by converting a compound of formula e(1) to the compound of formula f(1):



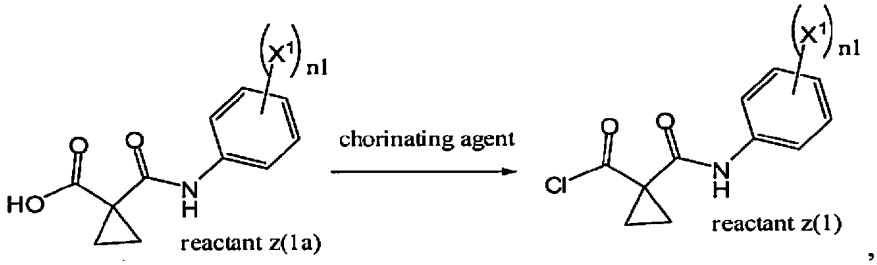

e(1) f(1),

wherein LG represents a leaving group. A non-limiting example of a leaving group that could be used in embodiment (D) of Aspect (1) include halo groups (such as Cl, Br or F) that

can be added by halogenating agents. Non-limiting examples of halogenating agents that can be used in embodiment (D) of Aspect (1) include chlorinating agents, such as $SOCl_2$, $SO_2Cl_2$, $COCl_2$, $PCl_5$, $POCl_3$, and the like.

**[0049]** The reaction in embodiment (D) of Aspect (1) of this disclosure is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions in embodiment (D) of Aspect (1) include the use of suitable solvents. Non-limiting example of suitable solvents that can be used in embodiment (D) of Aspect (1) during the halogenation of the compound of formula e(1) include a polar, aprotic solvent, such as $CH_3CN$, DMF, and the like, or mixtures thereof. In other embodiments, the chlorination can be carried out using $POCl_3$ in acetonitrile, $COCl_2$ in DMF, or $SOCl_2$ in DMF. The addition of the chlorination agent is advantageously carried out at a temperature ranging from about 60°C to about 90°C. In another embodiment, the addition of the chlorination agent can be carried out at a temperature ranging from about 70°C to about 85°C. In another embodiment, the addition of the chlorination agent can be carried out at a temperature ranging from about 74°C to about 80°C. The product can then be collected by filtration and purified using standard techniques.

**[0050]** In embodiment (E) of Aspect (1) of this disclosure, reactant z(1) can be made by reacting reactant z(1a) with a chlorinating agent to yield reactant z(1):

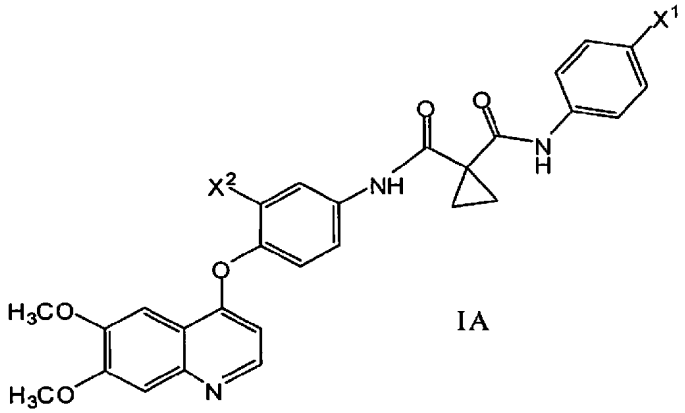



wherein $X^1$ is Br, Cl or F; and n1 is 1-2. Compounds of reactant z(1a) can be made according to the method described in Example 25 of WO 2005/030140 A2, and the skilled artisan would be able to make any necessary substitutions using commercially available starting materials to come up with various compounds within the scope of reactant z(1a). Example 25 in WO 2005/030140 A2 is incorporated herein by reference.

**[0051]** The reaction in embodiment (E) of Aspect (1) of this disclosure is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions in embodiment (E) of Aspect (1) include using a chlorinating agent such as $POCl_3$, oxalyl chloride, and the like. In another embodiment of embodiment (E) of Aspect (1), oxalyl chloride is used as a chlorinating agent. Non-limiting examples of suitable reaction

conditions in embodiment (E) of Aspect (1) include carrying out the reaction at a temperature in the range from about 0°C to about 25°C, or alternatively at a temperature in the range from about 5°C to about 20°C. Other non-limiting examples of suitable reaction conditions in embodiment (E) of Aspect include carrying out the reaction in a suitable solvent. Non-limiting examples of suitable solvents that can be used in embodiment (E) of Aspect (1) include polar, aprotic solvents such as halogenated hydrocarbons, *i.e.*, dichloromethane, chloroform; or ethers, i.e., $Et_2O$, dioxane, tetrahydrofuran (THF) containing catalytic DMF, and the like, or mixtures thereof. The resulting solution containing reactant z(1) can be used, without further processing, to make the compound of formula I in Aspect (1) of this disclosure.

**[0052]** In another embodiment of Aspect (1) of this disclosure, the compound of formula I is of formula I(A):



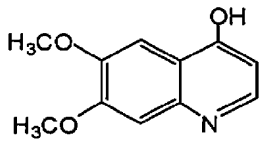

IA

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is H, Cl, Br or F; and

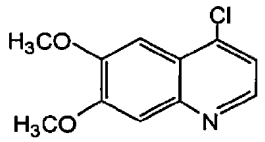
$X^2$ is H, Cl, Br or F. As mentioned above for the compound of formula I, the compound of formula I(A) can be in the free base form or it can converted to a pharmaceutically acceptable salt thereof. Accordingly, the compound of formula I(A) can be converted to its bis-maleate salt by the addition of maleic acid and a suitable solvent, or the compound of formula I(A) can be converted to its bis-phosphate salt by the addition of phosphoric acid and a suitable solvent.

**[0053]** In another embodiment of Aspect (1), embodiment (D) of this disclosure, the compound of formula e(1) is of formula e(2):



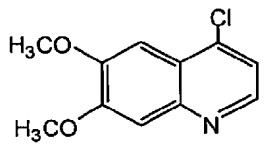

e(2) ;

and the compound of formula f(1) is of formula f(2):



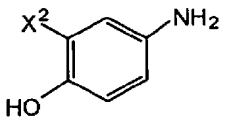

f(2) .

**[0054]** In another embodiment of Aspect (1), embodiment (C) of this disclosure, the compound of formula f(1) is of formula f(2):




f(2) ;

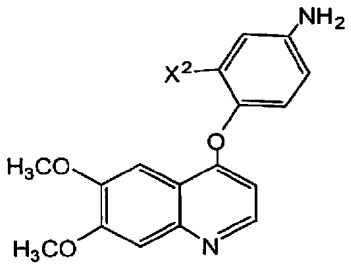
reactant y(1) is reactant (y)(2):




reactant (y)(2) ,

wherein $X^2$ is hydrogen or fluoro;

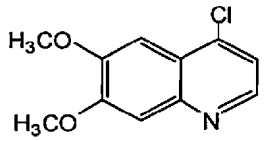
the compound of formula g(1) is of formula g(2):




g(2) .

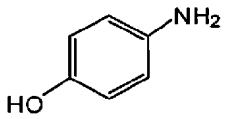
**[0055]** In a further embodiment of the previous embodiment, the reaction employs a non-nucleophilic base. In a further embodiment of the previous embodiment, the non-nucelophilic base is an alkali metal alkoxide; and the reaction is carried out in a polar solvent. In a further embodiment of the previous embodiment, the alkali metal alkoxide is sodium tert-butoxide, and the polar solvent is DMA.

**[0056]** In another embodiment of Aspect (1), embodiment (C) of this disclosure, the compound of formula f(1) is of formula f(2):




f(2) ;

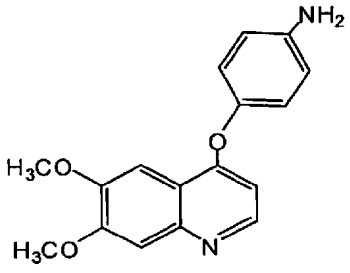
reactant y(1) is reactant (y)(3):




reactant (y)(3) ,

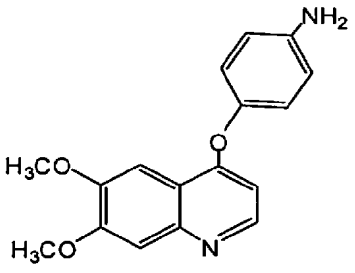
wherein $X^2$ is hydrogen or fluoro; and

the compound of formula g(1) is of formula g(3):



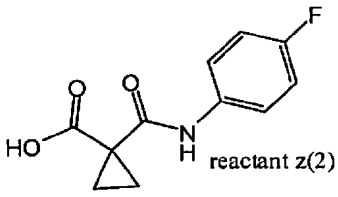

g(3) .

**[0057]** In another embodiment of Aspect (1) of this disclosure, the compound of formula g(1) is of formula g(3):



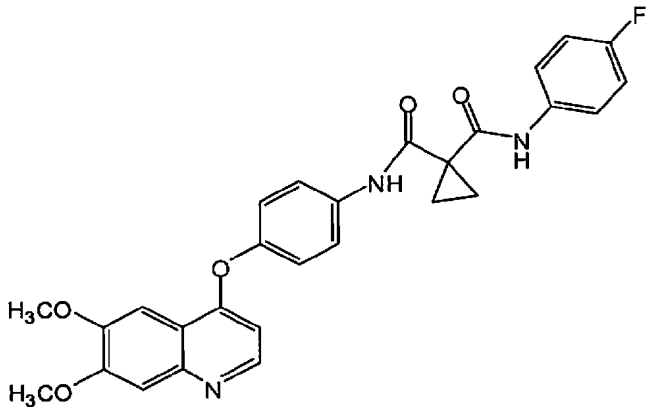
g(3) ;

reactant z(1) is reactant (z)(2):



reactant z(2) ; and

the compound of formula I is of formula I(B):

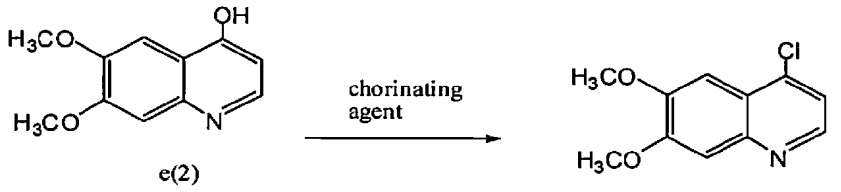


I(B).

**[0058]** In a further embodiment of the previous embodiment, the reaction is carried out in the presence of an inorganic base. In a further embodiment of the previous embodiment, the inorganic base is $K_2CO_3$, and the solvent employed in this reaction is a combination of THF and $H_2O$.

**[0059]** In another embodiment of Aspect (1) of this disclosure, $X^1$ and $X^2$ for each of formula g(1) and reactant z(1) are each selected from Cl or F. In another embodiment of Aspect (1) of this disclosure, $X^1$ and $X^2$ for each of formula g(2), and reactant z(1) are both F.

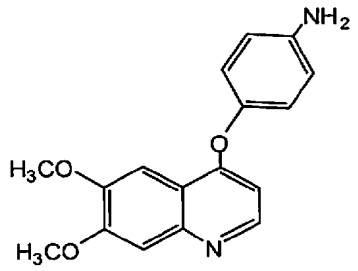
**[0060]** The compound of formula f(2),or a pharmaceutically acceptable salt thereof, can be made by converting the compound of formula e(2) to a compound of formula f(2) with a chlorinating agent in a suitable solvent:




e(2) f(2)

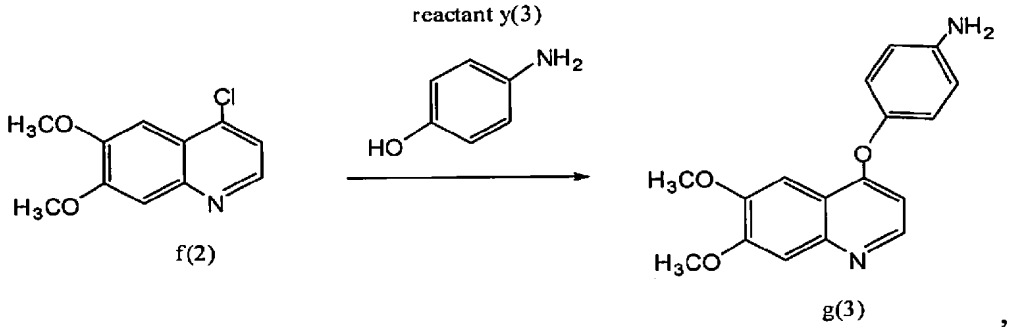
The compound of formula f(2) can be in its free base form or converted to a pharmaceutically acceptable salt thereof. The reaction conditions that can be used in this aspect include any of the reaction conditions disclosed in embodiment (E) of Aspect (1).

**[0061]** Aspect (2) of the disclosure relates to a method of preparing a compound of formula g(2):




g(2)

or a pharmaceutically acceptable salt thereof, the method comprising reacting the compound of formula f(2) with reactant y(3) under basic conditions in an appropriate solvent (2,6-lutidine is a sterically hindered organic mild base) to yield the compound of g(3):

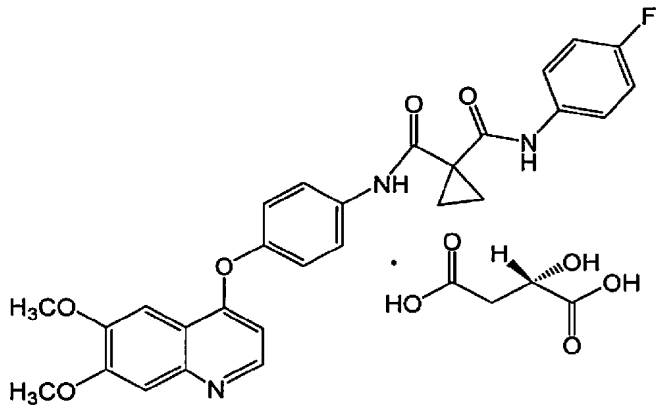



f(2) g(3)

The reaction conditions that can be used in this aspect include any of the reaction conditions disclosed in embodiment (C) of Aspect (1).

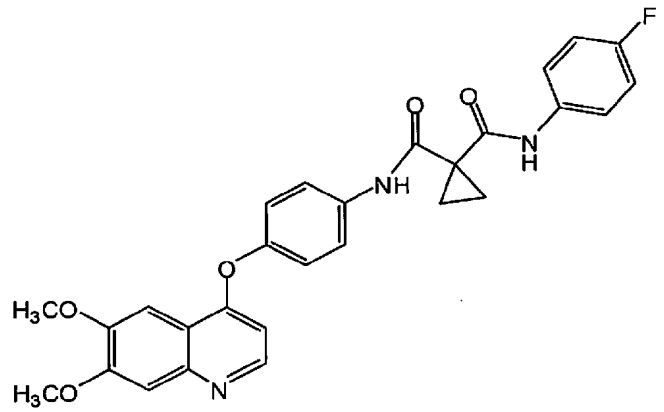
**[0062]** The reaction conditions that can be used in this aspect include any of the reaction conditions disclosed in alternative embodiments for embodiments (C) and (D) of Aspect (1).

**[0063]** As indicated above, in one aspect, the invention provides a method for preparing a compound of formula IB



Formula IB

from a compound of formula IA



Formula IA

comprising:

(a) heating and agitating a mixture comprising a compound of formula IA and L-malic acid, methylethyl ketone, and water; and

(b) cooling the mixture; and

(c) vacuum distilling the mixture successively; and

(d) isolating the compound of formula IB by filtration.

**[0064]** In one embodiment of this aspect, the compound of formula IA is admixed with a sufficient amount of L-malic acid in a methylethyl ketone/water (1:1) mixture. Alternatively, L-malic acid is added as a solution in water to a mixture of a compound of formula IA in methyl ethyl ketone. Generally the amount of L-malic is greater than 1 molar equivalent relative to the compound of formula IA. The mixture of the compound of formula IA and L-

malic acid in MEK/water is heated at about 40-70 °C and preferably at about 50-60 °C, and more preferably at about 55-60 °C with agitation, such as by stirring or the like, for from 1 to about 5 hours. At the end of the heating, the mixture is optionally clarified by filtering to give a clear solution. The resulting clear solution is then vacuum distilled from 1 to about 5 times at 150 to 200 mm Hg and a maximum jacket temperature of 55 °C to provide the desired crystalline compound of formula IB .

**[0065]** In one embodiment, L-malic acid is charged as a solution in water to the compound of formula IA. Generally the amount of L-malic is greater than 1 molar equivalent relative to the compound of formula IA. The mixture of the compound of formula IA and L-malic acid in MEK/water is heated at about 40-70 °C and preferably at about 50-60 °C, and more preferably at about 55-60 °C with agitation, such as by stirring or the like, for from 1 to about 5 hours. At the end of the heating, the mixture is optionally clarified by filtering to give a clear solution which is at a temperature of about 30-40 °C, and more preferably a t a temperature of about 33-37 °C. This clear solution is optionally seeded to facilitate crystallization. After seeding, the resulting mixture is vacuum distilled as provided above.

Definitions

**[0066]** As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise or they are expressly defined to mean something different.

**[0067]** The word "can" is used in a non-limiting sense and in contradistinction to the word "must." Thus, for example, in many aspects of the invention a certain element is described as "can" having a specified identity, which is meant to convey that the subject element is permitted to have that identity according to the invention but is not required to have it.

**[0068]** If a group "R" is depicted as "floating" on a ring system, then unless otherwise defined, the substituent(s) "R" can reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

**[0069]** When there are more than one such depicted "floating" groups, as for example in the formulae: where there are two groups, namely, the "R" and the bond indicating attachment to a parent structure; then, unless otherwise defined, the "floating" groups can

reside on any atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

**[0070]** Pharmaceutically acceptable salts include acid addition salts.

**[0071]** "Pharmaceutically acceptable acid addition salt" refers to those salts that retain the biological effectiveness of the free bases and that are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or mixtures thereof, as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like, or mixtures thereof.

**[0072]** The disclosure is further illustrated by the following examples, which are not to be construed as limiting the disclosure in scope or spirit to the specific procedures described in them.

**[0073]** Unless specified otherwise, the starting materials and various intermediates may be obtained from commercial sources, prepared from commercially available organic compounds, or prepared using well-known synthetic methods.

Experimental Procedures

**[0074]** The invention is illustrated further by the following examples in Scheme 1 and the description thereof, which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the invention, as demonstrated by the following examples. Those skilled in the art will also recognize that it may be necessary to utilize different solvents or reagents to achieve some of the above transformations.

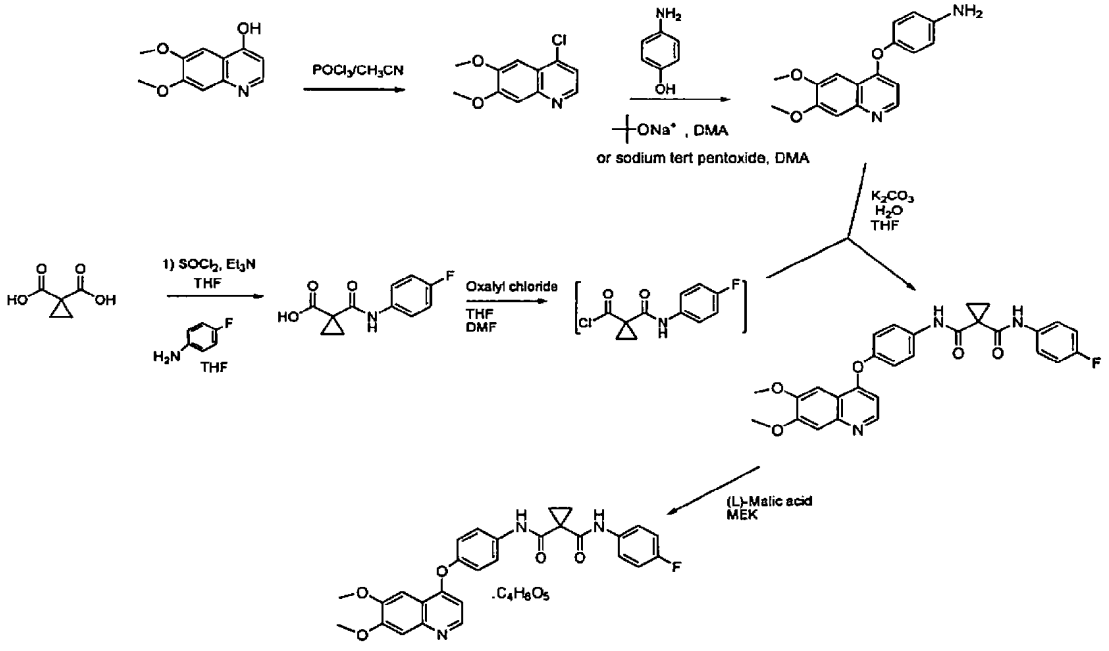
**[0075]** Unless otherwise specified, all reagents and solvents are of standard commercial grade and are used without further purification. The appropriate atmosphere to run the reaction under, for example, air, nitrogen, hydrogen, argon and the like, will be apparent to those skilled in the art.

**Example 1**

Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof.

[0076] A synthetic route that can be used for the preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Figure 1:

**Figure 1**




## Preparation of 4–Chloro–6,7–dimethoxy–quinoline

[0077] A reactor was charged sequentially with 6,7–dimethoxy–quinoline–4–ol (47.0 kg) and acetonitrile (318.8 kg). The resulting mixture was heated to approximately 60 °C and phosphorus oxychloride ($POCl_3$, 130.6 kg) was added. After the addition of $POCl_3$, the temperature of the reaction mixture was raised to approximately 77°C. The reaction was deemed complete (approximately 13 hours) when <3% of the starting material remained (in-process high-performance liquid chromatography [HPLC] analysis). The reaction mixture was cooled to approximately 2 – 7 °C and then quenched into a chilled solution of dichloromethane (DCM, 482.8 kg), 26 % $NH_4OH$ (251.3 kg), and water (900 L). The resulting mixture was warmed to approximately 20 – 25 °C, and phases were separated. The organic phase was filtered through a bed of AW hyflo super-cel NF (Celite; 5.4 kg) and the filter bed was washed with DCM (118.9 kg). The combined organic phase was washed with brine (282.9 kg) and mixed with water (120 L). The phases were separated and the organic phase was concentrated by vacuum distillation with the removal of solvent (approximately 95

L residual volume). DCM (686.5 kg) was charged to the reactor containing organic phase and concentrated by vacuum distillation with the removal of solvent (approximately 90 L residual volume). Methyl t-butyl ether (MTBE, 226.0 kg) was then charged and the temperature of the mixture was adjusted to – 20 to – 25 °C and held for 2.5 hours resulting in solid precipitate which was then filtered and washed with n-heptane (92.0 kg), and dried on a filter at approximately 25 °C under nitrogen to afford the title compound. (35.6 kg).

**Preparation of 4–(6, 7 –Dimethoxy–quinoline–4–yloxy)–phenylamine**

**[0078]** 4-Aminophenol (24.4 kg) dissolved in N,N-dimethylacetamide (DMA, 184.3 kg) was charged to a reactor containing 4-chloro-6,7-dimethoxyquinoline (35.3 kg), sodium t-butoxide (21.4 kg) and DMA (167.2 kg) at 20 – 25 °C. This mixture was then heated to 100 – 105°C for approximately 13 hours. After the reaction was deemed complete as determined using in-process HPLC analysis (<2% starting material remaining), the reactor contents were cooled at 15 to 20 °C and water (pre-cooled, 2 to 7 °C, 587 L) charged at a rate to maintain 15 to 30 °C temperature . The resulting solid precipitate was filtered, washed with a mixture of water (47 L) and DMA (89.1 kg) and finally with water (214 L). The filter cake was then dried at approximately 25°C on filter to yield crude 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine (59.4 kg wet, 41.6 kg dry calculated based on LOD). Crude 4–(6, 7 – dimethoxy–quinoline–4–yloxy)–phenylamine was refluxed (approximately 75 °C) in a mixture of tetrahydrofuran (THF, 211.4 kg) and DMA (108.8 kg) for approximately 1h and then cooled to 0 – 5°C and aged for approximately 1 h after which time the solid was filtered, washed with THF (147.6 kg) and dried on a filter under vacuum at approximately 25°C to yield 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine (34.0 kg).

**Alternative Preparation of 4–(6, 7 –Dimethoxy–quinoline–4–yloxy)–phenylamine**

**[0079]** 4-chloro-6,7-dimethoxyquinoline (34.8 kg) and 4-Aminophenol (30.8 kg) and sodium tert pentoxide (1.8 equivalents) 88.7 kg, 35 wt percent in THF) were charged to a reactor, followed by N,N-dimethylacetamide (DMA, 293.3 kg). This mixture was then heated to 105 – 115°C for approximately 9 hours. After the reaction was deemed complete as determined using in-process HPLC analysis (<2% starting material remaining), the reactor contents were cooled at 15 to 25 °C and water (315 kg) was added over a two hour period while maintaining the temperature between 20 and 30 °C. The reaction mixture was then agitated for an additional hour at 20 to 5°C. The crude product was collected by filtration and

washed with a mixture of 88kg water and 82.1 kg DMA, followed by 175 kg water. The product was dried on a filter drier for 53 hours. The LOD showed less than 1% w/w.

**[0080]** In an alternative procedure, 1.6 equivalents of sodium tert-pentoxide were used and the reaction temperature was increased from 110 – 120 °C. IN addition , the cool down temperature was increased to 35-40 °C and the starting temperature of the water addition was adjusted to 35-40 C, with an allowed exotherm to 45°C.

**Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid**

**[0081]** Triethylamine (19.5 kg) was added to a cooled (approximately 5 C) solution of cyclopropane–1,1–dicarboxylic acid (24.7 kg) in THF (89.6 kg) at a rate such that the batch temperature did not exceed 5°C. The solution was stirred for approximately 1.3 h, and then thionyl chloride (23.1 kg) was added, keeping the batch temperature below 10 C. When the addition was complete, the solution was stirred for approximately 4 h keeping temperature below 10 °C. A solution of 4–fluoroaniline (18.0 kg) in THF (33.1 kg) was then added at a rate such that the batch temperature did not exceed 10 C. The mixture was stirred for approximately 10 hours after which the reaction was deemed complete. The reaction mixture was then diluted with isopropyl acetate (218.1 kg). This solution was washed sequentially with aqueous sodium hydroxide (10.4 kg, 50 % dissolved in 119 L of water) further diluted with water (415 L), then with water (100 L) and finally with aqueous sodium chloride (20.0 kg dissolved in 100 L of water). The organic solution was concentrated by vacuum distillation (100 L residual volume) below 40 °C followed by the addition of n-heptane (171.4 kg), which resulted in the precipitation of solid. The solid was recovered by filtration and washed with n-Heptane (102.4 kg) resulting in wet crude, 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (29.0 kg). The crude, 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid was dissolved in methanol (139.7 kg) at approximately 25°C followed by the addition of water (320 L) resulting in slurry which was recovered by filtration, washed sequentially with water (20 L) and n-heptane (103.1 kg) and then dried on the filter at approximately 25 C under nitrogen to afford the title compound (25.4 kg).

**Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride**

**[0082]** Oxalyl chloride (12.6 kg) was added to a solution of 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (22.8 kg) in a mixture of THF (96.1 kg) and N, N-dimethylformamide (DMF; 0.23 kg) at a rate such that the batch temperature did not exceed 25 C. This solution was used in the next step without further processing.

**Alternative Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride**

**[0083]** A reactor was charged with 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (35 kg), 344 g DMF, and 175kg THF. The reaction mixture was adjusted to 12-17 °C and then to the reaction mixture was charged 19.9 kg of oxalyl chloride over a period of 1 hour. The reaction mixture was left stirring at 12-17 °C for 3 to 8 hours. This solution was used in the next step without further processing.

**Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide**

**[0084]** The solution from the previous step containing 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride was added to a mixture of compound 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (23.5 kg) and potassium carbonate (31.9 kg) in THF (245.7 kg) and water (116 L) at a rate such that the batch temperature did not exceed 30 °C. When the reaction was complete (in approximately 20 minutes), water (653 L) was added. The mixture was stirred at 20–25 C for approximately 10 hours, which resulted in the precipitation of the product. The product was recovered by filtration, washed with a pre-made solution of THF (68.6 kg) and water (256 L), and dried first on a filter under nitrogen at approximately 25°C and then at approximately 45 C under vacuum to afford the title compound (41.0 kg, 38.1 kg, calculated based on LOD).

**Alternative Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy–quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide**

**[0085]** A reactor was charged with 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (35.7 kg, 1 equivalent), followed by 412.9 kg THF. To the reaction mixture was charged a solution of 48.3 $K_2CO_3$ in 169 kg water. The acid chloride solution described in the Alternative Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride above was transferred to the reactor containing 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine while maintaining the temperature between 20-30 °C over a minimum of two hours. The reaction mixture was stirred at 20-25 °C for a minimum of three hours. The reaction temperature was then adjusted to 30-25 °C and the mixture was agitated. The agitation was stopped and the phases of the mixture were allowed to separate. The lower

aqueous phase was removed and discarded. To the remaining upper organic phase was added 804 kg water. The reaction was left stirring at 15-25 °C for a minimum of 16 hours.

**[0086]** The product precipitated. The product was filtered and washed with a mixture of 179 kg water and 157.9 THF in two portions. The crude product was dried under a vacuum for at least two hours. The dried product was then taken up in 285.1 kg THF. The resulting suspension was transferred to reaction vessel and agitated until the suspension became a clear (dissolved) solution, which required heating to 30-35 °C for approximately 30 minutes. 456 kg water were then added to the solution, as well as 20 kg SDAG-1 ethanol (ethanol denatured with methanol over two hours. The mixture was agitated at 15-25 °C fir at least 16 hours. The product was filtered and washed with a mixture of 143 kg water and 126.7 THF in two portions. The product was dried at a maximum temperature set point of 40 °C.

**[0087]** In an alternative procedure, the reaction temperature during acid chloride formation was adjusted to 10-15 °C. The recrystallization temperature was changed from 15-25 °C to 45-50 °C for 1 hour and then cooled to 15-25 °C over 2 hours.

**Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide, XL184 (L) malate salt**

**[0088]** Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide (1-5; 13.3 kg), L-malic acid (4.96 kg), methyl ethyl ketone (MEK; 188.6 kg) and water (37.3 kg) were charged to a reactor and the mixture was heated to reflux (approximately 74°C) for approximately 2 h. The reactor temperature was reduced to 50 to 55°C and the reactor contents were filtered. These sequential steps described above were repeated two more times starting with similar amounts of 1-5 (13.3 kg), L-Malic acid (4.96 kg), MEK (198.6 kg) and water (37.2 kg). The combined filtrate was azeotropically dried at atmospheric pressure using MEK (1133.2 kg) (approximate residual volume 711 L; KF $\leq$ 0.5 % w/w) at approximately 74°C. The temperature of the reactor contents was reduced to 20 to 25°C and held for approximately 4 hours resulting in solid precipitate which was filtered, washed with MEK (448 kg) and dried under vacuum at 50°C to afford the title compound (45.5 kg).

**Alternative Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide, XL184 (L) malate salt**

**[0089]** Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide (47.9 kg), L-malic acid (17.2), 658.2 kg methyl

ethyl ketone, and 129.1 kg water (37.3 kg) were charged to a reactor and the mixture was heated 50-55 °C for approximately 1-3 h, and then at 55-60 °C for an addition al 4-5 hours. The mixture was clarified by filtration through a 1 μm cartridge. The reactor temperature was adjusted to 20-25 °C and vacuum distilled with a vacuum at 150-200 mm Hg with a maximum jacket temperature of 55 °C to the volume range of 558-731 L.

**[0090]** The vacuum distillation was performed two more times with the charge of 380 kg and 380.2 kg methyl ethyl ketone, respectively. After the third distillation, the volume of the batch was adjusted to 18 v/w of Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy–quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide by charging 159.9 kg methyl ethyl ketone to give a total volume of 880L. An addition al vacuum distillation was carried out by adjusting 245.7 methyl ethyl ketone. The reaction mixture was left with moderate agitation at 20-25 °C for at least 24 hours. The product was filtered and washed with 415.1 kg methyl ethyl ketone in three portions. The product was dried under a vacuum with the jacket temperature set point at 45 °C.

**[0091]** In an alternative procedure, the order of addition was changes so that a solution of 17.7 kg L-malic acid dissolved in 129.9 kg water was added to Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide (48.7 kg) in methyl ethyl ketone (673.3 kg).

**[0092]** The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

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**FILING DATE:** *February 10, 2011*
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VIA EFS

February 10, 2011

Commissioner for Patents
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***Re:*** ***Application No.: To Be Determined***
***Inventors: To Be Determined***
***Filing Date: February 10, 2011***
***Title: c-Met Modulator Pharmaceutical Compositions***
***Our Docket. No.: 224990/11-XXXP/TBD***

Dear Sir:

The following documents are being electronically filed:

1. Cover Letter to the Commissioner for Patents;
2. Provisional Application for Patent Cover Sheet (PTO/SB/16);
3. Provisional Application; and
4. Certificate of Transmission under 37 C.F.R. §1.8(a).

It is believed that the filing fee required for this submission is $110. If there are any charges or credits regarding this filing, however, please apply them to Deposit Account 503145, referencing Attorney Docket 224990/11-XXXP/TBD.

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PTO/SB/16 (11-08)
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## Provisional Application for Patent Cover Sheet

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

### Inventor(s)

Inventor 1 — Remove

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| | |
|---|---|
| **Title of Invention** | C-MET MODULATOR PHARMACEUTICAL COMPOSITIONS |
| Attorney Docket Number (if applicable) | 224990/11-XXXP/TBD |

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Applicant claims small entity status under 37 CFR 1.27

- (●) Yes, applicant qualifies for small entity status under 37 CFR 1.27
- ( ) No

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| Signature | | | | Date (YYYY-MM-DD) | 2011-02-10 |
| First Name | Heidi | Last Name | Berven | Registration Number (If appropriate) | 48951 |

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| **First Named Inventor/Applicant Name:** | . . |
| **Customer Number:** | 91684 |
| **Filer:** | Heid Marie Berven/Lejla Duvnjak |
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| 1 | | EX11-XXXP_Application.pdf | 1732652<br>72faff57aaf4ff0b10f51969db2838b7d7003739 | yes | 21 |

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| Transmittal of New Application | 1 | 1 |
| Provisional Cover Sheet (SB16) | 2 | 3 |
| Specification | 4 | 17 |
| Claims | 18 | 19 |
| Abstract | 20 | 20 |
| Miscellaneous Incoming Letter | 21 | 21 |

**Warnings:**

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| 2 | Fee Worksheet (PTO-875) | fee-info.pdf | 29263<br>d94c8e7d515fb9881f701b60be7d9fe263c690ea | no | 2 |

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**ABSTRACT**

Pharmaceutical compositions and unit dosage forms comprising Compound (I) are disclosed.

What is claimed is:

1. A pharmaceutical composition as provided in Table 1.

**Table 1**

| Ingredient | % w/w |
|---|---|
| Compound (I) | 31.68 |
| Microcrystalline Cellulose (Avicel PH102) | 38.85 |
| Lactose anhydrous 60 M | 19.42 |
| Hydroxypropyl Cellulose, EXF | 3.00 |
| Croscarmellose Sodium | 3.00 |
| **Total Intra-granular** | **95.95** |
| Silicon dioxide, Colloidal PWD | 0.30 |
| Croscarmellose Sodium | 3.00 |
| Magnesium Stearate | 0.75 |
| **Total** | **100.00** |

2. A pharmaceutical composition as provided in Table 2.

**Table 2**

| Ingredient | (% w/w) |
|---|---|
| Compound (I) | 25.0-33.3 |
| Microcrystalline Cellulose, NF | q.s |
| Hydroxypropyl Cellulose, NF | 3 |
| Poloxamer, NF | 0-3 |
| Croscarmellose Sodium, NF | 6.0 |
| Colloidal Silicon Dioxide, NF | 0.5 |
| Magnesium Stearate, NF | 0.5-1.0 |
| Total | 100 |

3. The pharmaceutical composition of claims 1 or 2m, wherein Compound I is admixed with 100 ppm or less of 6,7–dimethoxy–quinoline–4–ol.

4. The pharmaceutical composition of claims 1 or 2m, wherein Compound I is admixed with 50 ppm or less of 6,7–dimethoxy–quinoline–4–ol.

5. The pharmaceutical composition of claims 1 or 2m, wherein Compound I is admixed with 25 ppm or less of 6,7–dimethoxy–quinoline–4–ol.

6. The pharmaceutical composition of claims 1 or 2m, wherein Compound I is admixed with 15 ppm or less of 6,7–dimethoxy–quinoline–4–ol.

7. The pharmaceutical composition of claims 1 or 2m, wherein Compound I is admixed with 10 ppm or less of 6,7–dimethoxy–quinoline–4–ol.

8. The pharmaceutical composition of claims 1 or 2m, wherein Compound I is admixed with 5 ppm or less of 6,7–dimethoxy–quinoline–4–ol.

# C-MET MODULATOR PHARMACEUTICAL COMPOSITIONS

## FIELD OF THE INVENTION

**[0001]** Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. One mechanism that can be exploited in cancer treatment is the modulation of protein kinase activity, because signal transduction through protein kinase activation is responsible for many of the characteristics of tumor cells. Protein kinase signal transduction is of particular relevance in, for example, renal, gastric, head and neck, lung, breast, prostate, and colorectal cancers; hepatocellular carcinoma; as well as in the growth and proliferation of brain tumor cells.

**[0002]** Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. For a detailed discussion of the receptor-type tyrosine kinases see Plowman et al., DN&P 7(6): 334-339, 1994. Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases, including, for example, immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, protein kinases are attractive targets for small molecule drug discovery. Particularly attractive targets for small-molecule modulation with respect to antiangiogenic and antiproliferative activity include receptor type tyrosine kinases c-Met, KDR, c-Kit, Axl, flt-3, and flt-4.

**[0003]** The kinase c-Met is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs) which include Met, Ron and Sea. The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenesis. Binding of HGF to c-Met induces activation of the receptor via autophosphorylation resulting in an increase of receptor dependent signaling, which promotes cell growth and invasion. Anti-HGF antibodies or HGF antagonists have been shown to inhibit tumor metastasis *in vivo* (See: Maulik et al Cytokine & Growth Factor Reviews 2002 13, 41-59). c-Met overexpression has been demonstrated on a wide variety of tumor types including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytomas, and glioblastomas. Additionally activating mutations

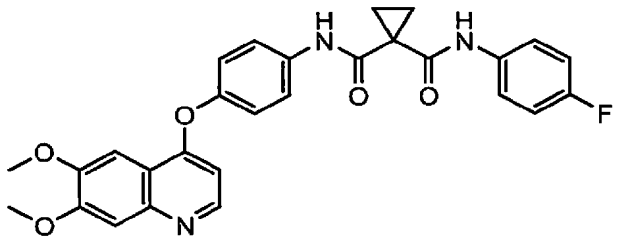
in the kinase domain of c-Met have been identified in hereditary and sporadic renal papilloma and squamous cell carcinoma. (See, e.g., Maulik et al., Cytokine & growth Factor reviews 2002 13, 41-59; Longati et al., Curr Drug Targets 2001, 2, 41-55; Funakoshi et al., Clinica Chimica Acta 2003 1-23).

**[0004]** Inhibition of epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A., Drug Disc. Technol. 2001 6, 1005-1024). Kinase KDR (refers to kinase insert domain receptor tyrosine kinase) and flt-4 (fms-like tyrosine kinase-4) are both VEGF receptors. Inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc. Technol. 2001 6, 1005-1024). EGF and VEGF receptors are desirable targets for small molecule inhibition. All members of the VEGF family stimulate cellular responses by binding to tyrosine kinase receptors (the VEGFRs) on the cell surface, causing them to dimerize and become activated through transphosphorylation. The VEGF receptors have an extracellular portion having immunoglobulin-like domains, a single transmembrane spanning region and an intracellular portion containing a split tyrosine-kinase domain. VEGF binds to VEGFR-1 and VEGFR-2. VEGFR-2 is known to mediate almost all of the known cellular responses to VEGF.

**[0005]** Kinase c-Kit (also called stem cell factor receptor or steel factor receptor) is a type 3 receptor tyrosine kinase (RTK) belonging to the platelet-derived growth factor receptor subfamily. Overexpression of c-Kit and c-Kit ligand has been described in variety of human diseases including human gastrointestinal stromal tumors, mastocytosis, germ cell tumors, acute myeloid leukemia (AML), NK lymphoma, small-cell lung cancer, neuroblastomas, gynecological tumors and colon carcinoma. Moreover, elevated expression of c-Kit may also relate to the development of neoplasia associated with neurofibromatosis type 1 (NF-1), mesenchymal tumors GISTs and mast cell disease, as well as other disorders associated with activated c-Kit.

**[0006]** Kinase Flt-3 (fms-like tyrosine kinase-3) is constitutively activated via mutation, either in the juxtamembrane region or in the activation loop of the kinase domain, in a large proportion of patients with AML (Reilly, Leuk. Lymphoma, 2003, 44: 1-7).

**[0007]** Accordingly, small-molecule compounds that specifically inhibit, regulate, and/or modulate the signal transduction of kinases, particularly including c-Met, VEGFR2, KDR, c-Kit, Axl, flt-3, and flt-4 described above, are particularly desirable as a means to treat or prevent disease states associated with abnormal cell proliferation and angiogenesis. One such small-molecule is Compound (I), which has the chemical structure:



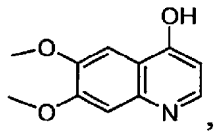
(I).

WO2005/030140 describes the synthesis of Compound (I) (Table 2, Compound 12, Example 48) and also discloses the therapeutic activity of this molecule to inhibit, regulate and/or modulate the signal transduction of kinases (Assays, Table 4, entry 289), the entire contents of which is incorporated herein by reference.

**[0008]** Although therapeutic efficacy is the primary concern for a therapeutic agent, the pharmaceutical composition can be equally important to its development. Generally, the drug developer endeavors to discover a pharmaceutical composition that possesses desirable properties such as satisfactory water-solubility (including rate of dissolution), storage stability, hygroscopicity, and reproducibility, all of which can impact the processability, manufacture, and/or bioavailability of the drug. Accordingly, discovery of pharmaceutical compositions that possess some or all of these desired properties is vital to drug development.

## SUMMARY OF THE INVENTION

**[0009]** These and other needs are met by the present invention which is directed to a pharmaceutical composition comprising compound II or a pharmaceutically acceptable salt

thereof admixed with less than 100 ppm 6,7–dimethoxy–quinoline–4–ol, the structure of which is  , and a pharmaceutically acceptable carrier.

**[0010]** In another aspect , the invention which is directed to a pharmaceutical composition comprising compound I or a pharmaceutically acceptable salt thereof admixed with less than 50 ppm 6,7–dimethoxy–quinoline–4–ol, and a pharmaceutically acceptable carrier.

**[0011]** In another aspect , the invention which is directed to a pharmaceutical composition comprising compound I or a pharmaceutically acceptable salt thereof admixed with less than 25 ppm 6,7–dimethoxy–quinoline–4–ol, and a pharmaceutically acceptable carrier.

**[0012]** In another aspect , the invention which is directed to a pharmaceutical composition comprising compound I or a pharmaceutically acceptable salt thereof admixed with less than 15 ppm 6,7–dimethoxy–quinoline–4–ol, and a pharmaceutically acceptable carrier.

**[0013]** In another aspect , the invention which is directed to a pharmaceutical composition comprising compound I or a pharmaceutically acceptable salt thereof admixed with less than 10 ppm 6,7–dimethoxy–quinoline–4–ol, and a pharmaceutically acceptable carrier.

**[0014]** In another aspect , the invention which is directed to a pharmaceutical composition comprising compound I or a pharmaceutically acceptable salt thereof admixed with less than 5 ppm 6,7–dimethoxy–quinoline–4–ol, and a pharmaceutically acceptable carrier.

**[0015]** In another aspect , the invention which is directed to a pharmaceutical composition comprising compound I L-malate salt admixed with less than 5 ppm 6,7–dimethoxy–quinoline–4–ol, and a pharmaceutically acceptable carrier.

**[0016]** In another aspect , the invention which is directed to a pharmaceutical composition as provided in Table 1.

**Table 1**

| Ingredient | % w/w |
|---|---|
| Compound (I) | 31.68 |
| Microcrystalline Cellulose (Avicel PH102) | 38.85 |
| Lactose anhydrous 60 M | 19.42 |
| Hydroxypropyl Cellulose, EXF | 3.00 |
| Croscarmellose Sodium | 3.00 |
| **Total Intra-granular** | **95.95** |
| Silicon dioxide, Colloidal PWD | 0.30 |
| Croscarmellose Sodium | 3.00 |
| Magnesium Stearate | 0.75 |
| **Total** | **100.00** |

wherein the compound or its pharmaceutically acceptable salt is admixed with 100 ppm or less 6,7–dimethoxy–quinoline–4–ol.

**[0017]** In another embodiment, the invention is also directed to a pharmaceutical composition as provided in Table 2.

**Table 2**

| Ingredient | (% w/w) |
|---|---|
| Compound (I) | 25.0-33.3 |
| Microcrystalline Cellulose, NF | q.s |
| Hydroxypropyl Cellulose, NF | 3 |
| Poloxamer, NF | 0-3 |
| Croscarmellose Sodium, NF | 6.0 |
| Colloidal Silicon Dioxide, NF | 0.5 |
| Magnesium Stearate, NF | 0.5-1.0 |
| Total | 100 |

wherein the compound or its pharmaceutically acceptable salt is admixed with 100 ppm or less 6,7–dimethoxy–quinoline–4–ol.

## DETAILED DESCRIPTION

**[0018]** Various carriers used in formulating pharmaceutically acceptable compositions and known techniques for their bulk preparation and subsequent production into unit dosage forms are disclosed in Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. D. B.

Troy, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York. The amount of carriers and excipients used in a formulation can be varied according to the amount of active ingredient used (that is, Compound (I)).

**Pharmaceutical Composition**

**[0019]** Compound (I) and various pharmaceutically acceptable salts of Compound (I) are disclosed in WO2005/0030140. The malate salt of Compound (I) is disclosed in PCT/US2010/021194 (filed January 15, 2010). Both references are incorporated by reference herein in their entirety.

**[0020]** In one embodiment, the pharmaceutical composition is a tablet.

**[0021]** In another embodiment, the pharmaceutical composition is a capsule.

**[0022]** In another embodiment of the pharmaceutical composition is provided by Tables 1 or 2, Compound (I) is the free base.

**[0023]** In another embodiment of the pharmaceutical composition is provided by Tables 1 or 2, Compound (I) is the malate salt.

**[0024]** In another embodiment of the pharmaceutical composition is provided by Tables 1 or 2, Compound (I) is the malate salt as the N-1 polymorph.

**[0025]** In another embodiment of the pharmaceutical composition is provided by Tables 1 or 2, Compound (I) is the malate salt as the N-2 polymorph.

**[0026]** In another embodiment, the pharmaceutical composition is provided by Tables 1 or 2, is administered as a tablet unit dosage form.

**[0027]** In another embodiment, of the pharmaceutical composition, the compound as defined in any of the previous embodiments is admixed with 100 ppm 6,7–dimethoxy–quinoline–4–ol.

**[0028]** In another embodiment, of the pharmaceutical composition, the compound as defined in any of the previous embodiments is admixed with 50 ppm 6,7–dimethoxy–quinoline–4–ol.

**[0029]** In another embodiment, of the pharmaceutical composition, the compound as defined in any of the previous embodiments is admixed with 25 ppm 6,7–dimethoxy–quinoline–4–ol.

**[0030]** In another embodiment, of the pharmaceutical composition, the compound as defined in any of the previous embodiments is admixed with 15 ppm 6,7–dimethoxy–quinoline–4–ol.

**[0031]** In another embodiment, of the pharmaceutical composition, the compound as defined in any of the previous embodiments is admixed with 10 ppm 6,7–dimethoxy–quinoline–4–ol.

**[0032]** In another embodiment, of the pharmaceutical composition, the compound as defined in any of the previous embodiments is admixed with 5 ppm 6,7–dimethoxy–quinoline–4–ol.

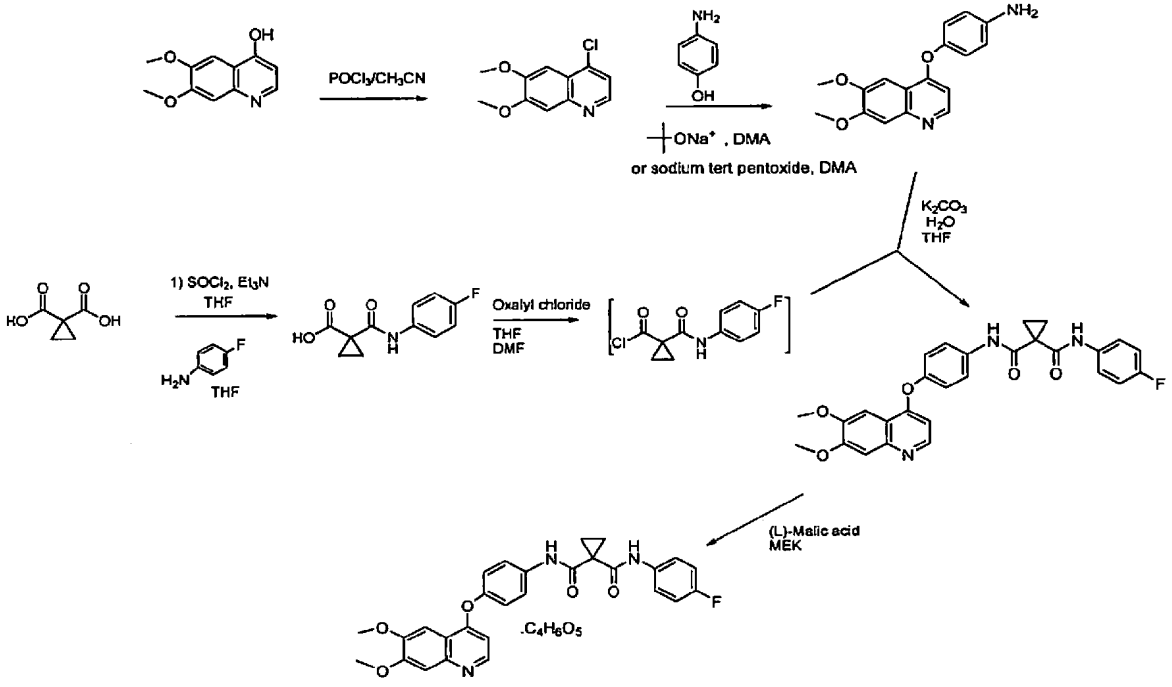
**[0033]** The following Examples illustrate the preparation of pharmaceutical compositions comprising Compound (I). The examples are not intended to be limiting to the scope of the invention in any respect, and should not be so construed.

## EXAMPLES

### Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof.

**[0034]** A synthetic route that can be used for the preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Figure 1:

**Figure 1**



**Preparation of 4–Chloro–6,7–dimethoxy–quinoline**

**[0035]** A reactor was charged sequentially with 6,7–dimethoxy–quinoline–4–ol (47.0 kg) and acetonitrile (318.8 kg). The resulting mixture was heated to approximately 60 °C and phosphorus oxychloride ($POCl_3$, 130.6 kg) was added. After the addition of $POCl_3$, the temperature of the reaction mixture was raised to approximately 77°C. The reaction was deemed complete (approximately 13 hours) when <3% of the starting material remained (in-process high-performance liquid chromatography [HPLC] analysis). The reaction mixture was cooled to approximately 2 – 7 °C and then quenched into a chilled solution of dichloromethane (DCM, 482.8 kg), 26 % $NH_4OH$ (251.3 kg), and water (900 L). The resulting mixture was warmed to approximately 20 – 25 °C, and phases were separated. The organic phase was filtered through a bed of AW hyflo super-cel NF (Celite; 5.4 kg) and the filter bed was washed with DCM (118.9 kg). The combined organic phase was washed with brine (282.9 kg) and mixed with water (120 L). The phases were separated and the organic phase was concentrated by vacuum distillation with the removal of solvent (approximately 95 L residual volume). DCM (686.5 kg) was charged to the reactor containing organic phase and concentrated by vacuum distillation with the removal of solvent (approximately 90 L residual volume). Methyl t-butyl ether (MTBE, 226.0 kg) was then charged and the temperature of the mixture was adjusted to – 20 to – 25 °C and held for 2.5 hours resulting in solid precipitate which was then filtered and washed with n-heptane (92.0 kg), and dried on a filter at approximately 25 °C under nitrogen to afford the title compound. (35.6 kg).

**Preparation of 4–(6, 7 –Dimethoxy–quinoline–4–yloxy)–phenylamine**

**[0036]** 4-Aminophenol (24.4 kg) dissolved in N,N-dimethylacetamide (DMA, 184.3 kg) was charged to a reactor containing 4-chloro-6,7-dimethoxyquinoline (35.3 kg), sodium t-butoxide (21.4 kg) and DMA (167.2 kg) at 20 – 25 °C. This mixture was then heated to 100 – 105°C for approximately 13 hours. After the reaction was deemed complete as determined using in-process HPLC analysis (<2% starting material remaining), the reactor contents were cooled at 15 to 20 °C and water (pre-cooled, 2 to 7 °C, 587 L) charged at a rate to maintain 15 to 30 °C temperature . The resulting solid precipitate was filtered, washed with a mixture of water (47 L) and DMA (89.1 kg) and finally with water (214 L). The filter cake was then dried at approximately 25°C on filter to yield crude 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine (59.4 kg wet, 41.6 kg

dry calculated based on LOD). Crude 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine was refluxed (approximately 75 °C) in a mixture of tetrahydrofuran (THF, 211.4 kg) and DMA (108.8 kg) for approximately 1h and then cooled to 0 – 5°C and aged for approximately 1 h after which time the solid was filtered, washed with THF (147.6 kg) and dried on a filter under vacuum at approximately 25°C to yield 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine (34.0 kg).

**Alternative Preparation of 4–(6, 7 –Dimethoxy–quinoline–4–yloxy)–phenylamine**

**[0037]** 4-chloro-6,7-dimethoxyquinoline (34.8 kg) and 4-Aminophenol (30.8 kg) and sodium tert pentoxide (1.8 equivalents) 88.7 kg, 35 wt percent in THF) were charged to a reactor, followed by N,N-dimethylacetamide (DMA, 293.3 kg). This mixture was then heated to 105 – 115°C for approximately 9 hours. After the reaction was deemed complete as determined using in-process HPLC analysis (<2% starting material remaining), the reactor contents were cooled at 15 to 25 °C and water (315 kg) was added over a two hour period while maintaining the temperature between 20 and 30 °C. The reaction mixture was then agitated for an additional hour at 20 to 5°C. The crude product was collected by filtration and washed with a mixture of 88kg water and 82.1 kg DMA, followed by 175 kg water. The product was dried on a filter drier for 53 hours. The LOD showed less than 1% w/w.

**[0038]** In an alternative procedure, 1.6 equivalents of sodium tert-pentoxide were used and the reaction temperature was increased from 110 – 120 °C. IN addition , the cool down temperature was increased to 35-40 °C and the starting temperature of the water addition was adjusted to 35-40 C, with an allowed exotherm to 45°C.

**Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid**

**[0039]** Triethylamine (19.5 kg) was added to a cooled (approximately 5 C) solution of cyclopropane–1,1–dicarboxylic acid (24.7 kg) in THF (89.6 kg) at a rate such that the batch temperature did not exceed 5°C. The solution was stirred for approximately 1.3 h, and then thionyl chloride (23.1 kg) was added, keeping the batch temperature below 10 C. When the addition was complete, the solution was stirred for approximately 4 h keeping temperature below 10 °C. A solution of 4–fluoroaniline (18.0 kg) in THF (33.1 kg) was then added at a rate such that the batch temperature did not exceed 10 C. The mixture was stirred for approximately 10

hours after which the reaction was deemed complete. The reaction mixture was then diluted with isopropyl acetate (218.1 kg). This solution was washed sequentially with aqueous sodium hydroxide (10.4 kg, 50 % dissolved in 119 L of water) further diluted with water (415 L), then with water (100 L) and finally with aqueous sodium chloride (20.0 kg dissolved in 100 L of water). The organic solution was concentrated by vacuum distillation (100 L residual volume) below 40 °C followed by the addition of n-heptane (171.4 kg), which resulted in the precipitation of solid. The solid was recovered by filtration and washed with n-Heptane (102.4 kg) resulting in wet crude, 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (29.0 kg). The crude, 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid was dissolved in methanol (139.7 kg) at approximately 25°C followed by the addition of water (320 L) resulting in slurry which was recovered by filtration, washed sequentially with water (20 L) and n-heptane (103.1 kg) and then dried on the filter at approximately 25 C under nitrogen to afford the title compound (25.4 kg).

**Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride**

**[0040]** Oxalyl chloride (12.6 kg) was added to a solution of 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (22.8 kg) in a mixture of THF (96.1 kg) and N, N-dimethylformamide (DMF; 0.23 kg) at a rate such that the batch temperature did not exceed 25 C. This solution was used in the next step without further processing.

**Alternative Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride**

**[0041]** A reactor was charged with 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (35 kg), 344 g DMF, and 175kg THF. The reaction mixture was adjusted to 12-17 °C and then to the reaction mixture was charged 19.9 kg of oxalyl chloride over a period of 1 hour. The reaction mixture was left stirring at 12-17 °C for 3 to 8 hours. This solution was used in the next step without further processing.

**Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide**

**[0042]** The solution from the previous step containing 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride was added to a mixture of compound 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (23.5 kg) and potassium carbonate (31.9 kg) in THF (245.7 kg)

and water (116 L) at a rate such that the batch temperature did not exceed 30 °C. When the reaction was complete (in approximately 20 minutes), water (653 L) was added. The mixture was stirred at 20–25 C for approximately 10 hours, which resulted in the precipitation of the product. The product was recovered by filtration, washed with a pre-made solution of THF (68.6 kg) and water (256 L), and dried first on a filter under nitrogen at approximately 25°C and then at approximately 45 C under vacuum to afford the title compound (41.0 kg, 38.1 kg, calculated based on LOD).

**Alternative Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy–quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide**

**[0043]** A reactor was charged with 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (35.7 kg, 1 equivalent), followed by 412.9 kg THF. To the reaction mixture was charged a solution of 48.3 $K_2CO_3$ in 169 kg water. The acid chloride solution of described in the Alternative Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride above was transferred to the reactor containing 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine while maintaining the temperature between 20-30 °C over a minimum of two hours. The reaction mixture was stirred at 20-25 °C for a minimum of three hours. The reaction temperature was then adjusted to 30-25 °C and the mixture was agitated. The agitation was stopped and the phases of the mixture were allowed to separate. The lower aqueous phase was removed and discarded. To the remaining upper organic phase was added 804 kg water. The reaction was left stirring at 15-25 °C for a minimum of 16 hours.

**[0044]** The product precipitated. The product was filtered and washed with a mixture of 179 kg water and 157.9 THF in two portions. The crude product was dried under a vacuum for at least two hours. The dried product was then taken up in 285.1 kg THF. The resulting suspension was transferred to reaction vessel and agitated until the suspension became a clear (dissolved) solution, which required heating to 30-35 °C for approximately 30 minutes. 456 kg water were then added to the solution, as well as 20 kg SDAG-1 ethanol (ethanol denatured with methanol over two hours. The mixture was agitated at 15-25 °C fir at least 16 hours. The product was filtered and washed with a mixture of 143 kg water and 126.7 THF in two portions. The product was dried at a maximum temperature set point of 40 °C.

**[0045]** In an alternative procedure, the reaction temperature during acid chloride formation was adjusted to 10-15 °C. The recrystallization temperature was changed from 15-25 °C to 45-50 °C for 1 hour and then cooled to 15-25 °C over 2 hours.

**Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide, XL184 (L) malate salt**

**[0046]** Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide (1-5; 13.3 kg), L-malic acid (4.96 kg), methyl ethyl ketone (MEK; 188.6 kg) and water (37.3 kg) were charged to a reactor and the mixture was heated to reflux (approximately 74°C) for approximately 2 h. The reactor temperature was reduced to 50 to 55°C and the reactor contents were filtered. These sequential steps described above were repeated two more times starting with similar amounts of 1-5 (13.3 kg), L-Malic acid (4.96 kg), MEK (198.6 kg) and water (37.2 kg). The combined filtrate was azeotropically dried at atmospheric pressure using MEK (1133.2 kg) (approximate residual volume 711 L; KF $\leq$ 0.5 % w/w) at approximately 74°C. The temperature of the reactor contents was reduced to 20 to 25°C and held for approximately 4 hours resulting in solid precipitate which was filtered, washed with MEK (448 kg) and dried under vacuum at 50°C to afford the title compound (45.5 kg).

**Alternative Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy–quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide, XL184 (L) malate salt**

**[0047]** Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide (47.9 kg), L-malic acid (17.2), 658.2 kg methyl ethyl ketone, and 129.1 kg water (37.3 kg) were charged to a reactor and the mixture was heated 50-55 °C for approximately 1-3 h, and then at 55-60 °C for an addition al 4-5 hours. The mixture was clarified by filtration through a 1 μm cartridge. The reactor temperature was adjusted to 20-25 °C and vacuum distilled with a vacuum at 150-200 mm Hg with a maximum jacket temperature of 55 °C to the volume range of 558-731 L.

**[0048]** The vacuum distillation was performed two more times with the charge of 380 kg and 380.2 kg methyl ethyl ketone, respectively. After the third distillation, the volume of the batch was adjusted to 18 v/w of Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide by charging 159.9 kg methyl ethyl ketone to

give a total volume of 880L. An addition al vacuum distillation was carried out by adjusting 245.7 methyl ethyl ketone. The reaction mixture was left with moderate agitation at 20-25 °C for at least 24 hours. The product was filtered and washed with 415.1 kg methyl ethyl ketone in three portions. The product was dried under a vacuum with the jacket temperature set point at 45 °C.

**[0049]** In an alternative procedure, the order of addition was changes so that a solution of 17.7 kg L-malic acid dissolved in 129.9 kg water was added to Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide (48.7 kg) in methyl ethyl ketone (673.3 kg).

**Pharmaceutical Compositions**

| Ingredient | (% w/w) |
|---|---|
| Compound (I) | 25.0-33.3 |
| Microcrystalline Cellulose, NF | q.s |
| Hydroxypropyl Cellulose, NF | 3 |
| Poloxamer, NF | 0-3 |
| Croscarmellose Sodium, NF | 6.0 |
| Colloidal Silicon Dioxide, NF | 0.5 |
| Magnesium Stearate, NF | 0.5-1.0 |
| Total | 100 |

**Example 2**

| Ingredient | % w/w |
|---|---|
| Compound (I) | 31.68 |
| Microcrystalline Cellulose (Avicel PH102) | 38.85 |
| Lactose anhydrous 60 M | 19.42 |
| Hydroxypropyl Cellulose, EXF | 3.00 |
| Croscarmellose Sodium | 3.00 |
| **Total Intra-granular** | **95.95** |
| Silicon dioxide, Colloidal PWD | 0.30 |
| Croscarmellose Sodium | 3.00 |
| Magnesium Stearate | 0.75 |
| **Total** | **100.00** |

**[0050]** The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with

reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

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| | | |
|---|---|---|
| International application number: | | **PCT/US2012/024591** |
| International filing date: | | **10 February 2012 (10.02.2012)** |
| Document type: | | **Certified copy of priority document** |
| Document details: | Country/Office: | **US** |
| | Number: | **61/441,527** |
| | Filing date: | **10 February 2011 (10.02.2011)** |
| Date of receipt at the International Bureau: | | **18 February 2012 (18.02.2012)** |

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a),(b) or (b-*bis*)

34, chemin des Colombettes
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# PCT

## REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/US12/24591
International Application No.

10 FEB 2012 (10.02.12)
International Filing Date

PCT INTERNATIONAL APPLICATION RO/US
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* EX10-039C-PC

**Box No. I TITLE OF INVENTION**

Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

**Box No. II APPLICANT** ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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Applicant's registration No. with the Office

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State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

**Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

**Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

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48,951

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E-mail address: patents@honigman.com

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*If none of the following sub-boxes is used, this sheet should not be included in the request.*

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Wilson, Jo Ann
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*US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

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This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

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This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

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This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

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Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

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☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

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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.

However,

☐ DE Germany **is not designated** for any kind of national protection

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☐ KR Republic of Korea **is not designated** for any kind of national protection

*(The check-boxes above may only be used to exclude (irrevocably) the designations concerned if, at the time of filing or subsequently under Rule 26bis.1, the international application contains in Box No. VI a priority claim to an earlier national application filed in the particular State concerned, in order to avoid the ceasing of the effect, under the national law, of this earlier national application.)*

**Box No. VI PRIORITY CLAIM**

The priority of the following earlier application(s) is hereby claimed:

| Filing date of earlier application *(day/month/year)* | Number of earlier application | Where earlier application is: | | |
|---|---|---|---|---|
| | | national application: country or Member of WTO | regional application: regional Office | international application: receiving Office |
| item (1) (10.02.2011) ~~10/02/2010~~ *10 February 2011 | 61/441,520 | US | | |
| item (2) ~~10/02/2010~~ (10.02.2011) *10 February 2011 | 61/441,527 | US | | |
| item (3) | | | | |

☐ Further priority claims are indicated in the Supplemental Box.

☐ The **International Bureau** is requested to obtain from a digital library, a certified copy of the earlier application(s) *(if the earlier application(s) is available to it from a digital library)* identified above as:*

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

☒ **The receiving Office** is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(if the earlier application(s) was filed with the Office which for the purposes of this international application is the receiving Office)* or to obtain a certified copy of the earlier application(s) from a digital library and transmit a copy of it to the International Bureau *(if the earlier application(s) is available to the receiving Office from a digital library)*, identified above as:*

☒ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

* Where the certified copy of the earlier application(s) is not stored in a digital library under the number of the earlier application indicated above but under the application number of another application which also claims priority from it, indicate that number in the supplemental sheet (item 4).

**Restore the right of priority:** the receiving Office is requested to restore the right of priority for the earlier application(s) identified above or in the Supplemental Box as item(s) (_____). *(See also the Notes to Box No. VI; further information must be provided to support a request to restore the right of priority.)*

**Incorporation by reference:** 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.

**Box No. VII INTERNATIONAL SEARCHING AUTHORITY**

**Choice of International Searching Authority (ISA)** *(if more than one International Searching Authority is competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA/ EP

**Box No. IX** CHECK LIST for EFS-Web filings - this sheet is only to be used when filing an international application with RO/US via EFS-Web

| This international application **contains** the following: | Number of sheets |
|---|---|
| (a) request form PCT/RO/101 (including any declarations and supplemental sheets) | 4 |
| (b) description (excluding any sequence listing part of the description, see (f), below) | 37 |
| (c) claims | 9 |
| (d) abstract | 1 |
| (e) drawings (if any) | |
| (f) sequence listing part of the description in the form of an **image file** (e.g. PDF) | |
| **Total number of sheets** (including the sequence listing part of the description if filed as an **image file**) | 51 |

(g) sequence listing part of the description

- ☐ filed in the form of an **Annex C/ST.25** text file
- ☐ WILL BE filed separately on physical data carrier(s), on the same day and in the form of an **Annex C/ST.25** text file

Indicate type and number of physical data carrier(s)

| This international application is **accompanied by** the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)* | Number of items |
|---|---|
| 1. ☐ fee calculation sheet | |
| 2. ☐ original separate power of attorney | |
| 3. ☒ original general power of attorney | 1 |
| 4. ☐ copy of general power of attorney; reference number: | |
| 5. ☐ statement explaining lack of signature | |
| 6. ☐ priority document(s) identified in Box No. VI as item(s) | |
| 7. ☐ Translation of international application into *(language)*: | |
| 8. ☐ separate indications concerning deposited microorganism or other biological material | |
| 9. ☐ *(only where item (f) is marked in the left column)* copy of the sequence listing in electronic form (Annex C/ST.25 text file) not forming part of the international application but **furnished only for the purposes of international search** under Rule 13*ter* | |
| 10. ☐ *(only where item (f) is marked in the left column)* a statement confirming that "the information recorded in electronic form submitted under Rule 13*ter* is identical to the sequence listing as contained in the international application" as filed via EFS-Web | |
| 11. ☐ copy of results of earlier search(es) (Rule 12*bis*.1(a)) | |
| 12. ☒ other *(specify)*: Cover Letter, Certificate of Transmissi | 2 |

**Figure of the drawings** which should accompany the abstract:

**Language of filing** of the international application:

**Box No. X** SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

*Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).*

Heidi M. Berven
Reg. No. 48951

Dated: February 10, 2012

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| | |
|---|---|
| 1. Date of actual receipt of the purported international application: 10 FEB 2012 (10.02.12) | 2. Drawings: ☐ received: ☐ not received: |
| 3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: | |
| 4. Date of timely receipt of the required corrections under PCT Article 11(2): | |
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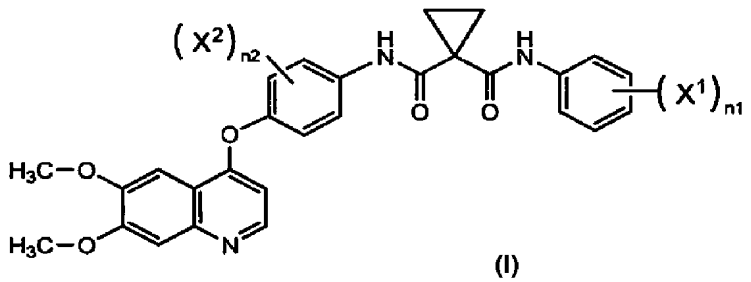
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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**Published**:

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

(54) Title: PROCESSES FOR PREPARING QUINOLINE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH COMPOUNDS




(I)

(57) Abstract: The present invention is directed to processes for making and compositions containing quinolines such as formula I or pharmaceutically acceptable salts thereof wherein: X1 is H, Br, CI, or X2 is H, Br, CI, or n1 is 1-2; and n2 is 1-2.

WO 2012/109510 A1

# PROCESSES FOR PREPARING QUINOLINE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH COMPOUNDS

## CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 61/441,520, filed February 10, 2011, and 61/441,527, filed February 10, 2011, which are incorporated herein by reference

## FIELD OF THE INVENTION

[0002] This disclosure relates to processes for preparing compounds useful for modulating protein kinase enzymatic activity. More specifically, this disclosure relates to processes for preparing quinolines that are useful for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration, and chemo-invasion and to pharmaceutical compositions containing such compounds.

## BACKGROUND OF THE INVENTION

[0003] Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. One mechanism that can be exploited in cancer treatment is the modulation of protein kinase activity because signal transduction through protein kinase activation is responsible for many of the characteristics of tumor cells. Protein kinase signal transduction is of particular relevance in, for example, renal, gastric, head and neck, lung, breast, prostate, and colorectal cancers; hepatocellular carcinoma; as well as in the growth and proliferation of brain tumor cells.

[0004] Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., DN&P 7(6): 334-339, 1994. Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases, including, for example, immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, protein kinases are attractive targets for small molecule drug discovery. Particularly attractive targets for small-molecule modulation with respect to antiangiogenic

and antiproliferative activity include receptor type tyrosine kinases c-Met, KDR, c-Kit, Axl, flt-3, and flt-4.

**[0005]** The kinase c-Met is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs) which include Met, Ron, and Sea. The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenesis. Binding of HGF to c-Met induces activation of the receptor via autophosphorylation, resulting in an increase of receptor dependent signaling, which promotes cell growth and invasion. Anti-HGF antibodies or HGF antagonists have been shown to inhibit tumor metastasis *in vivo* (See: Maulik et al Cytokine & Growth Factor Reviews 2002 13, 41-59). c-Met overexpression has been demonstrated on a wide variety of tumor types including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytomas, and glioblastomas. Additionally, activating mutations in the kinase domain of c-Met have been identified in hereditary and sporadic renal papilloma and squamous cell carcinoma. (See, e.g., Maulik et al., Cytokine & growth Factor reviews 2002 13, 41-59; Longati et al., Curr Drug Targets 2001, 2, 41-55; Funakoshi et al., Clinica Chimica Acta 2003 1-23).

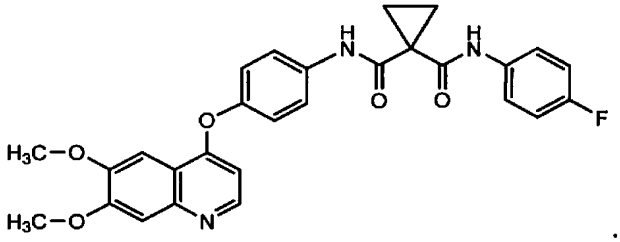
**[0006]** Inhibition of epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A., Drug Disc. Technol. 2001 6, 1005-1024). Kinase KDR (refers to kinase insert domain receptor tyrosine kinase) and flt-4 (fms-like tyrosine kinase-4) are both VEGF receptors. Inhibition of EGF, VEGF, and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc. Technol. 2001 6, 1005-1024). EGF and VEGF receptors are desirable targets for small molecule inhibition. All members of the VEGF family stimulate cellular responses by binding to tyrosine kinase receptors (the VEGFRs) on the cell surface, causing them to dimerize and become activated through transphosphorylation. The VEGF receptors have an extracellular portion with immunoglobulin-like domains, a single transmembrane spanning region, and an intracellular portion containing a split tyrosine-kinase domain. VEGF binds to VEGFR-1 and VEGFR-2. VEGFR-2 is known to mediate almost all of the known cellular responses to VEGF.

**[0007]** Kinase c-Kit (also called stem cell factor receptor or steel factor receptor) is a type 3 receptor tyrosine kinase (RTK) belonging to the platelet-derived growth factor receptor subfamily. Overexpression of c-Kit and c-Kit ligand has been described in variety of human

diseases, including human gastrointestinal stromal tumors, mastocytosis, germ cell tumors, acute myeloid leukemia (AML), NK lymphoma, small-cell lung cancer, neuroblastomas, gynecological tumors, and colon carcinoma. Moreover, elevated expression of c-Kit may also relate to the development of neoplasia associated with neurofibromatosis type 1 (NF-1), mesenchymal tumors GISTs, and mast cell disease, as well as other disorders associated with activated c-Kit.

**[0008]** Kinase Flt-3 (fms-like tyrosine kinase-3) is constitutively activated via mutation, either in the juxtamembrane region or in the activation loop of the kinase domain, in a large proportion of patients with AML (Reilly, Leuk. Lymphoma, 2003, 44: 1-7).

**[0009]** Small-molecule compounds that specifically inhibit, regulate, and/or modulate the signal transduction of kinases, such as c-Met, VEGFR2, KDR, c-Kit, Axl, flt-3, and flt-4 described above, are particularly desirable as a means to treat or prevent disease states associated with abnormal cell proliferation and angiogenesis. One such small-molecule is compound IA, which has the chemical structure:




IA

WO2005/030140 describes the synthesis of compound IA (Table 2, Compound 12, Example 48) and also discloses the therapeutic activity of this molecule to inhibit, regulate, and/or modulate the signal transduction of kinases (Assays, Table 4, entry 289), the entire contents of which is incorporated herein by reference.

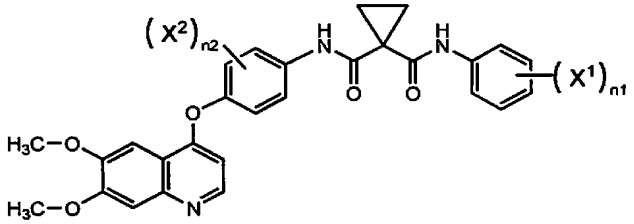
**[0010]** Although therapeutic efficacy is the primary concern for a therapeutic agent, the pharmaceutical composition can be equally important to its development. Generally, the drug developer endeavors to discover a pharmaceutical composition that possesses desirable properties, such as satisfactory water-solubility (including rate of dissolution), storage stability, hygroscopicity, and reproducibility, all of which can impact the processability, manufacture, and/or bioavailability of the drug.

**[0011]** Accordingly, there is a need for the discovery of new processes for making quinolines such as compound IA that minimize the formation of undesirable process contaminants or byproducts. There is also a need for new pharmaceutical compositions containing quinolines such as compound IA that are essentially free of process byproducts.

## SUMMARY OF THE INVENTION

**[0012]** These and other needs are met by the present disclosure, which is directed to processes for making and compositions containing quinolines or pharmaceutically acceptable salts thereof.

**[0013]** In one aspect, the disclosure relates to processes for preparing a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is H, Br, Cl, or F;

$X^2$ is H, Br, Cl, or F;

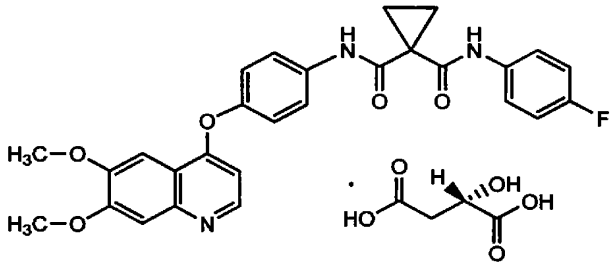
n1 is 1-2; and

n2 is 1-2.

**[0014]** Intermediates useful in preparing the above compounds are also disclosed.

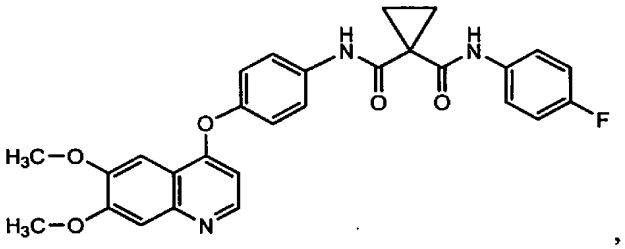
**[0015]** The compounds of formula I are useful as protein kinase modulators, and they inhibit various protein kinases including Ret and c-Met.

**[0016]** In another aspect, the disclosure provides a process for preparing compound IB:



IB

from compound IA:



IA,

comprising:

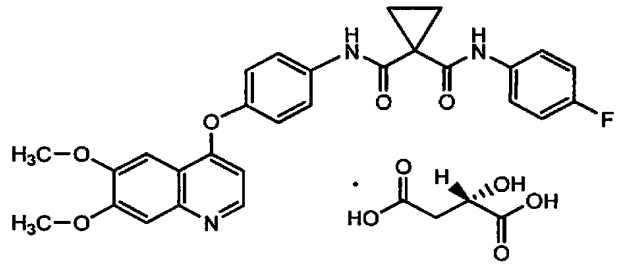
(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) vacuum distilling the mixture successively; and

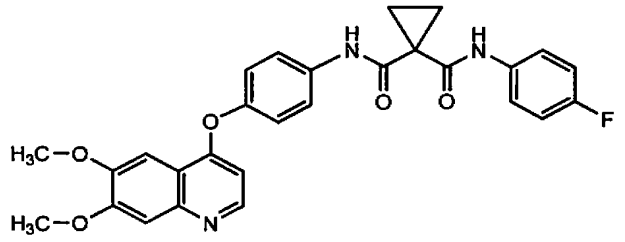
(d) isolating the compound of IB by filtration.

**[0017]** In another aspect, the disclosure provides a process for preparing compound IB:



IB

from compound IA:



IA,

comprising:

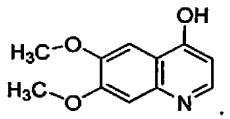
(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) seeding the mixture with compound IB;

(d) vacuum distilling the mixture; and

(e) isolating compound IB by filtration.

**[0018]** In another aspect, the disclosure provides compound I, IA, or IB admixed with less than 100 ppm 6,7-dimethoxy-quinoline-4-ol, the structure of which is  .

**[0019]** In another aspect, the disclosure provides pharmaceutical compositions containing the compound of formula I, compound IA, or compound IB for oral administration.

**[0020]** In another aspect, the disclosure provides a pharmaceutical tablet composition according to Table 1.

**Table 1**

| Ingredient | % w/w |
|---|---|
| Compound I | 31.68 |
| Microcrystalline Cellulose (MCC) (Avicel PH102) | 38.85 |
| Lactose anhydrous 60 M | 19.42 |
| Hydroxypropyl Cellulose, EXF | 3.00 |
| Croscarmellose Sodium | 3.00 |
| **Total Intra-granular** | **95.95** |
| Silicon dioxide, Colloidal PWD | 0.30 |
| Croscarmellose Sodium | 3.00 |
| Magnesium Stearate | 0.75 |
| **Total** | **100.00** |

**[0021]** In another aspect, the disclosure provides a pharmaceutical tablet composition according to Table 2.

**Table 2**

| Ingredient | (% w/w) |
|---|---|
| Compound I | 25.0-33.3 |
| Microcrystalline Cellulose, NF | q.s |
| Hydroxypropyl Cellulose, NF | 3 |
| Poloxamer, NF | 0-3 |
| Croscarmellose Sodium, NF | 6.0 |
| Colloidal Silicon Dioxide, NF | 0.5 |
| Magnesium Stearate, NF | 0.5-1.0 |
| Total | 100 |

**[0022]** In another aspect, the disclosure provides a pharmaceutical tablet composition according to Table 2A.

**Table 2A**

| **Ingredient** | **% w/w** |
|---|---|
| Compound IB (10 % drug load as Compound IA) | 12.67 |
| MCC | 51.52 |
| Lactose | 25.76 |
| Hydroxypropyl cellulose | 3.0 |
| Croscarmellose Sodium | 6.0 |
| Colloidal Silicon Dioxide | 0.3 |
| Magnesium Stearate | 0.75 |
| **Total** | **100** |

**[0023]** In another aspect, the disclosure provides a pharmaceutical capsule composition according to Table 3.

**Table 3**

| **Ingredient** | **mg/unit dose** |
|---|---|
| Compound IB (10 % drug load as Compound IA) | 25 |
| Silicified Microcrystalline Cellulose | 196.75 |
| Croscarmellose sodium | 12.5 |
| Sodium starch glycolate | 12.5 |
| Fumed Silica | 0.75 |
| Stearic acid | 2.5 |
| **Total Fill Weight** | 250 |

**[0024]** In another aspect, the disclosure provides a pharmaceutical capsule composition according to Table 4.

**Table 4**

| **Ingredient** | **mg/unit dose** |
|---|---|
| Compound IB (50 % drug load as Compound IA) | 100 |
| Silicified Microcrystalline Cellulose | 75.40 |
| Croscarmellose sodium | 10.00 |
| Sodium Starch Glycolate | 10.00 |
| Fumed silica | 0.6 |
| Stearic Acid | 4.0 |
| **Total Fill Weight** | 200 |

**[0025]** In another aspect, the disclosure provides a pharmaceutical capsule composition according to Table 5, wherein the IB weight equivalents are provided.

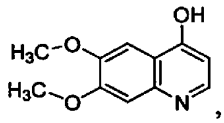
**Table 5**

| | mg/unit dose |
|---|---|
| **Ingredient** | **50mg** |
| Compound IB | 63.35 |
| Microcrystalline Cellulose | 95.39 |
| Croscarmellose sodium | 9.05 |
| Sodium starch glycolate | 9.05 |
| Fumed Silica | 0.54 |
| Stearic acid | 3.62 |
| **Total Fill Weight** | 181.00 |

**[0026]** In another aspect, the disclosure provides a pharmaceutical capsule composition according to Table 6, wherein the IB weight equivalents are provided.

**Table 6**

| | mg/unit dose |
|---|---|
| **Ingredient** | **60mg** |
| Compound IB | 73.95 |
| Microcrystalline Cellulose | 114.36 |
| Croscarmellose sodium | 10.85 |
| Sodium starch glycolate | 10.85 |
| Fumed Silica | 0.65 |
| Stearic acid | 4.34 |
| **Total Fill Weight** | 217.00 |

**[0027]** In another aspect, the invention is directed to a pharmaceutical composition comprising compound I, IA, or IB admixed with less than 100 ppm 6,7-dimethoxy-quinoline-4-ol, the structure of which is 

, and a pharmaceutically acceptable carrier.

**[0028]** There are many different aspects and embodiments of the disclosure described herein, and each aspect and each embodiment is non-limiting in regard to the scope of the disclosure. The terms "aspects" and "embodiments" are meant to be non-limiting regardless of where the terms "aspect" or "embodiment" appears in this specification. The transitional term "comprising," as used herein, which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements.

## DETAILED DESCRIPTION OF THE INVENTION

**Definitions**

**[0029]** As used herein, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise or they are expressly defined to mean something different.

**[0030]** The word "can" is used in a non-limiting sense and in contradistinction to the word "must." Thus, for example, in many aspects of the invention a certain element is described as "can" having a specified identity, which is meant to convey that the subject element is permitted to have that identity according to the invention but is not required to have it.

**[0031]** If a group "R" is depicted as "floating" on a ring system, then unless otherwise defined, the substituent(s) "R" can reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

**[0032]** When there are more than one such depicted "floating" groups, such as where there are two groups; then, unless otherwise defined, the "floating" groups can reside on any atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

**[0033]** "Pharmaceutically acceptable salts" include acid addition salts.

**[0034]** "Pharmaceutically acceptable acid addition salt" refers to those salts that retain the biological effectiveness of the free bases and that are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or mixtures thereof, as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like, or mixtures thereof.

**[0035]** "Essentially free" as used in the phrase "essentially free of process byproducts or contaminants," means that a compound or composition as disclosed here in is admixed with 200 parts per million (ppm) or less of such byproducts or contaminants.

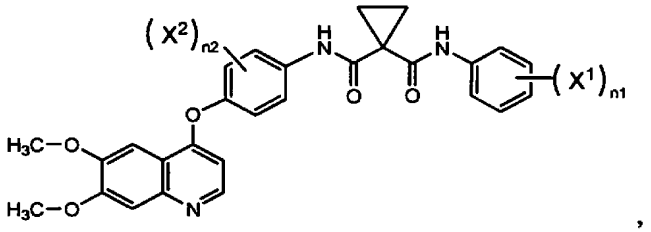
**[0036]** The disclosure is further illustrated by the following examples, which are not to be construed as limiting the disclosure in scope or spirit to the specific procedures described in them. Unless specified otherwise, the starting materials and various intermediates may be

obtained from commercial sources, prepared from commercially available organic compounds, or prepared using well-known synthetic processes.

**Processes**

**Aspect 1: Processes for Making Compounds of Formula I**

**[0037]** Aspect (1) of the invention relates to a process of preparing a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is H, Br, Cl, or F;

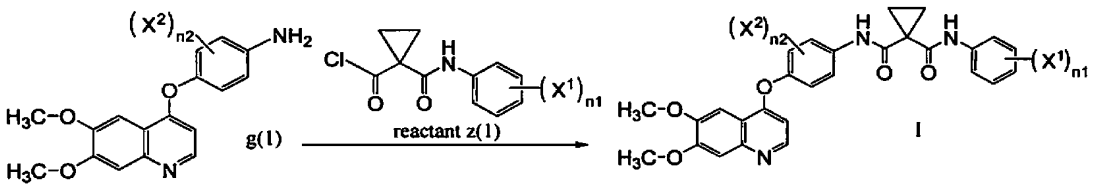
$X^2$ is H, Br, Cl, or F;

n1 is 1-2; and

n2 is 1-2;

the process comprising:

contacting the compound of formula g(1) with reactant z(1) to yield the compound of formula I:




**[0038]** The reaction is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions include using basic conditions. Non-limiting examples of basic conditions that can be used in Aspect (1) include the use of inorganic bases, such as aqueous KOH, NaOH, $K_2CO_3$, $Na_2CO_3$, $K_3PO_4$, $Na_3PO_4$, $K_2HPO_4$, $Na_2HPO_4$, and the like, or mixtures thereof. Other non-limiting examples of suitable reaction conditions include using suitable solvents. Non-limiting examples of suitable solvents that can be used include water miscible solvents, such as THF, acetone, ethanol, and the like, or mixtures thereof. Other non-limiting examples of suitable reaction conditions include using suitable temperatures. Suitable temperatures that may be used for the reaction include a

temperature at a range from about 10 °C to about 30 °C, or alternatively, at a range from about 15 °C to about 28 °C, or alternatively, at a range from about 20 °C to about 25 °C. The product formed by the reaction is in the free base form, and this free base form may be converted into a pharmaceutically acceptable salt thereof by processes known in the art. For example, the compound of formula I can be converted to the L-malate salt by the addition of L-malic acid and a suitable solvent.

**[0039]** Utilities of the compound of formula I are further described in WO 2005/030140 A2, which is incorporated herein by reference.

**Embodiments of Aspect (1) Part A**

**[0040]** In another embodiment of Aspect (1), $X^1$ is Cl or F.

**[0041]** In another embodiment of Aspect (1), $X^2$ is Cl or F.

**[0042]** In another embodiment of Aspect (1), $X^1$ is F.

**[0043]** In another embodiment of Aspect (1), $X^2$ is F.

**[0044]** In another embodiment of Aspect (1), $X^1$ is H.

**[0045]** In another embodiment of Aspect (1), $X^2$ is H.

**[0046]** In another embodiment of Aspect (1), n1 is 1.

**[0047]** In another embodiment of Aspect (1), n2 is 1.

**[0048]** In another embodiment of Aspect (1), n1 is 2.

**[0049]** In another embodiment of Aspect (1), n2 is 2.

**[0050]** All compounds of formula I for Aspect (1) disclosed above include any of the disclosed alternative embodiments in Part A for each of $X^1$, $X^2$, n1 or n2, in combination with any other of the disclosed alternative embodiments in Part A for each of $X^1$, $X^2$, n1, or n2, as well as a pharmaceutically acceptable salt of any such combination.

**Embodiments of Aspect (1) Part B**

**[0051]** In another embodiment of Aspect (1), n1 and n2 are each 1.

**[0052]** In another embodiment of Aspect (1), n1 and n2 are each 2.

**[0053]** In another embodiment of Aspect (1), n1 is 1; and n2 is 2.

**[0054]** In another embodiment of Aspect (1), n1 is 2 and n2 is 1.

**[0055]** In another embodiment of Aspect (1), $X^1$ is H; and $X^2$ is F.

**[0056]** In another embodiment of Aspect (1), $X^1$ is F; and $X^2$ is H.

**[0057]** In another embodiment of Aspect (1), $X^1$ and $X^2$ are each H.

**[0058]** In another embodiment of Aspect (1), $X^1$ and $X^2$ are each F.

[0059] In another embodiment of Aspect (1), $X^1$ is Cl; and $X^2$ is H.

[0060] In another embodiment of Aspect (1), $X^1$ is H; and $X^2$ is Cl.

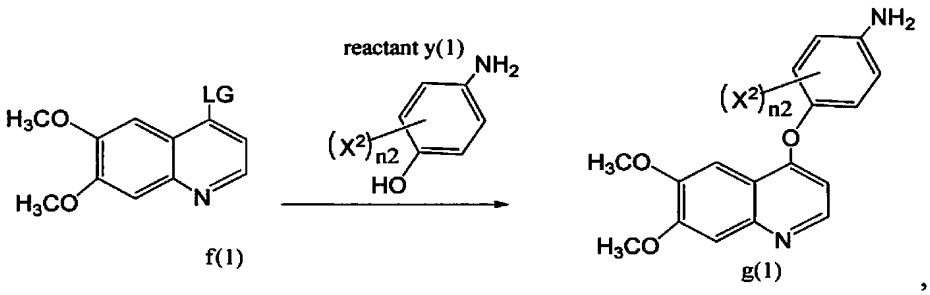
[0061] In another embodiment of Aspect (1), $X^1$ and $X^2$ are each Cl.

[0062] In another embodiment of Aspect (1), $X^1$ is Cl; and $X^2$ is F.

[0063] In another embodiment of Aspect (1), $X^1$ is F; and $X^2$ is Cl.

**Embodiments of Aspect (1) Part C**

[0064] In an embodiment of Aspect (1), the compound of formula g(1) can be made by reacting a compound of formula f(1) with reactant y(1) to yield the compound of g(1):




,

wherein LG represents a leaving group, and each of $X^2$, and n2 are as defined in Aspect (1), or as in any of the embodiments of Aspect (1) Part A. A non-limiting example of a leaving group includes a halo group such as Cl, Br, or F. Various compounds of reactant y(1) are commercially available, such as 2-fluoro-4-aminophenol and 4-aminophenol. Also, the skilled artisan would be able to make any variation of reactant y(1) using commercially available starting materials and by using known techniques to modify these commercially available starting materials to yield various compounds within the scope of reactant y(1).

[0065] The reaction in this embodiment is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions include using suitable solvents such as polar solvents. Non-limiting examples of polar solvents that can be used include tetrahydrofuran (THF), dimethylacetamide (DMA), dimethylsulfoxide (DMSO), dimethylformamide (DMF), ethyl acetate, N-methyl pyrrolidone (NMP), propylene carbonate, and the like, or mixtures thereof. In another embodiment, the polar solvent is dimethylacetamide (DMA). In another embodiment, the polar solvent is dimethylsulfoxide (DMSO). In another embodiment, the polar solvent is dimethylformamide (DMF). In another embodiment, the polar solvent is ethyl acetate. In another embodiment, the polar solvent is N-methyl pyrrolidone (NMP). In another embodiment, the polar solvent is propylene carbonate. In another embodiment, the solvent is a mixture of solvents, such as a mixture comprising THF and DMA.

[0066] The reactants f(1) and y(1) can be added together at a temperature ranging from about 10 °C to about 30 °C, or alternatively, from about 15 °C to about 28 °C, or alternatively, from about 20 °C to about 25 °C. The mixture is then heated to a temperature ranging from about 80 °C to about 125 °C, or alternatively, from about 95 °C to about 110 °C, or alternatively, from about 100 °C to about 105 °C, and the selected temperature is maintained until the reaction is complete.

[0067] Other non-limiting examples of suitable reaction conditions in this step of Aspect (1) include the use of a suitable base, such as a metal hydroxide or a non-nucleophilic base. Examples of metal hydroxides include sodium hydroxide or potassium hydroxide. Non-limiting examples of non-nucleophilic bases that can be used include lithium diisopropylamide, lithium tetramethylpiperidide, and alkali metal alkoxides such as sodium tert-butoxide, potassium tert-butoxide, sodium-pentoxide, and the like, or mixtures thereof. Preferably, the base is sodium tert-butoxide or sodium tert-pentoxide. In one embodiment, the base is sodium tert-pentoxide. Typically the sodium tert-pentoxide is commercially available as 35 weight percent solution of base in tetrahydrofuran, or as a 95 weight percent solid reagent. Preferably, the sodium tert-pentoxide is a 95 weight percent solid.

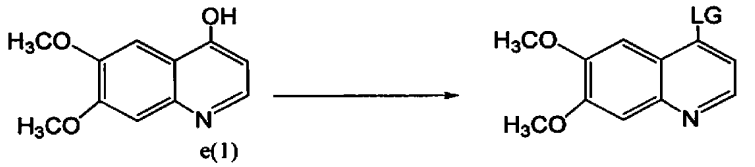
[0068] Typically, approximately 1.1 to 3.0 molar equivalents of base are used relative the moles of f(1) that are used. More preferably, 1.3 to 2.5 molar equivalents of base are used relative the moles of f(1) that are used. More preferably, 1.5 to 2.2 molar equivalents of base are used relative the moles of f(1) that are used. More preferably, 1.7 to 2.1 molar equivalents of base are used relative the moles of f(1) that are used.

[0069] Typically, the amount of molar equivalents of amino phenol that are used exceeds the molar equivalents of base that are used. In one embodiment, 1.1 to 2 molar equivalents of amino phenol are used relative to the molar equivalents of base that are used.

[0070] Once the reaction is substantially complete, the reaction mixture can be cooled to a temperature ranging from about 10 °C to about 25 °C. Precooled water can be charged at a rate to maintain a temperature that ranges from about 5 °C to about 35 °C. Alternatively, the precooled water can be charged at a rate to maintain a temperature that ranges from about 10 °C to about 25 °C. As a non-limiting example, the precooled water can be at a temperature ranging from about 0 °C to about 10 °C. As another non-limiting example, the precooled water can be at a temperature ranging from about 2 °C to about 7 °C. The precipitate can be collected by filtration under standard conditions and purified by standard purification techniques.

**Embodiments of Aspect (1) Part D**

**[0071]** In an embodiment of Aspect (1), the compound of formula f(1) can be made by converting a compound of formula e(1) to the compound of formula f(1):



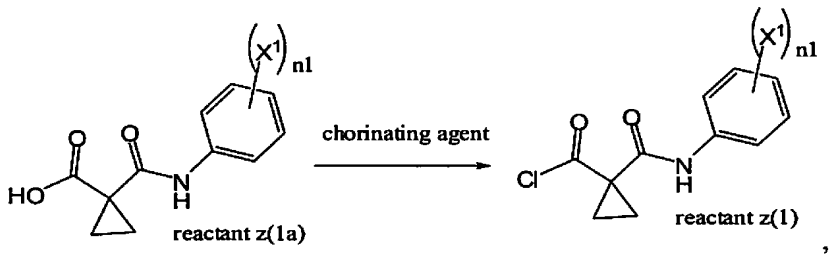

e(1) f(1),

wherein LG represents a leaving group. Non-limiting examples of leaving groups that can be used include halo groups (e.g., Cl, Br, or F) that can be added by halogenating agents. Non-limiting examples of halogenating agents that can be used include chlorinating agents, such as $SOCl_2$, $SO_2Cl_2$, $COCl_2$, $PCl_5$, $POCl_3$, and the like.

**[0072]** The reaction is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions in Part D of Aspect (1) include the use of suitable solvents. Non-limiting example of suitable solvents that can be used during the halogenation of the compound of formula e(1) include a polar, aprotic solvent, such as $CH_3CN$, DMF, and the like, or mixtures thereof. In other embodiments, the chlorination can be carried out using $POCl_3$ in acetonitrile, $COCl_2$ in DMF, or $SOCl_2$ in DMF. The addition of the chlorination agent is advantageously carried out at a temperature ranging from about 60 °C to about 90 °C. In another embodiment, the addition of the chlorination agent can be carried out at a temperature ranging from about 70 °C to about 85 °C. In another embodiment, the addition of the chlorination agent can be carried out at a temperature ranging from about 74 °C to about 80 °C. The product can then be collected by filtration and purified using standard techniques.

**Embodiments of Aspect (1) Part E**

**[0073]** In an embodiment of Aspect (1), reactant z(1) can be made by reacting reactant z(1a) with a chlorinating agent to yield reactant z(1):



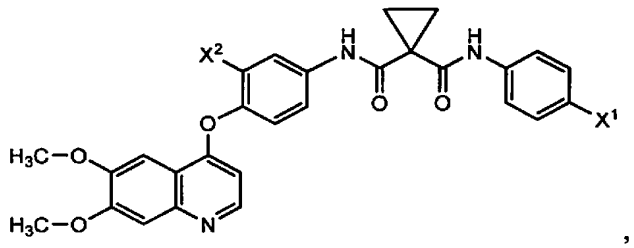

reactant z(1a) reactant z(1),

wherein $X^1$ is Br, Cl, or F; and n1 is 1-2. Compounds of reactant z(1a) can be made according to the process described in Example 25 of WO 2005/030140 A2, and the skilled artisan would be able to make any necessary substitutions using commercially available starting materials to come up with various compounds within the scope of reactant z(1a). Example 25 in WO 2005/030140 A2 is incorporated herein by reference.

**[0074]** The reaction is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions include using a chlorinating agent such as $POCl_3$, oxalyl chloride, and the like. In another embodiment, oxalyl chloride is used as a chlorinating agent. Non-limiting examples of suitable reaction conditions include carrying out the reaction at a temperature in the range from about 0 °C to about 25 °C, or alternatively at a temperature in the range from about 5 °C to about 20 °C. Other non-limiting examples of suitable reaction conditions include carrying out the reaction in a suitable solvent. Non-limiting examples of suitable solvents that can be used include polar aprotic solvents, such as halogenated hydrocarbons (e.g., dichloromethane and chloroform), ethers (e.g., $Et_2O$), dioxane, tetrahydrofuran (THF) containing catalytic DMF, and the like, or mixtures thereof. The resulting solution containing reactant z(1) can be used, without further processing, to make the compound of formula I.

**Other Embodiments of Aspect (1)**

**[0075]** In another embodiment of Aspect (1), the compound of formula I is a compound of formula IA-1:

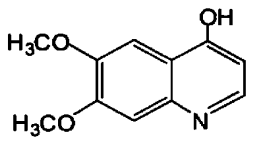



IA-1

or a pharmaceutically acceptable salt thereof, wherein:

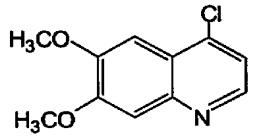
$X^1$ is H, Cl, Br, or F; and $X^2$ is H, Cl, Br, or F. Compound IA can be in the free base form or it can converted to a pharmaceutically acceptable salt thereof. Accordingly, compound IA can be converted to its L-malate salt by the addition of L-malic acid and a suitable solvent.

**[0076]** In another embodiment of Part D of Aspect (1), the compound of formula e(1) is compound e(2):



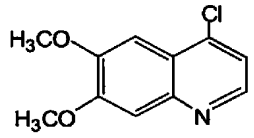
e(2) ;

and the compound of formula f(1) is compound f(2):



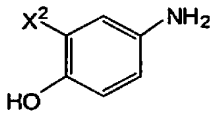
f(2) .

**[0077]** In another embodiment of Part C of Aspect (1), the compound of formula f(1) is compound f(2):



f(2) ;

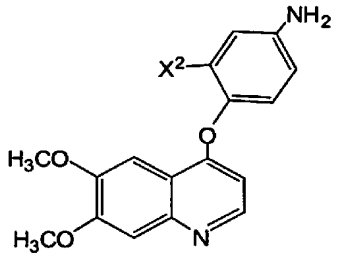
reactant y(1) is reactant (y)(2):



reactant (y)(2) ,

wherein $X^2$ is hydrogen or fluoro; and

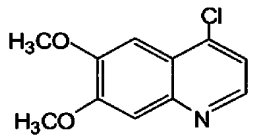
the compound of formula g(1) is of formula g(2):



g(2) .

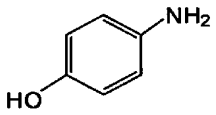
**[0078]** In a further embodiment, the reaction employs a non-nucleophilic base. In a further embodiment, the non-nucelophilic base is an alkali metal alkoxide; and the reaction is carried out in a polar solvent. In a further embodiment, the alkali metal alkoxide is sodium tert-butoxide, and the polar solvent is DMA.

**[0079]** In another embodiment of Part C of Aspect (1), the compound of formula f(1) is compound f(2):



f(2) ;

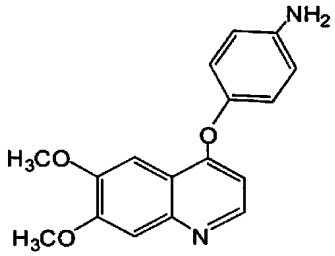
reactant y(1) is reactant (y)(3):



reactant (y)(3) ,

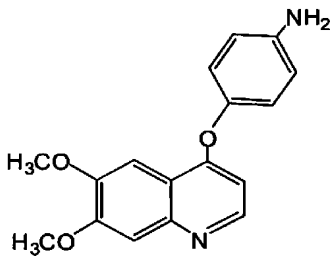
wherein $X^2$ is hydrogen or fluoro; and

the compound of formula g(1) is compound g(3):



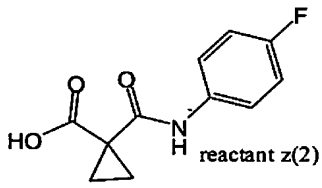
g(3) .

**[0080]** In another embodiment of Aspect (1) of this disclosure, the compound of formula g(1) is compound g(3):



g(3) ;

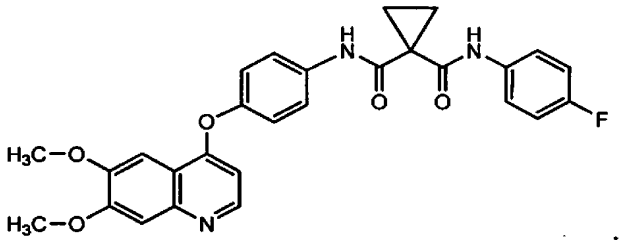
reactant z(1) is reactant (z)(2):




reactant z(2)

; and

the compound of formula I is compound IA:

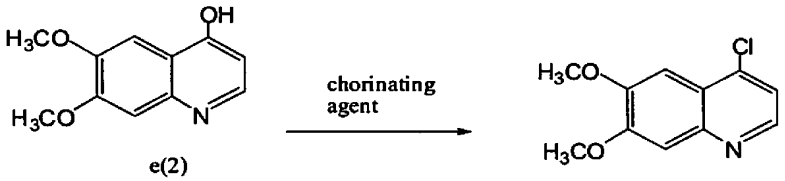



IA

**[0081]** In a further embodiment, the reaction is carried out in the presence of an inorganic base. In a further embodiment, the inorganic base is $K_2CO_3$, and the solvent employed in this reaction is a combination of THF and $H_2O$.

**[0082]** In another embodiment of Aspect (1) of this disclosure, $X^1$ and $X^2$ for each of formula g(1) and reactant z(1) are each selected from Cl or F. In another embodiment, $X^1$ and $X^2$ for each of formula g(2), and reactant z(1) are both F.

**[0083]** The compound of formula f(2),or a pharmaceutically acceptable salt thereof, can be made by converting the compound of formula e(2) to a compound of formula f(2) with a chlorinating agent in a suitable solvent:

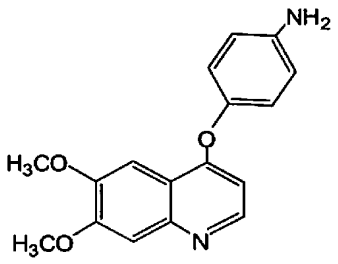



e(2) f(2)

The compound of formula f(2) can be in its free base form or converted to a pharmaceutically acceptable salt thereof. The reaction conditions that can be used in this aspect include any of the reaction conditions disclosed in Part E of Aspect (1).

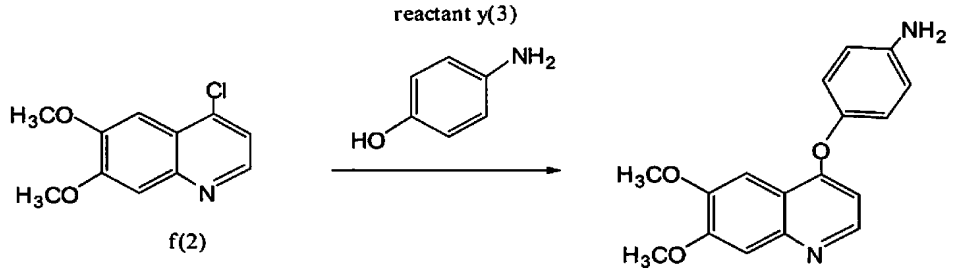
**Aspect 2: Processes for Making Compounds of Formula g(2)**

**[0084]** Aspect (2) of the disclosure relates to a process of preparing compound g(2):



g(2)

or a pharmaceutically acceptable salt thereof; the process comprising reacting compound f(2) with reactant y(3) under basic conditions (e.g., using 2,6-lutidine) in an appropriate solvent to yield compound g(3):



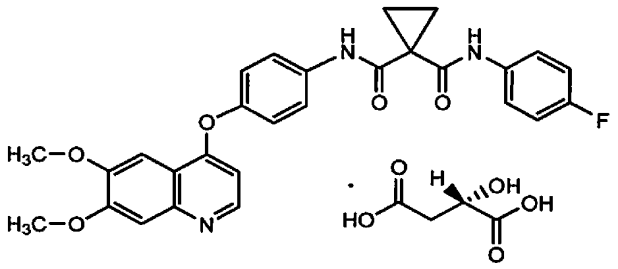

f(2) g(3)

The reaction conditions that can be used in this aspect include any of the reaction conditions disclosed in Part C of Aspect (1).

**[0085]** Alternative reaction conditions that can be used in this aspect include any of the reaction conditions disclosed in Parts C and D of Aspect (1).

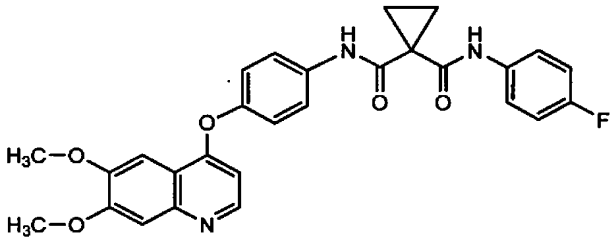
**Aspect 3: Processes for Making Compounds of IB**

**[0086]** As indicated above, in one aspect, the invention provides a process for preparing compound IB:



IB

from compound IA:



IA;

comprising:

(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) vacuum distilling the mixture successively; and

(d) isolating the compound of IB by filtration.

**[0087]** In one embodiment of this aspect, compound IA is admixed with a sufficient amount of L-malic acid in a methylethyl ketone (MEK)/water (1:1) mixture. Alternatively, L-malic acid is added as a solution in water to a mixture of compound IA in methyl ethyl ketone. Generally the amount of L-malic is greater than 1 molar equivalent relative to compound IA. The mixture of compound IA and L-malic acid in MEK/water is heated at about 40-70 °C, and preferably at about 50-60 °C, and more preferably at about 55-60 °C with agitation, such as by stirring or the like, for about 1 to about 5 hours. At the end of the heating, the mixture is optionally clarified by filtering to give a clear solution. The resulting clear solution is then vacuum distilled from 1 to about 5 times at 150 to 200 mm Hg and a maximum jacket temperature of 55 °C to provide the desired crystalline compound of IB.

**[0088]** In one embodiment, L-malic acid is charged as a solution in water to compound IA. Generally the amount of L-malic is greater than 1 molar equivalent relative to compound IA. The mixture of compound IA and L-malic acid in MEK/water is heated at about 40-70 °C, and preferably at about 50-60 °C, and more preferably at about 55-60 °C with agitation, such as by stirring or the like, for about 1 to about 5 hours. At the end of the heating, the mixture is optionally clarified by filtering to give a clear solution which is at a temperature of about 30-40 °C, and more preferably at a temperature of about 33-37 °C. This clear solution is optionally seeded to facilitate crystallization. After seeding, the resulting mixture is vacuum distilled as provided above.

**[0089]** In one embodiment, compound IB is in the N-1 form. In another embodiment, compound IB is in the N-2 form. In another embodiment, compound IB is a mixture of the N-1 form and the N-2 form. Processes for preparing the N-1 and N-2 forms of compound IB

are disclosed in WO 2010/083414 (PCT/US2010021194), the entire contents of which are incorporated herein by reference.

**[0090]** In another embodiment, the disclosure relates to compound IA or IB admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

**[0091]** In another embodiment, the disclosure relates to compound IA admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

**[0092]** In another embodiment, the disclosure relates to compound IB admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

**[0093]** In another embodiment, the disclosure relates to compound IB in the N-1 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

[0094] In another embodiment, the disclosure relates to compound IB in the N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

[0095] In another embodiment, the disclosure relates to compound IB as a mixture of the N-1 form and the N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

## Pharmaceutical Compositions

[0096] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound I, IA, or IB. Various carriers used in formulating pharmaceutically acceptable compositions and known techniques for their bulk preparation and subsequent production into unit dosage forms are employed to make the pharmaceutical compositions disclosed herein and are described in Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. D. B. Troy, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York. The amount of carriers and excipients used in a composition can be varied proportionally according to the amount of active ingredient used (that is, Compound I, IA or IB).

[0097] In one embodiment, the pharmaceutical composition is a tablet.

[0098] In another embodiment, the pharmaceutical composition is a capsule.

[0099] In another embodiment, the pharmaceutical composition comprises Compound IA.

[00100] In another embodiment, the pharmaceutical composition comprises Compound IB.

**[00101]** In another embodiment, the pharmaceutical composition comprises Compound IB. as the N-1 polymorph.

**[00102]** In another embodiment, the pharmaceutical composition comprises Compound IB as the N-2 polymorph.

**[00103]** In another embodiment, the pharmaceutical composition comprises Compound IB as a mixture of the N-1 form and the N-2 form.

**[00104]** In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; one or more fillers; one or more disintergrants; one or more glidants; and one or more lubricants.

**[00105]** In this embodiment, the filler comprises microcrystalline cellulose.

**[00106]** In this embodiment, the disintegrant comprises croscarmellose sodium.

**[00107]** In this embodiment, the disintegrant comprises croscarmellose sodium and sodium starch glycolate.

**[00108]** In this embodiment, the glidant comprises fumed silica.

**[00109]** In this embodiment, the lubricant comprises stearic acid.

**[00110]** In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; lactose; hydroxypropyl cellulose; croscarmellose sodium; colloidal silicon dioxide; and magnesium stearate.

**[00111]** In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; hydroxypropyl cellulose; a surfactant; croscarmellose sodium; colloidal silicon dioxide; and magnesium stearate.

**[00112]** In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; croscarmellose sodium; fumed silica; and stearic acid.

**[00113]** In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; anhydrous lactose; hydroxypropyl cellulose; croscarmellose sodium; silicon dioxide; and magnesium stearate.

**[00114]** In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; anhydrous lactose; hydroxypropyl cellulose; a surfactant; croscarmellose sodium; silicon dioxide; and magnesium stearate.

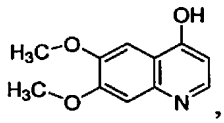
**[00115]** In another aspect, the disclosure provides a pharmaceutical composition according to Tables 1, 2, 2A, 3, 4, 5, and 6 as provided above. The compositions are prepared according to methods available to the skilled artisan. For example, the Tablet

formulations are prepared by combining, blending, and compacting the components of the tablet compositions. The capsule compositions are prepared by combining and blending the components and then placing the blend in a gelatin capsule.

**[00116]** For example, the 25 mg capsules (Table 3, 10 percent drug load formulation) are prepared as follows. The drug substance is delumped through a mill. The delumped drug substance is then co-screened with an equal volume Prosolv HD90. The excipients, except for stearic acid, are screened and charged to a blender along with the co-screened drug substance. The mixture is blended in a V-Blender. This process is repeated to manufacture a second sublot of unlubricated blend. The two sublots are then combined together in a V-blender and lubricated with stearic acid which has been co-screened with an equal volume of unlubricated blend. The final blend is then encapsulated into opaque, size 1 gelatin capsules using an automated capsule filling machine. The capsules are then weight sorted through an automatic weight sorter.

**[00117]** The 100-mg capsules (Table 4, 50% drug load formulation) are manufactured in two equal sublots of 5 kg of blend which are combined prior to lubricant blend The drug substance is delumped through a mill. The excipients, except for stearic acid, are screened and charged to the mixer along with the delumped drug substance. The mixture is blended with a high shear mixer. The process is repeated to manufacture a second sublot of unlubricated blend. The final blend is then encapsulated into Swedish oraopaque, size 1 gelatin capsules using an automated capsule filling machine. The capsuare then weight sorted through an automatic weight sorter.

**[00118]** The 50 and 60 mg capsules (Tables 5 and 6) are prepared in a similar fashion as the 25 and 100 mg capsules.

**[00119]** In another aspect, the disclosure relates to a pharmaceutical composition comprising a compound of Formula IA or IB and a pharmaceutically acceptable carrier admixed with less than 100 ppm of 6,7-dimethoxy-quinoline-4-ol. 6,7-dimethoxy-quinoline-4-ol, the structure of which is 

, can be used as reagent e(1) to make chloride f(1) and is a byproduct that may form during the synthesis of Compound IA or IB. Minimizing the concentration of contaminants or byproducts such as 6,7-dimethoxy-quinoline-4-ol in pharmaceutical compositions destined for human administration is desirable.

**[00120]** In one embodiment, the pharmaceutical composition as defined in any of the previous embodiments (for example, the pharmaceutical composition of Tables 1, 2, 2A, 3, 4, 5, and6) is admixed with 100 ppm 6,7-dimethoxy-quinoline-4-ol.

**[00121]** In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 50 ppm 6,7-dimethoxy-quinoline-4-ol.

**[00122]** In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 25 ppm 6,7-dimethoxy-quinoline-4-ol.

**[00123]** In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 15 ppm 6,7-dimethoxy-quinoline-4-ol.

**[00124]** In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 10 ppm 6,7-dimethoxy-quinoline-4-ol.

**[00125]** In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 5 ppm 6,7-dimethoxy-quinoline-4-ol.

**[00126]** In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 2.5 ppm 6,7-dimethoxy-quinoline-4-ol.

**[00127]** In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; one or more fillers; one or more disintergrants; one or more glidants; and one or more lubricants admixed with 100 ppm or less 6,7-dimethoxy-quinoline-4-ol.

**[00128]** In this embodiment, the filler comprises microcrystalline cellulose.

**[00129]** In this embodiment, the disintegrant comprises croscarmellose sodium.

**[00130]** In this embodiment, the disintegrant comprises croscarmellose sodium and sodium starch glycolate.

**[00131]** In this embodiment, the glidant comprises fumed silica.

**[00132]** In this embodiment, the lubricant comprises stearic acid.

**[00133]** In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; croscarmellose sodium; fumed silica; and stearic acid; admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment of this embodiment, the composition is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with

5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

**[00134]** In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; anhydrous lactose; hydroxypropyl cellulose; a surfactant; croscarmellose sodium; silicon dioxide; and magnesium stearate; admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment of this embodiment, the composition is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

**[00135]** In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; croscarmellose sodium; fumed silica; and stearic acid; ; admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment of this embodiment, the composition is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

## EXAMPLES

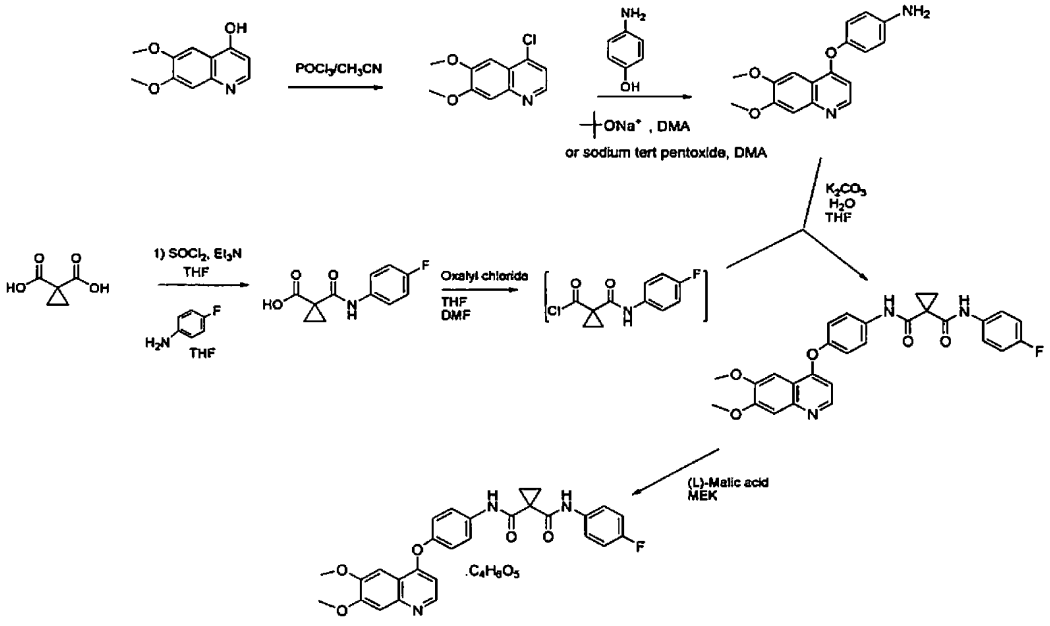
**[00136]** The invention is illustrated further by the following examples in Scheme 1 and the description thereof, which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the invention, as demonstrated by the following examples. Those skilled in the art will also recognize that it may be necessary to utilize different solvents or reagents to achieve some of the above transformations. Unless otherwise specified, all reagents and solvents are of standard commercial grade and are used without further purification. The

appropriate atmosphere to run the reaction under, for example, air, nitrogen, hydrogen, argon, and the like, will be apparent to those skilled in the art.

**Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof.**

**[00137]** A synthetic route that can be used for the preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Figure 1:

**Figure 1**




**Preparation of 4-Chloro-6,7-dimethoxy-quinoline**

**[00138]** A reactor was charged sequentially with 6,7-dimethoxy-quinoline-4-ol (47.0 kg) and acetonitrile (318.8 kg). The resulting mixture was heated to approximately 60 °C, and phosphorus oxychloride ($POCl_3$, 130.6 kg) was added. After the addition of $POCl_3$, the temperature of the reaction mixture was raised to approximately 77 °C. The reaction was deemed complete (approximately 13 hours) when less than 3% of the starting material remained (in-process high-performance liquid chromatography [HPLC] analysis). The reaction mixture was cooled to approximately 2 – 7 °C and then quenched into a chilled solution of dichloromethane (DCM, 482.8 kg), 26 % $NH_4OH$ (251.3 kg), and water (900 L). The resulting mixture was warmed to approximately 20 – 25 °C, and phases were separated.

The organic phase was filtered through a bed of AW hyflo super-cel NF (Celite; 5.4 kg) and the filter bed was washed with DCM (118.9 kg). The combined organic phase was washed with brine (282.9 kg) and mixed with water (120 L). The phases were separated and the organic phase was concentrated by vacuum distillation with the removal of solvent (approximately 95 L residual volume). DCM (686.5 kg) was charged to the reactor containing organic phase and concentrated by vacuum distillation with the removal of solvent (approximately 90 L residual volume). Methyl t-butyl ether (MTBE, 226.0 kg) was then charged and the temperature of the mixture was adjusted to -20 to -25 °C and held for 2.5 hours resulting in solid precipitate which was then filtered and washed with n-heptane (92.0 kg), and dried on a filter at approximately 25 °C under nitrogen to afford the title compound. (35.6 kg).

**Preparation of 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine**

**[00139]** 4-Aminophenol (24.4 kg) dissolved in N,N-dimethylacetamide (DMA, 184.3 kg) was charged to a reactor containing 4-chloro-6,7-dimethoxyquinoline (35.3 kg), sodium t-butoxide (21.4 kg) and DMA (167.2 kg) at 20-25 °C. This mixture was then heated to 100-105 °C for approximately 13 hours. After the reaction was deemed complete as determined using in-process HPLC analysis (<2% starting material remaining), the reactor contents were cooled at 15 to 20 °C and water (pre-cooled, 2 to 7 °C, 587 L) charged at a rate to maintain 15 to 30 °C temperature . The resulting solid precipitate was filtered, washed with a mixture of water (47 L) and DMA (89.1 kg) and finally with water (214 L). The filter cake was then dried at approximately 25 °C on filter to yield crude 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (59.4 kg wet, 41.6 kg dry calculated based on LOD). Crude 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine was refluxed (approximately 75 °C) in a mixture of tetrahydrofuran (THF, 211.4 kg) and DMA (108.8 kg) for approximately 1hour and then cooled to 0-5 °C and aged for approximately 1 h after which time the solid was filtered, washed with THF (147.6 kg) and dried on a filter under vacuum at approximately 25 °C to yield 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (34.0 kg).

**Alternative Preparation of 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine**

**[00140]** 4-chloro-6,7-dimethoxyquinoline (34.8 kg) and 4-aminophenol (30.8 kg) and sodium tert pentoxide (1.8 equivalents) 88.7 kg, 35 wt percent in THF) were charged to a reactor, followed by N,N-dimethylacetamide (DMA, 293.3 kg). This mixture was then heated to 105-115 °C for approximately 9 hours. After the reaction was deemed complete as

determined using in-process HPLC analysis (<2% starting material remaining), the reactor contents were cooled at 15 to 25 °C and water (315 kg) was added over a two hour period while maintaining the temperature between 20 and 30 °C. The reaction mixture was then agitated for an additional hour at 20 to 5 °C. The crude product was collected by filtration and washed with a mixture of 88 kg water and 82.1 kg DMA, followed by 175 kg water. The product was dried on a filter drier for 53 hours. The LOD showed less than 1% w/w.

**[00141]** In an alternative procedure, 1.6 equivalents of sodium tert-pentoxide were used and the reaction temperature was increased from 110-120 °C. In addition , the cool down temperature was increased to 35-40 °C and the starting temperature of the water addition was adjusted to 35-40 °C, with an allowed exotherm to 45 °C.

**Preparation of 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid**

**[00142]** Triethylamine (19.5 kg) was added to a cooled (approximately 5 C) solution of cyclopropane-1,1-dicarboxylic acid (24.7 kg) in THF (89.6 kg) at a rate such that the batch temperature did not exceed 5 °C. The solution was stirred for approximately 1.3 hours, and then thionyl chloride (23.1 kg) was added, keeping the batch temperature below 10 °C. When the addition was complete, the solution was stirred for approximately 4 h keeping temperature below 10 °C. A solution of 4–fluoroaniline (18.0 kg) in THF (33.1 kg) was then added at a rate such that the batch temperature did not exceed 10 °C. The mixture was stirred for approximately 10 hours after which the reaction was deemed complete. The reaction mixture was then diluted with isopropyl acetate (218.1 kg). This solution was washed sequentially with aqueous sodium hydroxide (10.4 kg, 50 % dissolved in 119 L of water) further diluted with water (415 L), then with water (100 L) and finally with aqueous sodium chloride (20.0 kg dissolved in 100 L of water). The organic solution was concentrated by vacuum distillation (100 L residual volume) below 40 °C followed by the addition of n-heptane (171.4 kg), which resulted in the precipitation of solid. The solid was recovered by filtration and washed with n-Heptane (102.4 kg) resulting in wet crude, 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (29.0 kg). The crude, 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid was dissolved in methanol (139.7 kg) at approximately 25 °C followed by the addition of water (320 L) resulting in slurry which was recovered by filtration, washed sequentially with water (20 L) and n-heptane (103.1 kg) and then dried on the filter at approximately 25 °C under nitrogen to afford the title compound (25.4 kg).

**Preparation of 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride**

**[00143]** Oxalyl chloride (12.6 kg) was added to a solution of 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (22.8 kg) in a mixture of THF (96.1 kg) and N, N-dimethylformamide (DMF; 0.23 kg) at a rate such that the batch temperature did not exceed 25 °C. This solution was used in the next step without further processing.

**Alternative Preparation of 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride**

**[00144]** A reactor was charged with 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (35 kg), 344 g DMF, and 175kg THF. The reaction mixture was adjusted to 12-17 °C and then to the reaction mixture was charged 19.9 kg of oxalyl chloride over a period of 1 hour. The reaction mixture was left stirring at 12-17 °C for 3 to 8 hours. This solution was used in the next step without further processing.

**Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (Compound IA)**

**[00145]** The solution from the previous step containing 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride was added to a mixture of compound 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (23.5 kg) and potassium carbonate (31.9 kg) in THF (245.7 kg) and water (116 L) at a rate such that the batch temperature did not exceed 30 °C. When the reaction was complete (in approximately 20 minutes), water (653 L) was added. The mixture was stirred at 20-25 °C for approximately 10 hours, which resulted in the precipitation of the product. The product was recovered by filtration, washed with a pre-made solution of THF (68.6 kg) and water (256 L), and dried first on a filter under nitrogen at approximately 25 °C and then at approximately 45 °C under vacuum to afford the title compound (41.0 kg, 38.1 kg, calculated based on LOD).

**Alternative Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide**

**[00146]** A reactor was charged with 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (35.7 kg, 1 equivalent), followed by 412.9 kg THF. To the reaction mixture was charged a solution of 48.3 $K_2CO_3$ in 169 kg water. The acid chloride solution of described in the Alternative Preparation of 1-(4–Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride above was transferred to the reactor containing 4-(6,7-dimethoxy-quinoline-4-yloxy)-

phenylamine while maintaining the temperature between 20-30 °C over a minimum of two hours. The reaction mixture was stirred at 20-25 °C for a minimum of three hours. The reaction temperature was then adjusted to 30-25 °C and the mixture was agitated. The agitation was stopped and the phases of the mixture were allowed to separate. The lower aqueous phase was removed and discarded. To the remaining upper organic phase was added 804 kg water. The reaction was left stirring at 15-25 °C for a minimum of 16 hours.

**[00147]** The product precipitated. The product was filtered and washed with a mixture of 179 kg water and 157.9 THF in two portions. The crude product was dried under a vacuum for at least two hours. The dried product was then taken up in 285.1 kg THF. The resulting suspension was transferred to reaction vessel and agitated until the suspension became a clear (dissolved) solution, which required heating to 30-35 °C for approximately 30 minutes. 456 kg water was then added to the solution, as well as 20 kg SDAG-1 ethanol (ethanol denatured with methanol over two hours. The mixture was agitated at 15-25 °C for at least 16 hours. The product was filtered and washed with a mixture of 143 kg water and 126.7 THF in two portions. The product was dried at a maximum temperature set point of 40 °C.

**[00148]** In an alternative procedure, the reaction temperature during acid chloride formation was adjusted to 10-15 °C. The recrystallization temperature was changed from 15-25 °C to 45-50 °C for 1 hour and then cooled to 15-25 °C over 2 hours.

**Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy- quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L) malate salt (Compound IB)**

**[00149]** Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (1-5; 13.3 kg), L-malic acid (4.96 kg), methyl ethyl ketone (MEK; 188.6 kg) and water (37.3 kg) were charged to a reactor and the mixture was heated to reflux (approximately 74 °C) for approximately 2 hours. The reactor temperature was reduced to 50 to 55 °C and the reactor contents were filtered. These sequential steps described above were repeated two more times starting with similar amounts of 1-5 (13.3 kg), L-Malic acid (4.96 kg), MEK (198.6 kg) and water (37.2 kg). The combined filtrate was azeotropically dried at atmospheric pressure using MEK (1133.2 kg) (approximate residual volume 711 L; KF $\leq$ 0.5 % w/w) at approximately 74 °C. The temperature of the reactor contents was reduced to 20 to 25 °C and held for approximately 4 hours resulting in solid precipitate which was filtered, washed with MEK (448 kg) and dried under vacuum at 50°C to afford the title compound (45.5 kg).

**Alternative Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L) malate salt**

**[00150]** Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (47.9 kg), L-malic acid (17.2), 658.2 kg methyl ethyl ketone, and 129.1 kg water (37.3 kg) were charged to a reactor and the mixture was heated 50-55 °C for approximately 1-3 hours, and then at 55-60 °C for an addition al 4-5 hours. The mixture was clarified by filtration through a 1 μm cartridge. The reactor temperature was adjusted to 20-25 °C and vacuum distilled with a vacuum at 150-200 mm Hg with a maximum jacket temperature of 55 °C to the volume range of 558-731 L.

**[00151]** The vacuum distillation was performed two more times with the charge of 380 kg and 380.2 kg methyl ethyl ketone, respectively. After the third distillation, the volume of the batch was adjusted to 18 v/w of Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide by charging 159.9 kg methyl ethyl ketone to give a total volume of 880L. An addition al vacuum distillation was carried out by adjusting 245.7 methyl ethyl ketone. The reaction mixture was left with moderate agitation at 20-25 °C for at least 24 hours. The product was filtered and washed with 415.1 kg methyl ethyl ketone in three portions. The product was dried under a vacuum with the jacket temperature set point at 45 °C.

**[00152]** In an alternative procedure, the order of addition was changed so that a solution of 17.7 kg L-malic acid dissolved in 129.9 kg water was added to Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (48.7 kg) in methyl ethyl ketone (673.3 kg).

**Preparation of Compound IB, Form N-1**

**[00153]** A solution was prepared by adding tetrahydrofuran (12 mL/g-bulk-LR (limiting reagent); 1.20 L) and N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (100 g; 1.00 equiv; 100.00 g) and (L)-malic acid (1.2 equiv (molar); 32.08 g) to a 1 L reactor. Water (0.5317 mL/g-bulk-LR; 53.17 mL) was added and the solution was heated to 60 °C and maintained at that temperature for one hour until the solids were fully dissolved. The solution was passed through a Polish Filter.

**[00154]** At 60 °C, acetonitrile (12 mL/g-bulk-LR; 1.20 L) was added over a period of 8 hours. The solution was held at 60 °C for 10 hours. The solution was then cooled to 20 °C and held for 1 hour. The solids were filtered and washed with acetonitrile (12 mL/g-bulk-LR;

1.20 L). The solids were dried at 60 °C (25 mm Hg) for 6 hours to afford compound (I), Form N-1 (108 g; 0.85 equivalent; 108.00 g; 85.22% yield) as a white crystalline solid.

**Alternate Preparation of Compound IB, Form N-1**

**[00155]** A solution was prepared with 190 mL tetrahydrofuran (110 mL), methyl isobutyl ketone, and 29 mL water. Next, 20 mL of this solution were transferred into an amber bottle, and then saturated by adding N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L)-malate until a thick slurry formed, and aging for at least 2 hours with stirring at room temperature. The solids were removed by filtration through a Buchner funnel, rendering a clear saturated solution.

**[00156]** Separately, a powder blend was made with known amounts of two batches of compound IB: (1) 300 mg of batch 1, which contained approximately 41% compound IB, Form N-1 and 59% compound IB, Form N-2 by Raman spectroscopy analysis, and (2) 200 mg of batch 2, which had a XPRD pattern similar to compound IB, Form N-2.

**[00157]** The compound IB, Form N-1 and compound (I), Form N-2 powder blend was added into the saturated solution, and the slurry was aged under magnetic stirring at room temperature for 25 days. The slurry was then sampled and filtered through a Buchner funnel to obtain 162 mg of wet cake. The wet cake was dried in a vacuum oven at 45 °C to afford 128 mg of crystalline compound IB in the N-1 form.

**Preparation of Crystalline Compound IB, Form N-2**

**Preparation of Crystalline Compound IB, Form N-2 Seed Crystals**

**[00158]** A solution was prepared by combining 20 ml of acetone and 300 mg of compound IA (N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide) in a 25ml screw capped vial. Next, 0.758ml of a 0.79M (L)-malic acid stock solution was added to the vial with magnetic stirring. The solution was then left stirring for 24 hours at ambient temperature. The sample was then suction filtered with 0.45μm PTFE filter cartridge and dried *in vacuo* at ambient temperature overnight.

**Preparation of Crystalline Compound IB, Form N-2.**

**[00159]** To a reactor were added N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (48 g; 1.00 equiv; 48.00 g) and tetrahydrofuran (16.5 mL/g-bulk-LR; 792.00 mL). The water content was adjusted to 1 wt% water. The solution was heated to 60 °C. Once dissolved, the solution was passed through a polish filter to provide the first solution.

[00160] In a separate reactor, (L)-malic acid (1.2 equiv (molar); 15.40 g) was dissolved into methyl isobutyl ketone (10 mL/g-bulk-LR; 480.00 mL) and tetrahydrofuran (1 mL/g-bulk-LR; 48.00 mL). Next, 50 mL of the (L)-malic acid solution was added to the first solution at 50 °C. Seed crystals were added (1%, 480 mg) and the malic acid solution was added at 50 °C dropwise via an addition funnel (1.3 ml/min over 3 hours). The slurry was held at 50 °C for 18 hours and then was cooled to 25 °C over 30 minutes. The solids were filtered, and washed with 20% tetrahydrofuran/methyl isobutyl ketone (10V, 480 mL). The solids were dried under vacuum at 60 °C for 5 hours to afford compound IB (55.7 g; 0.92 equivalent; 55.70 g; 91.56% yield) as an off-white crystalline solid.

**Stability Studies of Pharmaceutical Compositions**

[00161] The pharmaceutical capsule compositions of Tables 3 and 4 were prepared by mixing the ingredients according to processes known in the art.

**Table 3**

| Ingredient | mg/unit dose |
|---|---|
| Compound IB (10 % drug load as Compound IA) | 25 |
| Microcrystalline Cellulose | 196.75 |
| Croscarmellose sodium | 12.5 |
| Sodium starch glycolate | 12.5 |
| Fumed Silica | 0.75 |
| Stearic acid | 2.5 |
| **Total Fill Weight** | 250 |

**Table 4**

| Ingredient | mg/unit dose |
|---|---|
| Compound IB (50 % drug load as Compound IA) | 100 |
| Silicified Microcrystalline Cellulose | 75.40 |
| Croscarmellose sodium | 10.00 |
| Sodium Starch Glycolate | 10.00 |
| Fumed silica | 0.6 |
| Stearic Acid | 4.0 |
| **Total Fill Weight** | 200 |

[00162] The capsule compositions were subjected to stability studies to monitor the formation of 6,7-dimethoxy-quinoline-4-ol at various temperatures and relative humidities over time. The results are summarized in Tables 7A and 7B and Tables 8A and 8B.

**Table 7A: Stability of 25 Mg Capsules (Table 3)**

| | Conditions | Bottle A1 | Bottle A2 | Bottle A3 | Bottle A4 |
|---|---|---|---|---|---|
| | | PPM of 6,7-dimethoxy-quinoline-4-ol | | | |
| Initial T=0 | 25 °C/60% RH | 2 | 2 | 3 | 3 |
| 1 Month | 25 °C/60% RH | 3 | 4 | 5 | NA |
| | 30 °C/75% RH | 4 | 4 | NA | NA |
| | 40 °C/75% RH | 9 | 9 | 10 | NA |
| 3 Months | 25 °C/60% RH | 5 | 5 | 7 | NA |
| | 30 °C/75% RH | 7 | 6 | NA | NA |
| | 40 °C/75% RH | 22 | 23 | 24 | NA |
| 6 Months | 25 °C/60% RH | 6 | 6 | 7 | 7 (3M in blister) |
| | 30 °C/75% RH | 9 | 9 | NA | NA |
| | 40 °C/75% RH | 40 | 44 | 43 | 27 (3M in blister) |
| 9 Months | 25 °C/60% RH | 7 | 7 | 9 | 8 (6M in blister) |
| | 30 °C/75% RH | 13 | 12 | NA | NA |
| | 40 °C/75% RH | NA | NA | 68 | 60 (6M in blister) |

M=Months; NA=Not Applicable; RH= Relative Humidity; PPM= Parts per Million. A portion of Bottle A4 was repackaged in a blister pack after being stored in bottles for 3 months.

**Table 7B: Stability of 25 Mg Capsules (Table 3)**

| | Conditions | Bottle B1 | Bottle B | Bottle B3 | Bottle B4 |
|---|---|---|---|---|---|
| | | PPM of 6,7-dimethoxy-quinoline-4-ol | | | |
| Initial T=0 | 25 °C/60% RH | 3 | 1 | 2 | 2 |
| 1 Month | 25 °C/60% RH | <2 | <2 | <2 | NA |
| | 30 °C/75% RH | <2 | <2 | NA | NA |
| | 40 °C/75% RH | 2 | <2 | <2 | NA |
| 3 Months | 25 °C/60% RH | 2 | <2 | <2 | NA |
| | 30 °C/75% RH | 2 | <2 | NA | NA |
| | 40 °C/75% RH | 3 | <2 | <2 | NA |
| 6 Months | 25 °C/60% RH | <2 | <2 | <2 | <2 (3M in blister) |
| | 30 °C/75% RH | 2 | <2 | NA | NA |
| | 40 °C/75% RH | 4 | <2 | 3 | 3 (3M in blister) |
| 9 Months | 25 °C/60% RH | <2 | <2 | <2 | <2 (6M in blister) |
| | 30 °C/75% RH | 3 | <2 | NA | NA |
| | 40 °C/75% RH | NA | NA | 5 | 4 (6M in blister) |

A portion of Bottle B4 was repackaged in a blister pack after being stored in bottles for 3 months.

**Table 8A: Stability of 100 Mg Capsules (Table 4)**

| | Conditions | Bottle A1 | Blister A2 | Bottle A3 |
|---|---|---|---|---|
| | | PPM of 6,7-dimethoxy-quinoline-4-ol | | |
| Initial T=0 | 25 °C/60% RH | 4 | 4 | 6 |
| 1 Month | 25 °C/60% RH | 4 | 4 | 6 |
| | 30 °C/75% RH | 4 | NA | 6 |
| | 40 °C/75% RH | 6 | 6 | 9 |
| 3 Months | 25 °C/60% RH | 5 | 5 | 7 |
| | 30 °C/75% RH | 6 | NA | 7 |
| | 40 °C/75% RH | 10 | 10 | 12 |
| 6 Months | 25 °C/60% RH | 5 | 5 | |
| | 30 °C/75% RH | 6 | NA | |
| | 40 °C/75% RH | 11 | 17 | |

M=Months; NA=Not Applicable; RH= Relative Humidity; PPM= Parts per Million.

**Table 8B: Stability of 100 Mg Capsules (Table 4)**

| | Conditions | Bottle B1 | Blister B2 | Bottle B3 |
|---|---|---|---|---|
| | | PPM of 6,7-dimethoxy-quinoline-4-ol | | |
| Initial T=0 | 25 °C/60% RH | 1 | 1 | 2 |
| 1 Month | 25 °C/60% RH | <2 | <2 | <2 |
| | 30 °C/75% RH | <2 | <2 | 2 |
| | 40 °C/75% RH | <2 | <2 | 2 |
| 3 Months | 25 °C/60% RH | <2 | <2 | <2 |
| | 30 °C/75% RH | <2 | NA | <2 |
| | 40 °C/75% RH | <2 | <2 | 2 |
| 6 Months | 25 °C/60% RH | <2 | <2 | |
| | 30 °C/75% RH | <2 | NA | |
| | 40 °C/75% RH | 2 | 2 | |

M=Months; NA=Not Applicable; RH= Relative Humidity; PPM= Parts per Million.

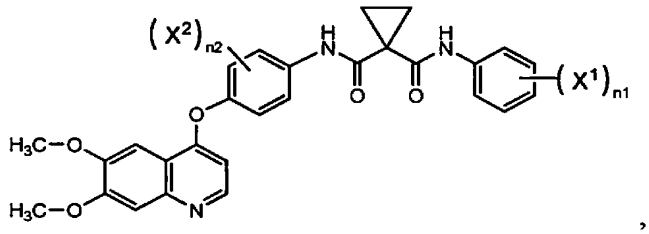
**[00163]** The results summarized in Tables 7A and 7B and 8A and 8B indicate that formation of 6,7-dimethoxy-quinoline-4-ol was minimized to 50 ppm or less over time in the capsule formulations.

**[00164]** The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that

changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled. All references cited herein are incorporated by reference in their entirety.

## CLAIMS

1. A process for preparing a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is H, Br, Cl, or F;

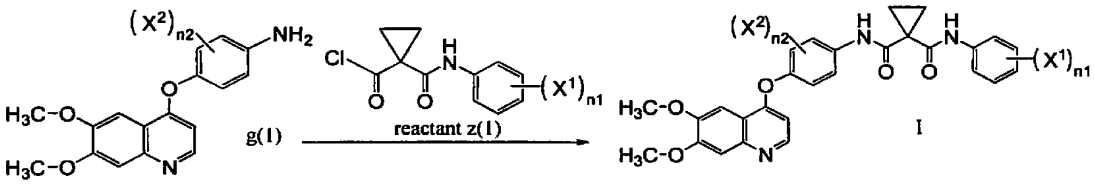
$X^2$ is H, Br, Cl, or F;

n1 is 1-2; and

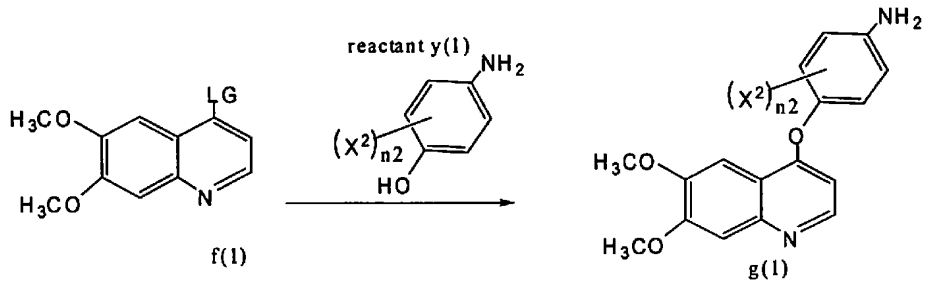
n2 is 1-2;

the process comprising:

contacting the compound of formula g(1) with reactant z(1) to yield the compound of formula I:

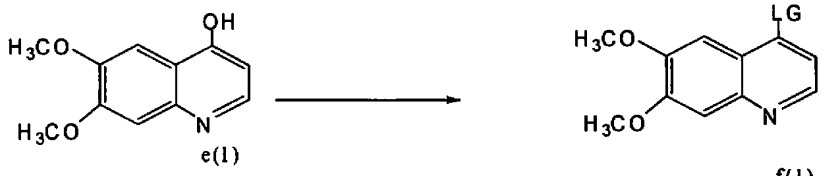



2. The process according to claim 1, wherein the compound of formula g(1) is made by reacting a compound of formula f(1) with reactant y(1) to yield the compound of formula g(1):



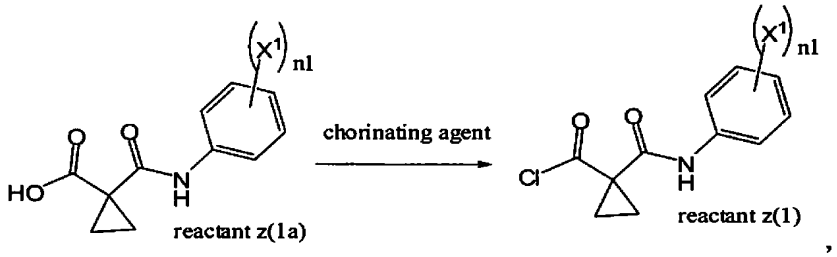

wherein LG represents a leaving group, and each $X^2$ and n2 are as defined in claim 1.

3. The process according to claim 2, wherein the compound of formula f(1) is made by converting compound e(1) to the compound of formula f(1):



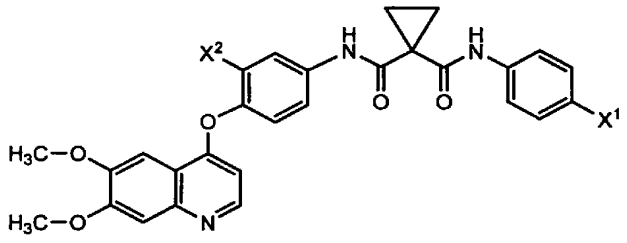

wherein LG represents a leaving group.

4. The process according to claim 1, wherein reactant z(1) is made by reacting reactant z(1a) with a chlorinating agent to yield reactant z(1):




wherein $X^1$ is Br, Cl, or F; and n1 is 1-2.

5. The process according to claim 1, wherein the compound of formula I is compound IA-1:



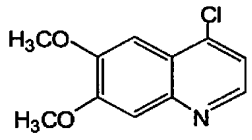

IA

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is H, Cl, Br, or F; and

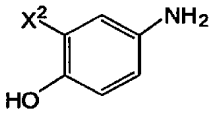
$X^2$ is H, Cl, Br, or F.

6. The process according to claim 5, wherein the compound of formula f(1) is compound f(2):



f(2) ;

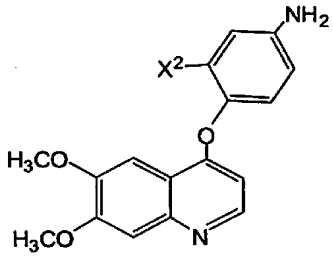
reactant y(1) is reactant (y)(2):



reactant (y)(2) ,

wherein $X^2$ is hydrogen or fluoro; and

the compound of formula g(1) is of formula g(2):



g(2) .

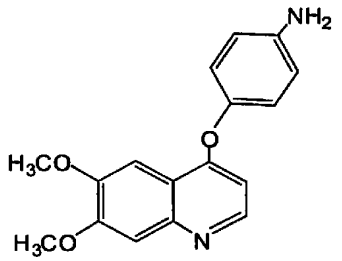
7. The process according to claim 6, wherein the reaction employs a non-nucleophilic base.

8. The process according to claim 7, wherein the non-nucleophilic base is an alkali metal alkoxide; and the reaction is carried out in a polar solvent.

9. The process according to claim 8, wherein the alkali metal alkoxide is sodium tert-butoxide, and the polar solvent is DMA.

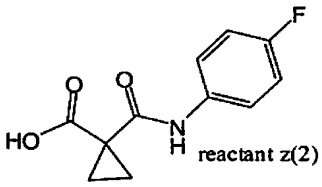
10. The process according to claim 8, wherein the alkali metal alkoxide is sodium tert-pentoxide, and the polar solvent is DMA.

11. The process according to claim 1, wherein the compound of formula g(1) is of compound g(3):



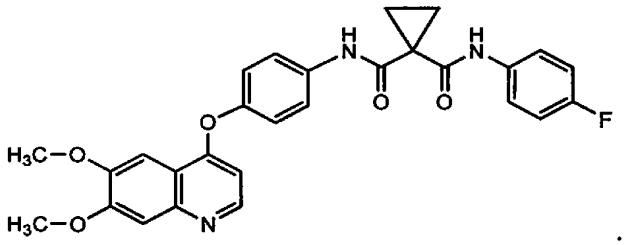
g(3) ;

reactant z(1) is reactant (z)(2):



reactant z(2) ; and

the compound of formula I is compound IA:

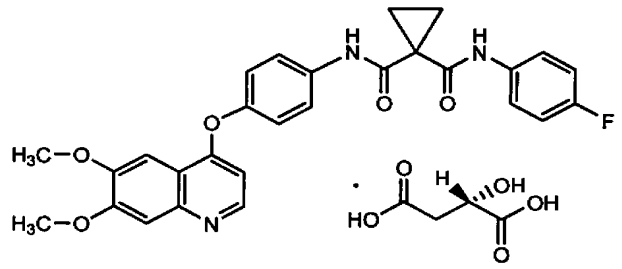


IA

12. The process according to claim 11, wherein the reaction is carried out in the presence of an inorganic base.

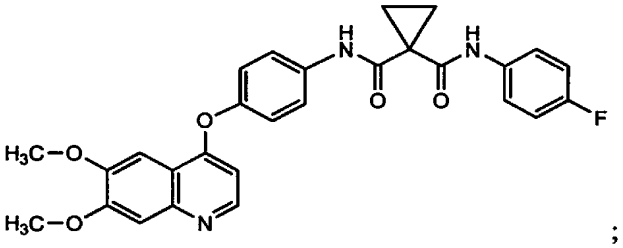
13. The process according to claim 12, wherein the inorganic base is $K_2CO_3$, and the solvent employed in this reaction is a combination of THF and $H_2O$.

14. A process for preparing compound IB:



IB

from compound IA:



;

IA

comprising:

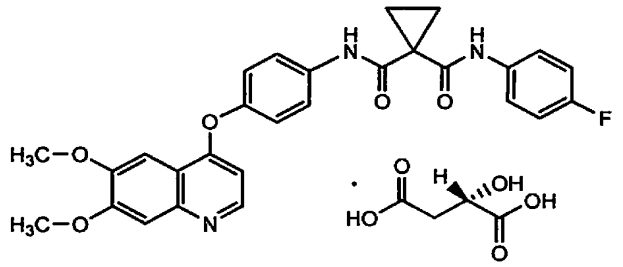
(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) vacuum distilling the mixture successively; and

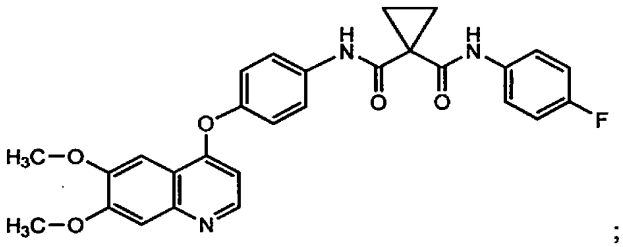
(d) isolating the compound of IB by filtration.

15. A process for preparing compound IB:



IB

from compound IA:



;

IA

comprising:

(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;
(b) cooling the mixture;
(c) seeding the mixture with the compound of IB;
(d) vacuum distilling the mixture; and
(e) isolating the compound of IB by filtration.

16. Compound IA or IB admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

17. Compound IB admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

18. Compound IB in the N-1 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

19. Compound IB in the N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

20. Compound IB as a mixture of the N-1 form and N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

21. A pharmaceutical composition according to Table 1.

**Table 1**

| Ingredient | % w/w |
|---|---|
| Compound I | 31.68 |
| Microcrystalline Cellulose (Avicel PH102) | 38.85 |
| Lactose anhydrous 60 M | 19.42 |
| Hydroxypropyl Cellulose, EXF | 3.00 |
| Croscarmellose Sodium | 3.00 |
| **Total Intra-granular** | **95.95** |
| Silicon dioxide, Colloidal PWD | 0.30 |
| Croscarmellose Sodium | 3.00 |
| Magnesium Stearate | 0.75 |
| **Total** | **100.00** |

22. A pharmaceutical composition according to Table 2.

**Table 2**

| Ingredient | (% w/w) |
|---|---|
| Compound I | 25.0-33.3 |
| Microcrystalline Cellulose, NF | q.s |
| Hydroxypropyl Cellulose, NF | 3 |
| Poloxamer, NF | 0-3 |
| Croscarmellose Sodium, NF | 6.0 |
| Colloidal Silicon Dioxide, NF | 0.5 |
| Magnesium Stearate, NF | 0.5-1.0 |
| Total | 100 |

23. A pharmaceutical composition according to Table 2A.

**Table 2A**

| **Ingredient** | **% w/w** |
|---|---|
| Compound IB (10 % drug load as Compound IA) | 12.67 |
| MCC | 51.52 |
| Lactose | 25.76 |
| Hydroxypropyl cellulose | 3.0 |
| Croscarmellose Sodium | 6.0 |
| Colloidal Silicon Dioxide | 0.3 |
| Magnesium Stearate | 0.75 |
| **Total** | **100** |

24. A pharmaceutical composition according to Table 3.

**Table 3**

| **Ingredient** | **mg/unit dose** |
|---|---|
| Compound IB (10 % drug load as Compound IA) | 25 |
| Silicified Microcrystalline Cellulose | 196.75 |
| Croscarmellose sodium | 12.5 |
| Sodium starch glycolate | 12.5 |
| Fumed Silica | 0.75 |
| Stearic acid | 2.5 |
| **Total Fill Weight** | 250 |

25. A pharmaceutical composition according to Table 4.

**Table 4**

| **Ingredient** | **mg/unit dose** |
|---|---|
| Compound IB (50 % drug load as Compound IA) | 100 |
| Silicified Microcrystalline Cellulose | 75.40 |
| Croscarmellose sodium | 10.00 |
| Sodium Starch Glycolate | 10.00 |
| Fumed silica | 0.6 |
| Stearic Acid | 4.0 |
| **Total Fill Weight** | 200 |

26. A pharmaceutical composition according to Table 5.

**Table 5**

| | **mg/unit dose** |
|---|---|
| **Ingredient** | **50mg** |
| Compound IB (10 % drug load as Compound IA) | 63.35 |
| Microcrystalline Cellulose | 95.39 |
| Croscarmellose sodium | 9.05 |
| Sodium starch glycolate | 9.05 |
| Fumed Silica | 0.54 |
| Stearic acid | 3.62 |
| **Total Fill Weight** | 181.00 |

27. A pharmaceutical composition according to Table 6.

**Table 6**

| | **mg/unit dose** |
|---|---|
| **Ingredient** | **60mg** |
| Compound IB | 73.95 |
| Microcrystalline Cellulose | 114.36 |
| Croscarmellose sodium | 10.85 |
| Sodium starch glycolate | 10.85 |
| Fumed Silica | 0.65 |
| Stearic acid | 4.34 |
| **Total Fill Weight** | 217.00 |

28. The pharmaceutical composition of claims 20-27 admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

29. The pharmaceutical composition of claims 20-27 admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

30. The pharmaceutical composition of claims 20-27 admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

31. The pharmaceutical composition of claims 20-27 admixed with 15 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

32. The pharmaceutical composition of claims 20-27 admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

33. The pharmaceutical composition of claims 20-27 admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

34. The pharmaceutical composition of claims 20-27 admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

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| PATENT APPLICATION FEE DETERMINATION RECORD<br>Substitute for Form PTO-875 | Application or Docket Number<br>13/984,559 | Filing Date<br>03/20/2014 | ☐ To be Mailed |
|---|---|---|---|

**ENTITY**: ☐ LARGE ☒ SMALL ☐ MICRO

## APPLICATION AS FILED – PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | RATE ($) | FEE ($) |
|---|---|---|---|---|
| ☐ BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | |
| ☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | |
| ☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | minus 20 = | * | X $ = | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | minus 3 = | * | X $ = | |
| ☐ 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

| 08/09/2013 | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|
| Total (37 CFR 1.16(i)) | * 34 | Minus | ** 34 | = 0 | X $40 = | 0 |
| Independent (37 CFR 1.16(h)) | * 15 | Minus | ***15 | = 0 | X $210 = | 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) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|
| Total (37 CFR 1.16(i)) | * | Minus | ** | = | X $ = | |
| Independent (37 CFR 1.16(h)) | * | Minus | *** | = | X $ = | |
| ☐ 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.

** 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 number found in the appropriate box in column 1.

LIE
/ADRIENE SELLMAN/

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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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>13/984,559 | Filing Date<br>03/20/2014 | ☐ To be Mailed |
|---|---|---|---|

**ENTITY**: ☐ LARGE ☒ SMALL ☐ MICRO

## APPLICATION AS FILED – PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | RATE ($) | FEE ($) |
|---|---|---|---|---|
| ☐ BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | |
| ☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | |
| ☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | minus 20 = | * | X $ = | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | minus 3 = | * | X $ = | |
| ☐ 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 | 10/01/2015 | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|
| | Total (37 CFR 1.16(i)) | * 4 | Minus | ** 34 | = 0 | X $40 = | 0 |
| | Independent (37 CFR 1.16(h)) | * 1 | Minus | ***15 | = 0 | X $210 = | 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) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|
| | Total (37 CFR 1.16(i)) | * | Minus | ** | = | X $ = | |
| | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | X $ = | |
| | ☐ 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.
** 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 number found in the appropriate box in column 1.

LIE
/HENRIETT K. DENDY/

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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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 13/984,559 | 03/20/2014 | Jo Ann Wilson | 224990/10-039C-US/343999 | 6725 |

91684 7590 06/09/2015

JONATHAN P. O'BRIEN, PH.D.
HONIGMAN MILLER SCHWARTZ AND COHN LLP
350 EAST MICHIGAN AVENUE, SUITE 300
Kalamazoo, MI 49007-3800

| EXAMINER | |
|---|---|
| ROZOF, TIMOTHY R | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1625 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 06/09/2015 | 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):

patent@honigman.com
hberven@honigman.com
cgregg-geist@honigman.com

| Office Action Summary | Application No. 13/984,559 | Applicant(s) WILSON, JO ANN | |
|---|---|---|---|
| | Examiner TIMOTHY R. ROZOF | Art Unit 1625 | AIA (First Inventor to File) Status No |

*-- 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 *March 20, 2015*.

☐ 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) *1-10,12-15,23 and 30-39* is/are pending in the application.

5a) Of the above claim(s) *1-10 and 12-15* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *23 and 30-39* 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 _____ 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 _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

## DETAILED ACTION

This is a response to Applicant's communication filed on March 20, 2015. Application No. 13/984,559 is a 371 of PCT/US12/24591, filed February 10, 2012, which claims the benefit of U.S. Provisional Applications Nos.: 61/441,520, February 10, 2011; and 61/441,527, filed February 10, 2011. In a preliminary amendment filed March 20, 2014, Applicant cancelled claims 11, 17, 18, 21, 22, and 24-27. In an amendment filed July 31, 2014, Applicant added new claims 35-39. In an amendment filed March 20, 2015, Applicant cancelled claims 16-19, 20, 28, and 29. Claims 1-10 and 12-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 31, 2014.

Claims 23 and 28-39 are examined below.

### *Rejections Withdrawn*

The rejection of claims 16, 19, 20, 23, and 28-29 under pre-AIA 35 U.S.C. 102(b) as being anticipated by Bannen et al., US2007/0054928 A1, is withdrawn in view of Applicant's March 20, 2015, Amendment & Remarks.

The rejections of claims 16, 19, 20, 23, and 28-29 under 35 U.S.C. 112, second paragraph, as being indefinite for improperly referring to "Compound IA or IB," as well

as “the N-2 form” and “the N-1 form,” elsewhere in the specification, is withdrawn in view of Applicant's March 2015, Amendment & Remarks.

***Rejection Maintained***

*Claim Rejections - 35 USC § 103(a)*

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

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 23, and 30-39 under pre-AIA 35 U.S.C. 103(a) as obvious over Bannen et al., US2007/0054928 A1, is maintained for reasons made of record. Applicant argues that there is no teaching or suggestion in Bannen of the need to minimize the degradation product (6,7-dimethoxy-quinoline-4-ol) in pharmaceutical formulations. Applicant's argument has been fully considered and is not persuasive.

Applicant argues that there is no teaching or suggestion in the prior art to minimize impurities to obtain a pharmaceutical grade formulation. However, the Bannen teaches that the compounds of the prior art are in *pure form and* in an appropriate pharmaceutical composition. See Id. para. [0297], p. 144. The prior art then teaches that the compositions can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Id. The prior art then list some, if not all, of these accepted modes of administration or agents, encompassing the additional elements of the composition of the present invention. Id., p. 144-145, paras.

[0297]-[0310]. Although, the prior art does not disclose the specific impurity, or degradation product (6,7-dimethoxy-quinoline-4-ol), the prior art is clear that any of the compositions it discloses are pharmaceutical grade, free of any impurity, let alone 6,7-dimethoxy-quinoline-4-ol. The discovery of a previously unappreciated property of a prior art composition does not render the old composition patentably new to the discoverer. MPEP 2112. I. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. MPEP 2112.II.

It is suggested that Applicant provide evidence demonstrating that the identification and removal of the degradation product from the known composition provides for some unexpected property to distinguish it from the composition of the prior art. Applicant has not demonstrated the level of scientific enquiry required to demonstrate unexpected superior results, such as a comparative study. See MPEP 716.02. The arguments of counsel cannot take the place of evidence in the record. MPEP 2145. Attorney statements which are not evidence, as in this case, must be supported by an appropriate affidavit or declaration. (Id.)

## ***Conclusion***

No claims are allowed.

**THIS ACTION IS MADE FINAL.** 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 mailing date of this final action.

***Contact Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY R. ROZOF whose telephone number is (571)270-5992. The examiner can normally be reached on Monday thru Friday, 9:00 am to 5:00 pm ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. 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 http://pair-direct.uspto.gov. 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.

/TIMOTHY R ROZOF/
Primary Examiner, Art Unit 1625

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

# BIB DATA SHEET

**CONFIRMATION NO. 6725**

| SERIAL NUMBER | FILING or 371(c) DATE | CLASS | GROUP ART UNIT | ATTORNEY DOCKET NO. |
|---|---|---|---|---|
| 13/984,559 | 03/20/2014 | 514 | 1625 | 224990/10-039C-US/343999 |
| | RULE | | | |

**APPLICANTS**

**INVENTORS**

Jo Ann Wilson, San Francisco, CA;

**** CONTINUING DATA ***************************

This application is a 371 of PCT/US12/24591 02/10/2012
which claims benefit of 61/441,520 02/10/2011
and claims benefit of 61/441,527 02/10/2011

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
04/01/2014

| Foreign Priority claimed | ☐ Yes ☑ No | | STATE OR COUNTRY | SHEETS DRAWINGS | TOTAL CLAIMS | INDEPENDENT CLAIMS |
|---|---|---|---|---|---|---|
| 35 USC 119(a-d) conditions met | ☐ Yes ☐ No | ☐ Met after Allowance | | | | |
| Verified and Acknowledged | /TIMOTHY R ROZOF/ Examiner's Signature | TRR Initials | CA | 0 | 25 | 6 |

**ADDRESS**

JONATHAN P. O'BRIEN, PH.D.
HONIGMAN MILLER SCHWARTZ AND COHN LLP
350 EAST MICHIGAN AVENUE, SUITE 300
Kalamazoo, MI 49007-3800
UNITED STATES

**TITLE**

Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

| FILING FEE RECEIVED | | |
|---|---|---|
| 3890 | FEES: Authority has been given in Paper<br>No._____ to charge/credit DEPOSIT ACCOUNT<br>No._____ for following: | ☐ All Fees<br>☐ 1.16 Fees (Filing)<br>☐ 1.17 Fees (Processing Ext. of time)<br>☐ 1.18 Fees (Issue)<br>☐ Other _____<br>☐ Credit |

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. 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 contains a valid OMB control number.

**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**
**(Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13984559 |
| Filing Date | 2014-03-20 |
| First Named Inventor | Jo Ann Wilson |
| Art Unit | 1625 |
| Examiner Name | Timothy R. Rozof |
| Attorney Docket Number | 224990/10-039C-US/343999 |

**U.S.PATENTS**

| 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 | 7166722 | | 2007-01-23 | MATSUNAGA et al. | |

If you wish to add additional U.S. Patent citation information please click the Add button.

**U.S.PATENT APPLICATION PUBLICATIONS**

| 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 | | | | | |

If you wish to add additional U.S. Published Application citation information please click the Add button.

**FOREIGN PATENT DOCUMENTS**

| 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 | 2005030140 | WO | | 2005-04-07 | BANNEN et al. | | ☐ |
| | 2 | 2011017639 | WO | | 2011-02-10 | AFTAB et al. | | ☐ |
| | 3 | 2012009722 | WO | | 2012-01-19 | WILSON | | ☐ |



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.R./

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13984559 |
| | Filing Date | 2014-03-20 |
| | First Named Inventor | Jo Ann Wilson |
| | Art Unit | 1625 |
| | Examiner Name | Timothy R. Rozof |
| | Attorney Docket Number | 224990/10-039C-US/343999 |

If you wish to add additional Foreign Patent Document citation information please click the Add button

**NON-PATENT LITERATURE DOCUMENTS**

| 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] |
|---|---|---|---|
| | 1 | | ☐ |

If you wish to add additional non-patent literature document citation information please click the Add button

**EXAMINER SIGNATURE**

| Examiner Signature | /Timothy Rozof/ | Date Considered | 06/03/2015 |
|---|---|---|---|

*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.GOVor 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.



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.R./

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13984559 |
| | Filing Date | 2014-03-20 |
| | First Named Inventor | Jo Ann Wilson |
| | Art Unit | 1625 |
| | Examiner Name | Timothy R. Rozof |
| | Attorney Docket Number | 224990/10-039C-US/343999 |

**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 | | Date (YYYY-MM-DD) | 2015-03-20 |
| Name/Print | Heidi Berven | Registration Number | 48951 |

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.**



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.R./

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13984559 | WILSON, JO ANN |
| | **Examiner** | **Art Unit** |
| | TIMOTHY R ROZOF | 1625 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 04/23/2014 | 10/04/2014 | 06/03/2015 | | | | | | |
| | 1 | ÷ | N | N | | | | | | |
| | 2 | ÷ | N | N | | | | | | |
| | 3 | ÷ | N | N | | | | | | |
| | 4 | ÷ | N | N | | | | | | |
| | 5 | ÷ | N | N | | | | | | |
| | 6 | ÷ | N | N | | | | | | |
| | 7 | ÷ | N | N | | | | | | |
| | 8 | ÷ | N | N | | | | | | |
| | 9 | ÷ | N | N | | | | | | |
| | 10 | ÷ | N | N | | | | | | |
| | 11 | - | - | - | | | | | | |
| | 12 | ÷ | N | N | | | | | | |
| | 13 | ÷ | N | N | | | | | | |
| | 14 | ÷ | N | N | | | | | | |
| | 15 | ÷ | N | N | | | | | | |
| | 16 | ÷ | ✓ | - | | | | | | |
| | 17 | - | - | - | | | | | | |
| | 18 | - | | - | | | | | | |
| | 19 | ÷ | ✓ | - | | | | | | |
| | 20 | ÷ | ✓ | - | | | | | | |
| | 21 | - | - | - | | | | | | |
| | 22 | - | - | - | | | | | | |
| | 23 | ÷ | ✓ | ✓ | | | | | | |
| | 24 | - | - | - | | | | | | |
| | 25 | - | - | - | | | | | | |
| | 26 | - | - | - | | | | | | |
| | 27 | - | - | - | | | | | | |
| | 28 | ÷ | ✓ | - | | | | | | |
| | 29 | ÷ | ✓ | - | | | | | | |
| | 30 | ÷ | ✓ | ✓ | | | | | | |
| | 31 | ÷ | ✓ | ✓ | | | | | | |
| | 32 | ÷ | ✓ | ✓ | | | | | | |
| | 33 | ÷ | ✓ | ✓ | | | | | | |
| | 34 | ÷ | ✓ | ✓ | | | | | | |
| | 35 | | ✓ | ✓ | | | | | | |
| | 36 | | ✓ | ✓ | | | | | | |

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13984559 | WILSON, JO ANN |
| | Examiner | Art Unit |
| | TIMOTHY R ROZOF | 1625 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 04/23/2014 | 10/04/2014 | 06/03/2015 | | | | | | |
| | 37 | | ✓ | ✓ | | | | | | |
| | 38 | | ✓ | ✓ | | | | | | |
| | 39 | | ✓ | ✓ | | | | | | |

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

Inventor: Jo Ann Wilson
Application No.: 13/984,559
Filed: March 20, 2014

Art Unit: 1625
Examiner: Timothy R. Rozof
Atty. Docket No.: 224990/10-039C-US/343999

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

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

**RESPONSE TO NON-FINAL REJECTION MAILED OCTOBER 8, 2014**

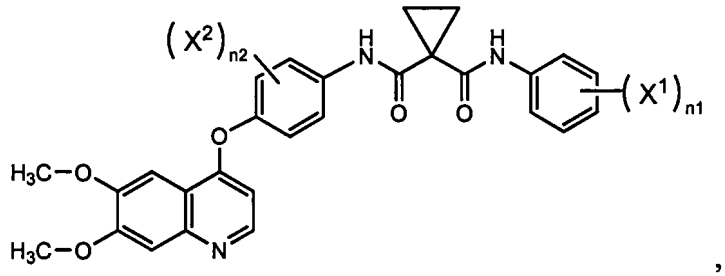
In response to the Non-Final Rejection, Applicant submits the following amendments.

Amendments to the claims begin on page 2.

Remarks begin on page 11.

## CLAIM AMENDMENTS

1. (Withdrawn) A process for preparing a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is H, Br, Cl, or F;

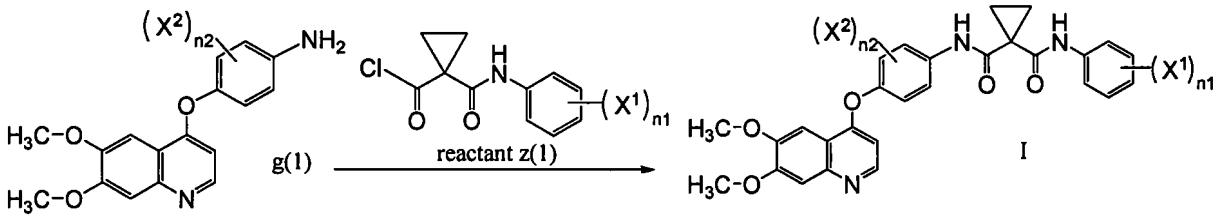
$X^2$ is H, Br, Cl, or F;

n1 is 1-2; and

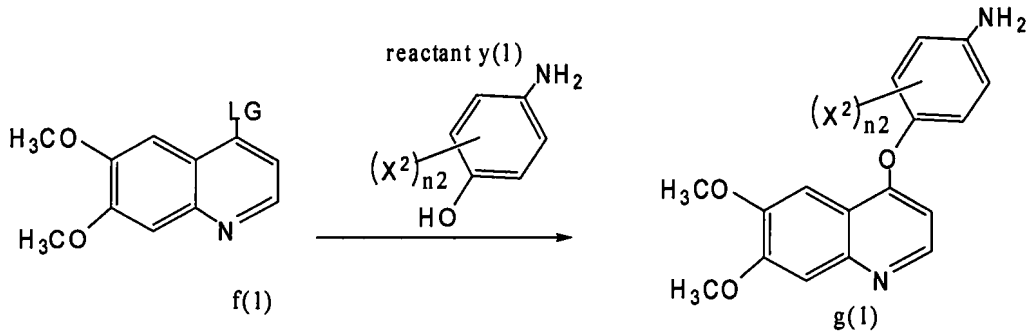
n2 is 1-2;

the process comprising:

contacting the compound of formula g(1) with reactant z(1) to yield the compound of formula I:

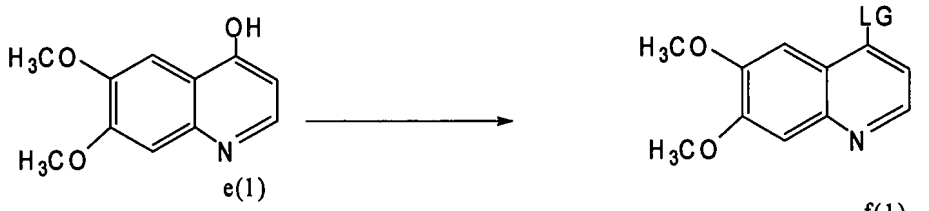



2. (Withdrawn) The process according to claim 1, wherein the compound of formula g(1) is made by reacting a compound of formula f(1) with reactant y(1) to yield the compound of formula g(1):



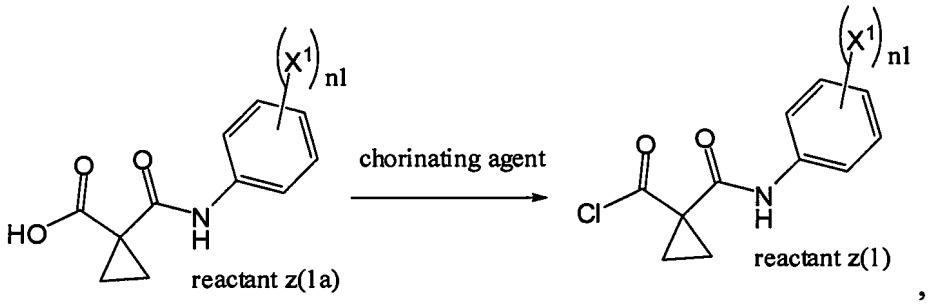
wherein LG represents a leaving group, and each $X^2$ and n2 are as defined in claim 1.

3. (Withdrawn) The process according to claim 2, wherein the compound of formula f(1) is made by converting compound e(1) to the compound of formula f(1):



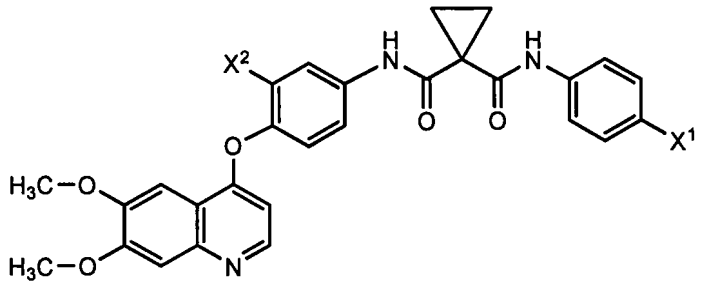

wherein LG represents a leaving group.

4. (Withdrawn) The process according to claim 1, wherein reactant z(1) is made by reacting reactant z(1a) with a chlorinating agent to yield reactant z(1):




wherein $X^1$ is Br, Cl, or F; and n1 is 1-2.

5. (Withdrawn) The process according to claim 1, wherein the compound of formula I is compound IA:



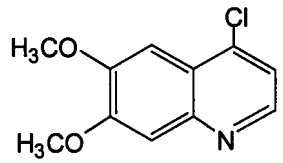

IA

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is H, Cl, Br, or F; and

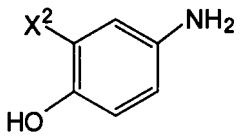
$X^2$ is H, Cl, Br, or F.

6. (Withdrawn) The process according to claim 5, wherein the compound of formula f(1) is compound f(2):



f(2) ;

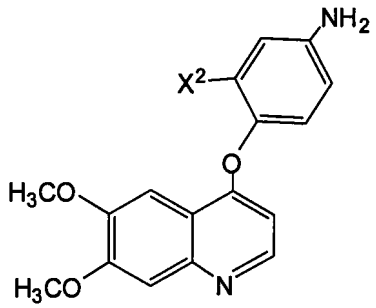
reactant y(1) is reactant (y)(2):



reactant (y)(2) ,

wherein $X^2$ is hydrogen or fluoro; and

the compound of formula g(1) is of formula g(2):



g(2) .

7. (Withdrawn) The process according to claim 6, wherein the reaction employs a non-nucleophilic base.

8. (Withdrawn) The process according to claim 7, wherein the non-nucleophilic base is an alkali metal alkoxide; and the reaction is carried out in a polar solvent.

9. (Withdrawn) The process according to claim 8, wherein the alkali metal alkoxide is sodium tert-butoxide, and the polar solvent is DMA.

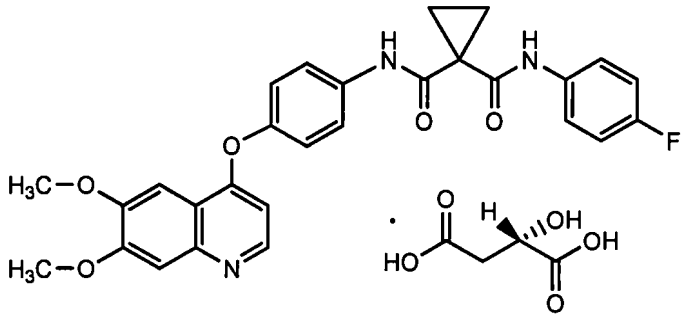
10. (Withdrawn) The process according to claim 8, wherein the alkali metal alkoxide is sodium tert-pentoxide, and the polar solvent is DMA.

11. Cancelled.

12. (Withdrawn) The process according to claim 1, wherein the reaction is carried out in the presence of an inorganic base.

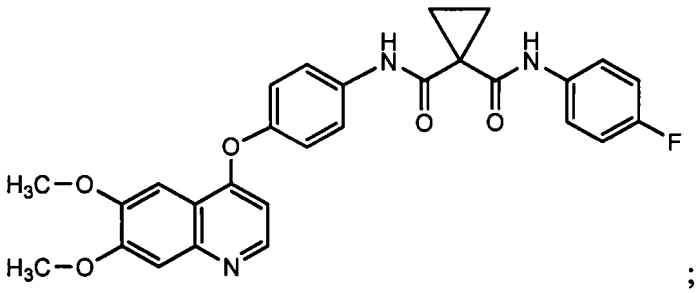
13. (Withdrawn) The process according to claim 12, wherein the inorganic base is $K_2CO_3$, and the solvent employed in this reaction is a combination of THF and $H_2O$.

14. (Withdrawn) A process for preparing compound IB:



IB

with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol from compound IA:



;

IA

comprising:

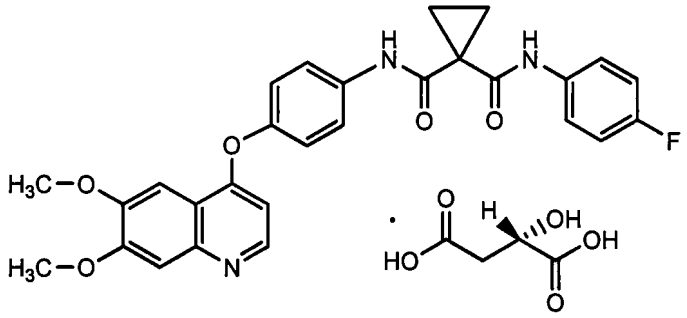
(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) vacuum distilling the mixture successively; and

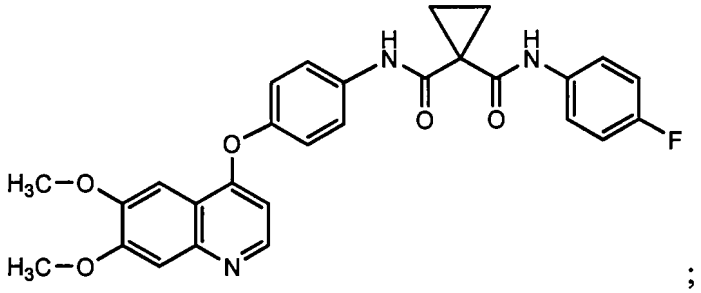
(d) isolating the compound of IB by filtration;.

15. (Withdrawn) The process of claim 14 for preparing compound IB:



IB

with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol from compound IA:



;

IA

comprising:

(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) seeding the mixture with the compound of IB;

(d) vacuum distilling the mixture; and

(e) isolating the compound of IB by filtration.

16-22. Cancelled.

23. (Currently Amended) A pharmaceutical composition selected from the group consisting of Table 2A, 3, 4, 5, and 6.

**Table 2A**

| **Ingredient** | **% w/w** |
|---|---|
| Compound IB (10 % drug load as Compound IA) | 12.67 |
| MCC | 51.52 |
| Lactose | 25.76 |
| Hydroxypropyl cellulose | 3.0 |
| Croscarmellose Sodium | 6.0 |
| Colloidal Silicon Dioxide | 0.3 |
| Magnesium Stearate | 0.75 |
| **Total** | **100** |

**Table 3**

| **Ingredient** | **mg/unit dose** |
|---|---|
| Compound IB (10 % drug load as Compound IA) | 25 |
| Silicified Microcrystalline Cellulose | 196.75 |
| Croscarmellose sodium | 12.5 |
| Sodium starch glycolate | 12.5 |
| Fumed Silica | 0.75 |
| Stearic acid | 2.5 |
| **Total Fill Weight** | 250 |

**Table 4**

| **Ingredient** | **mg/unit dose** |
|---|---|
| Compound IB (50 % drug load as Compound IA) | 100 |
| Silicified Microcrystalline Cellulose | 75.40 |
| Croscarmellose sodium | 10.00 |
| Sodium Starch Glycolate | 10.00 |
| Fumed silica | 0.6 |
| Stearic Acid | 4.0 |
| **Total Fill Weight** | 200 |

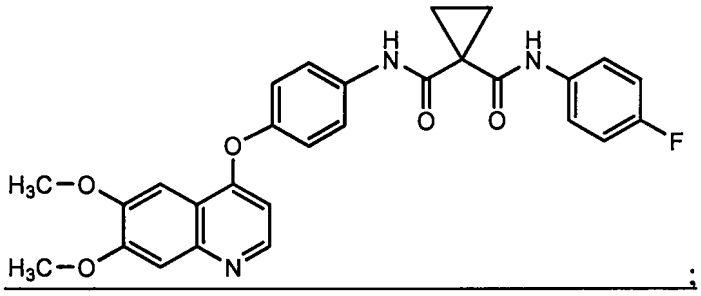
**Table 5**

| | **mg/unit dose** |
|---|---|
| **Ingredient** | **50mg** |
| Compound IB (10 % drug load as Compound IA) | 63.35 |
| Microcrystalline Cellulose | 95.39 |
| Croscarmellose sodium | 9.05 |
| Sodium starch glycolate | 9.05 |
| Fumed Silica | 0.54 |
| Stearic acid | 3.62 |
| **Total Fill Weight** | 181.00 |

**Table 6**

| | **mg/unit dose** |
|---|---|
| **Ingredient** | **60mg** |
| Compound IB | 73.95 |
| Microcrystalline Cellulose | 114.36 |
| Croscarmellose sodium | 10.85 |
| Sodium starch glycolate | 10.85 |
| Fumed Silica | 0.65 |
| Stearic acid | 4.34 |
| **Total Fill Weight** | 217.00 |

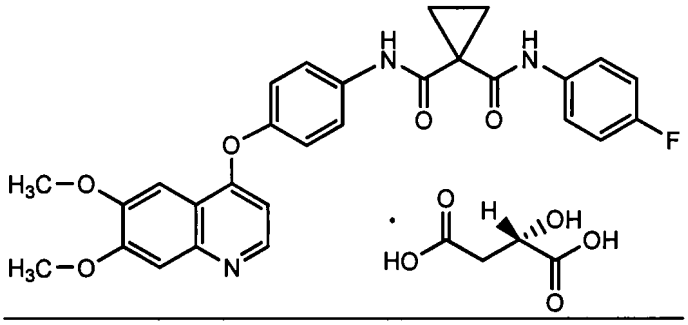
wherein Compound 1A has the structure:




;

IA;

compound IB has the structure:



IB;

and wherein the formation of 6,7-dimethoxy-quinoline-4-ol in the pharmaceutical formulation is minimized to 50 ppm or less over time.

24-29 Cancelled.

30. (Currently Amended) The pharmaceutical composition of claim 23 ~~admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol~~ wherein the formation of 6,7-dimethoxy-quinoline-4-ol in the pharmaceutical formulation is minimized to 25 ppm or less over time.

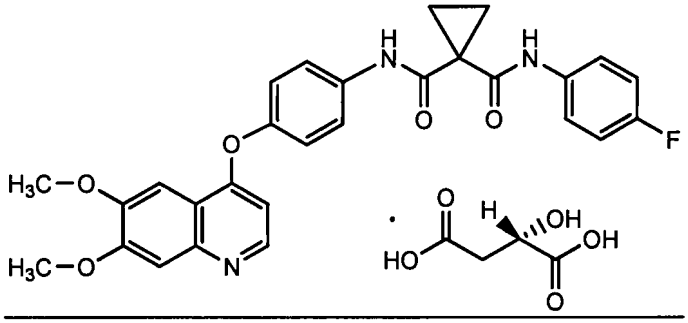
31. (Currently Amended) The pharmaceutical composition of claim 23 ~~admixed with 15 ppm or less of 6,7-dimethoxy-quinoline-4-ol~~ wherein the formation of 6,7-dimethoxy-quinoline-4-ol in the pharmaceutical formulation is minimized to 15 ppm or less over time.

32. (Currently Amended) The pharmaceutical composition of claim 23 ~~admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol~~ wherein the formation of 6,7-dimethoxy-quinoline-4-ol in the pharmaceutical formulation is minimized to 10 ppm or less over time.

33. (Currently Amended)The pharmaceutical composition of claim 23 ~~admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol~~ wherein the formation of 6,7-dimethoxy-quinoline-4-ol in the pharmaceutical formulation is minimized to 5 ppm or less over time.

34. (Currently Amended) The pharmaceutical composition of claim 23 ~~admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol~~ wherein the formation of 6,7-dimethoxy-quinoline-4-ol in the pharmaceutical formulation is minimized to 2.5 ppm or less over time.

35. (Currently Amended) A pharmaceutical composition comprising Compound IB; microcrystalline cellulose; croscarmellose sodium; sodium starch glycolate; fumed silica; and stearic acid; wherein Compound IB has the structure:



IB;

and wherein the formation of 6,7-dimethoxy-quinoline-4-ol in the pharmaceutical formulation is minimized to 50 ppm or less over time.

36. (Previously Presented) The pharmaceutical composition of claim 35, which is capsule composition.

37. (Previously Presented) The pharmaceutical composition of claim 36, comprising 25 mg or 100 mg of Compound 1B.

38. (Previously Presented) The pharmaceutical composition of claim 37 comprising 25 mg Compound IB, wherein formation of 6,7-dimethoxy-quinoline-4-ol is limited to 50 ppm over 9 months at temperatures of 25, 30, or 40 °C and relative humidities of 60 or 75 percent.

39. (Previously Presented) The pharmaceutical composition of claim 37 comprising 100 mg Compound IB, wherein formation of 6,7-dimethoxy-quinoline-4-ol is limited to 50 ppm over 6 months at temperatures of 25, 30, or 40 °C and relative humidities of 60 or 75 percent.

## REMARKS

**Claim Status**

Claims 1-10 and 12-15 are withdrawn.

Claims 11, 16-22, and 24-29 are cancelled.

Claims 36-39 are previously presented.

Claims 23 and 30-35 are currently amended to add the structures of Compounds IA and/or IB. Claims 23 and 30-35 are amended to add the limitation that formation of 6,7-dimethoxy-quinoline-4-ol in the pharmaceutical formulation is minimized over time. Support for this limitation is found in the specification as filed at page 36, paragraph 163. No new matter has been added to the currently amended claims.

Thus, claims 1-10. 12-15, 23, and 30-39 are currently pending.

The claim amendments are made in the interest of expediting prosecution. The Applicant does not intend to surrender any range of equivalents to which the Applicant would otherwise be entitled in view of the prior art, nor does the Applicant agree with the Examiner's comments or arguments about the art cited in the Office Action. Further, by the present amendment, it does not follow that the amended claims have become so perfect in their description that no one could devise an equivalent. After amendment, as before, limitations in the ability to describe the present invention in language in the patent claims naturally prevent the Applicant from capturing every nuance of the invention or describing with complete precision the range of its novelty or every possible equivalent. *See* Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 62 USPQ2d 1705 (2002). By amending the claims, the Applicant does not concede that patent coverage available to them would not extend as far as the original claim. The Applicant reserves the right to file divisional and/or continuation applications to pursue the breadth of the claims as filed. The Applicant respectfully requests the timely allowance of the amended claims.

**Claim Rejections under 35 USC § 102(b)**

The Examiner rejected claims 16, 19, 20, 23, and 28-29 under pre-AIA 35 USC 102(b) as being anticipated by Bannen et al., US2007/0054928A1. The Applicant respectfully disagrees.

The Application notes that according to MPEP 2133, a claimed invention is anticipated when a disclosure teaches every element of the claim. Bannen does not teach or otherwise disclose formulations comprising Compound IA or IB where formation of 6,7-dimethoxy-

quinoline-4-ol in the pharmaceutical formulation is minimized to 50 ppm or less over time. As a result, the claims are not anticipated by Bannen.

**Claim Rejections under 35 USC § 103(a)**

The Examiner rejected claims 16, 19, 20, 23, and 28-29 under pre-AIA 35 USC 102(b) as anticipated by or, in the alternative, under pre-AIA 35 USC 103(a) as obvious over Bannen et al., US2007/0054928A1. The Applicant respectfully disagrees.

The pharmaceutical formulations claimed by the Applicant are stable over various temperatures, times, and humidity levels, as demonstrated by the Applicant in the Stability Studies provided at pages 34-36 of the specification as filed, such that formation of 6,7-dimethoxy-quinoline-4-ol in the pharmaceutical formulation is minimized to 50 ppm or less over time. 6,7-dimethoxy-quinoline-4-ol is a degradation product that the Applicant sought to minimize in pharmaceutical formulations of Compound IA or IB. There is no teaching or suggestion in Bannen of the need to minimize this degradation product in pharmaceutical formulations. As a result, the Applicant respectfully submits that the claims are not obviated by Bannen.

**Claim Rejections under 35 USC § 112 Second Paragraph**

The Examiner rejected claims 16, 19, 20, 23, and 28-29 under 35 USC112, second paragraph, as being indefinite, since they did not provide the structures of Compounds IA or IB. In response, the Applicant has amended the claims to include the structures of Compound IA and/or IB. As a result, the Applicant requests removal of the rejection.

**INFORMATION DISCLOSURE STATEMENT**

The Applicant notes that the filing of the enclosed Information Disclosure Statement shall not be construed to be an admission that the information cited in the statement qualifies as prior art under 35 U.S.C. §§ 102 or 103, or is considered to be material to patentability as defined in §1.56(b).

**OTHER C-MET INHIBITOR CASES**

The Applicant wishes to make the Examiner aware of the Applicant's other applications related to c-Met inhibitors and their use in the treatment of cancer. For the Examiner's convenience, the Applicant is providing a list of the Applicant's applications directed to the

treatment of cancer using c-Met inhibitors. The Applicant understands the Examiner has electronic access to these applications and to the Office Actions that have issued in these applications, and has therefore not included copies with this Response. The Applicant will gladly provide the applications and Office Actions to the Examiner, however, upon request.

| **Application No.** | **Filing or 371 Date** | **Patent No.** | **Examiner** | **Status** |
|---|---|---|---|---|
| 10/573,336 | 09/18/2006 | | Koontz, Tammy J | Abandoned |
| 11/571,140 | 12/21/2006 | 7,977,345 | Moore, Susanna | Issued |
| 11/586,751 | 10/26/2006 | | Ward, Paul V. | Published |
| 11/753,462 | 05/24/2007 | 8,178,532 | Ward, Paul V | Issued |
| 11/753,503 | 05/24/2007 | 8,476,298 | Ward, Paul V | Issued |
| 11/753,514 | 05/24/2007 | 8,067,436 | Bernhardt, Emily A | Issued |
| 12/393,806 | 02/26/2009 | 7,579,473 | Seaman, D Margaret M | Issued |
| 12/435,473 | 05/05/2009 | | Pagonakis, Anna | Abandoned |
| 12/566,707 | 09/25/2009 | 8,314,232 | Rebecca L. Anderson | Issued |
| 12/911,442 | 10/25/2010 | | Ward, Paul, V. | Abandoned |
| 13/087,094 | 04/14/2011 | | Chickos, Sarah, J. | Abandoned |
| 13/129,183 | 05/13/2011 | | Seaman, D Margaret M | Abandoned |
| 13/132,650 | 06/03/2011 | | Seaman, D Margaret M | Abandoned |
| 13/145,054 | 10/20/2011 | 8,877,776 | Carter, Kendra D | Issued |
| 13/249,815 | 09/30/2011 | 8,497,284 | Bernhardt, Emily A | Issued |
| 13/384,451 | 07/12/2012 | 8,673,912 | Anderson, Rebecca L | Issued |
| 13/389,266 | 07/12/2012 | | Perreira, Melissa Jean | Published |
| 13/427,093 | 03/22/2012 | | Ward, Paul V | Abandoned |
| 13/438,964 | 04/04/2012 | | Brown-Pettigrew, Angela C | Published |
| 13/634,275 | 09/12/2012 | | Anderson, Rebecca L | Published |
| 13/753,031 | 01/29/2013 | | Pagonakis, Anna | Published |
| 13/753,146 | 01/29/2013 | | Pagonakis, Anna | Published |
| 13/810,537 | 01/16/2013 | | Soroush, Ali | Published |
| 13/810,546 | 01/16/2013 | | Branson, Daniel L | Published |
| 13/876,290 | 03/27/2013 | | Stone, Christopher R. | Published |
| 13/876,306 | 03/27/2013 | | Andrew P. Lee | Abandoned |
| 13/876,318 | 03/27/2013 | | Claytor, Deirdre Renee | Published |
| 13/888,592 | 05/07/2013 | | Paul V. Ward | Abandoned |
| 13/928,977 | 06/27/2013 | | Emily A. Bernhardt | Published |
| 13/984,559 | 08/09/2013 | | Timothy R. Rozof | Published |
| 13/988,561 | 05/21/2013 | | Sarah Pihonak | Published |
| 14/021,614 | 09/09/2013 | | Matos Negron, Taina Del Mar | Published |
| 14/115,236 | 11/01/2013 | | James D. Anderson | Published |
| 14/166,545 | 01/28/2014 | | Not Yet Assigned | Abandoned |
| 14/173,973 | 02/06/2014 | | Diana B. Johannsen | Published |

| Application No. | Filing or 371 Date | Patent No. | Examiner | Status |
|---|---|---|---|---|
| 14/340,871 | 07/25/2014 | | Kendra D. Carter | Published |
| 14/346,570 | 03/21/2014 | | Y Jean Marie Z Calvillo | Published |
| 14/353,251 | 04/21/2014 | | Oluwafemi L. Masha | Published |
| 14/356,927 | 05/08/2014 | | Not Yet Assigned | Published |
| 14/356,938 | 05/08/2014 | | Jeffrey Gerben Hoekstra | Published |
| 14/398,188 | 10/31/2014 | | Not Yet Assigned | Pending |
| 14/518,733 | 10/20/2014 | | Not Yet Assigned | Pending |

## CONCLUSION

It is believed that there are no fees associated with filing this response at this time. However, if there are credits or fees associated with this response please apply the credits or fees to Deposit Account No. 503145, referencing Attorney Docket Number 224990/10-039C-US/343999.

Respectfully submitted,

Date: March 20, 2015

//Heidi M. Berven//
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PTO/SB/08a (01-10)
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**(Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13984559 |
| Filing Date | 2014-03-20 |
| First Named Inventor | Jo Ann Wilson |
| Art Unit | 1625 |
| Examiner Name | Timothy R. Rozof |
| Attorney Docket Number | 224990/10-039C-US/343999 |

**U.S.PATENTS**

| 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 | 7166722 | | 2007-01-23 | MATSUNAGA et al. | |

If you wish to add additional U.S. Patent citation information please click the Add button.

**U.S.PATENT APPLICATION PUBLICATIONS**

| 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 | | | | | |

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**FOREIGN PATENT DOCUMENTS**

| 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 | 2005030140 | WO | | 2005-04-07 | BANNEN et al. | | ☐ |
| | 2 | 2011017639 | WO | | 2011-02-10 | AFTAB et al. | | ☐ |
| | 3 | 2012009722 | WO | | 2012-01-19 | WILSON | | ☐ |

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13984559 |
| | Filing Date | 2014-03-20 |
| | First Named Inventor | Jo Ann Wilson |
| | Art Unit | 1625 |
| | Examiner Name | Timothy R. Rozof |
| | Attorney Docket Number | 224990/10-039C-US/343999 |

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**NON-PATENT LITERATURE DOCUMENTS**

| 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] |
|---|---|---|---|
| | 1 | | ☐ |

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**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.GOVor 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 | 13984559 |
| | Filing Date | 2014-03-20 |
| | First Named Inventor | Jo Ann Wilson |
| | Art Unit | 1625 |
| | Examiner Name | Timothy R. Rozof |
| | Attorney Docket Number | 224990/10-039C-US/343999 |

**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 | | Date (YYYY-MM-DD) | 2015-03-20 |
| Name/Print | Heidi Berven | Registration Number | 48951 |

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.**

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# PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): 224990/10-039C-US/343999

Application Number: 13/984,559 | Filed: 03/20/2014

For: Exelixis, Inc.

Art Unit: 1625 | Examiner: Timothy R. Rozof

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

| | Fee | Small Entity Fee | Micro Entity Fee | |
|---|---|---|---|---|
| ☐ One month (37 CFR 1.17(a)(1)) | $200 | $100 | $50 | $ |
| ☐ Two months (37 CFR 1.17(a)(2)) | $600 | $300 | $150 | $ |
| ☑ Three months (37 CFR 1.17(a)(3)) | $1,400 | $700 | $350 | $ 700 |
| ☐ Four months (37 CFR 1.17(a)(4)) | $2,200 | $1,100 | $550 | $ |
| ☐ Five months (37 CFR 1.17(a)(5)) | $3,000 | $1,500 | $750 | $ |

☑ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 503145.

☑ Payment made via EFS-Web.

**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.**

I am the

☐ applicant.

☑ attorney or agent of record. Registration number 48951.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

| | |
|---|---|
| Signature | March 20, 2015 (Date) |
| Heidi Belven (Typed or printed name) | 269-337-7710 (Telephone Number) |

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.136(a). 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 6 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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | | |
|---|---|---|---|
| Inventors(s) | : Jo Ann Wilson | Art Unit | : 1625 |
| Serial No. | : 13/984,559 | Examiner | : Timothy R. Rozof |
| Filed | : March 20, 2014 | Docket No.: | 224990/10-039C-US/343999 |

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

**CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. §1.8(a)**

The undersigned hereby certifies that the following documents are being electronically filed in accordance with §1.6(a)(4), on the 20th day of March, 2015:

1. Cover Letter to the Commissioner;
2. Response to Non-Final Office Action dated October 8, 2014;
3. Information Disclosure Statement;
4. Foreign Patent References (5);
5. Petition for Extension of Time (PTO/SB/22); and
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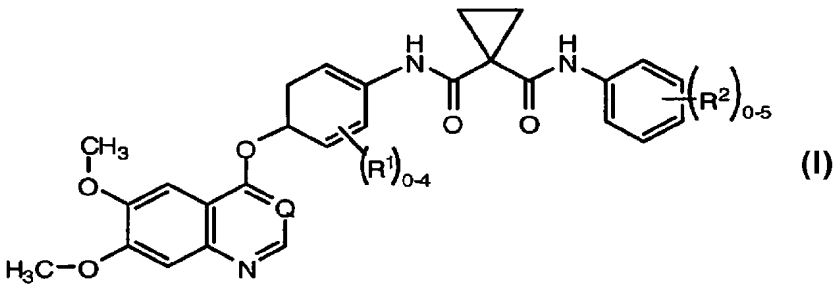
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(54) **Title**: METHODS OF USING C-MET MODULATORS




(I)

(57) **Abstract**: Methods of treating cancer by administering a compound of Formula (I), (Formula I) or a pharmaceutically acceptable salt or solvate thereof, in combination with other cancer treatments are described, wherein $R^1$ is halo; $R^2$ is halo; and Q is CH or N.

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# METHODS OF USING C-MET MODULATORS

## FIELD OF THE INVENTION

**[0001]** This invention relates to methods of using c-Met modulators, and specifically c-Met modulators in combination with other anti-cancer agents and/or radiation, which can be useful for the modulation of various cellular activities and for the treatment of various diseases as described in the specification.

## BACKGROUND OF THE INVENTION

**[0002]** Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. One mechanism that can be exploited in cancer treatment is the modulation of protein kinase activity because signal transduction through protein kinase activation is responsible for many of the characteristics of tumor cells. Protein kinase signal transduction is of particular relevance in, for example, thyroid, gastric, head and neck, lung, breast, prostate, and colorectal cancers, as well as in the growth and proliferation of brain tumor cells.

**[0003]** Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., DN&P 7(6): 334-339, 1994. Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases, including, for example, immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, protein kinases are attractive targets for small molecule drug discovery. Particularly attractive targets for small-molecule modulation with respect to antiangiogenic and antiproliferative activity include receptor type tyrosine kinases Ret, c-Met, and VEGFR2.

**[0004]** The kinase c-Met is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs) which include Met, Ron and Sea. The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenisis. Binding of HGF to c-Met

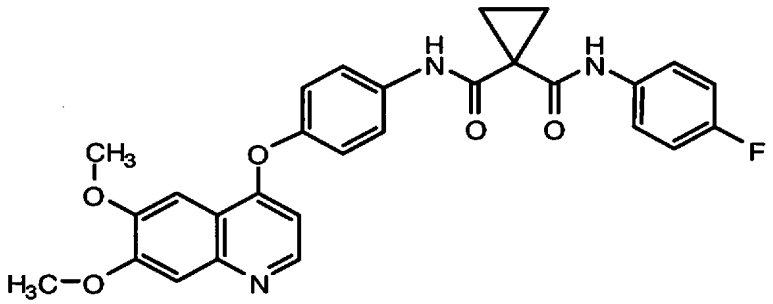
induces activation of the receptor via autophosphorylation resulting in an increase of receptor dependent signaling, which promotes cell growth and invasion. Anti-HGF antibodies or HGF antagonists have been shown to inhibit tumor metastasis in vivo (See: Maulik et al Cytokine & Growth Factor Reviews 2002 13, 41-59). c-Met, VEGFR2 and/or Ret overexpression has been demonstrated on a wide variety of tumor types including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytomas, and glioblastomas. The Ret protein is a transmembrane receptor with tyrosine kinase activity. Ret is mutated in most familial forms of medullary thyroid cancer. These mutations activate the kinase function of Ret and covert it into an oncogene product.

**[0005]** Inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc. Technol. 2001 6, 1005-1024).Kinase KDR (refers to kinase insert domain receptor tyrosine kinase) and flt-4 (fms-like tyrosine kinase-4) are both vascular endothelial growth factor (VEGF) receptors. Inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc. Technol. 2001 6, 1005-1024). EGF and VEGF receptors are desirable targets for small molecule inhibition.

**[0006]** Glioblastoma is the most aggressive form of primary brain tumor, with an incidence of 2.3 per 100,000 persons per year in the United Sates. The median survival time following diagnosis is 12-15 months with current standard of care involving surgery followed by radiation. It has been reported that targeting the MET pathway potentiates GBM response to gamma-radiation (Lal et al, 2005). It has also been report that MET expression correlate with high grade GBM tumors (Hirose et al, 1998) and expression of HGF and MET correlate with malignancy (Koochekpour et al, 1995; Abounader et al, 2001, Uchinokura et al, 2006). It has also been reported that the glioma derived stem cell factor induces angiogenesis within the brain. SCF and VEGF may have complementary roles in the robust angiogenic response in GBM (Sun et al, 2006).

**[0007]** Accordingly, small-molecule compounds that specifically inhibit, regulate and/or modulate the signal transduction of kinases, particularly including Ret, c-Met and VEGFR2 described above, are particularly desirable as a means to treat or prevent disease states associated

with abnormal cell proliferation and angiogenesis. One such small-molecule is N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, which has the chemical structure:




**[0008]** WO 2005/030140 describes the synthesis of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (Examples 25, 37, 38, and 48) and also discloses the therapeutic activity of this molecule to inhibit, regulate and/or modulate the signal transduction of kinases, (Assays, Table 4, entry 289). Compound (I) has been measured to have an c-Met $IC_{50}$ value of 1.3 nanomolar (nM) and a Ret $IC_{50}$ value of 5.2 nanomolar (nM).

**[0009]** Thus, finding new uses of compounds for treating diseases by using new combination therapies is desirable.

## SUMMARY OF THE INVENTION

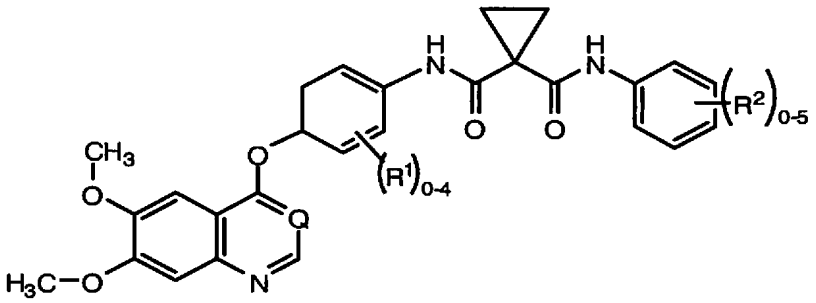
**[0010]** The summary of the invention only summarizes certain aspects of the invention and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below. All references cited in this specification are hereby incorporated by reference in their entirety. In the event of a discrepancy between the express disclosure of this specification and the references incorporated by reference, the express disclosure of this specification shall control.

**[0011]** One aspect of this disclosure relates to methods of treating diseases, as defined in the detailed description herein below. These methods of treatment include administering a Compound of Formula I, wherein the compound of Formula I is as define in the detailed description of the invention, to a patient in need of the treatment, in combination with either

temozolomide (TMZ) and/or radiation therapy (RT) and optionally one or more additional treatment(s), wherein the one or more additional treatment(s) are as described in the detailed description of the invention.

## DETAILED DESCRIPTION OF THE INVENTION

**[0012]** Aspect (I) of this disclosure relates to a method of treating a disease comprising administering to a patient in need of the treatment a compound of Formula I:



I

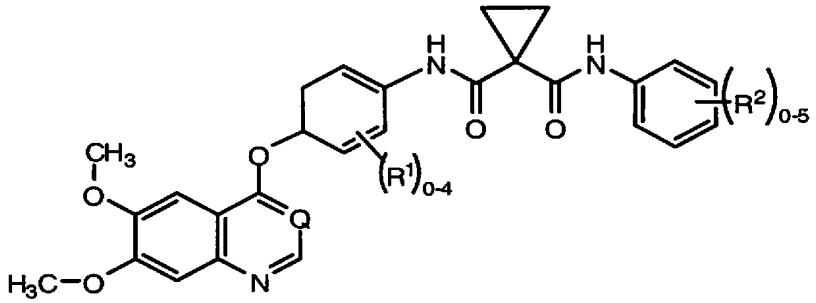
or a pharmaceutically acceptable salt thereof, in combination with temozolomide (TMZ) wherein:

$R^1$ is halo;

$R^2$ is halo; and

Q is CH or N.

**[0013]** Aspect (II) of this disclosure relates to a method of treating a disease comprising administering to a patient in need of the treatment a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, in combination with radiation therapy (RT) wherein:

$R^1$ is halo;

$R^2$ is halo; and

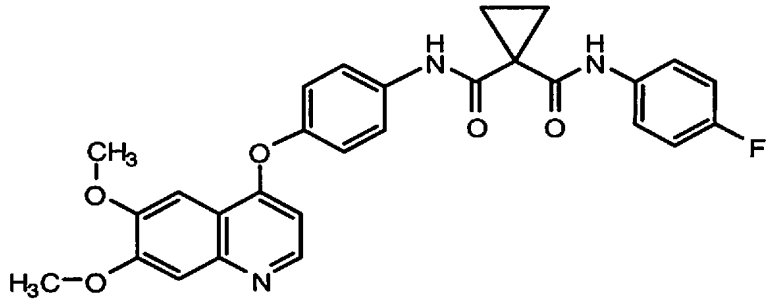
Q is CH or N.

**[0014]** In other embodiments of aspect (I) and Apsect (II) of this disclosure the compound of Formula I, or a pharmaceutically acceptable salt thereof, is a pharmaceutical composition which further comprises a pharmaceutically acceptable carrier, excipient, or diluent.

**[0015]** In other embodiments of Aspect (I), the method further comprises administereing to the patient one or more additional treatment(s), wherein the one or more treatment(s) are selected from (1) surgery, (2) one or more additional chemotherapeutic agent(s), (3) one or more hormone therapy(s), (4) one or more antibody(s), and (5) one or more immunotherapy(ies), (6) radioactive iodine therapy, and (7) radiation.

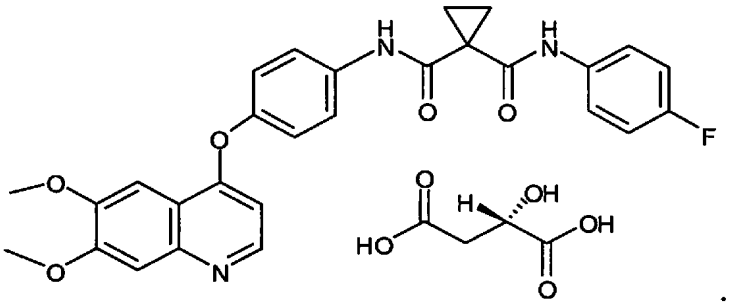
**[0016]** In other embodiments of Aspect (II), the method further comprises administereing to the patient one or more additional treatment(s), wherein the one or more treatment(s) are selected from (1) surgery, (2) one or more additional chemotherapeutic agent(s), (3) one or more hormone therapy(s), (4) one or more antibody(s), and (5) one or more immunotherapy(ies).

**[0017]** In other embodiments of Aspect (I) and Apsect (II), the compound of Formula I in any of the above embodiments is the following compound:




or a pharmaceutical salt thereof.

**[0018]** In other embodiments of Aspect (I) and Apsect (II), the compound of Formula I in any of the above embodiments is the following compound:



[0019] The compound of Formula (I), and all of the embodiments of the compound of Formula (I) as described herein, includes both the recited compounds as well as individual isomers and mixtures of isomers. In each instance, the compound of Formula (I) includes the pharmaceutically acceptable salts, hydrates, and/or solvates of the recited compounds and any individual isomers or mixture of isomers thereof.

## Abbreviations and Definitions

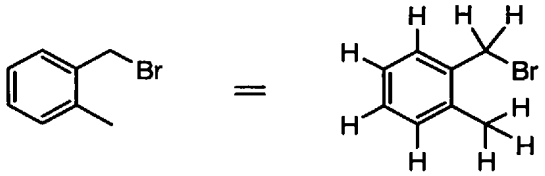
[0020] The following abbreviations and terms have the indicated meanings throughout:

| Abbreviation | Meaning |
|---|---|
| Ac | acetyl |
| Br | broad |
| °C | degrees Celsius |
| c- | cyclo |
| CBZ | CarboBenZoxy = benzyloxycarbonyl |
| d | doublet |
| dd | doublet of doublet |
| dt | doublet of triplet |
| DCM | dichloromethane |
| DME | 1,2-dimethoxyethane |
| DMF | *N,N*-dimethylformamide |
| DMSO | dimethyl sulfoxide |
| dppf | 1,1'-bis(diphenylphosphano)ferrocene |
| EI | Electron Impact ionization |

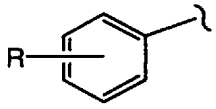
| Abbreviation | Meaning |
|---|---|
| g | gram(s) |
| Gy | Gray unit |
| h or hr | hour(s) |
| HPLC | high pressure liquid chromatography |
| L | liter(s) |
| M | molar or molarity |
| m | Multiplet |
| mg | milligram(s) |
| MGMT | $O^6$-Methylguanine methyltransferase |
| MHz | megahertz (frequency) |
| Min | minute(s) |
| mL | milliliter(s) |
| µL | microliter(s) |
| µM | Micromole(s) or micromolar |
| mM | Millimolar |
| mmol | millimole(s) |
| mol | mole(s) |
| MS | mass spectral analysis |
| N | normal or normality |
| nM | Nanomolar |
| NMR | nuclear magnetic resonance spectroscopy |
| q | Quartet |
| RT | Radiation Therapy |
| s | Singlet |
| t or tr | Triplet |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |

**[0021]** The symbol "-" means a single bond, "=" means a double bond.

**[0022]** When chemical structures are depicted or described, unless explicitly stated otherwise, all carbons are assumed to have hydrogen substitution to conform to a valence of four. For example, in the structure on the left-hand side of the schematic below there are nine hydrogens implied. The nine hydrogens are depicted in the right-hand structure. Sometimes a particular atom in a structure is described in textual formula as having a hydrogen or hydrogens as substitution (expressly defined hydrogen), for example, $-CH_2CH_2-$. It is understood by one of ordinary skill in the art that the aforementioned descriptive techniques are common in the chemical arts to provide brevity and simplicity to description of otherwise complex structures.

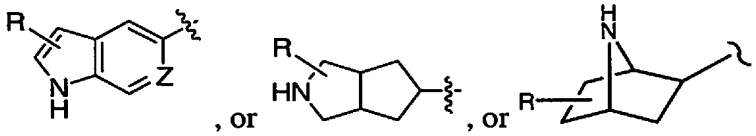


**[0023]** If a group "R" is depicted as "floating" on a ring system, as for example in the formula:



then, unless otherwise defined, a substituent "R" may reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

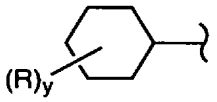
**[0024]** If a group "R" is depicted as floating on a fused ring system, as for example in the formulae:



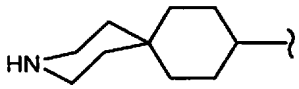
then, unless otherwise defined, a substituent "R" may reside on any atom of the fused ring system, assuming replacement of a depicted hydrogen (for example the -NH- in the formula above), implied hydrogen (for example as in the formula above, where the hydrogens are not shown but understood to be present), or expressly defined hydrogen (for example where in the formula above, "Z" equals =CH-) from one of the ring atoms, so long as a stable structure is

formed. In the example depicted, the "R" group may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formulas depicted above, there may more than one R group ($R_y$), wherein y is an integer of 1 or more. When y is 2, for example, then the two "R's" may reside on any two atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

**[0025]** When a group "R" is depicted as existing on a ring system containing saturated carbons, as for example in the formula:




where, in this example, "y" can be more than one, assuming each replaces a currently depicted, implied, or expressly defined hydrogen on the ring; then, unless otherwise defined, where the resulting structure is stable, two "R's" may reside on the same carbon. A simple example is when R is a methyl group; there can exist a geminal dimethyl on a carbon of the depicted ring (an "annular" carbon). In another example, two R's on the same carbon, including that carbon, may form a ring, thus creating a spirocyclic ring (a "spirocyclyl" group) structure with the depicted ring as for example in the formula:




**[0026]** "Halogen" or "halo" refers to fluorine, chlorine, bromine or iodine.

**[0027]** "Yield" for each of the reactions described herein is expressed as a percentage of the theoretical yield.

**[0028]** "Cancer" refers to cellular-proliferative disease states, including but not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hanlartoma, inesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous

adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis defornians), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastorna multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma], fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; Adrenal Glands: neuroblastoma; and breast cancer. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

**[0029]** "Hormone therapy" or "hormonal therapy" includes, for example, treatment with one or more of the following: steroids (e.g. dexamethasone), finasteride, tamoxifen, and an aromatase inhibitor.

**[0030]** "Patient" for the purposes of the present invention includes humans and other animals, particularly mammals, and other organisms. Thus the methods are applicable to both human therapy and veterinary applications. In another embodiment the patient is a mammal, and in another embodiment the patient is human.

**[0031]** A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference or S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 both of which are incorporated herein by reference.

**[0032]** Examples of pharmaceutically acceptable acid addition salts include those formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, 3-(4-hydroxybenzoyl)benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, p-toluenesulfonic acid, and salicylic acid and the like.

**[0033]** Examples of a pharmaceutically acceptable base addition salts include those formed when an acidic proton present in the parent compound is replaced by a metal ion, such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Specific salts are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to, salts of primary, secondary, and *tert*iary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins. Examples of organic bases include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol,

dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, tromethamine, *N*-methylglucamine, polyamine resins, and the like. Exemplary organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine.

**[0034]** "Platin(s)," and "platin-containing agent(s)" include, for example, cisplatin, carboplatin, and oxaliplatin.

**[0035]** "Prodrug" refers to compounds that are transformed (typically rapidly) *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis in blood. Common examples include, but are not limited to, ester and amide forms of a compound having an active form bearing a carboxylic acid moiety. Examples of pharmaceutically acceptable esters of the compounds of this invention include, but are not limited to, alkyl esters (for example with between about one and about six carbons) the alkyl group is a straight or branched chain. Acceptable esters also include cycloalkyl esters and arylalkyl esters such as, but not limited to benzyl. Examples of pharmaceutically acceptable amides of the compounds of this invention include, but are not limited to, primary amides, and secondary and tertiary alkyl amides (for example with between about one and about six carbons). Amides and esters of the compounds of the present invention may be prepared according to conventional methods. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference for all purposes.

**[0036]** "Taxane(s)" includes, for example, one or more of the following: Paclitaxel (Taxol®) and Docetaxel (Taxotere®).

**[0037]** "Therapeutically effective amount" is an amount of a compound of the invention, that when administered to a patient, ameliorates a symptom of the disease. A therapeutically effective amount is intended to include an amount of a compound alone or in combination with other active ingredients effective to modulate Ret, c-Met, and/or VEGFR2, or effective to treat or prevent cancer. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease state and its severity, the age of the patient to be treated, and the like. The therapeutically effective amount can be

determined routinely by one of ordinary skill in the art having regard to their knowledge and to this disclosure.

**[0038]** "Topoisomerase inhibitor" includes, for example, one or more of the following: amsacrine, camptothecin, etoposide, etoposide phosphate, exatecan, irinotecan, lurtotecan, and teniposide, and topotecan.

**[0039]** "Treating" or "treatment" of a disease, disorder, or syndrome, as used herein, includes (i) preventing the disease, disorder, or syndrome from occurring in a human, i.e. causing the clinical symptoms of the disease, disorder, or syndrome not to develop in an animal that may be exposed to or predisposed to the disease, disorder, or syndrome but does not yet experience or display symptoms of the disease, disorder, or syndrome; (ii) inhibiting the disease, disorder, or syndrome, *i.e.*, arresting its development; and (iii) relieving the disease, disorder, or syndrome, *i.e.*, causing regression of the disease, disorder, or syndrome. As is known in the art, adjustments for systemic versus localized delivery, age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by one of ordinary skill in the art.

## Additional Embodiments of the Invention

**[0040]** In another embodiment of Aspect (I) or Aspect (II) of this disclosure, the disease being treated is selected from astocytoma, glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components.

**[0041]** In another embodiment of Aspect (I) of this disclosure, the method further comprises administering radiation therapy to the patient.

**[0042]** In another embodiment of Aspect (I) of this disclosure, the disease is selected from astocytoma, glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendrogilial components; and the the method further comprises administering radiation therapy to the patient.

**[0043]** In another embodiment of Aspect (I) or Aspect (II) of this disclosure, the disease is selected from astocytoma, glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendrogilial components; and the the method further comprises administering surgury to the patient.

**[0044]** In another embodiment of Aspect (I) of this disclosure, the disease is selected from astocytoma, glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendrogilial components; and the the method further comprises administering radiation therapy and surgery to the patient.

**[0045]** Non-limiting examples of the additional chemotherapeutic agent(s) that can be used in any of the above embodiments include rapamycin, a rapamycin analogue, an alkylating agent(s), a taxane(s), and a platin(s). In chemotherapeutic agent(s) is selected from rapamycin, temozolomide, paclitaxel, docetaxel, carboplatin, cisplatin, oxaliplatin, gefitinib (Iressa®), erlotinib (Tarceva®), Zactima (ZD6474), HKI-272, pelitinib, canertinib, and lapatinib.

**[0046]** A non-limiting example of the antibody that can be used as the one or more additional treatments in Aspect (I) or Aspect (II) of this disclosure is panitumumab.

**[0047]** In another embodiment of Aspect (I) or (II) of this disclosure, the one or more additional treatments is one or more hormone therapy(s). Non-limiting examples of the hormone therapy(s) that can be used in this embodiment include tamoxifen, Toremifene (Fareston), Fulvestrant (Faslodex), Megestrol acetate (Megace), ovarian ablation, Raloxifene, a luteinizing hormone-releasing hormone (LHRH) analog (including goserelin and leuprolide), Megestrol acetate (Megace), and one or more aromatase inhibitor(s); in another embodiment, one or more of the aromatase inhibitor(s) is selected from letrozole (Femara), anastrozole (Arimidex), and exemestane (Aromasin). In another embodiment, one or more of the hormone therapy(s) is selected from tamoxifen and an aromatase inhibitor.

**[0048]** In another embodiment of Aspect (I) or Aspect (II) of this disclosure, the disease is an astrocytic tumor selected from astocytoma, glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components, and the one or more treatment(s) are selected from (1) surgery, (2) radiation, (3) one or more additional chemotherapeutic agent(s), (4) one or more anti-seizure agent(s), and (5) one or more agent(s) to reduce swelling. Non-limiting examples of the radiation treatment that can be used in this embodiment include external beam radiation, interstitial radiotherapy, and stereotactic radiosurgery. Non-limiting examples of the additional chemotherapeutic agent(s) that can be used in this embodiment include carmustine (BCNU), Erlotinib (Tarceva), bevacizumab, gefitinib (Iressa), rapamycin, cisplatin, BCNU, lomustine, procarbazine, and vincristine. A non-limiting examples of the antiseizure agent(s) that can be used in this embodiment is diphenylhydantoin (Dilantin). A non-limiting example of

the agent that can be used to reduce swelling in this embodiment include dexamethasone (Decadron).

**[0049]** In another embodiment of Aspect (I) of this disclosure, the one or more additional treatments are radiation and surgery.

**[0050]** In another embodiment of Aspect (I) of this disclosure, the one or more additional treatments are radiation and one or more additional chemotherapeutic agent(s).

**[0051]** In another embodiment of Aspect (I) or Aspect (II) of this disclosure, the one or more additional treatments are surgery and one or more additional chemotherapeutic agent(s).

**[0052]** In another embodiment, treatment for patients with GB comprises a (1) "concurrent phase," which is followed by a (2) "rest phase," which is followed by a (3) "maintenance phase."

**[0053]** The concurrent phase is followed by a (2) "rest phase which can range from about 2 weeks to about 8 weeks in duration. The rest phase is meant to allow for recovery from delayed toxicity, if present. In another embodiment, the rest phase can range from about 3 weeks to about 6 weeks in duration. In another embodiment, the rest phase is about 4 weeks in duration.

**[0054]** The rest phase is followed by a (3) "maintenance phase," during which patients receive active pharmaceutical ingredients for approximately twelve 28-day cycles, but can vary from about six to about twenty four 28-day cycles. In various embodiments, patients receive different amounts of the compound of Formula I at different times according to the phase of TMZ and radiation therapy.

**Concurrent Phase**

**[0055]** During the concurrent phase, the compound of Formula I, in one embodiment, can be administered to the patient concurrently with RT and TMZ for 3-12 weeks, or 4-10 weeks, or 6-7 weeks. In another embodiment, for patients having a mutation in the MGMT promoter wherein the mutated MGMT promoter is an unmethylated promoter, the compound of Formula I will be administered to the patient concurrently with RT for 6-7 weeks in the concurrent phase. The concurrent phase can range from about 3 weeks to about 12 weeks in duration. In another embodiment, the concurrent phase ranges from about 4 weeks to about 10 weeks in duration. In another embodiment, the concurrent phase ranges from about 6 weeks to about 8 weeks in duration. In another embodiment, the concurrent phase ranges from about 6 weeks to about 7 weeks in duration. During the concurrent phase, active pharmaceutical ingredients are given with (RT). In another embodiment, the active pharmaceutical ingredient(s) in the concurrent phase are TMZ and the compound of Formula I. In another embodiment, the active

pharmaceutical ingredient in the concurrent phase is TMZ provided that the compound of Formula I is at least one of the active pharmaceutical ingredients in the maintenance phase. In another embodiment, the active pharmaceutical ingredient in the concurrent phase is the compound of Formula I.

**Rest Phase**

**[0056]** During the rest phase, no RT, compounds of Formula I, or TMZ is administed to the patient. The rest phase can range from about 2 weeks to about 12 weeks. In another embodiment, the rest phase can range from about 3 weeks to about 6 weeks in duration. In another embodiment, the rest phase range is about 4 weeks in duration.

**Maintenance Phase**

**[0057]** In one embodiment of the maintenance phase, the compound of Formula I is administered to the patient. In another embodiment of the maintenance phase, temozolomide and the compound of Formula I are both administered to the patient. In another embodiment of the maintenance phase, temozolomide and the compound of Formula I are each administered to the patient for a period of time ranging from about 4 months to about 10 months. In another embodiment of the maintenance phase, temozolomide and the compound of Formula I are each administered to the patient for about 4 months. In another embodiment of the maintenance phase, temozolomide and the compound of Formula I are each administered to the patient for about 5 months. In another embodiment of the maintenance phase, temozolomide and the compound of Formula I are each administered to the patient for about 6 months. In another embodiment of the maintenance phase, temozolomide and the compound of Formula I are each administered to the patient for about 7 months. In another embodiment of the maintenance phase, temozolomide and the compound of Formula I are each administered to the patient for about 8 months. In another embodiment of the maintenance phase, temozolomide and the compound of Formula I are each administered to the patient for about 9 months. In another embodiment of the maintenance phase, temozolomide and the compound of Formula I are each administered to the patient for about 10 months. In another embodiment of the maintenance phase, the compound of Formula I is administered to the patient for period of time ranging from about 4 months to about 10 months. In another embodiment of the maintenance phase, the compound of Formula I is administered for about 4 months. In another embodiment of the maintenance phase, the

compound of Formula I is administered for about 5 months. In another embodiment of the maintenance phase, the compound of Formula I is administered for about 6 months. In another embodiment of the maintenance phase, the compound of Formula I is administered for about 7 months. In another embodiment of the maintenance phase, the compound of Formula I is administered for about 8 months. In another embodiment of the maintenance phase the compound of Formula I is administered for about 9 months. In another embodiment of the maintenance phase, the compound of Formula I is administered for 10 months.

**[0058]** During the maintenance phase, the compound of Formula I can be administered daily as a single oral agent as a 10-200 mg dosages (which can be in capsules or tablets). In another embodiment of the maintenance phase, the compound of Formula I can be administered daily as a single oral agent as a 25-125 mg dosage, or 25-100 mg dosage, (which can be in a capsule or tablet). Also during the maintenance phase, TMZ can be administered for 5 consecutive days and repeated every 28 days. TMZ, during the maintenance phase, can be administered to the patient as 5-300 mg dosages (which can be in capsules or tablets) to the patient.

**[0059]** For purposes of this disclosure, for all examples that are disclosed herein that refer to the compound of Formula I or temozolomide in dosage amounts in milligrams (mg), it is to be read as mg of the compound in question, and this dosage amount can be administered in any form, including tablet and capsule form. The examples of capsule or tablet forms, that are within the parenthesis after the dosage amounts, are non-limiting examples of how the dosages can be administered and these examples are meant to be non-limiting. For example, in the above embodiment, TMZ can be administered in other modes in addition to capsules or tablets, which are meant to be only non-limiting examples of how the dosage amount can be administered.

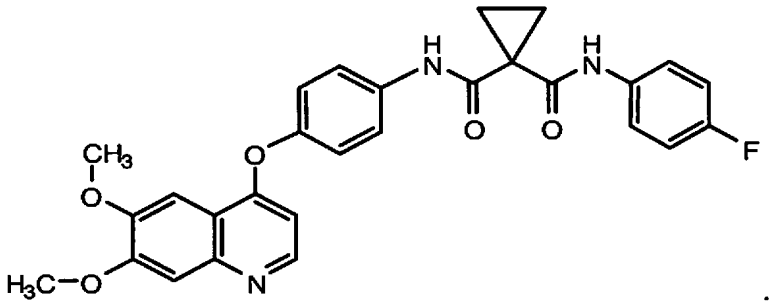
**[0060]** In non-limiting examples in all of the above embodiments (including the concurrent and maintenance phases), the compound of Formula I can be administered in 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 155 mg, 160 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, and 200 mg dosages (which can be in capsules or tablets).

**[0061]** In non-limiting examples in all of the above embodiments (including the concurrent and maintenance phases), TMZ can be administered in 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg,

150 mg, 155 mg, 160 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 205 mg, 210 mg, 215 mg, 220 mg, 225 mg, 230 mg, 235 mg, 240 mg, 245 mg, 250 mg, 255 mg, 260 mg, 265 mg, 260 mg, 275 mg, 280 mg, 285 mg, 290 mg, 295 mg, and 300 mg dosages (which can be in capsules or tablets).

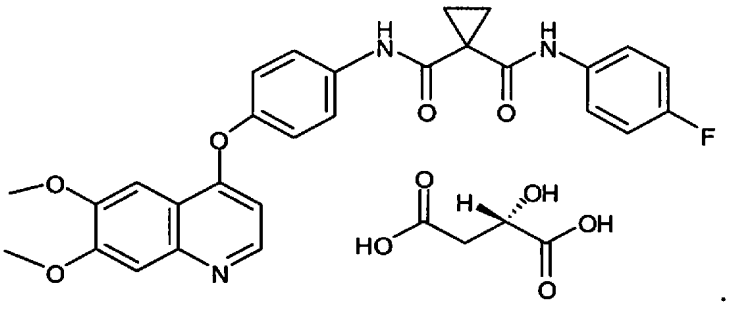
**[0062]** In another embodiment of Aspect (I) or Aspect (II) of this disclosure, the concurrent phase comprises administereing radiation and the compound of Formula I to the patient; the rest phase comprises not administering the compound of Formula I or radiation to the patient; and the maintenance phase comprises administereing the compound of Formula I to the patient. In one subembodiment of this embodiment, the concurrent phase can be 7-8 weeks in duration, the rest phase can be about 4 weeks in duration; and the maintence phase is of a duration sufficient slow down the cancer growth. In another subembodiment of this embodiment, the compound of Formula I is administered to the patient in 25-100 mg dosages, or 25-125 mg dosages, (which can be in capsules or tablets) daily during the concurrent phase; TMZ is administered to the patient in 5-180 mg dosages (which can be in capsules or tablets) daily to the patient during the concurrent phase; RT is administered to the patient during the concurrent phase using 1.8-2 Gy/fraction, daily for 5 days/week for a total dose of up to 60 Gy; the compound of Formula I is administered to the patient in 25-100 mg dosages, or 25-125 mg dosages, (which can be in capsules or tablets) daily during the maintenance phase; and TMZ is administered to the patient in 5-180 mg dosages (which can be in capsules or tablets) for 5 consecutive days and repeated every 28 days until the cancer growth is slowed down.

**[0063]** In other embodiments of any of the above embodiments of Aspect (I) and Aspect (II), the Compound of Formula I is the following compound:




or a pharmaceutical salt thereof.

**[0064]** In another embodiment, the compound of Formula I is the (L)-malate salt form of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide having the following structure:



## General Administration

**[0065]** In one aspect, the invention provides pharmaceutical compositions comprising a compound of Formula I as described above and a pharmaceutically acceptable carrier, excipient, or diluent. In certain other embodiments, administration is by the oral route. Administration of the compound of Formula I, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin dosages (which can be in capsules or tablets), powders, solutions, suspensions, or aerosols, or the like, specifically in unit dosage forms suitable for simple administration of precise dosages.

**[0066]** The compositions will include a conventional pharmaceutical carrier or excipient and a compound of Formula I as the/an active agent, and, in addition, may include carriers and adjuvants, etc.

**[0067]** Adjuvants include preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars,

sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

**[0068]** If desired, a pharmaceutical composition of the compound of Formula I may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylalted hydroxytoluene, etc.

**[0069]** The choice of formulation depends on various factors such as the mode of drug administration (e.g., for oral administration, formulations in the form of tablets, pills or capsules) and the bioavailability of the drug substance. Recently, pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from 10 to 1,000 nm in which the active material is supported on a crosslinked matrix of macromolecules. U.S. Pat. No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability.

**[0070]** Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

**[0071]** One specific route of administration is oral, using a convenient daily dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

**[0072]** Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b)

binders, as for example, cellulose derivatives, starch, alignates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

**[0073]** Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

**[0074]** Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. Such dosage forms are prepared, for example, by dissolving, dispersing, etc., the compound of Formula I, or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like; solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide; oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan; or mixtures of these substances, and the like, to thereby form a solution or suspension.

**[0075]** Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

**[0076]** Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the compound of Formula I with, for example, suitable non-irritating

excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

**[0077]** Dosage forms for topical administration of the compound of Formula I include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this dislcosure.

**[0078]** Compressed gases may be used to disperse the compound of Formula I in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

**[0079]** Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of Formula I, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of a compound(s) of Formula I, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

**[0080]** Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state in accordance with the teachings of this disclosure.

**[0081]** The compounds of this disclosure, or their pharmaceutically acceptable salts or solvates, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states, and the host undergoing therapy. The compound of Formula I can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is an example. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors

including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well known to one of ordinary skill in the art.

**[0082]** If formulated as a fixed dose, such combination products employ the compound of Formula I within the dosage range described above and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of Formula I may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

## General Synthesis

**[0083]** Compounds of this invention can be made by the synthetic procedures described below. These procdures are merely illustrative of some methods by which the compounds of Formula I can be synthesized, and various modifications to these procudures can be made. The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

**[0084]** The disclosure is further illustrated by the following examples, which are not to be construed as limiting the disclosure in scope or spirit to the specific procedures described in them.

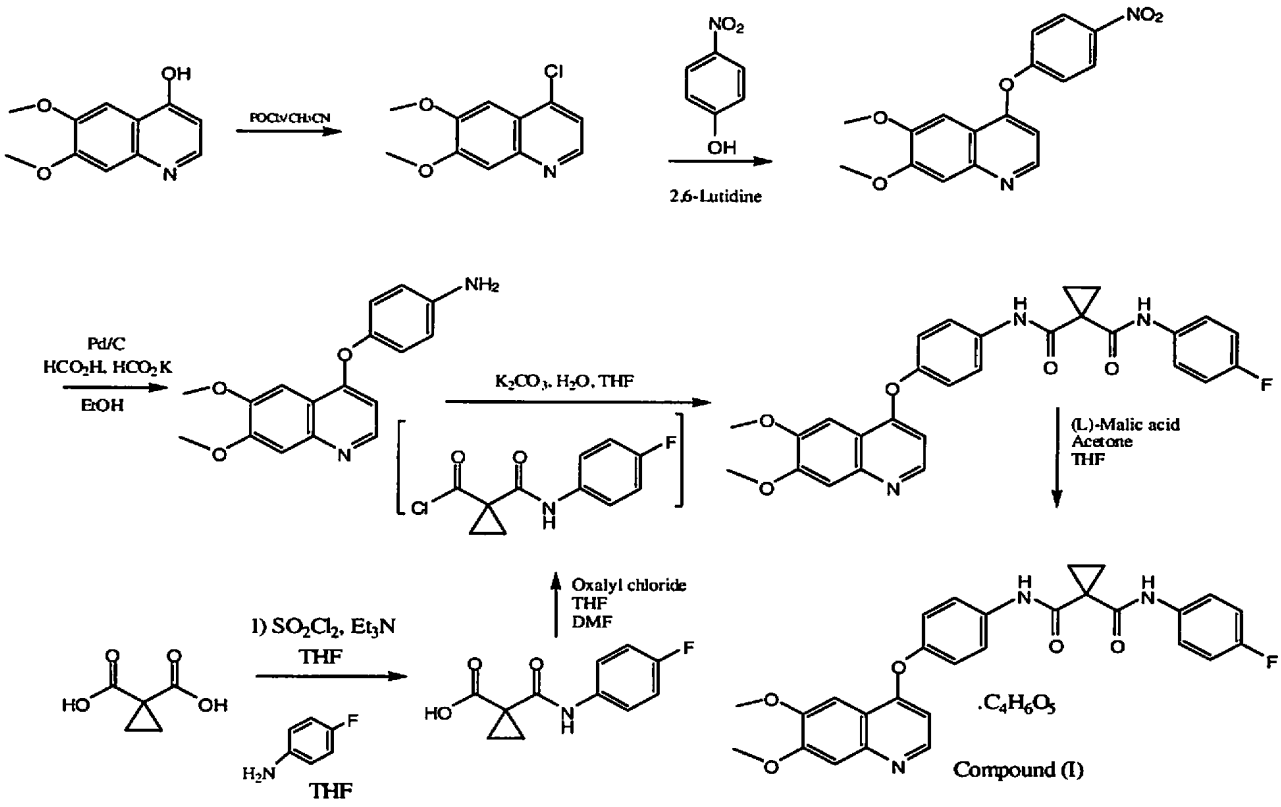
## EXAMPLES

### Example 1A

Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof.

**[0085]** A synthetic route that has been used for the preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Figure 1:

**FIGURE 1**




**[0086]** The process above is described in more detail below.

Preparation of 4–Chloro–6,7–dimethoxy–quinoline

**[0087]** A reactor was charged sequentially with 6,7–dimethoxy–quinoline–4–ol (10.0 kg) and acetonitrile (64.0 L). The resulting mixture was heated to approximately 65°C and phosphorus oxychloride ($POCl_3$, 50.0 kg) was added. After the addition of $POCl_3$, the temperature of the reaction mixture was raised to approximately 80°C. The reaction was deemed complete (approximately 9.0 hours) when <2% of the starting material remained (in process high-performance liquid chromotography [HPLC] analysis). The reaction mixture was cooled to approximately 10°C and then quenched into a chilled solution of dichloromethane (DCM, 238.0 kg), 30% $NH_4OH$ (135.0 kg), and ice (440.0 kg). The resulting mixture was warmed to approximately 14°C, and phases were separated. The organic phase was washed with water (40.0 kg) and concentrated by vacuum distillation with the removal of solvent (approximately 190.0 kg). Methyl-t-butyl ether (MTBE, 50.0 kg) was added to the batch, and the mixture was cooled to approximately 10°C, during which time the product crystallized out. The solids were

recovered by centrifugation, washed with n heptane (20.0 kg), and dried at approximately 40°C to afford the title compound (8.0 kg).

Preparation of 6,7–dimethyl–4–(4-nitro–phenoxy)–quinoline

**[0088]** A reactor was sequentially charged with 4–chloro–6,7–dimethoxy–quinoline (8.0 kg), 4 nitrophenol (7.0 kg), 4 dimethylaminopyridine (0.9 kg), and 2,6 lutidine (40.0 kg). The reactor contents were heated to approximately 147°C. When the reaction was complete (<5% starting material remaining as determined by in process HPLC analysis, approximately 20 hours), the reactor contents were allowed to cool to approximately 25°C. Methanol (26.0 kg) was added, followed by potassium carbonate (3.0 kg) dissolved in water (50.0 kg). The reactor contents were stirred for approximately 2 hours. The resulting solid precipitate was filtered, washed with water (67.0 kg), and dried at 25°C for approximately 12 hours to afford the title compound (4.0 kg).

Preparation of 4–(6,7 –dimethoxy–quinoline–4–yloxy)–phenylamine

**[0089]** A solution containing potassium formate (5.0 kg), formic acid (3.0 kg), and water (16.0 kg) was added to a mixture of 6,7-dimethoxy–4–(4-nitro–phenoxy)–quinoline (4.0 kg), 10% palladium on carbon (50% water wet, 0.4 kg) in tetrahydrofuran (40.0 kg) that had been heated to approximately 60°C. The addition was carried out such that the temperature of the reaction mixture remained approximately 60°C. When the reaction was deemed complete as determined using in-process HPLC analysis (<2% starting material remaining, typically 1 5 hours), the reactor contents were filtered. The filtrate was concentrated by vacuum distillation at approximately 35°C to half of its original volume, which resulted in the precipitation of the product. The product was recovered by filtration, washed with water (12.0 kg), and dried under vacuum at approximately 50°C to afford the title compound (3.0 kg).

Preparation of 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid

**[0090]** Triethylamine (8.0 kg) was added to a cooled (approximately 4°C) solution of commercially available cyclopropane–1,1–dicarboxylic acid (2 1, 10.0 kg) in THF (63.0 kg) at a rate such that the batch temperature did not exceed 10°C. The solution was stirred for approximately 30 minutes, and then thionyl chloride (9.0 kg) was added, keeping the batch temperature below 10°C. When the addition was complete, a solution of 4–fluoroaniline (9.0 kg) in THF (25.0 kg) was added at a rate such that the batch temperature did not exceed 10°C. The mixture was stirred for approximately 4 hours and then diluted with isopropyl acetate (87.0 kg).

This solution was washed sequentially with aqueous sodium hydroxide (2.0 kg dissolved in 50.0 L of water), water (40.0 L), and aqueous sodium chloride (10.0 kg dissolved in 40.0 L of water). The organic solution was concentrated by vacuum distillation followed by the addition of heptane, which resulted in the precipitation of solid. The solid was recovered by centrifugation and then dried at approximately 35°C under vacuum to afford the title compound. (10.0 kg).

Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride

**[0091]** Oxalyl chloride (1.0 kg) was added to a solution of 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (2.0 kg) in a mixture of THF (11 kg) and N, N-dimethylformamide (DMF; 0.02 kg) at a rate such that the batch temperature did not exceed 30°C. This solution was used in the next step without further processing.

Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

**[0092]** The solution from the previous step containing 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride was added to a mixture of 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (3.0 kg) and potassium carbonate (4.0 kg) in THF (27.0 kg) and water (13.0 kg) at a rate such that the batch temperature did not exceed 30°C. When the reaction was complete (in typically 10 minutes), water (74.0 kg) was added. The mixture was stirred at 15–30°C for approximately 10 hours, which resulted in the precipitation of the product. The product was recovered by filtration, washed with a pre made solution of THF (11.0 kg) and water (24.0 kg), and dried at approximately 65°C under vacuum for approximately 12 hours to afford the title compound (free base, 5.0 kg). $^1$H NMR (400 MHz, $d_6$-DMSO): δ 10.2 (s, 1H), 10.05 (s, 1H), 8.4 (s, 1H), 7.8 (m, 2H), 7.65 (m, 2H), 7.5 (s, 1H), 7.35 (s, 1H), 7.25 (m, 2H), 7.15(m, 2H), 6.4 (s, 1H), 4.0 (d, 6H), 1.5 (s, 4H). LC/MS: M+H= 502.

Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L) malate salt

**[0093]** A solution of L-malic acid (2.0 kg) in water (2.0 kg) was added to a solution of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide free base (1 5, 5.0 kg) in ethanol, maintaining a batch temperature of approximately 25°C. Carbon (0.5 kg) and thiol silica (0.1 kg) were then added, and the resulting mixture was heated to approximately 78°C, at which point water (6.0 kg) was added. The reaction mixture was then filtered, followed by the addition of isopropanol (38.0 kg), and was

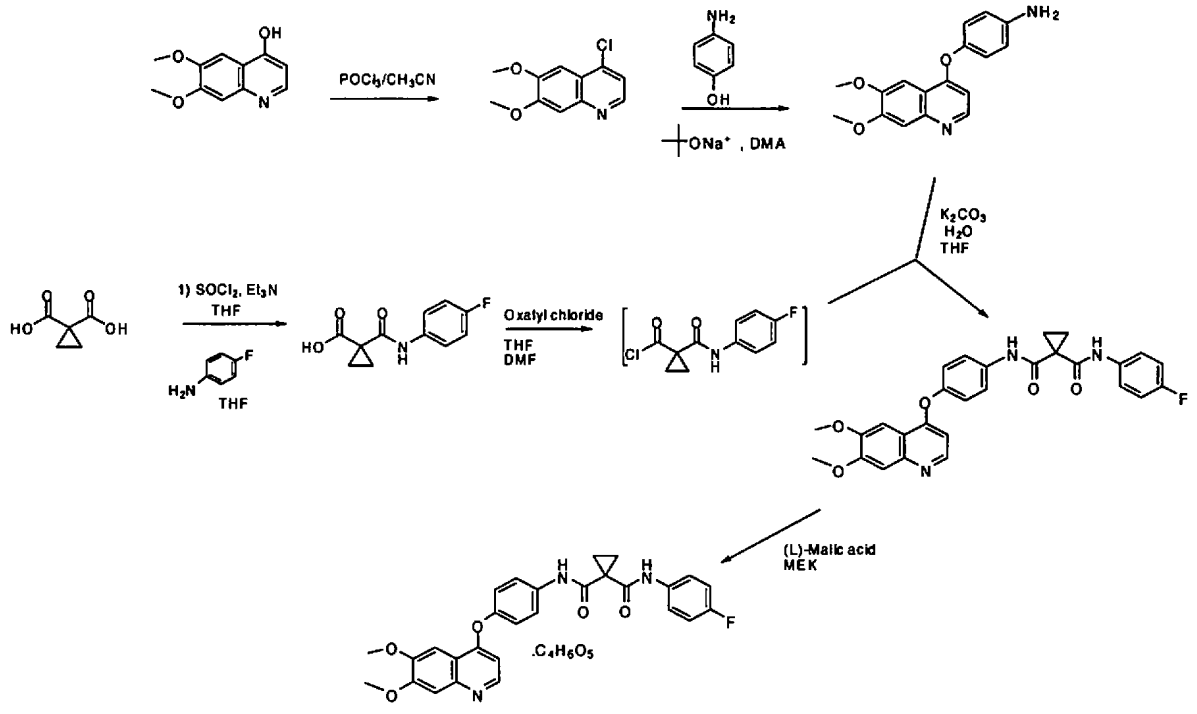
allowed to cool to approximately 25°C. The product was recovered by filtration and washed with isopropanol (20.0 kg) and dried at approximately 65°C to afford the title compound (5.0 kg).

## Example 1B

Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof.

**[0094]** Another synthetic route that has been used for the preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Figure 2:

**Figure 2**




Preparation of 4–Chloro–6,7–dimethoxy–quinoline

**[0095]** A reactor was charged sequentially with 6,7–dimethoxy–quinoline–4–ol (47.0 kg) and acetonitrile (318.8 kg). The resulting mixture was heated to approximately 60 °C and phosphorus oxychloride ($POCl_3$, 130.6 kg) was added. After the addition of $POCl_3$, the temperature of the reaction mixture was raised to approximately 77°C. The reaction was deemed complete (approximately 13 hours) when <3% of the starting material remained (in-process high-

performance liquid chromatography [HPLC] analysis). The reaction mixture was cooled to approximately 2 – 7 °C and then quenched into a chilled solution of dichloromethane (DCM, 482.8 kg), 26 % $NH_4OH$ (251.3 kg), and water (900 L). The resulting mixture was warmed to approximately 20 – 25 °C, and phases were separated. The organic phase was filtered through a bed of AW hyflo super-cel NF (Celite; 5.4 kg) and the filter bed was washed with DCM (118.9 kg). The combined organic phase was washed with brine (282.9 kg) and mixed with water (120 L). The phases were separated and the organic phase was concentrated by vacuum distillation with the removal of solvent (approximately 95 L residual volume). DCM (686.5 kg) was charged to the reactor containing organic phase and concentrated by vacuum distillation with the removal of solvent (approximately 90 L residual volume). Methyl t-butyl ether (MTBE, 226.0 kg) was then charged and the temperature of the mixture was adjusted to – 20 to – 25 °C and held for 2.5 hours resulting in solid precipitate which was then filtered and washed with n-heptane (92.0 kg), and dried on a filter at approximately 25 °C under nitrogen to afford the title compound. (35.6 kg).

Preparation of 4–(6, 7 –Dimethoxy–quinoline–4–yloxy)–phenylamine

**[0096]** 4-Aminophenol (24.4 kg) dissolved in N,N-dimethylacetamide (DMA, 184.3 kg) was charged to a reactor containing 4-chloro-6,7-dimethoxyquinoline (35.3 kg), sodium t-butoxide (21.4 kg) and DMA (167.2 kg) at 20 – 25 °C. This mixture was then heated to 100 – 105°C for approximately 13 hours. After the reaction was deemed complete as determined using in-process HPLC analysis (<2% starting material remaining), the reactor contents were cooled at 15 to 20 °C and water (pre-cooled, 2 to 7 °C, 587 L) charged at a rate to maintain 15 to 30 °C temperature . The resulting solid precipitate was filtered, washed with a mixture of water (47 L) and DMA (89.1 kg) and finally with water (214 L). The filter cake was then dried at approximately 25°C on filter to yield crude 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine (59.4 kg wet, 41.6 kg dry calculated based on LOD). Crude 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine was refluxed (approximately 75 °C) in a mixture of tetrahydrofuran (THF, 211.4 kg) and DMA (108.8 kg) for approximately 1h and then cooled to 0 – 5°C and aged for approximately 1 h after which time the solid was filtered, washed with THF (147.6 kg) and dried on a filter under vacuum at approximately 25°C to yield 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine (34.0 kg).

Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid

**[0097]** Triethylamine (19.5 kg) was added to a cooled (approximately 5 C) solution of cyclopropane–1,1–dicarboxylic acid (24.7 kg) in THF (89.6 kg) at a rate such that the batch temperature did not exceed 5°C. The solution was stirred for approximately 1.3 h, and then thionyl chloride (23.1 kg) was added, keeping the batch temperature below 10 C. When the addition was complete, the solution was stirred for approximately 4 h keeping the temperature below 10 °C. A solution of 4–fluoroaniline (18.0 kg) in THF (33.1 kg) was then added at a rate such that the batch temperature did not exceed 10 C. The mixture was stirred for approximately 10 hours after which the reaction was deemed complete. The reaction mixture was then diluted with isopropyl acetate (218.1 kg). This solution was washed sequentially with aqueous sodium hydroxide (10.4 kg, 50 % dissolved in 119 L of water) further diluted with water (415 L), then with water (100 L) and finally with aqueous sodium chloride (20.0 kg dissolved in 100 L of water). The organic solution was concentrated by vacuum distillation (100 L residual volume) below 40 °C followed by the addition of n-heptane (171.4 kg), which resulted in the precipitation of solid. The solid was recovered by filtration and washed with n-Heptane (102.4 kg) resulting in wet crude, 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (29.0 kg). The crude, 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid was dissolved in methanol (139.7 kg) at approximately 25°C followed by the addition of water (320 L) resulting in slurry which was recovered by filtration, washed sequentially with water (20 L) and n-heptane (103.1 kg) and then dried on the filter at approximately 25 C under nitrogen to afford the title compound (25.4 kg).

Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride

**[0098]** Oxalyl chloride (12.6 kg) was added to a solution of 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (22.8 kg) in a mixture of THF (96.1 kg) and N, N-dimethylformamide (DMF; 0.23 kg) at a rate such that the batch temperature did not exceed 25 C. This solution was used in the next step without further processing.

Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide

**[0099]** The solution from the previous step containing 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride was added to a mixture of compound 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (23.5 kg) and potassium carbonate (31.9 kg) in THF (245.7 kg) and water (116 L) at a rate such that the batch temperature did not exceed 30 °C. When the reaction was complete (in approximately 20 minutes), water (653 L) was added. The mixture was stirred at 20–25 C for approximately 10 hours, which resulted in the precipitation of the product.

The product was recovered by filtration, washed with a pre-made solution of THF (68.6 kg) and water (256 L), and dried first on a filter under nitrogen at approximately 25°C and then at approximately 45 C under vacuum to afford the title compound (41.0 kg, 38.1 kg, calculated based on LOD).

Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide, (L) malate salt

**[00100]** Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide (1-5; 13.3 kg), L-malic acid (4.96 kg), methyl ethyl ketone (MEK; 188.6 kg) and water (37.3 kg) were charged to a reactor and the mixture was heated to reflux (approximately 74°C) for approximately 2 h. The reactor temperature was reduced to 50 to 55°C and the reactor contents were filtered. These sequential steps described above were repeated two more times starting with similar amounts of 1-5 (13.3 kg), L-Malic acid (4.96 kg), MEK (198.6 kg) and water (37.2 kg). The combined filtrate was azeotropically dried at atmospheric pressure using MEK (1133.2 kg) (approximate residual volume 711 L; KF < 0.5 % w/w) at approximately 74°C. The temperature of the reactor contents was reduced to 20 to 25°C and held for approximately 4 hours resulting in solid precipitate which was filtered, washed with MEK (448 kg) and dried under vacuum at 50°C to afford the title compound (45.5 kg).

## EXAMPLE 2

Administration of the compound of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide during the Concurrent Phase to patients.

**[00101]** Example 2A: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 5, 20, 100, 250, 140 and 180 mg dosages (which can be

in capsules or tablets). In another embodiment, the starting dose of TMZ is 75 mg/m$^2$/day with concurrent RT for 6 weeks. For purposes of this patent application, the term "m$^2$" refers to body surface area in patients measured in square meters. Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00102]** Example 2B: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 5 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00103]** Example 2C: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 50 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 5 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00104]** Example 2D: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the

mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 75 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 5 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00105]** Example 2E: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 5 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00106]** Example 2F: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 20 mg dosages (which can be in capsules or tablets). Patients receive

RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00107]** Example 2G: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 50 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 20 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00108]** Example 2H: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 75 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 20 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00109]** Example 2I: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-

bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 20 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00110]** Example 2J: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 20 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00111]** Example 2K: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 100 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00112]** Example 2L: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent

phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 50 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 100 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00113]** Example 2M: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 75 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 100 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00114]** Example 2N: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 100 mg dosages (which can be in capsules or tablets).

Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00115]** Example 2O: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 100 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00116]** Example 2P: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 140 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00117]** Example 2Q: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-

bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 50 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 140 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00118]** Example 2R: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 75 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 140 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00119]** Example 2S: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 140 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00120]** Example 2T: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent

phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 140 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00121]** Example 2U: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 180 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00122]** Example 2V: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 50 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 180 mg dosages (which can be in capsules or tablets). Patients

receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00123]** Example 2W: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 75 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 180 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00124]** Example 2X: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 180 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00125]** Example 2Y: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-

bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 180 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00126]** Example 2Z: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 250 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00127]** Example 2AA: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 50 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 250 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00128]** Example 2AB: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent

phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 75 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 250 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00129]** Example 2AC: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 250 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

**[00130]** Example 2AD: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 250 mg dosages (which can be in capsules or tablets). Patients

receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

## EXAMPLE 3

Administration of the compound of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide during the Concurrent Phase to patients.

**[00131]** Example 3A: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 25 mg and 100 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 5, 20, 100, 250, 140, 180, and 200 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. In another embodiment, TMZ is administered in the amount of 200 $mg/m^2$/day given for 5 consecutive days and repeated every 28 days. For purposes of this disclosure, the term m2 is meant to mean body surface area in patients measured in square meters. The maintenance phase in Example 3A can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00132]** Example 3B: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 25 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 5 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in

Example 3B can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00133]** Example 3C: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 50 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 5 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3C can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00134]** Example 3D: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 75 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 5 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3D can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00135]** Example 3E: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 100 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the

mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 5 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3E can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00136]** Example 3F: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 25 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 20 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3F can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00137]** Example 3G: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 50 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 20 mg dosages (which can be in capsules

or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3G can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 82AD.

**[00138]** Example 3H: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 75 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 20 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3H can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00139]** Example 3I: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 100 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 20 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3I can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00140]** Example 3J: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 25 mg dosages (which can be

in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 100 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3J can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00141]** Example 3K: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 50 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 100 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3K can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00142]** Example 3L: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 75 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in

capsules or tablets). TMZ, when given, is supplied as 100 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3L can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00143]** Example 3M: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 100 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 100 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3M can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00144]** Example 3N: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 25 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 140 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3N can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00145]** Example 3O: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 50 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 140 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3O can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00146]** Example 3P: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 75 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 140 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3P can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00147]** Example 3Q: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 100 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-

bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 140 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3Q can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00148]** Example 3R: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 25 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 180 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3R can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00149]** Example 3S: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 50 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 180 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3S can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E,

2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00150]** Example 3T: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 75 mg dosages (which can be in a capsule or tablet). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 180 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3T can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00151]** Example 3U: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 100 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 180 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3U can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00152]** Example 3V: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 25 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead

receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied in doses of 200 mg/m$^2$/day given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3V can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00153]** Example 3W: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 50 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied in doses of 200 mg/m$^2$/day given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3W can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00154]** Example 3X: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 75 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied in doses of 200 mg/m$^2$/day given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3X can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00155]** Example 3Y: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 100 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied in doses of 200 mg/m$^2$/day given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3Y can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00156]** Example 3Z: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 25 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 250 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3Z can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00157]** Example 3AA: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 50 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 250 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3AA can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

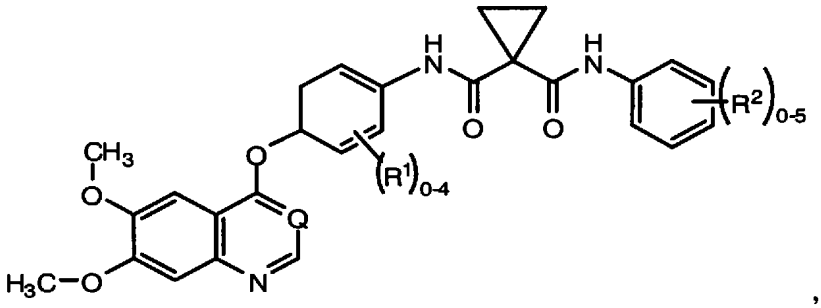
**[00158]** Example 3AB: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 75 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied in doses of 200 mg/m$^2$/day given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3AB can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00159]** Example 3AC: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 100 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 250 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3AC can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

**[00160]** The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

**What is claimed is:**

1. A method of treating cancer, wherein the method comprises administering to a patient in need of the treatment a compound of Formula I:



I

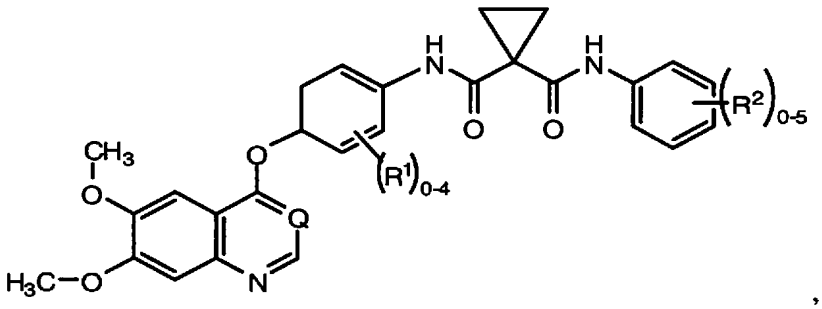
or a pharmaceutically acceptable salt thereof, in combination with temozolomide (TMZ) wherein:

$R^1$ is halo;

$R^2$ is halo; and

Q is CH or N.

2. A method of treating cancer, wherein the method comprises administering to a patient in need of the treatment a compound of Formula I:



I

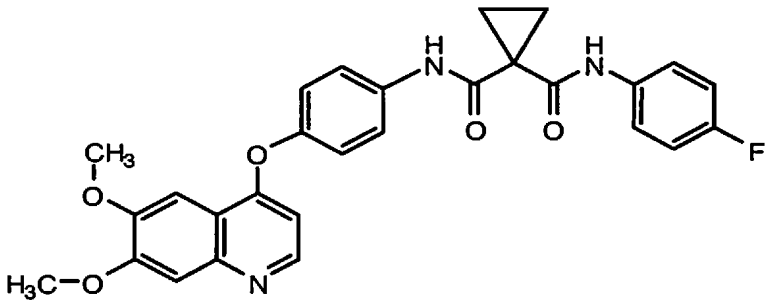
or a pharmaceutically acceptable salt thereof, in combination with radiation therapy (RT) wherein:

$R^1$ is halo;

$R^2$ is halo; and

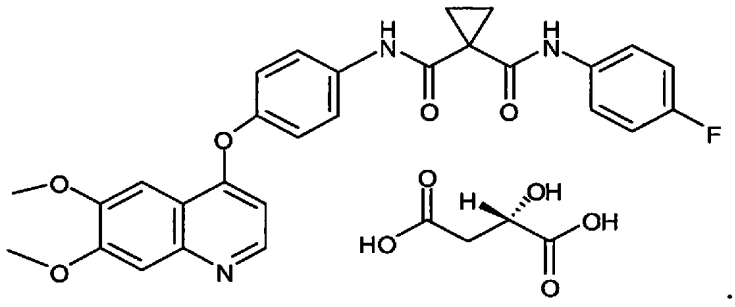
Q is CH or N.

3. The method according to any of claims 1-2, wherein the compound of Formula I is represented by the following structure:



or a pharmaceutically acceptable salt thereof.

4. The method according to any one of claims 1-2, wherein the compound of Formula I is represented by the following structure:



5. The method according to any one of claims 1-3, wherein the the compound of Formula I, or a pharmaceutically acceptable salt thereof, further comprises a pharmaceutically acceptable carrier, excipient, or diluent.

6. The method according to according to any one of claims 1 and 3-5, wherein the one or more additional treatment(s) are selected from (1) surgery, (2) one or more additional chemotherapeutic agent(s), (3) one or more hormone therapy(s), (4) one or more antibody(s), (5) one or more immunotherapy(ies), (6) radioactive iodine therapy, and (7) radiation.

7. The method according to any one of claims 1 and 3-6, wherein the one or more additional treatment(s) is radiation.

8. The method according to any one of claims 1-7 comprising administering a therapeutically effective dose of compound (I) or a pharmaceutically acceptable salt thereof.

9. The method according to any one of claims 1 and 3-8 comprising administering a therapeutically effective dose of TMZ.

10. The method according to any one of claims 2-9 comprising administering a therapeutically effective dose of radiation.

11. The method according to any one of claims 1-10, where the cancer is brain cancer.

12. The method according to any one of claims 1-11, where the cancer is selected from astocytoma, glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components.

13. The method according to any one of claims 1-12, wherein the method comprises (1) a concurrent phase, (2) a rest phase and (3) a maintenance phase, wherein:

the concurrent phase comprises administereing radiation and the compound of Formula I to the patient;

the rest phase comprises not administering the compound of Formula I or radiation to the patient; and

the maintenance phase comprises administereing the compound of Formula I to the patient.

14. The method according to any one of claims 1-13, wherein the concurrent phase is 7-8 weeks in duration, and the rest phase is about 4 weeks in duration; and the maintence phase is of a duration sufficient slow down the cancer growth.

15. The method according to any one of claims 1-14, wherein the compound of Formula I is administered to the patient in 25-125 mg dosages daily during the concurrent phase; TMZ is administered to the patient in 5-180 mg dosages daily to the patient during the concurrent phase; RT is administered to the patient during the concurrent phase using 1.8-2 Gy/fraction, daily for 5 days/week for a total dose of up to 60 Gy; the compound of Formula I is administered to the patient in 25-125 mg dosages daily during the maintenance phase; and TMZ is administered to the patient in 5-180 mg dosages for 5 consecutive days and repeated every 28 days until the cancer growth is slowed down.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/044749

**A. CLASSIFICATION OF SUBJECT MATTER**
INV. A61K31/47 A61K31/517 A61K45/06 A61P35/00
ADD.

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)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data, BEILSTEIN Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 2008/076415 A1 (EXELIXIS INC [US]; LAMB PETER [US]) 26 June 2008 (2008-06-26)<br>claim 1,<br>page 472<br>claims 26, 39 | 2,3,5-8,<br>10 |
| Y | WO 2005/030140 A2 (EXELIXIS INC [US]; BANNEN LYNNE CANNE [US]; CHAN DIVA SZE-MING [US]; C)<br>7 April 2005 (2005-04-07)<br>cited in the application<br>* abstract<br>page 157<br>claim 45 | 1-15 |

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[X] Further documents are listed in the continuation of Box C.

[X] 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 document 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

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 7 September 2010 | 15/09/2010 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Damiani, Federica |

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Form PCT/ISA/210 (second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/044749

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| Y | US 2006/199843 A1 (ZELDIS JEROME B [US])<br>7 September 2006 (2006-09-07)<br>paragraph [0203] | 1-15 |

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/044749

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
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| | | CA | 2671982 A1 | 26-06-2008 |
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| | | JP | 2008505907 T | 28-02-2008 |
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| US 2006199843 A1 | 07-09-2006 | NONE | | |

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18 July 2011 (18.07.2011)

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61/370,843 5 August 2010 (05.08.2010) US

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(74) Agent: **BERVEN, Heidi, M. Ph. D.**; Honigman Miller Schwartz and Cohn LLP, 350 East Michigan Ave., Suite 300, Kalamazoo, MI 49007-3800 (US).

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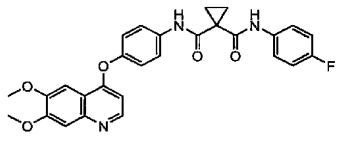
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: C-MET MODULATOR PHARMACEUTICAL COMPOSITIONS



Compound I

(57) Abstract: Pharmaceutical compositions and unit dosage forms comprising Compound (I) are disclosed.

WO 2012/009722 A1

# C-MET MODULATOR PHARMACEUTICAL COMPOSITIONS

## Cross-Reference to Related Applications

**[0001]** This application claims priority to U.S. Application Serial Number 61/365,253, filed July 16, 2010, and Application Serial Number 61/370,843, filed August 5, 2010, the entire contents of each of which are incorporated herein by reference.

## Field of the Invention

**[0002]** Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. One mechanism that can be exploited in cancer treatment is the modulation of protein kinase activity. Signal transduction through protein kinase activation is responsible for many of the characteristics of tumor cells. Protein kinase signal transduction is particularly relevant in, for example, renal cancer, gastric cancer, head and neck cancers, lung cancer, breast cancer, prostate cancer, colorectal cancers, and hepatocellular carcinoma, as well as in the growth and proliferation of brain tumor cells.

**[0003]** Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., DN&P 7(6): 334-339, 1994. Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth that is associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases, including, for example, immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Protein kinases are therefore attractive targets for small molecule drug discovery. Particularly attractive targets for small-molecule modulation with respect to antiangiogenic and antiproliferative activity include receptor type tyrosine kinases c-Met, KDR, c-Kit, Axl, flt-3, and flt-4.

**[0004]** The kinase c-Met is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs), which include Met, Ron, and Sea. The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenesis. Binding of HGF to c-Met induces activation of the receptor via autophosphorylation resulting in an increase of receptor dependent signaling, which promotes cell growth and invasion. Anti-HGF antibodies or HGF antagonists have been shown to inhibit tumor metastasis *in vivo* (See

Maulik et al Cytokine & Growth Factor Reviews 2002 13, 41-59). c-Met overexpression has been demonstrated on a wide variety of tumor types, including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytomas, and glioblastomas. Additionally, activating mutations in the kinase domain of c-Met have been identified in hereditary and sporadic renal papilloma and squamous cell carcinoma. (See, e.g., Maulik et al., Cytokine & growth Factor reviews 2002 13, 41-59; Longati et al., Curr Drug Targets 2001, 2, 41-55; Funakoshi et al., Clinica Chimica Acta 2003 1-23).

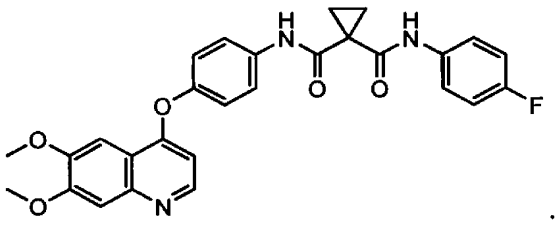
**[0005]** Inhibition of epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and ephrin signal transduction will prevent cell proliferation and angiogenesis, both of which are key cellular processes needed for tumor growth and survival (Matter A., Drug Disc. Technol. 2001 6, 1005-1024). Kinase KDR (refers to kinase insert domain receptor tyrosine kinase) and flt-4 (fms-like tyrosine kinase-4) are both VEGF receptors. EGF and VEGF receptors are desirable targets for small molecule inhibition. All members of the VEGF family stimulate cellular responses by binding to tyrosine kinase receptors (the VEGFRs) on the cell surface, which causes them to dimerize and become activated through transphosphorylation. The VEGF receptors have an extracellular portion with immunoglobulin-like domains, a single transmembrane spanning region, and an intracellular portion containing a split tyrosine-kinase domain. VEGF binds to VEGFR-1 and VEGFR-2. VEGFR-2 is known to mediate almost all of the known cellular responses to VEGF.

**[0006]** Kinase c-Kit (also called stem cell factor receptor or steel factor receptor) is a type 3 receptor tyrosine kinase (RTK) that belongs to the platelet-derived growth factor receptor subfamily. Overexpression of c-Kit and c-Kit ligand has been described in variety of human diseases, including human gastrointestinal stromal tumors, mastocytosis, germ cell tumors, acute myeloid leukemia (AML), NK lymphoma, small-cell lung cancer, neuroblastomas, gynecological tumors, and colon carcinoma. Moreover, elevated expression of c-Kit may also relate to the development of neoplasia associated with neurofibromatosis type 1 (NF-1), mesenchymal tumors GISTs, and mast cell disease, as well as other disorders associated with activated c-Kit.

**[0007]** Kinase Flt-3 (fms-like tyrosine kinase-3) is constitutively activated via mutation, either in the juxtamembrane region or in the activation loop of the kinase domain, in a large proportion of patients with AML (acute myeloid leukemia) (See Reilly, Leuk. Lymphoma, 2003, 44: 1-7).

**[0008]** Accordingly, small-molecule compounds that specifically inhibit, regulate, and/or modulate the signal transduction of kinases, including c-Met, VEGFR2, KDR, c-Kit, Axl, flt-

3, and flt-4, are particularly desirable as a means to treat or prevent disease states that are associated with abnormal cell proliferation and angiogenesis. One such small-molecule is Compound I, know also by its chemical name N-[4-[(6,7-Dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide which has the following chemical structure.



I

[0009] Compound I is disclosed and claimed in WO2005/030140, the entire contents of which is herein incorporated by reference. WO2005/030140 describes the synthesis of compound I (Table 2, Compound I2, Example 48) and discloses the therapeutic activity of this molecule to inhibit, regulate, and/or modulate the signal transduction of kinases (Assays, Table 4, entry 289). Compound I may be used as the malate salt.

[0010] Although therapeutic efficacy is the primary concern for a therapeutic agent, the pharmaceutical composition can be equally important to its development. Generally, drug developers endeavor to discover a pharmaceutical composition that possesses desirable properties, such as satisfactory water-solubility (including rate of dissolution), storage stability, hygroscopicity, and reproducibility, all of which can impact the processability, manufacture, and/or bioavailability of the drug. Accordingly, discovery of pharmaceutical compositions that possess some or all of these desired properties is vital to drug development.

## Summary of the Invention

[0011] These and other needs are met by the present disclosure, which is directed to a pharmaceutical composition comprising Compound I as provided in Table 1.

**Table 1**

| Ingredient | (% w/w) |
|---|---|
| Compound I | 31.68 |
| Microcrystalline Cellulose | 38.85 |
| Lactose anhydrous | 19.42 |
| Hydroxypropyl Cellulose | 3.00 |
| Croscarmellose Sodium | 3.00 |
| **Total Intra-granular** | **95.95** |
| Silicon dioxide, Colloidal | 0.30 |
| Croscarmellose Sodium | 3.00 |
| Magnesium Stearate | 0.75 |
| **Total** | **100.00** |

**[0012]** The disclosure is also directed to a pharmaceutical composition comprising Compound I as provided in Table 2.

**Table 2**

| Ingredient | (% w/w) |
|---|---|
| Compound I | 25.0-33.3 |
| Microcrystalline Cellulose | q.s |
| Hydroxypropyl Cellulose | 3 |
| Poloxamer | 0-3 |
| Croscarmellose Sodium | 6.0 |
| Colloidal Silicon Dioxide | 0.5 |
| Magnesium Stearate | 0.5-1.0 |
| Total | 100 |

**[0013]** The disclosure is further directed to a pharmaceutical composition comprising Compound I as provided in Table 3.

**Table 3**

| **Ingredient** | **Theoretical Quantity (mg/unit dose)** |
|---|---|
| Compound I | 100.0 |
| Microcrystalline Cellulose PH-102 | 155.4 |
| Lactose Anhydrous 60M | 77.7 |
| Hydroxypropyl Cellulose, EXF | 12.0 |
| Croscarmellose Sodium | 24 |
| Colloidal Silicon Dioxide | 1.2 |
| Magnesium Stearate (Non-Bovine) | 3.0 |
| Opadry Yellow | 16.0 |
| **Total** | **416** |

**[0014]** In one aspect, Compound I is present in Tables 1, 2, and 3 as the L-malate salt.

**[0015]** The disclosure is also directed to a process of preparing a pharmaceutical composition according to Tables 1, 2, or 3.

**[0016]** The disclosure is further directed to a method for treating cancer, comprising administering to a patient in need of such treatment a pharmaceutical composition according to Tables 1, 2, or 3. The disclosure is also directed to a method for treating cancer, comprising administering to a patient in need of such treatment a pharmaceutical composition according to Tables 1, 2, or 3 in combination with another therapeutic agent.

**[0017]** In these and other treatment aspects, the cancers to be treated include the cancers disclosed in WO2005/030140, including pancreatic cancer, kidney cancer, liver cancer, prostate cancer, gastric cancer, gastroesophageal cancer, melanoma, lung cancer, breast cancer, thyroid cancer, and astrocytic tumors. More particularly, the cancers include pancreatic cancer, hepatocellular carcinoma (HCC), renal cell carcinoma, castration-resistant prostate cancer (CRPC), gastric or gastroesophageal junction cancer, melanoma, small cell lung cancer (SCLC), ovarian cancer, primary peritoneal or fallopian tube carcinoma, estrogen receptor positive breast cancer, estrogen receptor/progesterone receptor/HER2-negative (triple-negative) breast cancer, inflammatory (regardless of receptor status) breast cancer histology, non-small cell lung cancer (NSCLC), and medullary thyroid cancer.

## Detailed Description

**[0018]** The disclosure is directed to a pharmaceutical formulation comprising Compound I and pharmaceutically acceptable filler, binder, disintegrant, glidant, and lubricant, and optionally a film coating material, each of which are described in greater detail in the following paragraphs. Examples of pharmaceutically acceptable fillers, binders, disintegrants, glidants, lubricants, and film coatings are set forth below and are described in more detail in the Handbook of Pharmaceutical Excipients, Second Edition, Ed. A. Wade and P. J. Weller, 1994, The Pharmaceutical Press, London, England. The term excipient as used herein refers to inert materials which impart satisfactory processing and compression characteristics into the formulation or impart desired physical characteristics to the finished table.

### Compound I Pharmaceutical Composition

**[0019]** The Compound I pharmaceutical composition is a tablet comprising Compound I and excipients selected from the group consisting of a filler, a binder, a disintegrant, a glidant, and a lubricant, and optionally may be coated or uncoated.

### Compound I

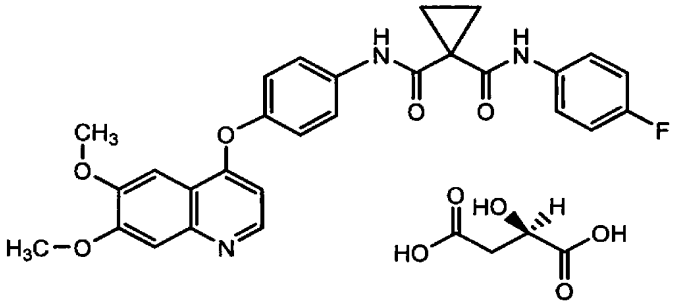
**[0020]** In one embodiment, the pharmaceutical composition comprises Compound I as the free base.

**[0021]** In another embodiment, the pharmaceutical composition comprises Compound I as a hydrate.

**[0022]** In another embodiment, the pharmaceutical composition comprises Compound I as a salt.

**[0023]** In another embodiment, the salt of Compound I is the malate salt.

**[0024]** In another embodiment, the malate salt is the L-malate salt of Compound I, which has the following structure.



**Compound I, L-Malate Salt**

**[0025]** In a further embodiment, the malate salt is the D-malate salt. In a further embodiment, the malate salt is the D,L-malate salt.

**[0026]** The malate salts of Compound I, particularly the L malate salt, have a preferred combination of pharmaceutical properties for development. Under the conditions of 25 °C/60 percent relative humidity (RH) and 40 °C/60 percent RH, the L-malate salt of Compound I showed no change in assay, purity, moisture, and dissolution. The DSC/TGA showed the L-malate salt of Compound I to be stable up to 185 °C. No solvent losses were observed. The uptake of water by the L-malate salt was reversible with a slight hysteresis. The amount of water taken up was calculated at about 0.60 weight percent at 90 percent RH. The L-malate salt was synthesized with good yield and purity greater than 90 percent and had sufficient solubility for use in a pharmaceutical composition. The amount of water associated with this salt was calculated at about 0.5 weight percent by Karl Fischer analysis and correlates with TGA and GVS analysis.

**[0027]** The L-malate salt of Compound I itself, and separately its crystalline and amorphous forms, exhibit beneficial properties over the free base and the other salts of Compound I. For example, the hydrochloride salt of Compound I exhibits undesirable moisture sensitivity, changing phase upon exposure to high humidity (75 percent RH) and high temperature (40°C). The maleate salt had low solubility. The tartrate salt had low crystallinity and low solubility. The phosphate salt exhibited an 8 percent weight gain due to absorption of $H_2O$, the highest among the salts tested.

**[0028]** The water solubility of the various salts was determined using 10 mg solids per mL water. The salts were prepared in a salt screen by reacting an acetone solution of the free base with stock tetrahydrofuran (THF) solutions of a range of acids in about a 1:1 molar ratio. The table below summarizes the water solubility and other data relating to the free base and each salt.

| | Solubility (mg/ml) | |
|---|---|---|
| Free base | <<0.001 | very low solubility |
| Propionate | <<0.001 | no salt formation; mixture of free base and acid |
| Acetate | <<0.001 | no salt formation; mixture of free base and acid |
| Succinate | 0.010 | no salt formation; mixture of free base and acid |
| Benzoate | 0.005 | no salt formation; mixture of free base and acid |
| L-Lactate | 0.015 | Amorphous, salt |
| Pyrroglutamate | 0.44 | Amorphous, salt |
| Glycolate | 0.016 | Amorphous, salt |
| L-Ascorbate | 0.053 | low crystallinity |
| Sulfate | 0.004 | Crystalline salt, low solubility |
| Tosylate | 0.007 | Crystalline salt, low solubility |
| Malonate | 0.003 | Crystalline salt, low solubility |
| 2,5dihydroxybenzoate | <<0.001 | Crystalline Salt, low solubility |
| Fumarate | 0.008 | Crystalline Salt, low solubility |
| Citrate | 0.002 | Crystalline Salt, low solubility |
| Mesylate | 0.175 | Crystalline Salt; possible sulfonic acid formation when made with alcohol |
| Esylate | 0.194 | Crystalline Salt; possible sulfonic acid formation when made with alcohol |
| Benzenesulfonate | 0.039 | Crystalline Salt; possible sulfonic acid formation when made with alcohol |
| Chloride | 0.070 | Crystalline but Hygroscopic; possible hydrate formation. Change in XRPD pattern upon exposure to humidity. |
| Maleate | 0.005 | Crystalline salt, possible hydrate formation; low solubility; different XRPD pattern observed upon scale up (possible polymorphism issue) |
| Phosphate | 0.026 | Crystalline but Hygroscopic. |
| L-Tartrate | 0.014 | Low degree of crystallinity; Hygroscopic. |
| L-Malate | 0.059 | Crystalline; non-Hygroscopic with no indication of hydrate formation. Suitable solubility, and chemical/physical stability. |

**[0029]** In another embodiment, the L-malate salt of Compound I is amorphous or in substantially amorphous form. "Substantially amorphous" means that more than 50 percent of the Compound I L-malate salt is amorphous.

**[0030]** In another embodiment, the L-malate salt of Compound I is crystalline or in substantially crystalline form. "Substantially crystalline" means that more than 50 percent of the L-malate salt of Compound I is crystalline. Two crystalline forms of the L-malate salt of Compound I are the N-1 and/or the N-2 crystalline forms.

**[0031]** Similarly, in another embodiment, the D-malate salt of Compound I is amorphous or in substantially amorphous form. "Substantially amorphous" means that more than 50 percent of the D-malate salt of Compound I is amorphous.

**[0032]** In another embodiment, the D-malate salt of Compound I is crystalline or in substantially crystalline form. "Substantially crystalline" means that more than 50 percent of the D-malate salt of Compound I is crystalline. Two crystalline forms of the D-malate salt of Compound I are the N-1 and/or the N-2 crystalline form.

**[0033]** Similarly, in another embodiment, the D,L-malate salt of Compound I is amorphous or in substantially amorphous form. "Substantially amorphous" means that more than 50 percent of the D,L-malate salt of Compound I is amorphous.

**[0034]** In another embodiment, the D,L-malate salt of Compound I is crystalline or in substantially crystalline form. "Substantially crystalline" means that more than 50 percent of the D,L-malate salt of Compound I is crystalline. Two crystalline forms of the D,L-malate salt of Compound I are the N-1 and/or the N-2 crystalline form.

**[0035]** As is known in the art, the crystalline D malate salt will form the same crystalline form and have the same properties as crystalline Compound I. See WO 2008/083319, which discusses the properties of crystalline enantiomers.

**[0036]** The crystalline N-1 form of the L-malate salt of Compound I and the N-1 form of the D-malate salt of Compound I may be characterized by at least one of the following:

(i) a solid state $^{13}C$ NMR spectrum with peaks at 18.1, 42.9, 44.5, 70.4, 123.2, 156.2, 170.8, 175.7, and 182.1 ppm, ± 0.2 ppm;

(ii) an x-ray powder diffraction pattern (CuKα λ=1.5418Å) comprising four or more peaks selected from: 6.4, 9.0, 12.0, 12.8, 13.5, 16.9, 19.4, 21.5, 22.8, 25.1, and 27.6 °2θ ± 0.2 °2θ, wherein measurement of the crystalline form is at an ambient room temperature;

(iii) a solid state $^{15}N$ NMR spectrum with peaks at 118.6, 119.6, 120.7, 134.8, 167.1, 176.0, and 180 ppm, ±0.2 ppm; and/or

**[0037]** Other solid state properties which may be used to characterize the crystalline N-1 forms of the L-malate salt of Compound I and the D-malate salt of Compound I are discussed in WO 2010/083414, the entire contents of which are incorporated herein by reference, and as described in the Examples below. For crystalline Compound I L-malate salt, the solid state phase and the degree of crystallinity remained unchanged after exposure to 75 percent RH at 40 °C for 1 week.

**[0038]** The crystalline N-2 forms of the L- and D-malate salts of Compound I as described here may be characterized by at least one of the following:

(i) a solid state $^{13}C$ NMR spectrum with peaks at 23.0, 25.9, 38.0, 54.4, 56.11, 41.7, 69.7, 102.0, 122.5, 177.3, 179.3, 180.0, and 180.3, ± 0.2 ppm;

(ii) an x-ray powder diffraction pattern (CuKα λ=1.5418Å) comprising four or more peaks selected from: 6.4, 9.1, 12.0, 12.8, 13.7, 17.1, 20.9, 21.9, 22.6, and 23.7 °2θ ± 0.2 °2θ, wherein measurement of the crystalline form is at an ambient room temperature;

(iii) a solid state $^{15}N$ NMR spectrum with peaks at 118.5, 120.8, 135.1, 167.3, and 180.1 ppm.

**[0039]** Other solid state properties may be used to characterize the crystalline N-2 forms of the L- and D-malate salts of Compound I are discussed in WO 2010/083414.

**[0040]** In another embodiment, the crystalline form of the L-malate salt of Compound I, as described herein in any of the aspects and/or embodiments, is substantially pure N-1 form.

**[0041]** In another embodiment, the disclosure relates to a crystalline form of the L-malate salt of Compound I in substantially pure N-2 form.

**[0042]** Another aspect of this disclosure relates to crystalline forms of the D,L-malate salt of Compound I. The D,L-malate salt is prepared from racemic malic acid. The crystalline N-1 form of the D,L malate salt may be characterized by at least one of the following:

(i) a solid state $^{13}C$ NMR spectrum with four or more peaks selected from 20.8, 26.2, 44.8, 55.7, 70.7, 100.4, 101.0, 114.7, 115.2, 116.0, 119.7, 120.4, 121.6, 124.4, 136.9, 138.9, 141.1, 145.7, 150.3, 156.5, 157.6, 159.6, 165.2, 167.4, 171.2, 176.3, 182.1 ppm, ± 0.2 ppm;

(ii) a powder x-ray diffraction pattern (CuKα λ=1.5418Å) comprising four or more 2θ values selected from: 12.8, 13.5, 16.9, 19.4, 21.5, 22.8, 25.1, and 27.6, ±0.2 °2θ, wherein measurement of the crystalline form is at temperature of room temperature; and/or

(iii) a solid state $^{15}N$ NMR spectrum with peaks at 119.6, 134,7, and 175.5 ppm, ± 0.2 ppm.

**[0043]** Other solid state properties may be used to characterize the crystalline N-1 form of the D,L malate salt of Compound I, as discussed in WO 2010/083414. In one embodiment, the N-1 Form of the D,L malate salt of Compound I is characterized by unit cell parameters approximately equal to the following:

Cell dimensions: a = 14.60 Å
b = 5.20 Å
c = 39.09 Å
α = 90.0°
β = 90.4°
γ = 90.0°
Space group: $P2_1/n$
Molecules of Compound I/unit cell: 4
Volume = 2969 $Å^3$
Density (calculated) = 1.422 $g/cm^3$

**[0044]** The unit cell parameters of Form N-1 of the D,L malate salt of Compound I were measured at a temperature of approximately 25°C, *e.g.*, ambient or room temperature.

**[0045]** Each of the N-1 and N-2 crystalline forms of the L-malate salt and the D-malate salt of Compound I and the crystalline form N-1 of the D,L malate salt of Compound I have unique characteristics that can distinguish them one from another. These characteristics can be understood by comparing the physical properties of the solid state forms. For example, Table 4 lists characteristic XRPD peak positions (°2θ±0.2 °2θ) for the crystalline D,L malate salt of Compound I, Form N-1 and Forms N-1 and N-2 of the crystalline L-malate salt of Compound I. Amorphous forms do not display reflection peaks in their XRPD patterns.

**Table 4**

**Characteristic diffraction peak positions (degrees 2θ±0.2 ) @ RT, based on pattern collected with a diffractometer (CuKα) with a spinning capillary.**

| Compound I L-Malate Salt Form N-1 | Compound I L-Malate Salt Form N-2 | Compound (III) D,L Malate Salt Form N-1 |
|---|---|---|
| 6.4 | 6.4 | 6.4 |
| 9.0 | 9.1 | 9.1 |
| 12.0 | 12.0 | 12.1 |
| 12.8 | 12.8 | 12.8 |
| 13.5 | 13.7 | 13.6 |
| 16.9 | 17.1 | 17.1 |
| 19.4* | 20.9* | 19.3 |
| 21.5* | 21.9* | 21.4 |
| 22.8* | 22.6 | 22.8 |
| 25.1* | 23.7 | 25.1 |
| 27.6* | -- | 27.6 |

*unique reflections between Compound I L-Malate Salt, Form N-1 and Compound I, L-Malate Salt, Form N-2.

**[0046]** The unique reflections between Forms N-1 and N-2 of the crystalline D-malate salt of Compound I are designated by an asterisk (*). As discussed above, the D-malate salt of Compound I is an enantiomer of the L-malate salt of Compound I and thus, Form N-1 of the D-malate salt of Compound I will have the same characteristic reflection pattern and unique peaks as those listed in Table 4 for the L-malate salt of Compound I, Form N-1. Likewise, Form N-2 of the D-malate salt of Compound I will have the same characteristic reflection pattern and unique peaks as those listed in Table 2 for the L-malate salt of Compound I, Form N-2. The L-and D-malate salts of Compound I are distinct from one another based on their absolute stereochemistry, i.e., the L-malate salt versus the D-malate salt, respectively. The crystalline D,L malate salt of Compound I, Form N-1, is distinct as the D,L-malate salt.

**[0047]** The characteristic peaks from the solid state NMR may also serve to distinguish the crystalline and amorphous forms disclosed herein. For example, Table 5 lists characteristic solid state $^{13}C$ NMR peaks for the crystalline D,L-malate salt of Compound I, Form N-1, crystalline L-malate salt of Compound I, Forms N-1 and N-2, and the amorphous form of Compound I.

**Table 5**

| **Solid State Carbon-13 NMR Resonances (ppm, ±0.2 ppm)** | | | |
|---|---|---|---|
| (I) Form N-1 | (I), Form N-2 | (III), Form N-1 | (I), Amorphous |
| 18.1 | 23.0 | 20.8 | 27.2 |
| 42.9 | 25.9 | 26.2 | 33.8 |
| 44.5 | 38.0 | 44.8 | 142.9 |
| 54.4 | 54.4 | 70.7 | -- |
| 56.1 | 56.1 | 114.7 | -- |
| 70.4 | 41.7 | 141.1 | -- |
| 123.2 | 69.7 | 145.7 | -- |
| 156.2 | 102.0 | 176.3 | -- |
| 170.8 | 122.5 | 182.1 | -- |
| 175.7 | 177.3 | -- | -- |
| 182.1 | 179.3 | -- | -- |
| -- | 180.0 | -- | -- |
| -- | 180.3 | -- | -- |

**[0048]** The solid state $^{19}F$ and $^{15}N$ NMR spectra, discussed below, provide data for similar comparison and characterization. As discussed above, being an enantiomer of the L-

malate salt of Compound I, crystalline Forms N-1 and N-2 and the amorphous form of the D-malate salt of Compound I have the same solid state NMR resonances, and unique peaks between them, as those provided for Forms N-1 and N-2 of crystalline L-malate salt of Compound I.

**[0049]** The crystalline form of the L-malate salt and/or the D-malate salt of Compound I can occur as mixtures. The mixtures may have from greater than zero weight percent to less than 100 weight percent of the L-malate salt form and from less than 100 weight percent to greater than zero weight percent D-malate salt form, based on the total weight of L-malate salt form and D-malate salt form. In another embodiment, the mixture comprises from about 1 to about 99 weight percent of the L-malate salt form and from about 99 to about 1 weight percent of the D-malate salt form, based on the total weight of the L-malate salt form and the D-malate salt form in said mixture. In a further embodiment, the mixture comprises from about 90 weight percent to less than 100 weight percent L-malate salt form and from greater than zero weight percent to about 10 weight percent D-malate salt form, based on the total weight of the L-malate salt form and the D-malate salt form. Accordingly, the mixture may have 1 to 10 percent by weight of the L-malate salt form; 11 to 20 percent by weight of the L-malate salt form; 21 to 30 percent by weight of the L-malate salt form; 31 to 40 percent by weight of the L-malate salt form; 41 to 50 percent by weight of the L-malate salt form; 51 to 60 percent by weight of the L-malate salt form; 61 to 70 percent by weight of the L-malate salt form; 71 to 80 percent by weight of the L-malate salt form; 81 to 90 percent by weight of the L-malate salt form; or 91 to 99 percent by weight of the L-malate salt form with the remaining weight percentage of malate salt being that of the D-malate salt form.

**Filler**

**[0050]** As indicated above, the pharmaceutical composition containing Compound I comprises a filler. Fillers are inert ingredients added to adjust the bulk in order to produce a size practical for compression. Examples of fillers include sodium starch glycolate, corn starch, talc, sucrose, dextrose, glucose, lactose, xylitol, fructose, sorbitol, calcium phosphate, calcium sulfate, calcium carbonate, and the like, or mixtures thereof. Microcrystalline cellulose may also be used as a filler and may be any suitable form of microcrystalline cellulose as is known and used in the tabletting art. Preferably, a mixture of lactose and microcrystalline cellulose is used as the filler. In one embodiment, the lactose is anhydrous lactose sold as Lactose 60M, which is readily commercially available from a number of

suppliers. In one embodiment, the microcrystalline cellulose is Avicel PH-102, which is also commercially available.

**[0051]** Preferably, filler(s) are present in an amount of from about 50 to about 70 percent, and more preferably from about 57 to about 67 percent, by weight on a solids basis of the directly compressible formulation. Preferably, lactose is present in an amount of from about 18 to 22 percent by weight. Preferably, the microcrystalline cellulose is present in an amount of from about 38 to 40 percent by weight.

**Binder**

**[0052]** The pharmaceutical composition containing Compound I also comprises a binder. Binders are added to powders to impart cohesive qualities to the powder, which allows the compressed tablet to retain its integrity. The binder can be any pharmaceutically acceptable binder available in the tabletting art, such as acacia, alginic acid, carbomer, carboxymethylcellulose sodium, dextrin, ethylcellulose, gelatin, guar gum, hydrogenated vegetable oil (type I), hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, liquid glucose, magnesium aluminaum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone, pregelatinized starch, sodium alginate, starch, zein, and the like, or mixtures thereof.

**[0053]** The preferred binder is hydroxypropyl cellulose preferably in an amount of from about 2 to about 4 percent by weight on a solid basis of the directly compressible formulation. In one embodiment, the hydroxypropyl cellulose is commercially available Klucel EXF.

**Disintegrant**

**[0054]** The pharmaceutical composition containing Compound I also comprises a disintegrant. A disintegrant is a substance or a mixture of substances added to facilitate breakup or disintegrate after administration. The disintegrant may be any pharmaceutically acceptable disintegrant available in the tabletting art, including alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium, crospovidone, guar gum, magnesium aluminum silicate, methylcellulose, microcrystalline cellulose, polyacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, starch, and the like, or mixtures thereof.

[0055] The preferred disintegrant is croscarmellose sodium, in an amount of from about 4 to about 8 percent by weight, on a solid basis of the directly compressible formulation. In one embodiment, the croscarmellose sodium is commercially available Ac-Di-Sol.

**Glidant**

[0056] The pharmaceutical composition containing Compound I also comprises a glidant. The glidant may be any pharmaceutically acceptable glidant which contributes to the compressibility, flowability, and homogeneity of the formulation and which minimizes segregation and does not significantly interfere with the release mechanism of the binders as set forth above. Preferably, the glidant is selected to improve the flow of the formulation. Silicon dioxide, particularly colloidal silicon dioxide, is preferred as a glidant.

[0057] The glidant is used in an amount of from about 0.2 to about 0.6 percent by weight on a solid basis of the directly compressible formulation.

**Lubricant**

[0058] The pharmaceutical composition containing Compound I also comprises a lubricant. Lubricants are employed to prevent adhesion of the tablet material to the surface of dyes and punches. The lubricant may be any pharmaceutically acceptable lubricant which substantially prevents segregation of the powder by contributing to homogeneity of the formulation and which exhibits good flowability. Preferably, the lubricant functions to facilitate compression of the tablets and ejection of the tablets from the die cavity. Such lubricants may be hydrophilic or hydrophobic, and examples include magnesium stearate, Lubritab.RTM., stearic acid, talc, and other lubricants known in the art or to be developed which exhibit acceptable or comparable properties, or mixtures thereof. Examples of lubricants include calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc, zinc stearate, and the like, or mixtures thereof.

[0059] The lubricant should be selected to aid in the flow of the powder in the hopper and into the die. Magnesium stearate exhibits excellent properties in combination with the other preferred excipients of the formulation. Magnesium stearate contributes to reducing friction between the die wall and tablet formulation during compression, as well as to the easy ejection of the Compound I tablets. It also resists adhesion to punches and dies.

[0060] Preferably, the lubricant is magnesium stearate (non-bovine) used in an amount of from about 0.5 to about 1.0 percent by weight on a solid basis of the directly compressible formulation.

**Film Coating**

[0061] The pharmaceutical composition containing Compound I also comprises an optional film coating. The film coat concentration can be about 1 to about 10 percent by weight on a solid basis of the directly compressible formulation. Film coating suspensions may include combinations of the following components: hypromeollose, carboxymethylcellulose sodium, carnauba wax, cellulose acetate phthalate, cetyl alcohol, confectioner's sugar, ethyl cellulose, gelatin, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, liquid glucose, maltodextrin, methyl cellulose, microcrystalline wax, Opadry and Opadry II, polymethacrylates, polyvinyl alcohol, shellac, sucrose, talc, titanium dioxide, and zein.

[0062] Preferably the film coating comprises commercially available Opadry Yellow. .

[0063] In one embodiment, the tablet composition comprises

30-32 percent by weight of Compound I in at least one of the forms disclosed herein;

50-70 percent by weight of a filler;

2-4 percent by weight of a binder;

4-8 percent by weight a disintegrant; and

0.2-0.6 percent by weight of a glidant; and 0.5-1 percent by weight of a lubricant.

[0064] In another embodiment, the tablet composition comprises:

30-32 percent by weight of Compound I in at least one of the forms disclosed herein;

50-70 percent by weight of a filler;

2-4 percent by weight of a binder;

4-8 percent by weight a disintegrant; and

0.2-0.6 percent by weigh of a glidant; and 0.5-1 percent by weight of a lubricant; wherein the composition is coated.

[0065] In another embodiment, the tablet composition comprises:

| Component | Weight/Weight Percent |
|---|---|
| Compound I | 25-29 |
| Microcrystalline Cellulose | q.s. |
| Lactose Anhydrous | 40-44 |
| Hydroxypropyl Cellulose | 2-4 |
| Croscarmellose Sodium | 2-8 |
| Colloidal Silicon Dioxide | 0.1-0.4 |
| Magnesium Stearate | 0.7-0.9 |
| Total | 100 |

[0066] In another embodiment, the tablet compositions of this disclosure contain from 10 to about 200 mg of Compound I in at least one of the forms described herein. In another embodiment, the tablet compositions of this disclosure contain from 20 to 100 mg of Compound I. In another embodiment, the tablet compositions contain 20, 25, 50, 60, 75, 80, or 100 mg of Compound I.

[0067] In other embodiments, the tablet compositions are summarized in Tables 1, 2, and 3. The compound I used in these and other compositions disclosed herein is the L-malate salt Compound I. In the tables, the weight of Compound I refers to the amount of N-[4-[(6,7-Dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide in the tablet. The skilled artisan will recognize that a certain amount of the Compound I L-malate salt is required to provide the weights listed in the tables. Thus, for example, in Table 3, 126.7 mg of Compound I L-malate salt is required to provide100 mg of Compound I. Proportionally smaller or larger amounts of Compound I L-malate salt are required for tablet compositions containing less or more of Compound I.

**Process**

[0068] In another aspect, the disclosure is directed to a process for making pharmaceutical formulations comprising Compound I. In one embodiment, the formulation is a tablet formulation.

[0069] In another embodiment, the process comprises mixing Compound I with one or more of the pharmaceutical excipients. The mixture is then taken up in an aqueous solution containing a binder to form a binder solution. The binder solution is granulated using a granulation technique known in the art. For example, the granulation method may comprise

wet high shear granulation using a wet high shear granulator. The resulting wet granules are then screened and dried using fluid bed drying or the like. The dried granules are then milled. The resulting dry milled granules are then mixed with a glidant and a disintegrant to form an extra-granular blend. A lubricant is then blended into the extraganular blend to form the final blend. The final blend is subsequently compressed to form the compressed tablet, which may be film coated.

**[0070]** More particularly, the process comprises delumping Compound I as needed prior to mixing with the excipients. Delumping ensures that the Compound I mixes homogeneously with the other excipients during the formulation process. Delumped Compound I is then mixed with microcrystalline cellulose, such as Avicel PH102, lactose (anhydrous, 60M), and croscarmellose sodium. This mixture is then combined with EXF grade hydroxypropoyl cellulose in water to form a binder solution, which is then wet high shear granulated. The resulting wet granules are wet screened and then fluid bed dried according to methods available to the skilled artisan. The resulting dried granules are milled and combined with colloidal silicon dioxide and croscarmellose sodium. Magnesium stearate is added to the mixture. This final blend is then ready for tablet compression. The resulting uncoated core tablets are subsequently film coated. The film coating comprises Opadry Yellow, which contains hypromellose, titanium dioxide, triacetin, and iron oxide yellow.

**[0071]** More particularly, the formulation process comprises:

a) Delumping unmilled Compound I;

b) Premixing the delumped Compound I with Avicel PH102, lactose anhydrous 60M, and croscarmellose sodium to form a binder solution;

c) Wet high shear granulation of the binder solution to produce wet granules;

d) Wet screening of the wet granules to produce wet screened granules;

e) Fluid bed drying of the wet screened granules to produce dried granules;

f) Dry milling of the dried granules to produce dried milled granules;

g) Blending the dried milled granules with colloidal silicon and croscarmellose to produce an extragranular blend;

h) Lubricant blending of the extragranular blend and magnesium stearate to produce a final blend;

i) Tablet compression of the final blend to form an uncoated core tablet; and

j) Film coating of the uncoated core tablet.

**Methods of Treatment**

**[0072]** Another aspect of this disclosure relates to a method of treating cancer, using a pharmaceutical composition containing Compound I in at least one of its forms, either alone or in combination with another therapeutic agent. The cancer being treated is selected from stomach cancer, esophageal carcinoma, kidney cancer, liver cancer, ovarian carcinoma, cervical carcinoma, large bowel cancer, small bowel cancer, brain cancer (including astrocytic tumor, which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components), lung cancer (including non-small cell lung cancer), bone cancer, prostate carcinoma, pancreatic carcinoma, skin cancer, bone cancer, lymphoma, solid tumors, Hodgkin's disease, non-Hodgkin's lymphoma, or thyroid cancer (including medullary thyroid cancer). More particularly, the cancer is pancreatic cancer, hepatocellular carcinoma (HCC), renal cell carcinoma, castration-resistant prostate cancer (CRPC), gastric or gastroesophageal junction cancer, melanoma, small cell lung cancer (SCLC), ovarian cancer, primary peritoneal or fallopian tube carcinoma, estrogen receptor positive breast cancer, estrogen receptor/progesterone receptor/HER2-negative (triple-negative) breast cancer, inflammatory (regardless of receptor status) breast cancer, non-small cell lung cancer (NSCLC), or medullary thyroid cancer.

**[0073]** Tyrosine kinase inhibitors have also been used to treat non-small cell lung cancer (NSCLC). Gefitinib and erlotinib are angiogenesis inhibitors that target receptors of an epidermal growth factor called tyrosine kinase. Erlotinib and Gefitinib are currently being used for treating NSCLC. Another aspect of this disclosure relates to a method of treating non-small cell lung cancer (NSCLC) comprising administering to the subject in need of the treatment a therapeutically effective amount of Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein, optionally in combination with Erlotinib or Gefitinib. In another embodiment, the combination is with Erlotinib.

**[0074]** In another embodiment, the cancer is non-small cell lung cancer (NSCLC), and the method comprises administering to the subject in need of the treatment a therapeutically effective amount of Erlotinib or Gefitinib in combination with at least one of the forms of Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein. The method of treatment may be practiced by administering a tablet formulation of at Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein.

**[0075]** Another aspect of this disclosure relates to a method of treating an astrocytic tumor (which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma

with oligodendroglial components) comprising administering to the subject in need of the treatment a therapeutically effective amount of Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein.

**[0076]** Another aspect of this disclosure relates to a method of treating thyroid cancer (including medullary thyroid cancer) comprising administering to the subject in need of the treatment a therapeutically effective amount of Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein.

**[0077]** Another aspect of this disclosure relates to a method of treating hepatocellular carcinoma comprising administering to the subject in need of the treatment a therapeutically effective amount of Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein.

**[0078]** Another aspect of this disclosure relates to a method of treating renal cell carcinoma comprising administering to the subject in need of the treatment a therapeutically effective amount of Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein.

**[0079]** Another aspect of this disclosure relates to a method of treating castration resistant prostate cancer comprising administering to the subject in need of the treatment a therapeutically effective amount of Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein. The amount administered can be a therapeutically effective amount.

**[0080]** Another aspect of this disclosure relates to a method of breast cancer comprising administering to the subject in need of the treatment a therapeutically effective amount of Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein.

**[0081]** Another aspect of this disclosure relates to a method of treating ovarian cancer comprising administering to the subject in need of the treatment a therapeutically effective amount of Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein.

**[0082]** Another aspect of this disclosure relates to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities. The method comprises administering to the subject in need of the treatment a therapeutically effective amount of Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein.

**[0083]** A "therapeutically effective amount of the active compounds", or a crystalline or amorphous form of the active compound(s) to inhibit, regulate, and/or modulate the signal transduction of kinases (discussed here concerning the pharmaceutical compositions) refers to an amount sufficient to treat a patient suffering from any of a variety of cancers associated with abnormal cell proliferation and angiogenesis. A therapeutically effective amount according to this disclosure is an amount therapeutically useful for the treatment or prevention of the disease states and disorders discussed herein. Compound I possess therapeutic activity to inhibit, regulate, and/or modulate the signal transduction of kinases such as described in WO 2005/030140.

**[0084]** The actual amount required for treatment of any particular patient will depend upon a variety of factors, including the disease state being treated and its severity; the specific pharmaceutical composition employed; the age, body weight, general health, sex, and diet of the patient; the mode of administration; the time of administration; the route of administration; the rate of excretion of the active compound(s), or a crystalline form of the active compound(s), according to this disclosure; the duration of the treatment; any drugs used in combination or coincidental with the specific compound employed; and other such factors well known in the medical arts. These factors are discussed in Goodman and Gilman's "The Pharmacological Basis of Therapeutics," Tenth Edition, A. Gilman, J.Hardman and L. Limbird, eds., McGraw-Hill Press, 155-173, 2001, which is incorporated herein by reference. The active compound(s) , or a crystalline form of active compound(s), according to this disclosure, and pharmaceutical compositions comprising them, may be used in combination with anticancer or other agents that are generally administered to a patient being treated for cancer. They may also be co-formulated with one or more of such agents in a single pharmaceutical composition.

## EXAMPLES

**[0085]** The disclosure is illustrated further by the following examples in Scheme 1 and the description thereof, which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the invention, as demonstrated by the following examples. Those skilled in the art will also recognize that it may be necessary to utilize different solvents or reagents to achieve some of the above transformations.

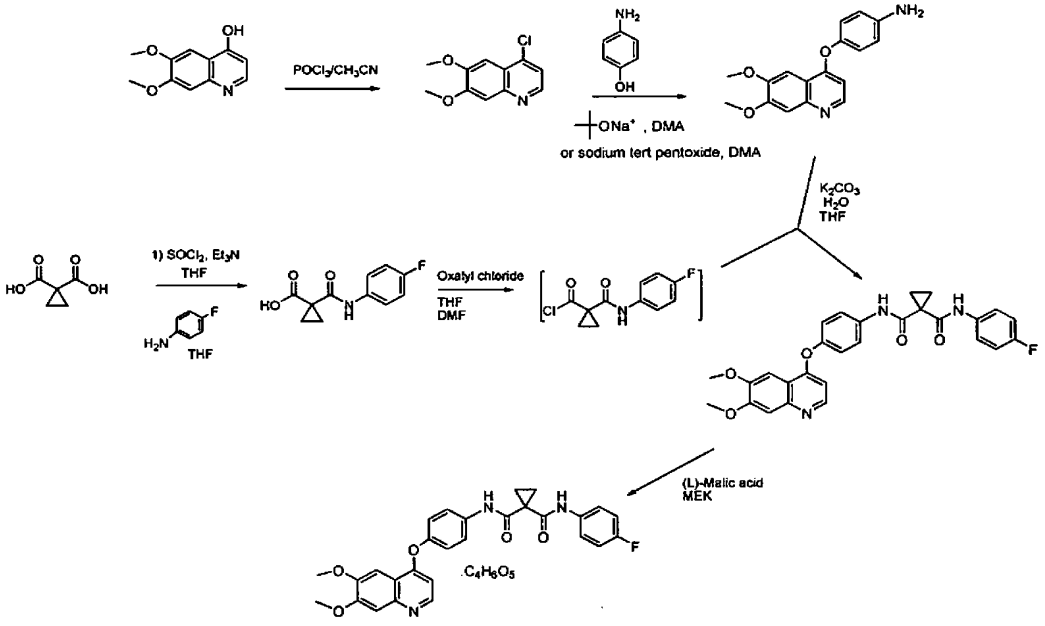
[0086] Unless otherwise specified, all reagents and solvents are of standard commercial grade and are used without further purification. The appropriate atmosphere to run the reaction under, for example, air, nitrogen, hydrogen, argon and the like, will be apparent to those skilled in the art.

## Example 1

### Preparation of Compound I and Compound I and the L-Malate Salt of Compound I

[0087] A synthetic route that can be used for the preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the L-malate salt thereof is depicted in Scheme 1.

**Scheme 1**




### Preparation of 4–Chloro–6,7–dimethoxy–quinoline

[0088] A reactor was charged sequentially with 6,7–dimethoxy–quinoline–4–ol (47.0 kg) and acetonitrile (318.8 kg). The resulting mixture was heated to approximately 60 °C, and phosphorus oxychloride ($POCl_3$, 130.6 kg) was added. After the addition of $POCl_3$, the temperature of the reaction mixture was raised to approximately 77 °C. The reaction was deemed complete (approximately 13 hours) when less than 3% of the starting material remained (in-process high-performance liquid chromatography [HPLC] analysis). The

reaction mixture was cooled to approximately 2–7 °C and then quenched into a chilled solution of dichloromethane (DCM, 482.8 kg), 26 % $NH_4OH$ (251.3 kg), and water (900 L). The resulting mixture was warmed to approximately 20 – 25 °C, and phases were separated. The organic phase was filtered through a bed of AW hyflo super-cel NF (Celite™; 5.4 kg), and the filter bed was washed with DCM (118.9 kg). The combined organic phase was washed with brine (282.9 kg) and mixed with water (120 L). The phases were separated, and the organic phase was concentrated by vacuum distillation with the removal of solvent (approximately 95 L residual volume). DCM (686.5 kg) was charged to the reactor containing organic phase and concentrated by vacuum distillation with the removal of solvent (approximately 90 L residual volume). Methyl t-butyl ether (MTBE, 226.0 kg) was then charged, and the temperature of the mixture was adjusted to –20 to –25 °C and held for 2.5 hours, resulting in solid precipitate which was then filtered and washed with n-heptane (92.0 kg) and dried on a filter at approximately 25 °C under nitrogen to afford the title compound. (35.6 kg).

**Preparation of 4–(6, 7 –Dimethoxy–quinoline–4–yloxy)–phenylamine**

**[0089]** 4-Aminophenol (24.4 kg) dissolved in N,N-dimethylacetamide (DMA, 184.3 kg) was charged to a reactor containing 4-chloro-6,7-dimethoxyquinoline (35.3 kg), sodium t-butoxide (21.4 kg), and DMA (167.2 kg) at 20–25 °C. This mixture was then heated to 100–105 °C for approximately 13 hours. After the reaction was deemed complete as determined using in-process HPLC analysis (less than 2% starting material remaining), the reactor contents were cooled at 15–20 °C, and water (pre-cooled, 2 to 7 °C, 587 L) was charged at a rate to maintain 15-30 °C temperature. The resulting solid precipitate was filtered and washed with a mixture of water (47 L) and DMA (89.1 kg) and again with water (214 L). The filter cake was then dried at approximately 25 °C on filter to yield crude 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine (59.4 kg wet, 41.6 kg dry calculated based on LOD). Crude 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine was refluxed (approximately 75 °C) in a mixture of tetrahydrofuran (THF, 211.4 kg) and DMA (108.8 kg) for approximately 1 hour, then cooled to 0–5 °C, and aged for approximately 1 hour, after which time the solid was filtered, washed with THF (147.6 kg), and dried on a filter under vacuum at approximately 25 °C to yield 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine (34.0 kg).

**Alternative Preparation of 4–(6, 7 –Dimethoxy–quinoline–4–yloxy)–phenylamine**

**[0090]** 4-chloro-6,7-dimethoxyquinoline (34.8 kg), 4-Aminophenol (30.8 kg), and sodium tert pentoxide (1.8 equivalents) 88.7 kg, 35 wt percent in THF) were charged to a reactor, followed by N,N-dimethylacetamide (DMA, 293.3 kg). This mixture was then heated to 105 – 115 °C for approximately 9 hours. After the reaction was deemed complete as determined using in-process HPLC analysis (less than 2 percent starting material remaining), the reactor contents were cooled at 15–25 °C, and water (315 kg) was added over a two hour period while maintaining the temperature between 20 and 30 °C. The reaction mixture was then agitated for an additional hour at 20 to 25°C. The crude product was collected by filtration and washed with a mixture of water (88 kg) and DMA (82.1 kg), followed by water (175 kg). The product was dried on a filter drier for 53 hours. The LOD showed less than 1% weight/weight (w/w).

**[0091]** In an alternative procedure, 1.6 equivalents of sodium tert-pentoxide were used, and the reaction temperature was increased from 110–120 °C. In addition, the cool down temperature was increased to 35-40 °C, and the starting temperature of the water addition was adjusted to 35-40 °C, with an allowed exotherm to 45°C.

**Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid**

**[0092]** Triethylamine (19.5 kg) was added to a cooled (approximately 5 °C) solution of cyclopropane–1,1–dicarboxylic acid (24.7 kg) in THF (89.6 kg) at a rate such that the batch temperature did not exceed 5 °C. The solution was stirred for approximately 1.3 hours, and then thionyl chloride (23.1 kg) was added, keeping the batch temperature below 10 °C. When the addition was complete, the solution was stirred for approximately 4 hours, keeping the temperature below 10 °C. A solution of 4–fluoroaniline (18.0 kg) in THF (33.1 kg) was then added at a rate such that the batch temperature did not exceed 10 °C. The mixture was stirred for approximately 10 hours, after which the reaction was deemed complete. The reaction mixture was then diluted with isopropyl acetate (218.1 kg). This solution was washed sequentially with aqueous sodium hydroxide (10.4 kg, 50 percent dissolved in 119 L of water) further diluted with water (415 L), then with water (100 L), and finally with aqueous sodium chloride (20.0 kg dissolved in 100 L of water). The organic solution was concentrated by vacuum distillation (100 L residual volume) below 40 °C, followed by the addition of n-heptane (171.4 kg), which resulted in the precipitation of solid. The solid was recovered by filtration and washed with n-Heptane (102.4 kg), resulting in wet crude, 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (29.0 kg). The crude, 1–(4–fluoro–

phenylcarbamoyl)–cyclopropanecarboxylic acid was dissolved in methanol (139.7 kg) at approximately 25 °C followed by the addition of water (320 L), resulting in slurry which was recovered by filtration, washed sequentially with water (20 L) and n-heptane (103.1 kg), and then dried on the filter at approximately 25 °C under nitrogen to afford the title compound (25.4 kg).

**Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride**

**[0093]** Oxalyl chloride (12.6 kg) was added to a solution of 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (22.8 kg) in a mixture of THF (96.1 kg) and N, N-dimethylformamide (DMF; 0.23 kg) at a rate such that the batch temperature did not exceed 25 °C. This solution was used in the next step without further processing.

**Alternative Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride**

**[0094]** A reactor was charged with 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (35 kg), DMF (344 g), and THF (175 kg). The reaction mixture was adjusted to 12-17 °C, and then to the reaction mixture was charged with oxalyl chloride (19.9 kg) over a period of 1 hour. The reaction mixture was left stirring at 12-17 °C for 3 to 8 hours. This solution was used in the next step without further processing.

**Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide**

**[0095]** The solution from the previous step containing 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride was added to a mixture of compound 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (23.5 kg) and potassium carbonate (31.9 kg) in THF (245.7 kg) and water (116 L) at a rate such that the batch temperature did not exceed 30 °C. When the reaction was complete (in approximately 20 minutes), water (653 L) was added. The mixture was stirred at 20–25 °C for approximately 10 hours, which resulted in the precipitation of the product. The product was recovered by filtration, washed with a pre-made solution of THF (68.6 kg) and water (256 L), and dried first on a filter under nitrogen at approximately 25 °C and then at approximately 45 °C under vacuum to afford the title compound (41.0 kg, 38.1 kg, calculated based on LOD).

**Alternative Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide**

**[0096]** A reactor was charged with 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (35.7 kg, 1 equivalent), followed by 412.9 kg THF. To the reaction mixture was charged a solution of 48.3 $K_2CO_3$ in 169 kg water. The acid chloride solution described in the Alternative Preparation of 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride above was transferred to the reactor containing 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine while maintaining the temperature between 20-30 °C over a minimum of two hours. The reaction mixture ws stirred at 20-25 °C for a minimum of three hours. The reaction temperature was then adjusted to 30-25 °C, and the mixture was agitated. The agitation was stopped, and the phases of the mixture were allowed to separate. The lower aqueous phase was removed and discarded. To the remaining upper organic phase was added water (804 kg). The reaction was left stirring at 15-25 °C for a minimum of 16 hours.

**[0097]** The product precipitated. The product was filtered and washed with a mixture of water (179 kg) and THF (157.9 kg) in two portions. The crude product was dried under a vacuum for at least two hours. The dried product was then taken up in THF (285.1 kg). The resulting suspension was transferred to reaction vessel and agitated until the suspension became a clear (dissolved) solution, which required heating to 30-35 °C for approximately 30 minutes. Water (456 kg) was then added to the solution, as well as SDAG-1 ethanol (20 kg) (ethanol denatured with methanol over two hours). The mixture was agitated at 15-25 °C for at least 16 hours. The product was filtered and washed with a mixture of 143 kg water (143 kg) and THF (126.7 kg) in two portions. The product was dried at a maximum temperature set point of 40 °C.

**[0098]** In an alternative procedure, the reaction temperature during acid chloride formation was adjusted to 10-15 °C. The recrystallization temperature was changed from 15-25 °C to 45-50 °C for 1 hour and then cooled to 15-25 °C over 2 hours.

**Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7- dimethoxy- quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L) malate salt**

**[0099]** Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy- quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (1-5; 13.3 kg), L-malic acid (4.96 kg), methyl ethyl ketone (MEK; 188.6 kg), and water (37.3 kg) were charged to a reactor, and the mixture was heated to reflux (approximately 74 °C) for approximately 2 hours. The reactor temperature was reduced to 50 to 55 °C, and the reactor contents were filtered. These sequential steps

described above were repeated two more times starting with similar amounts of 1-5 (13.3 kg), L-Malic acid (4.96 kg), MEK (198.6 kg), and water (37.2 kg). The combined filtrate was azeotropically dried at atmospheric pressure using MEK (1133.2 kg) (approximate residual volume 711 L; KF $\leq$ 0.5 % w/w) at approximately 74 °C. The temperature of the reactor contents was reduced to 20 to 25 °C and held for approximately 4 hours, resulting in solid precipitate which was filtered, washed with MEK (448 kg), and dried under vacuum at 50 °C to afford the title compound (45.5 kg).

**Alternative Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide, (L) malate salt**

**[00100]** Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide (47.9 kg), L-malic acid (17.2 kg), methyl ethyl ketone (658.2 kg), and water (129.1 kg) were charged to a reactor, and the mixture was heated 50-55 °C for approximately 1-3 hours, and then at 55-60 °C for an additional 4-5 hours. The mixture was clarified by filtration through a 1 μm cartridge. The reactor temperature was adjusted to 20-25 °C and vacuum distilled with a vacuum at 150-200 mm Hg with a maximum jacket temperature of 55 °C to the volume range of 558-731 L.

**[00101]** The vacuum distillation was performed two more times with the charge of 380 kg and 380.2 kg methyl ethyl ketone, respectively. After the third distillation, the volume of the batch was adjusted to 18 v/w of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide by charging methyl ethyl ketone (159.9 kg) to give a total volume of 880L. An additional vacuum distillation was carried out by adjusting methyl ethyl ketone (245.7 kg). The reaction mixture was left with moderate agitation at 20-25 °C for at least 24 hours. The product was filtered and washed with methyl ethyl ketone 415.1 kg) in three portions. The product was dried under a vacuum with the jacket temperature set point at 45 °C.

**[00102]** In an alternative procedure, the order of addition was changes so that a solution of L-malic acid (17.7 kg) dissolved in water (129.9 kg) was added to Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide (48.7 kg) in methyl ethyl ketone (673.3 kg).

**General Methods of Analysis of Crystalline Forms of Compound I and Compound I, Malate Salt**

**[00103]** Crystalline forms may be prepared by a variety of methods including, but not limited to, crystallization or recrystallization from a suitable solvent mixture, sublimation, growth from a melt, solid state transformation from another phase, crystallization from a supercritical fluid, and jet spraying. Techniques for crystallization or recrystallization of crystalline forms of a solvent mixture include, but are not limited to, evaporation of the solvent, decreasing the temperature of the solvent mixture, crystal seeding of a supersaturated solvent mixture of the compound and/or salt thereof, crystal seeding a supersaturated solvent mixture of the compound and/or a salt from thereof, freeze drying the solvent mixture, and adding antisolvents (countersolvents) to the solvent mixture. High throughput crystallization techniques may be employed to prepare crystalline forms including polymorphs.

**[00104]** Crystals of drugs, including polymorphs, their methods of preparation, and the characterization of drug crystals, are discussed in *Solid-State Chemistry of Drugs*, S.R. Byrn, R.R. Pfeiffer, and J.G. Stowell, 2nd Edition, SSCI, West Lafayette, Indiana (1999).

**[00105]** In a crystallization technique in which a solvent is employed, the solvent is typically chosen based on one or more factors including, but not limited to, solubility of the compound, crystallization technique utilized, and vapor pressure of the solvent. Combinations of solvents may be employed. For example, the compound may be solubilized in a first solvent to afford a solution, followed by the addition of an antisolvent to decrease the solubility of the compound in the solution and precipitate the formation of crystals. An antisolvent is a solvent in which a compound has low solubility.

**[00106]** In one method that can be used in preparing crystals, the L-malate salt of Compound I can be suspended and/or stirred in a suitable solvent to afford a slurry, which may be heated to promote dissolution. The term "slurry," as used herein, means a saturated solution of the compound, wherein such solution may contain an additional amount of compound to afford a heterogeneous mixture of compound and solvent at a given temperature.

**[00107]** Seed crystals may be added to any crystallization mixture to promote crystallization. Seeding may be employed to control growth of a particular polymorph and/or to control the particle size distribution of the crystalline product. Accordingly, calculation of the amount of seeds needed depends on the size of the seed available and the desired size of an average product particle as described, for example, in Programmed Cooling Batch Crystallizers," J.W. Mullin and J. Nyvlt, Chemical Engineering Science, 1971, 26, 3690377.

In general, seeds of small size are needed to effectively control the growth of crystals in the batch. Seeds of small size may be generated by sieving, milling, or micronizing large crystals, or by microcrystallizing a solution. In the milling or micronizing of crystals, care should be taken to avoid changing crystallinity from the desired crystalline form (i.e., changing to an amorphous or other polymorphic form).

**[00108]** A cooled crystallization mixture may be filtered under vacuum and the isolated solid product washed with a suitable solvent, such as, for example, cold recrystallization solvent. After washing, the product may be dried under a nitrogen purge to afford the desired crystalline form. The product may be analyzed by a suitable spectroscopic or analytical technique including, but not limited to, differential scanning calorimetry (DSC), x-ray powder diffraction (XRPD), and thermogravimetric analysis (TGA), to ensure that the crystalline form of the compound has been formed. The resulting crystalline form may be produced in an amount greater than about 70 weight percent isolated yield, based on the weight of the compound originally employed in the crystallization procedure, and preferably greater than about 90 weight percent isolated yield. Optionally, the product may be delumped by comilling or passing through a mesh screen.

**Preparation of Crystalline L-Malate Salt of Compound I**

**[00109]** The preparation of the captioned salt and its characterization is described above and in WO 2010/083414, the entire contents of which is incorporated by reference.

**Solid State Nuclear Magnetic Resonance (SSNMR)**

**[00110]** All solid-state $^{13}C$ NMR measurements were made with a Bruker DSX-400, 400 MHz NMR spectrometer. High resolution spectra were obtained using high-power proton decoupling, the TPPM pulse sequence, and ramp amplitude cross-polarization (RAMP-CP) with magic-angle spinning (MAS) at approximately 12 kHz (A.E. Bennett et al, *J. Chem. Phys.*, 1995, 103, 6951 and G. Metz, X. Wu and S.O. Smith, *J. Magn. Reson. A*,. 1994, 110, 219-227). Approximately 70 mg of sample, packed into a canister-design zirconia rotor, was used for each experiment. Chemical shifts (δ) were referenced to external adamantane with the high frequency resonance being set to 38.56 ppm (W.L. Earl and D.L. VanderHart, *J. Magn. Reson.*, 1982, 48, 35-54).

**L-Malate Salt of Compound I**

**[00111]** The solid state $^{13}C$ NMR spectrum of the crystalline L-malate salt of Compound I provides the following list of peaks, or a subset thereof, may be sufficient to characterize crystalline L-malate salt of Compound I.

**[00112]** SS $^{13}C$ NMR Peaks: 18.1, 20.6, 26.0, 42.9, 44.5, 54.4, 55.4, 56.1, 70.4, 99.4, 100.1, 100.6, 114.4, 114.9, 115.8, 119.6, 120.1, 121.6, 123.2, 124.1, 136.4, 138.6, 140.6, 145.4, 150.1, 150.9, 156.2, 157.4, 159.4, 164.9, 167.1, 170.8, 175.7, and 182.1 ppm, ± 0.2 ppm.

**[00113]** The solid state $^{15}N$ NMR spectrum of the crystalline L-malate salt of Compound I. provides peaks at 118.6, 119.6, 120.7, 134.8, 167.1, 176.0, and 180 ppm, ± 0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline L-malate salt of Compound I.

**[00114]** The solid state $^{19}F$ NMR spectrum of the crystalline L-malate salt of Compound I. provides peaks at -121.6, -120.8, and -118.0 ppm, ± 0.2 ppm.

**Thermal Characterization Measurements**

**Thermal Gravimetric Analysis (TGA)**

**[00115]** TGA measurements were performed in a TA Instruments™ model Q500 or 2950, employing an open pan setup. The sample (about 10-30 mg) was placed in a previously tared platinum pan. The weight of the sample was measured accurately and recorded to a thousand of a milligram. The furnace was purged with nitrogen gas at 100mL/min. Data were collected between room temperature and 300 °C at 10 °C/min heating rate.

**Differential Scanning Calorimetry (DSC) Analysis**

**[00116]** DSC measurements were performed in a TA Instruments™ models Q2000, 1000, or 2920, employing an open pan setup. The sample (about 2-6 mg) was weighed in an aluminum pan, accurately recorded to a hundredth of a milligram, and transferred to the DSC. The instrument was purged with nitrogen gas at 50mL/min. Data were collected between room temperature and 300 °C at a 10 °C/min heating rate. The plot was made with the endothermic peaks pointing down.

**L-Malate Salt of Compound I**

**[00117]** The TGA thermogram for the crystalline L-malate salt of Compound I, which shows a weight loss of approximately 0.4 weight percent at a temperature of 170 °C.

[00118] The DSC thermogram for the crystalline L-malate salt of Compound I, which showed a melting point of approximately 187 °C.

**Moisture Vapor Isotherm Measurements**

[00119] Moisture sorption isotherms were collected in a VTI SGA-100 Symmetric Vapor Analyzer using approximately 10 mg of sample. The sample was dried at 60 °C until the loss rate of less than or equal to 0.0005 weight percent per minute was obtained for 10 minutes. The sample was tested at 25 °C and a relative humidity (RH) of 3, 4, 5, 15, 25, 35, 45, 50, 65, 75, 85, and 95 percent. Equilibration at each RH was reached when the rate of less than or equal to 0.0003 weight percent per minute for 35 minutes was achieved, or at a maximum of 600 minutes.

[00120] All ranges disclosed herein are inclusive of the endpoints, and the endpoints are independently combinable with each other.

[00121] The use of the terms "a", "an", "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. Further, it should be noted that the terms "first," "second," and the like herein do not denote any order, quantity, or importance, but rather are used to distinguish one element from another. The modifier "about" used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (e.g., it includes the degree of error associated with measurement of the particular quantity).

[00122] The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

What is claimed is:

1. A pharmaceutical composition comprising:

| Ingredient | (% w/w) |
|---|---|
| Compound I | 31.68 |
| Microcrystalline Cellulose | 38.85 |
| Lactose anhydrous | 19.42 |
| Hydroxypropyl Cellulose | 3.00 |
| Croscarmellose Sodium | 3.00 |
| **Total Intra-granular** | **95.95** |
| Silicon dioxide, Colloidal | 0.30 |
| Croscarmellose Sodium | 3.00 |
| Magnesium Stearate | 0.75 |
| **Total** | **100.00** |

2. A pharmaceutical composition comprising:

| Ingredient | (% w/w) |
|---|---|
| Compound I | 25.0-33.3 |
| Microcrystalline Cellulose | q.s |
| Hydroxypropyl Cellulose | 3 |
| Poloxamer | 0-3 |
| Croscarmellose Sodium | 6.0 |
| Colloidal Silicon Dioxide | 0.5 |
| Magnesium Stearate | 0.5-1.0 |
| Total | 100 |

3. A pharmaceutical composition comprising:

| Ingredient | Theoretical Quantity (mg/unit dose) |
|---|---|
| Compound I | 100.0 |
| Microcrystalline Cellulose PH-102 | 155.4 |
| Lactose Anhydrous 60M | 77.7 |
| Hydroxypropyl Cellulose, EXF | 12.0 |
| Croscarmellose Sodium | 24 |
| Colloidal Silicon Dioxide | 1.2 |
| Magnesium Stearate (Non-Bovine) | 3.0 |
| Opadry Yellow | 16.0 |
| **Total** | **416** |

4. A pharmaceutical composition comprising:

30-32 percent by weight of Compound I in at least one of the forms disclosed herein;

50-70 percent by weight of a filler;

2-4 percent by weight of a binder;

4-8 percent by weight of a disintegrant; and

0.2-0.6 percent by weight of a glidant; and 0.5-1 percent by weight of a lubricant.

5. The pharmaceutical composition of claim 4, wherein Compound I is the free base.

6. The pharmaceutical composition of claim 4, wherein Compound I is a pharmaceutically acceptable salt.

7. The pharmaceutical composition of claim 4, wherein Compound I is the malate salt.

8. The pharmaceutical composition of claim 4, wherein Compound I is the L-, D-, or D,L malate salt, or mixtures thereof.

9. The pharmaceutical composition of claim 8, wherein the Compound I malate salt is in amorphous, substantially amorphous, crystalline, or substantially crystalline form.

10. The pharmaceutical composition of claim 8, wherein the Compound I malate salt is in crystalline or amorphous form.

11. The pharmaceutical composition of claim 4, wherein the filler is selected from the group consisting of sodium starch glycolate, corn starch, talc, sucrose, dextrose, glucose, lactose, xylitol, fructose, sorbitol, calcium phosphate, calcium sulfate, calcium carbonate, and microcrystalline cellulose, or mixtures thereof.

12. The pharmaceutical composition of claim 11, wherein the filler is comprises lactose and microcrystalline cellulose.

13. The pharmaceutical composition of claim 2, wherein the binder is selected from the group consisting of acacia, alginic acid, carbomer, carboxymethylcellulose sodium, dextrin, ethylcellulose, gelatin, guar gum, hydrogenated vegetable oil (type I), hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, liquid glucose, magnesium aluminaum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone, pregelatinized starch, sodium alginate, starch, and zein, or mixtures thereof.

14. The pharmaceutical composition of claim 13, wherein the binder is hydroxypropyl cellulose.

15 The pharmaceutical composition of claim 14, wherein the disintegrant is selected from the group consisting of alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium, crospovidone, guar gum, magnesium aluminum silicate, methylcellulose, microcrystalline cellulose, polyacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, and starch, or mixtures thereof.

16. The pharmaceutical composition of claim 15, wherein the disintegrant is croscarmellose sodium.

17. The pharmaceutical composition of claim 4, wherein the glidant is colloidal silicon dioxide.

18. The pharmaceutical composition of claim 4, wherein the lubricant is selected from the group consisting of magnesium stearate, Lubritab.RTM., stearic acid, and talc, or mixtures thereof.

19. The pharmaceutical composition of claim 4, wherein the lubricant is magnesium stearate.

20. The pharmaceutical composition of claim 4, further comprising a film coating.

21. The pharmaceutical composition of claim 20, wherein the film coating comprises Opadry Yellow.

22. The pharmaceutical formulation of claims 1-4 which is a tablet formulation.

23. A pharmaceutical composition comprising:

| Component | Weight/Weight Percent |
|---|---|
| Compound I | 25-29 |
| Microcrystalline Cellulose | q.s. |
| Lactose Anhydrous | 40-44 |
| Hydroxypropyl Cellulose | 2-4 |
| Croscarmellose Sodium | 2-8 |
| Colloidal Silicon Dioxide | 0.1-0.4 |
| Magnesium Stearate | 0.7-0.9 |
| Total | 100 |

24. The pharmaceutical composition of claim 22, further comprising a film coating.

25. The pharmaceutical composition of claim 24, wherein the film coating comprises Opadry yellow.

26. A method for treating cancer, comprising administering to a patient in need of such treatment a pharmaceutical composition of claim 1-4 or 23, alone or in combination with another therapeutic agent.

27. The method of claim 26, wherein the cancer is selected from the group consisting of pancreatic cancer, kidney cancer, liver cancer, prostate cancer, gastric cancer, gastroesophageal cancer, melanoma, lung cancer, breast cancer, thyroid cancer, and astrocytic tumors.

28. The method of claim 27, wherein the cancer is pancreatic cancer, hepatocellular carcinoma (HCC), renal cell carcinoma, castration-resistant prostate cancer (CRPC), gastric or gastroesophageal junction cancer, melanoma, small cell lung cancer (SCLC), ovarian cancer, primary peritoneal or fallopian tube carcinoma, estrogen receptor positive breast cancer, estrogen receptor/progesterone receptor/HER2-negative (triple-negative) breast cancer, inflammatory (regardless of receptor status) breast cancer, non-small cell lung cancer (NSCLC), or medullary thyroid cancer.

29. A process for manufacturing a pharmaceutical composition comprising Compound **I**, comprising the steps of:

a. Delumping unmilled Compound I;
b. Premixing the delumped Compound I with microcrystalline cellulose, anhydrous lactose , and croscarmellose sodium to form a binder solution;
c. Wet high shear granulation of the binder solution to produce wet granules;
d. Wet screening of the wet granules to produce wet screened granules;
e. Fluid bed drying of the wet screened granules to produce dried granules;
f. Dry milling of the dried granules to produce dried milled granules;
g. Blending the dried milled granules with colloidal silicon and croscarmellose to produce an extragranular blend;
h. Lubricant blending of the extragranular blend and magnesium stearate to produce a final blend; and
i. Tablet compression of the final blend to form an uncoated core tablet.

30. The process of claim 29, further comprising the step of film coating of the uncoated core tablet.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/044378

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/47
ADD.

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)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 2005/030140 A2 (EXELIXIS INC [US]; BANNEN LYNNE CANNE [US]; CHAN DIVA SZE-MING [US]; C) 7 April 2005 (2005-04-07) cited in the application table 2, compound 12 example 48 table 4, entry 289 paragraphs [0025], [0031], [0252], [0253] | 1-30 |

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[X] Further documents are listed in the continuation of Box C.

[X] 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 document 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 |
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| Name and mailing address of the ISA/ | Authorized officer |
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| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Sproll, Susanne |

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

International application No
PCT/US2011/044378

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| 60/535,377 | 9 January 2004 (09.01.2004) | US |
| 60/577,384 | 4 June 2004 (04.06.2004) | US |

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**Published:**
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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: C-MET MODULATORS AND METHODS OF USE

(57) Abstract: The present invention provides compounds for modulating protein kinase enzymatic activity for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration and chemoinvasion. More specifically, the invention provides quinazolines and quinolines which inhibit, regulate and/or modulate kinase receptor, particularly c-Met, KDR, c-Kit, flt-3 and flt-4, signal transduction pathways related to the changes in cellular activities as mentioned above, compositions which contain these compounds, and methods of using them to treat kinase-dependent diseases and conditions. The present invention also provides methods for making compounds as mentioned above, and compositions which contain these compounds.

WO 2005/030140 A2

# c-Met Modulators and Method of Use

## CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. provisional patent applications 60/506,181 filed on September 26, 2003, entitled "c-Met Modulators and Method of Use," naming Bannen, Lynne *et. al* as inventors, 60/535,377 filed on January 9, 2004, entitled "c-Met Modulators and Method of Use," naming Bannen, Lynne *et. al* as inventors and 60/577,384 filed on June 4, 2004, entitled "Synthesis of Quinoline and Quinazoline Kinase Modulators," naming Bannen, Lynne *et. al* as inventors; each of which is hereby incorporated by reference in its entirety for all purposes.

## FIELD OF THE INVENTION

[0002] This invention relates to compounds for modulating protein kinase enzymatic activity for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration and chemoinvasion. Even more specifically, the invention relates to quinazolines and quinolines which inhibit, regulate and/or modulate kinase receptor signal transduction pathways related to the changes in cellular activities as mentioned above, compositions which contain these compounds, methods of using them to treat kinase-dependent diseases and conditions, synthesis of the compounds as well as processes for formulating the compounds for pharmaceutical purposes.

## BACKGROUND OF THE INVENTION

[0003] Improvements in the specificity of agents used to treat cancer is of considerable interest because of the therapeutic benefits which would be realized if the side effects associated with the administration of these agents could be reduced. Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms.

[0004] Protein kinases are enzymes that catalyze the phosphorylation of proteins, in particular, hydroxy groups on tyrosine, serine and threonine residues of proteins. The consequences of this seemingly simple activity are staggering; cell differentiation and proliferation; i.e., virtually all aspects of cell life in one-way or another depend on protein kinase activity. Furthermore, abnormal protein kinase activity has been related to a host of

disorders, ranging from relatively non-life threatening diseases such as psoriasis to extremely virulent diseases such as glioblastoma (brain cancer).

[0005] Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases have an extracellular, a transmembrane, and an intracellular portion, while non-receptor type tyrosine kinases are wholly intracellular.

[0006] Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. In fact, about 20 different subfamilies of receptor-type tyrosine kinases have been identified. One tyrosine kinase subfamily, designated the HER subfamily, is comprised of EGFR (HER1), HER2, HER3, and HER4. Ligands of this subfamily of receptors identified so far include epithelial growth factor, TGF-alpha, amphiregulin, HB-EGF, betacellulin and heregulin. Another subfamily of these receptor-type tyrosine kinases is the insulin subfamily, which includes INS-R, IGF-IR, and IR-R. The PDGF subfamily includes the PDGF-alpha and beta receptors, CSFIR, c-Kit and FLK-II. Then there is the FLK family, which is comprised of the kinase insert domain receptor (KDR), fetal liver kinase-1 (FLK-1), fetal liver kinase-4 (FLK-4) and the fms-like tyrosine kinase-1 (flt-1). The PDGF and FLK families are usually considered together due to the similarities of the two groups. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., DN&P 7(6): 334-339, 1994, which is hereby incorporated by reference.

[0007] The non-receptor type of tyrosine kinases is also comprised of numerous subfamilies, including Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack, and LIMK. Each of these subfamilies is further sub-divided into varying receptors. For example, the Src subfamily is one of the largest and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, and Yrk. The Src subfamily of enzymes has been linked to oncogenesis. For a more detailed discussion of the non-receptor type of tyrosine kinases, see Bolen, Oncogene, 8:2025-2031 (1993), which is hereby incorporated by reference.

[0008] Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases. These include, but are not limited to: immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore,

both receptor and non-receptor protein kinases are attractive targets for small molecule drug discovery.

[0009] One particularly attractive goal for therapeutic use of kinase modulation relates to oncological indications. For example, modulation of protein kinase activity for the treatment of cancer has been demonstrated successfully with the FDA approval of Gleevec® (imatinib mesylate, produced by Novartis Pharmaceutical Corporation of East Hanover, NJ) for the treatment of Chronic Myeloid Leukemia (CML) and gastrointestinal stroma cancers (GIST). Gleevec is a c-Kit and Abl kinase inhibitor.

[0010] Modulation (particularly inhibition) of cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc Technol 2001 6, 1005-1024), is an attractive goal for development of small-molecule drugs. Anti-angiogenic therapy represents a potentially important approach for the treatment of solid tumors and other diseases associated with dysregulated vascularization, including ischemic coronary artery disease, diabetic retinopathy, psoriasis and rheumatoid arthritis. As well, cell antiproliferative agents are desirable to slow or stop the growth of tumors.

[0011] One particularly attractive target for small-molecule modulation, with respect to antiangiogenic and antiproliferative activity is c-Met. The kinase, c-Met, is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs) which include Met, Ron and Sea. Expression of c-Met occurs in a wide variety of cell types including epithelial, endothelial and mesenchymal cells where activation of the receptor induces cell migration, invasion, proliferation and other biological activities associated with "invasive cell growth." As such, signal transduction through c-Met receptor activation is responsible for many of the characteristics of tumor cells.

[0012] The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenisis, also known as "scatter factor" (SF). Binding of HGF to c-Met induces activation of the receptor via autophosphorylation resulting in an increase of receptor dependent signaling, which promotes cell growth and invasion. Anti-HGF antibodies or HGF antagonists have been shown to inhibit tumor metastasis *in vivo* (See: Maulik et al Cytokine & Growth Factor Reviews 2002 13, 41-59).

[0013] Tumor growth progression requires the recruitment of new blood vessels into the tumor from preexisting vessels as well as invasion, adhesion and proliferation of malignant cells. Accordingly, c-Met overexpression has been demonstrated on a wide

variety of tumor types including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytomas, and glioblastomas. Additionally activating mutations in the kinase domain of c-Met have been identified in hereditary and sporadic renal papilloma and squamous cell carcinoma. (See: Maulik et al Cytokine & growth Factor reviews 2002 13, 41-59; Longati et al Curr Drug Targets 2001, 2, 41-55; Funakoshi et al Clinica Chimica Acta 2003 1-23). Thus modulation of c-Met is desirable as a means to treat cancer and cancer-related disease.

**[0014]** The Eph receptors comprise the largest family of receptor tyrosine kinases and are divided into two groups, EphA and EphB, based on their sequence homology. The ligands for the Eph receptors are ephrin, which are membrane anchored. Ephrin A ligands bind preferentially to EphA receptors whilst ephrin B ligands bind to EphB receptors. Binding of ephrin to Eph receptors causes receptor autophosphorylation and typically requires a cell-cell interaction since both receptor and ligand are membrane bound.

**[0015]** Overexpression of Eph receptors has been linked to increased cell proliferation in a variety of tumors (Zhou R 1998 Pharmacol Ther. 77, 151-181; Kiyokawa E, Takai S, Tanaka M et al 1994 Cancer Res 54, 3645-3650; Takai N Miyazaki T, Fujisawa K, Nasu K and Miyakawa. 2001 Oncology reports 8, 567-573). The family of Eph receptor tyrosine kinases and their ephrin ligands play important roles in a variety of processes during embryonic development and also in pathological angiogenesis and potentially metastasis. Therefore modulation of Eph receptor kinase activity should provide means to treat or prevent disease states associated with abnormal cell proliferation such as those described above.

**[0016]** Inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc. Technol. 2001 6, 1005-1024). EGF and VEGF receptors are previously described targets for small molecule inhibition. KDR and flt-4 are both VEGF receptors

**[0017]** One particularly attractive target for small-molecule modulation is c-Kit. The proto-oncogene *c-Kit* was first identified as the oncogenic component of the acutely transforming Hardy-Zuckerman 4-feline sarcoma virus (Besmer et al Nature 1986 320:415-421). c-Kit (also called stem cell factor receptor or steel factor receptor) is a type 3 receptor tyrosine kinase (RTK) belonging to the platelet-derived growth factor receptor subfamily. c-Kit binds the ligand stem cell factor (SCF), and triggers its multiple signal

transduction pathways including Src family kinases, phosphatidyl-inositol 3 kinase, the Ras-Raf-Map kinase cascade, and phospholipase C (Broudy et al Blood 1999 94: 1979-1986; Lennartsson et al Oncogene 1999 18: 5546-5553 ; Timokhina et al EMBO J 1998 17;6250-6262; Chian et al Blood 2001 98(5)1365-1373; Blume-Jensen et al Curr Biol 1998 8:779-782; Kissel et al EMBO J 2000 19:1312-1326; Lennartsson et al. Oncogene 1999 18: 5546-5553; Sue et al Blood, 199892:1242-1149; Lev etal EMBO J 1991 10:647-654). c-Kit is required for normal hematopoiesis, melanonogenesis, and gametogenesis. c-Kit is expressed in mast cells, immature myeloid cells, melanocytes, epithelial breast cells and the interstitial cells of Cajal (ICC). In mast cells, it is required not only for the differentiation, maturation, chemotaxis, and haptotaxis but also for the promotion of survival and proliferation.

**[0018]** Mutations in c-Kit have been implicated in human disease. Mutations in the juxtamembrane domain are found in many human gastrointestinal stromal tumors, and mutations in the kinase domain are found in mastocytosis, germ cell tumors, acute myeloid leukemia (AML), NK lymphoma, and other hematologic disorders (Hirota et al Science 1998 279:577-580; Singer et al J Clin Oncol 2002 203898-3905; Longley et al Proc Natl Aca Sci USA 1999: 1609-1614; Tian et al Am J Pathol 1999 154: 1643-1647; Beghini et al Blood 2000 95:726-727; Hongyo et al Cancer Res 2000 60:2345-2347). These mutations result in ligand-independent tyrosine kinase activity, autophosphorylation of c-Kit, uncontrolled cell proliferation, and stimulation of downstream signaling pathways. Overexpression of c-Kit and c-Kit ligand have also been described in other tumors including small-cell lung cancer, neuroblastomas, gynecological tumors, and colon carcinoma, which might result in autocrine or paracrine c-Kit activation.

**[0019]** The overexpression of c-Kit has also been implicated in the development of neoplasia associated with neurofibromatosis type 1 (NF1). Mutations in the tumor suppressor gene *NF1* lead to a deficiency in neurofibromin, a GTPase-activating protein for Ras. This deficiency results in abnormal proliferation of Schwann cells in the peripheral nervous system, and predisposes affected individuals to peripheral nerve sheath tumors (neurofibromas), astrocytomas (optic pathway gliomas), learning disabilities, seizures, strokes, macrocephaly, vascular abnormalities, and juvenile myelomonocytic leukemia (Lynch & Gutmann Neurol Clin 2002 20:841-865). Genetic experiments in mice demonstrate that haploinsufficiency at *NF1* partially rescues some of the phenotypes associated with mutations in the gene for c-Kit, indicating that these genes function along

a common developmental pathway (Ingram, et al. J. Exp Med 2000 191:181-187). Also, c-Kit is expressed in schwannoma cells from NF1 patients, but not in normal schwann cells (Ryan et al. J Neurosci Res 1994 37:415-432). These data indicate that elevated c-Kit expression and sensitivity to stem cell factor may play important roles in the development of proliferative disorders associated with NF-1. Therefore, c-Kit inhibitors may be effective chemotherapeutic agents for treating patients with NF-1.

**[0020]** GISTs are the most common mesenchymal tumors of the gastrointestinal tract, and they are generally resistant to chemotherapy and radiation therapy. However, recent results with the c-Kit/BCR-Abl inhibitor STI571 indicate that targeting c-Kit may be an effective therapeutic strategy for this disease (Eisenberg & Mehren Expert Opin Pharmacother 2003 4:869-874). Malignant mast cell disease often suggests an extremely poor prognosis, and no reliable effective chemotherapeutic agents have been identified (Marone et al Leuk Res 2001 25:583-594). Systemic mast cell disorders have been treated with interferon-alpha, although the effectiveness of this therapy has been variable (Lehmann & Lammle Ann Hematol 1999 78:483-484; Butterfield Br J Dermatol 1998 138: 489-495). Therefore, activated c-Kit might serve as a therapeutic target in GISTs and mast cell disease, as well as other disorders associated with activated c-Kit.

**[0021]** Flt-3 is normally expressed on hematopoietic progenitor cells and a subset of mature myeloid and lymphoid cells, where it modulates cell survival and proliferation. Flt-3 is constitutively activated via mutation, either in the juxtamembrane region or in the activation loop of the kinase domain, in a large proportion of patients with AML (Reilly Leuk Lymphoma 2003 44: 1-7). Also, mutations in flt-3 are significantly correlated with poor prognosis in AML patients (Sawyers Cancer Cell 2002 1: 413-415).

**[0022]** Accordingly, the identification of small-molecule compounds that specifically inhibit, regulate and/or modulate the signal transduction of kinases, particularly including c-Met, KDR, c-Kit, flt-3, and flt-4, is desirable as a means to treat or prevent disease states associated with abnormal cell proliferation and angiogenesis, and is an object of this invention.

**[0023]** Quinolines and quinazolines bearing substitution, for example at the two, four, six and seven positions of their fused ring system have been shown to be particularly attractive targets for kinase inhibition by a number of groups. Conventional quinoline and quinazoline kinase inhibitors typically have fairly simple substitution about the quinoline or quinazoline fused ten-membered ring system, but recently more complex molecules are

being disclosed. For example, we have previously disclosed, in U.S. provisional patent applications 60/506,181 and 60/535,377 which are both incorporated by reference herein in their entirety for all purposes, that certain quinolines and quinazolines are particularly well suited as kinase modulators, more particularly inhibitors of for example c-Met, KDR, c-Kit, flt-3, and flt-4. These molecules in some cases are particularly complex and although they can be made via conventional methods, more efficient routes are desirable, especially in a pharmaceutical setting.

**[0024]** Conventional methods of making quinolines and quinazolines with the aforementioned substitution patterns usually involve linear construction of a quinoline or quinazoline template upon which relatively simple substitutions are appended. With the advent of more complex substitution about such quinolines and quinazolines (*vide supra*), for example side chains containing cyclic and bicyclic systems with multiple functional groups, conventional methods of synthesis become problematic due to the linear or serial reactions used. Indeed, as such molecules become more complex and the utility of such complex groups is realized, the quinoline and quinazoline ring system becomes more of a sub-structure than a main structure of such inhibitors. Thus it is desirable to find more efficient methods of synthesis, particularly convergent syntheses which are an object of this invention.

## SUMMARY OF THE INVENTION

**[0025]** In one aspect, the present invention provides compounds for modulating kinase activity and methods of treating diseases mediated by kinase activity utilizing the compounds and pharmaceutical compositions thereof. Diseases mediated by kinase activity include, but are not limited to, diseases characterized in part by migration, invasion, proliferation and other biological activities associated with invasive cell growth. In particular to this invention is modulation, even more particularly inhibition, of c-Met, KDR, c-Kit, flt-3, and flt-4.

**[0026]** In another aspect, the invention provides methods of screening for modulators of c-Met, KDR, c-Kit, flt-3, and flt-4 activity. The methods comprise combining a composition of the invention, a kinase, e.g. c-Met, KDR, c-Kit, flt-3, or flt-4, and at least one candidate agent and determining the effect of the candidate agent on the c-Met, KDR, c-Kit, flt-3, or flt-4, activity.

**[0027]** In yet another aspect, the invention also provides pharmaceutical kits comprising one or more containers filled with one or more of the ingredients of pharmaceutical

compounds and/or compositions of the present invention, including, one or more kinase, e.g. c-Met, KDR, c-Kit, flt-3, or flt-4, enzyme activity modulators as described herein. Such kits can also include, for example, other compounds and/or compositions (e.g., diluents, permeation enhancers, lubricants, and the like), a device(s) for administering the compounds and/or compositions, and written instructions in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which instructions can also reflects approval by the agency of manufacture, use or sale for human administration.

**[0028]** In another aspect, the invention also provides a diagnostic agent comprising a compound of the invention and, optionally, pharmaceutically acceptable adjuvants and excipients.

**[0029]** In still yet another aspect, the present invention provides processes for making compounds, and pharmaceutical compositions thereof, for modulating kinase activity and treating diseases mediated by kinase activity. In particular to this invention are methods for making quinolines and quinazolines used for modulation of kinase activity, even more particularly inhibition of kinase activity, and yet even more particularly inhibition of c-Met, KDR, c-Kit, flt-3, and flt-4.

**[0030]** These and other features and advantages of the present invention will be described in more detail below with reference to the associated drawings.

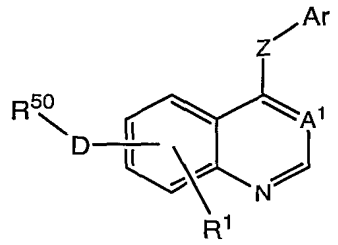
## DETAILED DESCRIPTION OF THE INVENTION

**[0031]** The compositions of the invention are used to treat diseases associated with abnormal and or unregulated cellular activities. Disease states which can be treated by the methods and compositions provided herein include, but are not limited to, cancer (further discussed below), immunological disorders such as rheumatoid arthritis, graft-host diseases, multiple sclerosis, psoriasis; cardiovascular diseases such as artheroscrosis, myocardioinfarction, ischemia, stroke and restenosis; other inflammatory and degenerative diseases such as interbowel diseases, osteoarthritus, macular degeneration, diabetic retinopathy.

**[0032]** It is appreciated that in some cases the cells may not be in a hyper- or hypo-proliferative and/or migratory state (abnormal state) and still require treatment. For example, during wound healing, the cells may be proliferating "normally", but

proliferation and migration enhancement may be desired. Alternatively, reduction in "normal" cell proliferation and/or migration rate may be desired.

**[0033]** Thus, in one aspect the present invention comprises a compound for modulating kinase activity according to Formula **I**,



**I**

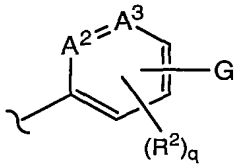
or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

$R^1$ is selected from -H, halogen, $-OR^3$, $-NO_2$, $-NH_2$, $-NR^3R^4$, and optionally substituted lower alkyl;

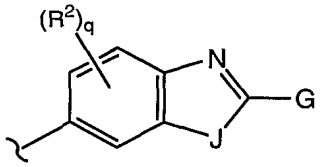
$A^1$ is selected from =N-, =C(H)-, and =C(CN)-;

Z is selected from $-S(O)_{0-2}-$, -O-, and $-NR^5-$;

Ar is either a group of formula **II**, or of formula **III**,



**II**



**III**

wherein,

$R^2$ is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

q is 0 to 4;

G is a group -B-L-T, wherein

B is selected from absent, $-N(R^{13})-$, $-N(SO_2R^{13})-$, -O-, $-S(O)_{0-2}-$, and -C(=O)-;

L is selected from absent, $-C(=S)N(R^{13})-$, $-C(=NR^{14})N(R^{13})-$, $-SO_2N(R^{13})-$, $-SO_2-$, $-C(=O)N(R^{13})-$, $-N(R^{13})-$, $-C(=O)C_{1-2}alkylN(R^{13})-$, $-N(R^{13})C_{1-2}alkylC(=O)-$, $-C(=O)C_{0-1}alkylC(=O)N(R^{13})-$, $-C_{0-4}alkylene-$, $-C(=O)C_{0-1}alkylC(=O)OR^3-$,

$-C(=NR^{14})C_{0-1}alkylC(=O)-$, $-C(=O)-$, $-C(=O)C_{0-1}alkylC(=O)-$, and an optionally substituted four to six-membered heterocyclyl containing between one and three annular heteroatoms including at least one nitrogen; and

T is selected from -H, $-R^{13}$, $-C_{0-4}alkyl$, $-C_{0-4}alkylQ$, $-OC_{0-4}alkylQ$, $-C_{0-4}alkylOQ$, $-N(R^{13})C_{0-4}alkylQ$, $-SO_2C_{0-4}alkylQ$, $-C(=O)C_{0-4}alkylQ$, $-C_{0-4}alkylN(R^{13})Q$, and $-C(=O)N(R^{13})C_{0-4}alkylQ$, wherein each of the aforementioned $C_{0-4}alkyl$ is optionally substituted;

J is selected from $-S(O)_{0-2}-$, -O-, and $-NR^{15}-$;

$R^3$ is -H or $R^4$;

$R^4$ is selected from optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, and optionally substituted lower heterocyclylalkyl; or

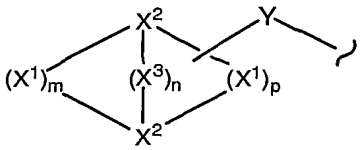
$R^3$ and $R^4$, when taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclyl, said optionally substituted five- to seven-membered heterocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

$A^2$ and $A^3$ are each independently selected from $=N-$, $=C(R^2)-$;

$R^5$ is -H or optionally substituted lower alkyl;

D is selected from -O-, $-S(O)_{0-2}-$, and $-NR^{15}-$;

$R^{50}$ is either $R^3$, or according to formula **IV**;




**IV**

wherein $X^1$, $X^2$, and optionally $X^3$, represent the atoms of a saturated bridged ring system, said saturated bridged ring system comprising up to four annular heteroatoms represented by any of $X^1$, $X^2$, and $X^3$; wherein,

each $X^1$ is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

each $X^2$ is independently an optionally substituted bridgehead methine or a bridgehead nitrogen;

each $X^3$ is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

Y is either:

an optionally substituted lower alkylene linker, between D and either 1) any annular atom of the saturated bridged ring system, except $X^2$ when $X^2$ is a bridgehead nitrogen, or 2) any heteroatom, represented by any of $R^6$ or $R^7$; provided there are at least two carbon atoms between D and any annular heteroatom of the saturated bridged ring system or any heteroatom represented by any of $R^6$ or $R^7$;

or Y is absent, when Y is absent, said saturated bridged ring system, is directly attached to D via an annular carbon of said saturated bridged ring system, unless D is $-SO_2-$, in which case said saturated bridged ring system, is directly attached to D via an any annular atom of said saturated bridged ring system;

m and p are each independently 1-4;

n is 0-2, when n = 0, then there is a single bond between the two bridgehead $X^2$'s;

$R^6$ and $R^7$ are each independently selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^4$, $-SO_2NR^3R^4$, $-CO_2R^3$, $-C(O)NR^3R^4$, $-N(R^3)SO_2R^4$, $-N(R^3)C(O)R^3$, $-NCO_2R^3$, $-C(O)R^3$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, optionally substituted lower heterocyclylalkyl, and a bond to either Y or D; or

$R^6$ and $R^7$, when taken together are oxo; or

$R^6$ and $R^7$, when taken together with a common carbon to which they are attached, form a optionally substituted three- to seven-membered spirocyclyl, said optionally substituted three- to seven-membered spirocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

$R^8$ is selected from $-R^3$, Y, $-SO_2NR^3R^4$, $-CO_2R^4$, $-C(O)NR^3R^3$, $-SO_2R^4$, and $-C(O)R^3$;

$R^{13}$ is selected from -H, $-C(=O)R^3$, $-C(=O)OR^3$, $-C(=O)SR^3$, $-SO_2R^4$, $-C(=O)N(R^3)R^3$, and optionally substituted lower alkyl,

two $R^{13}$, together with the atom or atoms to which they are attached, can combine to form a heteroalicyclic optionally substituted with between one and four of $R^{60}$, said heteroalicyclic can have up to four annular heteroatoms, and said heteroalicyclic can have an aryl or heteroaryl fused thereto, in which case said aryl or heteroaryl is optionally substituted with an additional one to four of $R^{60}$;

$R^{14}$ is selected from -H, $-NO_2$, $-NH_2$, $-N(R^3)R^4$, -CN, $-OR^3$, optionally substituted lower alkyl, optionally substituted heteroalicyclylalkyl, optionally substituted aryl, optionally substituted arylalkyl and optionally substituted heteroalicyclic;

$R^{15}$ is a group $-M^1-M^2$, wherein $M^1$ is selected from absent, $-C(=S)N(R^{13})-$, $-C(=NR^{14})N(R^{13})-$, $-SO_2N(R^{13})-$, $-SO_2-$, $-C(=O)N(R^{13})-$, $-C(=O)C(=O)N(R^{13})-$, $-C_{0-4}$alkylene-, -C(=O)-, and an optionally substituted four to six-membered hetercyclyl annular containing between one and three heteratoms including at least one nitrogen; and $M^2$ is selected from -H, $-C_{0-6}$alkyl, alkoxy, $-C(=O)C_{0-4}$alkylQ, $-C_{0-4}$alkylQ, $-OC_{0-4}$alkylQ-, $-N(R^{13})C_{0-4}$alkylQ-, and $-C(=O)N(R^{13})C_{0-4}$alkylQ; and

Q is a five- to ten-membered ring system, optionally substituted with between zero and four of $R^{20}$;

$R^{20}$ is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

$R^{60}$ is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroarylalkyl, and optionally substituted arylalkyl;

two of $R^{60}$, when attached to a non-aromatic carbon, can be oxo;

with the proviso, only when Ar is according to formula **II**, if Y is a $C_{1-6}$ alkylene; Z is -NH- or $-N(CH_3)-$; $R^1$ is a $C_{1-6}$alkyl optionally substituted in the 2-position by -OH or a $C_{1-4}$alkoxy group; $R^2$ is -H or halogen; n = 0; and the atoms, $X^1$, of one bridge of the saturated bridged ring system, when combined with both bridgehead atoms, $X^2$, of the saturated bridged ring system, represent:

1) either a pyrrolidine or a piperidine, and any atom, $X^1$ or $X^2$, of either of said pyrrolidine or said piperidine is attached to Y, then the other bridge of said saturated bridged ring system cannot be any one of $-OC(O)CH_2-$,

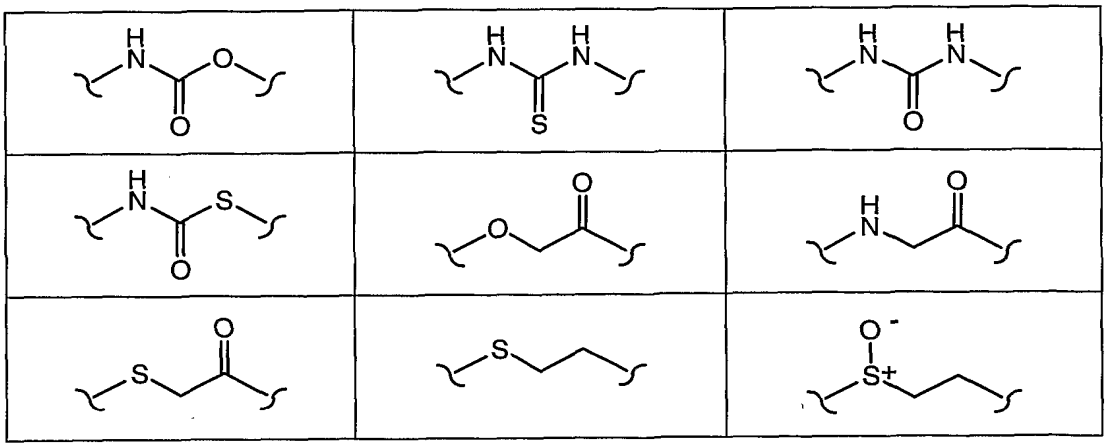
$-CH_2OC(O)-$, $-OC(O)CH_2CH_2-$, $-CH_2OC(O)CH_2-$, $-CH_2CH_2OC(O)-$, $-OC(O)CH_2NH-$, $-OC(O)CH_2N(C_{1-4}alkyl)-$, and $-OC(O)CH_2O-$; or

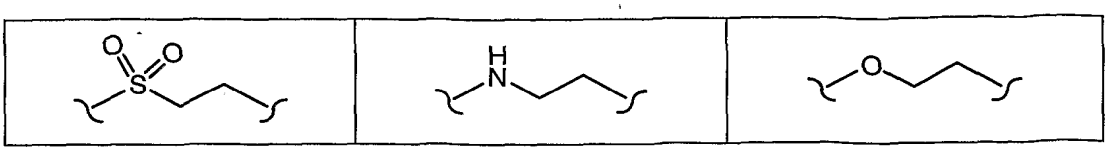
2) either a piperazine or a 4-($C_{1-4}$alkyl)-piperazine, and any atom, $X^1$ or $X^2$, of either of said piperazine or said 4-($C_{1-4}$alkyl)-piperazine is attached to Y, then the other bridge of said saturated bridged ring system, only when attached via the 2- and the 3-position of either of said piperazine or said 4-($C_{1-4}$alkyl)-piperazine, cannot be one of $-CH_2OC(O)CH_2-$, $-CH_2CH_2OC(O)-$, and either of the two aforementioned bridges optionally substituted by one or two $C_{1-2}$alkyl groups; or

3) a piperazine, and any atom, $X^1$ or $X^2$, of said piperazine is attached to Y, then the other bridge of said saturated bridged ring system, only when attached via the 3- and the 4-position of said piperazine, cannot be one of $-C(O)OCH_2CH_2-$, $-CH_2OC(O)CH_2-$, and either of the two aforementioned bridges optionally substituted by one or two $C_{1-2}$alkyl groups, and only when either of the two aforementioned bridges are attached to the 3-position of said piperazine via their left-hand end as depicted above; or

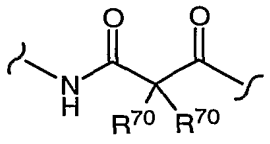
4) a 2-oxomorpholine, said 2-oxomorpholine attached to Y via its 4-position, then the other bridge of said saturated bridged ring system, only when attached via the 5- and the 6-position of said 2-oxomorpholine, cannot be one of $-(CH_2)_g-$, $-CH_2WCH_2-$, $-CH_2WCH_2CH_2-$, and $-CH_2CH_2WCH_2-$, wherein W is -O-, $-S(O)_{0-2}-$, -NH-, or $-N(C_{1-4}alkyl)-$ wherein g is 2, 3, or 4;

and with the proviso that when Z is-O-, Ar is according to formula **II**, and the portion of G directly attached to Ar is selected from:



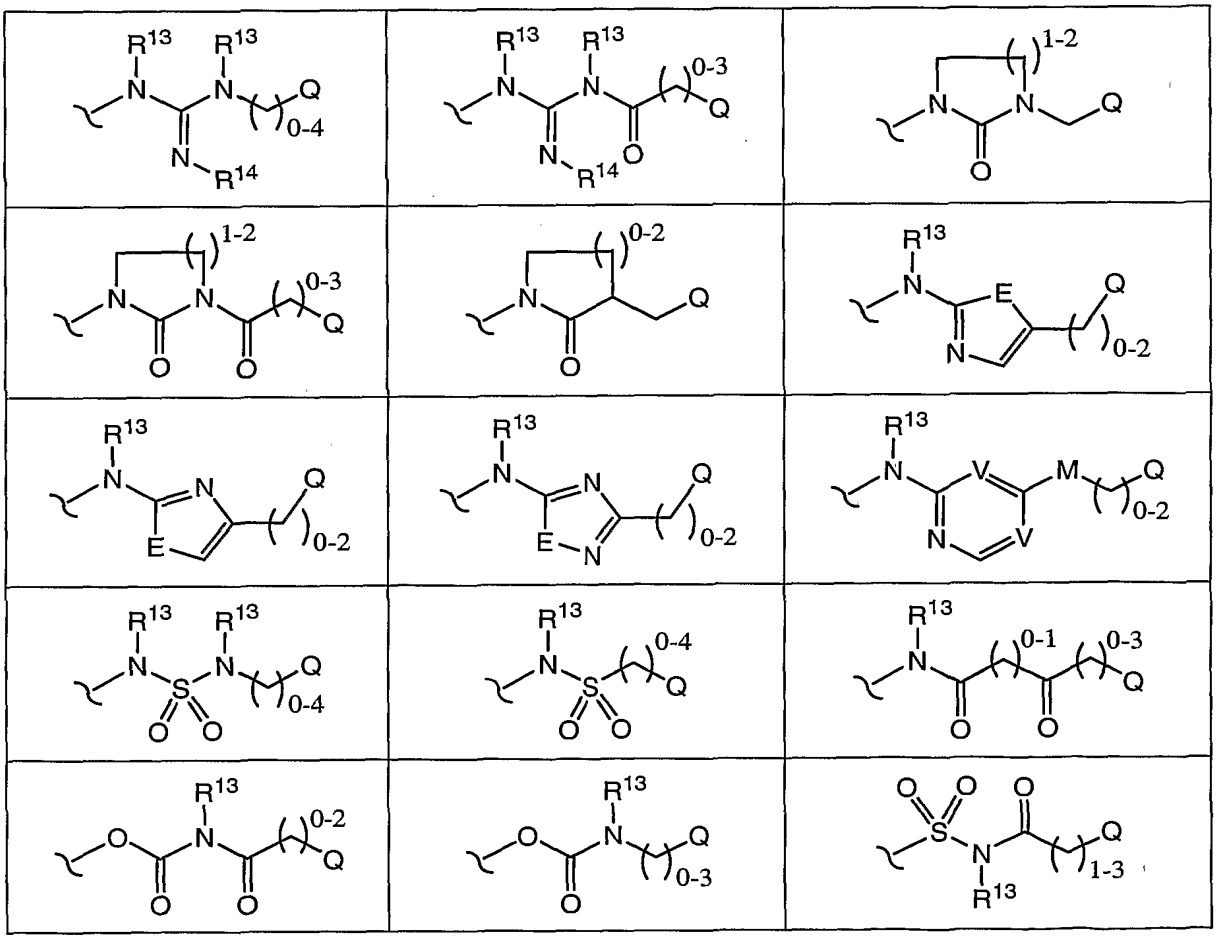


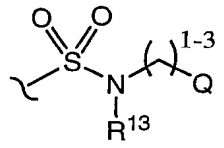
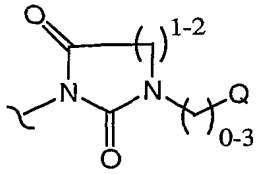
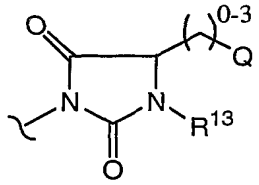
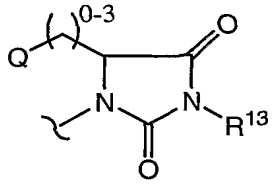
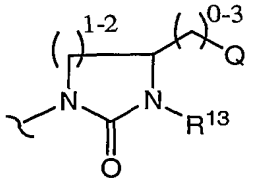
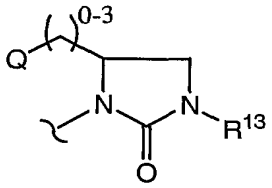
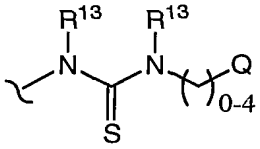
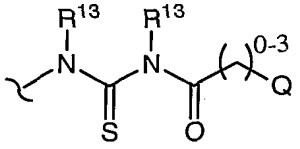
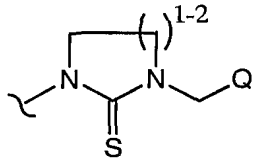
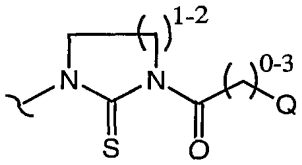
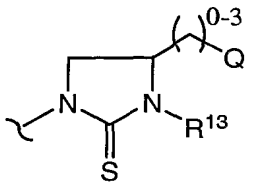
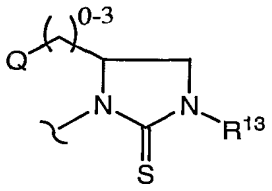
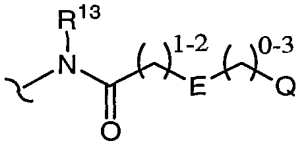
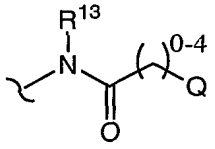
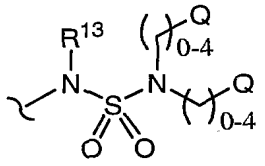
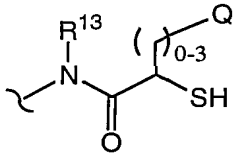
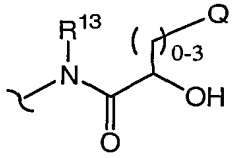
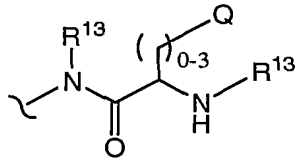
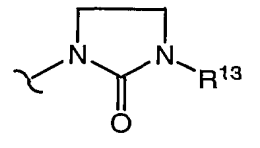
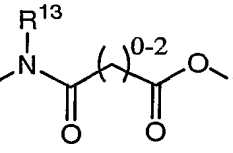
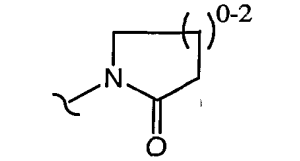
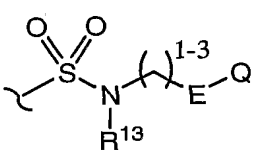
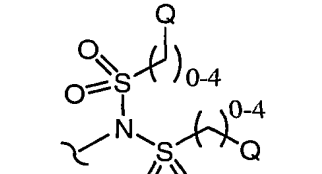
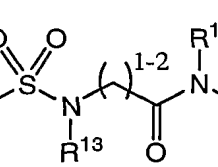
then $R^{50}$ must be of formula **IV**;

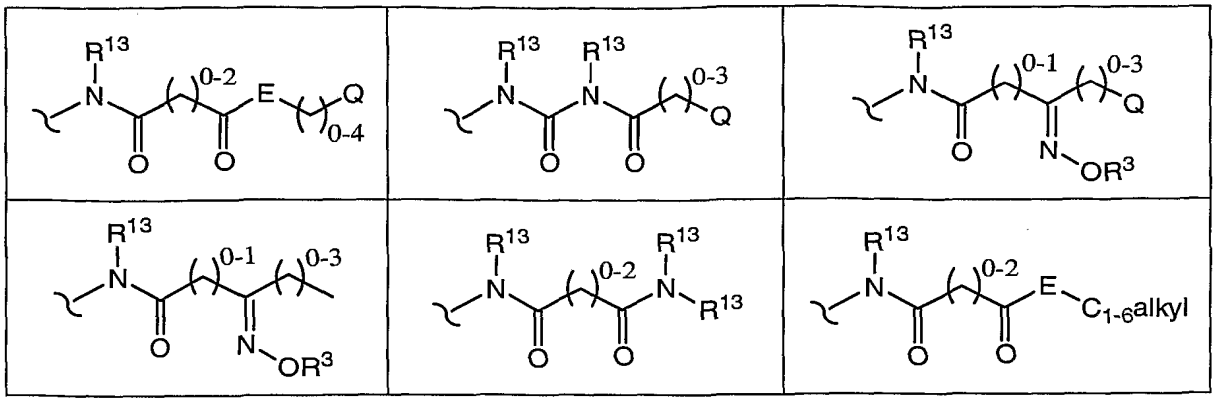
and with the proviso that when Ar is phenylene or substituted phenylene, Z is -S(O)$_{0-2}$- or -O-, then the portion of G directly attached to Ar cannot contain  , when $R^{70}$ is selected from -H, $C_{1-4}$alkyl, and $C_{1-4}$alkoxyl.

**[0034]** In one example, the compound is according to paragraph [0033], wherein Z is either -O- or -$NR^5$-.

**[0035]** In another example, the compound is according to paragraph [0034], wherein G is selected from the following:

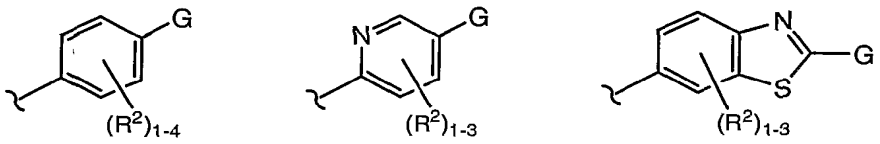


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wherein wherein Q, $R^{20}$, and $R^{13}$ are as defined above; each E is selected from -O-, -N($R^{13}$)-, -$CH_2$-, and -S(O)$_{0-2}$-; M is selected from -O-, -N($R^{13}$)-, -$CH_2$-, and -C(=O)N($R^{13}$)-; each V is independently either =N- or =C(H)-; each methylene in any of the above formulae is independently optionally substituted with $R^{25}$; and $R^{25}$ is selected from halogen, trihalomethyl, -CN, -$NO_2$, -$NH_2$, -$OR^3$, -$NR^3R^4$, -S(O)$_{0-2}R^3$, -$SO_2NR^3R^3$, -$CO_2R^3$, -C(O)$NR^3R^3$, -N($R^3$)$SO_2R^3$, -N($R^3$)C(O)$R^3$, -N($R^3$)$CO_2R^3$, -C(O)$R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; two of $R^{25}$, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic, two of $R^{25}$ on a single carbon can be oxo.

**[0036]** In another example, the compound is according to paragraph [0035], wherein Ar is according to one of formula **IIa**, **IIb**, and **IIIa**.



**IIa** **IIb** **IIIa**

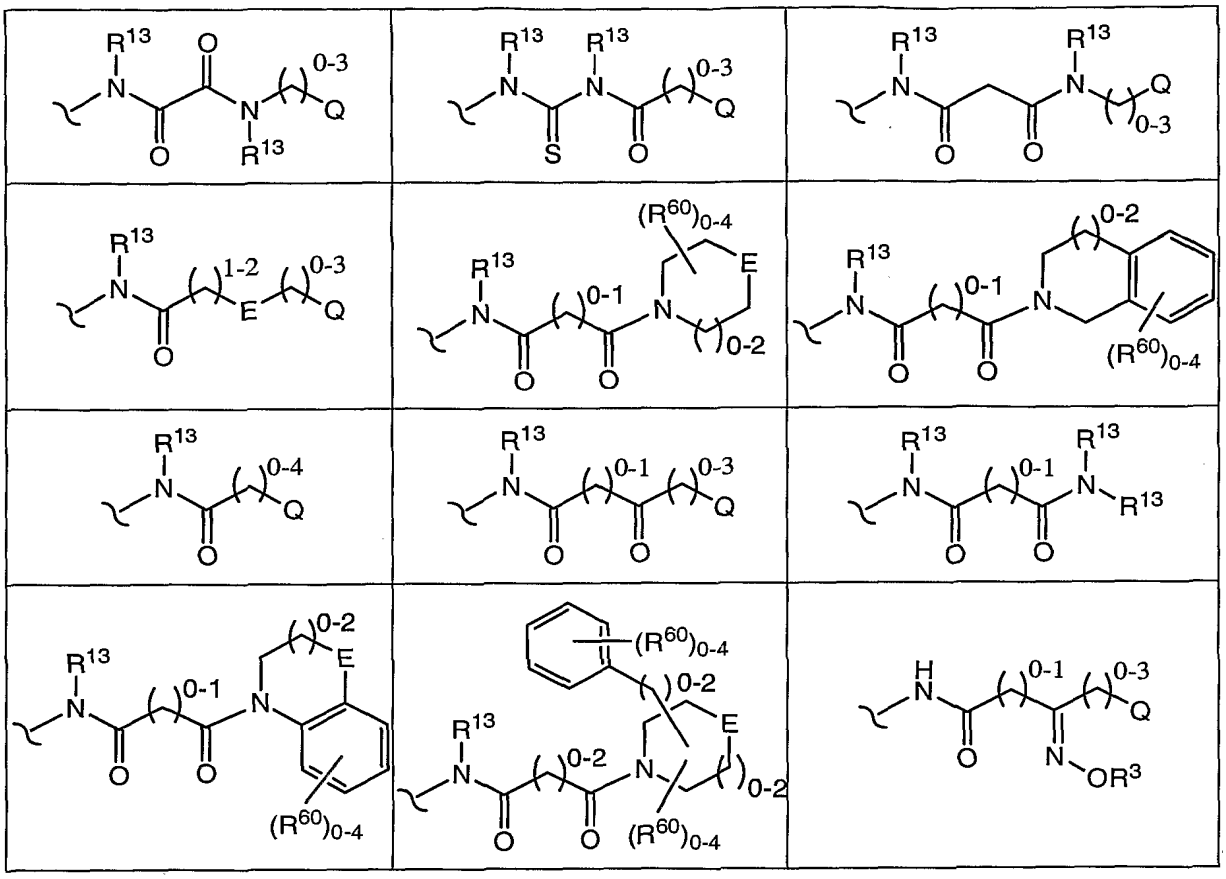
**[0037]** In another example, the compound is according to paragraph [0036], wherein D is -O- and $R^1$ is -$OR^3$.

**[0038]** In another example, the compound is according to paragraph [0037], wherein -O-$R^{50}$ and $R^1$ are interchangeably located at the 6-position and 7-position of the quinazoline or quinoline according to formula **I**.

**[0039]** In another example, the compound is according to paragraph [0038], wherein $R^1$ is -OH or -$OC_{1-6}$alkyl.

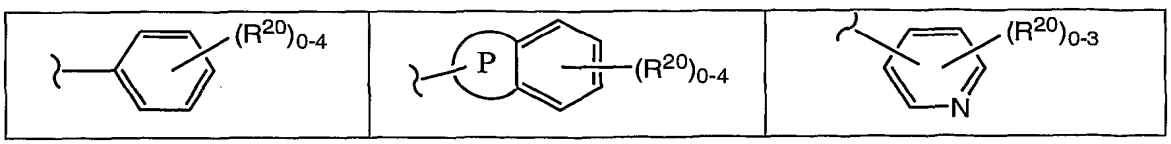
**[0040]** In another example, the compound is according to paragraph [0039], wherein $A^1$ is =N- or =C(H)-.

**[0041]** In another example, the compound is according to paragraph [0040], wherein G is selected from:



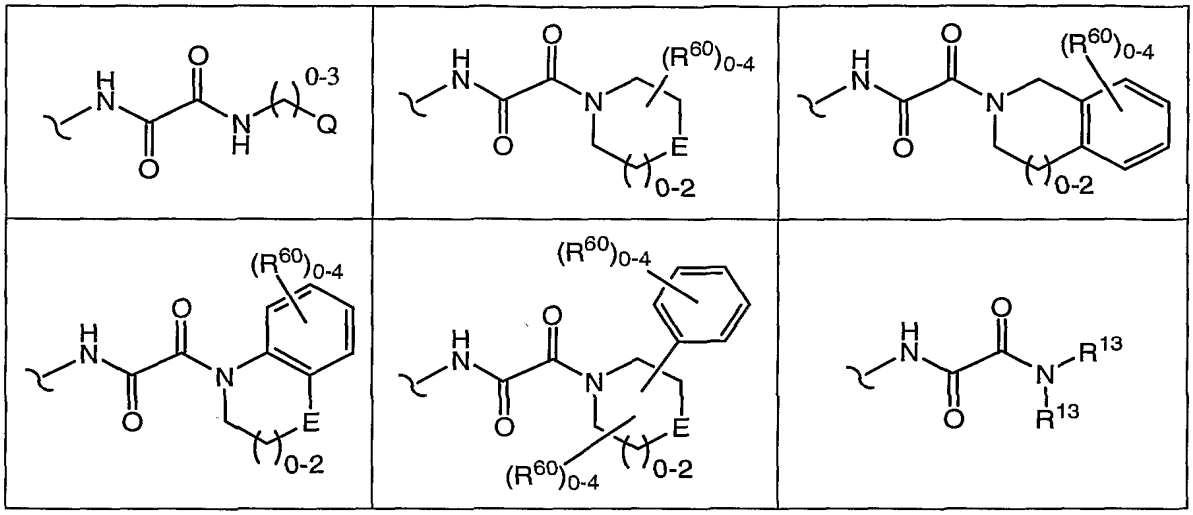
wherein Q, $R^{20}$, $R^{13}$, E, and $R^{60}$ are as defined above; each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with $R^{25}$; and $R^{25}$ is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; two of $R^{25}$, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic.

**[0042]** In another example, the compound is according to paragraph [0041], wherein Q is selected from:



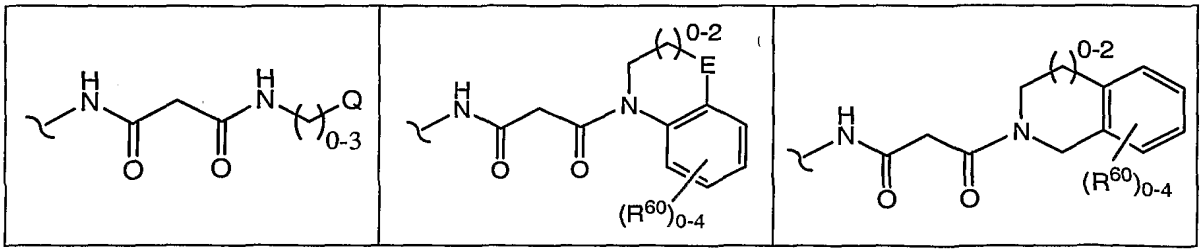
wherein $R^{20}$ is defined as above, and P is a five- to seven-membered ring, including the two shared carbons of the aromatic ring to which P is fused, P optionally containing between one and three heteroatoms.

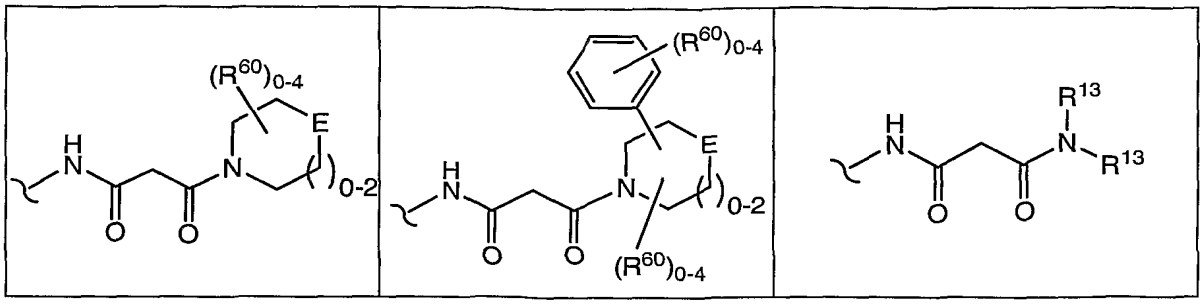
**[0043]** In another example, the compound is according to paragraph [0042], wherein Ar is according to formula **IIa**, and G is selected from:



wherein Q, $R^{20}$, $R^{13}$, E, and $R^{60}$ are as defined above, and each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with $R^{25}$; and $R^{25}$ is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; two of $R^{25}$, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic.

**[0044]** In another example, the compound is according to paragraph [0042], wherein Ar is according to formula **IIb**, and G is selected from:





wherein Q, $R^{20}$, $R^{13}$, E, and $R^{60}$ are as defined above, and each methylene in any of the above formulae, other than those depicted in a ring, is independently optionally substituted with $R^{25}$; and $R^{25}$ is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; two of $R^{25}$, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic.

**[0045]** In another example, the compound is according to paragraph [0044], wherein the methylene between the two carbonyls of the depicted formulae is di-substituted with either optionally substituted lower alkyl, or an optionally substituted spirocycle.

**[0046]** In another example, the compound is according to either [0043] or paragraph [0044], wherein $R^{50}$ is a heteroalicylic or a $C_{1-6}$alkyl-heteroalicylic.

**[0047]** In another example, the compound is according to paragraph [0046], wherein at least one of $R^2$ is halogen.

**[0048]** In another example, the compound is according to paragraph [0046], wherein $R^{50}$ is according to formula **IV**.

**[0049]** In another example, the compound is according to paragraph [0048], wherein the saturated bridged ring system according to formula **IV** has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], [3.1.0], [3.3.3], [3.3.2], [3.3.1], [3.2.2], [3.2.1], [2.2.2], and [2.2.1].

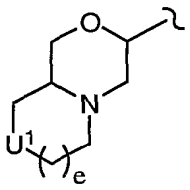
**[0050]** In another example, the compound is according to paragraph [0049], wherein Y is selected from $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2-$, $-CH_2-$, and absent.

**[0051]** In another example, the compound is according to paragraph [0050], wherein n is 0 and the saturated bridged ring system according to formula **IV** has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], and [3.1.0].

**[0052]** In another example, the compound is according to paragraph [0051], wherein said saturated bridged ring system contains at least one annular nitrogen or at least one annular oxygen.

**[0053]** In another example, the compound is according to paragraph [0052], wherein said saturated bridged ring system contains $-NR^8-$, wherein $R^8$ is selected from -H, optionally substituted lower alkyl, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.

**[0054]** In another example, the compound is according to paragraph [0052], wherein said saturated bridged ring system is of formula **V**,



**V**

wherein $U^1$ is selected from -O-, $-S(O)_{0-2}-$, $-NR^8-$, $-CR^6R^7-$, and absent; and e is 0 or 1.

**[0055]** In another example, the compound is according to paragraph [0054], wherein Y is $-CH_2-$.

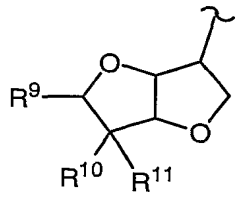
**[0056]** In another example, the compound is according to paragraph [0055], wherein $U^1$ is $-NR^8-$, wherein $R^8$ is selected from -H, optionally substituted lower alkyl, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.

**[0057]** In another example, the compound is according to paragraph [0055], wherein $U^1$ is -O-.

**[0058]** In another example, the compound is according to paragraph [0055], wherein $U^1$ is absent.

**[0059]** In another example, the compound is according to paragraph [0052], wherein Y is selected from $-CH_2CH_2-$, $-CH_2-$, and absent.

**[0060]** In another example, the compound is according to paragraph [0059], wherein said saturated bridged ring system is of formula **VI**,



VI

wherein $R^9$, $R^{10}$, and $R^{11}$ are each independently selected from -H, and $-OR^{12}$; or

$R^9$ is selected from -H, and $-OR^{12}$, and $R^{10}$ and $R^{11}$, when taken together, are either an optionally substituted alkylidene or an oxo;

$R^{12}$ is selected from -H, $-C(O)R^3$, optionally substituted lower alkylidyne, optionally substituted lower arylalkylidyne, optionally substituted lower heterocyclylalkylidyne, optionally substituted lower alkylidene, optionally substituted lower alkylidenearyl, optionally substituted lower alkylideneheterocyclyl, optionally substituted lower alkyl, optionally substituted lower alkylaryl, optionally substituted aryl, optionally substituted lower heterocyclylalkyl, and optionally substituted heterocyclyl;

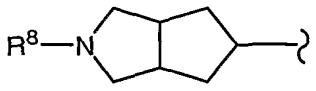
or two $R^{12}$'s, when taken together, form 1) a corresponding spirocyclic ketal when said two $R^{12}$'s stem from $R^{10}$ and $R^{11}$, or 2) a corresponding cyclic ketal when said two $R^{12}$'s stem from $R^9$ and one of $R^{10}$ and $R^{11}$.

**[0061]** In another example, the compound is according to paragraph [0060], wherein one of $R^{10}$ and $R^{11}$ is $-OR^{12}$, wherein $R^{12}$ is selected from -H, $-C(O)R^3$, and optionally substituted lower alkyl; and $R^9$ and the other of $R^{10}$ and $R^{11}$ are both -H.

**[0062]** In another example, the compound is according to paragraph [0061], wherein Y is either $-CH_2-$ or absent.

**[0063]** In another example, the compound is according to paragraph [0062], wherein $R^9$ is an alkyl group containing at least one fluorine substitution thereon.

**[0064]** In another example, the compound is according to paragraph [0053], wherein said saturated bridged ring system is of formula **VII**.

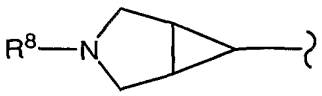



VII

**[0065]** In another example, the compound is according to paragraph [0064], wherein Y is either $-CH_2-$ or absent.

**[0066]** In another example, the compound is according to paragraph [0065], wherein $R^8$ is methyl or ethyl.

**[0067]** In another example, the compound is according to paragraph [0053], wherein said saturated bridged ring system is of formula **VIII**.

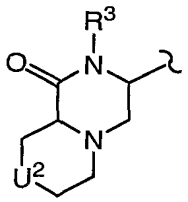


**VIII**

**[0068]** In another example, the compound is according to paragraph [0067], wherein Y is $-CH_2-$.

**[0069]** In another example, the compound is according to paragraph [0068], wherein $R^8$ is methyl or ethyl.

**[0070]** In another example, the compound is according to paragraph [0052], wherein said saturated bridged ring system is of formula **IX**



**IX**

wherein $U^2$ is selected from -O-, $-S(O)_{0-2}-$, $-NR^8-$, $-CR^6R^7-$, and absent.

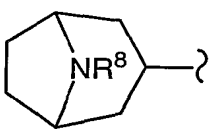
**[0071]** In another example, the compound is according to paragraph [0070], wherein $R^3$ of formula **IX** is selected from -H and optionally substituted alkyl.

**[0072]** In another example, the compound is according to paragraph [0071], wherein $U^2$ is either $-CR^6R^7-$ or absent.

**[0073]** In another example, the compound is according to paragraph [0072], wherein $U^2$ is either $-CH_2-$ or absent.

**[0074]** In another example, the compound is according to paragraph [0073], wherein Y is $-CH_2-$.

**[0075]** In another example, the compound is according to paragraph [0053], wherein said saturated bridged ring system is according to formula **X**.



X

**[0076]** In another example, the compound is according to paragraph [0075], wherein $R^8$ is methyl or ethyl.

**[0077]** In another example, the compound is according to paragraph [0033], selected from Table 1.

**Table 1**

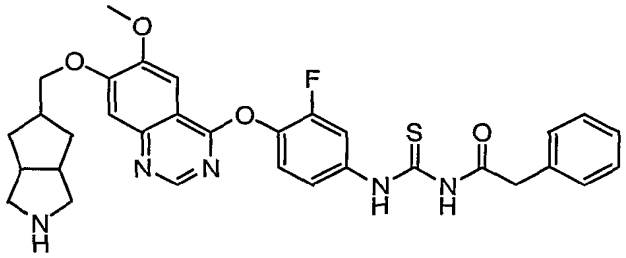
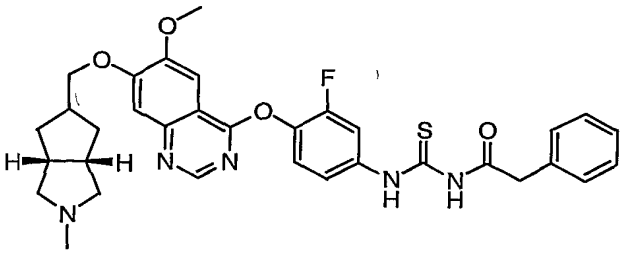
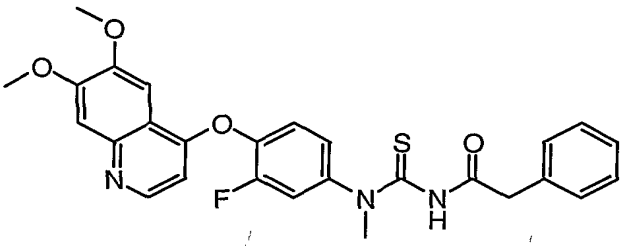
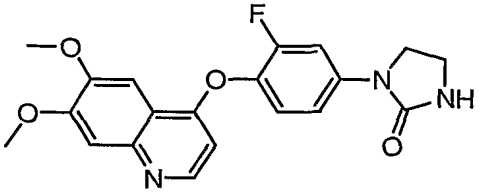
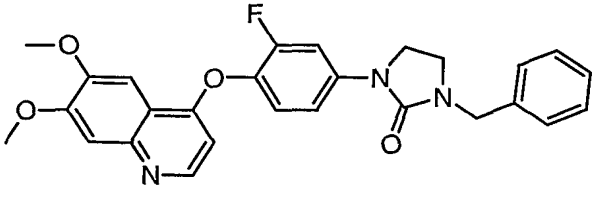
| Entry | Name | Structure |
|---|---|---|
| 1 | N-[({3-fluoro-4-[(6-(methyloxy)-7-{[(3aR,6aS)-octahydrocyclopenta[c]pyrrol-5-ylmethyl]oxy}quinazolin-4-yl)oxy]phenyl}amino)carbonothioyl]-2-phenylacetamide |  |
| 2 | N-{[(3-fluoro-4-{[7-({[(3aR,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide |  |
| 3 | N-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)(methyl)amino]carbonothioyl}-2-phenylacetamide |  |
| 4 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)imidazolidin-2-one |  |
| 5 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)imidazolidin-2-one |  |

**Table 1**

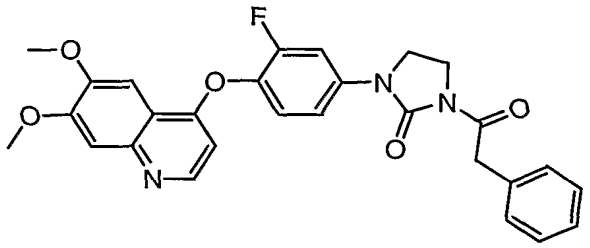
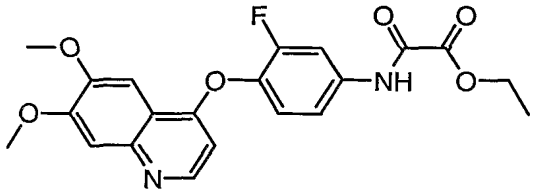
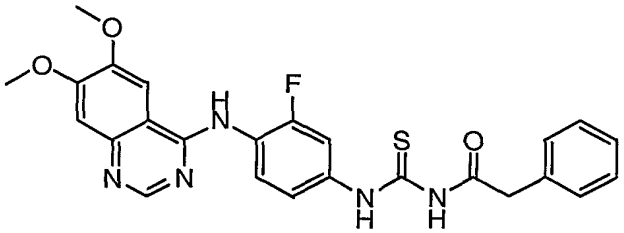
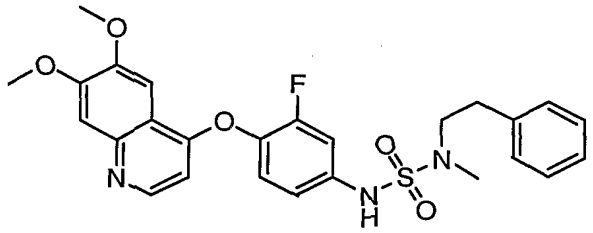
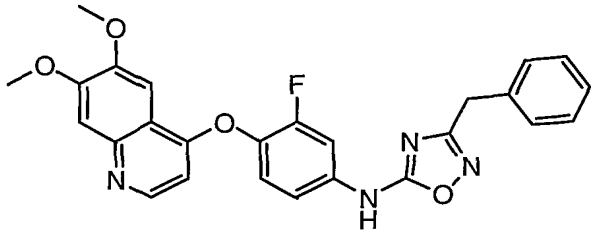
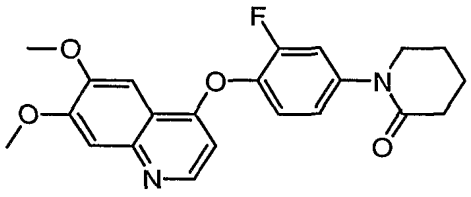
| Entry | Name | Structure |
|---|---|---|
| 6 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylacetyl)imidazolidin-2-one |  |
| 7 | ethyl [(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](oxo)acetate |  |
| 8 | N-{[(4-{[6,7-bis(methyloxy)quinazolin-4-yl]amino}-3-fluorophenyl)amino]carbonothioyl}-2-phenylacetamide |  |
| 9 | N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-methyl-N-(2-phenylethyl)sulfamide |  |
| 10 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)-1,2,4-oxadiazol-5-amine |  |
| 11 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)piperidin-2-one |  |

**Table 1**

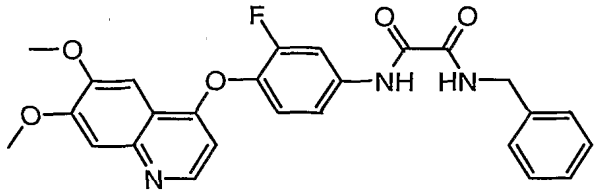
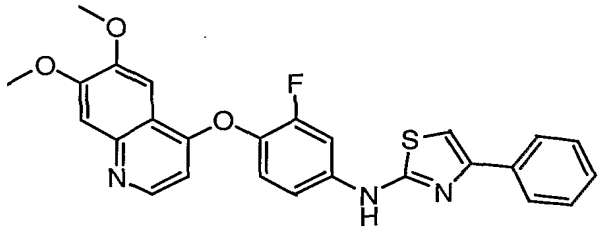
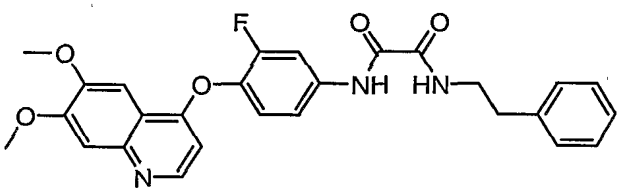
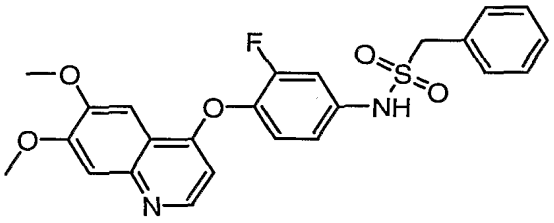
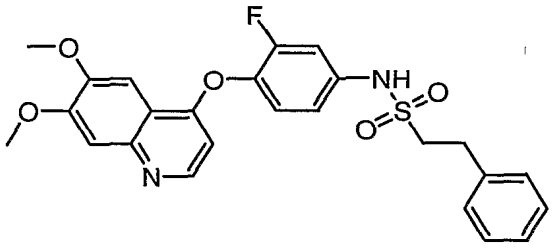
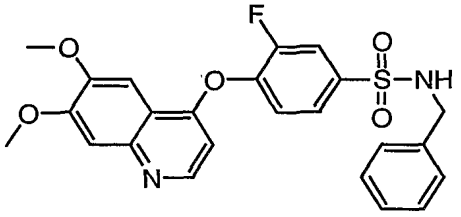
| Entry | Name | Structure |
|---|---|---|
| 12 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(phenylmethyl)ethanediamide |  |
| 13 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-phenyl-1,3-thiazol-2-amine |  |
| 14 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylethyl)ethanediamide |  |
| 15 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-1-phenylmethanesulfonamide |  |
| 16 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-2-phenylethanesulfonamide |  |
| 17 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(phenylmethyl)benzenesulfonamide |  |

**Table 1**

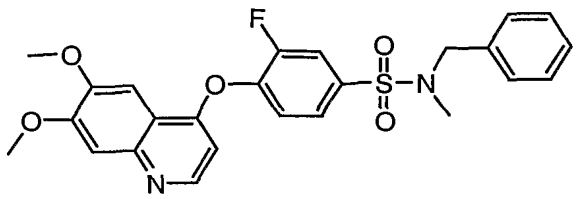
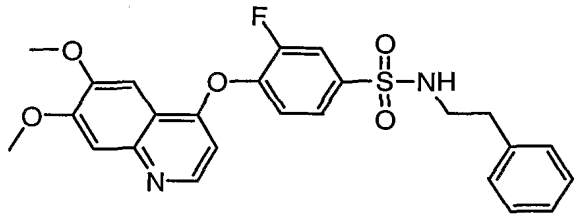
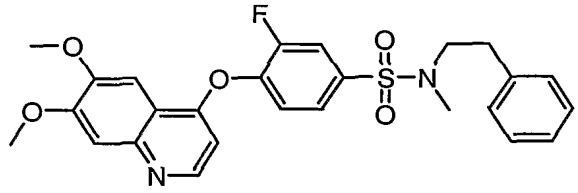
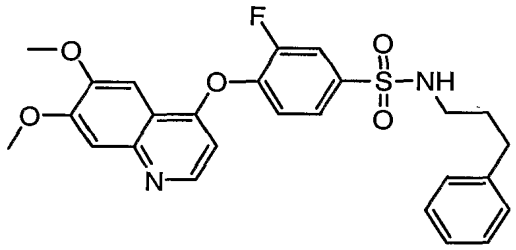
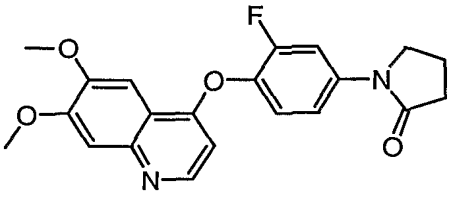
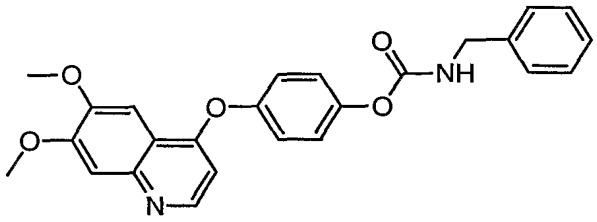
| Entry | Name | Structure |
|---|---|---|
| 18 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(phenylmethyl)benzenesulfonamide |  |
| 19 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(2-phenylethyl)benzenesulfonamide |  |
| 20 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(2-phenylethyl)benzenesulfonamide |  |
| 21 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(3-phenylpropyl)benzenesulfonamide |  |
| 22 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)pyrrolidin-2-one |  |
| 23 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (phenylmethyl)carbamate |  |

**Table 1**

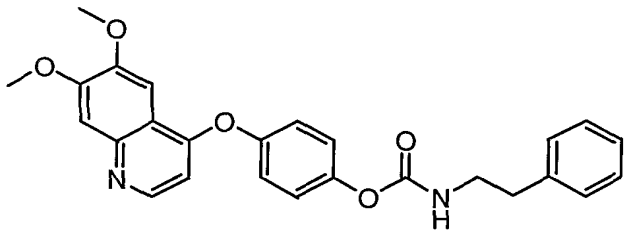
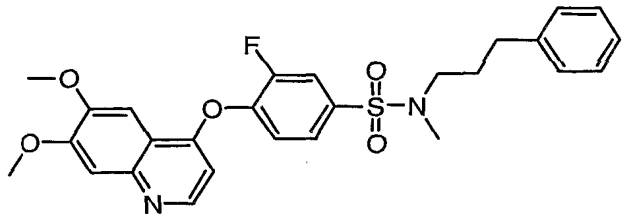
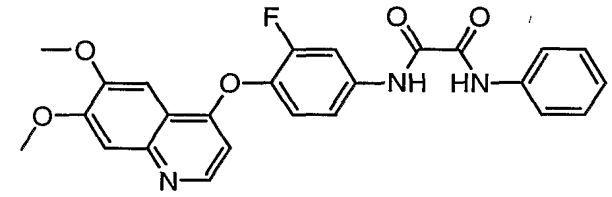
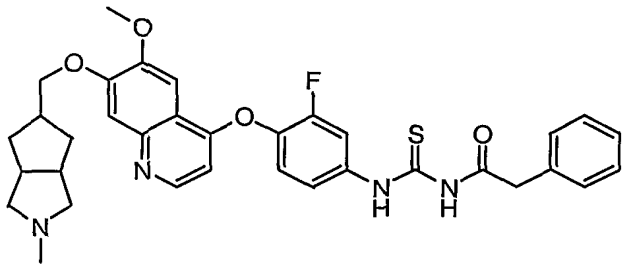
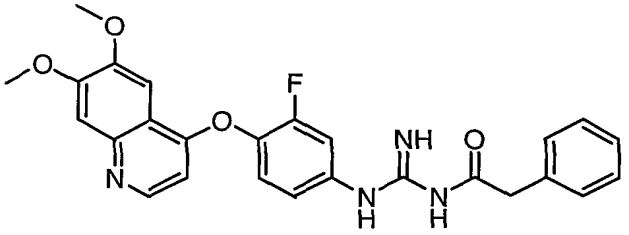
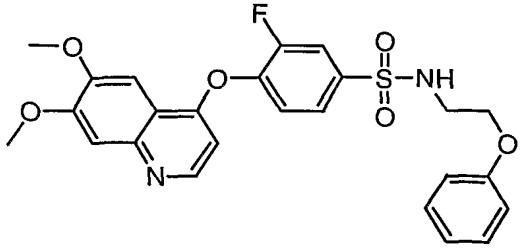
| Entry | Name | Structure |
|---|---|---|
| 24 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (2-phenylethyl)carbamate |  |
| 25 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(3-phenylpropyl)benzenesulfonamide |  |
| 26 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-phenylethanediamide |  |
| 27 | N-{[(3-fluoro-4-{[7-{[(2-methyloctahydrocyclopenta[c]pyrrol-5-yl)methyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide |  |
| 28 | N-[(Z)-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](imino)methyl]-2-phenylacetamide |  |
| 29 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-[2-(phenyloxy)ethyl]benzenesulfonamide |  |

**Table 1**

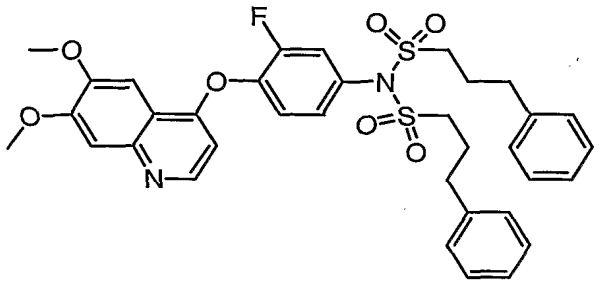
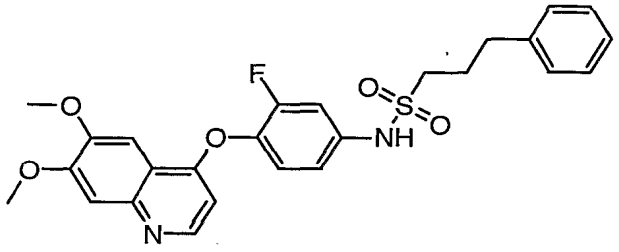
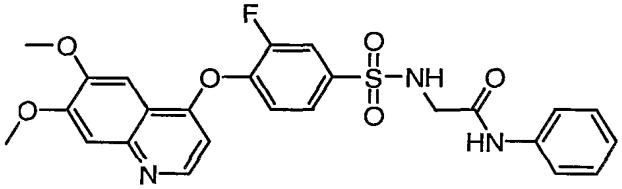
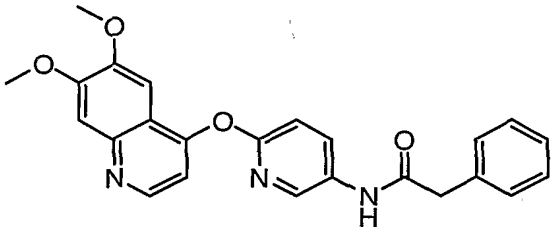
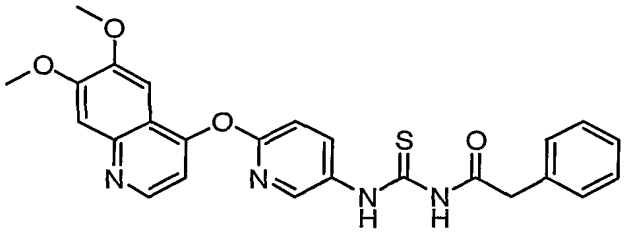
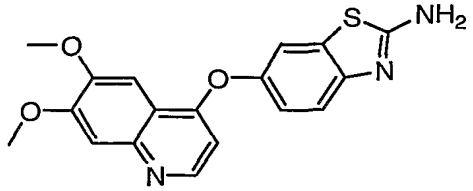
| Entry | Name | Structure |
|---|---|---|
| 30 | N,N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-bis-(3-phenylpropane-1-sulfonamide) |  |
| 31 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-phenylpropane-1-sulfonamide |  |
| 32 | N2-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)sulfonyl]-N1-phenylglycinamide |  |
| 33 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-2-phenylacetamide |  |
| 34 | N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide |  |
| 35 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-amine |  |

**Table 1**

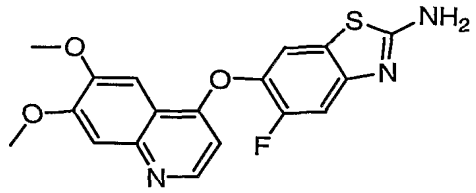
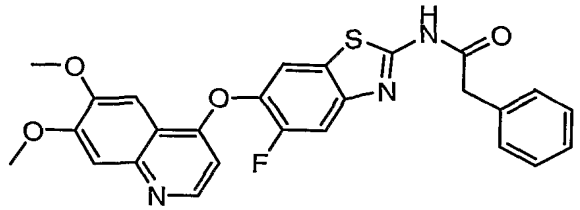
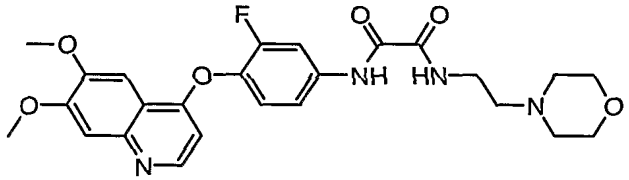
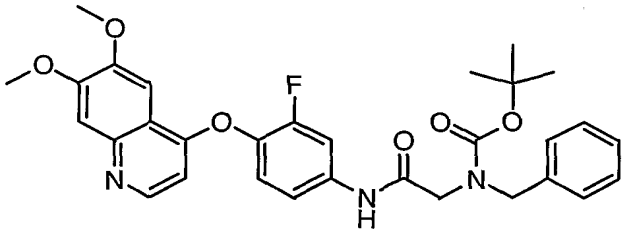
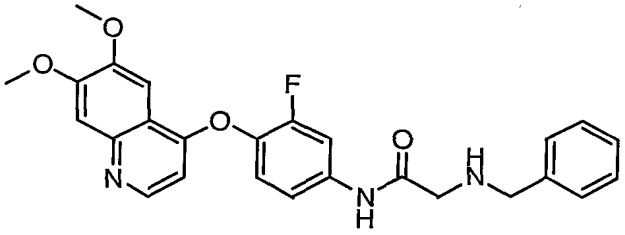
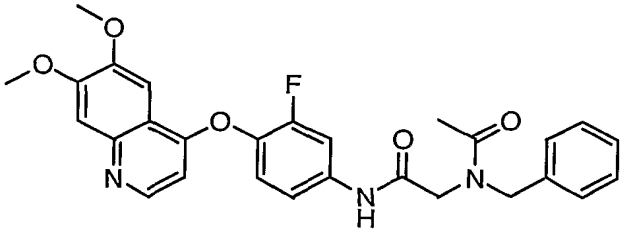
| Entry | Name | Structure |
|---|---|---|
| 36 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-amine |  |
| 37 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-phenylacetamide |  |
| 38 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-morpholin-4-ylethyl)ethanediamide |  |
| 39 | benzyl-{[4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylcarbamoyl]-methyl}-carbamic acid tert-butyl ester |  |
| 40 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(phenylmethyl)glycinamide |  |
| 41 | N2-acetyl-N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(phenylmethyl)glycinamide |  |

**Table 1**

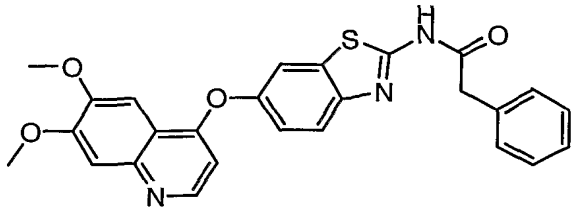
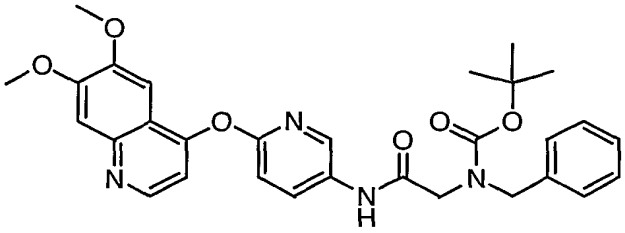
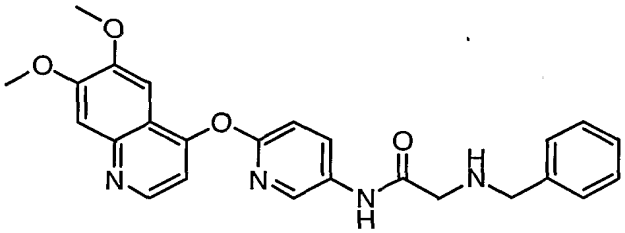
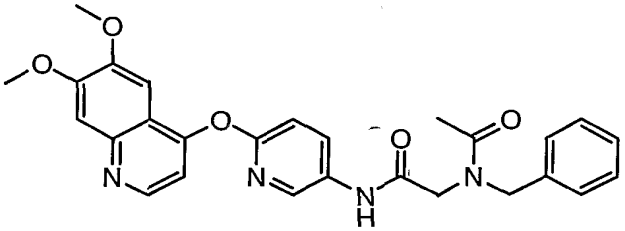
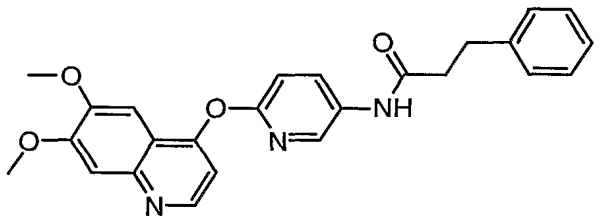
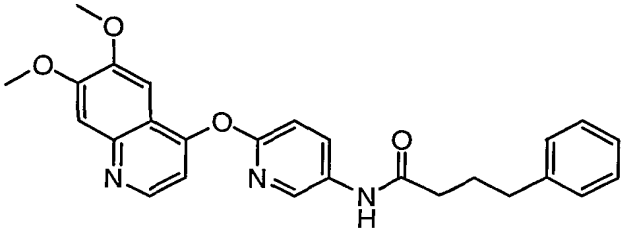
| Entry | Name | Structure |
|---|---|---|
| 42 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-yl)-2-phenylacetamide |  |
| 43 | benzyl-{[6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylcarbamoyl]-methyl}-carbamic acid tert-butyl ester |  |
| 44 | N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-(phenylmethyl)glycinamide |  |
| 45 | N2-acetyl-N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-(phenylmethyl)glycinamide |  |
| 46 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-3-phenylpropanamide |  |
| 47 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-4-phenylbutanamide |  |

**Table 1**

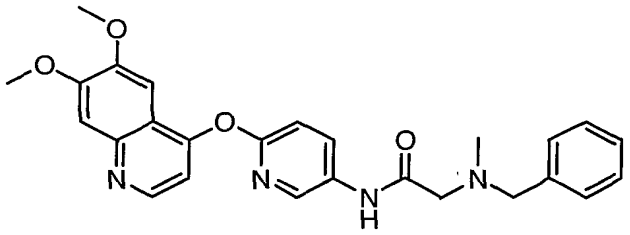
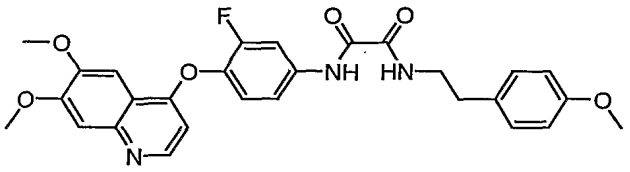
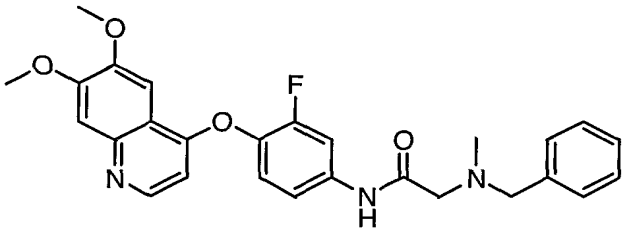
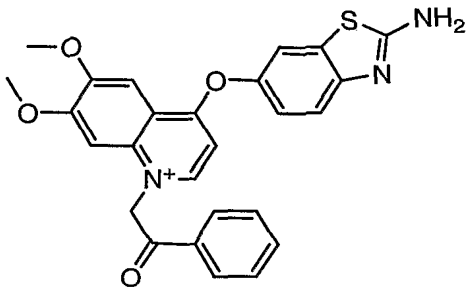
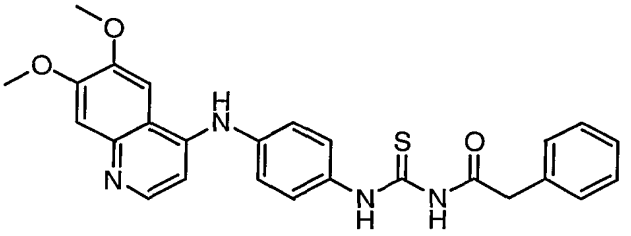
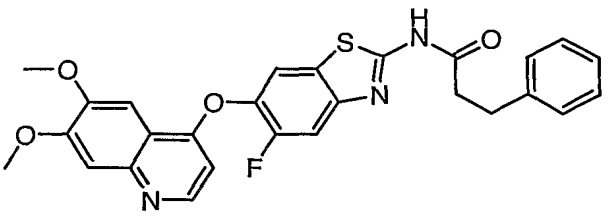
| Entry | Name | Structure |
|---|---|---|
| 48 | N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-methyl-N2-(phenylmethyl)glycinamide |  |
| 49 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{2-[4-(methyloxy)phenyl]ethyl}ethanediamide |  |
| 50 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-(phenylmethyl)glycinamide |  |
| 51 | 4-[(2-amino-1,3-benzothiazol-6-yl)oxy]-6,7-bis(methyloxy)-1-(2-oxo-2-phenylethyl)quinolinium |  |
| 52 | N-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]amino}phenyl)amino]carbonothioyl}-2-phenylacetamide |  |
| 53 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-3-phenylpropanamide |  |

**Table 1**

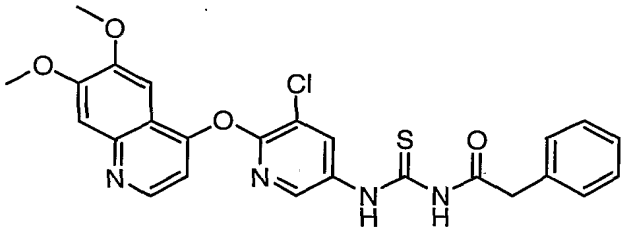
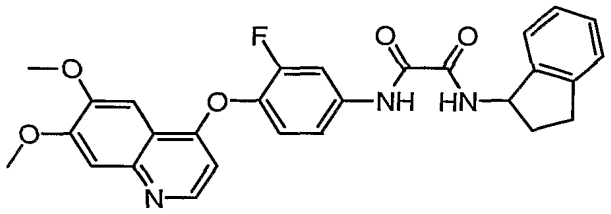
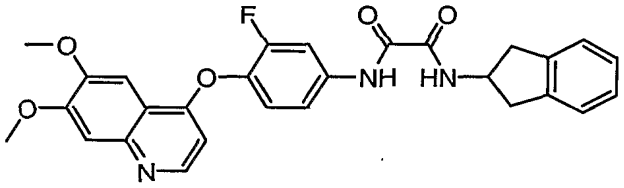
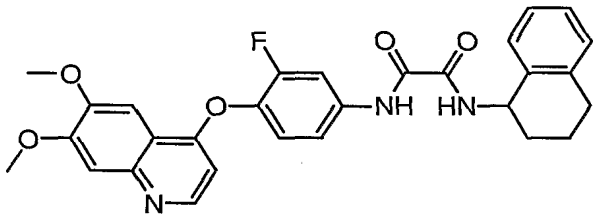
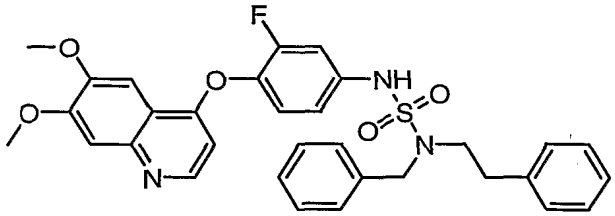
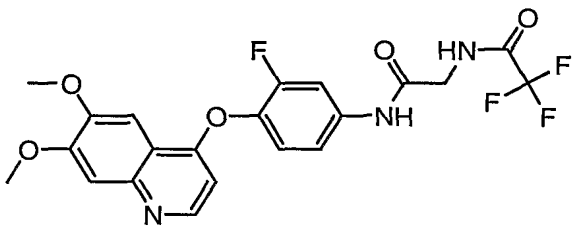
| Entry | Name | Structure |
|---|---|---|
| 54 | N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide |  |
| 55 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2,3-dihydro-1H-inden-1-yl)ethanediamide |  |
| 56 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2,3-dihydro-1H-inden-2-yl)ethanediamide |  |
| 57 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydronaphthalen-1-yl)ethanediamide |  |
| 58 | N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-(2-phenylethyl)-N-(phenylmethyl)sulfamide |  |
| 59 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(trifluoroacetyl)glycinamide |  |

**Table 1**

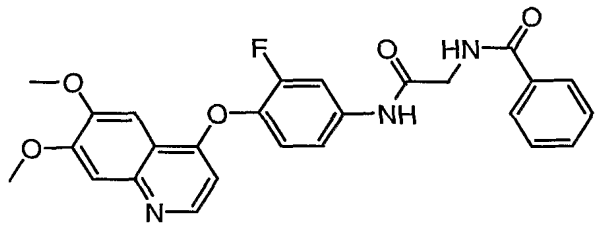
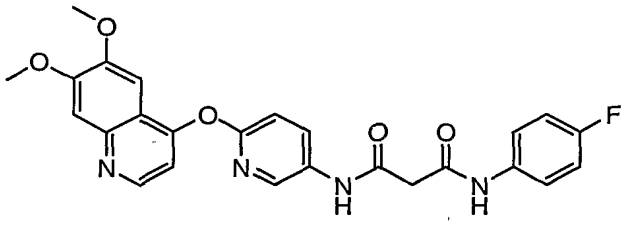
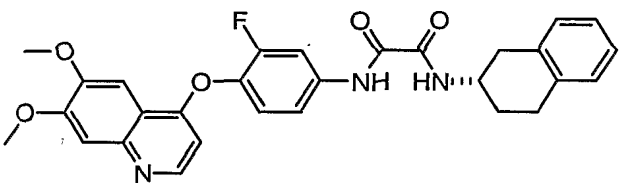
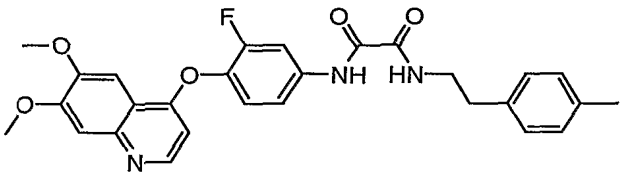
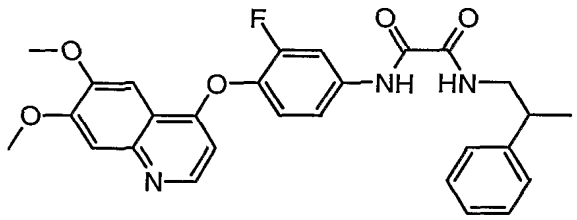
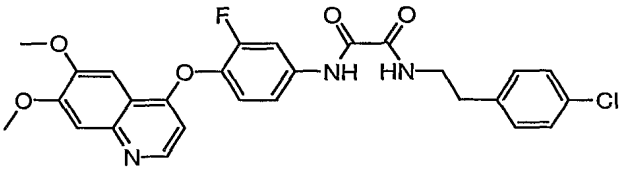
| Entry | Name | Structure |
|---|---|---|
| 60 | N-{[4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylcarbamoyl]-methyl}-benzamide |  |
| 61 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N'-(4-fluorophenyl)propanediamide |  |
| 62 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2S)-1,2,3,4-tetrahydronaphthalen-2-yl]ethanediamide |  |
| 63 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(4-methylphenyl)ethyl]ethanediamide |  |
| 64 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylpropyl)ethanediamide |  |
| 65 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(4-chlorophenyl)ethyl]ethanediamide |  |

**Table 1**

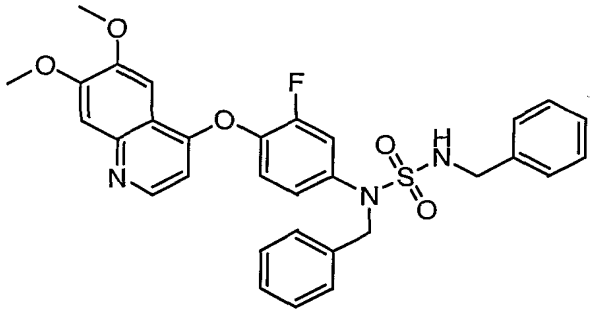
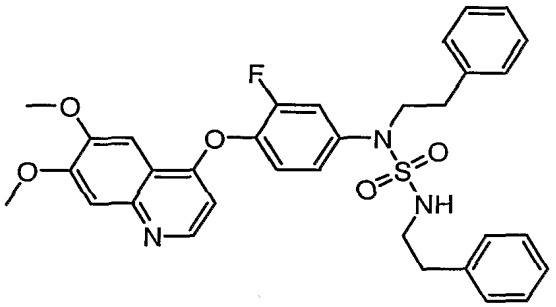
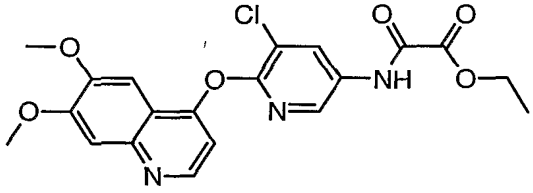
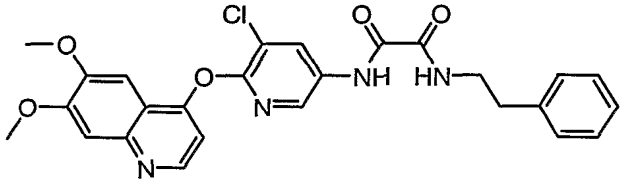
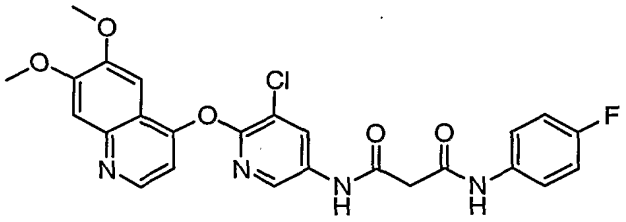
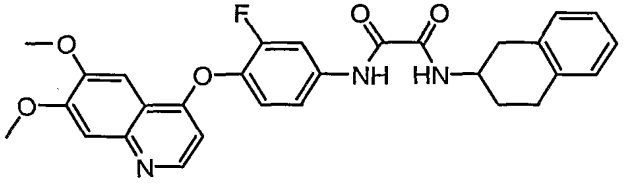
| Entry | Name | Structure |
|---|---|---|
| 66 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(phenylmethyl)sulfamide |  |
| 67 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(2-phenylethyl)sulfamide |  |
| 68 | ethyl [(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino](oxo)acetate |  |
| 69 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)ethanediamide |  |
| 70 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)propanediamide |  |
| 71 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydronaphthalen-2-yl)ethanediamide |  |

**Table 1**

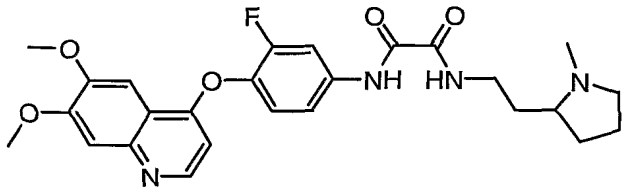
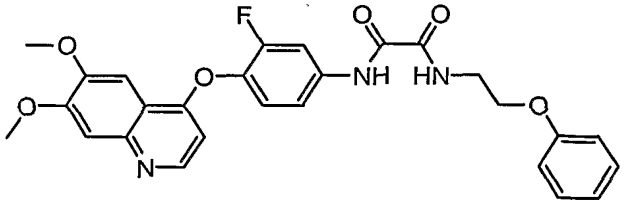
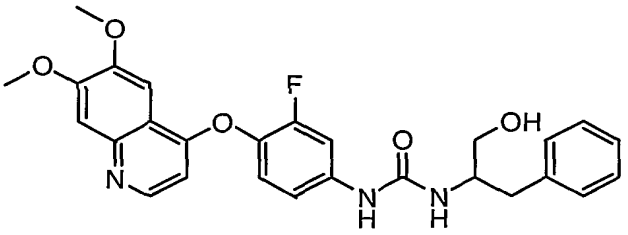
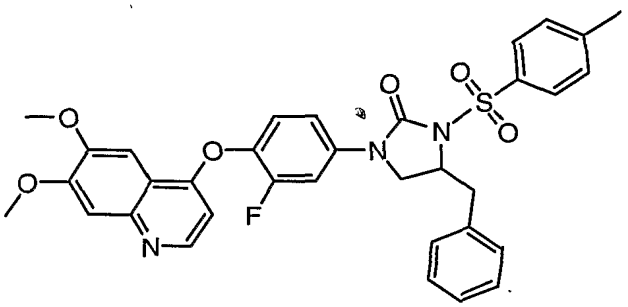
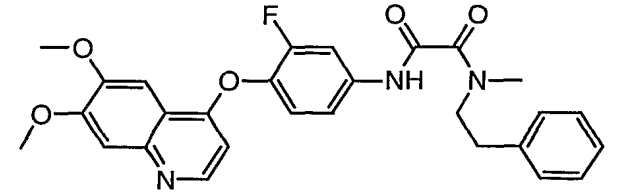
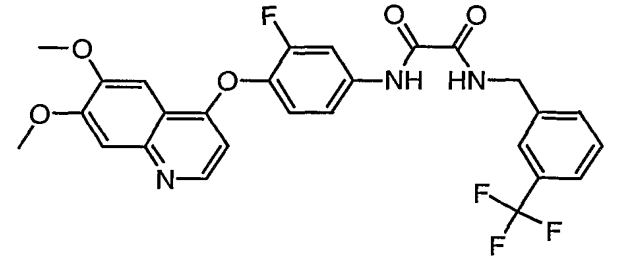
| Entry | Name | Structure |
|---|---|---|
| 72 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(1-methylpyrrolidin-2-yl)ethyl]ethanediamide |  |
| 73 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(phenyloxy)ethyl]ethanediamide |  |
| 74 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-hydroxy-1-(phenylmethyl)ethyl]urea |  |
| 75 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one |  |
| 76 | N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-methyl-N-(2-phenylethyl)ethanediamide |  |
| 77 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{[3-(trifluoromethyl)phenyl]methyl}ethanediamide |  |

**Table 1**

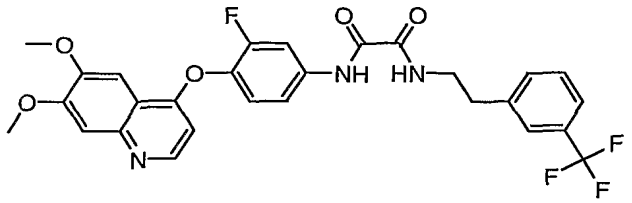
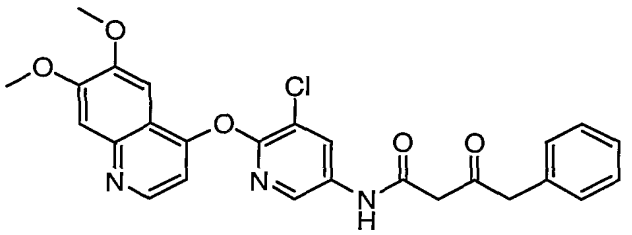
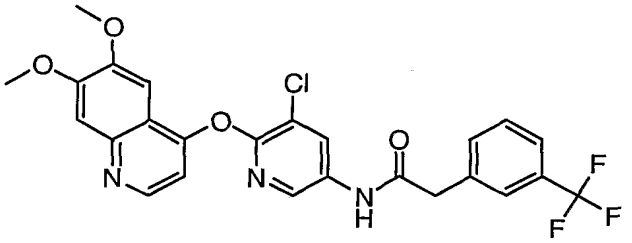
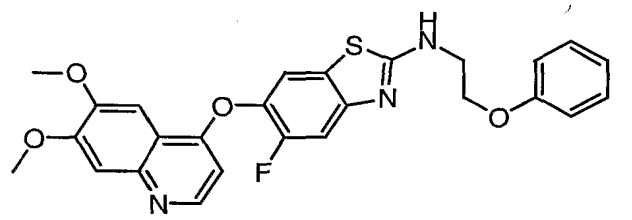
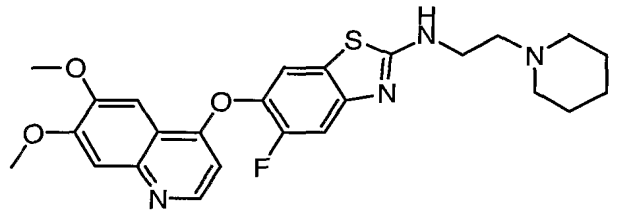
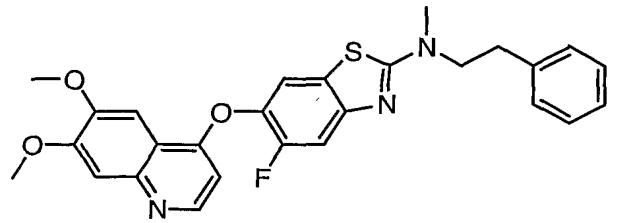
| Entry | Name | Structure |
|---|---|---|
| 78 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{2-[3-(trifluoromethyl)phenyl]ethyl}ethanediamide |  |
| 79 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-3-oxo-4-phenylbutanamide |  |
| 80 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-2-[3-(trifluoromethyl)phenyl]acetamide |  |
| 81 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-[2-(phenyloxy)ethyl]-1,3-benzothiazol-2-amine |  |
| 82 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-piperidin-1-ylethyl)-1,3-benzothiazol-2-amine |  |
| 83 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-methyl-N-(2-phenylethyl)-1,3-benzothiazol-2-amine |  |

**Table 1**

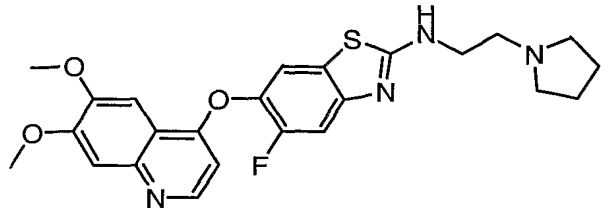
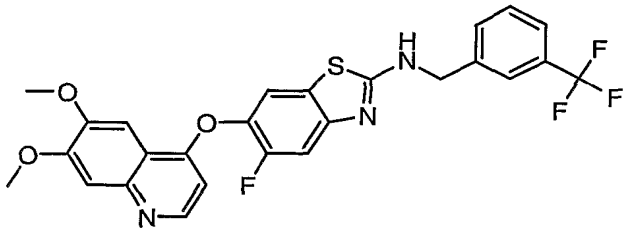
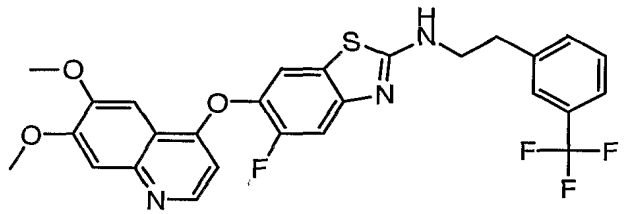
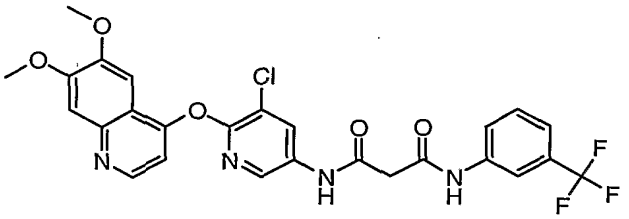
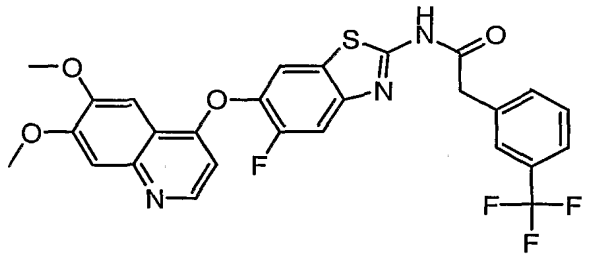
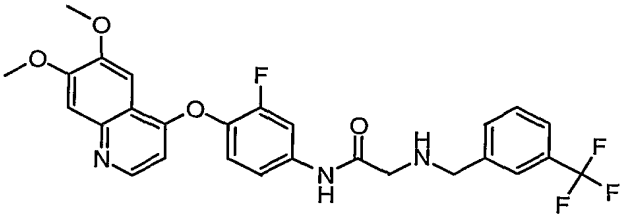
| Entry | Name | Structure |
|---|---|---|
| 84 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-pyrrolidin-1-ylethyl)-1,3-benzothiazol-2-amine |  |
| 85 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-{[3-(trifluoromethyl)phenyl]methyl}-1,3-benzothiazol-2-amine |  |
| 86 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-{2-[3-(trifluoromethyl)phenyl]ethyl}-1,3-benzothiazol-2-amine |  |
| 87 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-[3-(trifluoromethyl)phenyl]propanediamide |  |
| 88 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3-(trifluoromethyl)phenyl]acetamide |  |
| 89 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-{[3-(trifluoromethyl)phenyl]methyl}glycinamide |  |

**Table 1**

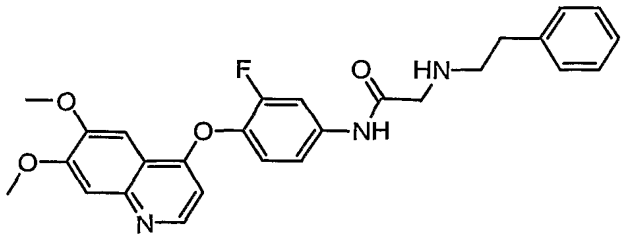
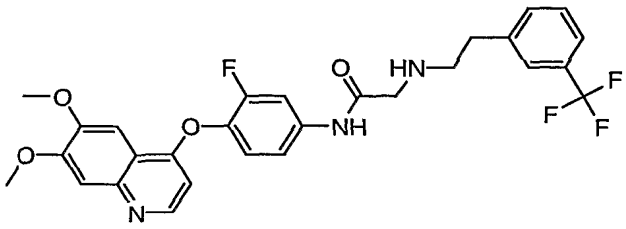
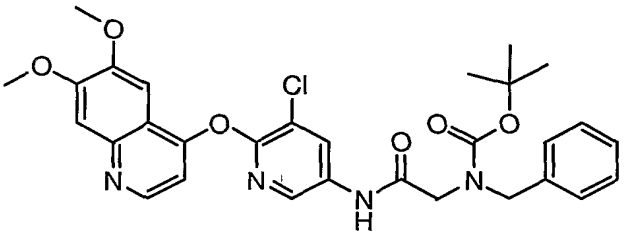
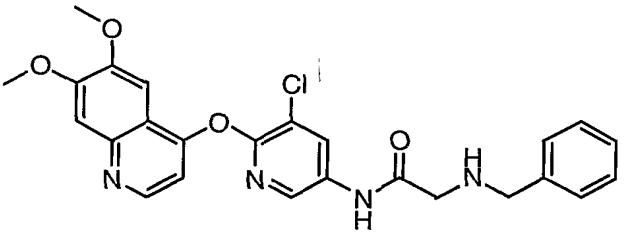
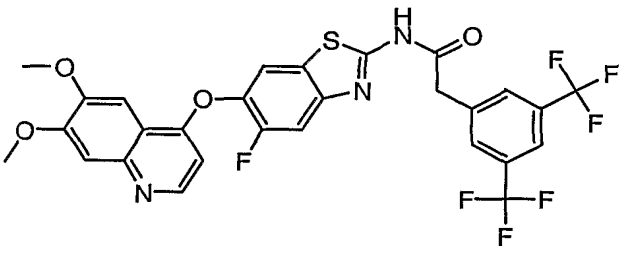
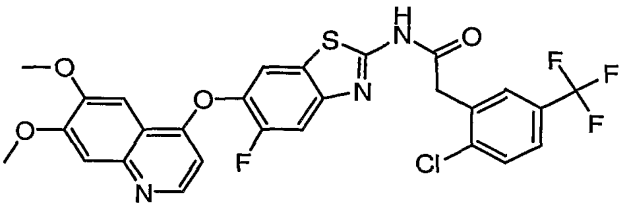
| Entry | Name | Structure |
|---|---|---|
| 90 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(2-phenylethyl)glycinamide |  |
| 91 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide |  |
| 92 | benzyl-{[5-chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylcarbamoyl]-methyl}-carbamic acid tert-butyl ester |  |
| 93 | N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N2-(phenylmethyl)glycinamide |  |
| 94 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3,5-bis(trifluoromethyl)phenyl]acetamide |  |
| 95 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[2-chloro-5-(trifluoromethyl)phenyl]acetamide |  |

**Table 1**

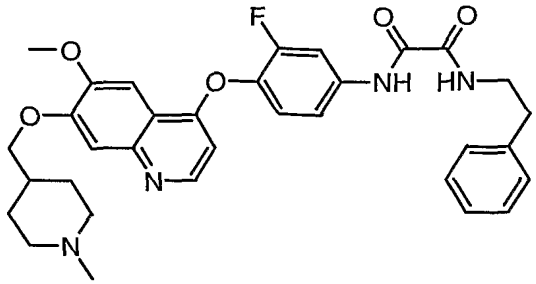
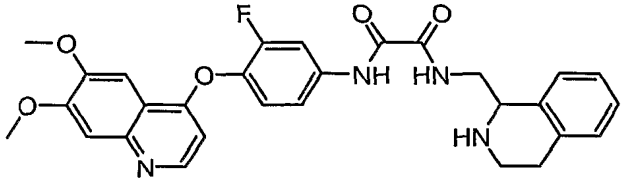
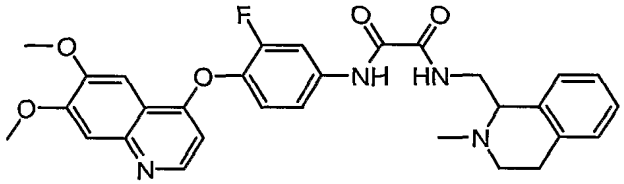
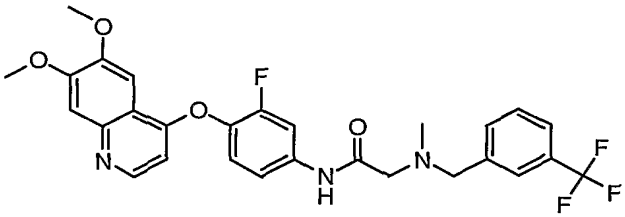
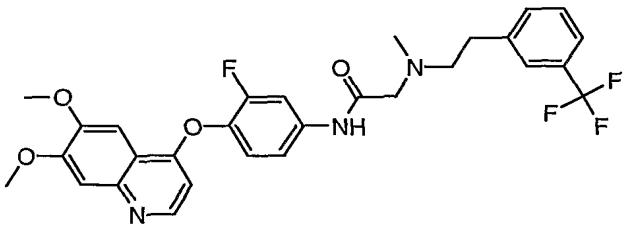
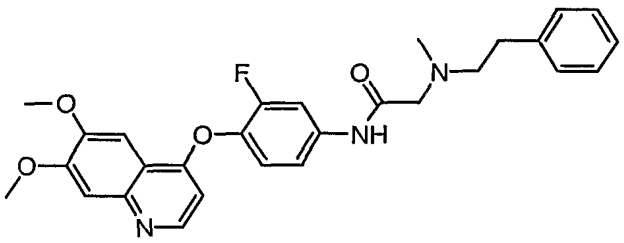
| Entry | Name | Structure |
|---|---|---|
| 96 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(2-phenylethyl)ethanediamide |  |
| 97 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)ethanediamide |  |
| 98 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]ethanediamide |  |
| 99 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-{[3-(trifluoromethyl)phenyl]methyl}glycinamide |  |
| 100 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide |  |
| 101 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-(2-phenylethyl)glycinamide |  |

**Table 1**

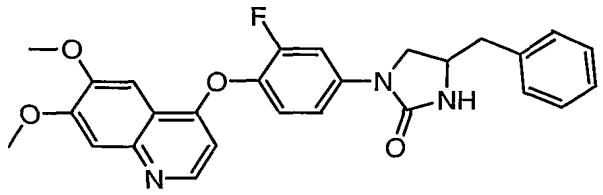
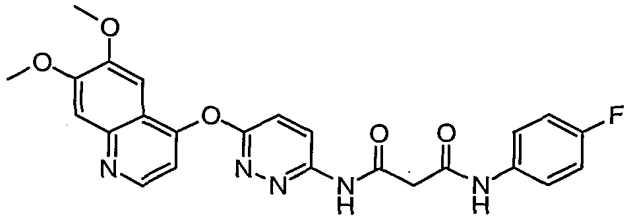
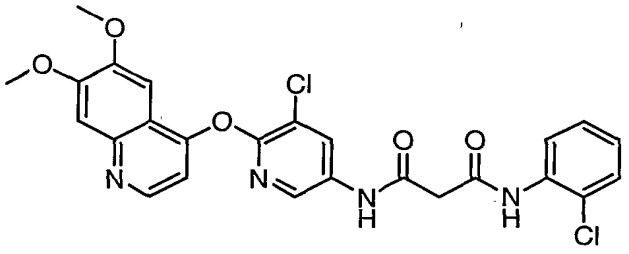
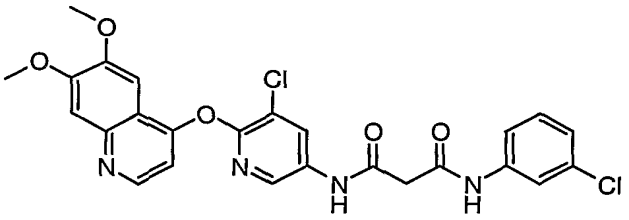
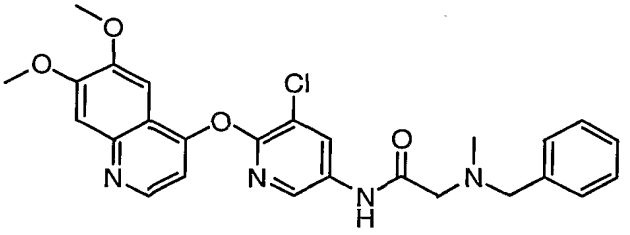
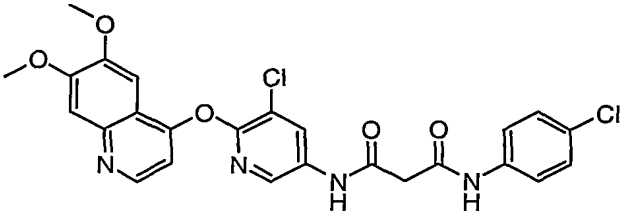
| Entry | Name | Structure |
|---|---|---|
| 102 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-(phenylmethyl)imidazolidin-2-one |  |
| 103 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridazin-3-yl)-N'-(4-fluorophenyl)propanediamide |  |
| 104 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-chlorophenyl)propanediamide |  |
| 105 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(3-chlorophenyl)propanediamide |  |
| 106 | N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N2-methyl-N2-(phenylmethyl)glycinamide |  |
| 107 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-chlorophenyl)propanediamide |  |

**Table 1**

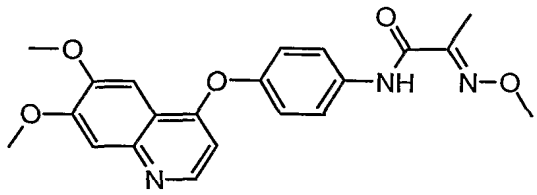
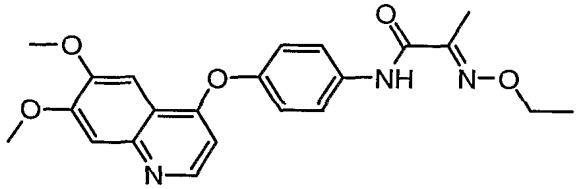
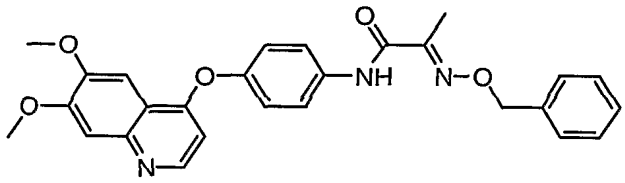
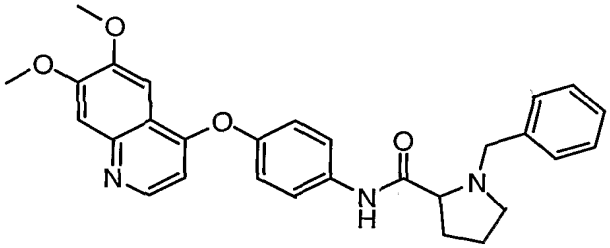
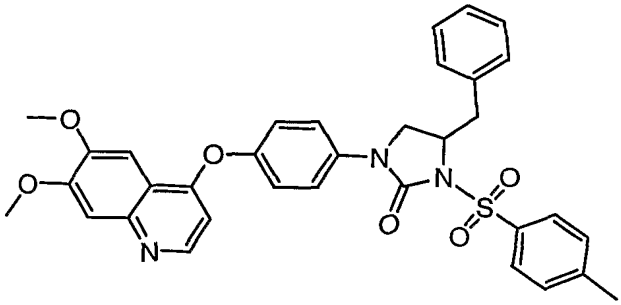
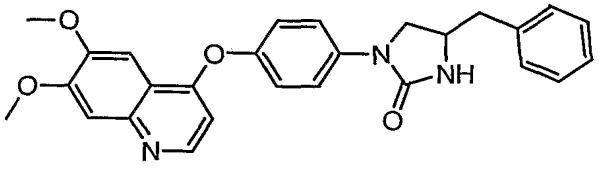
| Entry | Name | Structure |
|---|---|---|
| 108 | (2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(methyloxy)imino]propanamide |  |
| 109 | (2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(ethyloxy)imino]propanamide |  |
| 110 | (2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-{[(phenylmethyl)oxy]imino}propanamide |  |
| 111 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-1-(phenylmethyl)prolinamide |  |
| 112 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one |  |
| 113 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)imidazolidin-2-one |  |

**Table 1**

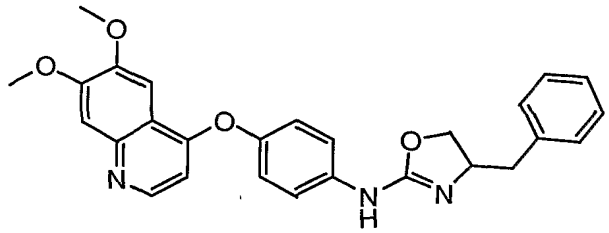
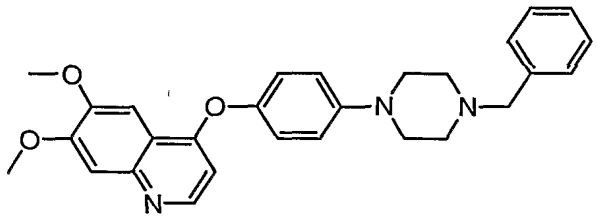
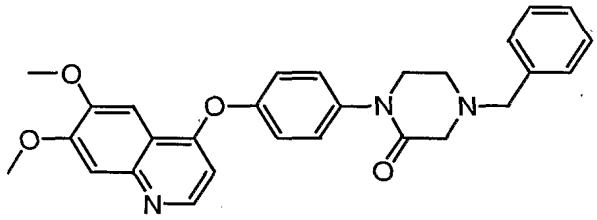
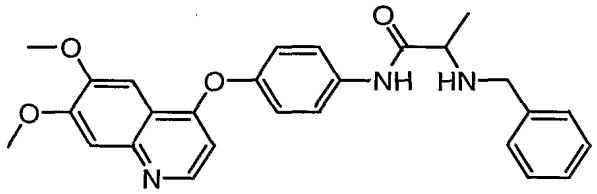
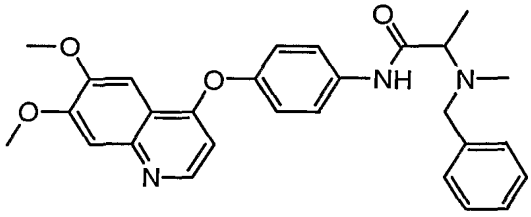
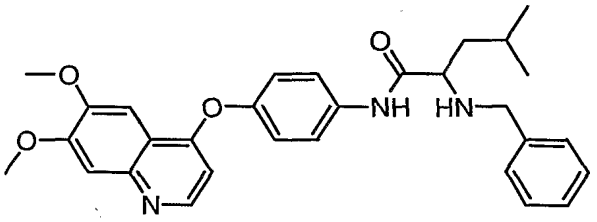
| Entry | Name | Structure |
|---|---|---|
| 114 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)-4,5-dihydro-1,3-oxazol-2-amine |  |
| 115 | 6,7-bis(methyloxy)-4-({4-[4-(phenylmethyl)piperazin-1-yl]phenyl}oxy)quinoline |  |
| 116 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)piperazin-2-one |  |
| 117 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)alaninamide |  |
| 118 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-methyl-N2-(phenylmethyl)alaninamide |  |
| 119 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)leucinamide |  |

**Table 1**

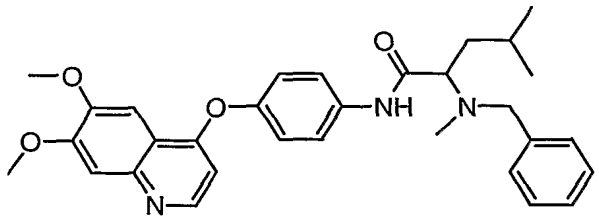
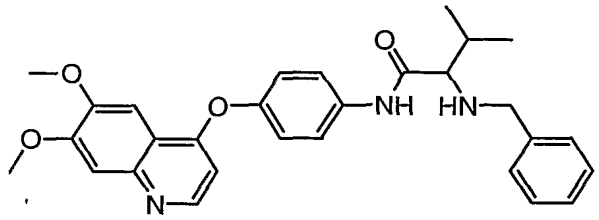
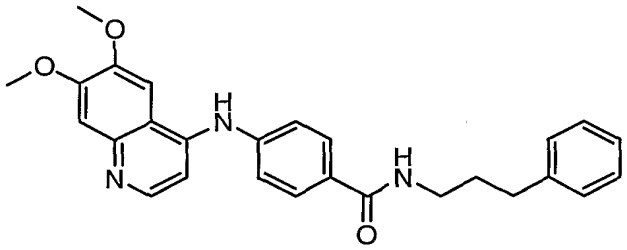
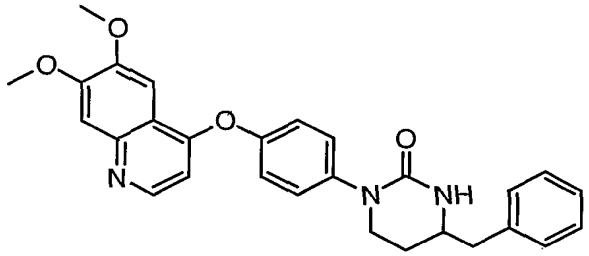
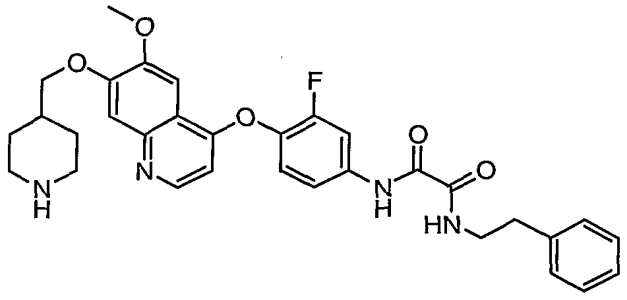
| Entry | Name | Structure |
|---|---|---|
| 120 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-methyl-N2-(phenylmethyl)leucinamide |  |
| 121 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)valinamide |  |
| 122 | 4-(6,7-dimethoxy-quinolin-4-ylamino)-N-(3-phenyl-propyl)-benzamide |  |
| 123 | 4-benzyl-1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-tetrahydro-pyrimidin-2-one |  |
| 124 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide |  |

**Table 1**

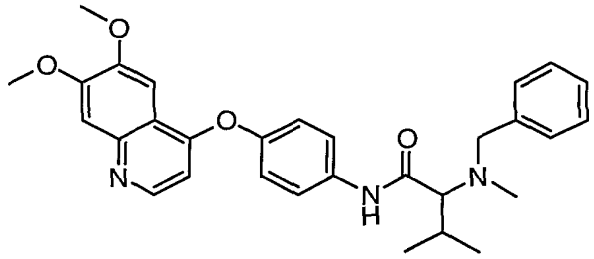
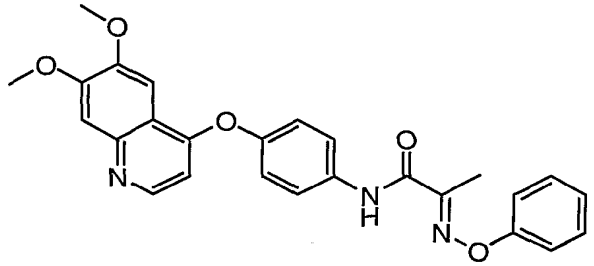
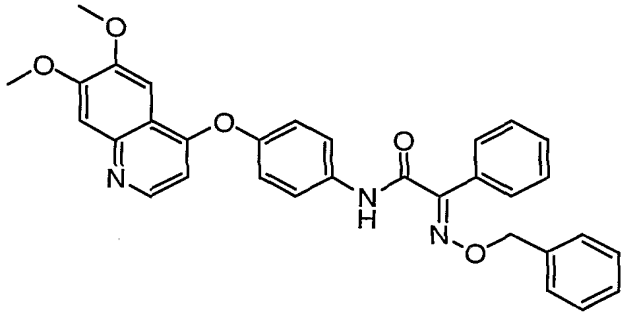
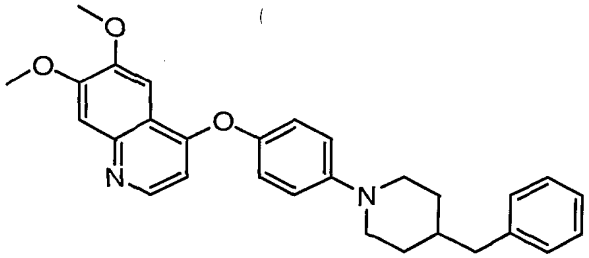
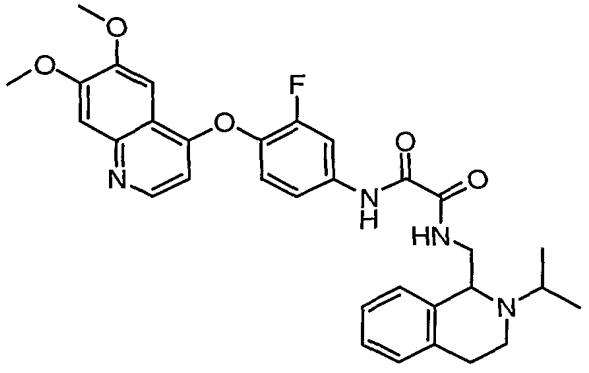
| Entry | Name | Structure |
|---|---|---|
| 125 | 2-(Benzyl-methyl-amino)-N-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-3-methyl-butyramide (note: Alphabetic order of prefixes ignored while selecting parent chain) |  |
| 126 | N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenyl]-2-phenoxyimino-propionamide |  |
| 127 | 2-Benzyloxyimino-N-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-2-phenyl-acetamide |  |
| 128 | 4-[4-(4-Benzyl-piperidin-1-yl)-phenoxy]-6,7-dimethoxy-quinoline |  |
| 129 | N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-oxalamide |  |

**Table 1**

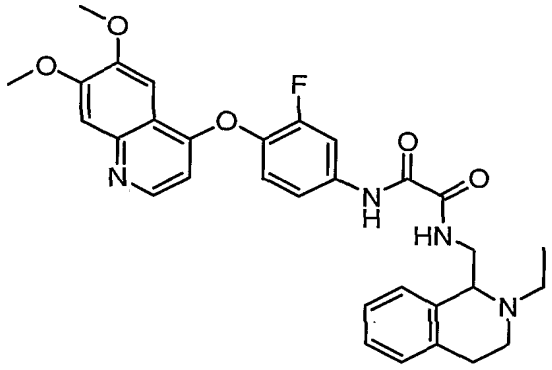
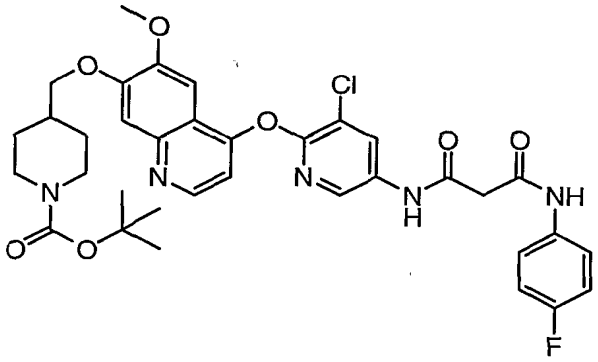
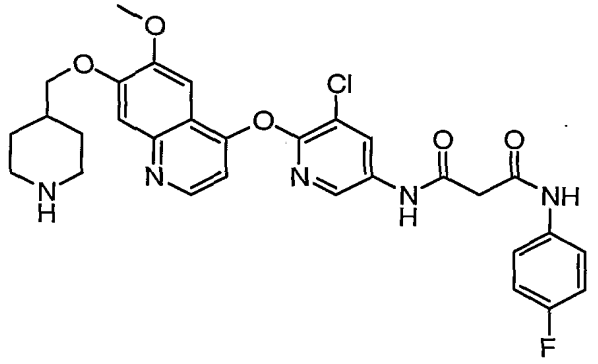
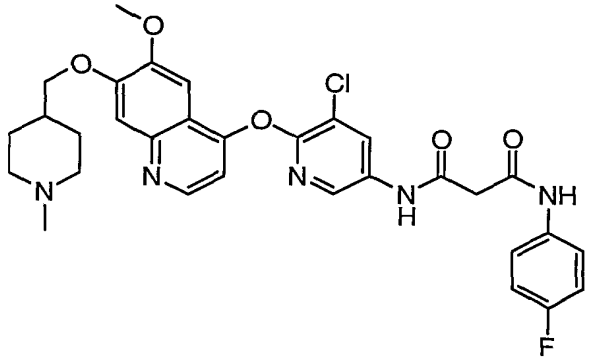
| Entry | Name | Structure |
|---|---|---|
| 130 | N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-oxalamide |  |
| 131 | 4-(4-{3-Chloro-5-[2-(4-fluoro-phenylcarbamoyl)-acetylamino]-pyridin-2-yloxy}-6-methoxy-quinolin-7-yloxymethyl)-piperidine-1-carboxylic acid tert-butyl ester |  |
| 132 | N-{5-Chloro-6-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide |  |
| 133 | N-{5-Chloro-6-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide |  |

**Table 1**

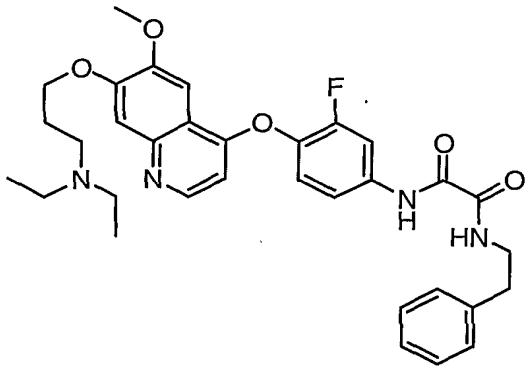
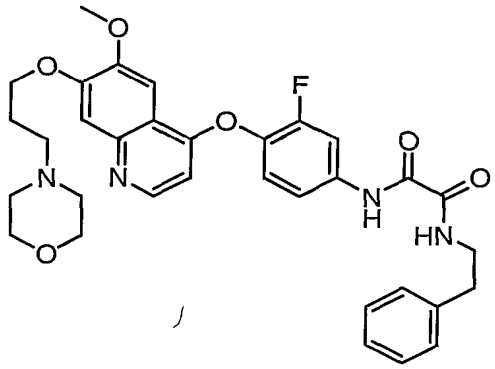
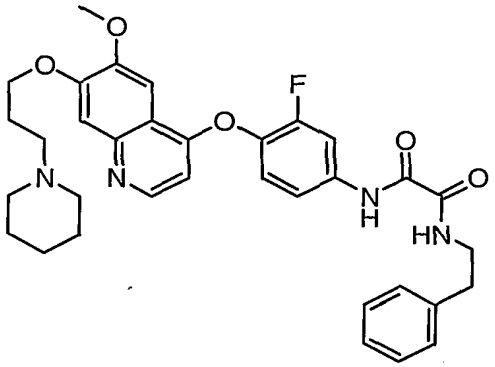
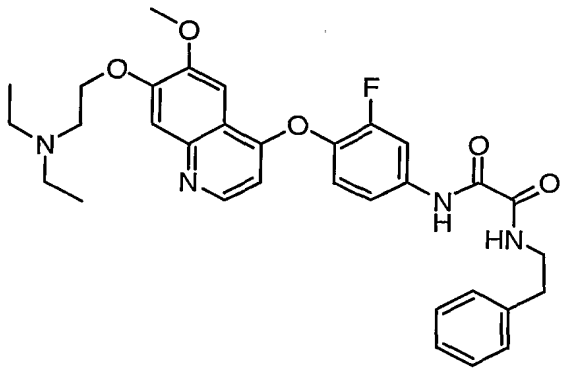
| Entry | Name | Structure |
|---|---|---|
| 134 | N-{4-[7-(3-Diethylamino-propoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide |  |
| 135 | N-{3-Fluoro-4-[6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide |  |
| 136 | N-{3-Fluoro-4-[6-methoxy-7-(3-piperidin-1-yl-propoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide |  |
| 137 | N-{4-[7-(2-Diethylamino-ethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide |  |

**Table 1**

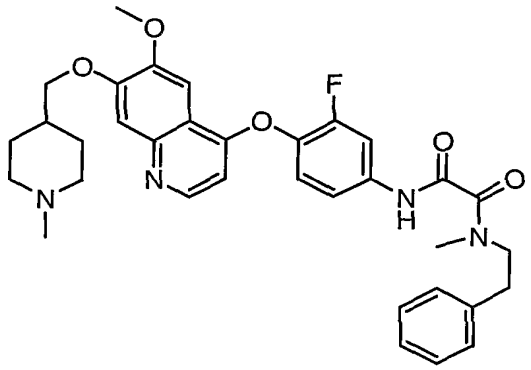
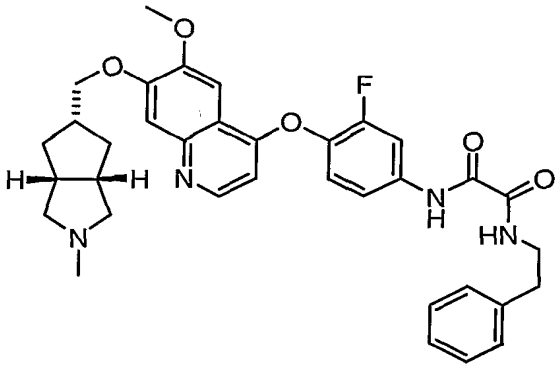
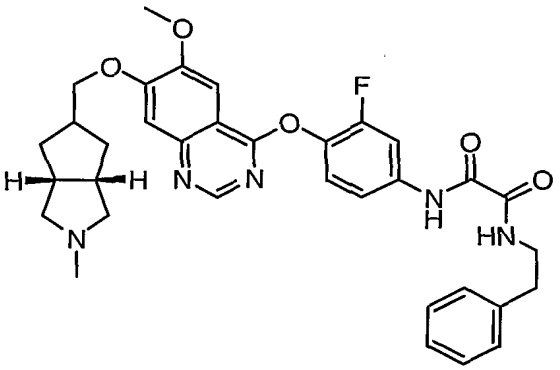
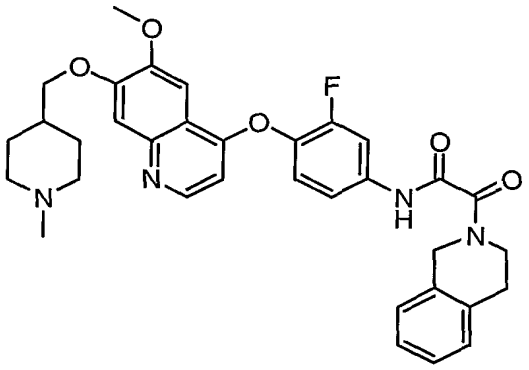
| Entry | Name | Structure |
|---|---|---|
| 138 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-methyl-N'-phenethyl-oxalamide |  |
| 139 | N-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide |  |
| 140 | N-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide |  |
| 141 | 2-(3,4-Dihydro-1H-isoquinolin-2-yl)-N-{3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-acetamide |  |

**Table 1**

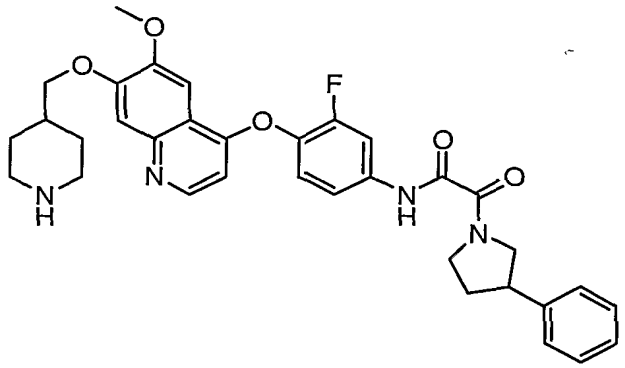
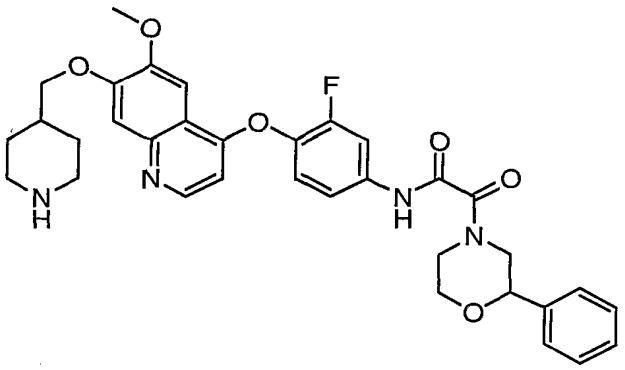
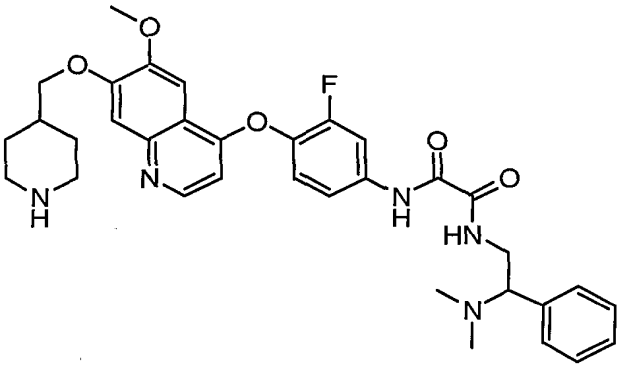
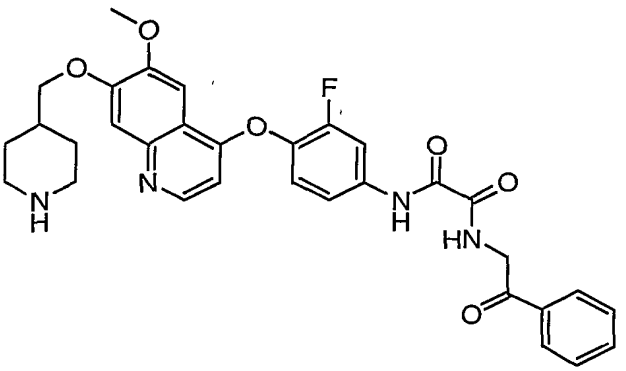
| Entry | Name | Structure |
|---|---|---|
| 142 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-(3-phenyl-pyrrolidin-1-yl)-acetamide |  |
| 143 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-(2-phenyl-morpholin-4-yl)-acetamide |  |
| 144 | N-(2-Dimethylamino-2-phenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 145 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-oxo-2-phenyl-ethyl)-oxalamide |  |

**Table 1**

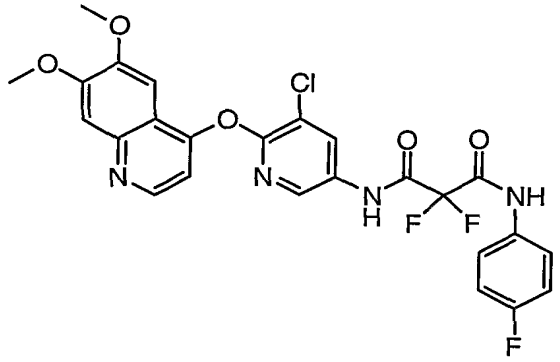
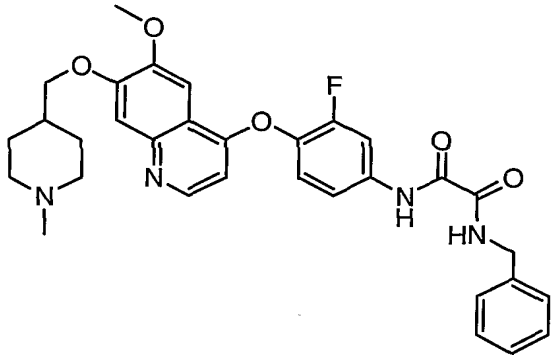
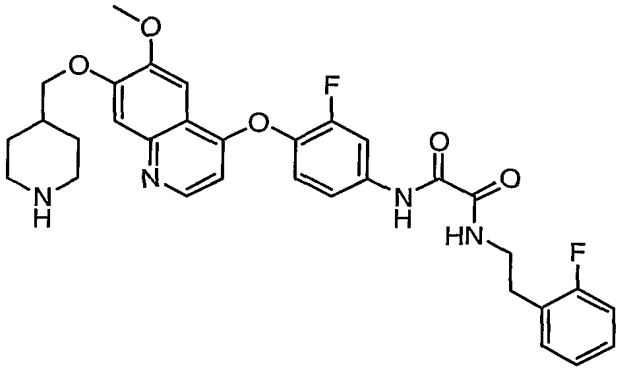
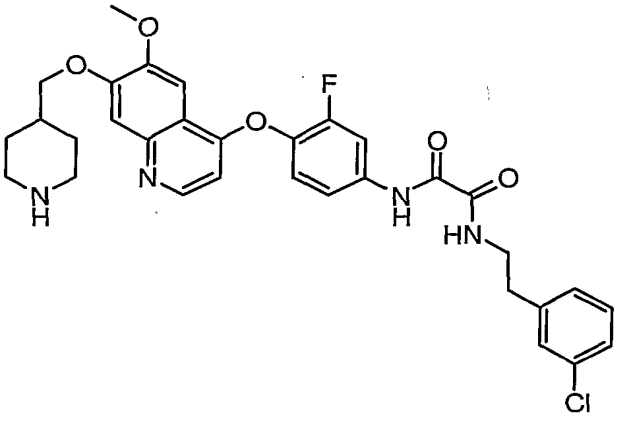
| Entry | Name | Structure |
|---|---|---|
| 146 | N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-2,2-difluoro-N'-(4-fluoro-phenyl)-malonamide |  |
| 147 | N-Benzyl-N'-{3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 148 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-fluoro-phenyl)-ethyl]-oxalamide |  |
| 149 | N-[2-(3-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

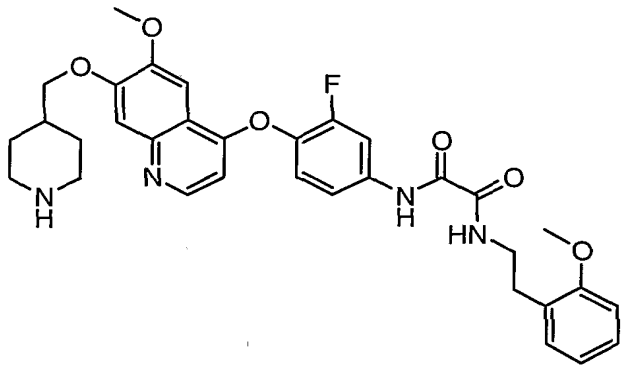
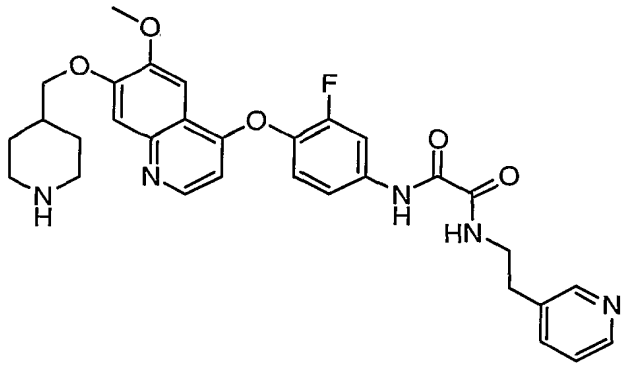
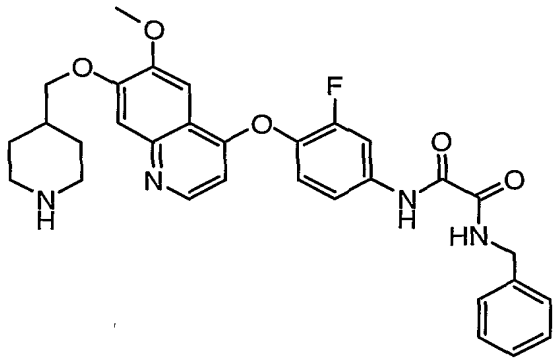
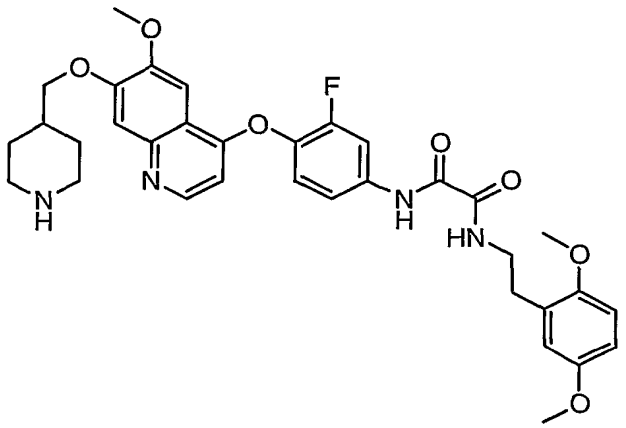
| Entry | Name | Structure |
|---|---|---|
| 150 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-methoxy-phenyl)-ethyl]-oxalamide |  |
| 151 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-3-yl-ethyl)-oxalamide |  |
| 152 | N-Benzyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 153 | N-[2-(2,5-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

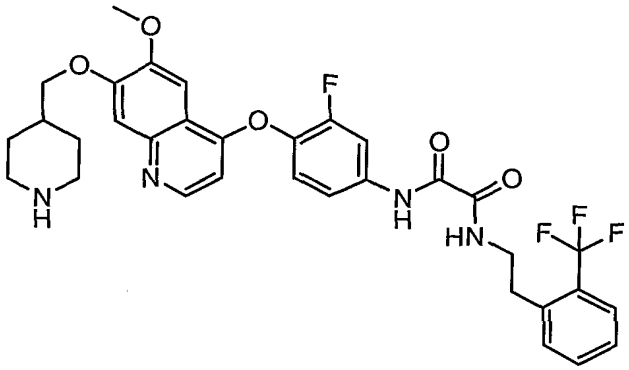
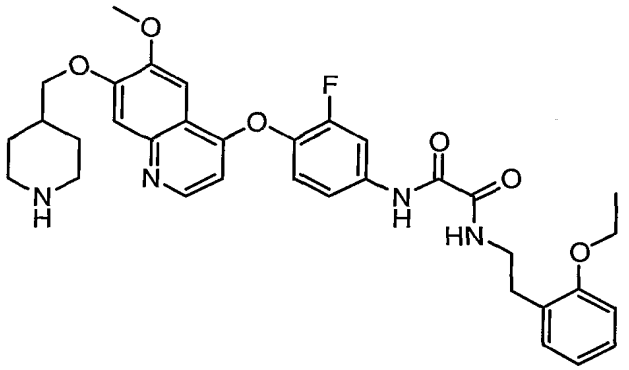
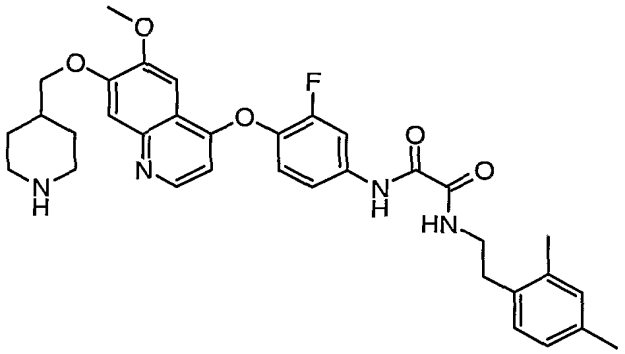
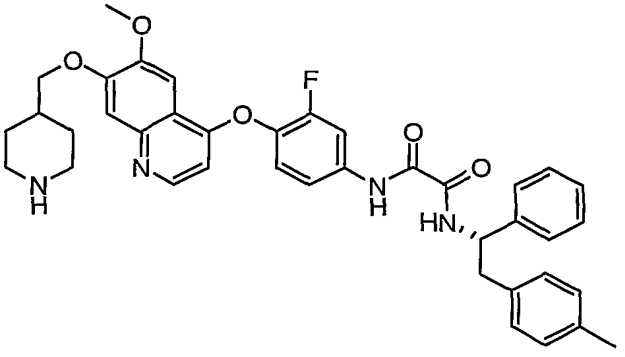
| Entry | Name | Structure |
|---|---|---|
| 154 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-trifluoromethyl-phenyl)-ethyl]-oxalamide |  |
| 155 | N-[2-(2-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 156 | N-[2-(2,4-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 157 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*S* -phenyl-2-p-tolyl-ethyl)-oxalamide |  |

**Table 1**

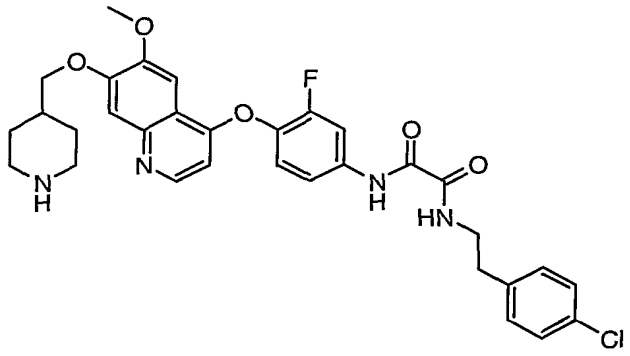
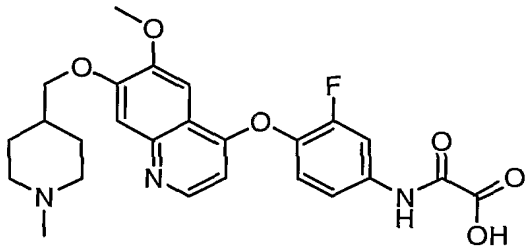
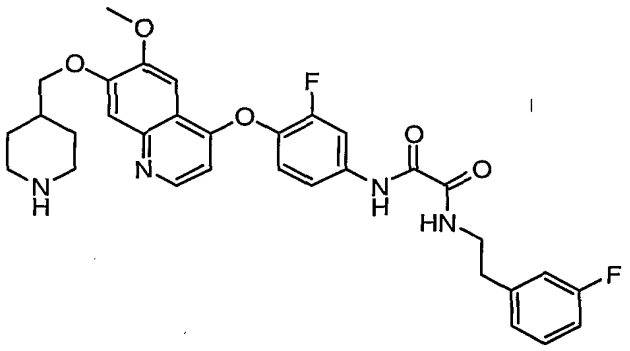
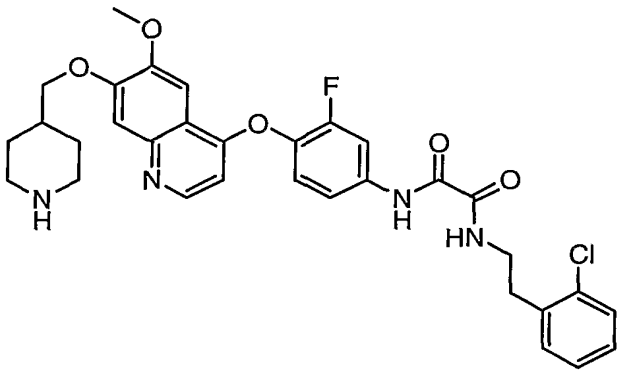
| Entry | Name | Structure |
|---|---|---|
| 158 | N-[2-(4-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 159 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamic acid |  |
| 160 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-fluoro-phenyl)-ethyl]-oxalamide |  |
| 161 | N-[2-(2-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

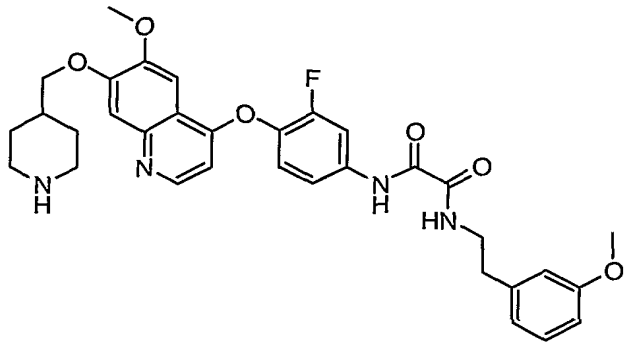
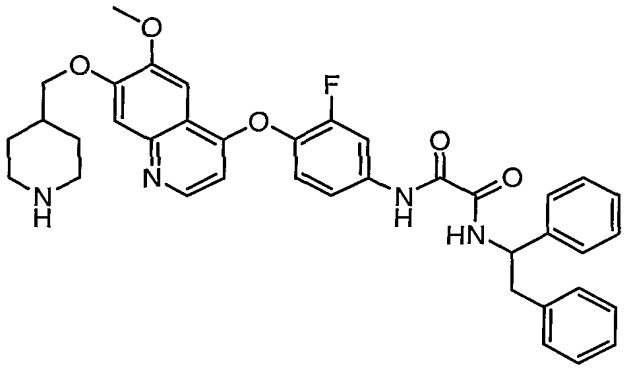
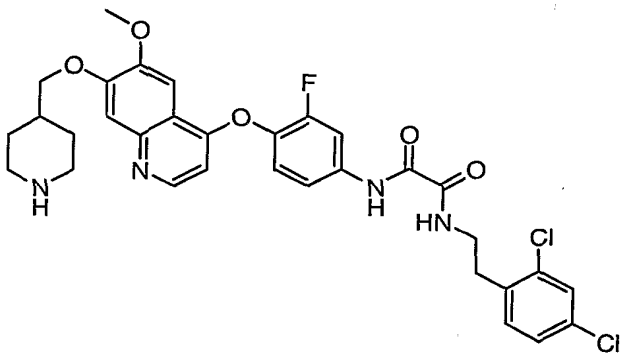
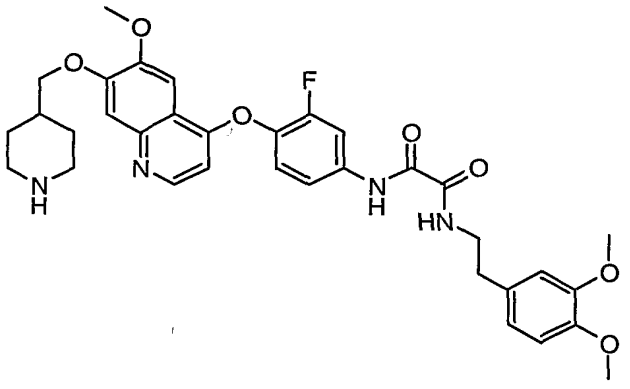
| Entry | Name | Structure |
|---|---|---|
| 162 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-methoxy-phenyl)-ethyl]-oxalamide |  |
| 163 | N-(1,2-Diphenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 164 | N-[2-(2,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 165 | N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

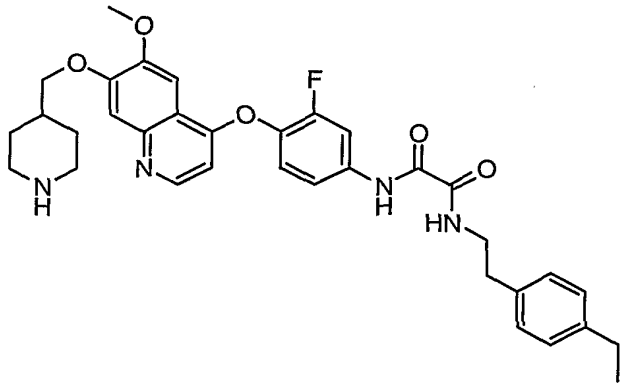
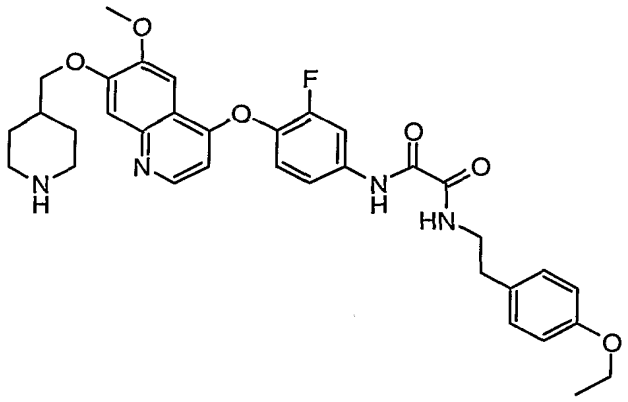
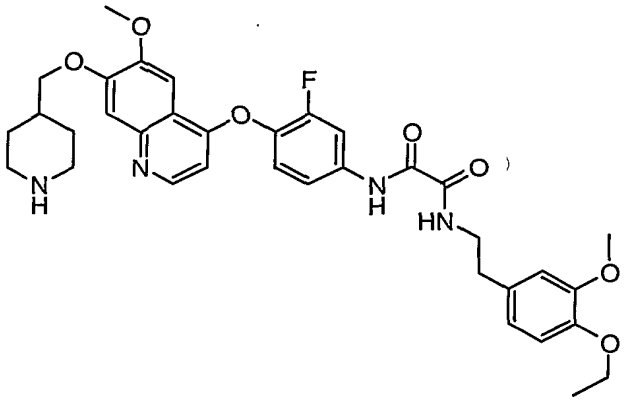
| Entry | Name | Structure |
|---|---|---|
| 166 | N-[2-(4-Ethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 167 | N-[2-(4-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 168 | N-[2-(4-Ethoxy-3-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

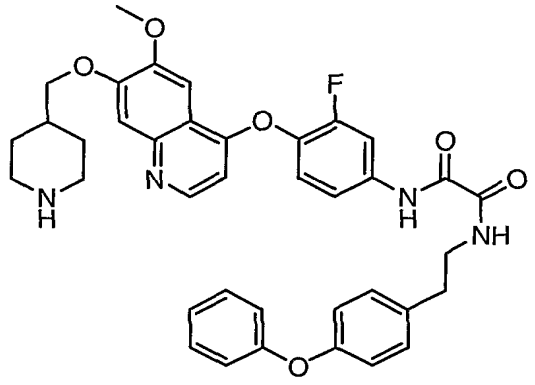
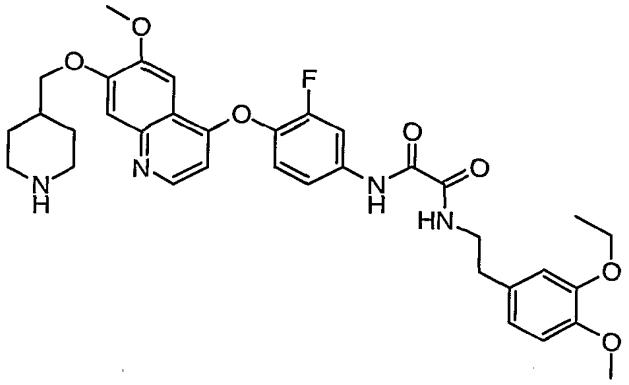
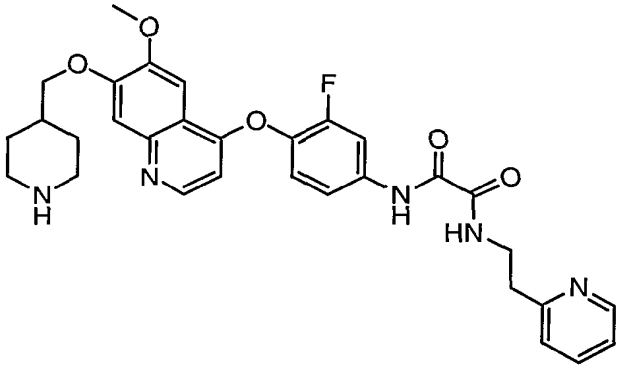
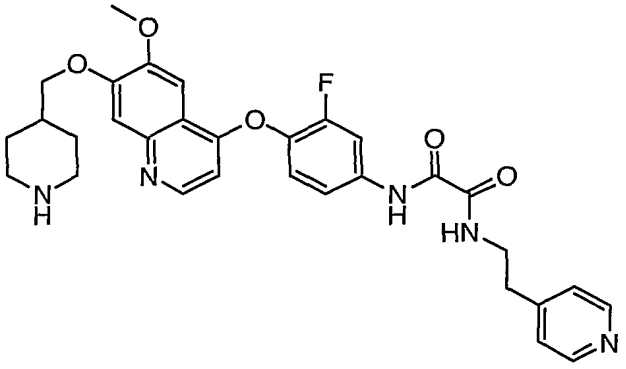
| Entry | Name | Structure |
|---|---|---|
| 169 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-phenoxy-phenyl)-ethyl]-oxalamide |  |
| 170 | N-[2-(3-Ethoxy-4-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 171 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-2-yl-ethyl)-oxalamide |  |
| 172 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-4-yl-ethyl)-oxalamide |  |

**Table 1**

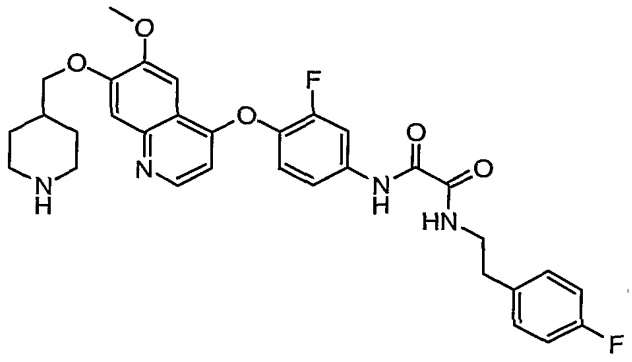
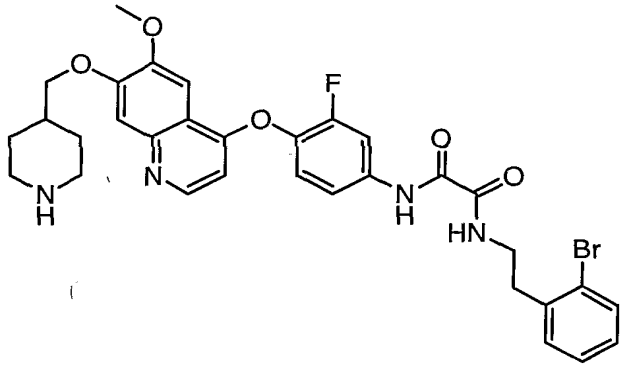
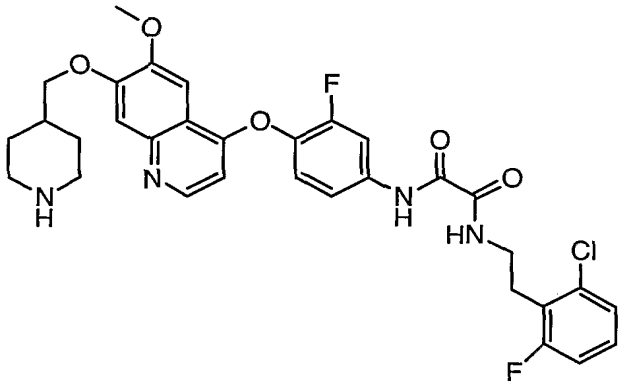
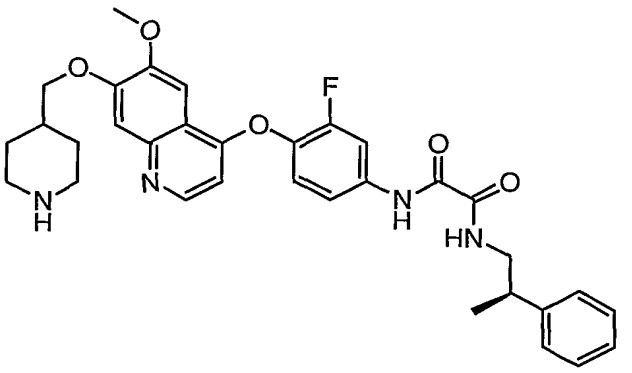
| Entry | Name | Structure |
|---|---|---|
| 173 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-fluoro-phenyl)-ethyl]-oxalamide |  |
| 174 | N-[2-(2-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 175 | N-[2-(2-Chloro-6-fluoro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 176 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2*R*-phenyl-propyl)-oxalamide |  |

**Table 1**

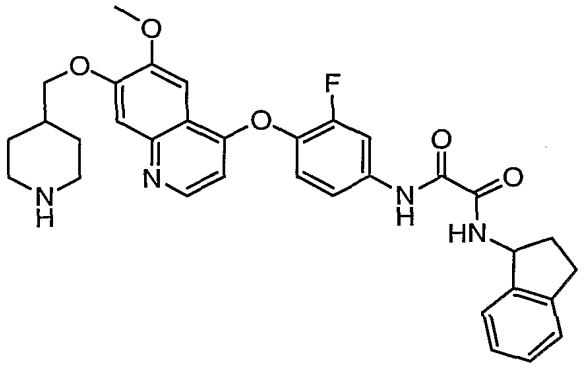
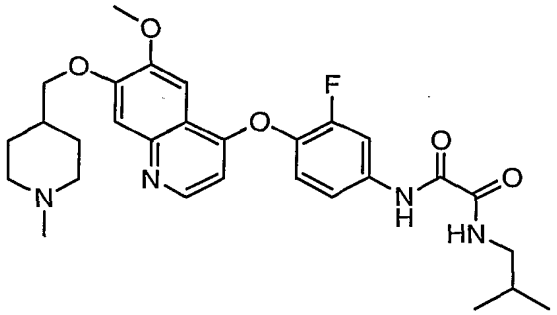
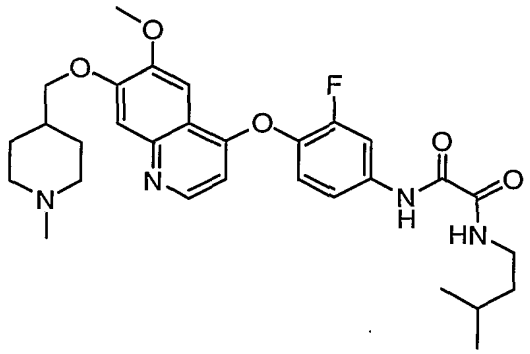
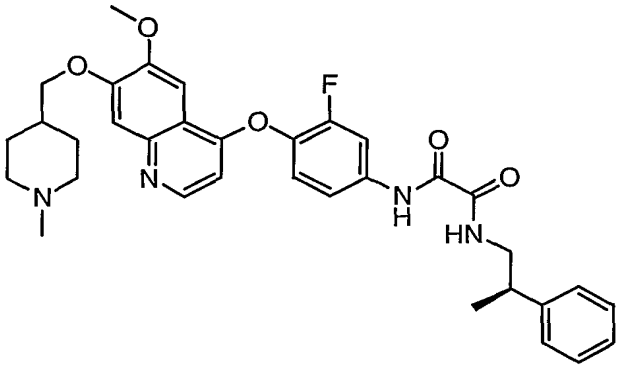
| Entry | Name | Structure |
|---|---|---|
| 177 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-indan-1-yl-oxalamide |  |
| 178 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-isobutyl-oxalamide |  |
| 179 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-butyl)-oxalamide |  |
| 180 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2*R*-phenyl-propyl)-oxalamide |  |

**Table 1**

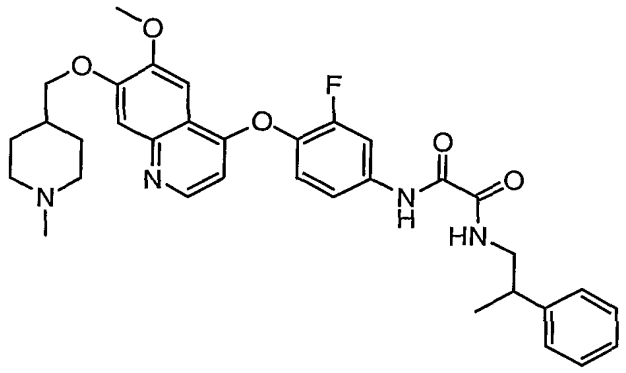
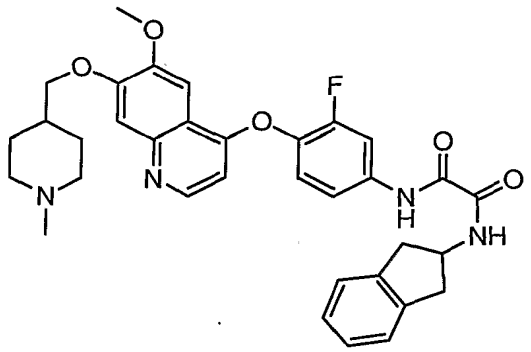
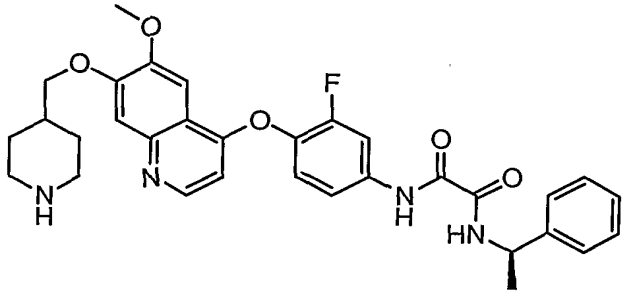
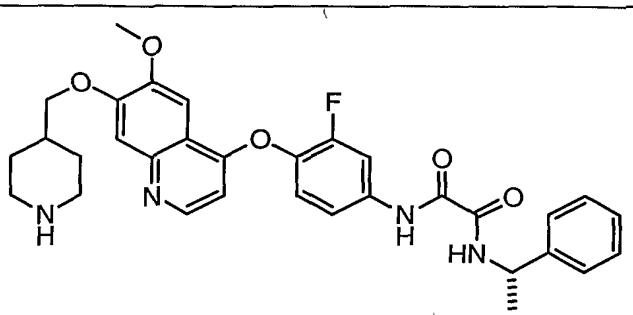
| Entry | Name | Structure |
|---|---|---|
| 181 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenyl-propyl)-oxalamide |  |
| 182 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-indan-2-yl-oxalamide |  |
| 183 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*R*-phenyl-ethyl)-oxalamide |  |
| 184 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*S*-phenyl-ethyl)-oxalamide |  |

**Table 1**

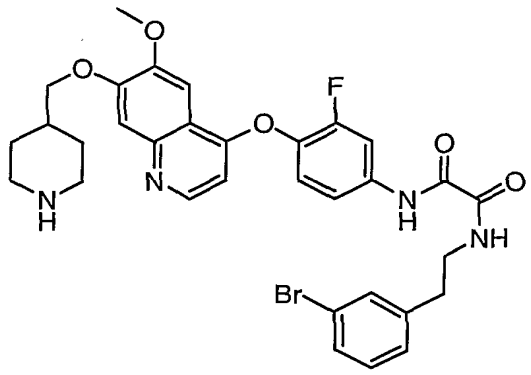
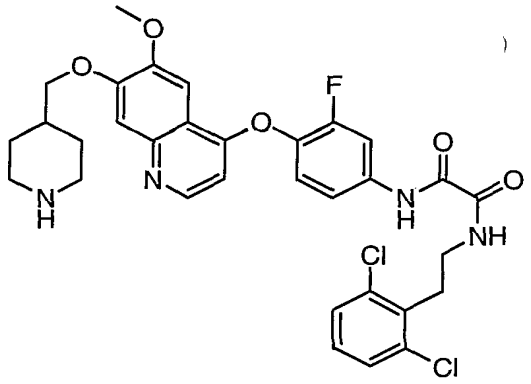
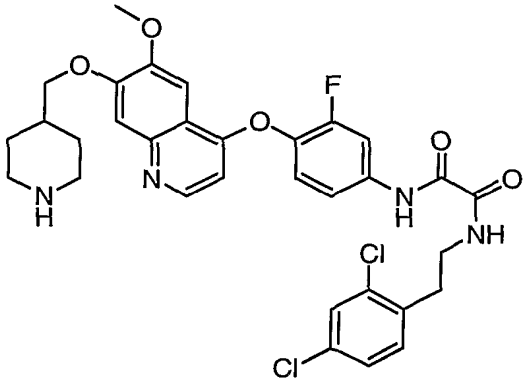
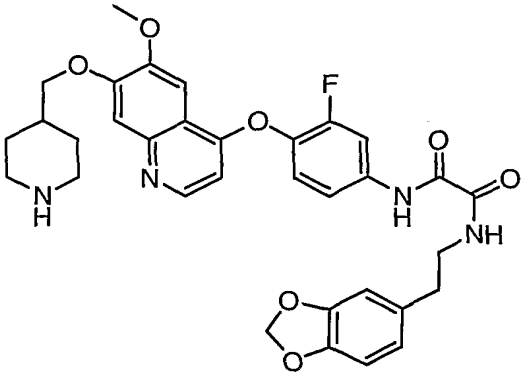
| Entry | Name | Structure |
|---|---|---|
| 185 | N-[2-(3-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 186 | N-[2-(2,6-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 187 | N-[2-(2,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 188 | N-(2-Benzo[1,3]dioxol-5-yl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

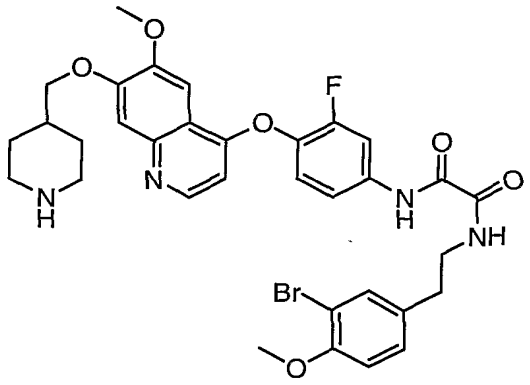
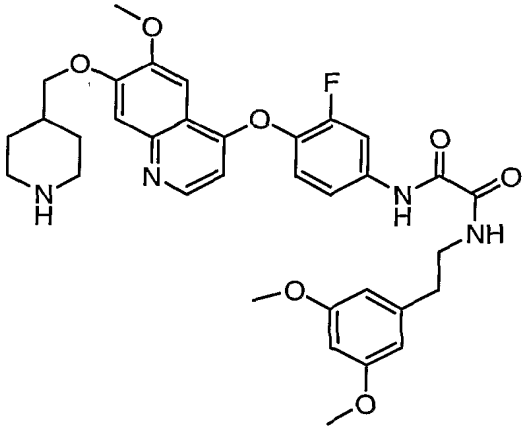
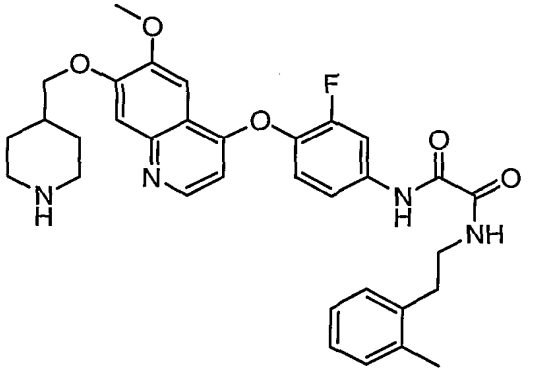
| Entry | Name | Structure |
|---|---|---|
| 189 | N-[2-(3-Bromo-4-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 190 | N-[2-(3,5-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 191 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-o-tolyl-ethyl)-oxalamide |  |

**Table 1**

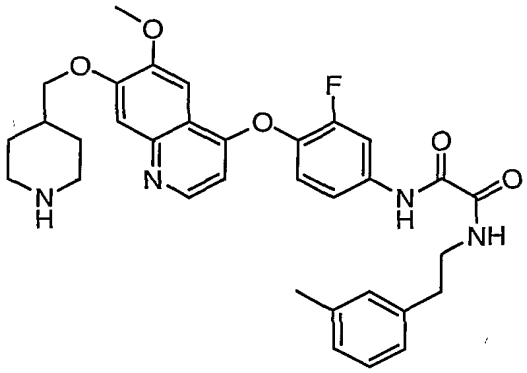
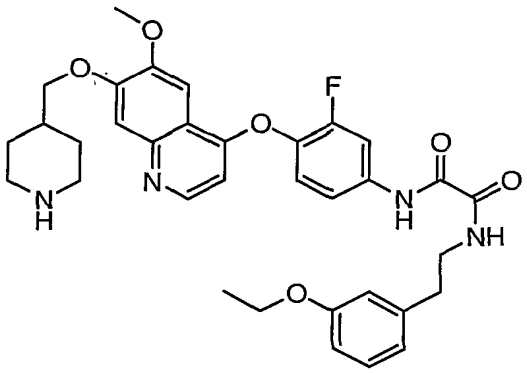
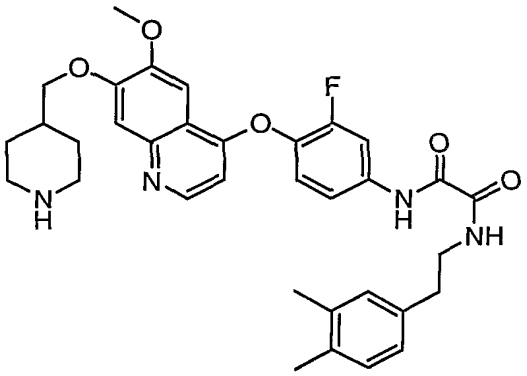
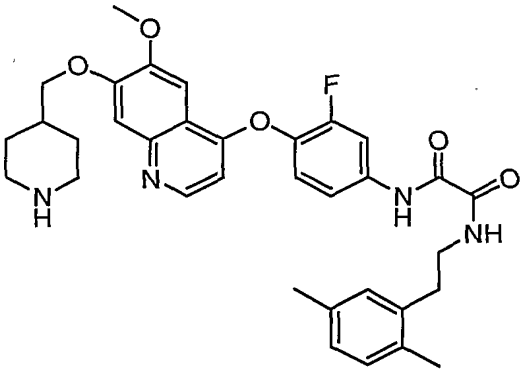
| Entry | Name | Structure |
|---|---|---|
| 192 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-m-tolyl-ethyl)-oxalamide |  |
| 193 | N-[2-(3-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 194 | N-[2-(3,4-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 195 | N-[2-(2,5-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

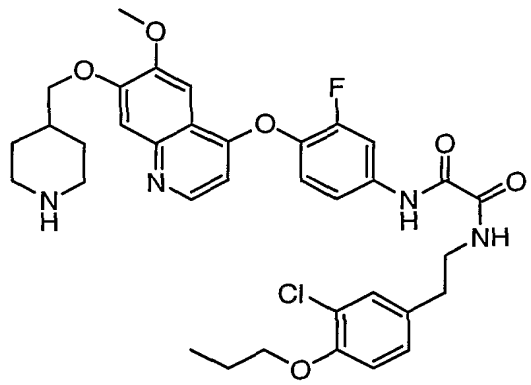
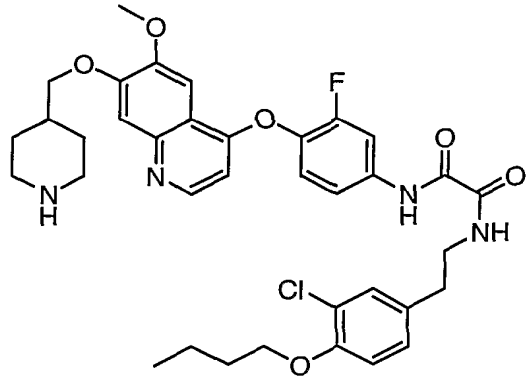
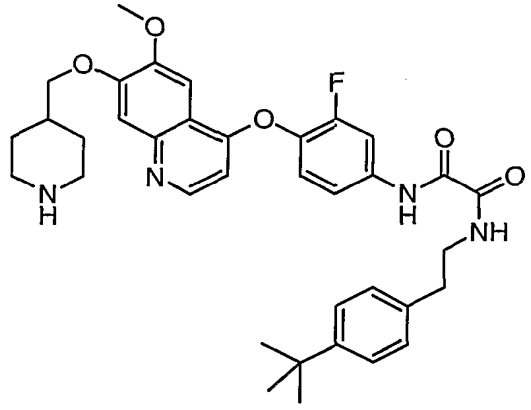
| Entry | Name | Structure |
|---|---|---|
| 196 | N-[2-(3-Chloro-4-propoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 197 | N-[2-(4-Butoxy-3-chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 198 | N-[2-(4-tert-Butyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

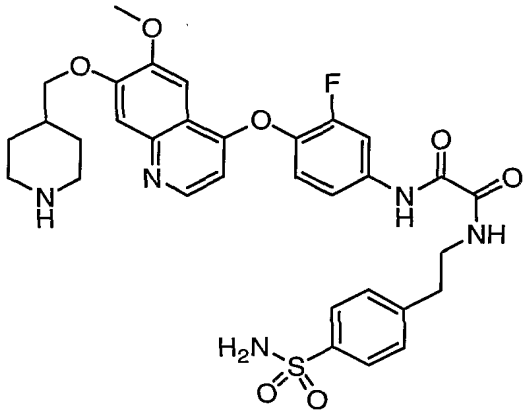
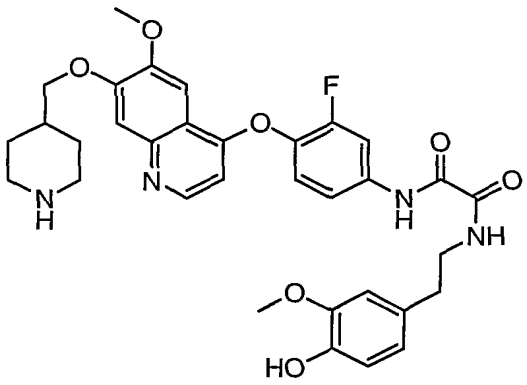
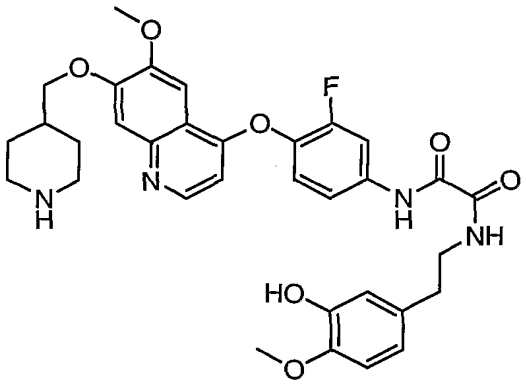
| Entry | Name | Structure |
|---|---|---|
| 199 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-sulfamoyl-phenyl)-ethyl]-oxalamide |  |
| 200 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-hydroxy-3-methoxy-phenyl)-ethyl]-oxalamide |  |
| 201 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-hydroxy-4-methoxy-phenyl)-ethyl]-oxalamide |  |

**Table 1**

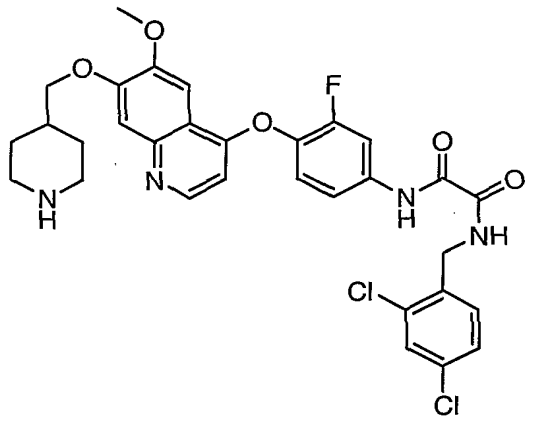
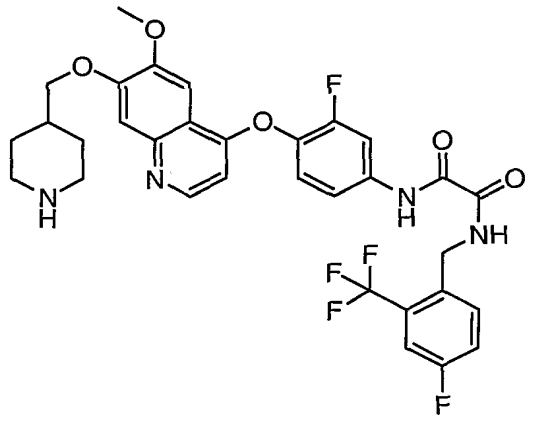
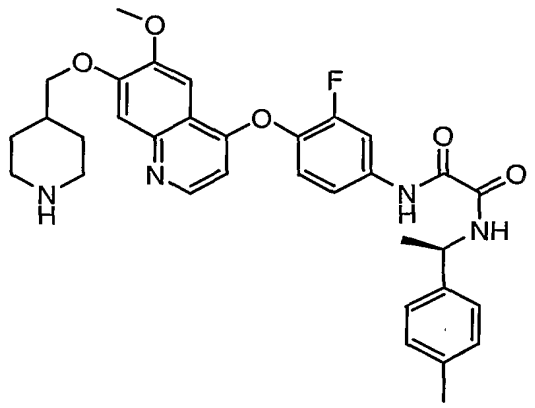
| Entry | Name | Structure |
|---|---|---|
| 202 | N-(2,4-Dichloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 203 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-fluoro-2-trifluoromethyl-benzyl)-oxalamide |  |
| 204 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-p-tolyl-ethyl)-oxalamide |  |

**Table 1**

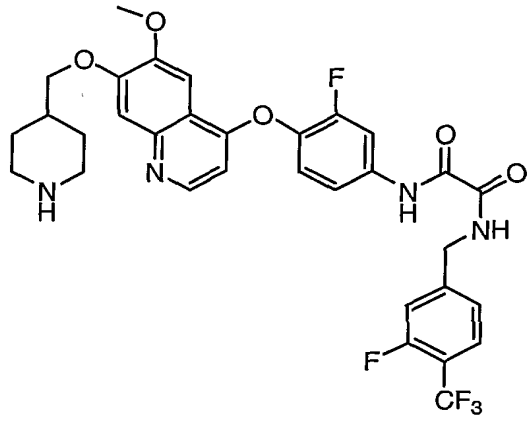
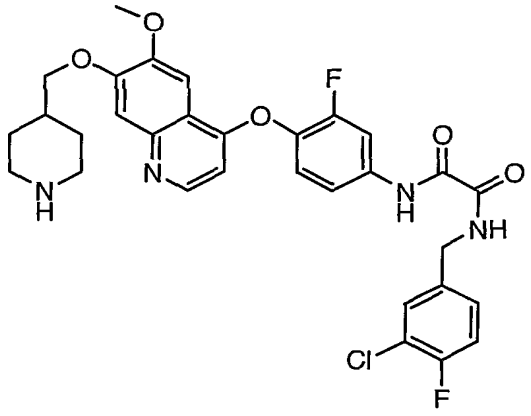
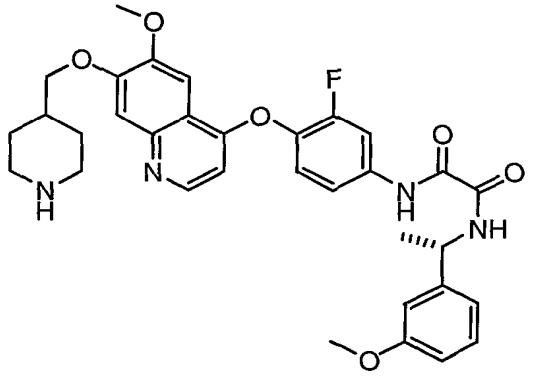
| Entry | Name | Structure |
|---|---|---|
| 205 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-4-trifluoromethyl-benzyl)-oxalamide |  |
| 206 | N-(3-Chloro-4-fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 207 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[1-(3-methoxy-phenyl)-ethyl]-oxalamide |  |

**Table 1**

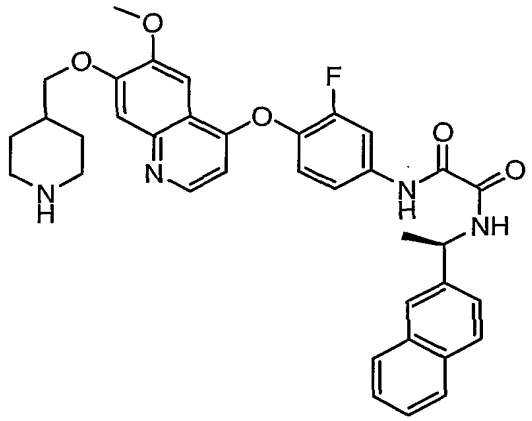
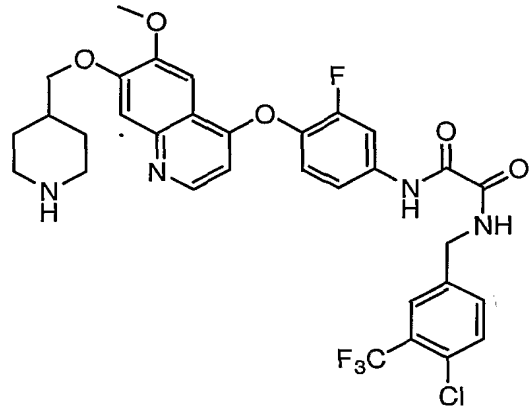
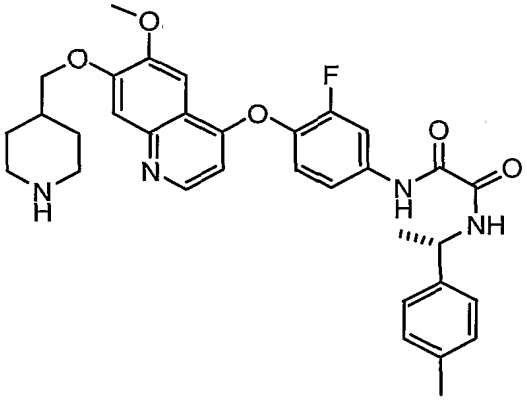
| Entry | Name | Structure |
|---|---|---|
| 208 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-naphthalen-2-yl-ethyl)-oxalamide |  |
| 209 | N-(4-Chloro-3-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 210 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-p-tolyl-ethyl)-oxalamide |  |

**Table 1**

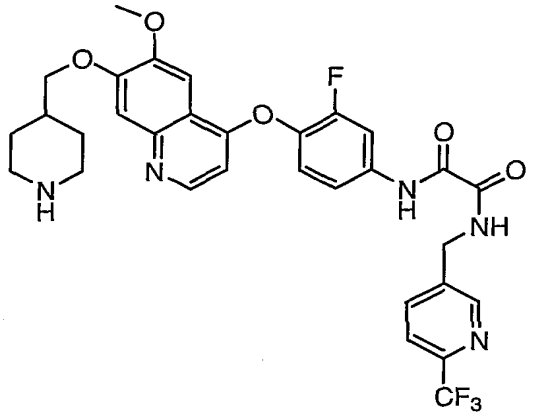
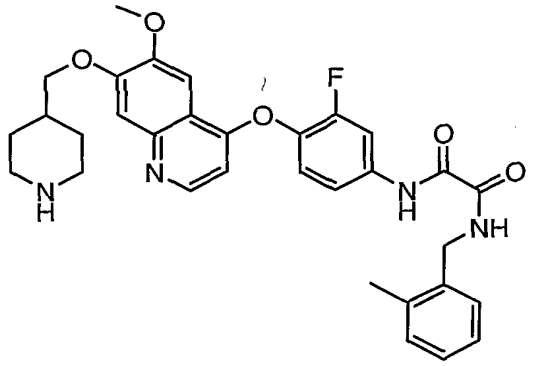
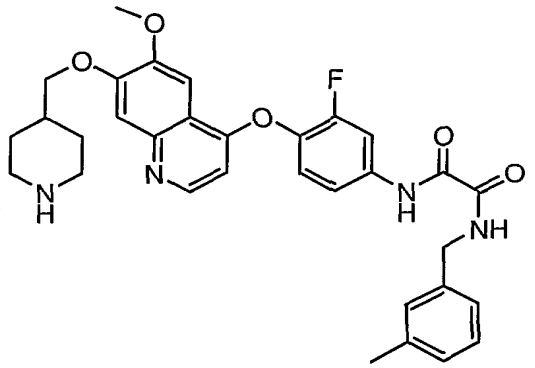
| Entry | Name | Structure |
|---|---|---|
| 211 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(6-trifluoromethyl-pyridin-3-ylmethyl)-oxalamide |  |
| 212 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methyl-benzyl)-oxalamide |  |
| 213 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-benzyl)-oxalamide |  |

**Table 1**

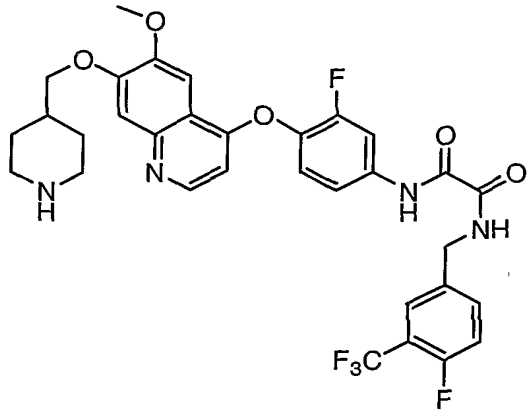
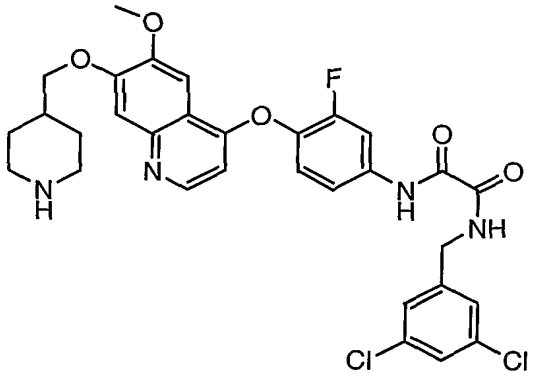
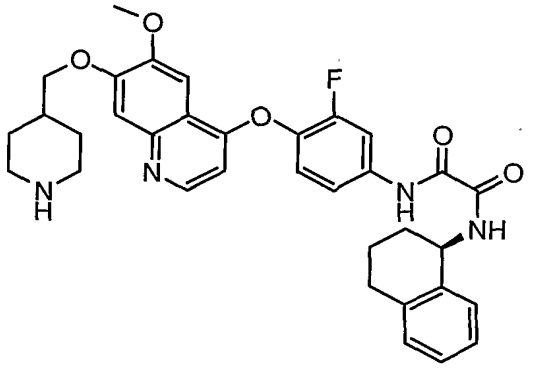
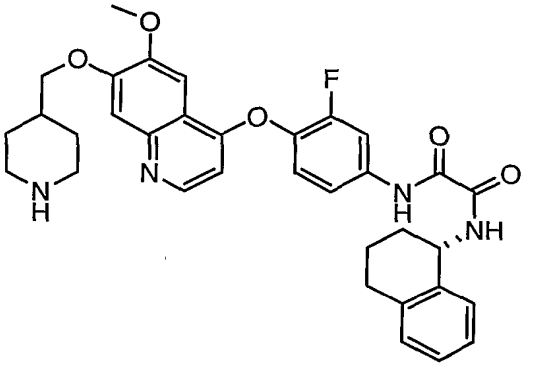
| Entry | Name | Structure |
|---|---|---|
| 214 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-fluoro-3-trifluoromethyl-benzyl)-oxalamide |  |
| 215 | N-(3,5-Dichloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 216 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R,2,3,4-tetrahydro-naphthalen-1-yl)-oxalamide |  |
| 217 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1S,2,3,4-tetrahydro-naphthalen-1-yl)-oxalamide |  |

**Table 1**

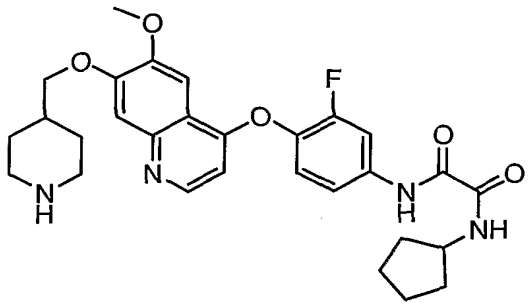
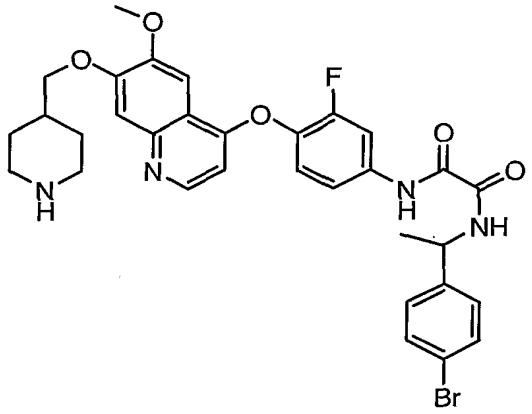
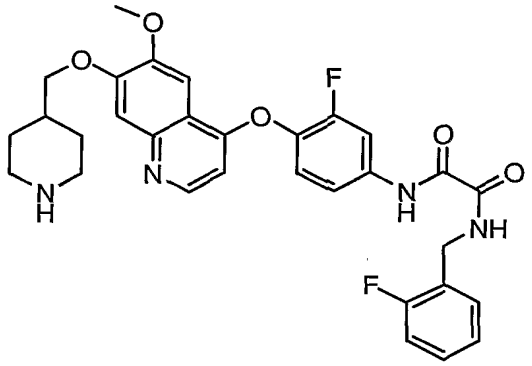
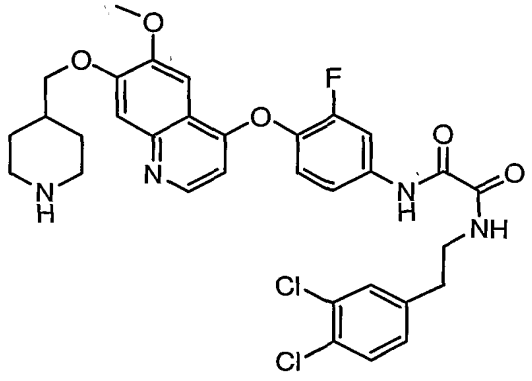
| Entry | Name | Structure |
|---|---|---|
| 218 | N-Cyclopentyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 219 | N-[1-(4-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 220 | N-(2-Fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 221 | N-[2-(3,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

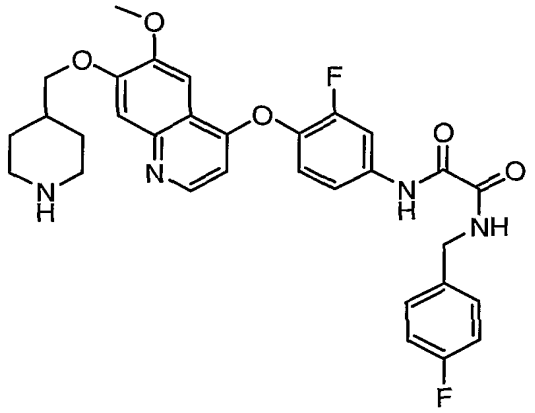
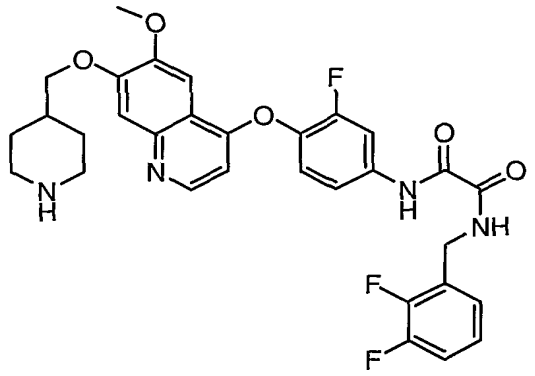
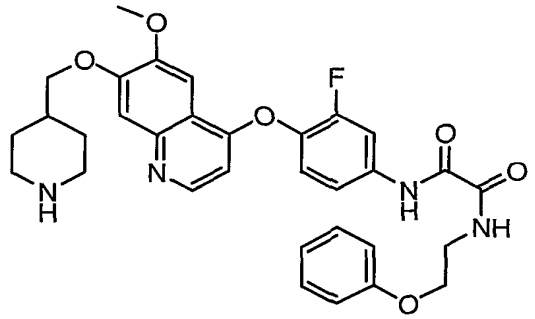
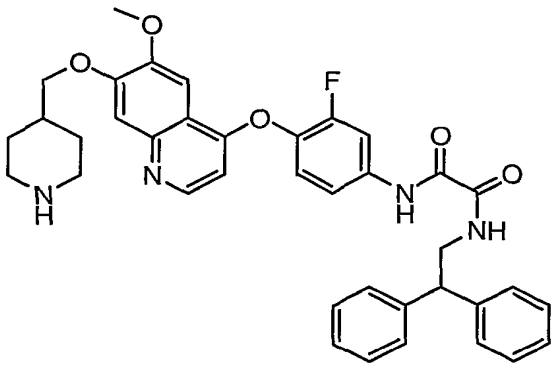
| Entry | Name | Structure |
|---|---|---|
| 222 | N-(4-Fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 223 | N-(2,3-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 224 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenoxy-ethyl)-oxalamide |  |
| 225 | N-(2,2-Diphenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

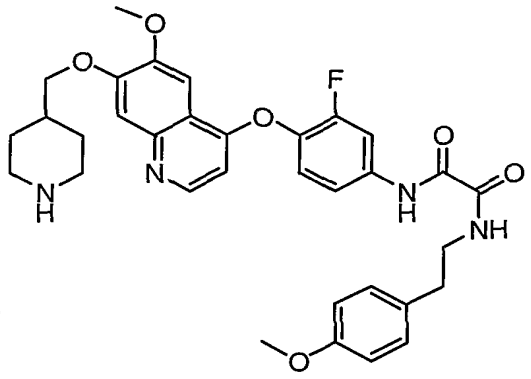
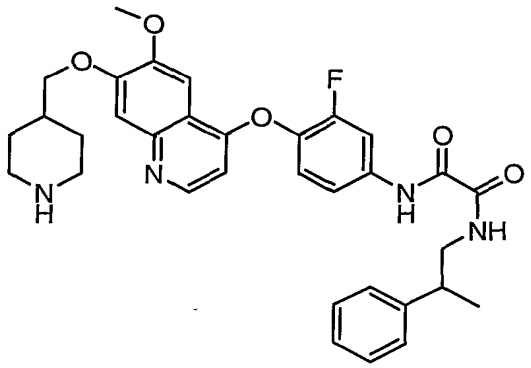
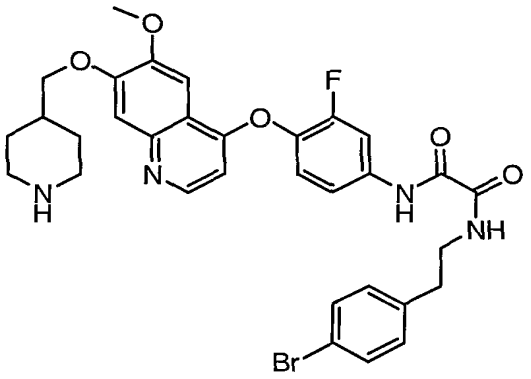
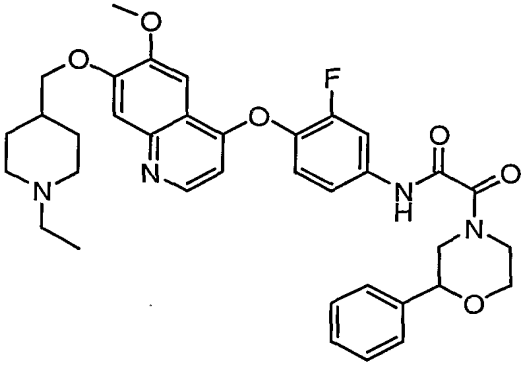
| Entry | Name | Structure |
|---|---|---|
| 226 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-methoxy-phenyl)-ethyl]-oxalamide |  |
| 227 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenyl-propyl)-oxalamide |  |
| 228 | N-[2-(4-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 229 | N-{4-[7-(1-Ethyl-piperidin-4-ylmethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-2-oxo-2-(2-phenyl-morpholin-4-yl)-acetamide |  |

**Table 1**

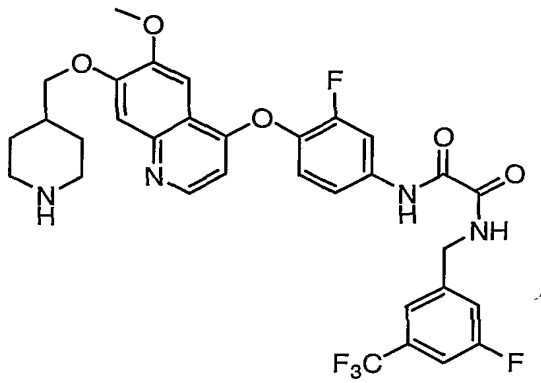
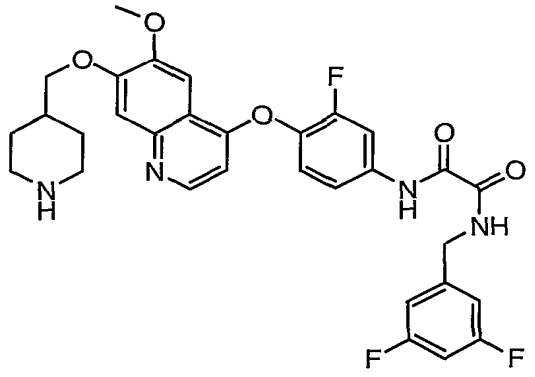
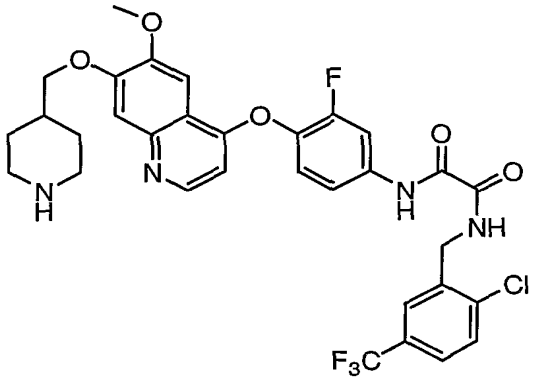
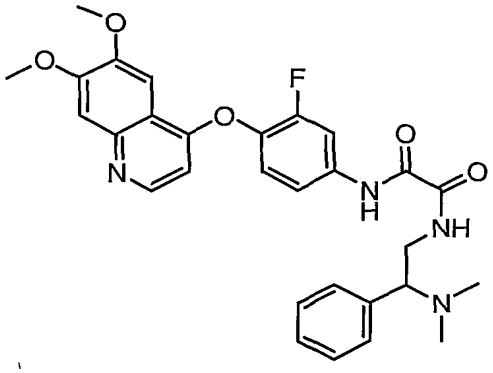
| Entry | Name | Structure |
|---|---|---|
| 230 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-5-trifluoromethyl-benzyl)-oxalamide |  |
| 231 | N-(3,5-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 232 | N-(2-Chloro-5-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 233 | N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-dimethylamino-2-phenyl-ethyl)-oxalamide |  |

**Table 1**

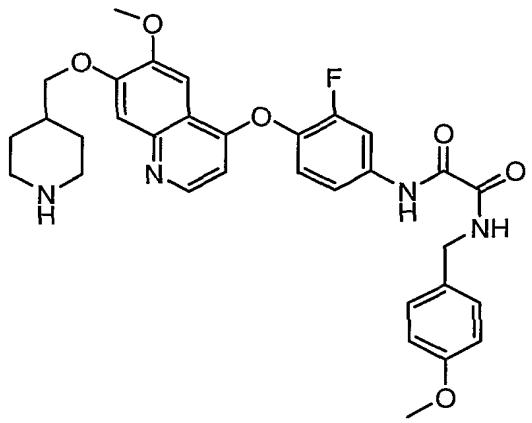
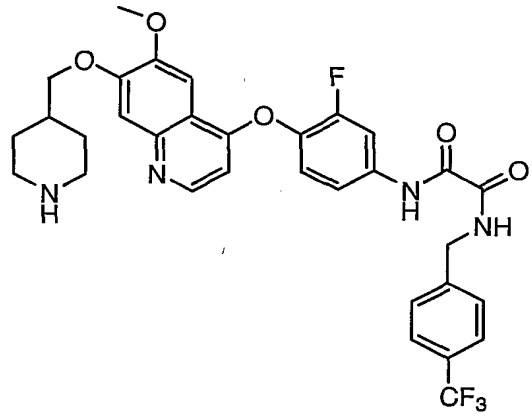
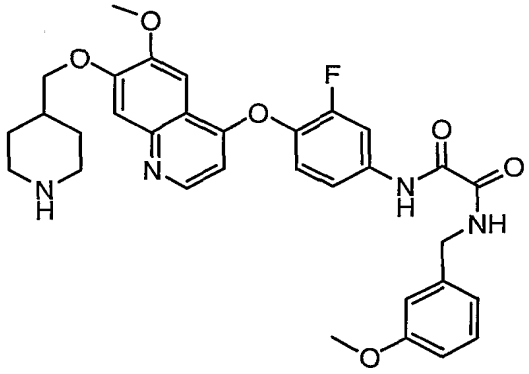
| Entry | Name | Structure |
|---|---|---|
| 234 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-methoxy-benzyl)-oxalamide |  |
| 235 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethyl-benzyl)-oxalamide |  |
| 236 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methoxy-benzyl)-oxalamide |  |

**Table 1**

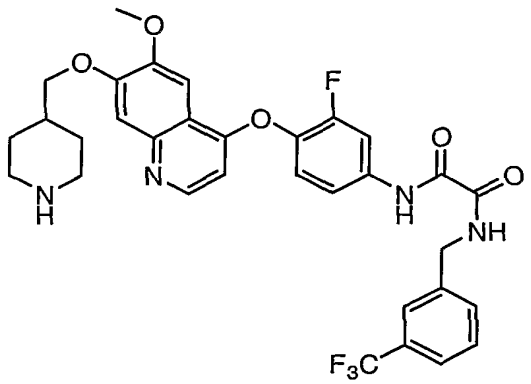
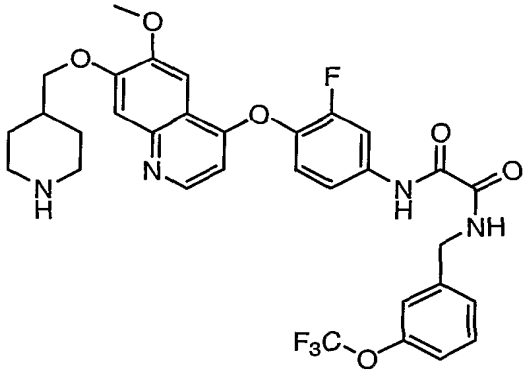
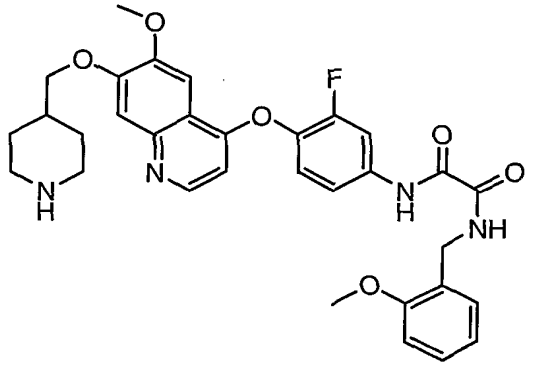
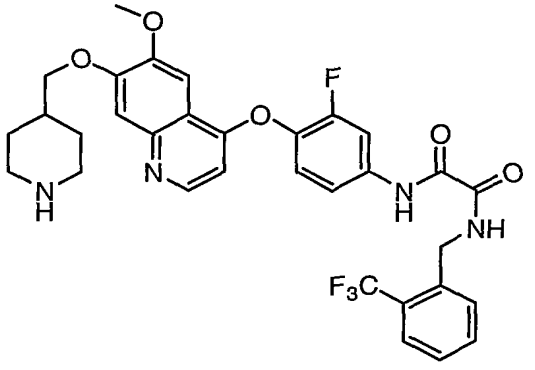
| Entry | Name | Structure |
|---|---|---|
| 237 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-trifluoromethyl-benzyl)-oxalamide |  |
| 238 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-trifluoromethoxy-benzyl)-oxalamide |  |
| 239 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methoxy-benzyl)-oxalamide |  |
| 240 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-trifluoromethyl-benzyl)-oxalamide |  |

**Table 1**

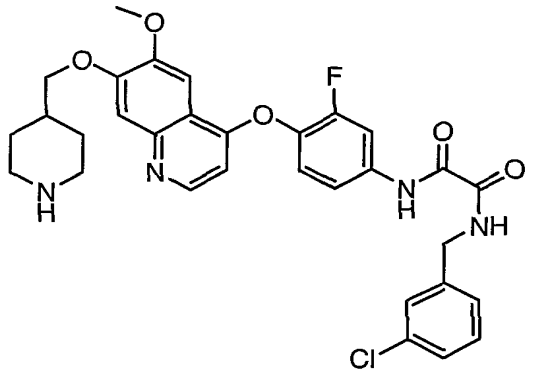
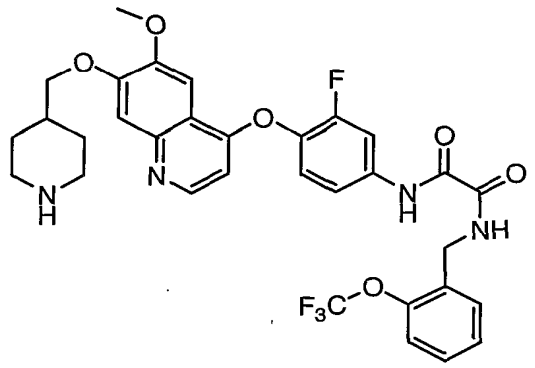
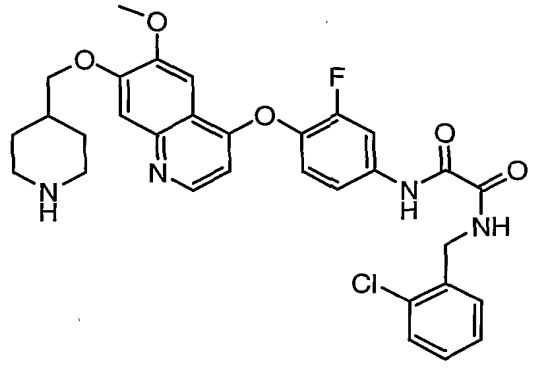
| Entry | Name | Structure |
|---|---|---|
| 241 | N-(3-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 242 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-trifluoromethoxy-benzyl)-oxalamide |  |
| 243 | N-(2-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

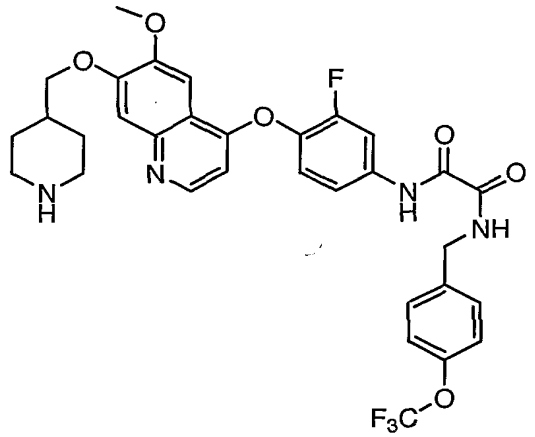
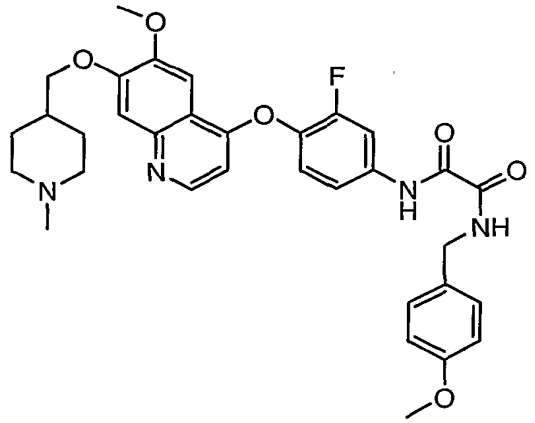
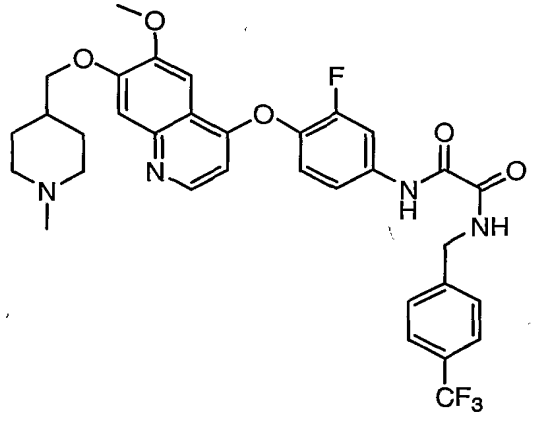
| Entry | Name | Structure |
|---|---|---|
| 244 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethoxy-benzyl)-oxalamide |  |
| 245 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-methoxy-benzyl)-oxalamide |  |
| 246 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethyl-benzyl)-oxalamide |  |

**Table 1**

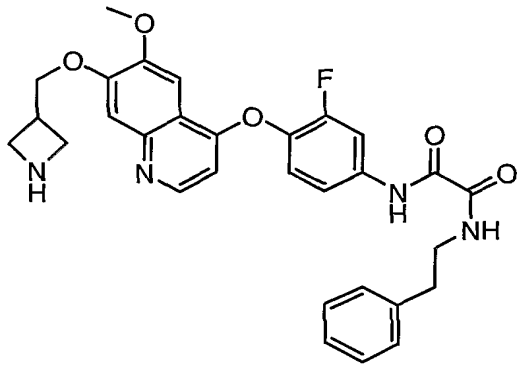
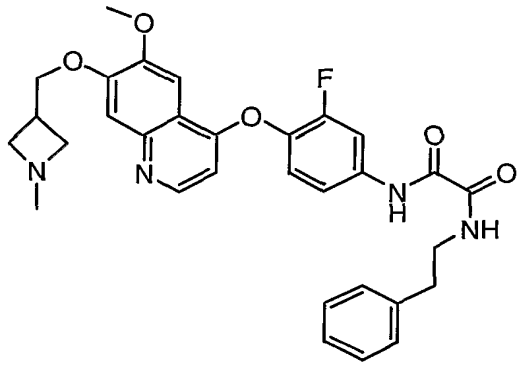
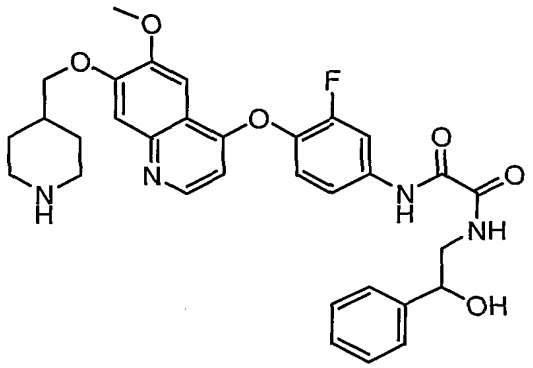
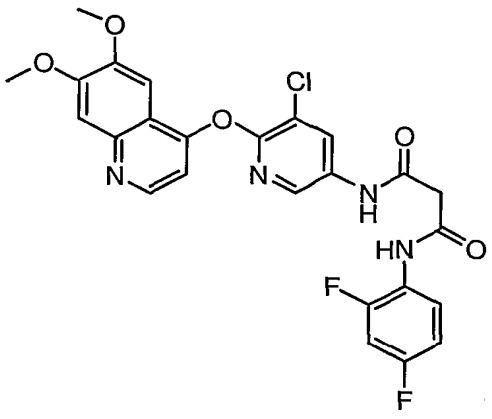
| Entry | Name | Structure |
|---|---|---|
| 247 | N-{4-[7-(Azetidin-3-ylmethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide |  |
| 248 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-azetidin-3-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide |  |
| 249 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-hydroxy-2-phenyl-ethyl)-oxalamide |  |
| 250 | N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(2,4-difluoro-phenyl)-malonamide |  |

**Table 1**

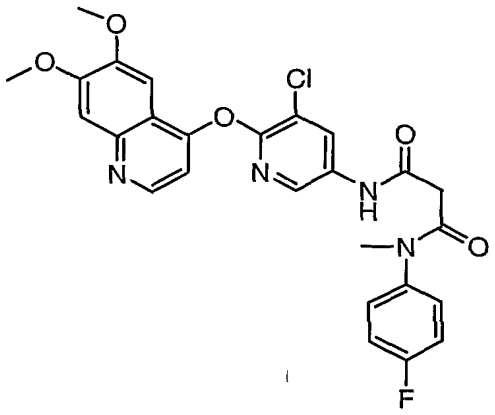
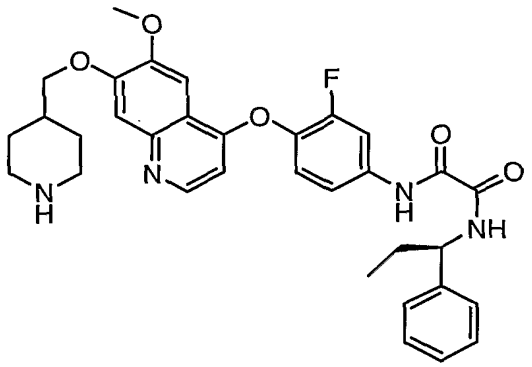
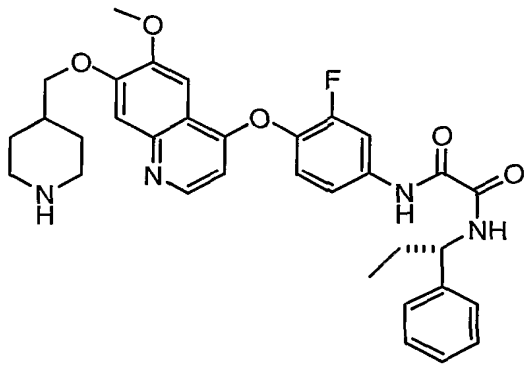
| Entry | Name | Structure |
|---|---|---|
| 251 | N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(4-fluoro-phenyl)-N'-methyl-malonamide |  |
| 252 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R-phenyl-propyl)-oxalamide |  |
| 253 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R-phenyl-propyl)-oxalamide |  |

**Table 1**

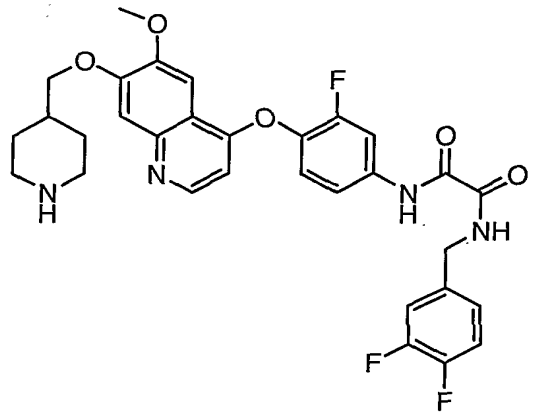
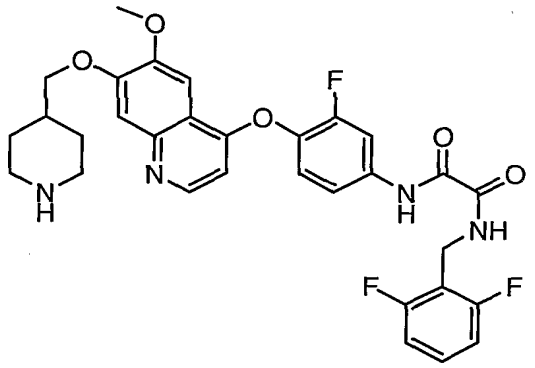
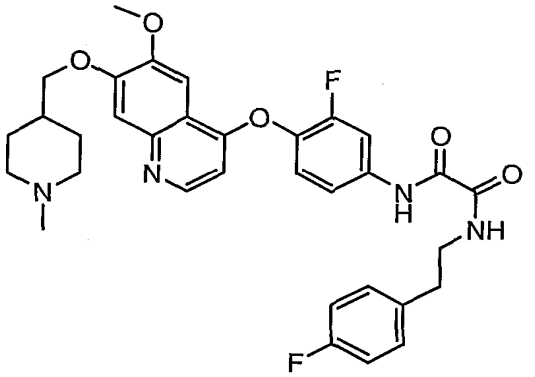
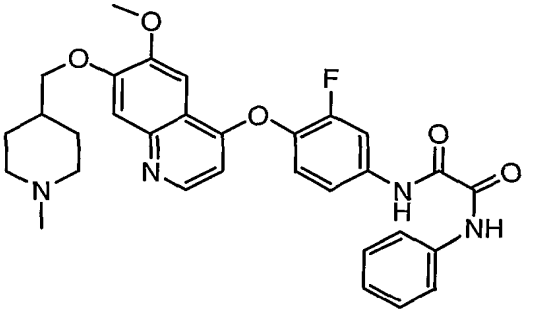
| Entry | Name | Structure |
|---|---|---|
| 254 | N-(3,4-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 255 | N-(2,6-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 256 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-fluoro-phenyl)-ethyl]-oxalamide |  |
| 257 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenyl-oxalamide |  |

**Table 1**

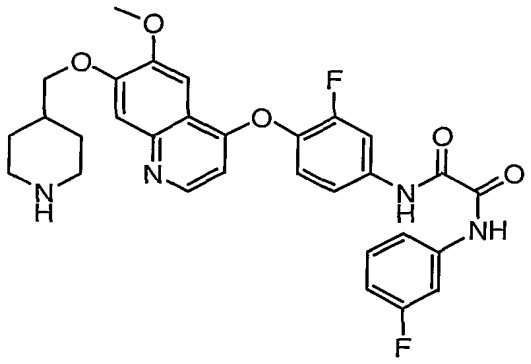
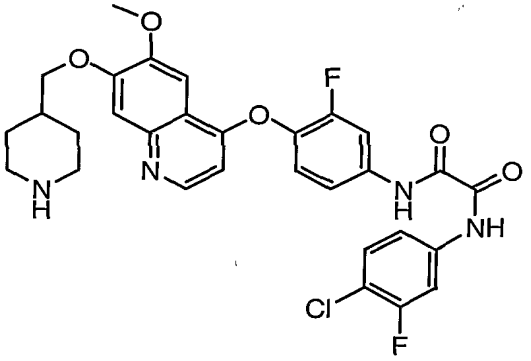
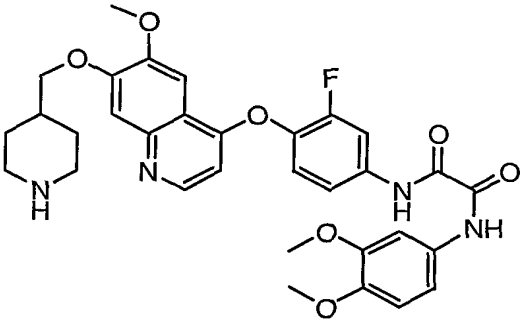
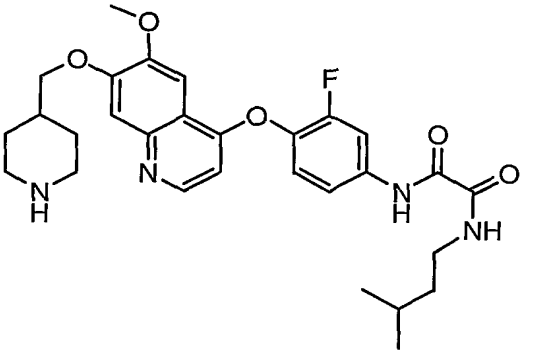
| Entry | Name | Structure |
|---|---|---|
| 258 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-phenyl)-oxalamide |  |
| 259 | N-(4-Chloro-3-fluoro-phenyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 260 | N-(3,4-Dimethoxy-phenyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 261 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-butyl)-oxalamide |  |

**Table 1**

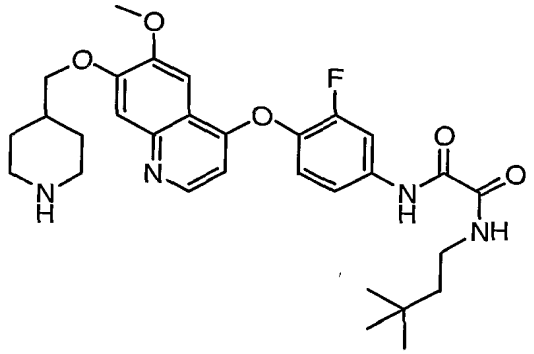
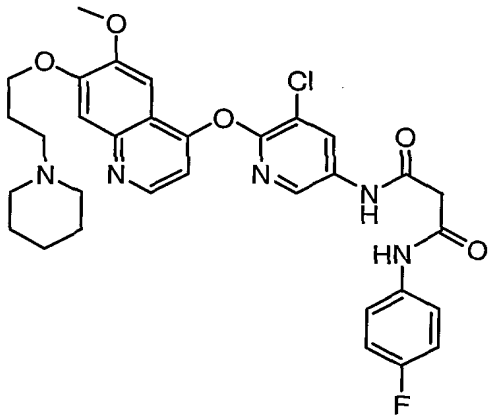
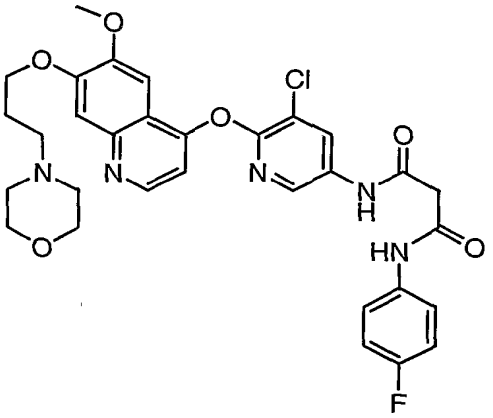
| Entry | Name | Structure |
|---|---|---|
| 262 | N-(3,3-Dimethyl-butyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 263 | N-{5-Chloro-6-[6-methoxy-7-(3-piperidin-1-yl-propoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide |  |
| 264 | N-{5-Chloro-6-[6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide |  |

**Table 1**

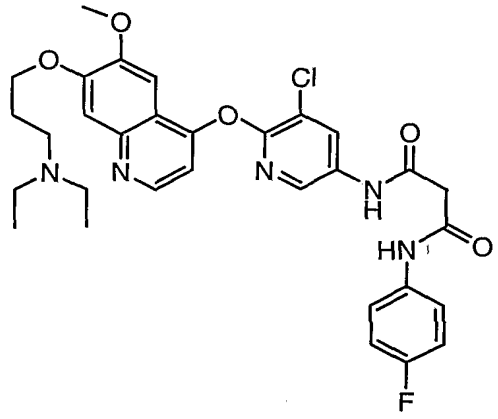
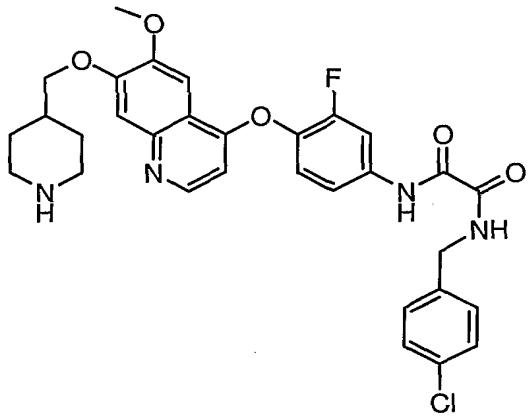
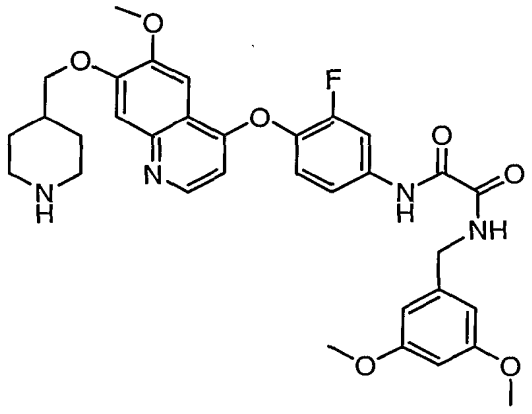
| Entry | Name | Structure |
|---|---|---|
| 265 | N-{5-Chloro-6-[7-(3-diethylamino-propoxy)-6-methoxy-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide |  |
| 266 | N-(4-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 267 | N-(3,5-Dimethoxy-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

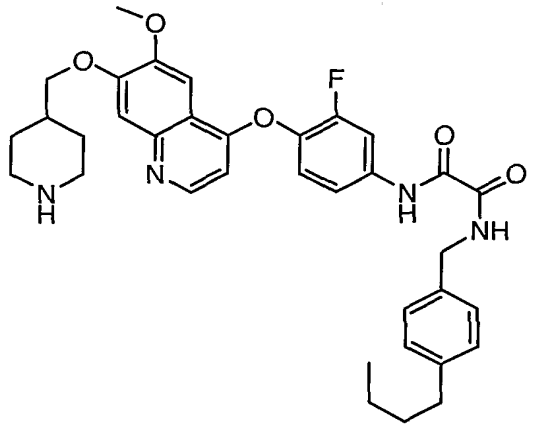
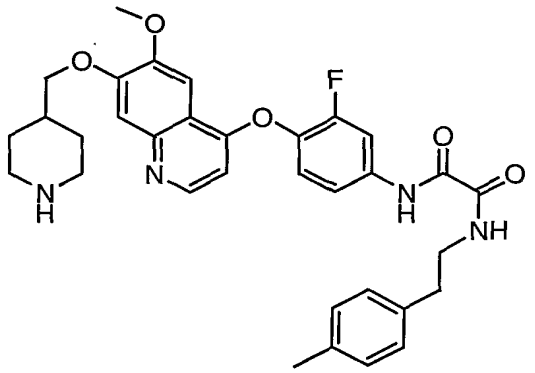
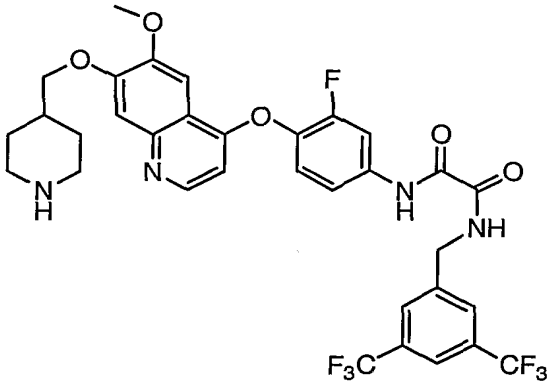
| Entry | Name | Structure |
|---|---|---|
| 268 | N-(4-Butyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 269 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-p-tolyl-ethyl)-oxalamide |  |
| 270 | N-(3,5-Bis-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

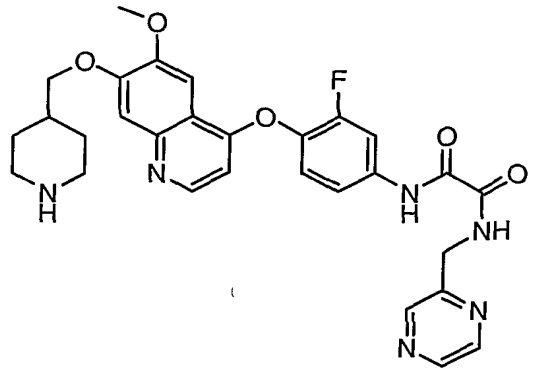
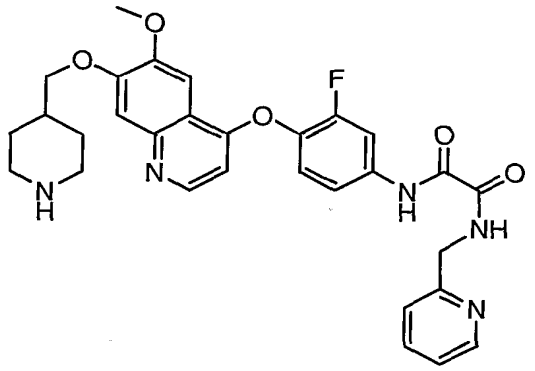
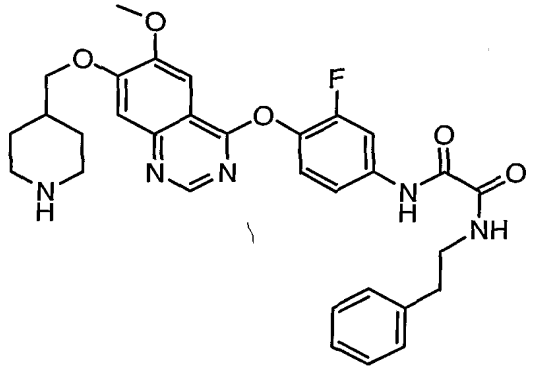
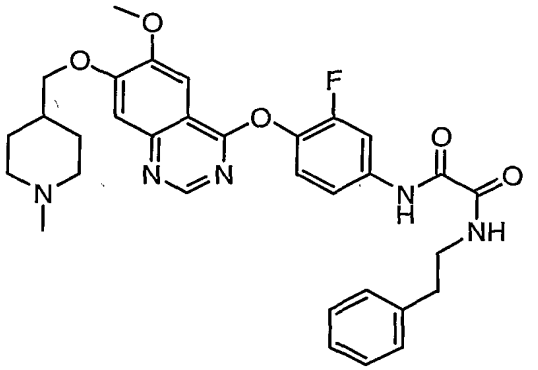
| Entry | Name | Structure |
|---|---|---|
| 271 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-pyrazin-2-ylmethyl-oxalamide |  |
| 272 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-pyridin-2-ylmethyl-oxalamide |  |
| 273 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide |  |
| 274 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide |  |

**Table 1**

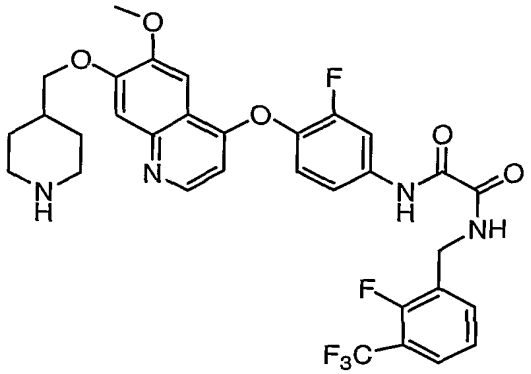
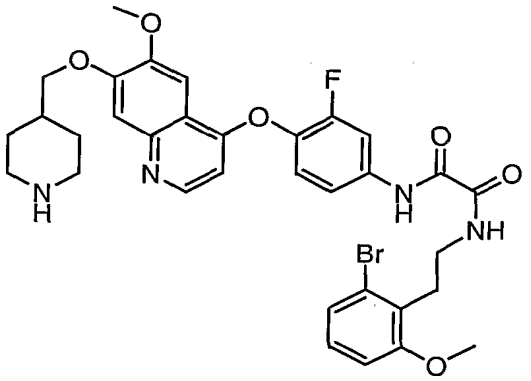
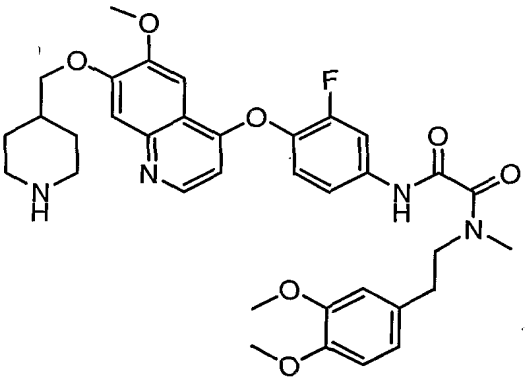
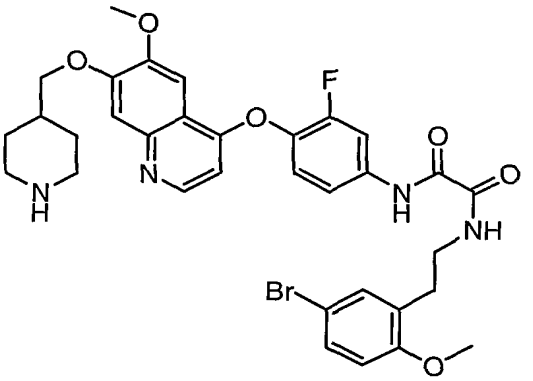
| Entry | Name | Structure |
|---|---|---|
| 275 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-fluoro-3-trifluoromethyl-benzyl)-oxalamide |  |
| 276 | N-[2-(2-Bromo-6-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 277 | N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N-methyl-oxalamide |  |
| 278 | N-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

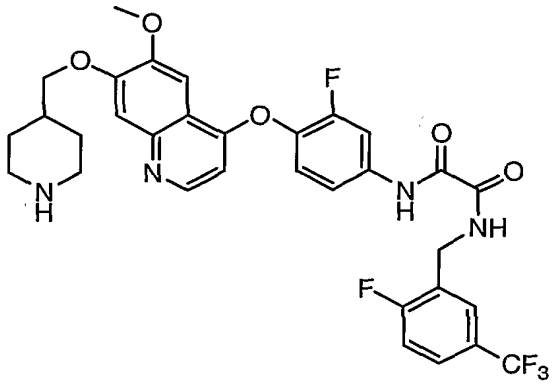
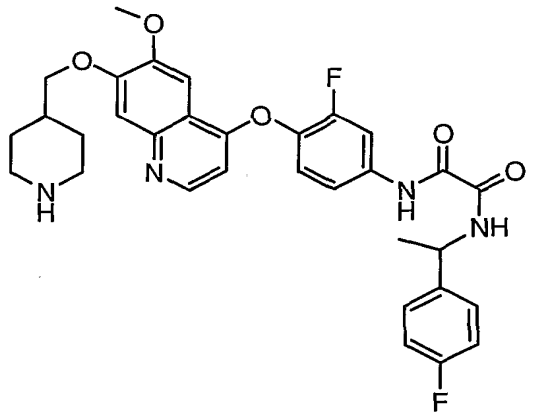
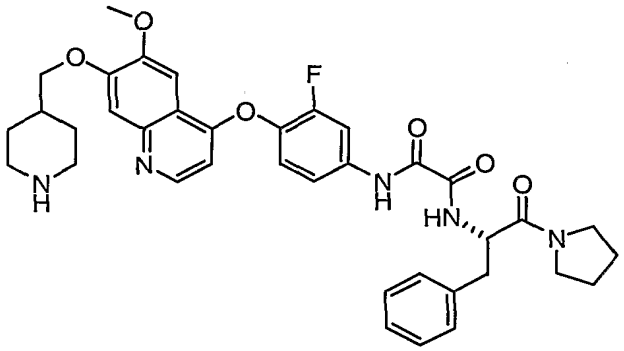
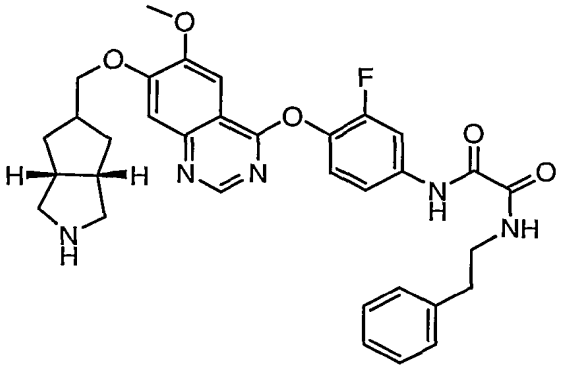
| Entry | Name | Structure |
|---|---|---|
| 279 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-fluoro-5-trifluoromethyl-benzyl)-oxalamide |  |
| 280 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[1-(4-fluoro-phenyl)-ethyl]-oxalamide |  |
| 281 | N-(1S-Benzyl-2-oxo-2-pyrrolidin-1-yl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 282 | N-{3-Fluoro-4-[6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide |  |

**Table 1**

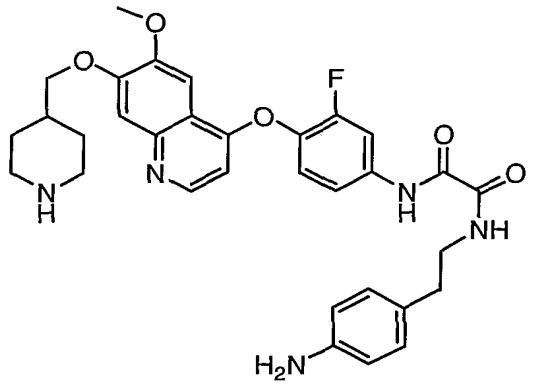
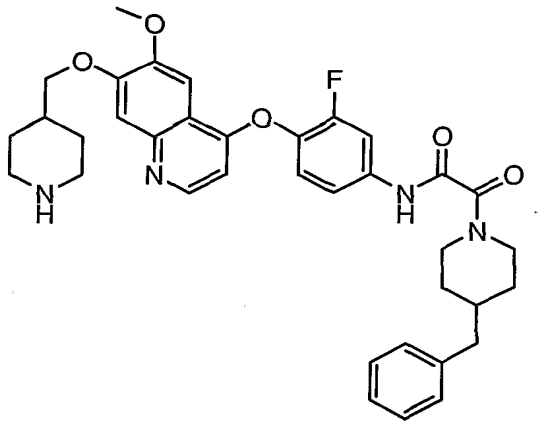
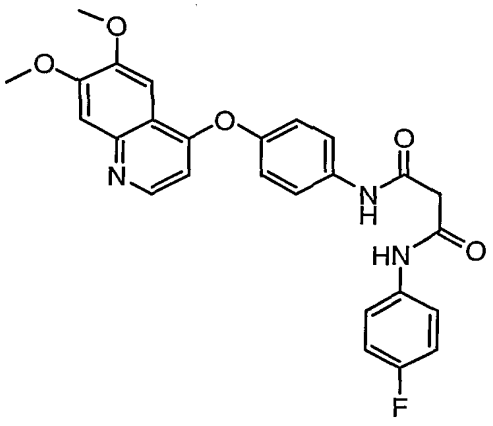
| Entry | Name | Structure |
|---|---|---|
| 283 | N-[2-(4-Amino-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 284 | 2-(4-Benzyl-piperidin-1-yl)-N-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-acetamide |  |
| 285 | N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenyl]-N'-(4-fluoro-phenyl)-malonamide |  |

**Table 1**

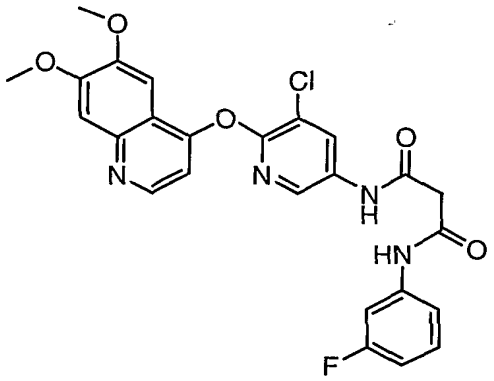
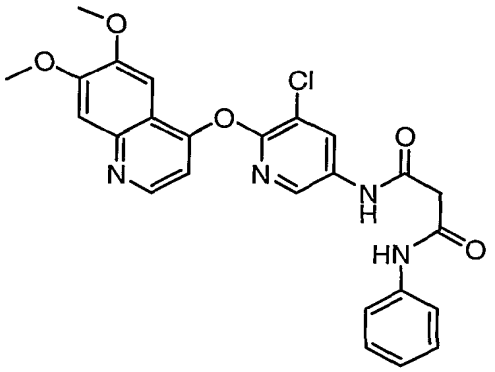
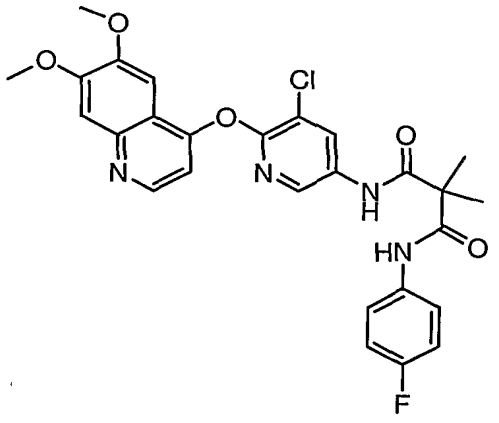
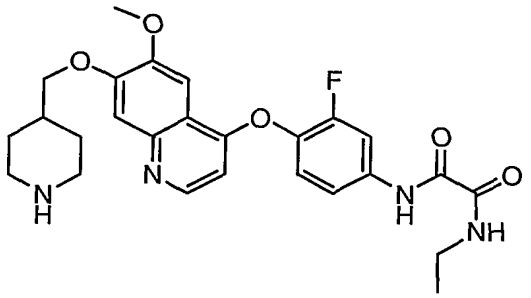
| Entry | Name | Structure |
|---|---|---|
| 286 | N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(3-fluoro-phenyl)-malonamide |  |
| 287 | N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-phenyl-malonamide |  |
| 288 | N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(4-fluoro-phenyl)-2,2-dimethyl-malonamide |  |
| 289 | N-Ethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

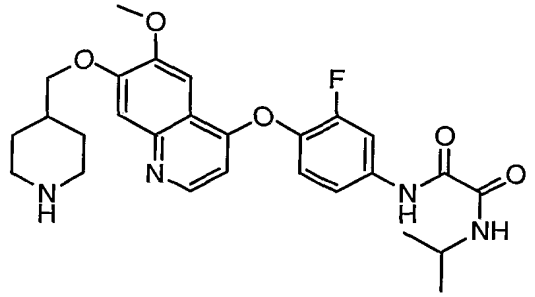
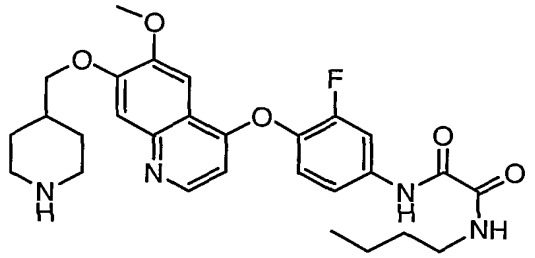
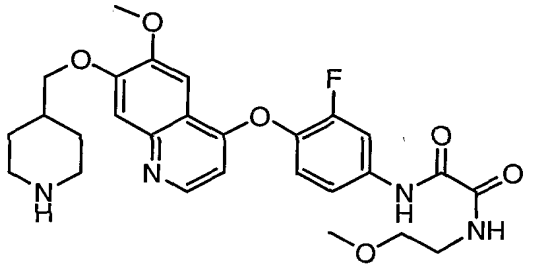
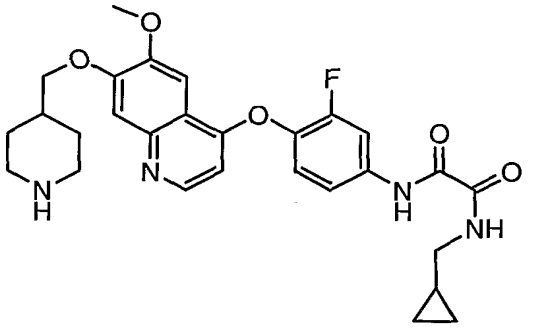
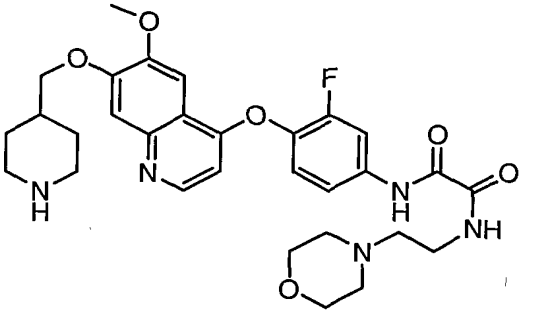
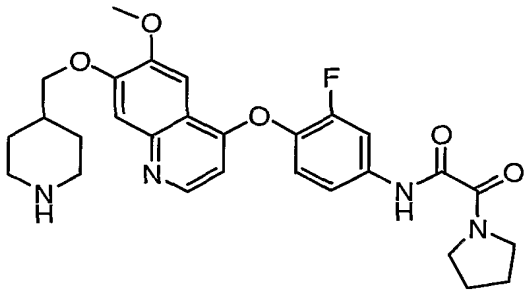
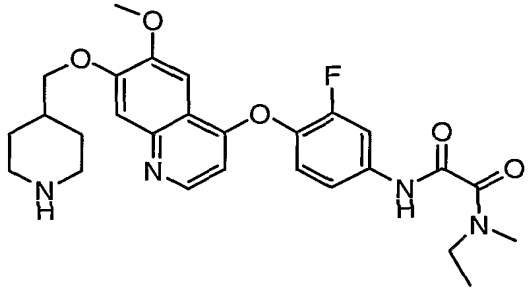
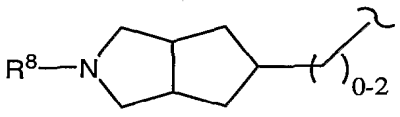
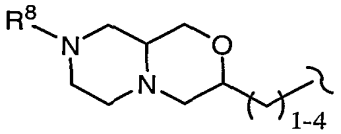
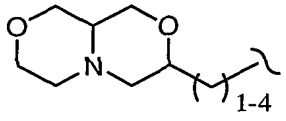
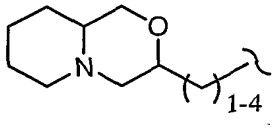
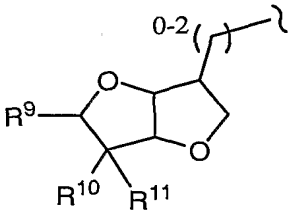
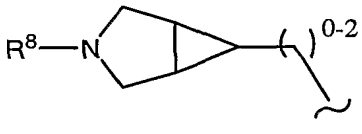
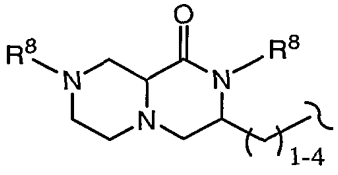
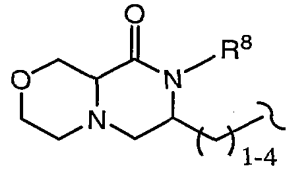
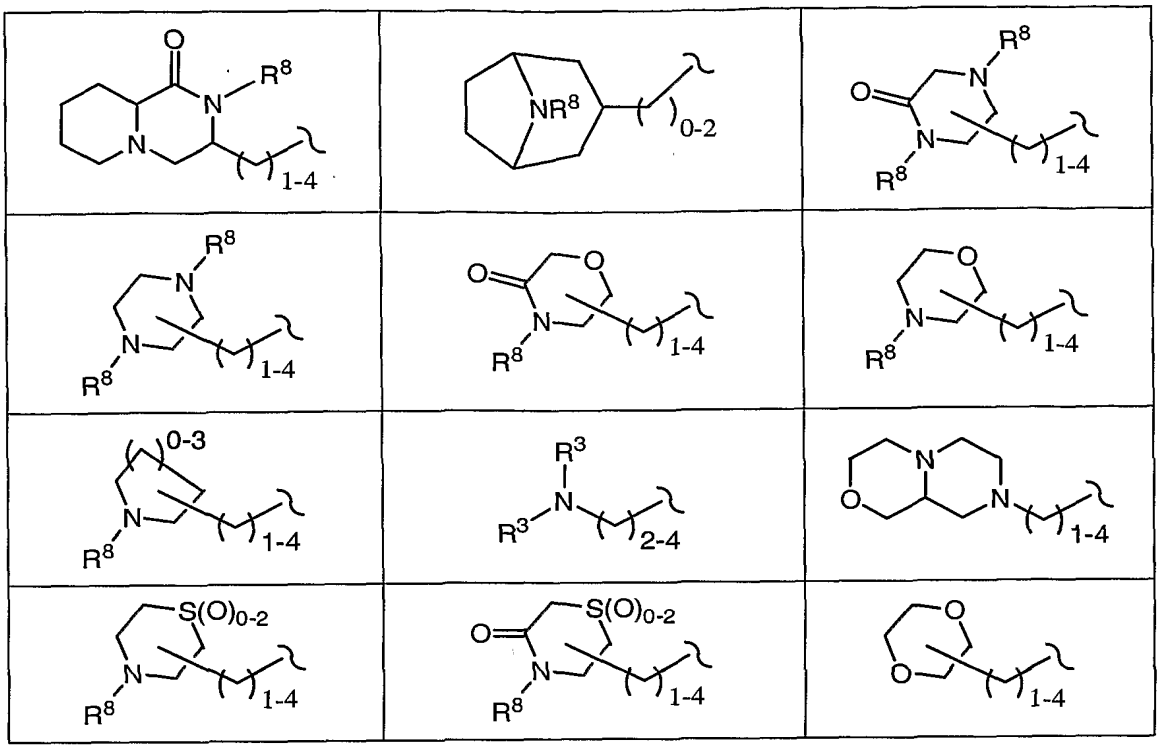
| Entry | Name | Structure |
|---|---|---|
| 290 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-isopropyl-oxalamide |  |
| 291 | N-Butyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 292 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methoxy-ethyl)-oxalamide |  |
| 293 | N-Cyclopropylmethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 294 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-morpholin-4-yl-ethyl)-oxalamide |  |

**Table 1**

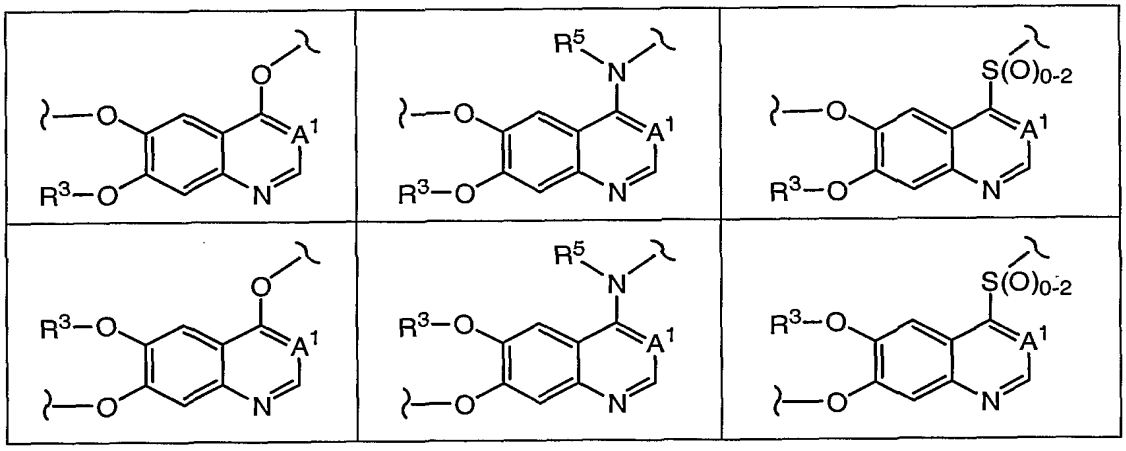
| Entry | Name | Structure |
|---|---|---|
| 295 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-pyrrolidin-1-yl-acetamide |  |
| 296 | N-Ethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N-methyl-oxalamide |  |

**[0078]** In another aspect, the invention comprises a compound for modulating kinase activity of formula A-B-C, or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein, A is selected from:

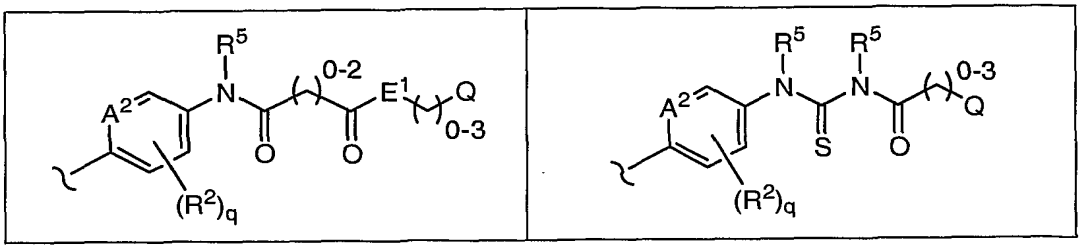
| | | |
|---|---|---|
| $-R^3$ |  |  |
|  |  |  |
|  |  |  |

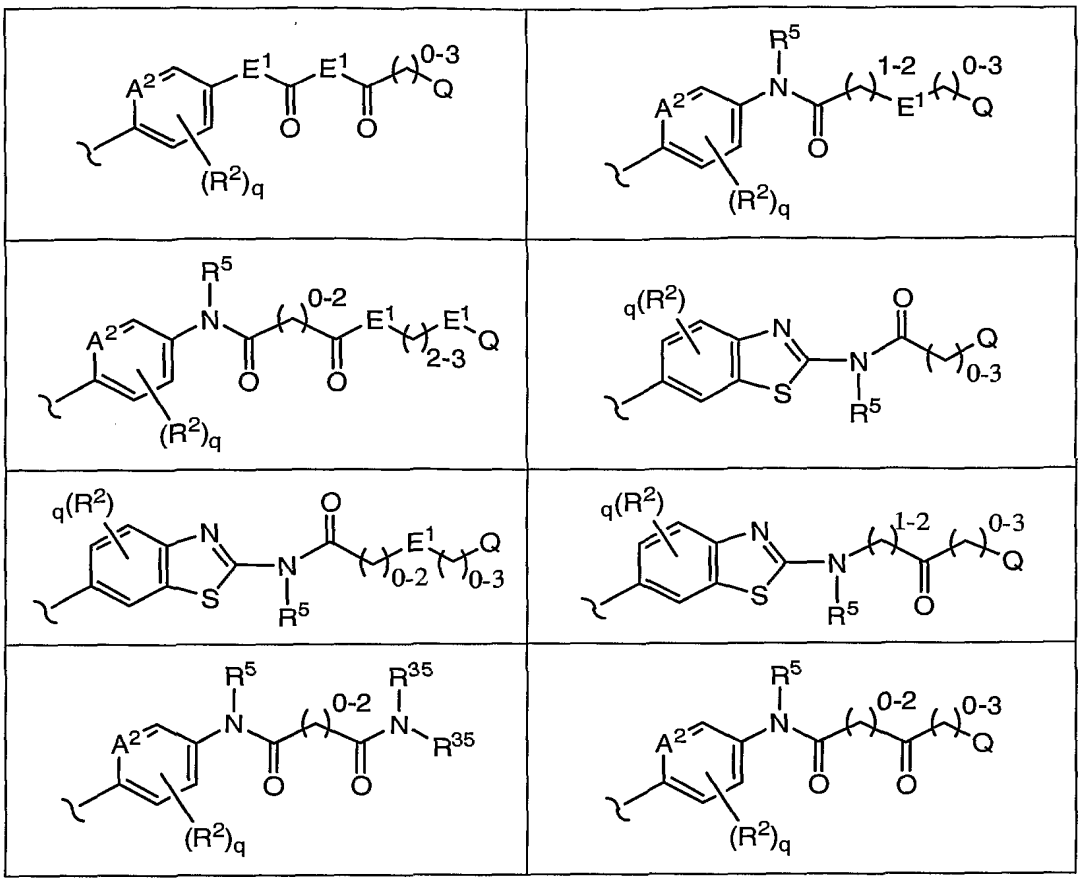


B is selected from:



and, C is selected from:





wherein $R^2$ is selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

q is 0 to 2;

each $R^3$ is independently selected from –H, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted arylalkyl, and optionally substituted heteroarylalkyl;

two $R^3$, together with the nitrogen to which they are attached, form a four- to seven-membered heteroalicyclic, said four- to seven-membered heteroalicyclic optionally containing one additional heteroatom; when one said additional heteroatom is a nitrogen, then said nitrogen is optionally substituted with a group selected from -H, trihalomethyl, $-SO_2R^5$, $-SO_2NR^5R^5$, $-CO_2R^5$, $-C(O)NR^5R^5$, $-C(O)R^5$, and optionally substituted lower alkyl;

each $R^{35}$ is independently selected from -H, $-C(=O)R^3$, $-C(=O)OR^3$, $-C(=O)SR^3$, $-SO_2R^3$, $-C(=O)N(R^3)R^3$, and optionally substituted lower alkyl;

two $R^{35}$, together with the nitrogen to which they are attached, can combine to form a heteroalicyclic optionally substituted with between one and four of $R^{60}$, said heteroalicyclic may have an additional annular heteroatom, and said heteroalicyclic may have an aryl fused thereto, said aryl optionally substituted with an additional one to four of $R^{60}$;

$A^1$ is selected from =N-, =C(H)-, and =C(CN)-;

$A^2$ is either =N- or =C(H)-;

$R^5$ is -H or optionally substituted lower alkyl;

$R^8$ is selected from $R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$;

$R^9$, $R^{10}$, and $R^{11}$ are each independently selected from -H, and $-OR^{12}$; or

$R^9$ is selected from -H, and $-OR^{12}$, and $R^{10}$ and $R^{11}$, when taken together, are either an optionally substituted alkylidene or an oxo; and

$R^{12}$ is selected from -H, $-C(O)R^3$, optionally substituted lower alkylidyne, optionally substituted lower arylalkylidyne, optionally substituted lower heterocyclylalkylidyne, optionally substituted lower alkylidene, optionally substituted lower alkylidenearyl, optionally substituted lower alkylideneheterocyclyl, optionally substituted lower alkyl, optionally substituted lower alkylaryl, optionally substituted aryl, optionally substituted lower heterocyclylalkyl, and optionally substituted heterocyclyl;

or two $R^{12}$'s, when taken together, form 1) a corresponding spirocyclic ketal when said two $R^{12}$'s stem from $R^{10}$ and $R^{11}$, or 2) a corresponding cyclic ketal when said two $R^{12}$'s stem from $R^9$ and one of $R^{10}$ and $R^{11}$;

$E^1$ is selected from -O-, $-CH_2-$, $-N(R^5)-$, and $-S(O)_{0-2}-$;

Q is a five- to ten-membered ring system, optionally substituted with between zero and four of $R^{20}$;

$R^{20}$ is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

$R^{60}$ is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$,

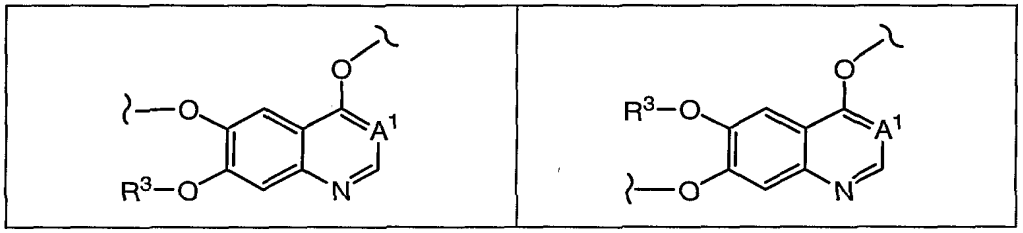
$-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroarylalkyl, and optionally substituted arylalkyl;

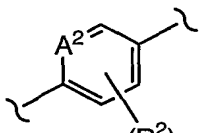
two of $R^{60}$, when attached to a non-aromatic carbon, can be oxo;

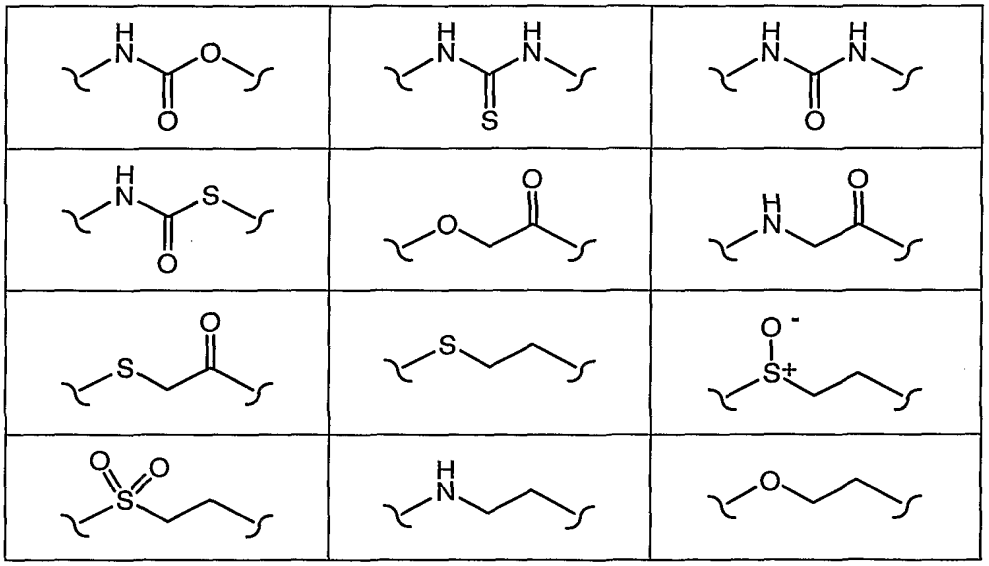
each methylene in any of the above formulae is independently optionally substituted with $R^{25}$;

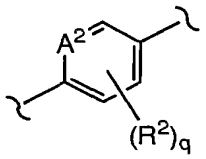
each $R^{25}$ is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; two of $R^{25}$, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic, two of $R^{25}$ on a single carbon can be oxo;

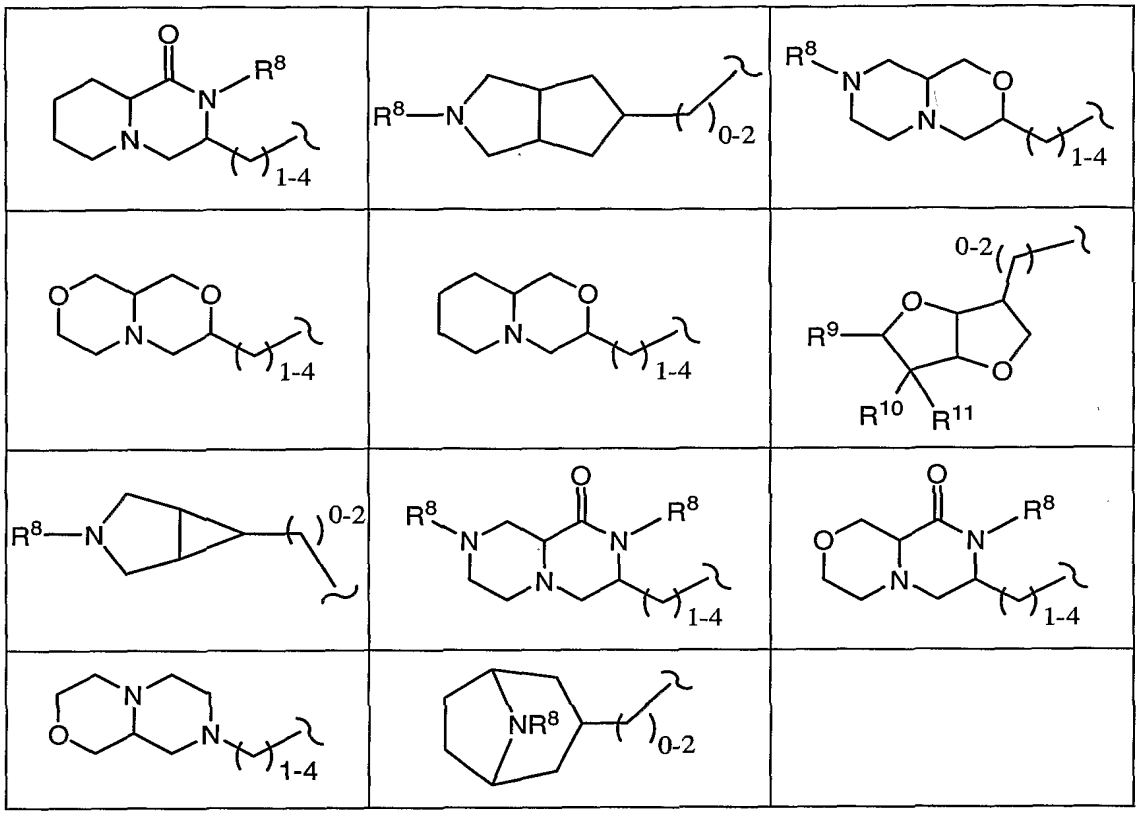
with the proviso that when B is selected from:

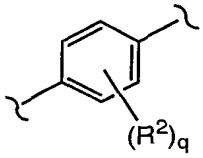


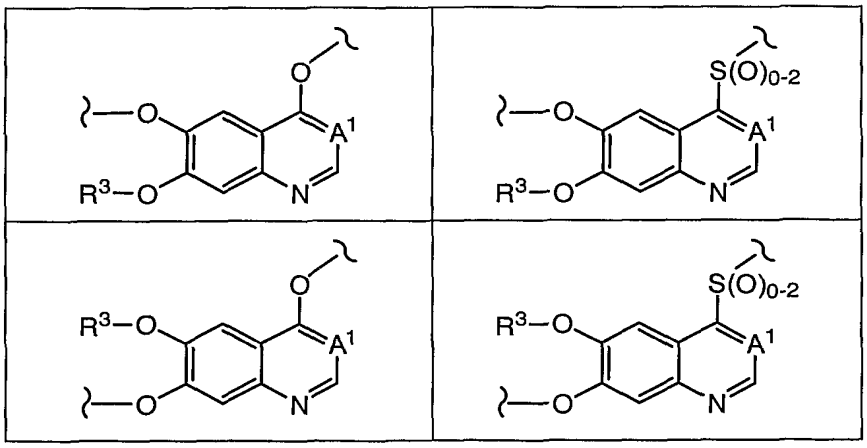
and C contains  , and the remaining portion of C contains one of:

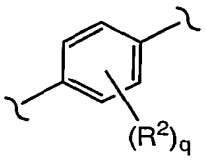
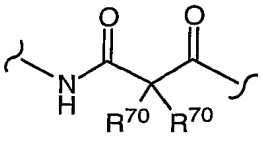


directly attached to  , then A must be one of:



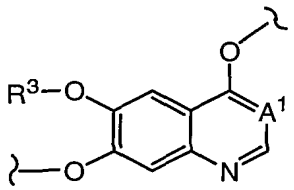
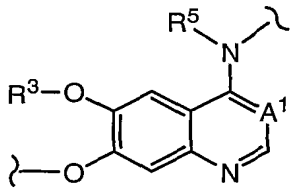
and with the proviso that when C contains  , and B is selected from:



then the portion of C directly attached to  cannot contain  , when $R^{70}$ is selected from -H, $C_{1-4}$alkyl, and $C_{1-4}$alkoxyl.

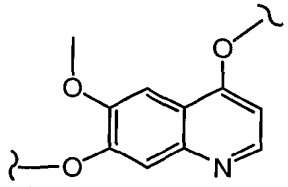
**[0079]** In another example the compound is according to paragraph [0078], wherein Q is selected from phenyl, napthyl, 1,2,3,4-tetrahydronaphthyl, indanyl, benzodioxanyl, benzofuranyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroisoquinolyl, pyrrolyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, tetrahydropyridinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxazolidinyl, triazolyl, isoxazolyl, isoxazolidinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, benzothieliyl, and oxadiazolyl; each optionally substituted with between one and four of $R^{20}$; wherein each $R^{20}$ is independently selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl.

**[0080]** In another example the compound is according to paragraph [0079], wherein B is either of the following:

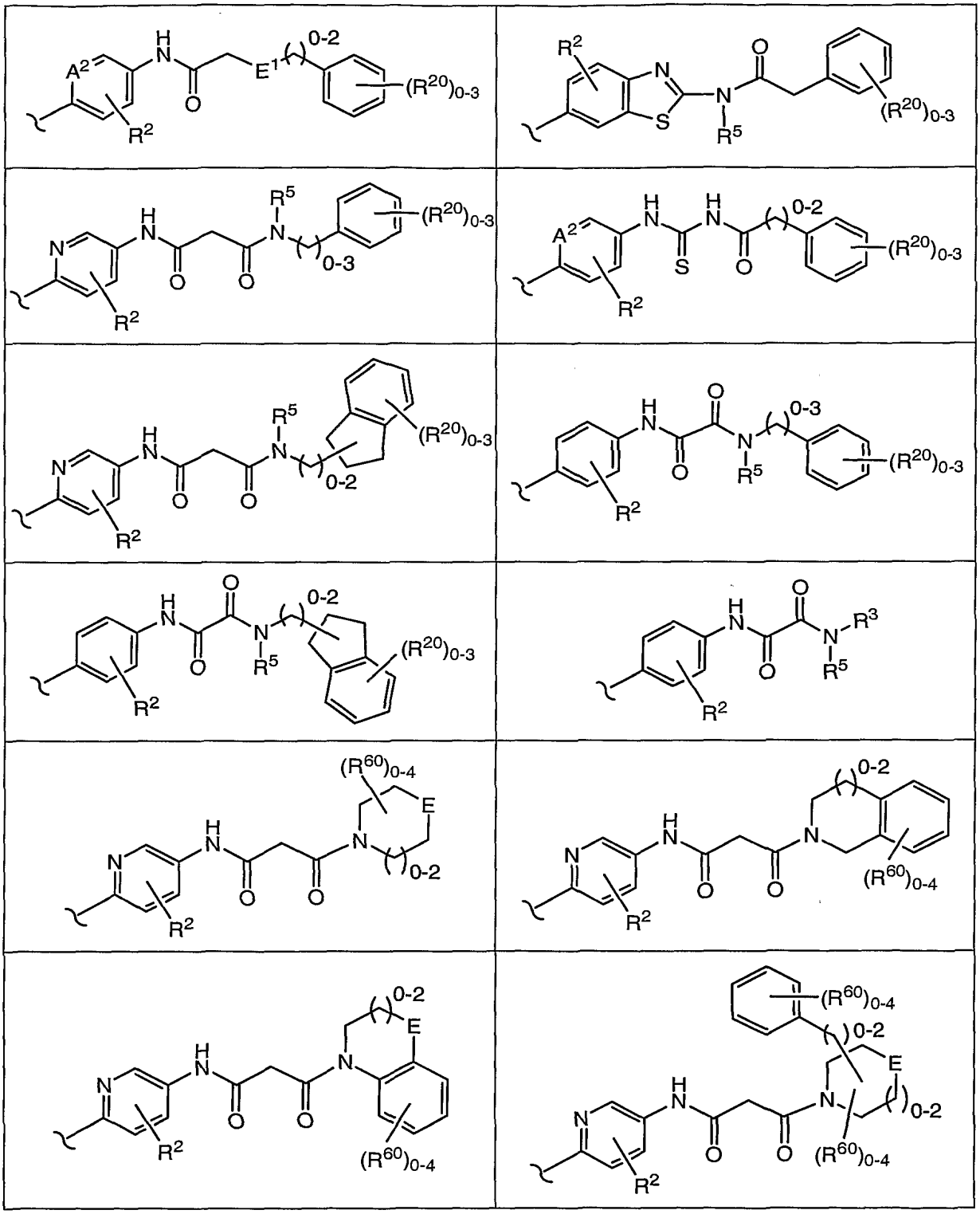



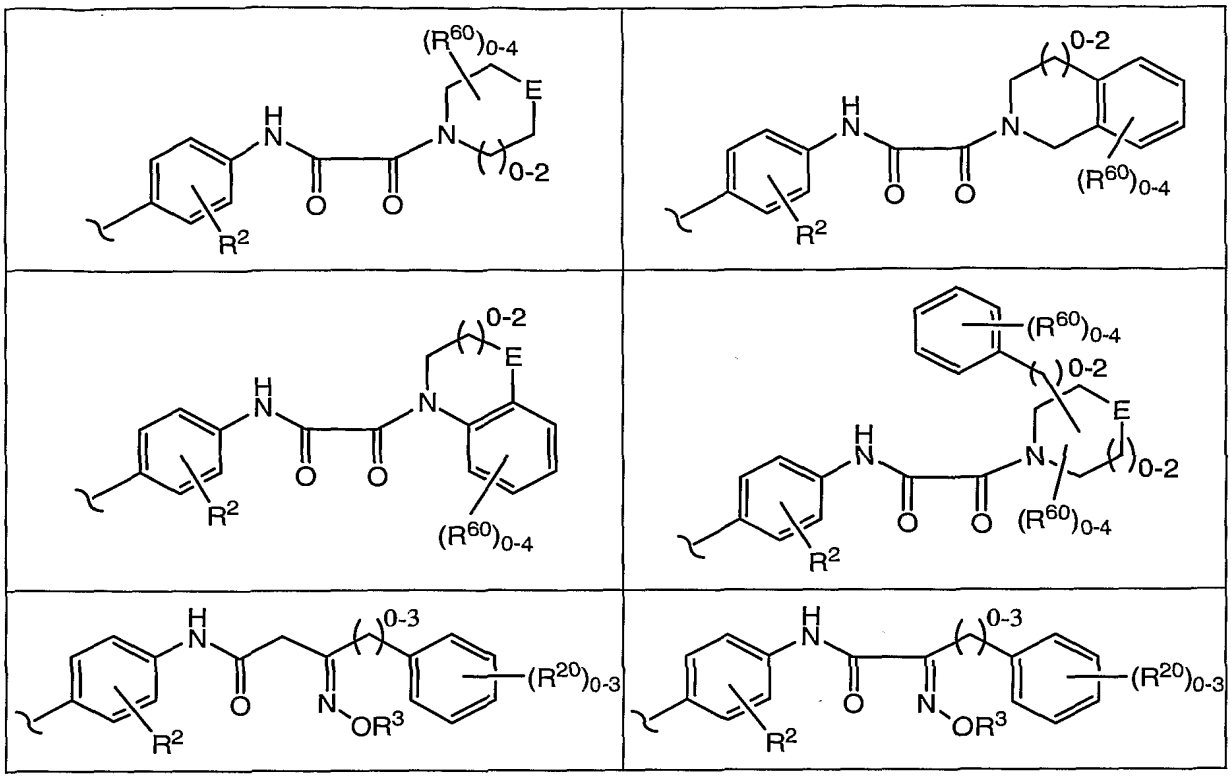
wherein $A^1$ is either =N- or =C(H)-.

**[0081]** In another example the compound is according to paragraph [0080], wherein B is



**[0082]** In another example the compound is according to paragraph [0081], wherein C is selected from:





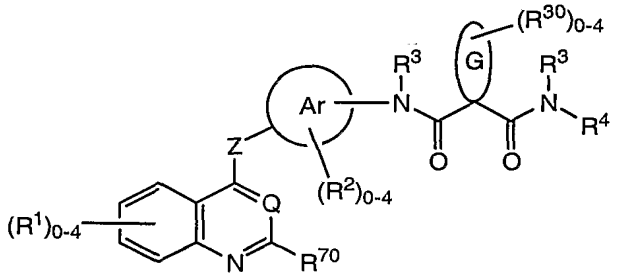
wherein $R^2$, $R^3$, $R^5$, $R^{20}$, $R^{25}$ and $R^{60}$ are as defined above.

**[0083]** In another example the compound is according to paragraph [0082], $R^2$ is selected from halogen, trihalomethyl, -CN, $-NO_2$, $-OR^3$, $-NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl

**[0084]** In another example the compound is according to paragraph [0083], wherein $R^2$ is halogen.

**[0085]** In another example the compound is according to paragraph [0084], wherein $R^2$ is either fluorine or chlorine.

**[0086]** In another aspect, the invention comprises a compound for modulating kinase activity according to Formula **XI**,



**XI**

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

each $R^1$ is independently selected from halogen, $-OR^3$, $-NO_2$, $-NH_2$, $-NR^3R^4$, $-D-R^{50}$ and optionally substituted $C_{1-6}$alkyl;

$R^{70}$ is selected from -H, halogen, $-OR^3$, $-S(O)_{0-2}R^3$, $-NO_2$, $-NH_2$, $-NR^3R^4$, and optionally substituted $C_{1-6}$alkyl;

Q is selected from =N-, =C(H)-, and =C(CN)-;

Z is selected from $-S(O)_{0-2}$-, -O-, and $-NR^5$-;

Ar is either a five- or six-membered arylene or a five- or six-membered heteroarylene containing between one and three heteroatoms;

G is either an optionally substituted cycloalkyl or an optionally substituted heteroalicyclic;

each $R^2$ is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted $C_{1-6}$alkyl;

each $R^3$ is independently -H or $R^4$;

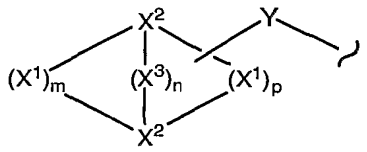
each $R^4$ is independently selected from optionally substituted $C_{1-6}$alkyl, optionally substituted aryl, optionally substituted aryl $C_{1-6}$alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl $C_{1-6}$alkyl; or

$R^3$ and $R^4$, when taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclyl, said optionally substituted five- to seven-membered heterocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

$R^5$ is -H or optionally substituted $C_{1-6}$alkyl;

each D is independently selected from $-O-$, $-S(O)_{0-2}$-, and $-NR^5$-;

each $R^{50}$ is independently either $R^3$, or according to formula **XII**;




**XII**

wherein $X^1$, $X^2$, and optionally $X^3$, represent the atoms of a saturated bridged ring system, said saturated bridged ring system comprising up to four annular heteroatoms represented by any of $X^1$, $X^2$, and $X^3$; wherein,

each $X^1$ is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

each $X^2$ is independently an optionally substituted bridgehead methine or a bridgehead nitrogen;

each $X^3$ is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

Y is either:

an optionally substituted lower alkylene linker, between D and either 1) any annular atom of the saturated bridged ring system, except $X^2$ when $X^2$ is a bridgehead nitrogen, or 2) any heteroatom, represented by any of $R^6$ or $R^7$; provided there are at least two carbon atoms between D and any annular heteroatom of the saturated bridged ring system or any heteroatom represented by any of $R^6$ or $R^7$;

or Y is absent, when Y is absent, said saturated bridged ring system, is directly attached to D via an annular carbon of said saturated bridged ring system, unless D is $-SO_2-$, in which case said saturated bridged ring system, is directly attached to D via an any annular atom of said saturated bridged ring system;

m and p are each independently one to four;

n is zero to two, when n equals zero, then there is a single bond between the two bridgehead $X^2$'s;

$R^6$ and $R^7$ are each independently selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^4$, $-SO_2NR^3R^4$, $-CO_2R^3$, $-C(O)NR^3R^4$, $-N(R^3)SO_2R^4$, $-N(R^3)C(O)R^3$, $-NCO_2R^3$, $-C(O)R^3$, optionally substituted $C_{1-6}$alkyl, optionally substituted aryl, optionally substituted aryl $C_{1-6}$alkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl $C_{1-6}$alkyl, and a bond to either Y or D; or

$R^6$ and $R^7$, when taken together are oxo; or

$R^6$ and $R^7$, when taken together with a common carbon to which they are attached, form a optionally substituted three- to seven-membered spirocyclyl, said optionally substituted three- to seven-membered spirocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

$R^8$ is selected from $-R^3$, Y, $-SO_2NR^3R^4$, $-CO_2R^4$, $-C(O)NR^3R^3$, $-SO_2R^4$, and $-C(O)R^3$; and

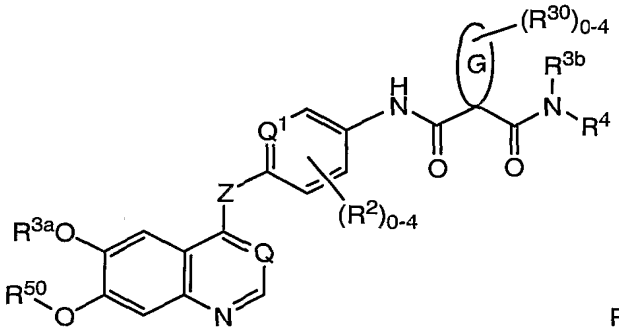
each $R^{30}$ is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted $C_{1-6}$alkyl.

**[0087]** In one example, the compound is according to paragraph [0086], wherein Z is either -O- or $-NR^5-$.

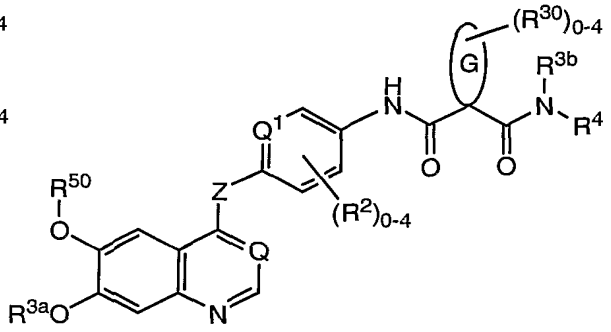
**[0088]** In another example, the compound is according to paragraph [0087], wherein at least one of $R^1$ is $-D-R^{50}$.

**[0089]** In another example, the compound is according to paragraph [0088], wherein D is -O- and at least one other $R^1$ is $-OR^3$.

**[0090]** In another example, the compound is according to paragraph [0089], of formula **XIIIa** or **XIIIb**:



**XIIIa**



**XIIIb**

wherein $Q^1$ is either =N- or =C(H)-.

**[0091]** In another example, the compound is according to paragraph [0090], wherein $R^{50}$ is selected from $C_{1-6}$alkyl optionally substituted with at least one of optionally substituted amino, optionally substituted $C_{1-6}$alkyl amino, optionally substituted $C_{1-6}$dialkyl amino, optionally substituted heteroalicylic, and a group of formula **XII**.

**[0092]** In another example, the compound is according to paragraph [0091], wherein $R^{3a}$ is $C_{1-6}$alkyl.

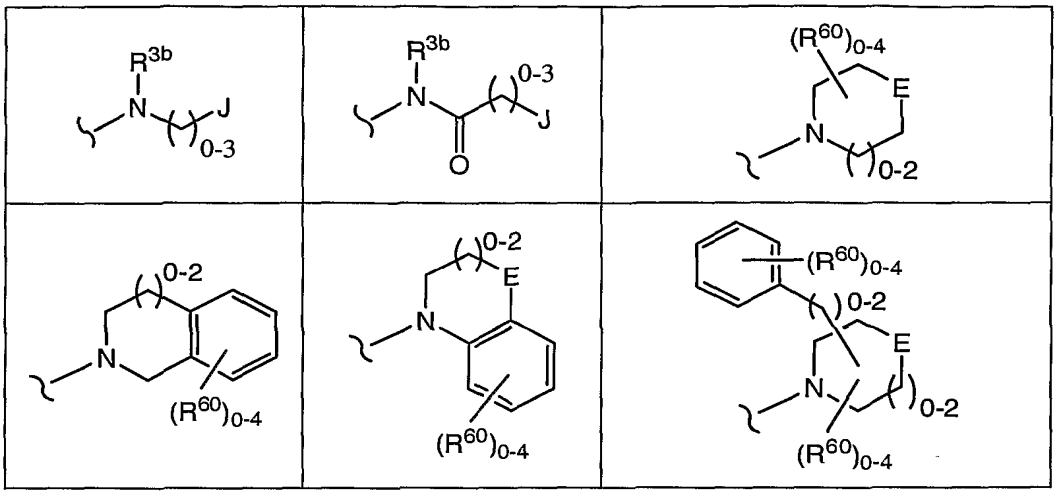
**[0093]** In another example, the compound is according to paragraph [0092], wherein Z is -O-.

**[0094]** In another example, the compound is according to paragraph [0093], wherein G is selected from cyclopropyl, aziradine, cyclobutyl, and azetidine, each optionally substituted with between zero and four of $R^{30}$.

**[0095]** In another example, the compound is according to paragraph [0094], wherein Q is either =N- or =C(H)-.

**[0096]** In another example, the compound is according to paragraph [0095], wherein $R^2$ is selected from -H, halogen, $C_{1-6}$ alkyl and perfluoro $C_{1-6}$ alkyl.

**[0097]** In another example, the compound is according to paragraph [0096], wherein $-N(R^{3b})R^4$ is selected from the following:



wherein J, is a five- to ten-membered ring, optionally substituted with between zero and five of $R^{20}$;

each $R^{20}$ is independently selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted $C_{1-6}$alkyl, optionally substituted aryl, optionally substituted aryl $C_{1-6}$alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl $C_{1-6}$alkyl;

two of $R^{20}$, together with the atom or atoms to which they are attached, combine to form an optionally substituted three- to seven-membered heteroalicyclic, said optionally substituted three- to seven-membered heteroalicyclic either spiro- to J or fused to J;

E is selected from -O-, $-N(R^5)$-, $-CH_2$-, and $-S(O)_{0-2}$-;

each $R^{60}$ is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted $C_{1-6}$alkyl, optionally substituted aryl, optionally substituted heteroaryl $C_{1-6}$alkyl, and optionally substituted aryl $C_{1-6}$alkyl;

each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with $R^{25}$; and

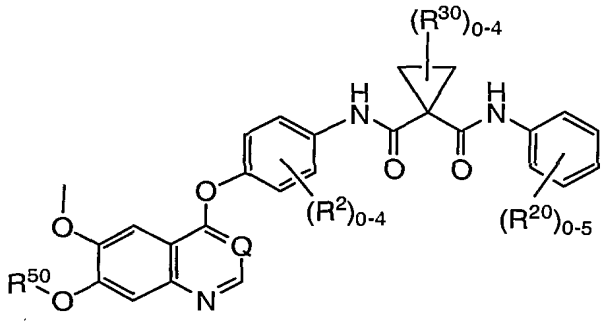
$R^{25}$ is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted aryl $C_{1-6}$alkyl, heteroaryl $C_{1-6}$alkyl, and optionally substituted $C_{1-6}$alkyl; or

two of $R^{25}$, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic;

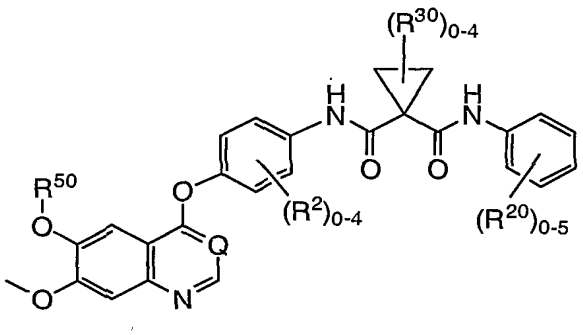
$R^{3b}$ is equivalent to $R^3$ as defined above; and

$R^4$ and $R^5$ are as defined above.

**[0098]** In another example, the compound is according to paragraph [0097], of formula **XIVa** or **XIVb**:



**XIVa**



**XIVb**

**[0099]** In another example, the compound is according to paragraph [0098], wherein $R^{50}$ is $C_{1-6}$alkyl optionally substituted with a group selected from optionally substituted amino, an optionally substituted alkylamino, optionally substituted dialkylamino, and optionally substituted heteroalicylic.

**[0100]** In another example, the compound is according to paragraph [0099], wherein the heteroalicyclic portion of said optionally substituted heteroalicyclic of $R^{50}$ is selected from the group consisting of piperidine, piperazine, morpholine, thiomorpholine, thiomorpholine 1-oxide, thiomorpholine 1,1-dioxide, 2-oxo-morpholine, pyrrolidine, and azepine.

**[0101]** In another example, the compound is according to paragraph [0099], wherein $R^{50}$ is according to formula **XII**.

**[0102]** In another example, the compound is according to paragraph [0101], wherein the saturated bridged ring system according to formula **XII** has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], [3.1.0], [3.3.3], [3.3.2], [3.3.1], [3.2.2], [3.2.1], [2.2.2], and [2.2.1].

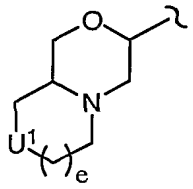
**[0103]** In another example, the compound is according to paragraph [0102], wherein Y is selected from $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2-$, $-CH_2-$, and absent.

**[0104]** In another example, the compound is according to paragraph [0103], wherein n is 0 and the saturated bridged ring system according to formula **XII** has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], and [3.1.0].

**[0105]** In another example, the compound is according to paragraph [0104], wherein said saturated bridged ring system contains at least one annular nitrogen or at least one annular oxygen.

**[0106]** In another example, the compound is according to paragraph [0105], wherein said saturated bridged ring system contains $-NR^8-$, wherein $R^8$ is selected from -H, optionally substituted $C_{1-6}$alkyl, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.

**[0107]** In another example, the compound is according to paragraph [0105], wherein said saturated bridged ring system is of formula **XV**,




**XV**

wherein $U^1$ is selected from $-O-$, $-S(O)_{0-2}-$, $-NR^8-$, $-CR^6R^7-$, and absent; and e is 0 or 1.

**[0108]** In another example, the compound is according to paragraph [0107], wherein Y is $-CH_2-$.

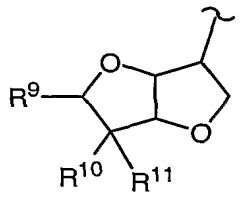
**[0109]** In another example, the compound is according to paragraph [0108], wherein $U^1$ is $-NR^8-$, wherein $R^8$ is selected from -H, optionally substituted lower alkyl, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.

**[0110]** In another example, the compound is according to paragraph [0108], wherein $U^1$ is $-O-$.

**[0111]** In another example, the compound is according to paragraph [0108], wherein $U^1$ is absent.

**[0112]** In another example, the compound is according to paragraph [0103], wherein Y is selected from $-CH_2CH_2-$, $-CH_2-$, and absent.

**[0113]** In another example, the compound is according to paragraph [0112], wherein said saturated bridged ring system is of formula **XVI**,



**XVI**

wherein $R^9$, $R^{10}$, and $R^{11}$ are each independently selected from -H, and $-OR^{12}$; or

$R^9$ is selected from -H, and $-OR^{12}$, and $R^{10}$ and $R^{11}$, when taken together, are either an optionally substituted alkylidene or an oxo;

$R^{12}$ is selected from -H, $-C(O)R^3$, optionally substituted lower alkylidyne, optionally substituted lower arylalkylidyne, optionally substituted lower heterocyclylalkylidyne, optionally substituted lower alkylidene, optionally substituted lower alkylidenearyl, optionally substituted lower alkylideneheterocyclyl, optionally substituted lower alkyl, optionally substituted lower alkylaryl, optionally substituted aryl, optionally substituted lower heterocyclylalkyl, and optionally substituted heterocyclyl;

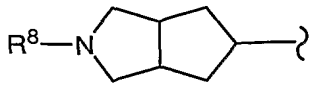
or two $R^{12}$'s, when taken together, form 1) a corresponding spirocyclic ketal when said two $R^{12}$'s stem from $R^{10}$ and $R^{11}$, or 2) a corresponding cyclic ketal when said two $R^{12}$'s stem from $R^9$ and one of $R^{10}$ and $R^{11}$.

**[0114]** In another example, the compound is according to paragraph [0113], wherein one of $R^{10}$ and $R^{11}$ is $-OR^{12}$, wherein $R^{12}$ is selected from -H, $-C(O)R^3$, and optionally substituted lower alkyl; and $R^9$ and the other of $R^{10}$ and $R^{11}$ are both -H.

**[0115]** In another example, the compound is according to paragraph [0114], wherein Y is either $-CH_2-$ or absent.

**[0116]** In another example, the compound is according to paragraph [0113], wherein $R^9$ is an alkyl group containing at least one fluorine substitution thereon.

**[0117]** In another example, the compound is according to paragraph [0106], wherein said saturated bridged ring system is of formula **XVII**.



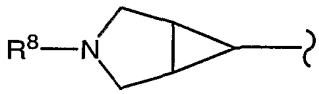
**XVII**

**[0118]** In another example, the compound is according to paragraph [0117], wherein Y is either $-CH_2-$ or absent.

**[0119]** In another example, the compound is according to paragraph [0118], wherein $R^8$ is methyl or ethyl.

**[0120]** In another example, the compound is according to paragraph [0119], wherein at least one of $R^2$ is halogen.

**[0121]** In another example, the compound is according to paragraph [0106], wherein said saturated bridged ring system is of formula **XVIII**.

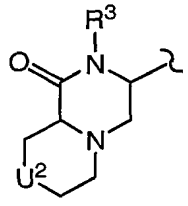


**XVIII**

**[0122]** In another example, the compound is according to paragraph [0121], wherein Y is $-CH_2-$.

**[0123]** In another example, the compound is according to paragraph [0122], wherein $R^8$ is methyl or ethyl.

**[0124]** In another example, the compound is according to paragraph [0105], wherein said saturated bridged ring system is of formula **XIX**



**XIX**

wherein $U^2$ is selected from -O-, $-S(O)_{0-2}-$, $-NR^8-$, $-CR^6R^7-$, and absent.

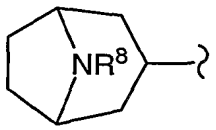
**[0125]** In another example, the compound is according to paragraph [0124], wherein $R^3$ of formula **XIX** is selected from -H and optionally substituted alkyl.

**[0126]** In another example, the compound is according to paragraph [0125], wherein $U^2$ is either $-CR^6R^7-$ or absent.

**[0127]** In another example, the compound is according to paragraph [0126], wherein $U^2$ is either $-CH_2-$ or absent.

**[0128]** In another example, the compound is according to paragraph [0127], wherein Y is $-CH_2-$.

**[0129]** In another example, the compound is according to paragraph [0106], wherein said saturated bridged ring system is according to formula **XX**.




**XX**

**[0130]** In another example, the compound is according to paragraph [0129], wherein $R^8$ is methyl or ethyl.

**[0131]** In another example, the compound is according to any of paragraphs [0099] – [0130], wherein $R^2$ is selected from $C_{1-6}$ alkyl, perfluoro $C_{1-6}$ alkyl, and halogen.

**[0132]** In another example, the compound is according to paragraph [0131], wherein $R^2$ is selected from perfluoro $C_{1-3}$ alkyl and halogen.

**[0133]** In another example, the compound is according to any of paragraphs [0099] – [0130], wherein $R^{20}$ is selected from halogen, $-CN$, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, optionally substituted heterocyclyl, and optionally substituted heterocyclyl $C_{1-6}$alkyl, and (two of $R^{20}$) together with the atom or atoms to which they are attached, an optionally substituted three- to six-membered heteroalicyclic, said optionally substituted three- to six-membered heteroalicyclic fused to the phenyl as in **XIVa** or **XIVb**.

**[0134]** In another example, the compound is according to paragraph [0133], wherein $R^{20}$ is selected from halogen, $-NR^3R^4$, optionally substituted heterocyclyl, and optionally substituted heterocyclyl $C_{1-6}$alkyl, and (two of $R^{20}$) together with the atom or atoms to which they are attached, an optionally substituted five- to six-membered heteroalicyclic, said optionally substituted five- to six-membered heteroalicyclic fused to the phenyl as in **XIVa** or **XIVb**.

**[0135]** In another example, the compound is according to paragraph [0134], wherein $R^2$ is selected from $C_{1-6}$ alkyl, perfluoro $C_{1-6}$ alkyl, and halogen.

**[0136]** In another example, the compound is according to paragraph [0135], wherein $R^2$ is selected from perfluoro $C_{1-3}$ alkyl and halogen.

**[0137]** In another example, the compound is according to paragraph [0086], selected from Table 2.

**Table 2**

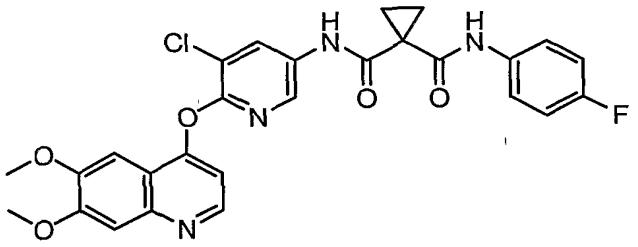
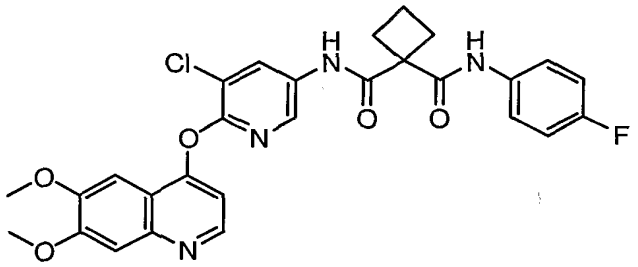
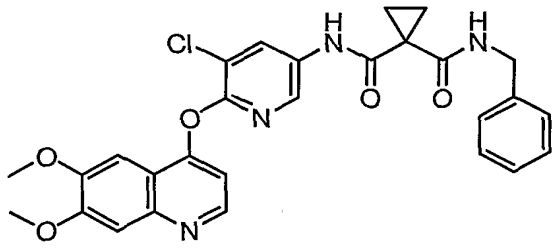
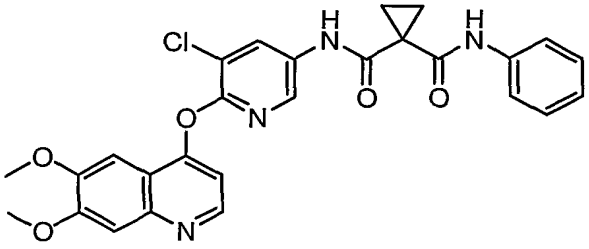
| Entry | Name | Structure |
|---|---|---|
| 1 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 2 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide |  |
| 3 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(phenylmethyl)cyclopropane-1,1-dicarboxamide |  |
| 4 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-phenylcyclopropane-1,1-dicarboxamide |  |

**Table 2**

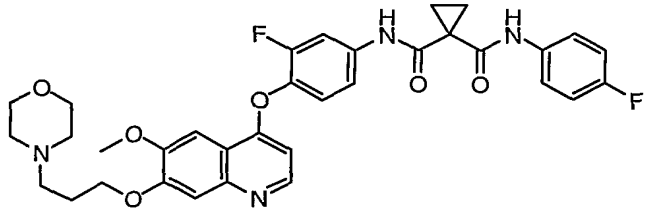
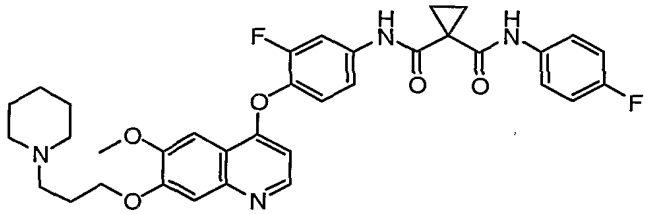
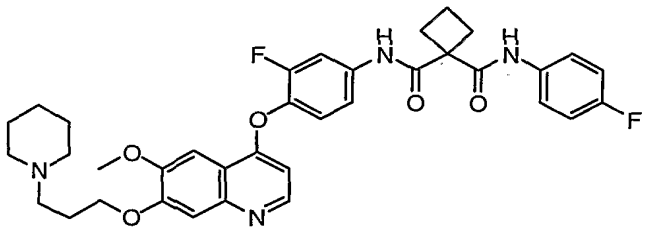
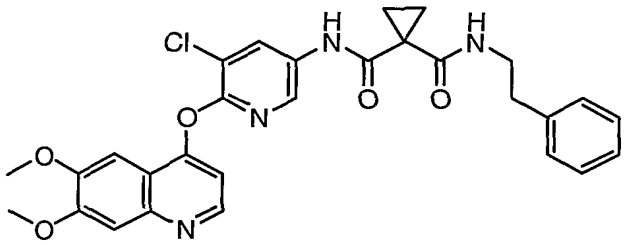
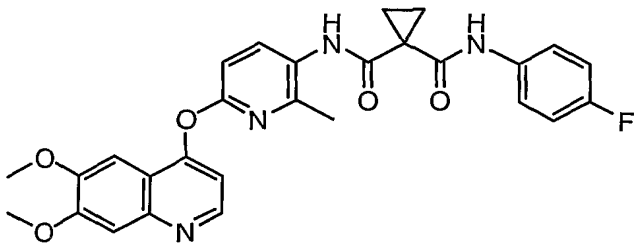
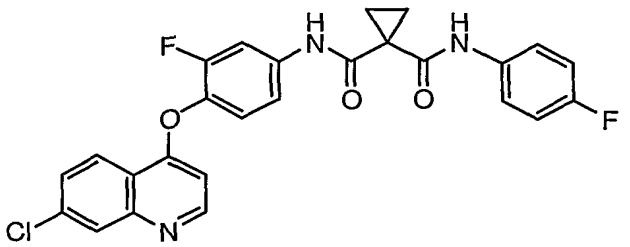
| Entry | Name | Structure |
|---|---|---|
| 5 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 6 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 7 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide |  |
| 8 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)cyclopropane-1,1-dicarboxamide |  |
| 9 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 10 | N-{4-[(7-chloroquinolin-4-yl)oxy]-3-fluorophenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |

**Table 2**

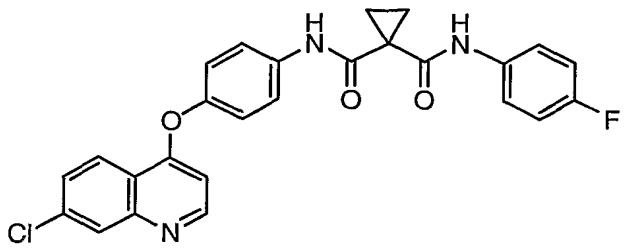
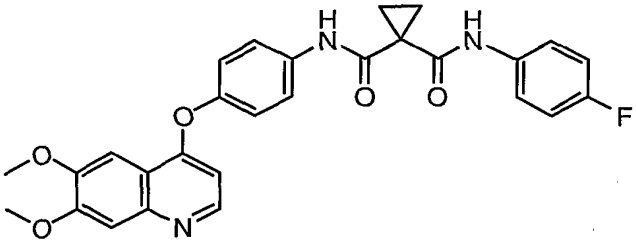
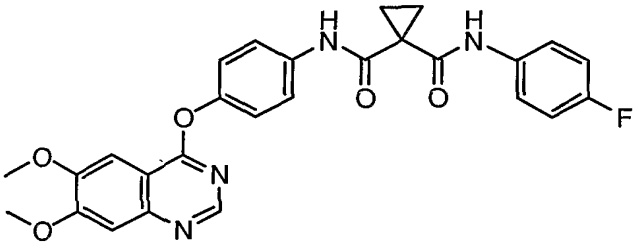
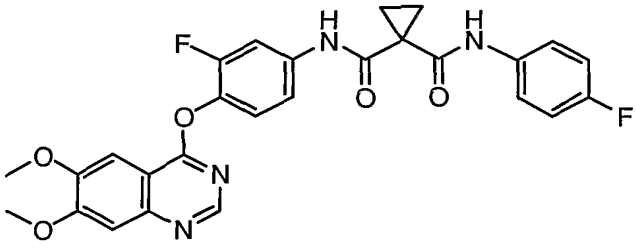
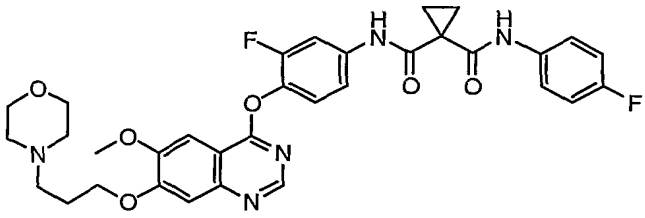
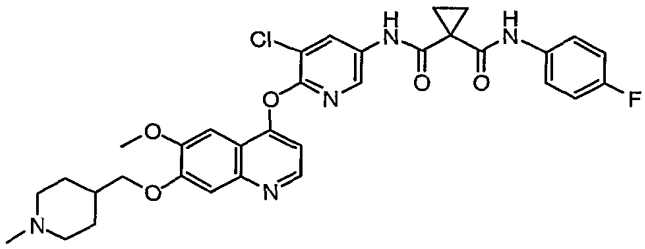
| Entry | Name | Structure |
|---|---|---|
| 11 | N-{4-[(7-chloroquinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 12 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 13 | N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 14 | N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 15 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 16 | N-{5-chloro-6-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]pyridin-3-yl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |

**Table 2**

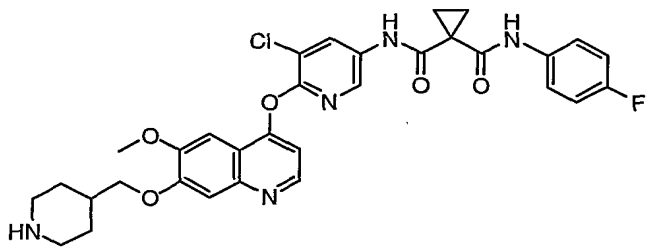
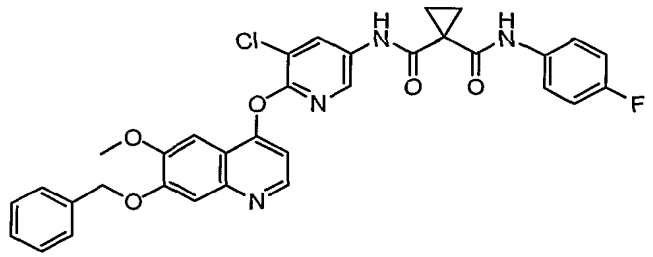
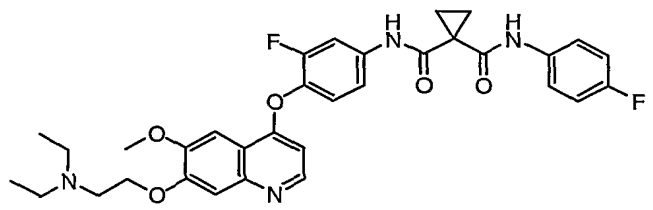
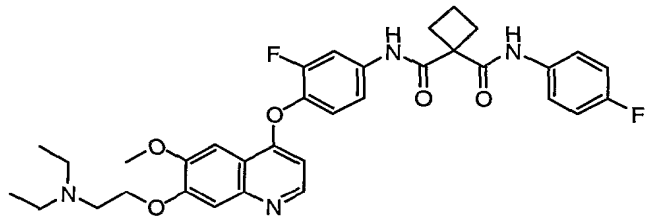
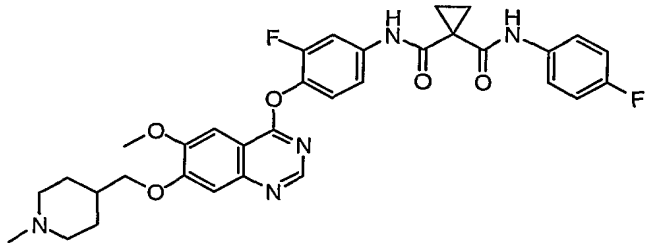
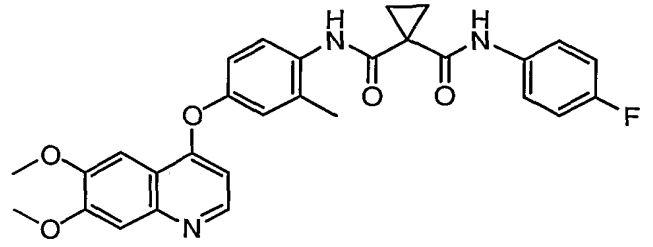
| Entry | Name | Structure |
|---|---|---|
| 17 | N-[5-chloro-6-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 18 | N-[5-chloro-6-({6-(methyloxy)-7-[(phenylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 19 | N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 20 | N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide |  |
| 21 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 22 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |

**Table 2**

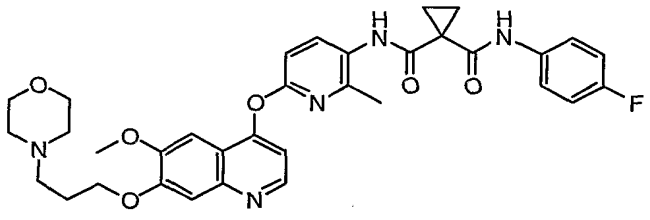
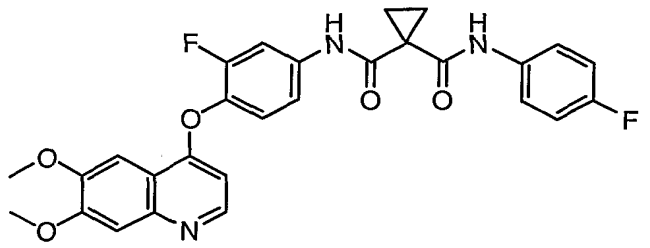
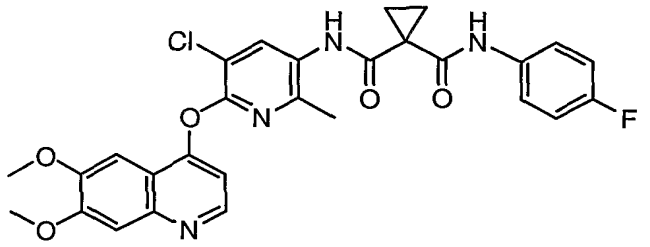
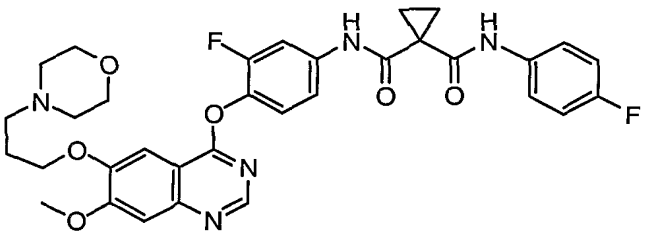
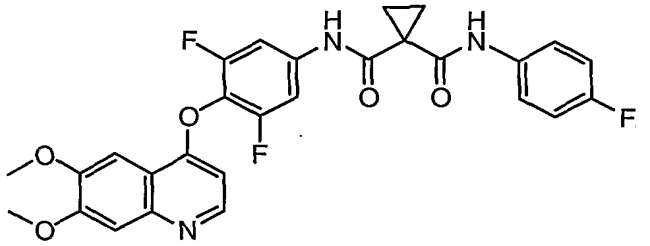
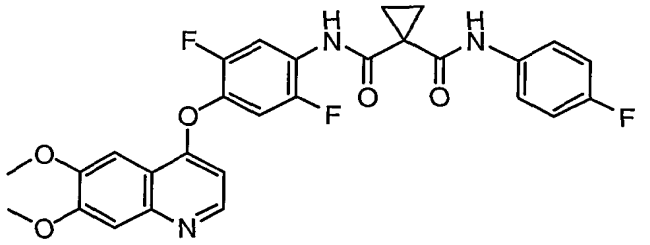
| Entry | Name | Structure |
|---|---|---|
| 23 | N-(4-fluorophenyl)-N'-[2-methyl-6-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]cyclopropane-1,1-dicarboxamide |  |
| 24 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 25 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloro-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 26 | N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 27 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 28 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |

**Table 2**

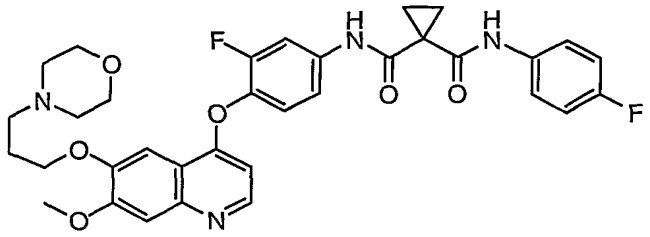
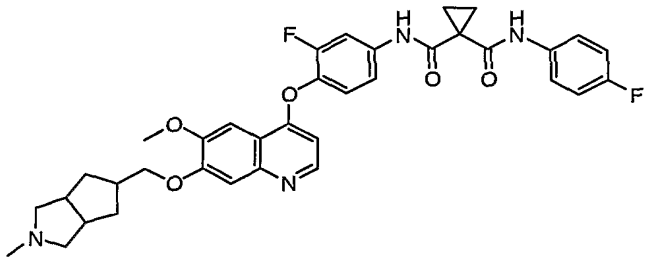
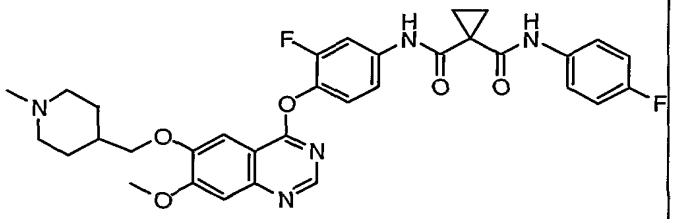
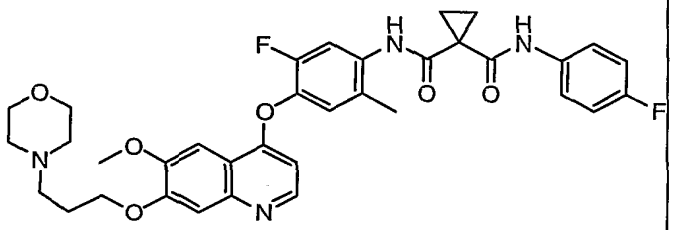
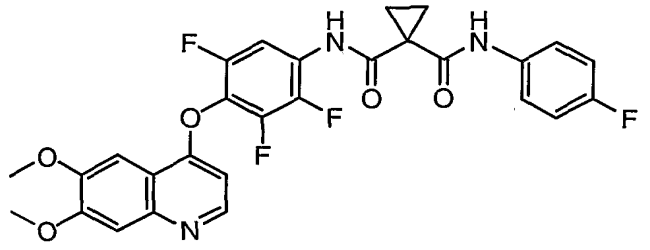
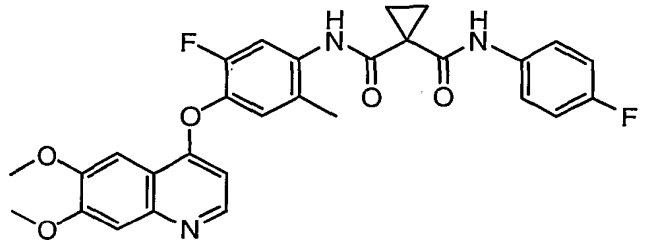
| Entry | Name | Structure |
|---|---|---|
| 29 | N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 30 | N-{3-fluoro-4-[(6-(methyloxy)-7-(2-methyl octahydrocyclo-penta[c]pyrrol-5-ylmethoxy)quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 31 | N-{3-fluoro-4-[(7-(methyloxy)-6-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 32 | N-[5-fluoro-2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 33 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,3,5-trifluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 34 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |

**Table 2**

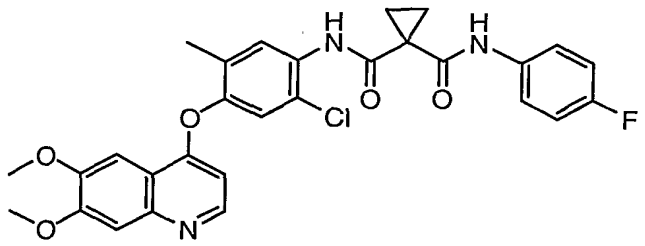
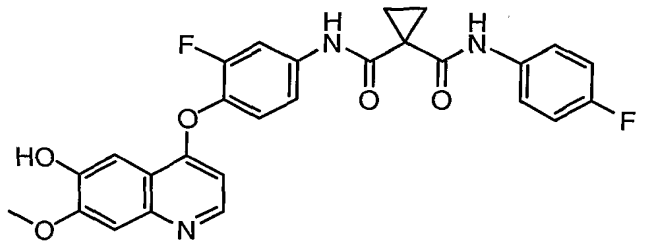
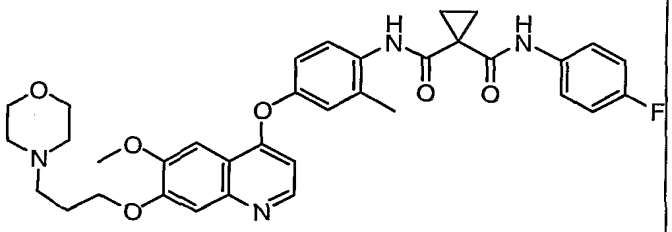
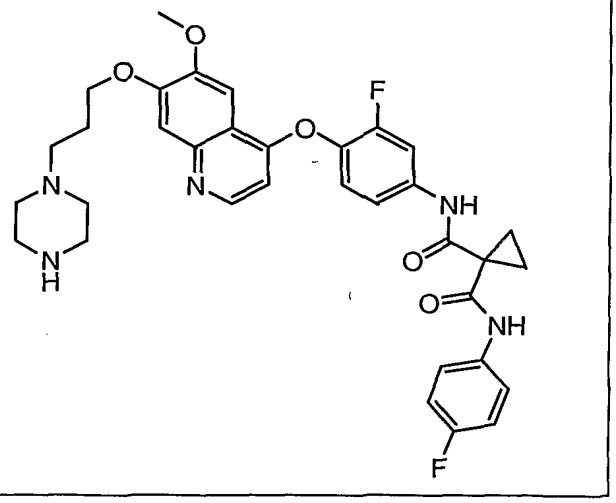
| Entry | Name | Structure |
|---|---|---|
| 35 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 36 | N-(3-fluoro-4-{[6-hydroxy-7-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 37 | N-(4-fluorophenyl)-N'-[2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide |  |
| 38 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |

**Table 2**

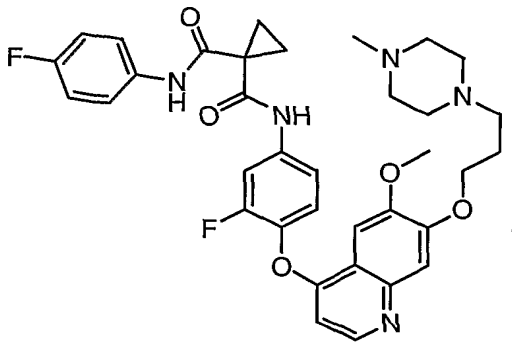
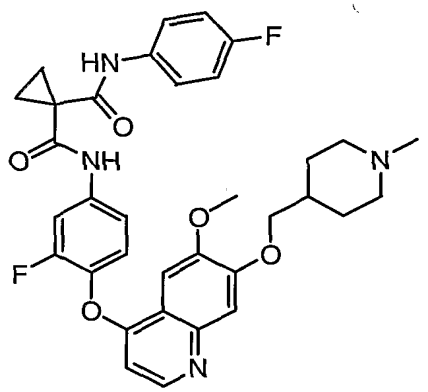
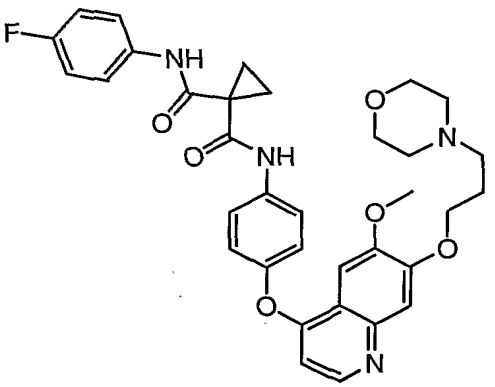
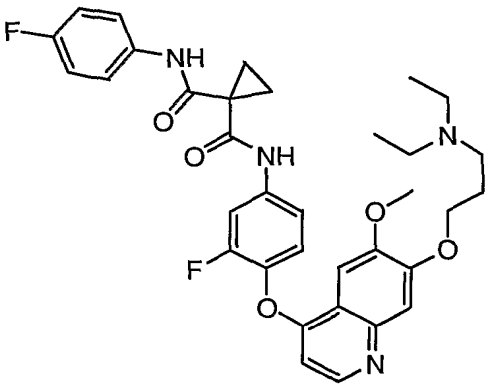
| Entry | Name | Structure |
|---|---|---|
| 39 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 40 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 41 | N-(4-fluorophenyl)-N'-[4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide |  |
| 42 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |

**Table 2**

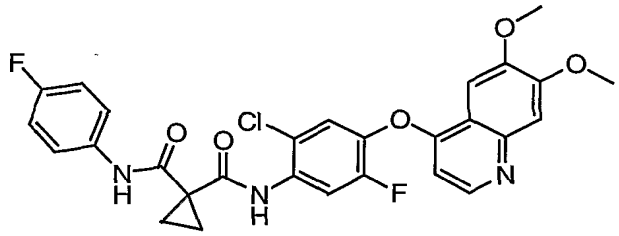
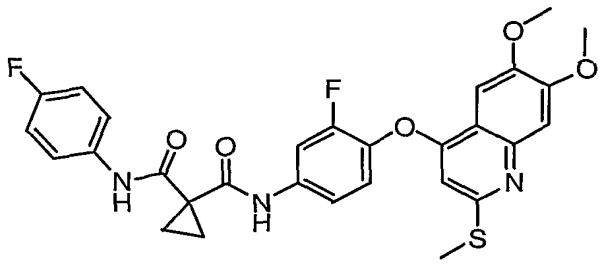
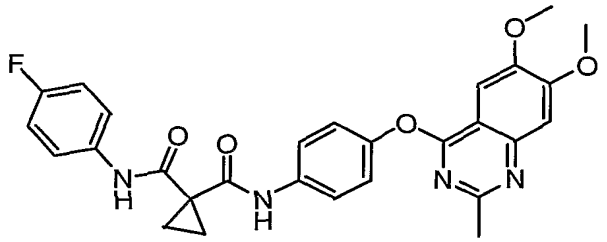
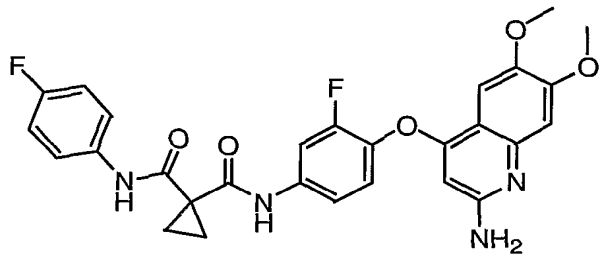
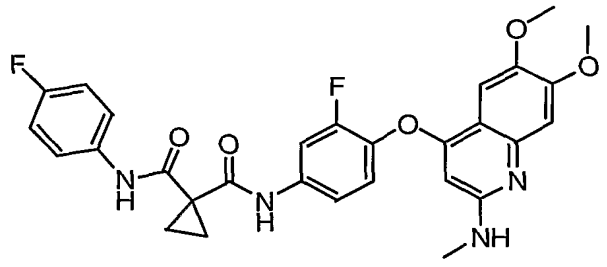
| Entry | Name | Structure |
|---|---|---|
| 43 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 44 | N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 45 | N-(4-fluorophenyl)-N'-(4-{[2-methyl-6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide |  |
| 46 | N-(4-{[2-amino-6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 47 | N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |

**Table 2**

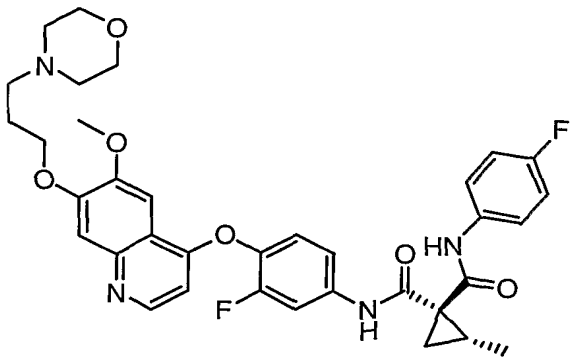
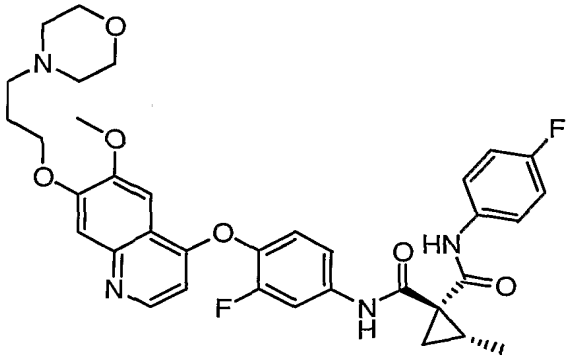
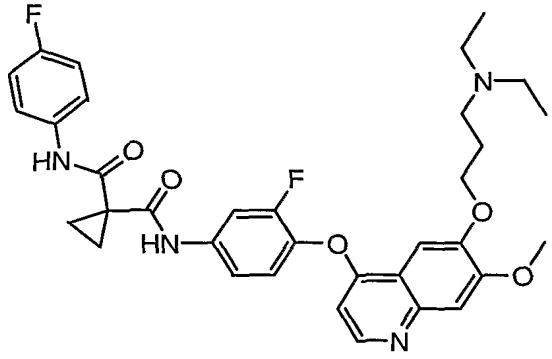
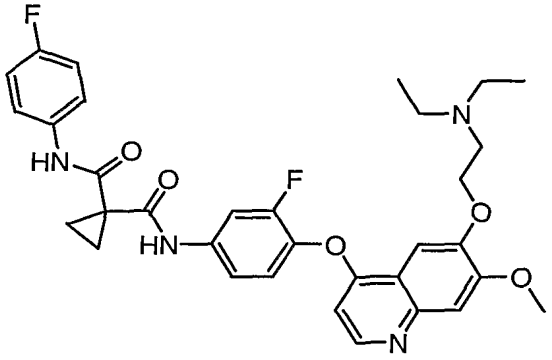
| Entry | Name | Structure |
|---|---|---|
| 48 | (1S,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |
| 49 | (1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |
| 50 | N-(4-{[6-{[3-(diethylamino)propyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 51 | N-(4-{[6-{[2-(diethylamino)ethyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |

**Table 2**

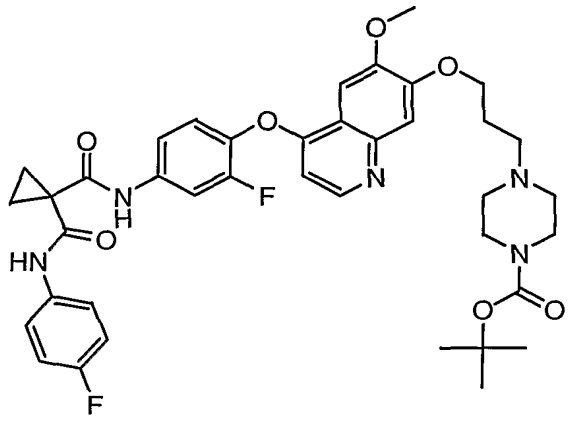
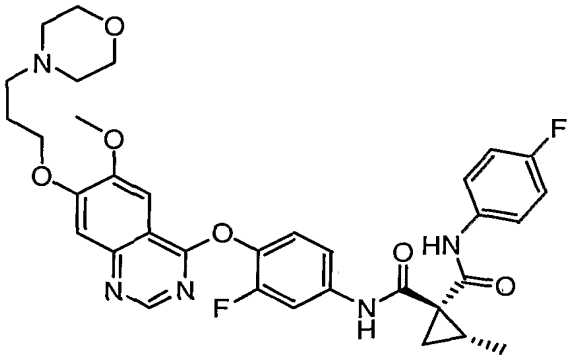
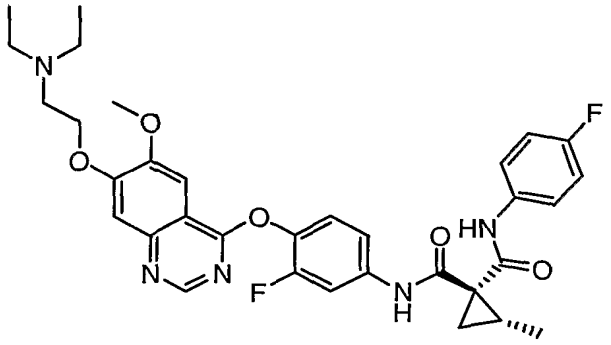
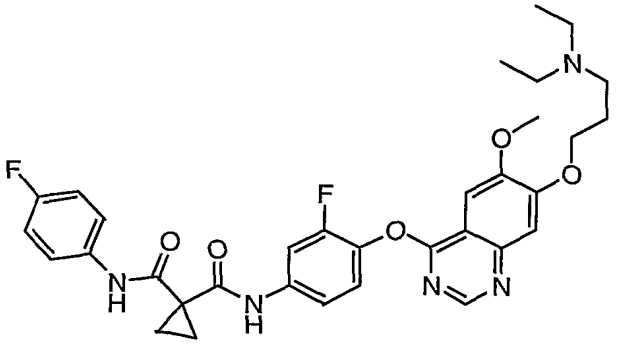
| Entry | Name | Structure |
|---|---|---|
| 52 | 1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[(1-{[(4-fluorophenyl)amino]carbonyl}cyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate |  |
| 53 | (1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |
| 54 | (1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |
| 55 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |

**Table 2**

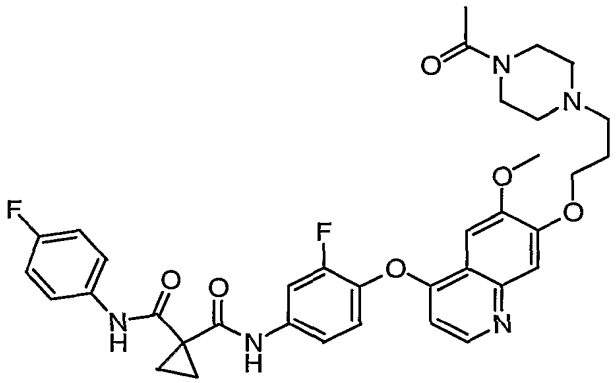
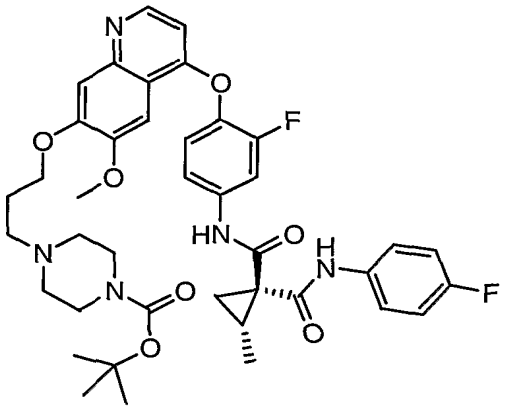
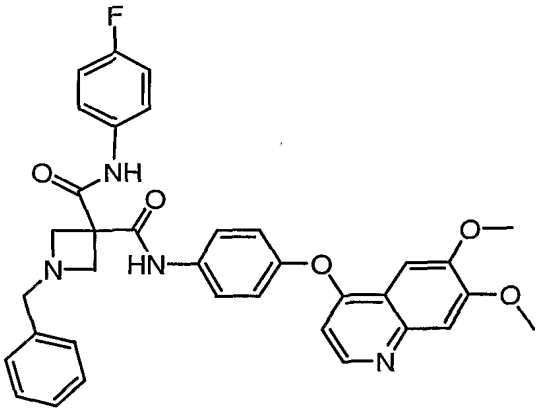
| Entry | Name | Structure |
|---|---|---|
| 56 | N-(4-{[7-{[3-(4-acetylpiperazin-1-yl)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 57 | 1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[((1R,2R)-1-{[(4-fluorophenyl)amino]carbonyl}-2-methylcyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate |  |
| 58 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide |  |

**Table 2**

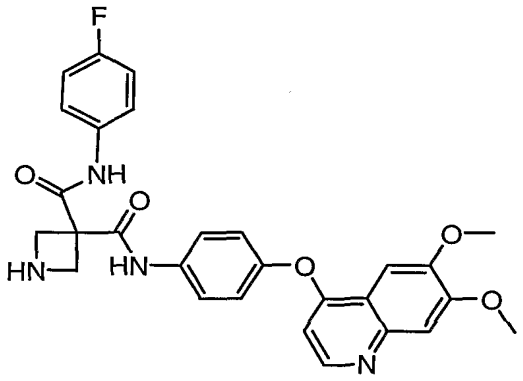
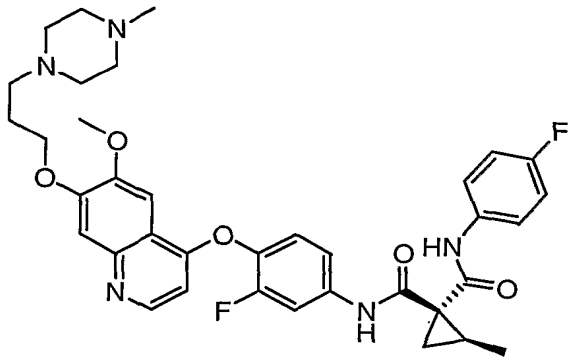
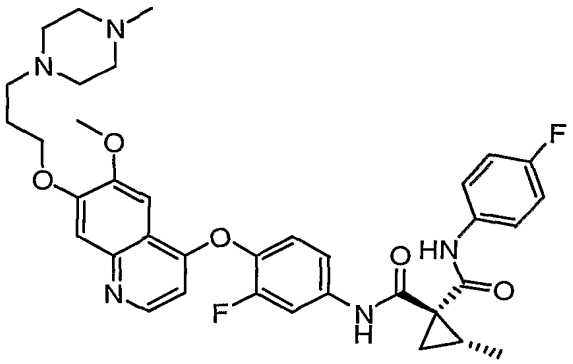
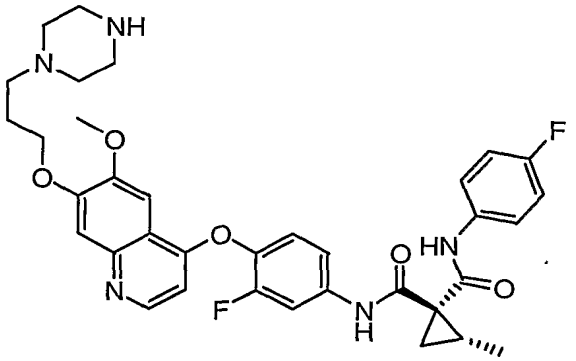
| Entry | Name | Structure |
|---|---|---|
| 59 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)azetidine-3,3-dicarboxamide |  |
| 60 | (1R,2S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |
| 61 | (1R,2R)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |
| 62 | (1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |

**Table 2**

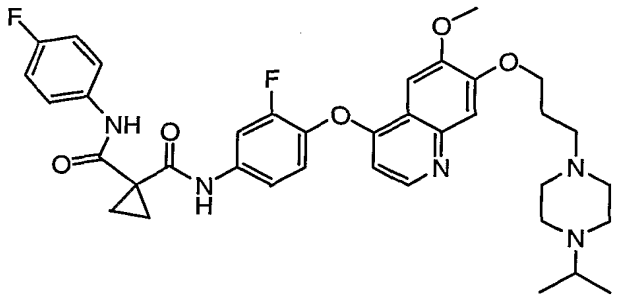
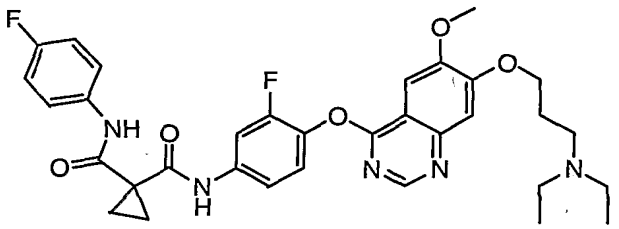
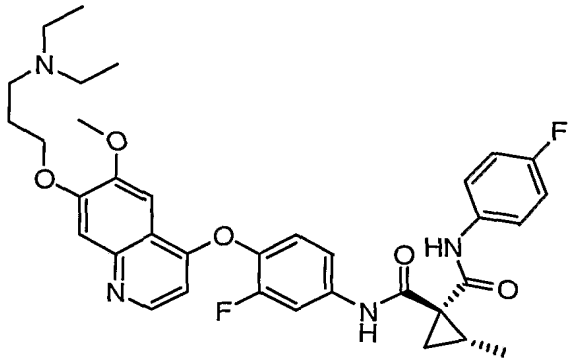
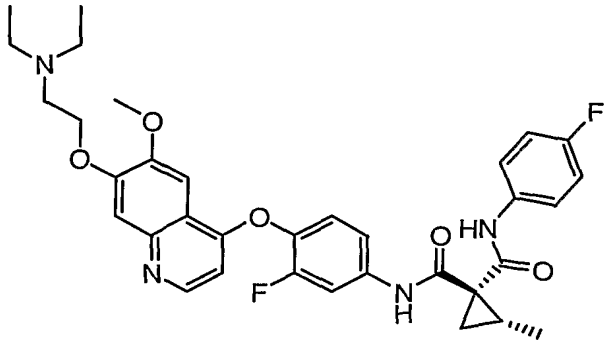
| Entry | Name | Structure |
|---|---|---|
| 63 | N-(3-fluoro-4-{[7-({3-[4-(1-methylethyl)piperazin-1-yl]propyl}oxy)-6-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 64 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 65 | (1R,2R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |
| 66 | (1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |

**Table 2**

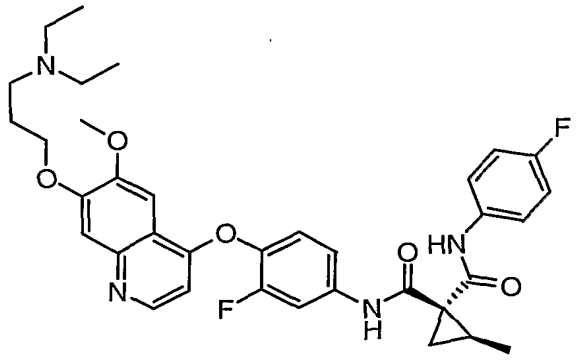
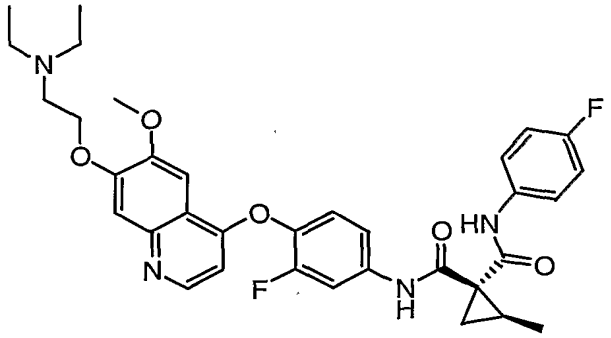
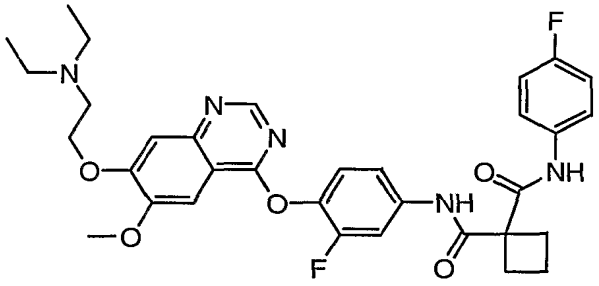
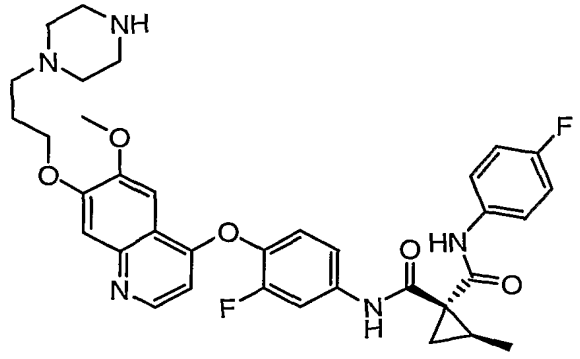
| Entry | Name | Structure |
|---|---|---|
| 67 | (1R,2S)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |
| 68 | (1R,2S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |
| 69 | N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide |  |
| 70 | (1R,2S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |

**Table 2**

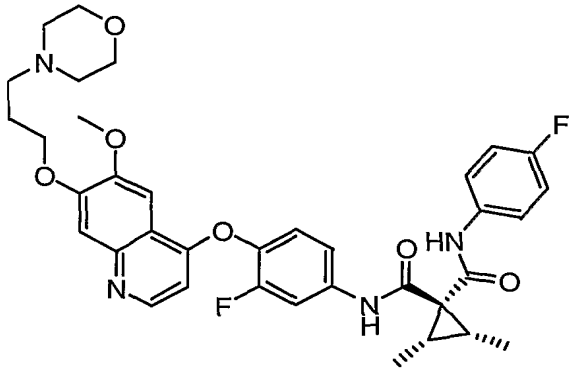
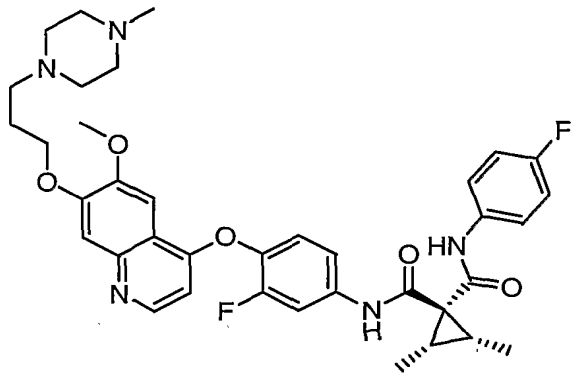
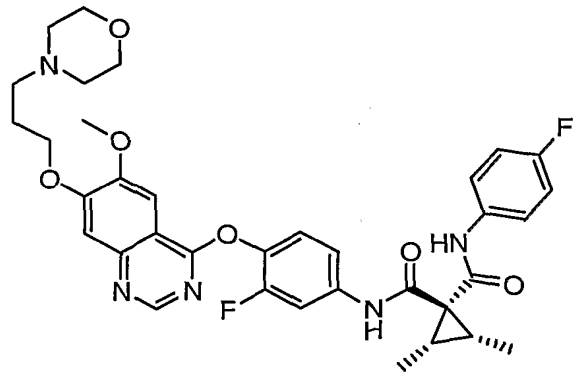
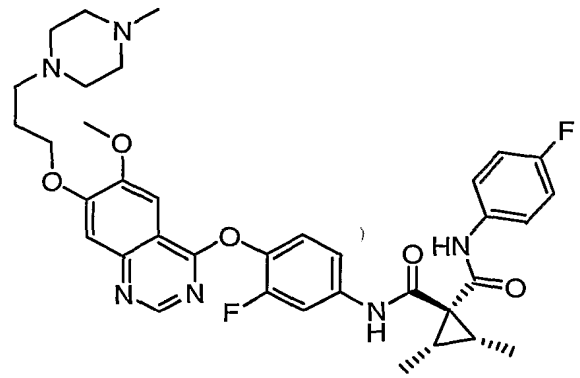
| Entry | Name | Structure |
|---|---|---|
| 71 | (1R,2R,3S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |
| 72 | (1R,2R,3S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |
| 73 | (1R,2R,3S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |
| 74 | (1R,2R,3S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |

**Table 2**

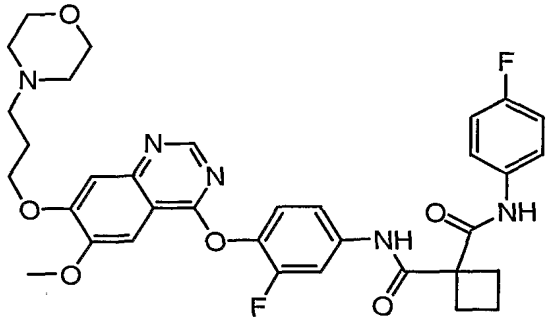
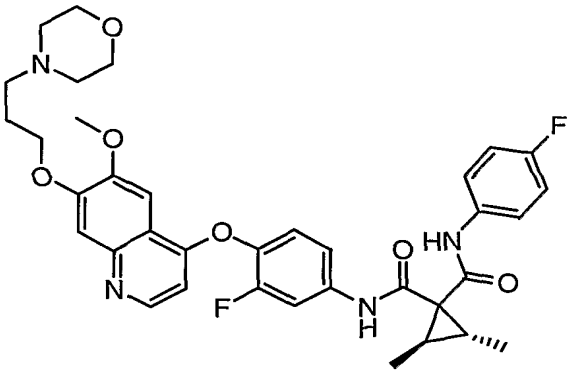
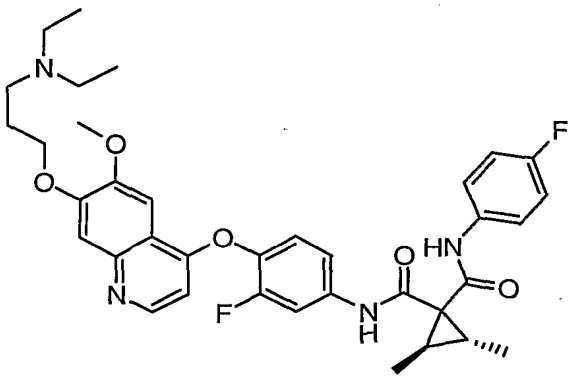
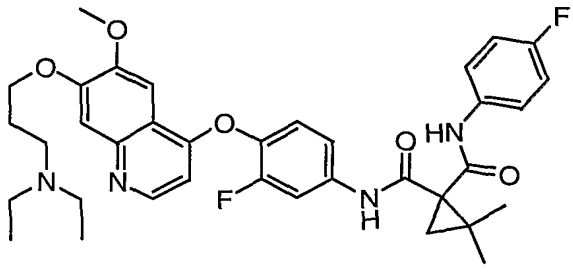
| Entry | Name | Structure |
|---|---|---|
| 75 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide |  |
| 76 | (2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |
| 77 | (2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |
| 78 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide |  |

**Table 2**

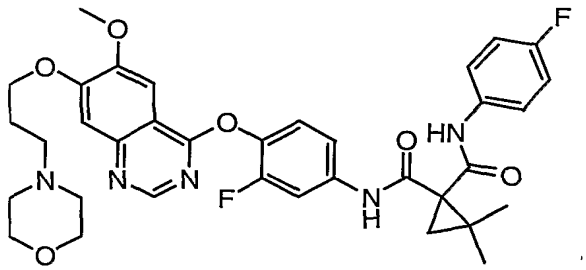
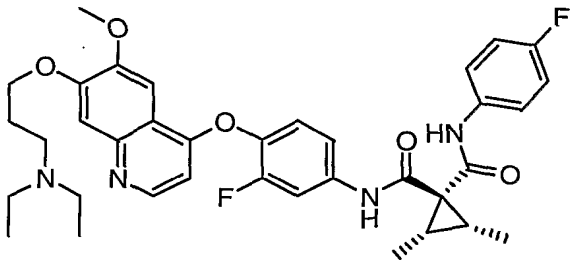
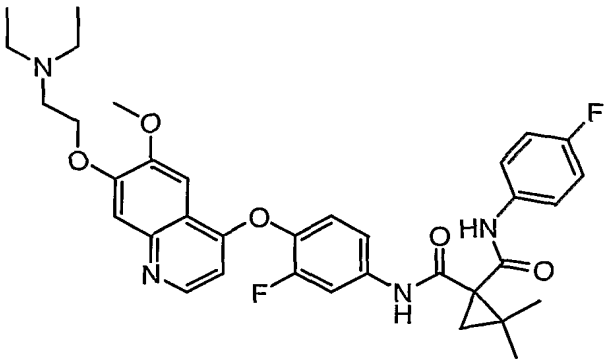
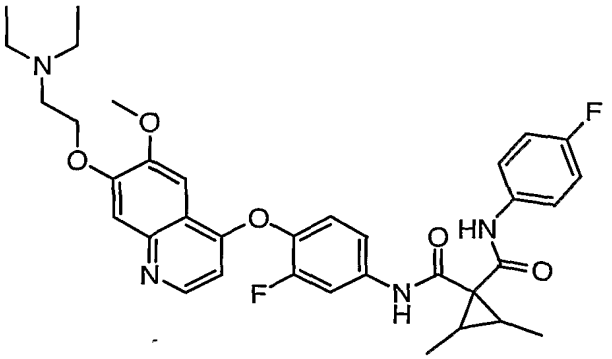
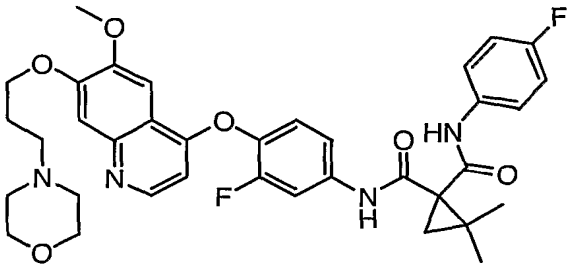
| Entry | Name | Structure |
|---|---|---|
| 79 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide |  |
| 80 | (1R,2R,3S)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |
| 81 | N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide |  |
| 82 | (1R,2R,3S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |
| 83 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide |  |

**Table 2**

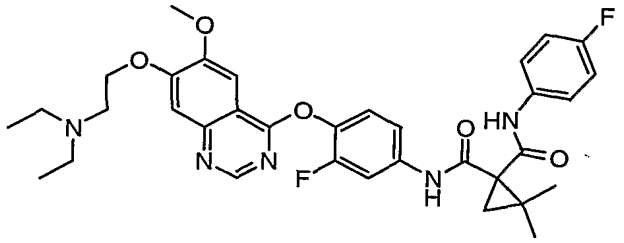
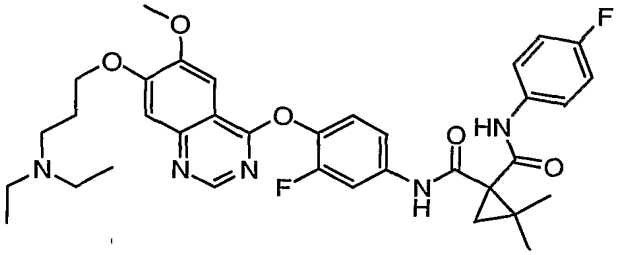
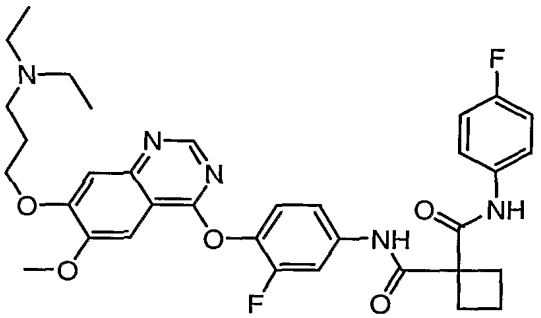
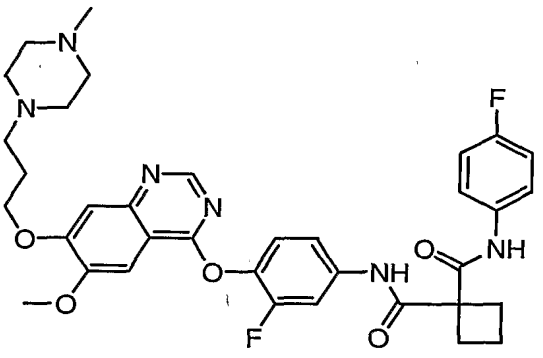
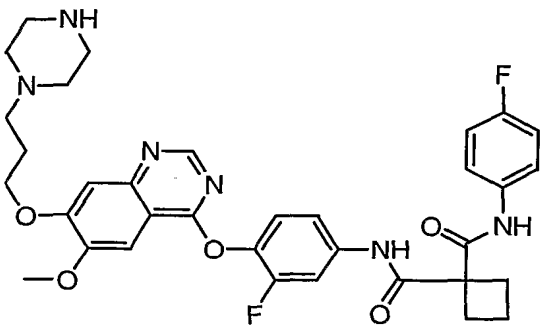
| Entry | Name | Structure |
|---|---|---|
| 84 | N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide |  |
| 85 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide |  |
| 86 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide |  |
| 87 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide |  |
| 88 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide |  |

**Table 2**

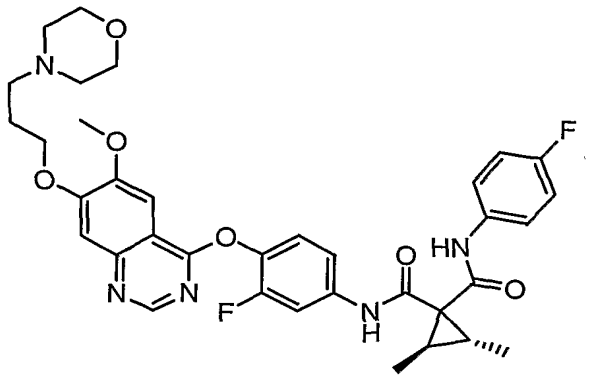
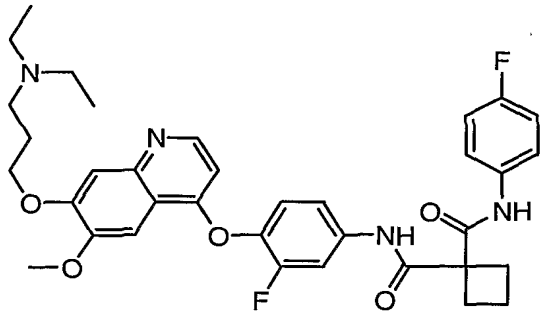
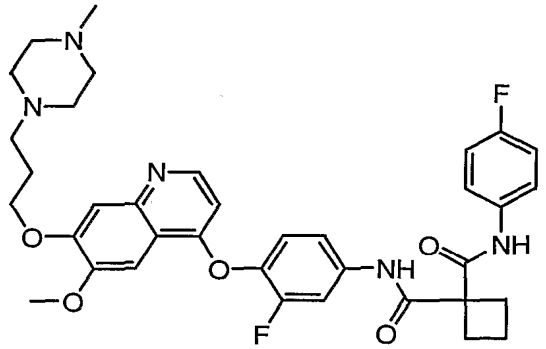
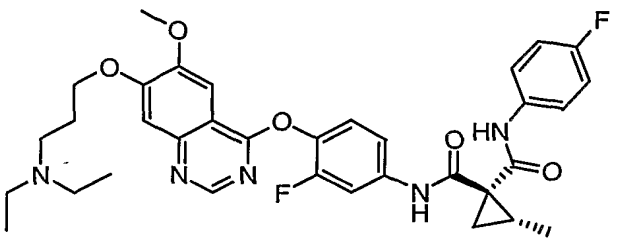
| Entry | Name | Structure |
|---|---|---|
| 89 | (2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |
| 90 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide |  |
| 91 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide |  |
| 92 | (1R,2R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |

**Table 2**

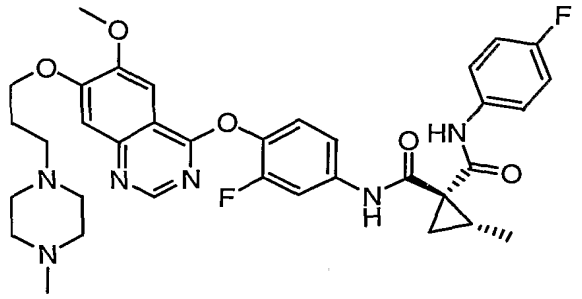
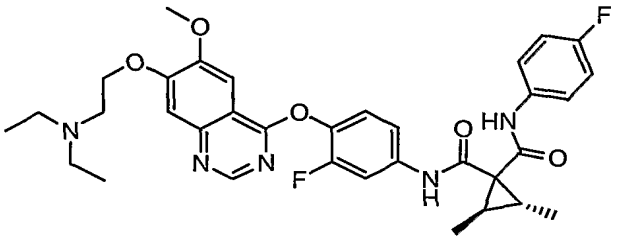
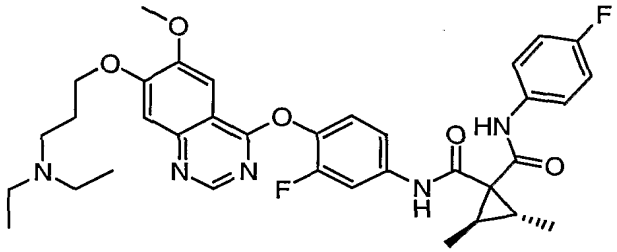
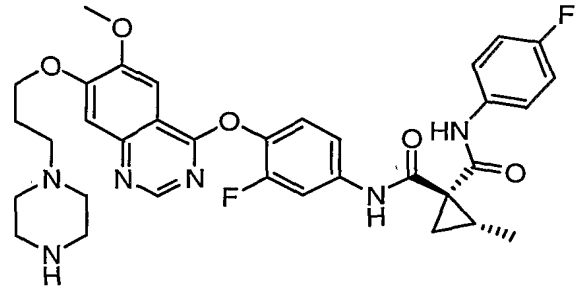
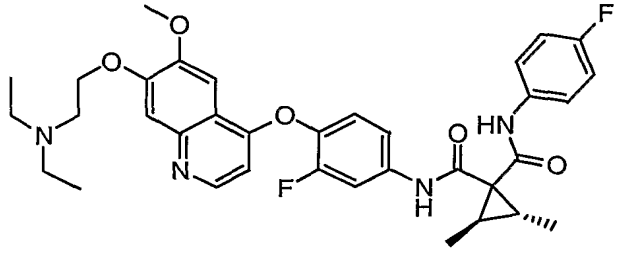
| Entry | Name | Structure |
|---|---|---|
| 93 | (1R,2R)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |
| 94 | (2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |
| 95 | (2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |
| 96 | (1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |
| 97 | (2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |

**Table 2**

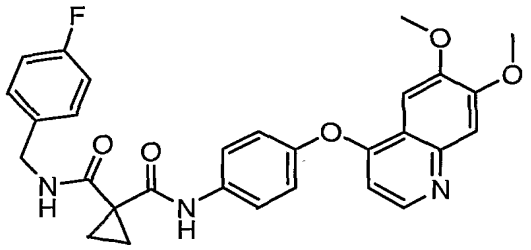
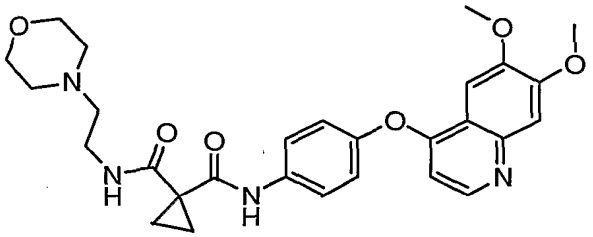
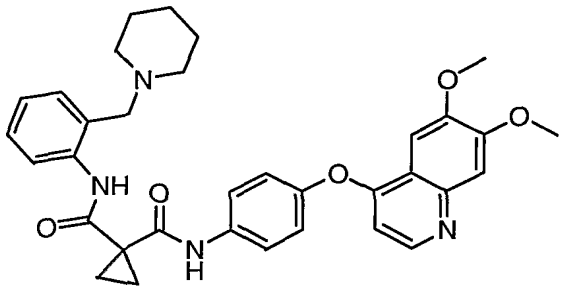
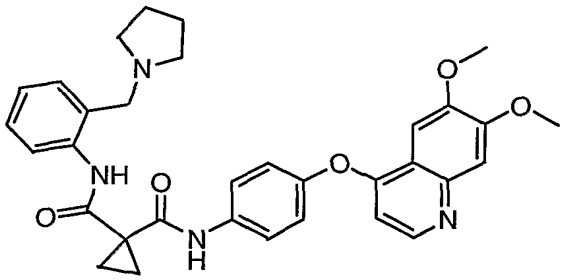
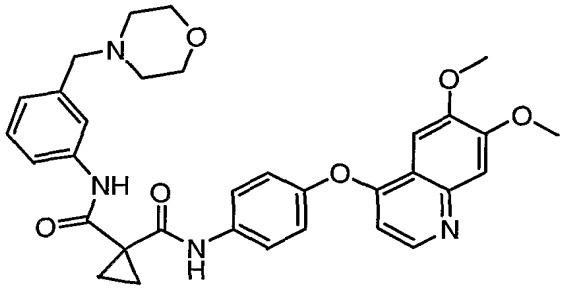
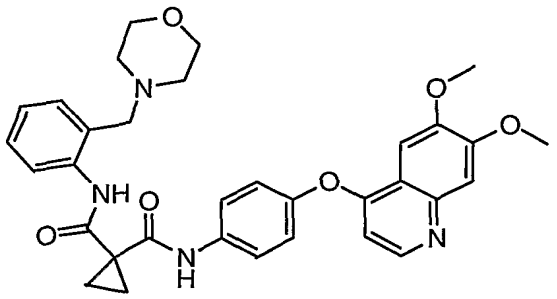
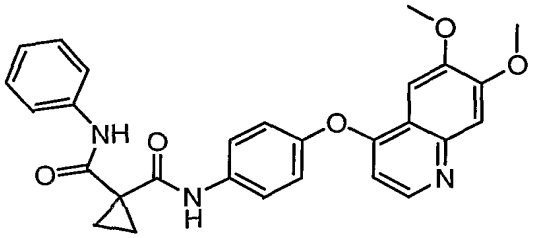
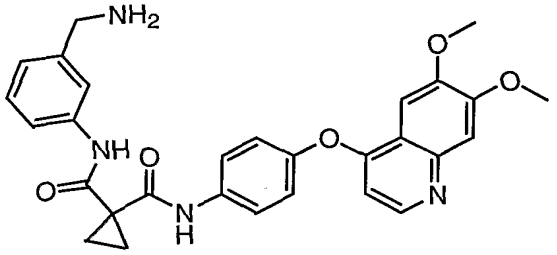
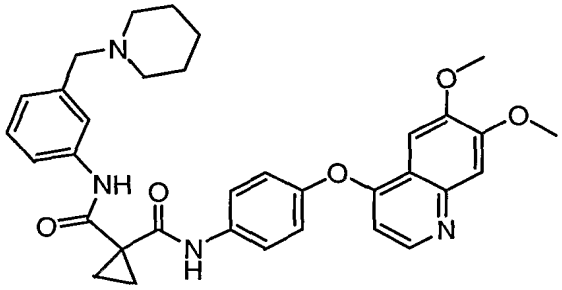
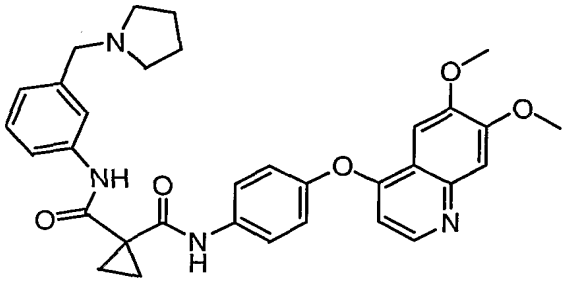
| Entry | Name | Structure |
|---|---|---|
| 98 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[(4-fluorophenyl)methyl]cyclopropane-1,1-dicarboxamide |  |
| 99 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(2-morpholin-4-ylethyl)cyclopropane-1,1-dicarboxamide |  |
| 100 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide |  |
| 101 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide |  |
| 102 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide |  |

**Table 2**

| Entry | Name | Structure |
|---|---|---|
| 103 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide |  |
| 104 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-phenylcyclopropane-1,1-dicarboxamide |  |
| 105 | N-[3-(aminomethyl)phenyl]-N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide |  |
| 106 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide |  |
| 107 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide |  |

[0176] Another aspect of the invention is a pharmaceutical composition comprising a compound according to any one of paragraphs [0033]-[0120] and a pharmaceutically acceptable carrier.

[0177] Another aspect of the invention is a metabolite of the compound or the pharmaceutical composition according to any one of paragraphs [0022]-[0122].

[0178] Another aspect of the invention is a method of modulating the *in vivo* activity of a kinase, the method comprising administering to a subject an effective amount of the compound or the pharmaceutical composition according to any of paragraphs [0033]-[0121].

[0179] Another aspect of the invention is the method according to paragraph [0123], wherein modulating the *in vivo* activity of the kinase comprises inhibition of said kinase.

[0180] Another aspect of the invention is the method according to paragraph [0124], wherein the kinase is at least one of c-Met, KDR, c-Kit, flt-3, and flt-4.

[0181] Another aspect of the invention is the method according to paragraph [0125], wherein the kinase is c-Met.

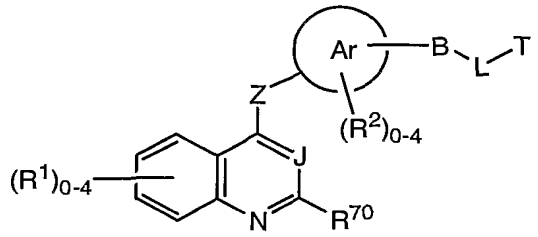
[0182] Another aspect of the invention is a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities, the method comprising administering, to a mammal in need thereof, a therapeutically effective amount of the compound or the pharmaceutical composition as described in any one of paragraphs [0033]-[0121].

[0183] Another aspect of the invention is a method of screening for a modulator of a kinase, said kinase selected from c-Met, KDR, c-Kit, flt-3, and flt-4, the method comprising combining a compound according to any one of paragraphs [0033]-[0120], and at least one candidate agent and determining the effect of the candidate agent on the activity of said kinase.

[0184] Another aspect of the invention is a method of inhibiting proliferative activity in a cell, the method comprising administering an effective amount of a composition comprising a compound according any one of paragraphs [0033]-[0120] to a cell or a plurality of cells.

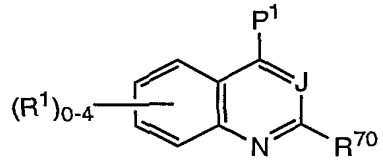
[0185] As mentioned, although improved quinolines and quinazolines of the invention can be made via conventional serial methods, due to their complex structure, more efficient

routes are desirable, particularly convergent syntheses. Thus, the present invention also comprises a process for preparing a compound of Formula **XXI**,

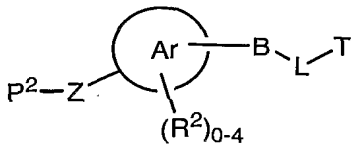


**XXI**

comprising reaction of a compound of Formula **XXII**, with a compound of Formula **XXIII**



**XXII**



**XXIII**

wherein,

each $R^1$ is independently selected from halogen, $-OR^3$, $-NO_2$, $-NH_2$, $-NR^3R^3$, $-D-R^{50}$ and optionally substituted $C_{1-6}$alkyl;

$R^{70}$ is selected from -H, halogen, $-OR^3$, $-S(O)_{0-2}R^3$, $-NO_2$, $-NH_2$, $-NR^3R^3$, and optionally substituted $C_{1-6}$alkyl;

J is selected from =N-, =C(H)-, =C(halogen)-, and =C(CN)-;

Z is selected from $-S(O)_{0-2}-$, -O-, and $-NR^5-$;

each $R^5$ is independently selected from -H, optionally substituted $C_{1-6}$alkyl, optionally substituted aryl, and optionally substituted aryl $C_{1-6}$alkyl;

Ar is either a five- to ten-membered arylene or a five- to ten-membered heteroarylene containing between one and three heteroatoms;

$R^2$ is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted $C_{1-6}$alkyl;

each $R^3$ is independently selected from -H, $-Si(R^5)(R^5)R^5$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted arylalkyl, and optionally substituted heteroarylalkyl;

two $R^3$, together with the nitrogen to which they are attached, form a four- to seven-membered heteroalicyclic, said four- to seven-membered heteroalicyclic optionally containing one additional heteroatom; when one said additional heteroatom is a nitrogen, then said nitrogen is optionally substituted with a group selected from -H, trihalomethyl, $-SO_2R^5$, $-SO_2NR^5R^5$, $-CO_2R^5$, $-C(O)NR^5R^5$, $-C(O)R^5$, and optionally substituted lower alkyl;

B is selected from absent, $-N(R^{13})-$, $-N(SO_2R^{13})-$, -O-, $-S(O)_{0-2}-$, and -C(=O)-;

L is selected from absent, $-C(=S)N(R^{13})-$, $-C(=NR^{14})N(R^{13})-$, $-SO_2N(R^{13})-$, $-SO_2-$, $-C(=O)N(R^{13})-$, $-N(R^{13})-$, $-C(=O)C_{1-2}alkylN(R^{13})-$, $-N(R^{13})C_{1-2}alkylC(=O)-$, $-C(=O)C_{0-1}alkylC(=O)N(R^{13})-$, -C(=O)-, $-C_{0-4}alkylene-$, $-C(=O)C_{0-1}alkylC(=O)OR^3-$, $-C(=NR^{14})C_{0-1}alkylC(=O)-$, $-C(=O)C_{0-1}alkylC(=O)-$, and an optionally substituted four- to six-membered heterocyclyl containing between one and three annular heteroatoms and comprising at least one nitrogen;

T is selected from -H, $-R^{13}$, $-C_{0-4}alkyl$, $-C_{0-4}alkylQ$, $-OC_{0-4}alkylQ$, $-C_{0-4}alkylOQ$, $-N(R^{13})C_{0-4}alkylQ$, $-SO_2C_{0-4}alkylQ$, $-C(=O)C_{0-4}alkylQ$, $-C_{0-4}alkylN(R^{13})Q$, and $-C(=O)N(R^{13})C_{0-4}alkylQ$, wherein each of the aforementioned $C_{0-4}alkyl$ is optionally substituted;

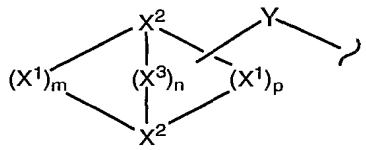
Q is a five- to ten-membered ring system, optionally substituted with between zero and four of $R^{20}$;

each $R^{20}$ is independently selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted $C_{1-6}alkyl$, optionally substituted aryl, optionally substituted aryl $C_{1-6}alkyl$, optionally substituted heterocyclyl, and optionally substituted heterocyclyl $C_{1-6}alkyl$;

two of $R^{20}$, together with the atom or atoms to which they are attached, combine to form an optionally substituted three- to seven-membered heteroalicyclic, said optionally substituted three- to seven-membered heteroalicyclic either spiro- to Q or fused to Q;

D is selected from -O-, $-S(O)_{0-2}-$, and $-NR^{15}-$;

$R^{50}$ is either $R^3$, or according to formula **XXIV**;



**XXIV**

wherein $X^1$, $X^2$, and optionally $X^3$, represent the atoms of a saturated bridged ring system, said saturated bridged ring system comprising up to four annular heteroatoms represented by any of $X^1$, $X^2$, and $X^3$; wherein,

each $X^1$ is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

each $X^2$ is independently an optionally substituted bridgehead methine or a bridgehead nitrogen;

each $X^3$ is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

Y is either:

an optionally substituted $C_{1-6}$alkylene linker, between D and either 1) any annular atom of the saturated bridged ring system, except $X^2$ when $X^2$ is a bridgehead nitrogen, or 2) any heteroatom, represented by any of $R^6$ or $R^7$; provided there are at least two carbon atoms between D and any annular heteroatom of the saturated bridged ring system or any heteroatom represented by any of $R^6$ or $R^7$;

or Y is absent, when Y is absent, said saturated bridged ring system, is directly attached to D via an annular carbon of said saturated bridged ring system, unless D is $-SO_2-$, in which case said saturated bridged ring system, is directly attached to D via an any annular atom of said saturated bridged ring system;

m and p are each independently one to four;

n is zero to two, when n is zero, then there is a single bond between the two bridgehead $X^2$'s;

$R^6$ and $R^7$ are each independently selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-NCO_2R^3$, $-C(O)R^3$, optionally substituted $C_{1-6}$alkyl, optionally substituted aryl, optionally substituted aryl $C_{1-6}$alkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl a $C_{1-6}$lkyl, and a bond to either Y or D; or

$R^6$ and $R^7$, when taken together are oxo; or

$R^6$ and $R^7$, when taken together with a common carbon to which they are attached, form a optionally substituted three- to seven-membered spirocyclyl, said optionally substituted three- to seven-membered spirocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

$R^8$ is selected from $-R^3$, Y, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$;

$R^{13}$ is selected from -H, $-C(=O)R^3$, $-C(=O)OR^3$, $-C(=O)SR^3$, $-SO_2R^3$, $-C(=O)N(R^3)R^3$, and optionally substituted $C_{1-6}$alkyl;

two $R^{13}$, together with the atom or atoms to which they are attached, can combine to form a heteroalicyclic optionally substituted with between one and four of $R^{60}$, said heteroalicyclic comprising up to four annular heteroatoms, and said heteroalicyclic optionally comprising an aryl or heteroaryl fused thereto, in which case said aryl or heteroaryl is optionally substituted with an additional one to four of $R^{60}$;

$R^{14}$ is selected from -H, $-NO_2$, $-NH_2$, $-N(R^3)R^3$, -CN, $-OR^3$, optionally substituted $C_{1-6}$alkyl, optionally substituted heteroalicyclyl $C_{1-6}$alkyl, optionally substituted aryl, optionally substituted aryl $C_{1-6}$alkyl and optionally substituted heteroalicyclic;

$R^{15}$ is a group $-M^1-M^2$, wherein $M^1$ is selected from absent, $-C(=S)N(R^{13})-$, $-C(=NR^{14})N(R^{13})-$, $-SO_2N(R^{13})-$, $-SO_2-$, $-C(=O)N(R^{13})-$, $-C(=O)C(=O)N(R^{13})-$, $-C_{0-4}$alkylene-, -C(=O)-, and an optionally substituted four to six-membered heterocyclyl containing between one and three heteroatoms but comprising at least one nitrogen; and $M^2$ is selected from -H, $-C_{0-6}$alkyl, alkoxy, $-C(=O)C_{0-4}$alkylQ, $-C_{0-4}$alkylQ, $-OC_{0-4}$alkylQ-, $-N(R^{13})C_{0-4}$alkylQ-, and $-C(=O)N(R^{13})C_{0-4}$alkylQ;

$R^{60}$ is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted $C_{1-6}$alkyl, optionally substituted aryl, optionally substituted heteroaryl $C_{1-6}$alkyl, and optionally substituted aryl $C_{1-6}$alkyl;

two of $R^{60}$, when attached to a non-aromatic carbon, can be oxo;

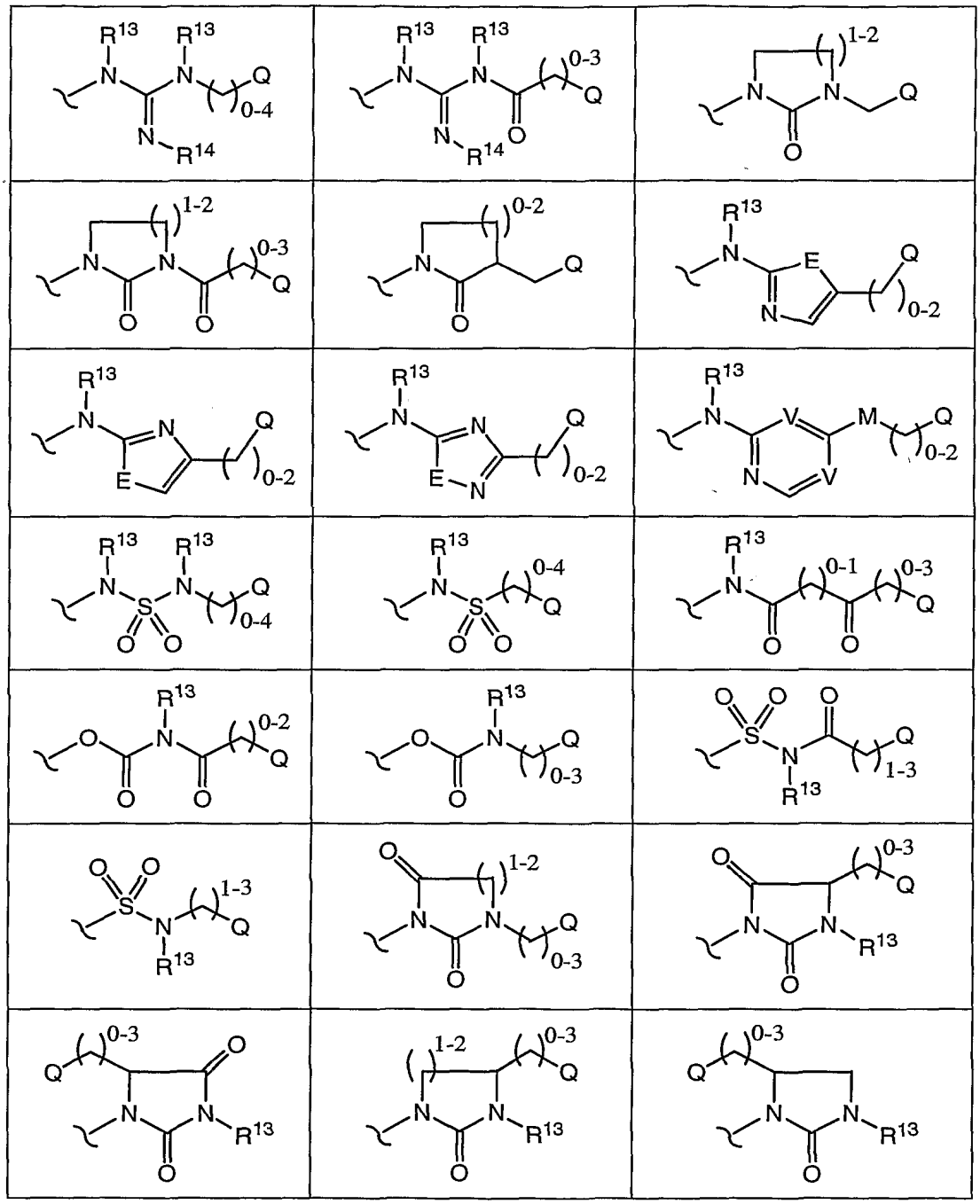
$P^1$ is a suitable leaving group; and

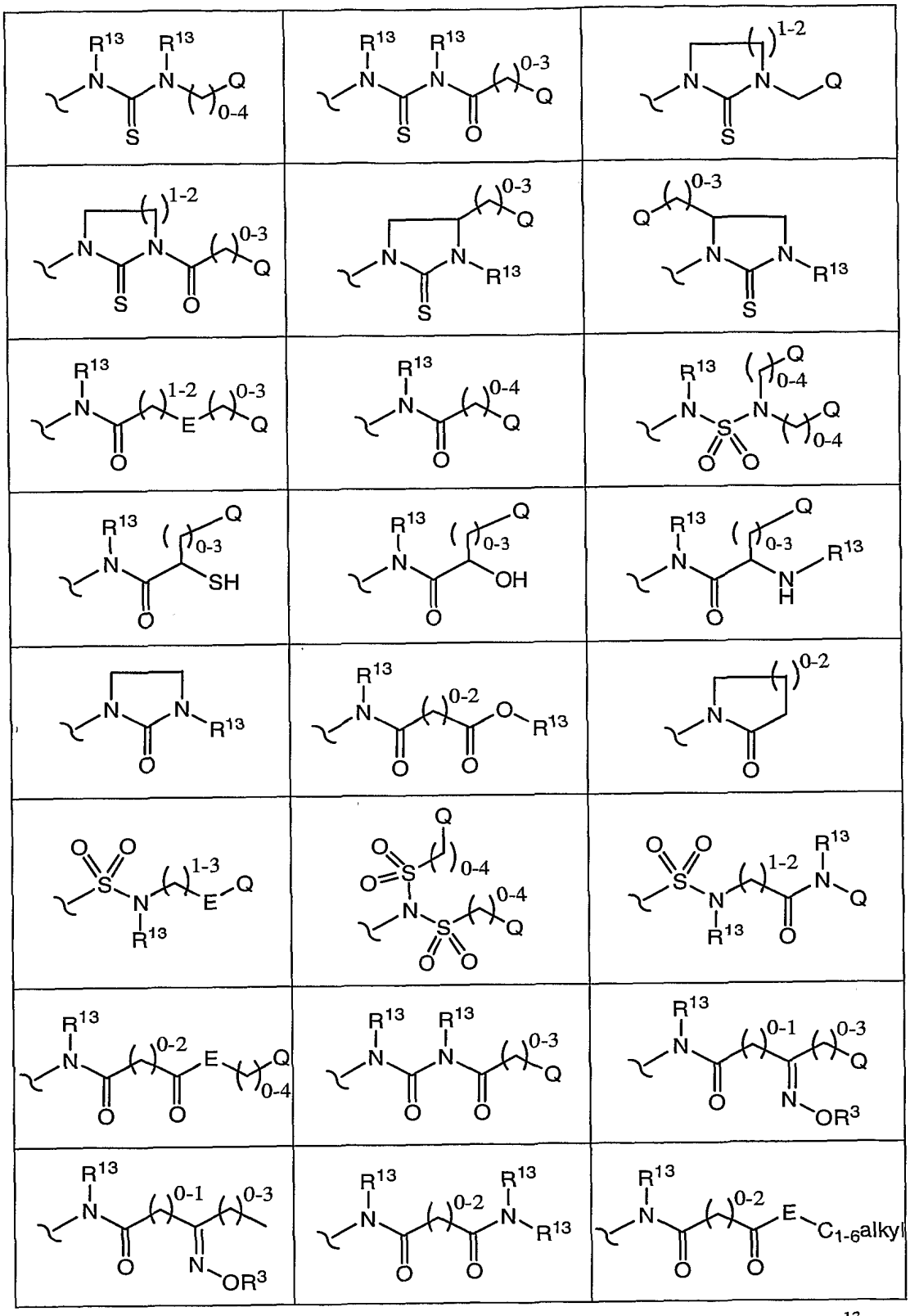
$P^2$ is selected from -H, a metal, and a group removed *in-situ* when combining **XXII** and **XXIII** to make **XXI**.

**[0131]** In one example, the process is according to paragraph [0130], wherein Ar is *para*-phenylene as defined by the substitution pattern of -Z- and -B-L-T about said phenylene.

**[0132]** In another example, the process is according to paragraph [0131], wherein Z is either -O- or $-NR^5-$.

**[0133]** In another example, the process is according to paragraph [0132], wherein -B-L-T is selected from the following:





wherein Q, $R^{20}$, and $R^{13}$ are as defined above; each E is selected from -O-, -N($R^{13}$)-, -$CH_2$, and -$S(O)_{0-2}$-; M is selected from -O-, -N($R^{13}$)-, -$CH_2$-, and -C(=O)N($R^{13}$)-; each V is independently either =N- or =C(H)-; each methylene in any of the above formulae is

independently optionally substituted with $R^{25}$; and $R^{25}$ is selected from halogen, trihalomethyl, -CN, -$NO_2$, -$NH_2$, -$OR^3$, -$NR^3R^3$, -$S(O)_{0-2}R^3$, -$SO_2NR^3R^3$, -$CO_2R^3$, -$C(O)NR^3R^3$, -$N(R^3)SO_2R^3$, -$N(R^3)C(O)R^3$, -$N(R^3)CO_2R^3$, -$C(O)R^3$, optionally substituted aryl, optionally substituted aryl $C_{1-6}$alkyl, heteroaryl $C_{1-6}$alkyl, and optionally substituted $C_{1-6}$alkyl; two of $R^{25}$, together with the carbon or carbons to which they are attached, can combine to form an optionally substituted three- to seven-membered alicyclic or heteroalicyclic; two of $R^{25}$ on a single carbon can be oxo.

**[0134]** In another example, the process is according to paragraph [0133], wherein there is one of $R^1$ that is -D-$R^{50}$ and another of $R^1$ that is -$OR^{3a}$.

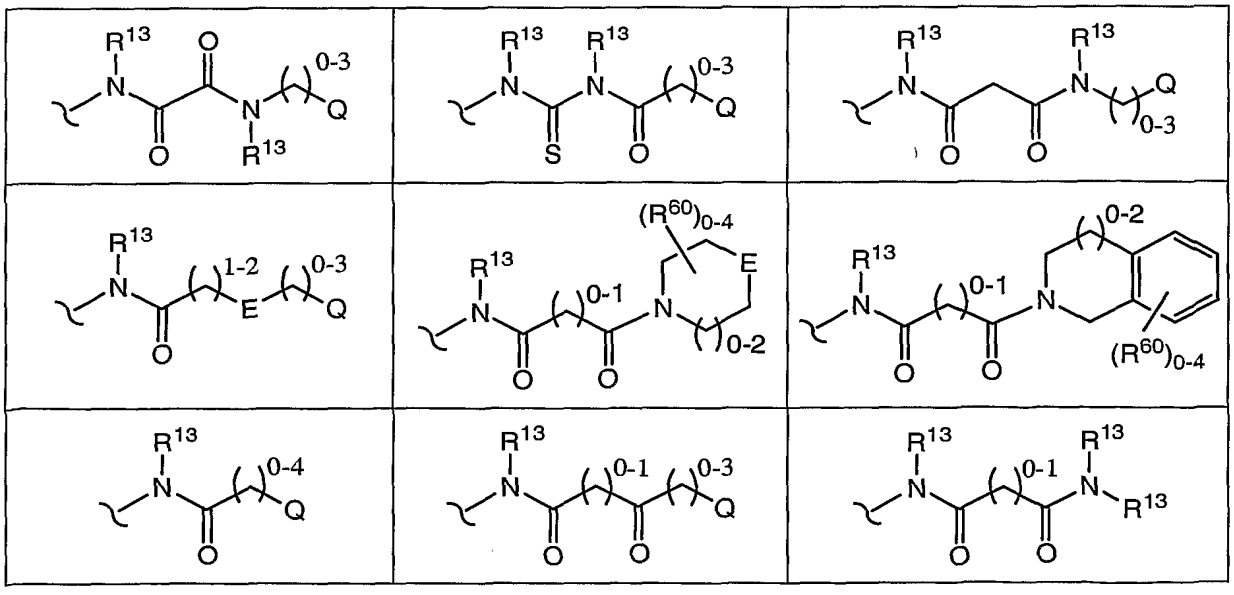
**[0135]** In another example, the process is according to paragraph [0134], wherein D is -O-.

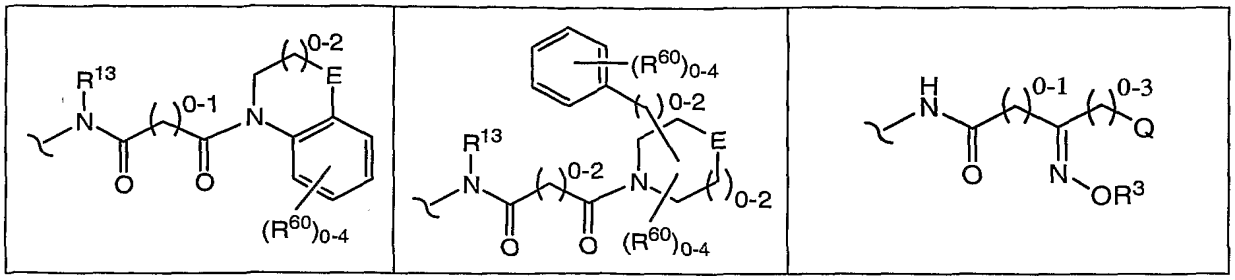
**[0136]** In another example, the process is according to paragraph [0135], wherein -O-$R^{50}$ and -$OR^{3a}$ are interchangeably located at the 6-position and 7-position of the quinazoline or quinoline according to Formula **XXI**.

**[0137]** In another example, the process is according to paragraph [0136], wherein -$OR^{3a}$ is selected from -OH, -$OSi(R^5)(R^5)R^5$, and optionally substituted -$OC_{1-6}$alkyl.

**[0138]** In another example, the process is according to paragraph [0137], wherein J is =N- or =C(H)-.

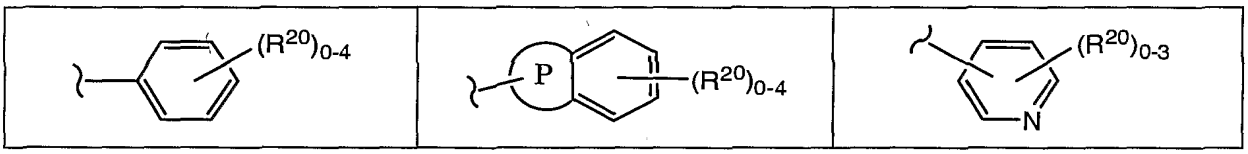
**[0139]** In another example, the process is according to paragraph [0138], wherein -B-L-T is selected from:





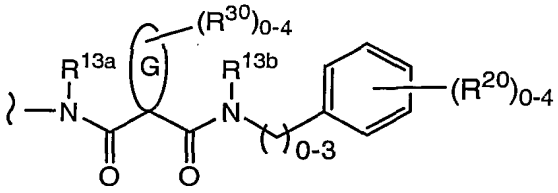
wherein Q, $R^{20}$, $R^{13}$, E, and $R^{60}$ are as defined above; each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with $R^{25}$; and $R^{25}$ is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted aryl $C_{1-6}$alkyl, heteroaryl $C_{1-6}$alkyl, and optionally substituted $C_{1-6}$alkyl; two of $R^{25}$, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered optionally substituted alicyclic or heteroalicyclic.

**[0140]** In another example, the process is according to paragraph [0139], wherein Q is selected from the following three formula:

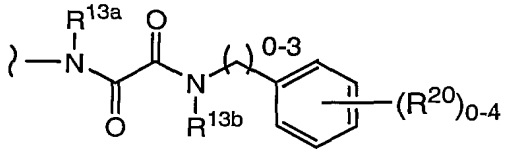


wherein $R^{20}$ is defined as above, and P is a five- to seven-membered ring, including the two shared carbons of the aromatic ring to which P is fused, P optionally containing between one and three heteroatoms.

**[0141]** In another example, the process is according to paragraph [0140], wherein -B-L-T is either of formula **XXV** or formula **XXVI**,



**XXV**

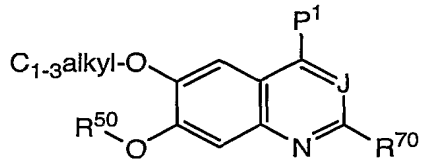


**XXVI**

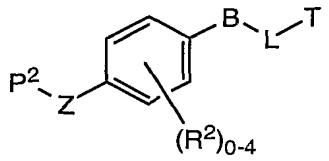
wherein $R^{20}$ is defined as above; G is either an optionally substituted cycloalkyl or an optionally substituted heteroalicyclic; each $R^{30}$ is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally

substituted $C_{1-6}$alkyl; and $R^{3a}$ and $R^{3b}$ are each independently selected from -H and optionally substituted $C_{1-6}$alkyl.

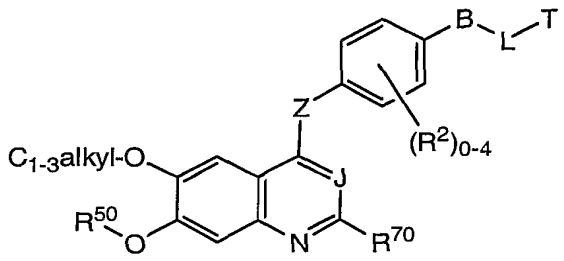
**[0142]** In another example, the process is according to paragraph [0141], wherein a compound of formula **XXIIa** is combined with a compound of formula **XXIIIa** to make a compound of formula **XXIa**,



**XXIIa**



**XXIIIa**



**XXIa**

wherein -B-L-T, Z, J, $R^{50}$, and $R^2$ are as defined above; $R^{70}$ is selected from -H, $-NO_2$, $-NH_2$, and $-NR^3R^3$; provided when Z is $-N(R^5)-$ that $R^5$ is selected from -H, $C_{1-3}$alkyl, and aryl $C_{1-3}$alkyl; $P^1$ is selected from halogen, optionally substituted alkyl-$S(O)_{0-2}$-, optionally substituted arylsulfonate, optionally substituted alkylsulfonate, a group containing boron, an azide, a group containing phosphorus, and a metal; and $P^2$ is selected from -H and a metal.

**[0143]** In another example, the process is according to paragraph [0142], wherein $P^2$ is selected from -H, lithium, sodium, potassium, cesium, copper, palladium, and titanium.

**[0144]** In another example, the process is according to paragraph [0143], wherein Z is -O-.

**[0145]** In another example, the process is according to paragraph [0144], wherein $P^1$ is selected from chlorine, bromine, a toluene sulfonate, and trifluoromethansulfonate.

**[0146]** In another example, the process is according to paragraph [0145], wherein $R^{70}$ is -H.

**[0147]** In another example, the process is according to paragraph [0146], wherein J is =C(H)-.

**[0148]** In another example, the process is according to paragraph [0147], wherein $R^2$ is selected from $C_{1-6}$ alkyl, perfluoro $C_{1-6}$ alkyl, and halogen.

**[0149]** In another example, the process is according to paragraph [0148], wherein **XXIIa** and **XXIIIa** are heated together, optionally with a base, optionally with microwave radiation, to form **XXIa**.

**[0150]** In another example, the process is according to paragraph [0149], wherein the base is selected from an organic base, an inorganic base, and a combination of an organic base and an inorganic base.

**[0151]** In another example, the process is according to paragraph [0150], wherein the base is selected from 2,6-lutidine, 4-N,N-dimethylaminopyridine, and a metal carbonate.

**[0152]** In another example, the process is according to paragraph [0151], wherein **XXIIa** and **XXIIIa** are heated together in a solvent with said base, at between about 40°C and 200°C for between about one hour and twenty-four hours to form **XXIa**.

**[0153]** In another example, the process is according to paragraph [0152], wherein the solvent is an organic solvent.

**[0154]** In another example, the process is according to paragraph [0153], wherein one molar equivalent of **XXIIa** is combined with between about one quarter and four molar equivalents of **XXIIIa**.

**[0155]** In another example, the process is according to paragraph [0154], wherein one molar equivalent of **XXIIa** is combined with more than one but less than two molar equivalents of **XXIIIa**.

**[0156]** In another example, the process is according to paragraph [0155], wherein **XXIIa** is combined with **XXIIIa** and said base in an aromatic solvent to form a mixture, and said mixture is heated to between about 100°C and 200°C for between about one and ten hours to form **Ia**.

**[0157]** In another example, the process is according to paragraph [0156], wherein the aromatic solvent is an optionally substituted benzene.

**[0158]** In another example, the process is according to paragraph [0157], wherein the aromatic solvent is bromobenzene.

**[0159]** In another example, the process is according to paragraph [0158], wherein the base is 4-N,N-dimethylaminopyridine.

**[0160]** In another example, the process is according to paragraph [0159], wherein said mixture is heated to reflux for between about three and seven hours.

**[0161]** In another example, the process is according to paragraph [0160], wherein said mixture is heated to reflux for between about four and six hours.

**[0162]** In another example, the process is according to paragraph [0155], wherein **XXIIa** is combined with **XXIIIa** and said base in a non-aromatic solvent to form a mixture, and said mixture is heated to between about 40°C and 100°C for between about one and twenty hours to form **XXIa**.

**[0163]** In another example, the process is according to paragraph [0162], wherein the non-aromatic solvent comprises a functional group selected from an amide, and ether, a nitrile, a halide, an ester, an amine, and a ketone.

**[0164]** In another example, the process is according to paragraph [0163], wherein the non-aromatic solvent is N,N-dimethylacetamide.

**[0165]** In another example, the process is according to paragraph [0164], wherein the base is potassium carbonate.

**[0166]** In another example, the process is according to paragraph [0165], wherein said mixture is heated to about 50°C between about ten and twenty hours.

**[0167]** In another example, the process is according to paragraph [0166], wherein the aromatic solvent is an optionally substituted pyridine.

**[0168]** In another example, the process is according to paragraph [0167], wherein the aromatic solvent is 2,6-lutidine.

**[0169]** In another example, the process is according to paragraph [0168], wherein the base is 2,6-lutidine.

**[0170]** In another example, the process is according to paragraph [0169], wherein said mixture is heated to reflux for between about three and seven hours.

**[0171]** In another example, the process is according to paragraph [0170], wherein said mixture is heated to reflux for between about four and six hours.

**[0172]** In another example, the process is according to paragraph [0154], wherein one molar equivalent of **XXIIIa** is combined with more than one but less than two molar equivalents of **XXIIa**.

**[0173]** In another example, the process is according to paragraph [0172], wherein **XXIIa** is combined with **XXIIIa** and said base in an aromatic solvent to form a mixture, and said mixture is heated to between about 100°C and 200°C for between about ten and twenty hours to form **XXIa**.

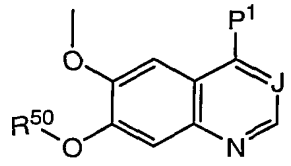
**[0174]** In another example, the process is according to paragraph [0173], wherein the aromatic solvent is an optionally substituted pyridine.

**[0175]** In another example, the process is according to paragraph [0174], wherein the aromatic solvent is 2,6-lutidine.

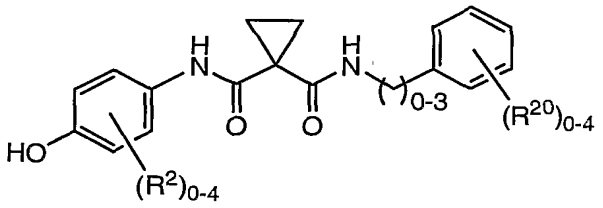
**[0176]** In another example, the process is according to paragraph [0175], wherein the base is 2,6-lutidine.

**[0177]** In another example, the process is according to paragraph [0176], wherein said mixture is heated to between about 150°C and 200°C for between about fifteen and twenty hours.

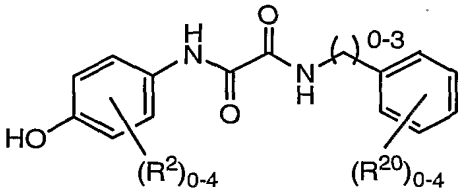
**[0178]** In another example, the process is according to any of paragraphs [0149] – [0177], wherein a compound of formula **XXIIb** is substituted for the compound of formula **XXIIa**, and either a compound of formula **XXIIIb** or a compound of formula **XXIIIc** is substituted for the compound of formula **XXIIIa**, in order to make a compound of formula **XXIb** or a compound of formula **XXIc**, respectively,



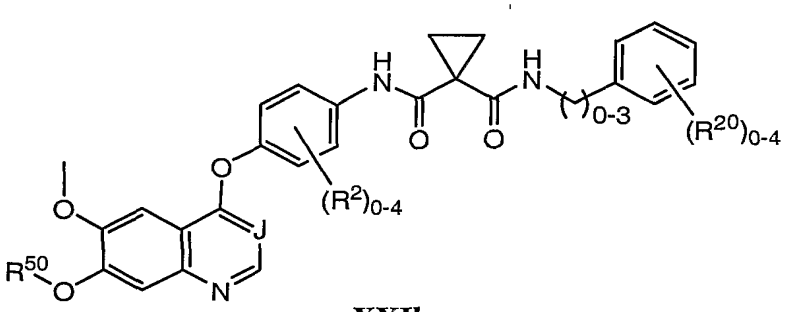

**XXIIb**



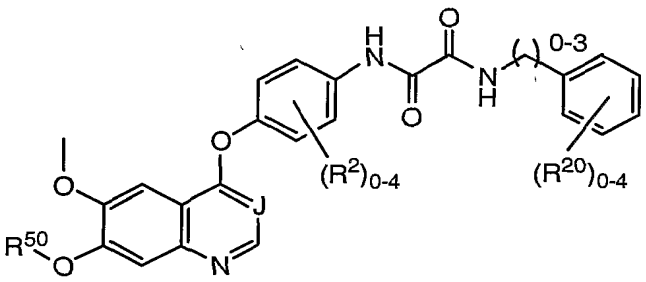

**XXIIIb**




**XXIIIc**



**XXIb**



**XXIc**

wherein J, $R^{50}$, $R^{20}$ and $R^2$ are as defined above.

**[0179]** In another example, the process is according to paragraph [0178], wherein $R^2$, if present, is halogen.

**[0180]** In another example, the process is according to paragraph [0179], wherein $R^2$, if present, is fluorine.

**[0181]** In another example, the process is according to paragraph [0180], wherein $R^2$, if present, is up to two fluorines *ortho* to the oxygen of the phenylene to which $R^2$ is attached.

**[0182]** In another example, the process is according to paragraph [0130], used to make a compound listed in either Table 1 or Table 2.

**[0183]** In another example the process is according to any of paragraphs [0130] - [0182], further comprising converting said compound to a pharmaceutically acceptable salt, hydrate, or prodrug thereof.

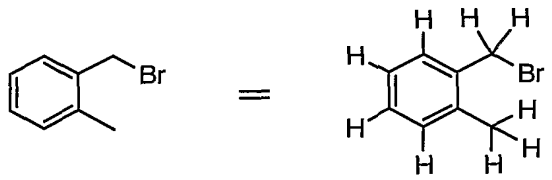
**Definitions**

**[0184]** As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in

which they are used indicates otherwise or they are expressly defined to mean something different.

**[0185]** The symbol "-" means a single bond, "=" means a double bond, "≡" means a triple bond. The symbol "〰" refers to a group on a double-bond as occupying either position on the terminus of a double bond to which the symbol is attached; that is, the geometry, *E*- or *Z*-, of the double bond is ambiguous. When a group is depicted removed from its parent formula, the "〜" symbol will be used at the end of the bond which was theoretically cleaved in order to separate the group from its parent structural formula.

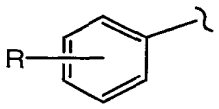
**[0186]** When chemical structures are depicted or described, unless explicitly stated otherwise, all carbons are assumed to have hydrogen substitution to conform to a valence of four. For example, in the structure on the left-hand side of the schematic below there are nine hydrogens implied. The nine hydrogens are depicted in the right-hand structure. Sometimes a particular atom in a structure is described in textual formula as having a hydrogen or hydrogens as substitution (expressly defined hydrogen), for example, $-CH_2CH_2-$. It is understood by one of ordinary skill in the art that the aforementioned descriptive techniques are common in the chemical arts to provide brevity and simplicity to description of otherwise complex structures.




**[0187]** In this application, some ring structures are depicted generically and will be described textually. For example, in the schematic below, if in the structure on the left, ring A is used to describe a "spirocyclyl," then if ring A is cyclopropyl, there are at most four hydrogens on ring A (when "R" can also be -H). In another example, as depicted on the right side of the schematic below, if ring B is used to describe a "phenylene" then there can be at most four hydrogens on ring B (assuming depicted cleaved bonds are not C-H bonds).

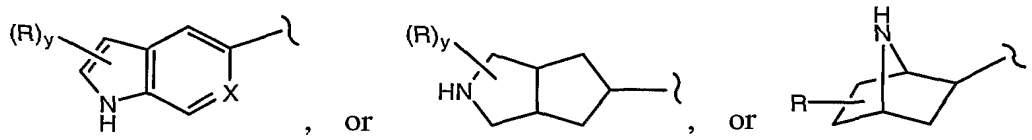



**[0188]** If a group "R" is depicted as "floating" on a ring system, as for example in the formula:



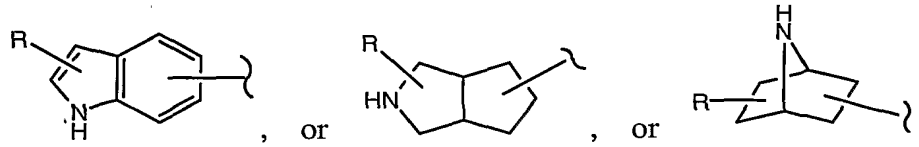
then, unless otherwise defined, a substituent "R" may reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

**[0189]** If a group "R" is depicted as floating on a fused ring system, as for example in the formulae:



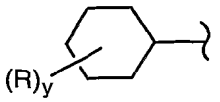
then, unless otherwise defined, a substituent "R" may reside on any atom of the fused ring system, assuming replacement of a depicted (for example the -NH- in the formula above), implied (for example as in the formula above, where the hydrogens are not shown but understood to be present), or expressly defined hydrogen (for example where in the formula above, "X" equals =CH-) from one of the ring atoms, so long as a stable structure is formed. In the example depicted, the "R" group may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formula depicted above, when y is 2 for example, then the two "R's" may reside on any two atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

**[0190]** When there are more than one such depicted "floating" groups, as for example in the formulae:

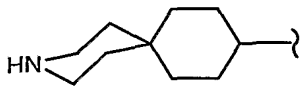


where there are two groups, namely, the "R" and the bond indicating attachment to a parent structure; then, unless otherwise defined, the "floating" groups may reside on any atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

**[0191]** When a group "R" is depicted as existing on a ring system containing saturated carbons, as for example in the formula:




where, in this example, "y" can be more than one, assuming each replaces a currently depicted, implied, or expressly defined hydrogen on the ring; then, unless otherwise defined, where the resulting structure is stable, two "R's" may reside on the same carbon. A simple example is when R is a methyl group; there can exist a geminal dimethyl on a carbon of the depicted ring (an "annular" carbon). In another example, two R's on the same carbon, including that carbon, may form a ring, thus creating a spirocyclic ring (a "spirocyclyl" group) structure with the depicted ring as for example in the formula:




**[0192]** "Alkyl" is intended to include linear, branched, or cyclic hydrocarbon structures and combinations thereof, inclusively. For example, "$C_8$ alkyl" may refer to an *n*-octyl, *iso*-octyl, cyclohexylethyl, and the like. Lower alkyl refers to alkyl groups of from one to six carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *s*-butyl, *t*-butyl, isobutyl, pentyl, hexyl and the like. Higher alkyl refers to alkyl groups containing more that eight carbon atoms. Exemplary alkyl groups are those of $C_{20}$ or below. Cycloalkyl is a subset of alkyl and includes cyclic hydrocarbon groups of from three to thirteen carbon atoms. Examples of cycloalkyl groups include c-propyl, c-butyl, c-pentyl, norbornyl, adamantyl and the like. In this application, alkyl refers to alkanyl, alkenyl, and alkynyl residues (and combinations thereof); it is intended to include cyclohexylmethyl, vinyl, allyl, isoprenyl, and the like. Thus when an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed; thus, for example, either "butyl" or "$C_4$ alkyl" is meant to include *n*-butyl, *sec*-butyl, isobutyl, *t*-butyl, isobutenyl and but-2-yne radicals; and for example, "propyl" or "$C_3$ alkyl" each include *n*-propyl, propenyl, and isopropyl.

**[0193]** "Alkylene" refers to straight or branched chain divalent radical consisting solely of carbon and hydrogen atoms, containing no unsaturation and having from one to ten carbon atoms, for example, methylene, ethylene, propylene, *n*-butylene and the like. Alkylene is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, fully saturated. Examples of alkylene include ethylene

(-$CH_2CH_2$-), propylene (-$CH_2CH_2CH_2$-), dimethylpropylene (-$CH_2C(CH_3)_2CH_2$-), and cyclohexylpropylene (-$CH_2CH_2CH(C_6H_{13})$).

**[0194]** "Alkylidene" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms, having from two to ten carbon atoms, for example, ethylidene, propylidene, *n*-butylidene, and the like. Alkylidene is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, double bond unsaturation. The unsaturation present includes at least one double bond.

**[0195]** "Alkylidyne" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms having from two to ten carbon atoms, for example, propylid-2-ynyl, *n*-butylid-1-ynyl, and the like. Alkylidyne is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, triple bond unsaturation. The unsaturation present includes at least one triple bond.

**[0196]** Any of the above radicals, "alkylene," "alkylidene" and "alkylidyne," when optionally substituted, may contain alkyl substitution which itself contains unsaturation. For example, 2-(2-phenylethynyl-but-3-enyl)-naphthalene (IUPAC name) contains an *n*-butylid-3-ynyl radical with a vinyl substituent at the 2-position of said radical.

**[0197]** "Alkoxy" or "alkoxyl" refers to the group -O-alkyl, for example including from one to eight carbon atoms of a straight, branched, cyclic configuration, unsaturated chains, and combinations thereof attached to the parent structure through an oxygen atom. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like. Lower-alkoxy refers to groups containing one to six carbons.

**[0198]** "Substituted alkoxy" refers to the group -O-(substituted alkyl), the substitution on the alkyl group generally containing more than only carbon (as defined by alkoxy). One exemplary substituted alkoxy group is "polyalkoxy" or -O-optionally substituted alkylene-optionally substituted alkoxy, and includes groups such as -$OCH_2CH_2OCH_3$, and glycol ethers such as polyethyleneglycol and -$O(CH_2CH_2O)_xCH_3$, where x is an integer of between about two and about twenty, in another example, between about two and about ten, and in a further example between about two and about five. Another exemplary substituted alkoxy group is hydroxyalkoxy or -$OCH_2(CH_2)_yOH$, where y is for example an

integer of between about one and about ten, in another example y is an integer of between about one and about four.

**[0199]** "Acyl" refers to groups of from one to ten carbon atoms of a straight, branched, cyclic configuration, saturated, unsaturated and aromatic and combinations thereof, attached to the parent structure through a carbonyl functionality. One or more carbons in the acyl residue may be replaced by nitrogen, oxygen or sulfur as long as the point of attachment to the parent remains at the carbonyl. Examples include acetyl, benzoyl, propionyl, isobutyryl, *t*-butoxycarbonyl, benzyloxycarbonyl and the like. Lower-acyl refers to groups containing one to six carbons.

**[0200]** "α-Amino Acids" refer to naturally occurring and commercially available amino acids and optical isomers thereof. Typical natural and commercially available α-amino acids are glycine, alanine, serine, homoserine, threonine, valine, norvaline, leucine, isoleucine, norleucine, aspartic acid, glutamic acid, lysine, omithine, histidine, arginine, cysteine, homocysteine, methionine, phenylalanine, homophenylalanine, phenylglycine, ortho-tyrosine, meta-tyrosine, para-tyrosine, tryptophan, glutamine, asparagine, proline and hydroxyproline. A "side chain of an α-amino acid" refers to the radical found on the α-carbon of an α-amino acid as defined above, for example, hydrogen (for glycine), methyl (for alanine), benzyl (for phenylalanine), and the like.

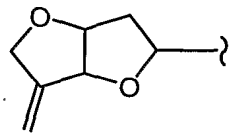
**[0201]** "Amino" refers to the group $-NH_2$. "Substituted amino," refers to the group -N(H)R or –N(R)R where each R is independently selected from the group: optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted heterocyclyl, acyl, carboxy, alkoxycarbonyl, sulfanyl, sulfinyl and sulfonyl, for example, diethylamino, methylsulfonylamino, furanyl-oxy-sulfonamino.

**[0202]** "Aryl" refers to aromatic six- to fourteen-membered carbocyclic ring, for example, benzene, naphthalene, indane, tetralin, fluorene and the like, univalent radicals. As univalent radicals, the aforementioned ring examples are named, phenyl, naphthyl, indanyl, tetralinyl, and fluorenyl.

**[0203]** "Arylene" generically refers to any aryl that has at least two groups attached thereto. For a more specific example, "phenylene" refers to a divalent phenyl ring radical. A phenylene, thus may have more than two groups attached, but is defined by a minimum of two non-hydrogen groups attached thereto.

[0204] "Arylalkyl" refers to a residue in which an aryl moiety is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne radical. Examples include benzyl, phenethyl, phenylvinyl, phenylallyl and the like. Both the aryl, and the corresponding alkylene, alkylidene, or alkylidyne radical portion of an arylalkyl group may be optionally substituted. "Lower arylalkyl" refers to an arylalkyl where the "alkyl" portion of the group has one to six carbons; this can also be refered to as $C_{1-6}$ arylalkyl.

[0205] "Exo-alkenyl" refers to a double bond that emanates from an annular carbon, and is not within the ring system, for example the double bond depicted in the formula below.



[0206] In some examples, as appreciated by one of ordinary skill in the art, two adjacent groups on an aromatic system may be fused together to form a ring structure. The fused ring structure may contain heteroatoms and may be optionally substituted with one or more groups. It should additionally be noted that saturated carbons of such fused groups (i.e. saturated ring structures) can contain two substitution groups.

[0207] "Fused-polycyclic" or "fused ring system" refers to a polycyclic ring system that contains bridged or fused rings; that is, where two rings have more than one shared atom in their ring structures. In this application, fused-polycyclics and fused ring systems are not necessarily all aromatic ring systems. Typically, but not necessarily, fused-polycyclics share a vicinal set of atoms, for example naphthalene or 1,2,3,4-tetrahydro-naphthalene. A spiro ring system is not a fused-polycyclic by this definition, but fused polycyclic ring systems of the invention may themselves have spiro rings attached thereto via a single ring atom of the fused-polycyclic.

[0208] "Halogen" or "halo" refers to fluorine, chlorine, bromine or iodine. "Haloalkyl" and "haloaryl" refer generically to alkyl and aryl radicals that are substituted with one or more halogens, respectively. Thus, "dihaloaryl," "dihaloalkyl," "trihaloaryl" etc. refer to aryl and alkyl substituted with a plurality of halogens, but not necessarily a plurality of the same halogen; thus 4-chloro-3-fluorophenyl is within the scope of dihaloaryl.

[0209] "Heteroarylene" generically refers to any heteroaryl that has at least two groups attached thereto. For a more specific example, "pyridylene" refers to a divalent pyridyl

ring radical. A pyridylene, thus may have more than two groups attached, but is defined by a minimum of two non-hydrogen groups attached thereto.

[0210] "Heteroatom" refers to O, S, N, or P.

[0211] "Heterocyclyl" refers to a stable three- to fifteen-membered ring radical that consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclyl radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused or bridged ring systems as well as spirocyclic systems; and the nitrogen, phosphorus, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized to various oxidation states. In a specific example, the group $-S(O)_{0-2}-$, refers to -S- (sulfide), -S(O)- (sulfoxide), and $-SO_2-$ (sulfone). For convenience, nitrogens, particularly but not exclusively, those defined as annular aromatic nitrogens, are meant to include their corresponding *N*-oxide form, although not explicitly defined as such in a particular example. Thus, for a compound of the invention having, for example, a pyridyl ring; the corresponding pyridyl-*N*-oxide is meant to be included as another compound of the invention. In addition, annular nitrogen atoms may be optionally quaternized; and the ring radical may be partially or fully saturated or aromatic. Examples of heterocyclyl radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofuranyl, carbazoyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, tetrahydroisoquinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxazolidinyl, triazolyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothieliyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, dioxaphospholanyl, and oxadiazolyl.

[0212] "Heteroalicyclic" refers specifically to a non-aromatic heterocyclyl radical. A heteroalicyclic may contain unsaturation, but is not aromatic.

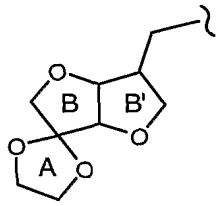
[0213] "Heteroaryl" refers specifically to an aromatic heterocyclyl radical.

[0214] "Heterocyclylalkyl" refers to a residue in which a heterocyclyl is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne radical. Examples include (4-methylpiperazin-1-yl) methyl, (morpholin-4-yl) methyl, (pyridine-4-yl) methyl, 2-(oxazolin-2-yl) ethyl, 4-(4-methylpiperazin-1-yl)-2-butenyl, and the like. Both the heterocyclyl, and the corresponding alkylene, alkylidene, or alkylidyne radical portion of a heterocyclylalkyl group may be optionally substituted. "Lower heterocyclylalkyl" refers to a heterocyclylalkyl where the "alkyl" portion of the group has one to six carbons. "Heteroalicyclylalkyl" refers specifically to a heterocyclylalkyl where the heterocyclyl portion of the group is non-aromatic; and "heteroarylalkyl" refers specifically to a heterocyclylalkyl where the heterocyclyl portion of the group is aromatic Such terms may be described in more than one way, for example, "lower heterocyclylalkyl" and "heterocyclyl $C_{1-6}$alkyl" are equivalent terms.

[0215] "Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. One of ordinary skill in the art would understand that, with respect to any molecule described as containing one or more optional substituents, that only sterically practical and/or synthetically feasible compounds are meant to be included. "Optionally substituted" refers to all subsequent modifiers in a term, for example in the term "optionally substituted aryl$C_{1-8}$ alkyl," optional substitution may occur on both the "$C_{1-8}$ alkyl" portion and the "aryl" portion of the molecule; and for example, optionally substituted alkyl includes optionally substituted cycloalkyl groups, which in turn are defined as including optionally substituted alkyl groups, potentially *ad infinitum*. A list of exemplary optional substitution are listed below in the definition of "substituted."

[0216] "Saturated bridged ring system" refers to a bicyclic or polycyclic ring system that is not aromatic. Such a system may contain isolated or conjugated unsaturation, but not aromatic or heteroaromatic rings in its core structure (but may have aromatic substitution thereon). For example, hexahydro-furo[3,2-b]furan, 2,3,3a,4,7,7a-hexahydro-1H-indene, 7-aza-bicyclo[2.2.1]heptane, and 1,2,3,4,4a,5,8,8a-octahydro-naphthalene are all included in the class "saturated bridged ring system."

[0217] "Spirocyclyl" or "spirocyclic ring" refers to a ring originating from a particular annular carbon of another ring. For example, as depicted below, a ring atom of a saturated bridged ring system (rings B and B'), but not a bridgehead atom, can be a shared atom between the saturated bridged ring system and a spirocyclyl (ring A) attached thereto. A spirocyclyl can be carbocyclic or heteroalicyclic.




[0218] "Substituted" alkyl, aryl, and heterocyclyl, refer respectively to alkyl, aryl, and heterocyclyl, wherein one or more (for example up to about five, in another example, up to about three) hydrogen atoms are replaced by a substituent independently selected from: optionally substituted alkyl (for example, fluoromethyl), optionally substituted aryl (for example, 4-hydroxyphenyl), optionally substituted arylalkyl (for example, 1-phenyl-ethyl), optionally substituted heterocyclylalkyl (for example, 1-pyridin-3-yl-ethyl), optionally substituted heterocyclyl (for example, 5-chloro-pyridin-3-yl or 1-methyl-piperidin-4-yl), optionally substituted alkoxy, alkylenedioxy (for example methylenedioxy), optionally substituted amino (for example, alkylamino and dialkylamino), optionally substituted amidino, optionally substituted aryloxy (for example, phenoxy), optionally substituted arylalkyloxy (for example, benzyloxy), carboxy (-$CO_2H$), carboalkoxy (that is, acyloxy or -OC(=O)R), carboxyalkyl (that is, esters or -$CO_2R$), carboxamido, benzyloxycarbonylamino (CBZ-amino), cyano, acyl, halogen, hydroxy, nitro, sulfanyl, sulfinyl, sulfonyl, thiol, halogen, hydroxy, oxo, carbamyl, acylamino, and sulfonamido.

[0219] "Suitable leaving group" is defined as the term would be understood by one of ordinary skill in the art; that is, a carbon with such a group attached, upon reaction wherein a new bond is to be formed, loses such a group upon formation of the new bond. The invention pertains particularly with respect convergent synthesis, to reactions where such a leaving group is bonded to a reaction partner that is aromatic, undergoes a bond-forming reaction and remains aromatic. A typical example of such a reaction is a nucleophilic aromatic substitution reaction, as would be understood by one of ordinary skill in the art. However, the invention is not limited to such mechanistic restrictions; for example, reactions where there is, for example, an insertion reaction (for example by a transition metal) into the bond between the aromatic reaction partner and its leaving group

followed by reductive coupling can also be used within the scope of the invention. Examples of suitable leaving groups include halogens, optionally substituted aryl or alkyl sulfonates, phosphonates, azides, $RS(O)_{0-2}$- where R is, for example optionally substituted alkyl, optionally substituted aryl, or optionally substituted heteroaryl.

**[0220]** "Sulfanyl" refers to the groups: -S-(optionally substituted alkyl), -S-(optionally substituted aryl), and -S-(optionally substituted heterocyclyl).

**[0221]** "Sulfinyl" refers to the groups: -S(O)-H, -S(O)-(optionally substituted alkyl), -S(O)-optionally substituted aryl), and -S(O)-(optionally substituted heterocyclyl).

**[0222]** "Sulfonyl" refers to the groups: $-S(O_2)$-H, $-S(O_2)$-(optionally substituted alkyl), $-S(O_2)$-optionally substituted aryl), $-S(O_2)$-(optionally substituted heterocyclyl), $-S(O_2)$-(optionally substituted alkoxy), $-S(O_2)$-optionally substituted aryloxy), and $-S(O_2)$-(optionally substituted heterocyclyloxy).

**[0223]** "Yield" for each of the reactions described herein is expressed as a percentage of the theoretical yield.

**[0224]** Some of the compounds of the invention may have imino, amino, oxo or hydroxy substituents off aromatic heterocyclyl systems. For purposes of this disclosure, it is understood that such imino, amino, oxo or hydroxy substituents may exist in their corresponding tautomeric form, i.e., amino, imino, hydroxy or oxo, respectively.

**[0225]** Compounds of the invention are named according to systematic application of the nomenclature rules agreed upon by the International Union of Pure and Applied Chemistry (IUPAC), International Union of Biochemistry and Molecular Biology (IUBMB), and the Chemical Abstracts Service (CAS).

**[0226]** The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms, oxidized sulfur atoms or quaternized nitrogen atoms in their structure.

**[0227]** The compounds of the invention and their pharmaceutically acceptable salts may exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. The compounds may also exist as geometric isomers. All such single stereoisomers, racemates and mixtures thereof, and geometric isomers are intended to be within the scope of this invention.

[0228] It is assumed that when considering generic descriptions of compounds of the invention for the purpose of constructing a compound, such construction results in the creation of a stable structure. That is, one of ordinary skill in the art would recognize that there can theoretically be some constructs which would not normally be considered as stable compounds (that is, sterically practical and/or synthetically feasible, *supra*).

[0229] When a particular group with its bonding structure is denoted as being bonded to two partners; that is, a divalent radical, for example, -$OCH_2$-, then it is understood that either of the two partners may be bound to the particular group at one end, and the other partner is necessarily bound to the other end of the particular group, unless stated explicitly otherwise. Stated another way, divalent radicals are not to be construed as limited to the depicted orientation, for example "-$OCH_2$-" is meant to mean not only "-$OCH_2$-" as drawn, but also "-$CH_2O$-."

[0230] Methods for the preparation and/or separation and isolation of single stereoisomers from racemic mixtures or non-racemic mixtures of stereoisomers are well known in the art. For example, optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. Enantiomers (R- and S-isomers) may be resolved by methods known to one of ordinary skill in the art, for example by: formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallization, selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where a desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step may be required to liberate the desired enantiomeric form. Alternatively, specific enantiomer may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting on enantiomer to the other by asymmetric transformation. For a mixture of enantiomers, enriched in a particular enantiomer, the major component enantiomer may be further enriched (with concomitant loss in yield) by recrystallization.

[0231] "Patient" for the purposes of the present invention includes humans and other animals, particularly mammals, and other organisms. Thus the methods are applicable to

both human therapy and veterinary applications. In a preferred embodiment the patient is a mammal, and in a most preferred embodiment the patient is human.

[0232] "Kinase-dependent diseases or conditions" refer to pathologic conditions that depend on the activity of one or more protein kinases. Kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including proliferation, adhesion, migration, differentiation and invasion. Diseases associated with kinase activities include tumor growth, the pathologic neovascularization that supports solid tumor growth, and associated with other diseases where excessive local vascularization is involved such as ocular diseases (diabetic retinopathy, age-related macular degeneration, and the like) and inflammation (psoriasis, rheumatoid arthritis, and the like).

[0233] While not wishing to be bound to theory, phosphatases can also play a role in "kinase-dependent diseases or conditions" as cognates of kinases; that is, kinases phosphorylate and phosphatases dephosphorylate, for example protein substrates. Therefore compounds of the invention, while modulating kinase activity as described herein, may also modulate, either directly or indirectly, phosphatase activity. This additional modulation, if present, may be synergistic (or not) to activity of compounds of the invention toward a related or otherwise interdependent kinase or kinase family. In any case, as stated previously, the compounds of the invention are useful for treating diseases characterized in part by abnormal levels of cell proliferation (i.e. tumor growth), programmed cell death (apoptosis), cell migration and invasion and angiogenesis associated with tumor growth.

[0234] "Therapeutically effective amount" is an amount of a compound of the invention, that when administered to a patient, ameliorates a symptom of the disease. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease state and its severity, the age of the patient to be treated, and the like. The therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

[0235] "Cancer" refers to cellular-proliferative disease states, including but not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma),

alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hanlartoma, inesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinorna, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinorna, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [neplrroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis defornians), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastorna multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, SertoliLeydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma], fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma,

dermatofibroma, keloids, psoriasis; and Adrenal lands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

[0236] "Pharmaceutically acceptable acid addition salt" refers to those salts that retain the biological effectiveness of the free bases and that are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

[0237] "Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Exemplary salts are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins, and the like. Exemplary organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine. (See, for example, S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 which is incorporated herein by reference.)

[0238] "Prodrug" refers to compounds that are transformed (typically rapidly) *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis in blood. Common examples include, but are not limited to, ester and amide forms of a compound having an active form bearing a carboxylic acid moiety. Examples of pharmaceutically acceptable esters of the compounds of this invention include, but are not limited to, alkyl esters (for example with between about one and about six carbons) wherein the alkyl group is a straight or branched chain. Acceptable esters also include cycloalkyl esters and

arylalkyl esters such as, but not limited to benzyl. Examples of pharmaceutically acceptable amides of the compounds of this invention include, but are not limited to, primary amides, and secondary and tertiary alkyl amides (for example with between about one and about six carbons). Amides and esters of the compounds of the present invention may be prepared according to conventional methods. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference for all purposes.

**[0239]** "Metabolite" refers to the break-down or end product of a compound or its salt produced by metabolism or biotransformation in the animal or human body; for example, biotransformation to a more polar molecule such as by oxidation, reduction, or hydrolysis, or to a conjugate (see Goodman and Gilman, "The Pharmacological Basis of Therapeutics" 8.sup.th Ed., Pergamon Press, Gilman et al. (eds), 1990 for a discussion of biotransformation). As used herein, the metabolite of a compound of the invention or its salt may be the biologically active form of the compound in the body. In one example, a prodrug may be used such that the biologically active form, a metabolite, is released *in vivo*. In another example, a biologically active metabolite is discovered serendipitously, that is, no prodrug design *per se* was undertaken. An assay for activity of a metabolite of a compound of the present invention is known to one of skill in the art in light of the present disclosure.

**[0240]** In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

**[0241]** In addition, it is intended that the present invention cover compounds made either using standard organic synthetic techniques, including combinatorial chemistry or by biological methods, such as bacterial digestion, metabolism, enzymatic conversion, and the like.

**[0242]** "Treating" or "treatment" as used herein covers the treatment of a disease-state in a human, which disease-state is characterized by abnormal cellular proliferation, and invasion and includes at least one of: (i) preventing the disease-state from occurring in a human, in particular, when such human is predisposed to the disease-state but has not yet

been diagnosed as having it; (ii) inhibiting the disease-state, i.e., arresting its development; and (iii) relieving the disease-state, i.e., causing regression of the disease-state. As is known in the art, adjustments for systemic versus localized delivery, age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by one of ordinary skill in the art.

**[0243]** One of ordinary skill in the art would understand that certain crystallized, protein-ligand complexes, in particular c-Met, c-Kit, KDR, flt-3, or flt-4-ligand complexes, and their corresponding x-ray structure coordinates can be used to reveal new structural information useful for understanding the biological activity of kinases as described herein. As well, the key structural features of the aforementioned proteins, particularly, the shape of the ligand binding site, are useful in methods for designing or identifying selective modulators of kinases and in solving the structures of other proteins with similar features. Such protein-ligand complexes, having compounds of the invention as their ligand component, are an aspect of the invention.

**[0244]** As well, one of ordinary skill in the art would appreciate that such suitable x-ray quality crystals can be used as part of a method of identifying a candidate agent capable of binding to and modulating the activity of kinases. Such methods may be characterized by the following aspects: a) introducing into a suitable computer program, information defining a ligand binding domain of a kinase in a conformation (e.g. as defined by x-ray structure coordinates obtained from suitable x-ray quality crystals as described above) wherein the computer program creates a model of the three dimensional structures of the ligand binding domain, b) introducing a model of the three dimensional structure of a candidate agent in the computer program, c) superimposing the model of the candidate agent on the model of the ligand binding domain, and d) assessing whether the candidate agent model fits spatially into the ligand binding domain. Aspects a-d are not necessarily carried out in the aforementioned order. Such methods may further entail: performing rational drug design with the model of the three-dimensional structure, and selecting a potential candidate agent in conjunction with computer modeling.

**[0245]** Additionally, one skilled in the art would appreciate that such methods may further entail: employing a candidate agent, so-determined to fit spatially into the ligand binding domain, in a biological activity assay for kinase modulation, and determining whether said candidate agent modulates kinase activity in the assay. Such methods may also include

administering the candidate agent, determined to modulate kinase activity, to a mammal suffering from a condition treatable by kinase modulation, such as those described above.

[0246] Also, one skilled in the art would appreciate that compounds of the invention can be used in a method of evaluating the ability of a test agent to associate with a molecule or molecular complex comprising a ligand binding domain of a kinase. Such a method may be characterized by the following aspects: a) creating a computer model of a kinase binding pocket using structure coordinates obtained from suitable x-ray quality crystals of the kinase, b) employing computational algorithms to perform a fitting operation between the test agent and the computer model of the binding pocket, and c) analyzing the results of the fitting operation to quantify the association between the test agent and the computer model of the binding pocket.

**General Administration**

[0247] Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages.

[0248] The compositions will include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc. Compositions of the invention may be used in combination with anticancer or other agents that are generally administered to a patient being treated for cancer. Adjuvants include preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form

can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0249] If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylalted hydroxytoluene, etc.

[0250] Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

[0251] One preferable route of administration is oral, using a convenient daily dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

[0252] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alignates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[0253] Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[0254] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. Such dosage forms are prepared, for example, by dissolving, dispersing, etc., a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like; solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide; oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan; or mixtures of these substances, and the like, to thereby form a solution or suspension.

[0255] Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

[0256] Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the compounds of the present invention with for example suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

[0257] Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

[0258] Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

[0259] Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state in accordance with the teachings of this invention.

[0260] The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states, and the host undergoing therapy. The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is an example. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well known to one of ordinary skill in the art.

**Utility of compounds of the invention as screening agents**

[0261] To employ the compounds of the invention in a method of screening for candidate agents that bind to, for example c-Met, KDR, c-Kit, flt-3, or flt-4, the protein is bound to a support, and a compound of the invention is added to the assay. Alternatively, the

compound of the invention is bound to the support and the protein is added. Classes of candidate agents among which novel binding agents may be sought include specific antibodies, non-natural binding agents identified in screens of chemical libraries, peptide analogs, etc. Of particular interest are screening assays for candidate agents that have a low toxicity for human cells. A wide variety of assays may be used for this purpose, including labeled in vitro protein-protein binding assays, electrophoretic mobility shift assays, immunoassays for protein binding, functional assays (phosphorylation assays, etc.) and the like.

**[0262]** The determination of the binding of the candidate agent to, for example, c-Met, KDR, c-Kit, flt-3, or flt-4 protein may be done in a number of ways. In one example, the candidate agent (the compound of the invention) is labeled, for example, with a fluorescent or radioactive moiety and binding determined directly. For example, thus may be done by attaching all or a portion of the c-Met, KDR, c-Kit, flt-3, or flt-4 protein to a solid support, adding a labeled agent (for example a compound of the invention in which at least one atom has been replaced by a detectable isotope), washing off excess reagent, and determining whether the amount of the label is that present on the solid support. Various blocking and washing steps may be utilized as is known in the art.

**[0263]** By "labeled" herein is meant that the compound is either directly or indirectly labeled with a label which provides a detectable signal, e.g., radioisotope, fluorescent tag, enzyme, antibodies, particles such as magnetic particles, chemiluminescent tag, or specific binding molecules, etc. Specific binding molecules include pairs, such as biotin and streptavidin, digoxin and antidigoxin etc. For the specific binding members, the complementary member would normally be labeled with a molecule which provides for detection, in accordance with known procedures, as outlined above. The label can directly or indirectly provide a detectable signal.

**[0264]** In some embodiments, only one of the components is labeled. For example, c-Met, KDR, c-Kit, flt-3, or flt-4 protein may be labeled at tyrosine positions using $^{125}I$, or with fluorophores. Alternatively, more than one component may be labeled with different labels; using $^{125}I$ for the proteins, for example, and a fluorophor for the candidate agents.

**[0265]** The compounds of the invention may also be used as competitors to screen for additional drug candidates. "Candidate bioactive agent" or "drug candidate" or grammatical equivalents as used herein describe any molecule, e.g., protein, oligopeptide, small organic molecule, polysaccharide, polynucleotide, etc., to be tested for bioactivity.

They may be capable of directly or indirectly altering the cellular proliferation phenotype or the expression of a cellular proliferation sequence, including both nucleic acid sequences and protein sequences. In other cases, alteration of cellular proliferation protein binding and/or activity is screened. In the case where protein binding or activity is screened, some embodiments exclude molecules already known to bind to that particular protein. Exemplary embodiments of assays described herein include candidate agents, which do not bind the target protein in its endogenous native state, termed herein as "exogenous" agents. In one example, exogenous agents further exclude antibodies to c-Met, KDR, c-Kit, flt-3, or flt-4.

**[0266]** Candidate agents can encompass numerous chemical classes, though typically they are organic molecules having a molecular weight of more than about 100 daltons and less than about 2,500 daltons. Candidate agents comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding and lipophilic binding, and typically include at least an amine, carbonyl, hydroxyl, ether, or carboxyl group, for example at least two of the functional chemical groups. The candidate agents often comprise cyclical carbon or heterocyclyl structures and/or aromatic or polyaromatic structures substituted with one or more of the above functional groups. Candidate agents are also found among biomolecules including peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs, or combinations thereof.

**[0267]** Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural or synthetically produced libraries and compounds are readily modified through conventional chemical, physical and biochemical means. Known pharmacological agents may be subjected to directed or random chemical modifications, such as acylation, alkylation, esterification, amidification to produce structural analogs.

**[0268]** In one example, the binding of the candidate agent is determined through the use of competitive binding assays. In this example, the competitor is a binding moiety known to bind to c-Met, KDR, c-Kit, flt-3, or flt-4, such as an antibody, peptide, binding partner, ligand, etc. Under certain circumstances, there may be competitive binding as between the

candidate agent and the binding moiety, with the binding moiety displacing the candidate agent.

[0269] In some embodiments, the candidate agent is labeled. Either the candidate agent, or the competitor, or both, is added first to for example c-Met, KDR, c-Kit, flt-3, or flt-4 for a time sufficient to allow binding, if present. Incubations may be performed at any temperature that facilitates optimal activity, typically between 4°C and 40°C

[0270] Incubation periods are selected for optimum activity, but may also be optimized to facilitate rapid high throughput screening. Typically between 0.1 and 1 hour will be sufficient. Excess reagent is generally removed or washed away. The second component is then added, and the presence or absence of the labeled component is followed, to indicate binding.

[0271] In one example, the competitor is added first, followed by the candidate agent. Displacement of the competitor is an indication the candidate agent is binding to c-Met, KDR, c-Kit, flt-3, or flt-4 and thus is capable of binding to, and potentially modulating, the activity of the c-Met, KDR, c-Kit, flt-3, or flt-4. In this embodiment, either component can be labeled. Thus, for example, if the competitor is labeled, the presence of label in the wash solution indicates displacement by the agent. Alternatively, if the candidate agent is labeled, the presence of the label on the support indicates displacement.

[0272] In an alternative embodiment, the candidate agent is added first, with incubation and washing, followed by the competitor. The absence of binding by the competitor may indicate the candidate agent is bound to c-Met, KDR, c-Kit, flt-3, or flt-4 with a higher affinity. Thus, if the candidate agent is labeled, the presence of the label on the support, coupled with a lack of competitor binding, may indicate the candidate agent is capable of binding to c-Met, KDR, c-Kit, flt-3, or flt-4.

[0273] It may be of value to identify the binding site of c-Met, KDR, c-Kit, flt-3, or flt-4. This can be done in a variety of ways. In one embodiment, once c-Met, KDR, c-Kit, flt-3, or flt-4 has been identified as binding to the candidate agent, the c-Met, KDR, c-Kit, flt-3, or flt-4 is fragmented or modified and the assays repeated to identify the necessary components for binding.

[0274] Modulation is tested by screening for candidate agents capable of modulating the activity of c-Met, KDR, c-Kit, flt-3, or flt-4 comprising the steps of combining a candidate agent with c-Met, KDR, c-Kit, flt-3, or flt-4, as above, and determining an alteration in the

biological activity of the c-Met, KDR, c-Kit, flt-3, or flt-4. Thus, in this embodiment, the candidate agent should both bind to (although this may not be necessary), and alter its biological or biochemical activity as defined herein. The methods include both *in vitro* screening methods and *in vivo* screening of cells for alterations in cell viability, morphology, and the like.

**[0275]** Alternatively, differential screening may be used to identify drug candidates that bind to native c-Met, KDR, c-Kit, flt-3, or flt-4, but cannot bind to modified c-Met, KDR, c-Kit, flt-3, or flt-4.

**[0276]** Positive controls and negative controls may be used in the assays. For example, all control and test samples are performed in at least triplicate to obtain statistically significant results. Incubation of samples is for a time sufficient for the binding of the agent to the protein. Following incubation, samples are washed free of non-specifically bound material and the amount of bound, generally labeled agent determined. For example, where a radiolabel is employed, the samples may be counted in a scintillation counter to determine the amount of bound compound.

**[0277]** A variety of other reagents may be included in the screening assays. These include reagents like salts, neutral proteins, e.g., albumin, detergents, etc which may be used to facilitate optimal protein-protein binding and/or reduce non-specific or background interactions. Also reagents that otherwise improve the efficiency of the assay, such as protease inhibitors, nuclease inhibitors, anti-microbial agents, etc., may be used. The mixture of components may be added in any order that provides for the requisite binding.

**Abbreviations and their Definitions**

**[0278]** The following abbreviations and terms have the indicated meanings throughout.

| Abbreviation | Meaning |
|---|---|
| Ac | acetyl |
| ATP | adenosine triphosphate |
| BNB | 4-bromomethyl-3-nitrobenzoic acid |
| Boc | t-butyloxy carbonyl |

| Abbreviation | Meaning |
|---|---|
| br | broad |
| Bu | butyl |
| °C | degrees Celsius |
| c- | cyclo |
| CBZ | CarboBenZoxy = benzyloxycarbonyl |
| d | doublet |
| dd | doublet of doublet |
| dt | doublet of triplet |
| DBU | Diazabicyclo[5.4.0]undec-7-ere |
| DCM | dichloromethane = methylene chloride = $CH_2Cl_2$ |
| DCE | dichloroethylene |
| DEAD | diethyl azodicarboxylate |
| DIC | diisopropylcarbodiimide |
| DIEA | N,N-diisopropylethyl amine |
| DMAP | 4-N,N-dimethylaminopyridine |
| DMF | N,N-dimethylfonnamide |
| DMSO | dimethyl sulfoxide |
| DVB | 1,4-divinylbenzene |
| EEDQ | 2-ethoxy-l-ethoxycarbonyl-1,2-dihydroquinoline |
| EI | Electron Impact ionization |
| Et | ethyl |
| Fmoc | 9-fluorenylmethoxycarbonyl |
| g | gram(s) |
| GC | gas chromatography |
| h or hr | hour(s) |
| HATU | 0-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate |
| HMDS | hexamethyldisilazane |
| HOAc | acetic acid |
| HOBt | hydroxybenzotriazole |
| HPLC | high pressure liquid chromatography |

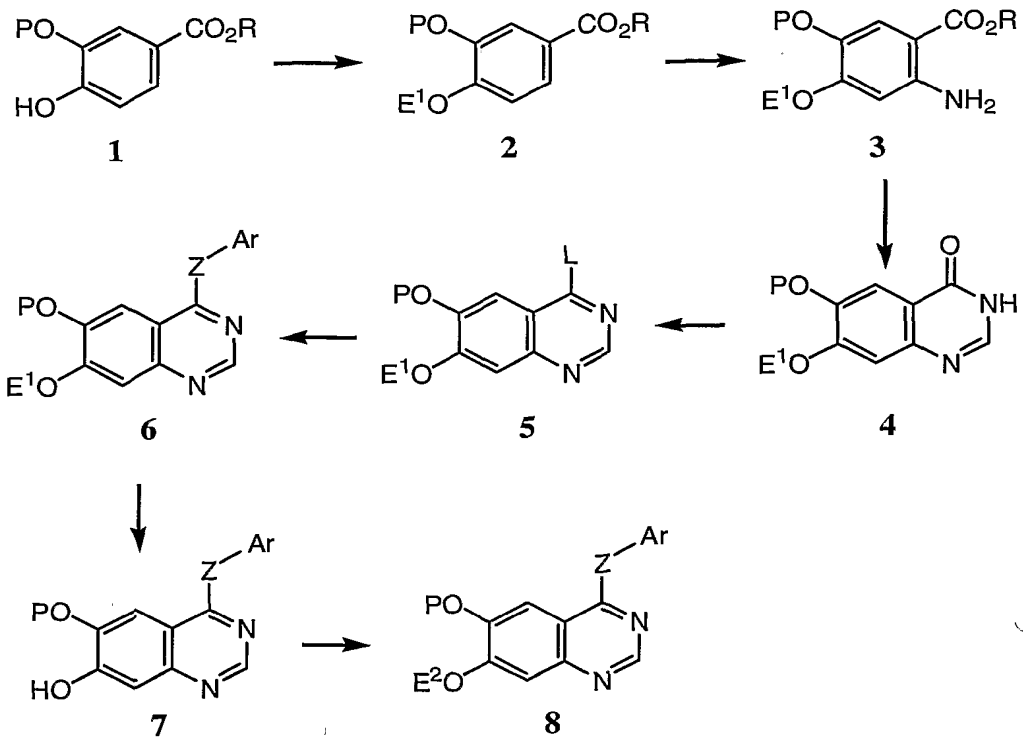
| Abbreviation | Meaning |
|---|---|
| L | liter(s) |
| M | molar or molarity |
| m | multiplet |
| Me | methyl |
| mesyl | methanesulfonyl |
| mg | milligram(s) |
| MHz | megahertz (frequency) |
| Min | minute(s) |
| mL | milliliter(s) |
| mM | millimolar |
| mmol | millimole(s) |
| mol | mole(s) |
| MS | mass spectral analysis |
| MTBE | methyl t-butyl ether |
| N | normal or normality |
| NBS | N-bromosuccinimide |
| NCS | N-chlorosuccinimide |
| nM | nanomolar |
| NMO | N-methylmorpholine oxide |
| NMR | nuclear magnetic resonance spectroscopy |
| PEG | polyethylene glycol |
| pEY | poly-glutamine, tyrosine |
| Ph | phenyl |
| PhOH | phenol |
| PfP | pentafluorophenol |
| PfPy | pentafluoropyridine |
| PPTS | Pyridinium p-toluenesulfonate |
| Py | pyridine |
| PyBroP | bromo-tris-pyrrolidino-phosphonium hexafluorophosphate |
| q | quartet |

| Abbreviation | Meaning |
|---|---|
| RT | Room temperature |
| Sat'd | saturated |
| s | singlet |
| s- | secondary |
| t- | tertiary |
| t or tr | triplet |
| TBDMS | t-butyldimethylsilyl |
| TES | triethylsilane |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TMOF | trimethyl orthoformate |
| TMS | trimethylsilyl |
| tosyl | p-toluenesulfonyl |
| Trt | triphenylmethyl |
| uL | microliter(s) |
| uM | Micromole(s) or micromolar |

**Synthesis of Compounds**

**[0279]** Schemes 1 and 2 depict general synthetic routes for compounds of the invention and are not intended to be limiting. More specifically, Scheme 1 depicts synthesis of quinazoline compounds, and Scheme 2 depicts synthesis of quinoline compounds. Specific examples are described subsequently to these general synthetic descriptions so as to allow one skilled in the art to make and use either quinazolines or quinolines of the invention.

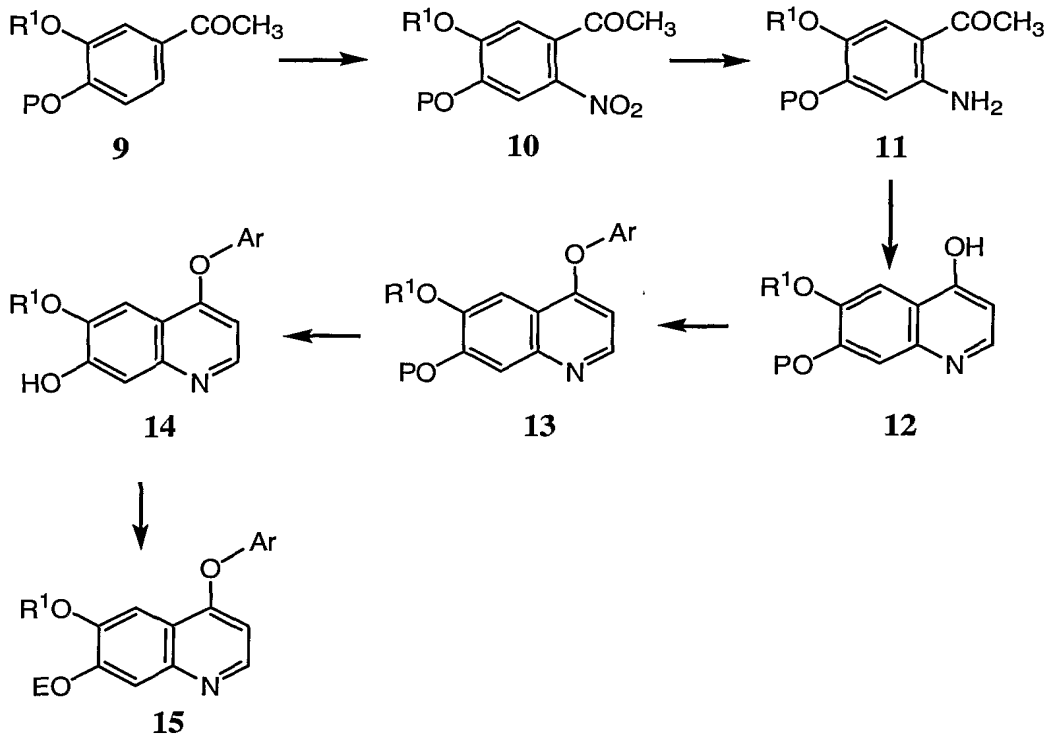
Scheme 1




[0280] Referring to Scheme 1, a benzoic ester **1**, where R is typically but not necessarily a methyl radical and P is typically but not necessarily an alkyl group, is O-alkylated at the oxygen *para* to the carboxylate group with an electrophile to afford a substituted derivative **2**. P is typically a lower alkyl group, but may be a protecting group that is removed later in a synthesis. When P is a lower alkyl group it may possess functionality initially, or be derivitized to contain such functionality at various stages of the synthesis. The group, $E^1$, may represent either a protecting group, e.g. benzyl, or a group that either has moieties present in compounds of the invention or possesses functionality that serve as a precursors to such groups. Aromatic ring nitration and reduction of the corresponding nitro group are carried out in a regio- and chemoselective manner by methods well known in the art to give anthranilate derivative **3**. Formation of quinazolin-4-one **4** is carried out by methods well known in the art, for example by heating **3** in formamide solution in the presence of ammonium formate or for example by heating directly with formamidine hydrochloride. Introduction of 4-position functionality groups is carried out by methods known in the art. For example, quinazolin-4-one **4** is converted to an intermediate quinazoline **5**, where "L" represents a leaving group, e.g. chlorine. Quinazoline **5** is then converted to **6** by reaction with a range of nucleophiles, e.g. amines, alcohols, and thiols. After formation of **6**, group "Z" is either left "as is" or converted at some subsequent stage to a derivative thereof. For example when Z is -NH-, then the hydrogen on the nitrogen

may optionally be replaced with an alkyl group, or when Z is sulfur, then that sulfur atom may be oxidized to, for example, a sulfone. Structure **6** may represent compounds of the invention or, for example when $E^1$ serves as a protecting group, $E^1$ may be removed to provide phenol **7**. Introduction of a group $E^2$ is carried out by methods well established in the art; for example alkylation with an appropriately derivatized alkyl halide (or mesylate or the like) to give **8** which also represents compounds of the invention.

Scheme 2




**[0281]** Scheme 2 shows a general route used to make exemplary quinolines of the invention. For example, compound **9** contains an alkyl group, $R^1$, a protecting group, P. The arrangement of the protected and alkylated phenolic oxygens may vary from the pattern depicted in compound **9**. Compound **9** is nitrated to provide compound **10**. The nitro group of compound **10** is reduced to give aniline **11**. Compound **11** is treated, for example, with ethyl formate under basic conditions followed by acidification and isolation to form 4-hydroxy quinoline **12**. Quinoline **12** may be converted to compounds of the invention in a number of ways. For example, the 4-oxygen is used as a nucleophile in a nucleophilic aromatic substitution reaction to form quinoline-aryl-ether **13**. In another example, compound **13** is further derivatized, via removal of protecting group P, to afford compound **14**. The 7-hydroxy of compound **14** is alkylated, for example with electrophile E, to provide a compound of the invention. As discussed in relation to Scheme 1,

variations on any of the above steps are possible, and intermediates in these schemes, for example compounds **12**, **13**, and **14** may also be compounds of the invention according to formula **I**. Also, for example, the 4-hydroxy quinoline compound **12** are converted to a corresponding 4-nitrogen or 4-sulfur quinoline using chemistry known in the art to make compounds of the invention, or alternatively the corresponding 4-nitrogen or 4-sulfur quinolines are made via routes analogous to that depicted in Schemes 1 and 2.

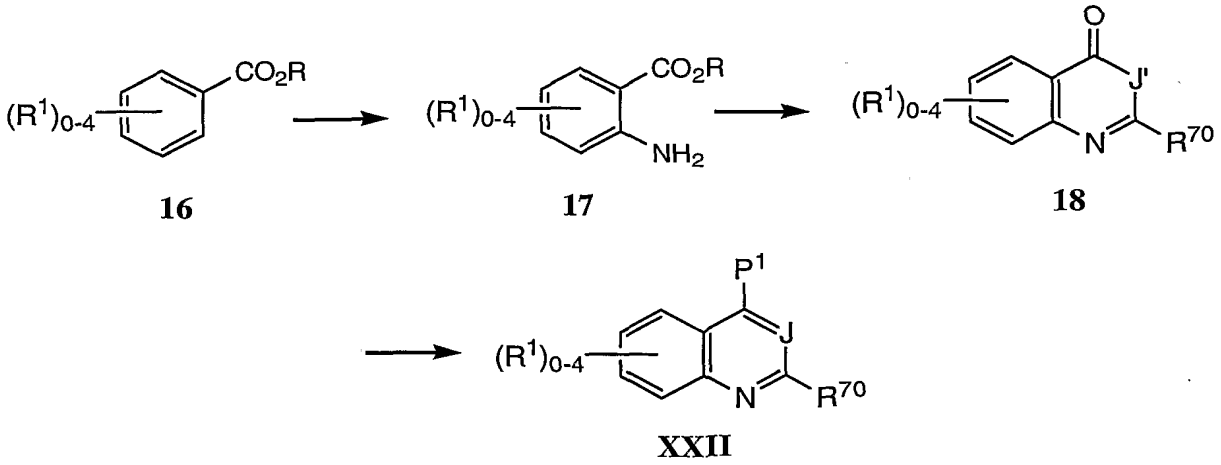
**[0282]** Schemes 1 and 2 are illustrative of quinolines and quinazolines having oxygen substitution at their respective 6- and 7-positions; the invention is not so limited, but rather is intended to encompass quinolines and quinazolines not necessarily having substitution, oxygen or otherwise, at their respective 6- or 7-positions.

**[0283]** Schemes 3 and 4 depict generalized synthetic routes to show the process of the invention to make compounds of formua **XXI** and is not intended to be limiting. More specifically, Schemes 3 and 4 depict convergent syntheses of quinoline and quinazoline compounds as described herein. Specific examples are described subsequently to this general synthetic description so as to allow one of ordinary skill in the art to practice the invention.

**[0284]** Referring to Scheme 3, a benzoic ester **16** for example, where R is typically but not necessarily a methyl radical and $R^1$ is typically but not necessarily one or more alkoxy or hydroxy groups. In a typical synthesis, at least one of $R^1$ within Scheme 3 is a hydroxyl which is converted (or protected )via one or more steps to a group important to the activity of the compounds as described as kinase modulators (in the case that -OH itself is desired in the final compound, then deprotection affords the -OH, *vide supra*). Preferably, but not necessarily, this group is complete once the synthesis of **XXII** is complete. By building desired complexity into **XXII** prior to combination with **XXIII**, convergent syntheses' advantages over serial syntheses are realized more fully. Regioselective aromatic ring nitration, and reduction of the corresponding nitro group, are carried out in a regio- and chemoselective manner by methods well known in the art to give anthranilate derivative **17**. Formation of quinazoline or quinoline 4-one **18** is carried out by methods well known in the art. For example by heating **17** in formamide solution in the presence of ammonium formate, or by heating **17** with formamidine hydrochloride, the quinazoline-4-one analog is made. In another example **17** is treated, for example, with ethyl formate under basic conditions followed by acidification and isolation to form the 4-hydroxy quinoline analog (a tautomer of the 4-one). In this scheme J' represents either carbon or nitrogen atom with

the appropriate number of hydrogens to fill their respective normal valence bonding schemes; J' is a precursor to J. Radicals J and $R^{70}$ are in accord with formula **XXI**. Introduction of 4-position functionality is carried out by methods known in the art. For example, 4-one **18** is converted to **XXII**, where "$P^1$" represents a suitable leaving group (in accord with formula **XXI**), e.g. chlorine (via dehydration/chlorination of **18** to give **XXII**). In another example, a 4-hydroxy analog is converted to a sulfonyl ester, e.g. the trifluoromethane sulfonate.

Scheme 3

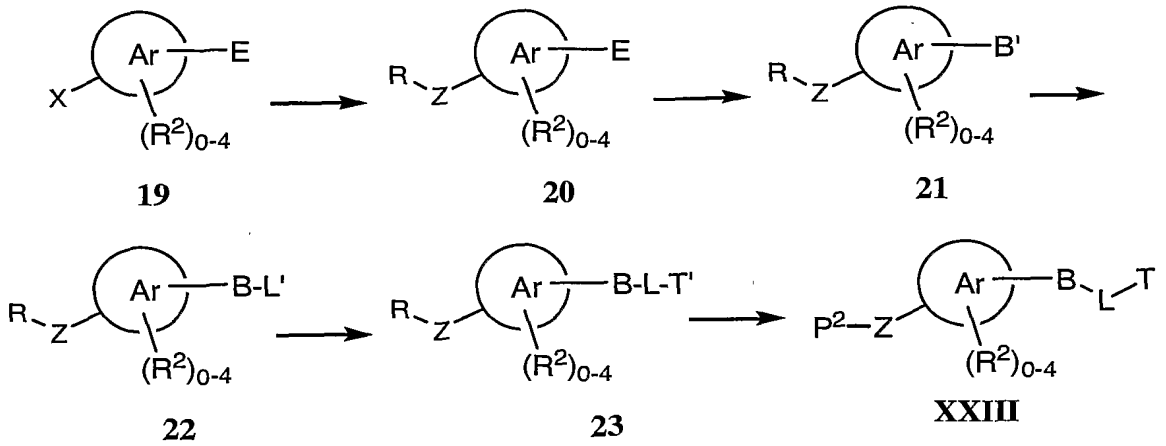



**16** **17** **18**

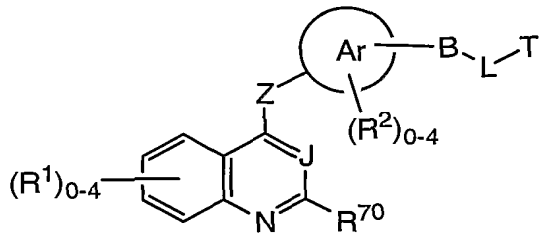
**XXII**

**[0285]** Scheme 4 shows a general route used to make compounds of formula **XXIII**. For example, aromatic compound **19**, where "X" is a leaving group, such as fluorine and "E" is an electron withdrawing group such as nitro, is converted to **20** by reaction with a range of nucleophiles, e.g. amines, alcohols, and thiols (where "Z" is oxygen, nitrogen (substituted or not), or sulfur). In this case, "R" represents a removable group, for example benzyl. In a typical synthesis, after formation of **20**, group "E" is either left "as is" or converted at some subsequent stage to a derivative thereof. In the example depicted, E is converted to B', a precursor to B in accord with formula **XXI**, to make **21**. For example if E is a nitro, then B' could might be an amino group, made via reduction of the nitro group. Structure **21** may be further derivitized by synthesis of –B-L-T in accord with formula **XXI**. In scheme 4, this is depicted as a serial process whereby L', a precursor to L, is introduced to give **22**, followed by introduction of T' (a precursor to T) to give **23**. In some cases, -L-T is preformed and appended to B. One of ordinary skill in the art would appreciate that variations on any of the above steps are possible. Compound **23** is converted to **XXIII** via conversion of T' to T and introduction of $P^2$ (for example, when R is benzyl, removal of the benzyl after completion of –B-L-T).

Scheme 4




[0286] As discussed above, one aspect of the invention encompasses combination of **XXII** and **XXIII** to make compounds of formula **XXI**. Because of the diversity and complexity of compounds described for kinase modulation (*vide supra*), methods of the invention provide advantages to serial synthesis.



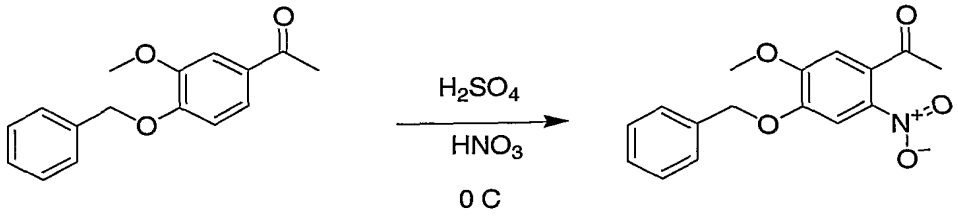

**XXI**

**Examples**

[0287] The following examples serve to more fully describe the manner of using the above-described invention, as well as to set forth the best modes contemplated for carrying out various aspects of the invention. It is understood that these examples in no way serve to limit the true scope of this invention, but rather are presented for illustrative purposes. All references cited herein are incorporated by reference in their entirety. Generally, but not necessarily, each example set out below describes a multi-step synthesis as outlined above.

**Quinoline and Quinazoline Syntheses**

**Example 1**

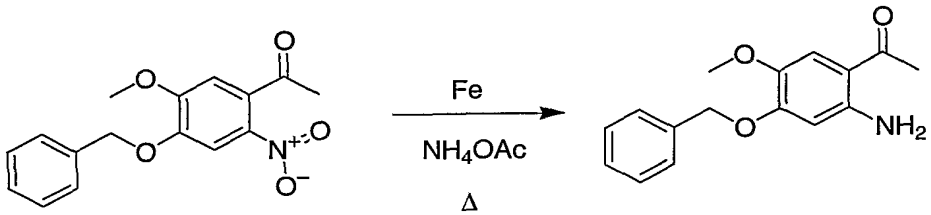



**[0288]** Synthesis of 1-(4-Benzyloxy-5-methoxy-2-nitro-phenyl)-ethanone. 1-(4-Benzyloxy-3-methoxy-phenyl)-ethanone (200 mmol, 51.3 g) dissolved in DCM (750ml) and the mixture cooled to 0° C. Nitric acid (90%, 300 mmol, 14 ml) was added dropwise to the cooled solution over 20 minutes. Sulfuric acid (96.2%, 300 mmol, 8.75 ml) was then added dropwise over 40 minutes at 0° C.

**[0289]** Additional nitric acid (200 mmol, 9.4 ml) was added dropwise over 20 minutes. The reaction mixture was diluted with water (300 ml) and wash with water (3 X 200 ml), Sat. NaHCO3 (4 X 200 ml, or until neutral). The organic layer was dried over Na2SO4 and concentrated.

**[0290]** The crude mixture was recrystallized with DMF to give 22.5 g of the nitro product. The DMF layer was concentrated and recrystallized with ethyl acetate to give additional 8.75g of the product. The ethyl acetate layer was concentrated and purified on silica column using 20% EtOAc/hexanes to gave another 4.75 g of the product. Total yield is 36 g, (~60%). 1H NMR (CDCl3): 7.647 (1H, s), 7.446-7.333 (5H, m), 6.745 (1H, s), 5.210 (2H, s), 3.968 (3H, s), 2.487 (3H, s).

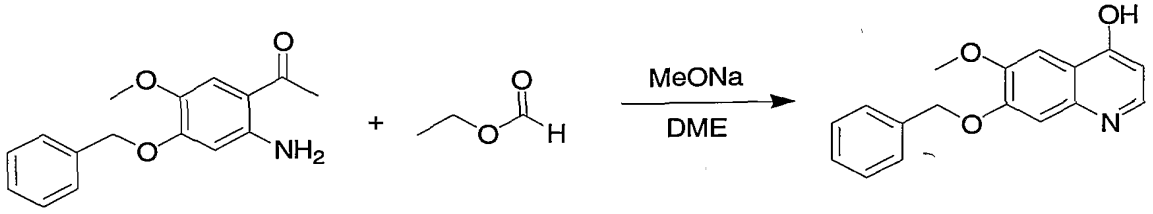
**Example 2**




**[0291]** Synthesis of 1-(2-Amino-4-benzyloxy-5-methoxy-phenyl)-ethanone. A Mixture of iron powder (477 mmol, 27 g), ammonium acetate (500 mmol, 31.g), 1-(4-Benzyloxy-5-methoxy-2-nitro-phenyl)-ethanone (120 mmol, 36 g), toluene (500 ml) and water (500 ml) was refluxed overnight, or until completion. The mixture was filtered through celite and

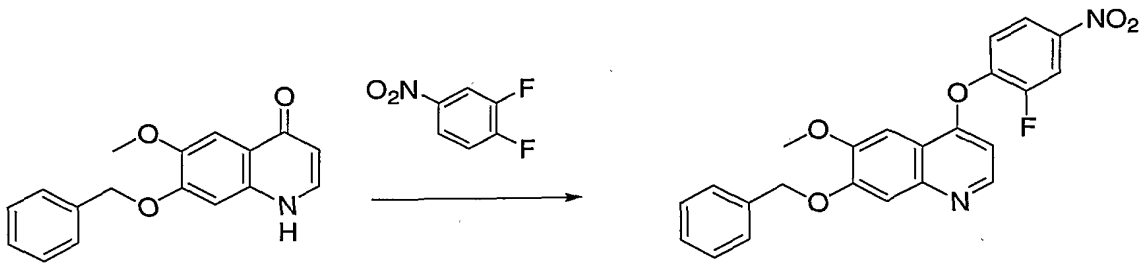
washed with EtOAc. The organic layer was washed with water and Sat. NaCl, dried over Na2SO4, and concentrated to afford the product, 90%. 1H NMR (CDCl3): 7.408-7.298 (5H, m), 7.130 (1H, s), 6.155 (2H, br), 6.104 (1H, s), 5.134 (2H, s), 3.834 (3H, s), 2.507 (3H, s). LC/MS (M+1 = 272).

**Example 3**




**[0292]** Synthesis of 7-Benzyloxy-6-methoxy-quinolin-4-ol. To a solution of 1-(2-Amino-4-benzyloxy-5-methoxy-phenyl)-ethanone (108 mmol, 29.3 g) in DME (700 ml) was added sodium methoxide (432 mmol, 23.35 g). The mixture was stirred for 30 minutes. Ethyl formate (540 mmol, 44 ml) was added and the mixture was stirred overnight. (Additional sodium methoxide may be needed if reaction is not complete as monitored by LC/MS.) After the reaction was completion, the mixture was diluted with water (40 ml) and acidified to neutral with 1M HCl. The precipitate was filtered and washed with water, dried *in vacuo* to afford 22g (72%) of 7-benzyloxy-6-methoxy-quinolin-4-ol. 1H NMR (CDCl3): 10.7 (1H, br), 7.703 (1H, s), 7.493-7.461 (1H, t), 7.431-7.413 (2H, br d), 7.372-7.333 (2H, t), 7.296-7.283 (1H, d), 6.839 (1H, s), 6.212-6.193 (1H, d), 5.212 (2H, s), 3.965 (3H, s). LC/MS (M+1 = 282).

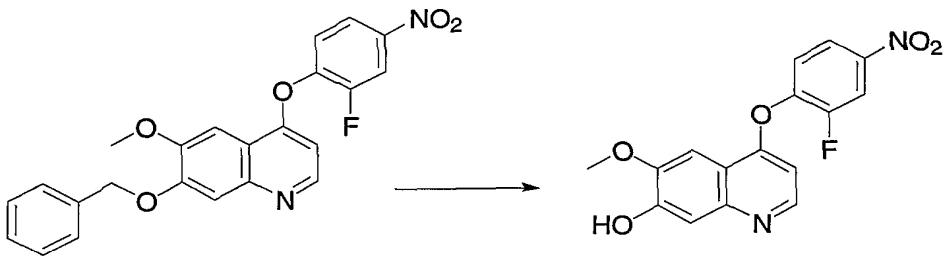
**Example 4**




**[0293]** 7-Benzyloxy-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinoline. To a round bottom flask equipped with a magnetic stir bar was added 7-Benzyloxy-6-methoxy-1H-quinolin-4-one (12.2 g, 43.3 mmol, 1.0 eq.), acetonitrile (150ml), DMF (150ml) and

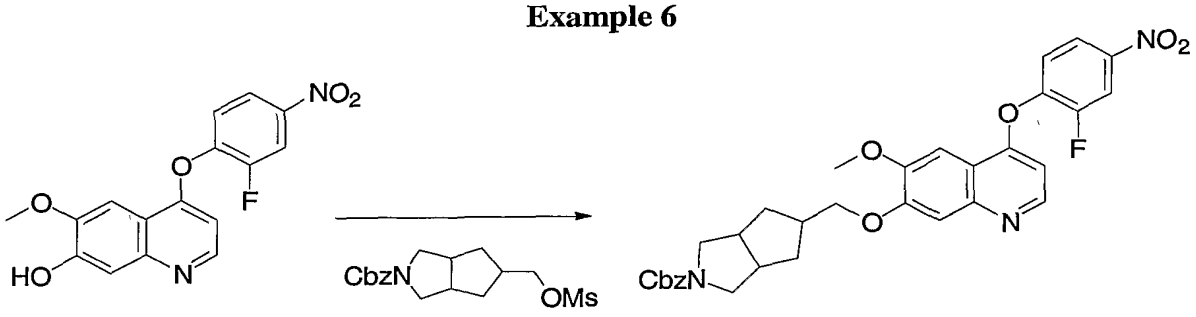
cesium carbonate (28.2 g, 86.5 mmol, 2.0 eq). The mixture was stirred at room temperature for 30 minutes at which time 1,2-difluoro-4-nitro-benzene (7.57 g, 47.6 mmol, 1.1 eq) was added over a 10 minute period. After 2 hours the reaction was complete at which time 75% of the MeCN and DMF was removed and the resulting solution was poured over into ice water. The solid was filtered and dried and further columned with a biotage system. The eluent was 1:3 ethyl acetate/hexane. Removal of the solvent afforded 7-Benzyloxy-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinoline as a pale green solid (7.4 g, 41% yield). $^1$H NMR (400 MHz, $CDCl_3$): 8.53 (d, 1H), 8.42 (dd, 1H), 8.16 (m, 1H), 7.5 (m, 8H), 6.76 (d, 1H), 5.31 (s, 2H), 3.92 (s, 3H); MS (EI) for $C_{23}H_{27}FN_2O_5$: 421 ($MH^+$).

**Example 5**



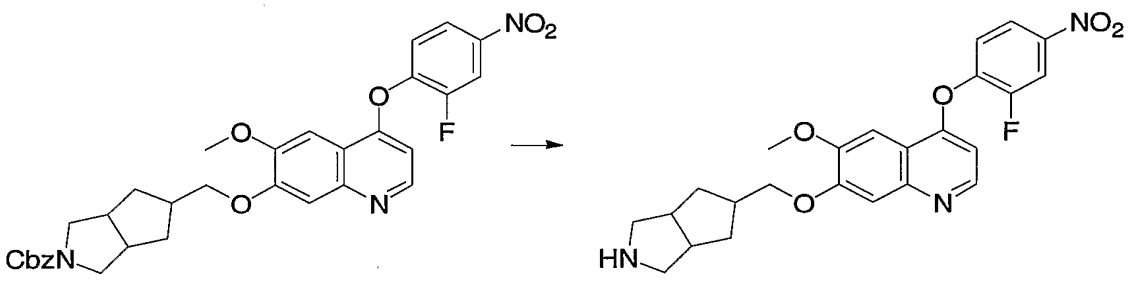

**[0294]** 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-ol. To a round bottom flask equipped with a magnetic stir bar was added 7-benzyloxy-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinoline (2.9 g, 6.9 mmol, 1.0eq) and 33% HBr in acetic acid (30 ml). The mixture was stirred at room temperature for 3 hours and diluted with ether to give a pale white solid. The solid was filtered, washed with ether and dried to yield 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-ol as a pale white solid (2.74 g, 97.5% yield). $^1$H NMR (400 MHz, $CDCl_3$): 11.89 (bs, 1H), 8.87 (d, 1H), 8.57 (d, 1H), 8.30 (d, 1H), 7.89 (m, 1H), 7.73 (s, 1H), 7.55 (s, 1H), 4.03 (s, 3H); MS (EI) for $C_{16}H_{11}FN_2O_5$: 421 ($M+H^+$).

**Example 6**



[0295] 5-[4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-yloxymethyl]-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester. To a round bottom flask equipped with a magnetic stir bar was added 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-ol (2.74 g, 6.7 mmol, 1.0 eq.), DMA (30ml) and cesium carbonate (6.6 g, 20.2 mmol, 3.0 eq). The mixture was stirred at room temperature for 30 minutes at which time 5-methanesulfonyloxymethyl-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester (2.6 g, 7.3 mmol, 1.1 eq) was added. The reaction was heated to $75^0$ C and allowed to stir overnight. After allowing the reaction to cool to room temperature the reaction was poured into water. The solid was filtered and was then dissolved in EtOAc and washed 2X water, 1X brine and dried over $NaSO_4$. The solvent was removed to yield 5-[4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-yloxymethyl]-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester as a cream solid (3.7 g, 94% yield). $^1$H NMR (400 MHz, $CDCl_3$): 8.55 (d, 1H), 8.15 (d, 1H), 8.09 (d, 1H), 7.32 (m, 8H), 6.52 (d, 1H), 5.11 (d, 2H), 4.13 (d, 2H), 3.95 (s, 3H), 3.57 (m, 2H), 3.43 (m, 2H), 2.93 (m, 3H), 2.16 (m, 2H), 1.39 (m, 2H); MS (EI) for $C_{32}H_{30}FN_3O_7$: 588 ($M+H^+$).

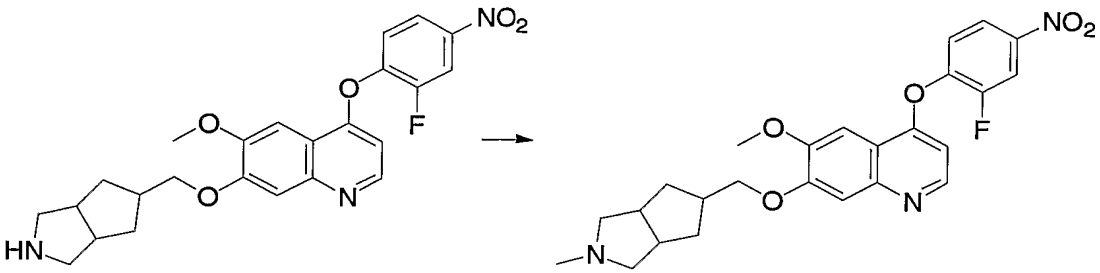
**Example 7**




[0296] 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinoline. To a round bottom flask equipped with a magnetic stir bar was added 5-[4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-yloxymethyl]-hexahydrocyclopenta-[c]pyrrole-2-carboxylic acid benzyl ester (2.5 g, 4.1 mmol, 1.0eq), 33% HBr in acetic acid (5 ml) and acetic acid (5 ml). The mixture was stirred at room temperature for 1 hour and diluted with EtOAc to give a pale orange solid. The solid was filtered, washed with EtOAc and dried, giving 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinoline (2.1 g, 95% yield). $^1$H NMR (400 MHz, $CDCl_3$): 8.83 (d, 1H), 8.32 (m, 2H), 8.02 (s, 1H), 7.76 (t, 1H), 7.65 (s, 1H), 6.89 (d,

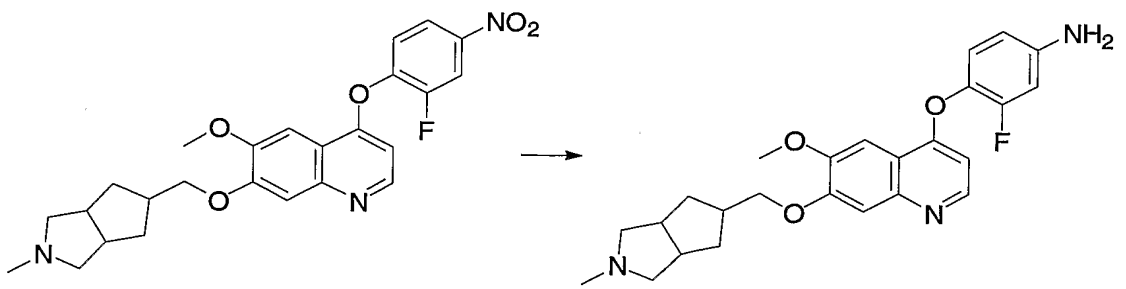
1H), 5.3 (d, 2H), 4.11 (m, 3H), 3.26 (m, 4H), 2.95 (m, 2H), 2.68 (m, 3H), 2.36 (m, 2H), 1.68 (m, 2H); MS (EI) for $C_{24}H_{24}FN_3O_5$: 454 ($M+H^+$).

**Example 8**



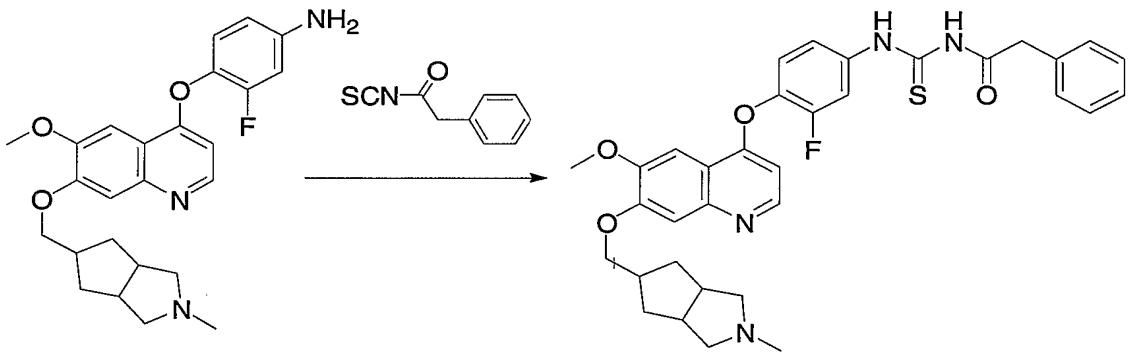
**[0297]** 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinoline. To a round bottom flask equipped with a magnetic stir bar was added 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinoline (2.1 g, 3.9 mmol, 1.0 eq.) and acetonitrile/water 1:1 (5ml, 5ml). The reaction mixture was then cooled to $0^0$ C and 37% solution of formaldehyde in water was added (0.2 g, 7.8 mmol, 2.0 eq). While keeping the temperature at $0^0$C $Na(OAc)_3BH$ was added (4.4g, 20.7 mmol, 3.0 eq). After 1 hour the pH was adjusted to 10 and the aqueous was extracted 2 x DCM (100 ml). Removal of the DCM resulted in a white solid. The compound was further purified with a biotage system using an eluent EtOAc and 5% MeOH, affording 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-7-(2-methyl-octahydrocyclopenta-[c]pyrrol-5-ylmethoxy)-quinoline (0.9 g, 50% yield). ). $^1$H NMR (400 MHz, $CDCl_3$): 8.57 (d, 1H), 8.14 (dd, 1H), 8.12 (dd, 1H), 7.41 (s, 2H), 7.34 (t, 1H), 6.54 (d, 1H), 4.19 (d, 2H), 4.01 (s, 3H), 2.61 (m, 4H), 2.43 (m, 1H), 2.33 (s, 3H), 2.11 (m, 4H), 1.32 (m, 2H); MS (EI) for $C_{25}H_{26}FN_3O_5$: 468 ($M+H^+$).

**Example 9**



[0298] 3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenylamine. To a par hydrogenation reaction vessel was added 4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinoline (0.800 g, 1.6 mmol, 1.0 eq.), DMF (50 ml), EtoAc (50ml), MeOH (50ml), TEA (5ml) and 10% Pd/C (200 mg). The vessel was placed on the par hydrogenator at 35 psi overnight. The Pd was filtered and the solvent removed to give 3-fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenylamine as an off yellow solid (0.78 g, 99% yield). $^1$H NMR (400 MHz, $CDCl_3$): 8.45 (d, 1H), 7.57 (s, 1H), 7.36 (s, 1H), 7.05 (t, 1H), 6.54 (m, 2H), 6.39 (d, 1H), 4.16 (d, 2H), 4.01 (s, 3H), 3.81 (m, 3H), 2.61 (m, 3H), 2.41 (m, 1H), 2.29 (s, 3H), 2.23 (m, 2H), 1.32 (m, 2H); MS (EI) for $C_{25}H_{28}FN_3O_3$: 438 ($M+H^+$).

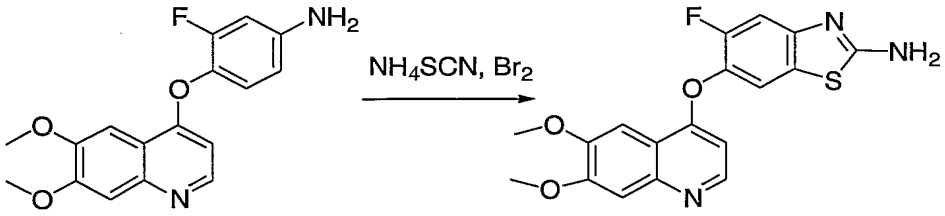
**Example 10**




[0299] 1-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea. To a round bottom flask equipped with a magnetic stir bar was added 3-fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenylamine (0.78 mg, 1.7 mmol, 1.0 eq.), toluene (10ml), ethanol (10ml) and phenyl-acetyl isothiocyanate (1.64 g, 9.2 mmol, 4.5 eq). The reaction mixture was stirred at room temperature overnight. After removal of the solvent the product was purified with a biotage system using an eluent EtOAc and 4% TEA (2L) then EtOAc, 4% TEA, 1% MeOH (1L). The solvent was removed to give 1-{3-fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea (0.5 g, 50% yield). $^1$H NMR (400 MHz, DMSO): 8.48 (d, 1H), 7.92 (dd, 1H), 7.53 (s, 1H), 7.40 (m, 4H), 7.33 (d, 2H), 7.23 (m, 2H), 6.54 (d, 2H), 6.39 (d, 1H), 4.21 (d, 2H), 4.02 (s, 3H), 3.81 (m, 3H),

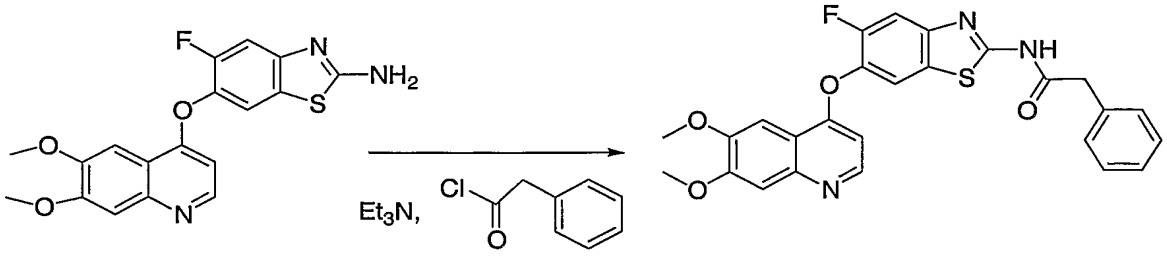
2.87 (d, 2H), 2.73 (m, 4H), 2.53 (m, 1H), 2.27 (m, 2H), 2.01 (s, 3H), 1.36 (m, 2H); MS (EI) for $C_{34}H_{35}FN_4O_4S$: 615 ($M+H^+$).

**Example 11**




**[0300]** 6-(6,7-Dimethoxy-quinolin-4-yloxy)-5-fluoro-benzothiazol-2-ylamine. 4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylamine (1.00g, 3.18mmol) was dissolved in AcOH (8.0ml), to which was added $NH_4SCN$ (486mg, 6.38mmol) and the mixture cooled in an ice bath. $Br_2$ (0.33ml, 6.42mmol) in AcOH (0.33ml) was added dropwise with stirring. After addition was complete, the reaction mixture was stirred at room temperature. After one hour, more $NH_4SCN$ (1.0g, 13.1mmol) was added, followed by more $Br_2$ (0.33ml, 6.42mmol) in AcOH (0.33ml), dropwise with stirring. The reaction mixture was then heated to reflux for several minutes. Upon cooling to room temperature, solids were filtered and washed with AcOH, followed by $H_2O$. The volume of the filtrate was reduced *in vacuo* and the pH adjusted to pH 9-10 with 1.0N NaOH. The resulting solids were filtered, washed with $H_2O$, and dried under high vacuum to give 6-(6,7-dimethoxy-quinolin-4-yloxy)-5-fluoro-benzothiazol-2-ylamine (568mg, 48%). $^1$H-NMR (400MHz, DMSO): 8.45 (d, 1H), 7.82 (d, 1H), 7.73 (br s, 2H), 7.53 (s, 1H), 7.38 (m, 2H), 6.44 (d, 1H), 3.94 (s, 6H). LC/MS Calcd for $[M+H]^+$ 372.1, found 372.2

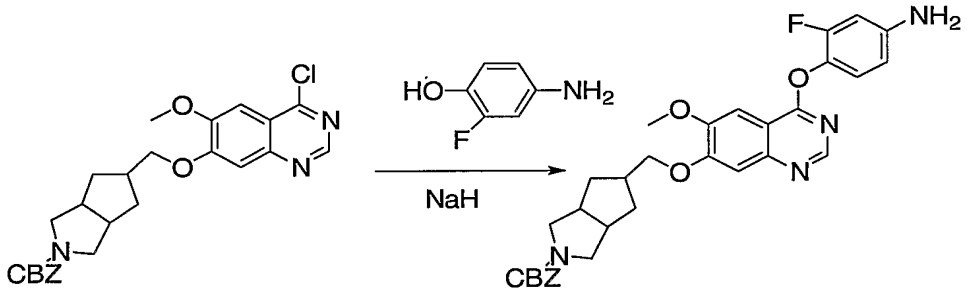
**Example 12**




**[0301]** N-[6-(6,7-Dimethoxy-quinolin-4-yloxy)-5-fluoro-benzothiazol-2-yl]-2-phenyl-acetamide. 6-(6,7-dimethoxy-quinolin-4-yloxy)-5-fluoro-benzothiazol-2-ylamine (95mg,

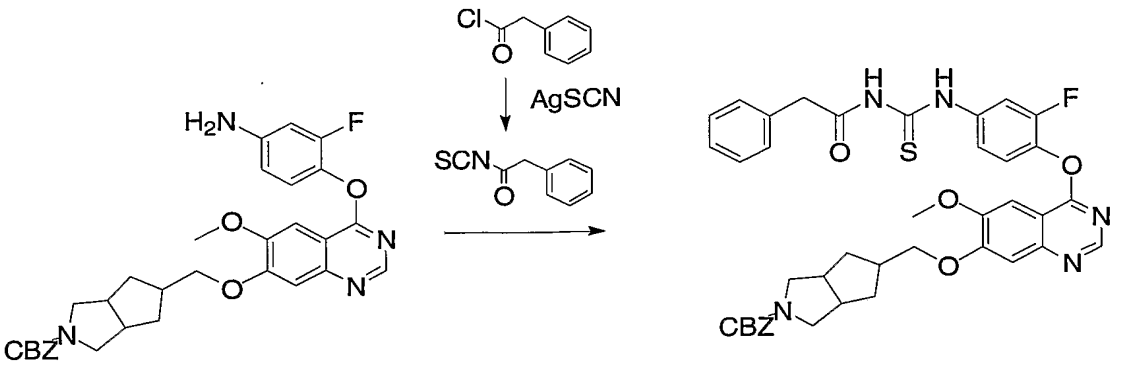
0.25mmol), $Et_3N$ (0.10ml, 0.72mmol), phenylacetyl chloride (0.044ml, 0.33mmol), and THF (1.0ml) were combined and stirred at room temperature for 1 hr. Additional phenylacetyl chloride (0.044ml, 0.33mmol) was added and the mixture heated to reflux for 1-2 hrs. After cooling to room temperature, the reaction mixture was diluted with 1:1 AcCN:$H_2O$ (1.0ml) and the resulting solids filtered, washed with 1:1 AcCN:$H_2O$ and dried under high vacuum to give N-[6-(6,7-dimethoxy-quinolin-4-yloxy)-5-fluoro-benzothiazol-2-yl]-2-phenyl-acetamide (72mgs, 59%). $^1$H-NMR (400MHz, DMSO): 12.80 (s, 1H), 8.54 (d, 1H), 8.18 (d, 1H), 7.91 (d, 1H), 7.60 (s, 1H), 7.45 (s, 1H), 7.34 (m, 4H), 7.28 (m, 1H), 6.60 (d, 1H), 3.98 (s, 3H), 3.96 (s, 3H), 3.86 (s, 2H). LC/MS Calcd for $[M+H]^+$ 490.1, found 490.0.

**Example 13**



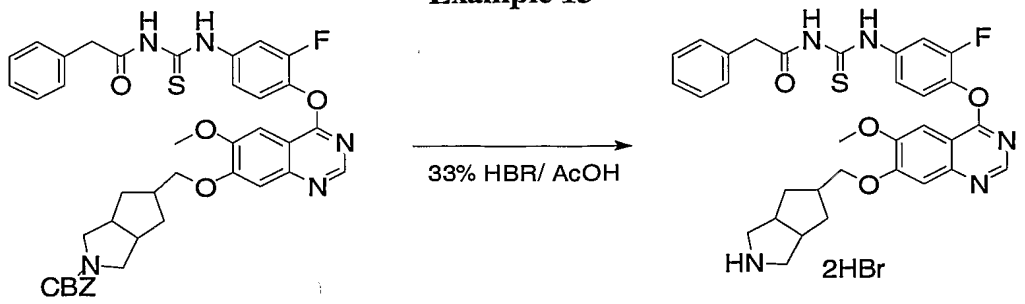

**[0302]** 5-[4-(4-Amino-2-fluoro-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester. 4-Amino-2-fluoro-phenol (1.53g, 12.0mmol) was dissolved in dry DMF (30ml) to which was added 60% NaH (774mg, 19.3mmol). After the mixture was stirred at room temperature for several minutes, a suspension of 5-(4-chloro-6-methoxy-quinazolin-7-yloxymethyl)-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester (4.70g, 6.7mmol) in dry DMF (40ml) was added. The reaction mixture was stirred at room temperature for 1-2 hrs, then diluted with EtOAc and washed with sat'd $NaHCO_3$ (3x), $H_2O$ (1x), sat'd NaCl (1x), dried ($Na_2SO_4$), and concentrated *in vacuo* to give crude 5-[4-(4-amino-2-fluoro-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester (5.6g, ~100%) which was used in the next reaction without further purification. $^1$H-NMR (400MHz, DMSO): 8.50 (s, 1H), 7.48 (s, 1H), 7.34 (m, 5H), 7.28 (m, 1H), 7.02 (t, 1H), 6.48 (dd, 1H), 6.40 (dd, 1H), 5.40 (br s, 2H), 5.05 (s, 2H), 4.16 (d, 2H), 3.92 (s, 3H), 3.48 (m, 2H), 3.30 (m, 2H), 2.65 (m, 2H), 2.52 (m, 1H), 2.10 (m, 2H), 1.30 (m, 2H). LC/MS Calcd for $[M+H]^+$ 559.2, found 559.4.

**Example 14**



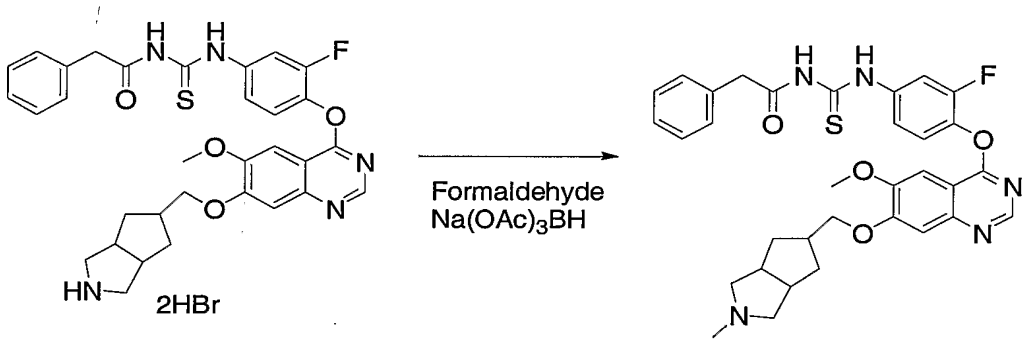

**[0303]** 5-{4-[2-Fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-6-methoxy-quinazolin-7-yloxymethyl}-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester. Phenylacetyl chloride (2.65ml, 20.0mmol) and AgSCN (4.92g, 29.6mmol) were combined in dry toluene (50ml) and heated to reflux for 2 hrs. The reaction mixture was allowed to cool to room temperature, the solids were filtered through celite and the filtrate concentrated *in vacuo*. The resulting oil was combined with 5-[4-(4-amino-2-fluoro-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester (5.6g, 10mmol) in 1:1 EtOH:toluene (100ml) and the mixture stirred at room temperature for 1-2 hrs. The reaction mixture was diluted with EtOAc and washed with sat'd $NaHCO_3$ (3x), $H_2O$ (1x), sat'd NaCl (1x), dried ($Na_2SO_4$), and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (3:1 EtOAc:hexanes) to give 5-{4-[2-fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-6-methoxy-quinazolin-7-yloxymethyl}-hexahydrocyclopenta[c]pyrrole-2-carboxylic acid benzyl ester (3.61g, 49%) as a dark brown foam. $^1$H-NMR (400MHz, DMSO): 12.44 (s, 1H), 11.80 (s, 1H), 8.54 (s, 1H), 7.90 (m, 1H), 7.53 (s, 1H), 7.48 (m, 2H), 7.38 (s, 1H), 7.34 (m, 7H), 7.28 (m, 3H), 5.05 (s, 2H), 4.16 (d, 2H), 3.94 (s, 3H), 3.72 (s, 2H), 3.48 (m, 2H), 3.30 (m, 2H), 2.65 (m, 2H), 2.52 (m, 1H), 2.10 (m, 2H), 1.30 (m, 2H). LC/MS Calcd for $[M+H]^+$ 736.2, found 736.0.

**Example 15**



**[0304]** 1-{3-Fluoro-4-[6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea, dihydrobromide salt. 5-{4-[2-Fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-6-methoxy-quinazolin-7-yloxymethyl}-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester (3.3g, 4.5mmol) was dissolved in AcOH (70ml) to which was added 33%HBr in AcOH (12ml). The reaction mixture was stirred at room temperature for 1 hr, diluted with $Et_2O$ (1000ml) and the resulting solids filtered, washed with $Et_2O$, and dried under high vacuum to give the 1-{3-fluoro-4-[6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea, dihydrobromide salt (3.4g, 100%). $^1$H-NMR (400MHz, DMSO): 12.42 (s, 1H), 11.80 (s, 1H), 8.84 (br s, 2H), 8.64 (s, 1H), 7.92 (m, 1H), 7.59 (s, 1H), 7.49 (m, 2H), 7.41 (s, 1H), 7.33 (m, 4H), 7.27 (m, 1H), 4.17 (d, 2H), 3.95 (s, 3H), 3.73 (s, 2H), 3.17 (m, 2H), 3.10 (m, 2H), 2.83 (m, 2H), 2.45 (m, 1H), 2.15 (m, 2H), 1.30 (m, 2H). LC/MS Calcd for $[M+H]^+$ 602.2, found 602.1.

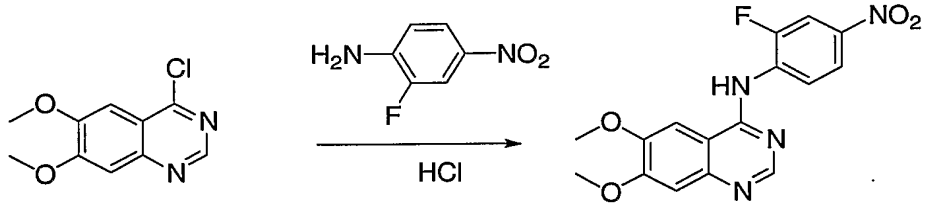
**Example 16**




**[0305]** 1-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea. 1-{3-Fluoro-4-[6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea, dihydrobromide salt (3.4g, 4.5mmol) was dissolved in in a combination of AcCN (100ml), $H_2O$ (30ml), and AcOH (2.45ml). Formaldehyde (37% in $H_2O$, 855ml, 10.5mmol) was added and the mixture cooled in an ice bath. $Na(OAC)_3BH$ (2.99g, 14.1mmol) was added and the reaction mixture was stirred at 0 C for 1 hr, followed by stirring at room temperature for 2 hrs. The reaction mixture was neutralized with the addition of sat'd $NaHCO_3$ and then concentrated *in vacuo*. The resulting aqueous mixture was extracted with $CH_2Cl_2$ (3x). The combined extractions were washed with sat'd $NaHCO_3$ (1x), sat'd NaCl (1x), dried ($Na_2SO_4$), and concentrated *in vacuo*. The

resulting residue was purified by flash chromatography (100% EtOAc, followed by 4% $Et_3N$ in EtOAc) to give the free base of 1-{3-fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea (1.13g, 40%). The free base was converted to the HCl salt by dissolving the free base in a mixture of 1:1 AcCN:$H_2O$ containing 2-3 equivalents of 1 N HCl and lyophilizing to give the HCl salt of 1-{3-fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea as a white solid. $^1$H-NMR (400MHz, DMSO): 12.44 (s, 1H), 11.83 (s, 1H), 10.24 (br s, 1H), 8.59 (s, 1H), 7.93 (m, 1H), 7.59 (s, 1H), 7.50 (m, 2H), 7.42 (s, 1H), 7.36 (m, 4H), 7.30 (m, 1H), 4.20 (m, 2H), 3.95 (s, 3H), 3.73 (s, 2H), 3.39 (m, 2H), 3.06 (m, 2H), 2.95-2.77 (m, 5H), 2.35 (m, 1H), 2.15 (m, 2H), 1.45 (m, 2H). LC/MS Calcd for $[M+H]^+$ 616.2, found 616.2. Alternatively, the free base was converted to the acetate salt by dissolving the free base in a mixture of MeOH and $CH_2Cl_2$ to which was added 3 equivalents of acetic acid. The resulting mixture was concentrated *in vacuo* and the resulting residue lyophilized from 1:1 AcCN:$H_2O$ to give the acetate salt of 1-{3-fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea as a white solid. $^1$H-NMR (400MHz, $CDCl_3$): d 12.45 (s, 1H), 8.65 (s, 1H), 7.98 (dd, 1H), 7.50 (s, 1H), 7.40 (m, 4H), 7.29 (m, 4H), 4.17 (d, 2H), 4.05 (s, 3H), 3.75 (s, 2H), 2.93 (m, 2H), 2.80 (m, 2H), 2.72 (m, 2H), 2.53 (s, 3H), 2.47 (m, 1H), 2.25 (m, 2H), 2.02 (s, 3H), 1.35 (m, 2H). LC/MS Calcd for $[M+H]^+$ 616.2, found 616.2.

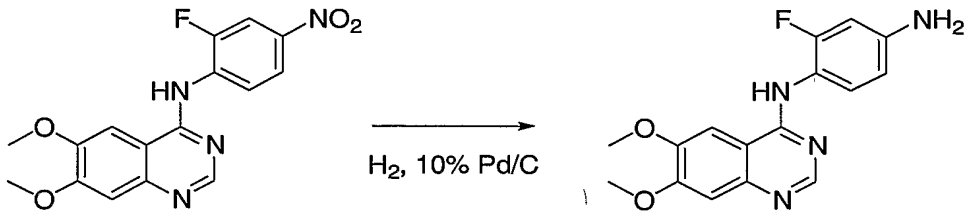
**Example 17**




**[0306]** (6,7-Dimethoxy-quinazolin-4-yl)-(2-fluoro-4-nitro-phenyl)-amine. A mixture of 4-chloro-6,7-dimethoxy-quinazoline (548mg, 2.4mmol), 2-fluoro-4-nitro-phenylamine (392mg, 2.5mmol), AcCN (10ml), and conc'd HCl (0.050ml) was heated to reflux for several hrs. After the reaction mixture was allowed to cool to room temperature, the resulting solids were filtered, washed with AcCN and air-dried to give (6,7-dimethoxy-quinazolin-4-yl)-(2-fluoro-4-nitro-phenyl)-amine (673mgs, 80%). $^1$H-NMR (400MHz,

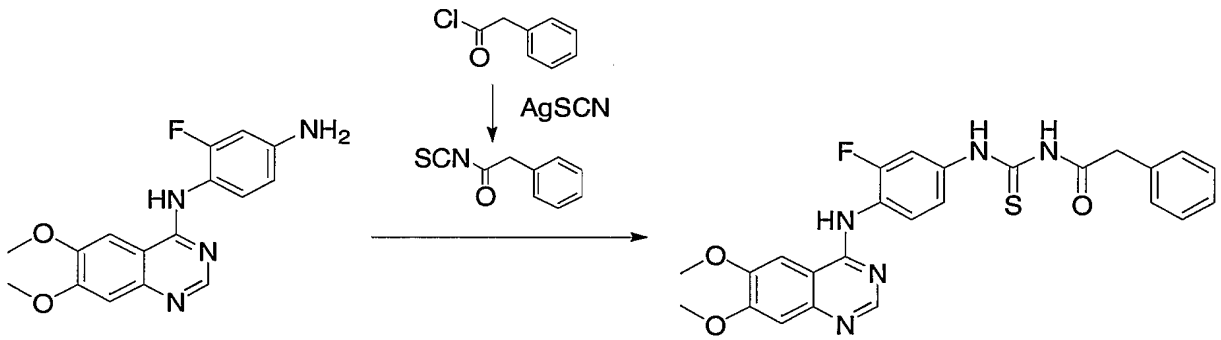
DMSO): 12.18 (br s, 1H), 8.91 (s, 1H), 8.45 (s, 1H), 8.36 (dd, 1H), 8.24 (dd, 1H), 7.91 (dd, 1H), 7.44 (s, 1H), 4.04 (s, 3H), 4.02 (s, 3H). LC/MS Calcd for $[M+H]^+$ 345.1, found 345.4.

**Example 18**




**[0307]** N[1]-(6,7-Dimethoxy-quinazolin-4-yl)-2-fluoro-benzene-1,4-diamine. (6,7-Dimethoxy-quinazolin-4-yl)-(2-fluoro-4-nitro-phenyl)-amine (673mg, 1.95mmol) was dissolved in a combination of DMF (20ml) and MeOH (20ml), to which was added 10% Pd/C (227mg). The mixture was shaken under an atmosphere of $H_2$ on a Parr hydrogenator at 40psi for 3hrs. The reaction mixture was filtered through celite and the filtrate concentrated *in vacuo*. The resulting residue was triturated in EtOAc/$Et_2O$. The resulting solids were filtered, washed with $Et_2O$, and dried under vacuum to give N[1]-(6,7-dimethoxy-quinazolin-4-yl)-2-fluoro-benzene-1,4-diamine (398mg, 65%) which was used in the next reaction without further purification. $^1$H-NMR (400MHz, DMSO): 10.80 (br s, 1H), 10.30 (br s, 1H), 8.63 (s, 1H), 8.15 (s, 1H), 7.33 (s, 1H), 7.15 (m, 1H), 6.45 (m, 1H), 3.96 (s, 6H). LC/MS Calcd for $[M+H]^+$ 315.1, found 315.4.

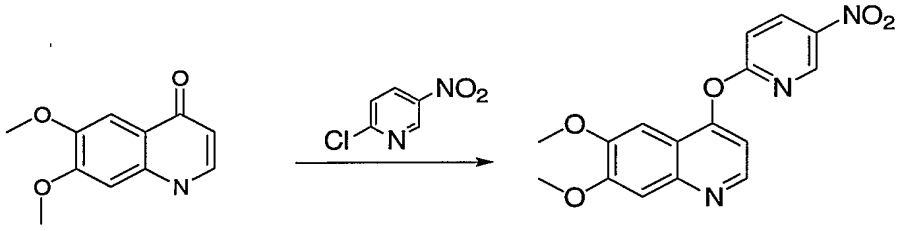
**Example 19**




**[0308]** 1-[4-(6,7-Dimethoxy-quinazolin-4-ylamino)-3-fluoro-phenyl]-3-phenylacetyl-thiourea. Phenylacetyl chloride (0.18ml, 1.4mmol) and AgSCN (338mg, 2.0mmol) were

combined in dry toluene (5ml) and heated to reflux for 2 hrs. The reaction mixture was allowed to cool to room temperature, the solids were filtered through celite and the filtrate concentrated *in vacuo*. The resulting oil was combined with $N^1$-(6,7-Dimethoxy-quinazolin-4-yl)-2-fluoro-benzene-1,4-diamine (398mg, 1.3mmol) in 1:1:2 EtOH:toluene:MeOH (30ml) and the mixture stirred at room temperature overnight. The resulting solids were filtered and washed with toluene, followed by hexanes. The solids were dissolved/suspended in a mixture of EtOAc/MeOH. Insoluble material was filtered and the filtrate concentrated *in vacuo*. The resulting solids were once again dissolved/suspended in a mixture of EtOAc/MeOH. In soluble material was filtered and the filtrate concentrated *in vacuo* to give 1-[4-(6,7-dimethoxy-quinazolin-4-ylamino)-3-fluoro-phenyl]-3-phenylacetyl-thiourea (105mg, 17%). $^1$H-NMR (400MHz, DMSO): 12.53 (s, 1H), 11.86 (s, 1H), 11.44 (br s, 1H), 8.81(s, 1H), 8.25 (s, 1H), 7.94 (dd, 1H), 7.54 (m, 2H), 7.16 (m, 5H), 7.10 (m, 1H), 4.02 (s, 6H), 3.84 (s, 2H). LC/MS Calcd for $[M+H]^+$ 492.1, found 492.4.

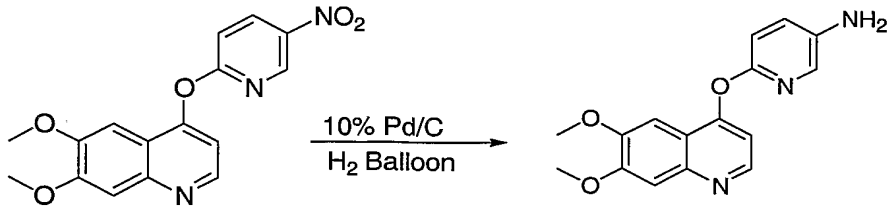
**Example 20**




**[0309]** 6,7-Dimethoxy-4-(5-nitro-pyridin-2-yloxy)-quinoline. To a round bottom flask equipped with a magnetic stir bar was added 6,7-dimethoxy-1*H*-quinolin-4-one (1.8 g, 8.77 mmol, 1.0 eq.), anhydrous acetonitrile (90 mL) and $Cs_2CO_3$ (3.13 g, 9.65 mmole, 1.1 eq.). The reaction mixture was stirred at room temperature for 5 minutes. Then, 2-Cl-5-nitropyridine (1.53 g, 9.65 mmol, 1.1 eq.) was added. The reaction mixture was stirred at room temperature for 16 hours. The solids were then filtered off and the filtrate was concentrated via rotary evaporation. The resulting material was taken up in EtOAc, and again the solids were filtered off. The EtOAc filtrate was concentrated. Purification was done on Biotage with solvent system EtOAc 100%. The collected pure fractions were concentrated and dried on high vacuum overnight to give 6,7-dimethoxy-4-(5-nitro-pyridin-2-yloxy)-quinoline as a yellow foam solid (0.902 g, 31.4% yield). $^1$H NMR (400

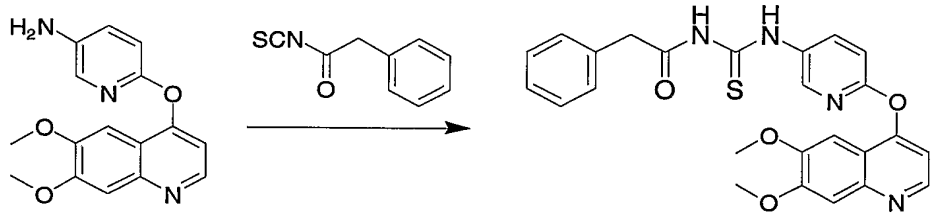
MHz, CDCl3): 9.08 (d, 1H), 8.74 (d, 1H), 8.60 (dd, 1H), 7.49 (s, 1H), 7.26 (d, 1H), 7.16 (s, 1H), 7.07 (d, 1H), 4.06 (s, 3H), 3.95 (s, 3H); MS (EI) for $C_{16}H_{13}N_3O_5$: 328 ($M+H^+$).

**Example 21**




**[0310]** 6-(6,7-Dimethoxy-quinolin-4-yloxy)-pyridin-3-ylamine. To a round bottom flask equipped with a magnetic stir bar was added 6,7-dimethoxy-4-(5-nitro-pyridin-2-yloxy)-quinoline (0.46 g, 1.41 mmol, 1.0 eq.), and THF (10 mL), MeOH (4 mL), DMF (2 mL), and TEA (2 mL). The 6,7-Dimethoxy-4-(5-nitro-pyridin-2-yloxy)-quinoline was dissolved completely in the above solution mixture, and was flushed with nitrogen for at least 5 minutes. The Pd/C (10% by weight) (0.090 g, 20% by weight) was then added. A balloon filled with $H_2$ was connected to the flask after the nitrogen was vacuumed out. The reaction mixture was stirred at room temperature for 4 hours. The palladium was filtered out through Celite, and the filtrated was collected and concentrated via rotary evaporation. The resulting oil-like product was taken up into 5 mL of water and 1 mL of acetonitrile and lyophilized to yield 6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylamine as a light brown solid (0.411 g, 98.1%). $^1H$ NMR (400 MHz, CDCl3): 8.54 (d, 1H), 7.85 (d, 1H), 7.53 (s, 1H), 7.41 (s, 1H), 7.18 (dd, 1H), 6.96 (d, 1H), 6.61 (d, 1H), 4.05 (s, 3H), 4.03 (s, 3H), 3.73 (s, 2H); MS (EI) for $C_{16}H_{15}N_3O_3$: 298 ($M+H^+$).

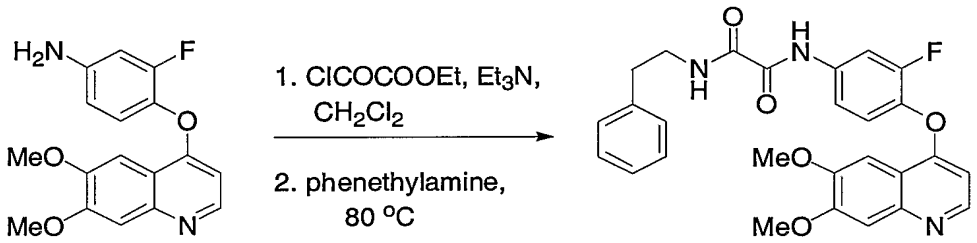
**Example 22**




**[0311]** 1-[6-(6,7-Dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-3-phenylacetyl-thiourea. To a round bottom flask equipped with a magnetic stir bar was added 6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylamine (85 mg, 0.0285 mmol, 1.0 eq.), and Phenyl-acetyl

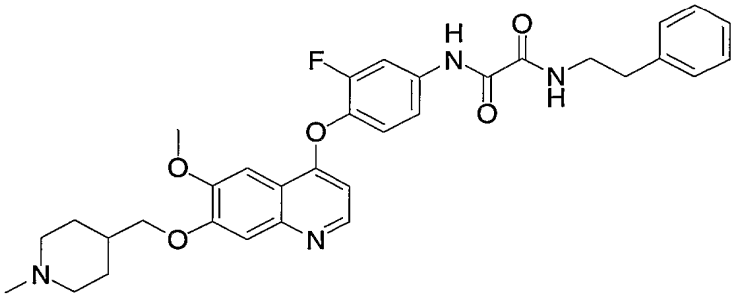
isothiocyanate (256 mg, 1.44 mmol, 5.0 eq.) dissolved in EtOAc/MeOH 50:50 (2 mL). The reaction mixture was sittred at room temperature for 12 hours, and the solvent was evaporated via rotary evaporation. Purification was done on Biotage with solvent system 95% EtOAc, 4% TEA and 1% MeOH. The combined pure fractions were concentrated and dried under vacuum overnight to yield 1-[6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-3-phenylacetyl-thiourea as a light yellow solid (40.4 mg, 29.7%). $^1$H NMR (400 MHz, CDCl3): 8.65 (d, 1H), 8.33 (d, 1H), 8.27 (dd, 1H), 7.35 (m, 7H), 7.15 (d, 1H), 6.92 (d, 1H), 4.05 (s, 3H), 3.99 (s, 3H), 3.76 (s, 2H); MS (EI) for $C_{25}H_{22}N_4O_4S$: 475 ($M+H^+$).

**Example 23**




**[0312]** N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-phenethyl-oxalamide. To a solution of 4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylamine (263 mg, 0.83 mmol) and $Et_3N$ (0.223 ml, 1.67 mmol) in $CH_2Cl_2$ (10 mL) was added dropwise a solution of ethyl oxalyl chloride in $CH_2Cl_2$ (1 mL). The stirring was continued for 0.5 h at rt. The reaction mixture was then washed with aqueous saturated $NaHCO_3$ and dried over $NaSO_4$. Removal of the solvent gave the crude oxamate, which was treated with neat phenethylamine (1.0 g, 8.3 mmol) at 80 °C for 3 h. Purification by flash column chromatography (hexanes:EtOAc = 1:3) gave N-[4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-phenethyl-oxalamide (310 mg, 76%). $^1$H NMR (400 MHz, $CDCl_3$) δ 9.35 (br s, 1 H), 8.70 (d, $J$ = 6.3 Hz, 1 H), 7.83 (dd, $J$ = 11.9, 2.5 Hz, 1 H), 7.60-7.54 (m, 2 H), 7.43 (s, 1 H), 7.38-7.32 (m, 3 H), 7.30-7.20 (m, 4 H), 6.41 (d, $J$ = 5.3 Hz, 1 H), 4.07 (s, 3 H), 4.05 (s, 3 H), 3.67 (dt, $J$ = 7.0, 7.0 Hz, 2 H), 2.92 (t, $J$ = 7.2 Hz, 2 H). LC-MS: 490 $[M+H]^+$

**Example 24**



**[0313]** N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxyl-phenyl}-N'-phenethyl-oxalamide. To a flask containing 7-benzyloxy-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinoline (850 mg, 2.0 mmol) was added 20 mL of 30% HBr in AcOH. The resulted solution was stirred for 4 h at rt; at this time, a large amount of precipitate formed. The crude product was filtered, washed with $Et_2O$ and dried in air, giving 4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-7-hydroxyquinoline (609 mg, 92% yield).

**[0314]** To a solution of the 4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-7-hydroxyquinoline (609 mg, 1.8 mmol) in DMF (9 mL) was added $K_2CO_3$ (1.24 g, 9.0 mmol) and N-Boc-4-piperidinemethanol mesylate (732 mg, 2.5 mmol). The mixture was then stirred at 80 °C for 2.5 h. After it was cooled to rt, the mixture was loaded directly to a Biotage column, and eluted with solvents (hexanes:EtOAc = 1:3). The resulting product, 4-[4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-yloxymethyl]-piperidine-1-carboxylic acid tert-butyl ester, was obtained as a solid (556 mg, 56%).

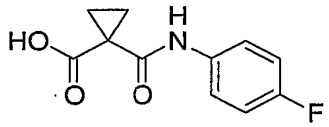
**[0315]** To a solution of 4-[4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-yloxymethyl]-piperidine-1-carboxylic acid tert-butyl ester (305 mg, 0.58 mmol) in $CH_2Cl_2$ (1 mL) was added 0.4 mL of TFA. The reaction mixture was stirred for 1.5 h and the solvents were removed under reduced pressure. The crude product was treated with $NaBH(OAc)_3$ (381 mg, 1.80 mmol) and formaldehyde (0.5 mL, 37% in $H_2O$). The stirring was continued for 12 h. The reaction was quenched with sat. aqueous $NaHCO_3$. 15% NaOH was added until PH = 14. The product was extracted with EtOAc. Removal of the solvent *in vacuo* gave the crude product, 4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinoline, (240 mg, 93%), which was used directly in the next reaction.

**[0316]** To a solution of 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinoline (240 mg, 0.54 mmol) in EtOH (20 mL) was added 10% Pd/C (50

mg). The mixture was then hydrogenated on a Parr hydrogenator (40 psi) for 10 h. AcOH was added to dissolve the intermediate (mostly the hydroxylamine) and the hydrogenation was continued for additional 12 h. LC-MS was used to monitor the reaction progress. The solvents were removed under reduced pressure and the resulting crude product of 3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenylamine (about 220 mg) was used directly in the next reaction.

**[0317]** To a 0 °C solution of 3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenylamine (66 mg, 0.13 mmol) and $Et_3N$ (0.34 mL) in $CH_2Cl_2$ (6 mL) was added slowly ethyl oxalyl chloride (98 mg). The reaction mixture was stirred at rt for 30 min, then diluted with $CH_2Cl_2$ and washed with sat. aqueous $NaHCO_3$. After dried over $MgSO_4$ and concentrated, the crude ethyl oxamate was reacted with phenethylamine (80 mg, 0.64 mmol) at 80 °C for 2 h. Purification by HPLC gave product, N-{3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide (52 mg, 68% yield). $^1H$ NMR (400 MHz) δ 9.38 (br s, 1 H), 8.48 (d, J = 5.2 Hz, 1 H), 7.83 (dd, J = 11.7, 2.6 Hz, 1 H), 7.59 (t, J = 6.2 Hz, 1 H), 7.55 (s, 1 H), 7.40-7.20 (8 H), 6.39 (d, J = 5.3 Hz, 1 H), 4.06 (d, J = 6.6 Hz, 2 H), 4.04 (s, 3 H), 3.67 (q, J = 6.8 Hz, 2 H), 2.98 (br d, J = 11.5 Hz, 2 H), 2.92 (t, J = 7.0 Hz, 2 H), 2.34 (s, 3 H), 2.10-1.80 (m, 5 H), 1.60-1.54 (m, 2 H).

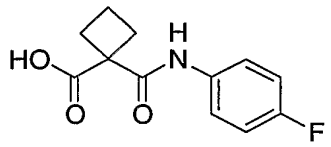
**Example 25**




**[0318]** 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid. The title compound was prepared based on a modified procedure of Shih and Rankin [*Synthetic Communications*, 1996, 26(4), 833-836]: To a mixture of cyclopropane-1,1-dicarboxylic acid (21.2 g, 0.163 mol, 1.0 eq.) in anhydrous THF (200 mL) under nitrogen was added dropwise triethylamine (16.49 g, 0.163 mol, 1.0 eq.) with stirring for 30 minutes at 0°C, followed by the addition of thionyl chloride (19.39 g, 0.163 mol, 1.0 eq.) with stirring for another 30 minutes at 0°C. To the resulting mixture under nitrogen was added dropwise a solution of 4-fluoroaniline (19.92 g, 0.179 mol, 1.1 eq.) in anhydrous THF (100 mL) with stirring for 1.5 hours at 0°C. The reaction mixture was diluted with ethyl acetate and

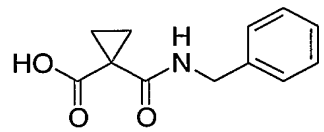
washed with 1N NaOH. The layers were separated, and the ethyl acetate layer was concentrated in vacuo to give a brownish solid. The brownish solid was washed with small amount of cold ethyl acetate, filtered and dried under vacuum to yield 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid as a white solid (23.71 g, 65.18%). $^1$H NMR (400 MHz, $CD_3OD$): 7.57-7.53 (m, 2H), 7.05-7.00 (m, 2H) 1.46-1.43 (m, 2H), 1.40-1.37 (m, 2H).

**Example 26**




**[0319]** 1-(4-Fluoro-phenylcarbamoyl)-cyclobutanecarboxylic acid. To a mixture of cyclobutane-1,1-dicarboxylic acid (10.0 g, 69.4 mmol, 1.0 eq.) in anhydrous THF (100 mL) under nitrogen was added dropwise triethylamine (7.02 g, 69.4 mmol, 1.0 eq.) with stirring for 30 minutes at 0°C, followed by the addition of thionyl chloride (8.25 g, 69.4 mmol, 1.0 eq.) with stirring for another 30 minutes at 0°C. To the resulting mixture under nitrogen was added dropwise a solution of 4-fluoroaniline (8.48 g, 76.3 mmol, 1.1 eq.) in anhydrous THF (50 mL) with stirring for 1.5 hours at 0°C. The reaction mixture was diluted with ethyl acetate and extracted with 2N NaOH. The aqueous phase was titrated with 2N HCl to pH 1-2 and then extracted with ethyl acetate. The organic phase was dried with sodium sulfate and concentrated in vacuo to give 1-(4-fluoro-phenylcarbamoyl)-cyclobutanecarboxylic acid as a light pink solid (5.75 g, 34.9%). $^1$H NMR (400 MHz, $CDCl_3$ w/1drop $CD_3OD$): 7.53-7.48 (m, 2H), 7.06-7.00 (m, 2H), 2.81-2.63 (m, 4H), 2.14-2.02 (m, 2H).

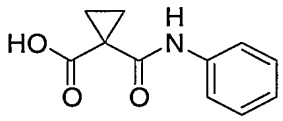
**Example 27**




**[0320]** 1-Benzylcarbamoyl-cyclopropanecarboxylic acid. The title compound was prepared based on a modified procedure of Shih and Rankin [*Synthetic Communications*, 1996, 26(4), 833-836]: To a mixture of cyclopropane-1,1-dicarboxylic acid (5.0 g, 38.4

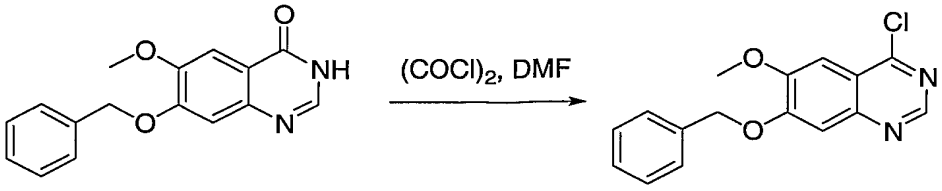
mmol, 1.0 eq.) in anhydrous THF (50 mL) under nitrogen was added dropwise triethylamine (3.89 g, 38.4 mmol, 1.0 eq.) with stirring for 30 minutes at 0°C, followed by the addition of thionyl chloride (4.57 g, 38.4 mmol, 1.0 eq.) with stirring for another 30 minutes at 0°C. To the resulting mixture under nitrogen was added dropwise a solution of benzylamine **5** (4.53 g, 42.3 mmol, 1.1 eq.) in anhydrous THF (25 mL) with stirring for 1.5 hours at 0°C. The reaction mixture was diluted with ethyl acetate and extracted with 2N NaOH (to pH 10). The aqueous phase was titrated with 2N HCl to pH 1-2 and then extracted with ethyl acetate. The organic phase was dried with sodium sulfate and concentrated in vacuo to give 1-Benzylcarbamoyl-cyclopropanecarboxylic acid as a white solid (4.39 g, 52.15%). $^1$H NMR (400 MHz, $CDCl_3$): 8.44 (br s, 1H), 7.37-7.33 (m, 2H), 7.32-7.26 (m, 3H), 1.82-1.70 (m, 4H).

**Example 28**



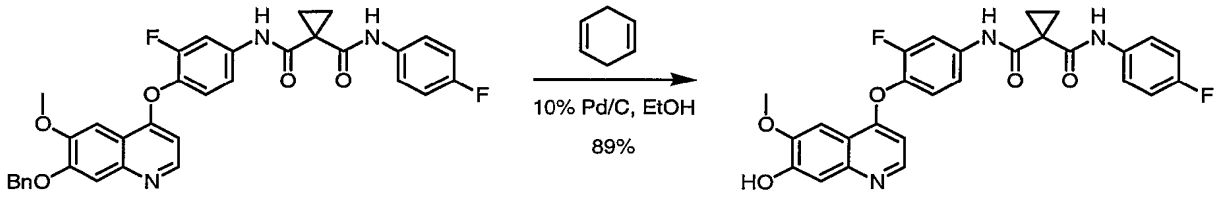

**[0321]** 1-Phenylcarbamoyl-cyclopropanecarboxylic acid. To a mixture of cyclopropane-1,1-dicarboxylic acid (5.29 g, 40.7 mmol, 1.0 eq.) in anhydrous THF (50 mL) under nitrogen was added dropwise triethylamine (4.12 g, 40.7 mmol, 1.0 eq.) with stirring for 30 minutes at 0°C, followed by the addition of thionyl chloride (4.84 g, 40.7 mmol, 1.0 eq.) with stirring for another 30 minutes at 0°C. To the resulting mixture under nitrogen was added dropwise a solution of phenylamine 9 (4.17 g, 44.8 mmol, 1.1 eq.) in anhydrous THF (25 mL) with stirring for 1.5 hours at 0°C. The reaction mixture was diluted with ethyl acetate and extracted with 2N NaOH (to pH >10). The aqueous phase was titrated with 2N HCl to pH 1-2 and then extracted with ethyl acetate. The organic phase was dried with sodium sulfate and concentrated in vacuo to give 1-phenylcarbamoyl-cyclopropanecarboxylic acid as a white solid (5.08 g, 60.8%). $^1$H NMR (400 MHz, $CDCl_3$): 10.50 (br s, 1H), 7.56-7.54 (m, 2H), 7.35-7.31 (m, 2H), 7.15-7.10 (m, 1H), 1.94-1.91 (m, 2H), 1.82-1.79 (m, 2H).

**Example 29**




**[0322]** 7-Benzyloxy-4-chloro-6-methoxy-quinoline. Dry DMF (8.0ml, 103mmol) was dissolved in dry $CHCl_3$ (40ml) and cooled in an ice bath. Oxalyl chloride (9.0ml, 105mmol) in $CH_2Cl_2$ (10ml) was added dropwise with stirring at 0C. When the bubbling had ceased, this solution was added slowly to an ice-cold solution of 7-benzyloxy-6-methoxy-3H-quinazolin-4-one (10.0g, 35.4mmol) in dry $CHCl_3$ (60ml) and the mixture was then heated to reflux for 2-3hrs. After cooling to room temperature, $H_2O$ (100ml) was added and the phases were separated. The aqueous phase was further extracted with $CHCl_3$ (2x). The combined $CHCl_3$ extractions were washed with sat'd NaCl (1x), dried ($Na_2SO_4$) and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (1:1 hexanes:EtOAc, followed by 100%EtOAc) to give 7-benzyloxy-4-chloro-6-methoxy-quinoline (5.11g, 48%). LC/MS Calcd for $[M+H]^+$ 301.1, found 301.1.

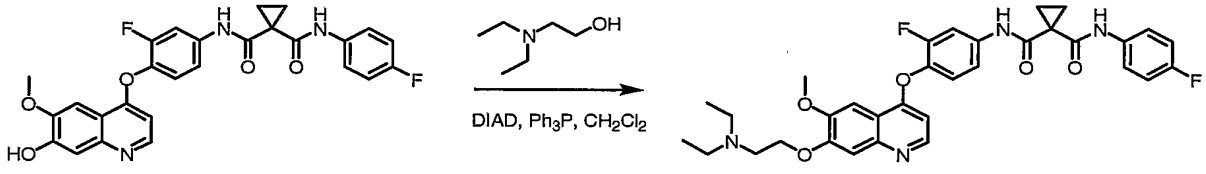
**Example 30**




**[0323]** Cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide(4-fluoro-phenyl)-amide. To a solution of cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide (1.18g, 2.0 mmol) in EtOH (20 mL) was added 1,4-cyclohexadiene (2.0 mL, 20 mmol) and 10% Pd/C (300 mg). The reaction mixture was then heated to reflux and the stirring was continued for 2 h. It was cooled to room temperature, filtered through celite and washed with MeOH. The MeOH solution was then concentrated under reduced pressure. The residue was taken into EtOAc (200 mL).

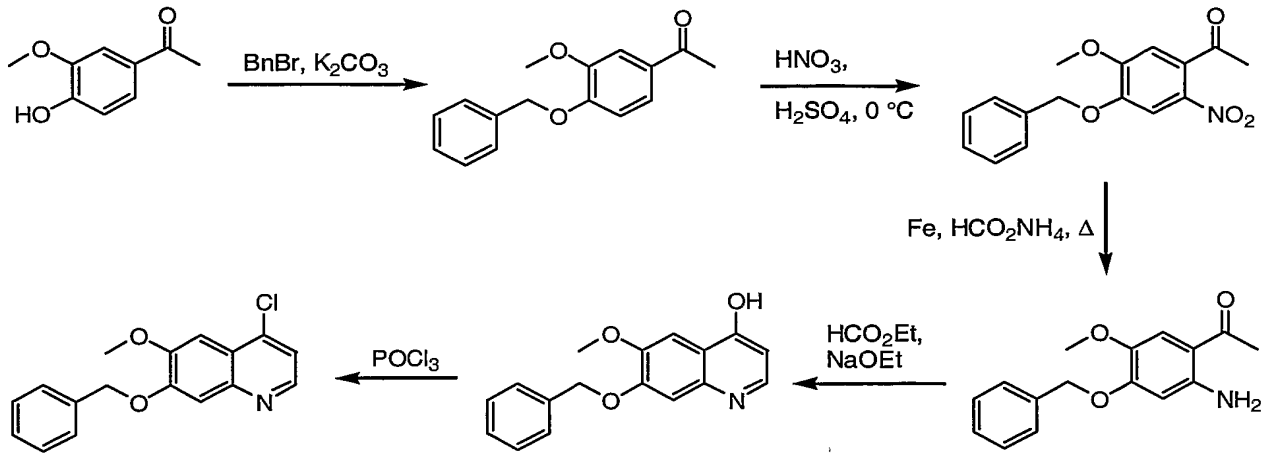
The EtOAc solution was washed with water, and dried over $Na_2SO_4$. Removal of the solvent under reduced pressure gave 900 mg (89%) of the crude product (90% purity by analytical HPLC), which was used in the next reaction without further purification.

**Example 31**




**[0324]** N-(4-{[7-{[2-(Diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a mixture of cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide(4-fluoro-phenyl)-amide (186 mg, 0.36 mmol) in $CH_2Cl_2$ (10 mL) was added 2-(diethylamino)ethanol (63 mg, 0.54 mmol), and $PPh_3$ (141 mg, 0.54 mmol). DIAD (109 mg, 0.54 mmol) was then added as a $CH_2Cl_2$ (1 mL) solution. The resulted solution was stirred at room temperature for 2 h and the solvent was removed under reduced pressure. To the residue was added 1 N HCl (50 mL), and it was washed with EtOAc (50 mL x 2). The aqueous phase was basified by adding 15% NaOH aqueous solution until pH =11-13, and then extracted with ether (50 mL x 2). The combined organic layer was dried (MgSO4), and concentrated in vacuo. The residue was purified on preparative HPLC to give N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluoro-phenyl)cyclopropane-1,1-dicarboxamide (74 mg, 34%) as a pale yellow solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.40 (br s, 1 H), 10.02 (br s, 1 H), 8.47 (d, $J$ = 5.2 Hz, 1 H), 7.91 (br d, $J$ = 13.9 Hz, 1 H), 7.54-7.52 (m, 2 H), 7.55-7.50 (m, 1 H), 7.52 (s, 1 H), 7.50-7.40 (m, 1 H), 7.41 (s, 1 H), 7.16 (br t, $J$ = 8.7 Hz, 2 H), 6.41 (br d, $J$ = 4.7 Hz, 1 H), 4.18 (t, $J$ = 6.0 Hz, 2 H), 3.94 (s, 3 H), 2.87 (br t, $J$ = 6.3 Hz, 2 H), 2.59 (q, $J$ = 7.1 Hz, 4 H), 1.47 (br s, 4 H), 1.00 (t, $J$ = 7.0 Hz, 6 H).

**Example 32**




**[0325]** 1-(4-Benzyloxy-3-methoxyphenyl)ethanone. A solution of 4-hydroxy-3-methoxyacetophenone (40 g, 240 mmol), benzyl bromide (31.4 mL, 260 mmol) and potassium carbonate (99.6 g, 360 mmol) in DMF (800 mL) was heated to 40 °C overnight. The solution was cooled to room temperature, poured over ice and the resultant solid was filtered. This material was washed with water and dried to give 1-(4-benzyloxy-3-methoxyphenyl)ethanone (61 g, 99 %).

**[0326]** 1-(4-Benzyloxy-5-methoxy-2-nitrophenyl)ethanone. A stirred solution of 1-(4-benzyloxy-3-methoxyphenyl)ethanone (51.3 g, 200 mmol) in dichloromethane (750 mL) was cooled to 0 °C. Nitric acid (90 %, 14 mL, 300 mmol) was added dropwise to the cooled solution over 20 min. Sulfuric acid (96.2 %, 16.3 mL, 300 mmol) was then added dropwise over 40 min at 0 °C. Additional nitric acid (9.4 mL, 200 mmol) was added dropwise over 20 min. The reaction mixture was washed with water (3 x 200 mL), and saturated sodium bicarbonate (4 x 200 mL, or until neutral). The organic layer was dried over $Na_2SO_4$ and concentrated. The crude mixture was recrystallized from DMF to give 1-(4-benzyloxy-5-methoxy-2-nitrophenyl)ethanone (36 g, 60 %). $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.45-7.33 (m, 5H), 6.74 (s, 1H), 5.21 (s, 2H), 3.97 (s, 3H), 2.49 (s, 3H).

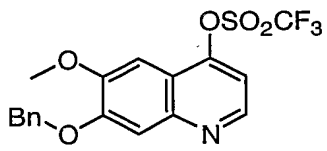
**[0327]** 1-(2-Amino-4-benzyloxy-5-methoxyphenyl)ethanone. A mixture of iron powder (27 g, 0.48 g atoms), ammonium formate (31 g, 500 mmol), 1-(4-benzyloxy-5-methoxy-2-nitrophenyl)ethanone (36 g, 120 mmol), toluene (500 mL) and water (500 mL) was heated to reflux overnight. The mixture was filtered through celite and washed with ethyl acetate. The combined organic layers were washed with water and brine. The organic layer was

dried over $Na_2SO_4$ and concentrated to afford 1-(2-amino-4-benzyloxy-5-methoxyphenyl)ethanone (29.3 g, 90 %). $^1$H NMR ($CDCl_3$): δ 7.41-7.30 (m, 5H), 7.13 (s, 1H), 6.16 (br s, 2H), 6.10 (s, 1H), 5.13 (s, 2H), 3.83 (s, 3H), 2.51 (s, 3H). LC/MS (M+H = 272).

**[0328]** 7-Benzyloxy-6-methoxyquinolin-4-ol. Sodium ethoxide (74.8 g, 1.1 mol) was added to a solution of 1-(2-amino-4-benzyloxy-5-methoxyphenyl)ethanone (29.3 g, 108 mmol) in DME (700 mL) and stirred for 30 min. Ethyl formate (44 mL, 540 mmol) was added and the mixture was stirred overnight (in case of incomplete reaction, additional sodium ethoxide can be added and the reaction monitored by LC/MS). After the reaction was complete, the mixture was diluted with water (40 mL) and acidified to neutral pH with 1M HCl. The solid was filtered, washed with water and dried to afford 7-benzyloxy-6-methoxyquinolin-4-ol (22 g, 72%). $^1$H NMR (400 MHz, $CDCl_3$): δ 10.7 (br s, 1H), 7.70 (s, 1H), 7.49-7.46 (t, 1H), 7.43-7.41 (br d, 2H), 7.37-7.33 (t, 2H), 7.30-7.28 (d, 1H), 6.84 (s, 1H), 6.21-6.19 (d, 1H), 5.21 (s, 2H), 3.96 (s, 3H). LC/MS (M+H = 282).

**[0329]** 7-Benzyloxy-4-chloro-6-methoxyquinoline. Phosphorus oxychloride (300 mL) was added to 7-benzyloxy-6-methoxyquinolin-4-ol (40 g, 140 mmol) and the mixture heated to reflux for 2 h. The mixture was carefully poured into a mixture of ice and sodium carbonate. The solution was adjusted to pH 8 with the addition of solid sodium bicarbonate and stirred at room temperature overnight. The solid was filtered and washed with water and dried to give 7-benzyloxy-4-chloro-6-methoxyquinoline as a pale brown solid (40.2 g, 95%). $^1$H NMR (400 MHz, $d_6$-DMSO): δ 8.61 (s, 1H), 7.57-7.37 (m, 8H), 5.32 (s, 2H), 3.98 (s, 3H); $^{13}$C NMR (100 MHz, $d_6$-DMSO): δ 152.4, 151.5, 148.5, 146.2, 139.6, 137.0, 129.2, 128.8, 121.7, 120.4, 110.1, 101.9, 70.8, 56.5; IR ($cm^{-1}$): 2359, 2341, 1506, 1456, 1435, 1252, 1227, 1146, 999, 845, 752, 698, 667; LC/MS (M+H = 300).

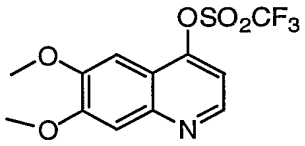
**Example 33**




**[0330]** Trifluoromethanesulfonic acid 7-benzyloxy-6-methoxy-quinolin-4-yl ester. To a dry 2L RBF containing 7-benzyloxy-6-methoxyquinolin-4-ol (75.3 g, 267 mmol) was added DCM (1 L), 4-dimethylaminopyridine (3.28 g, 26.8 mmol) and 2,6-lutidine (62 mL,

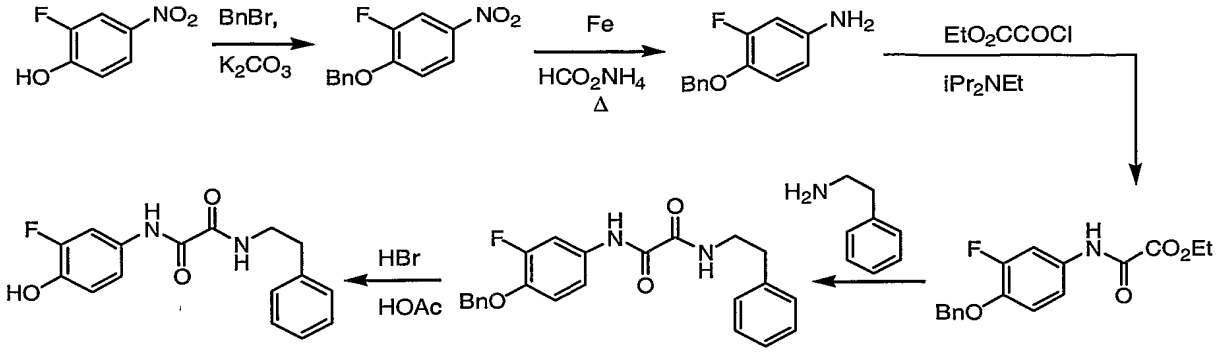
534 mmol). The mixture was cooled to –20°C by controlled addition of dry ice to an acetone bath. Trifluoromethanesulfonyl chloride (37 mL, 350 mmol) was added dropwise to the cooled solution with magnetic stirring over 25 minutes. After addition was complete, the mixture was stirred in bath for 20 minutes, then at room temperature for 3 hours. LCMS indicated reaction completion. The reaction mixture was concentrated *in vacuo* and placed under high vacuum to remove residual 2,6-lutidine. To the resulting brown solids was added methanol (3.5 L). The resulting slurry was stirred with mechanical stirrer for 30 min before adding water (1.5 L). The solids were isolated by filtration, followed by a water wash. The resulting solid was dried under high vacuum overnight yielding trifluoromethanesulfonic acid 7-benzyloxy-6-methoxy-quinolin-4-yl ester as a light brown solid (92.2 g, 83.8%). $^1$H NMR (400MHz, DMSO, $d_6$): δ 8.82 (d, 1H), 7.67 (s, 1H), 7.59 (d, 1H), 7.54-7.52 (m, 2H), 7.46-7.42 (m, 2H), 7.39-7.36 (m, 1H), 7.23 (s, 1H), 5.35 (s, 2H), 3.97 (s, 3H). LC/MS: M+H = 414.

**Example 34**




**[0331]** Trifluoromethanesulfonic acid 6,7-dimethoxyquinolin-4-yl ester from 6,7-Dimethoxy-quinolin-4-ol. To a dry 1L RBF containing 6,7-dimethoxy-quinolin-4-ol (20.9 g, 102 mmol), which can be prepared according to the procedure of Riegel, B. *(J. Amer. Chem. Soc.* 1946, *68*, 1264), was added DCM (500 mL), 4-dimethylaminopyridine (1.24 g, 10 mmol) and 2,6-lutidine (24 mL, 204 mmol). The mixture was vigorously stirred at RT. Trifluoromethanesulfonyl chloride (14 mL, 132 mmol) was added dropwise to the solution. After addition was complete, the mixture was stirred ice bath for 2 to 3 hrs. On LC/MS indicating the reaction completion, the reaction mixture was concentrated *in vacuo* and placed under high vacuum to remove residual 2,6-lutidine. To the resulting brown solids was added methanol (250 mL). The resulting slurry was stirred for 30 min before adding water (1 L). The solids were isolated by filtration, followed by a water wash. The resulting solid was dried under high vacuum overnight yielding trifluoromethanesulfonic acid 6, 7-dimethoxy-quinolin-4-yl ester as a light brown solid (27 g, 80%). $^1$H NMR (400MHz, DMSO, $d_6$): δ 8.82 (d, 1H), 7.59 (m, 2H), 7.20 (s, 1H), 3.97 (d, 6H). LC/MS: M+H = 338.

**Example 35**




**[0332]** 1-Benzyloxy-2-fluoro-4-nitrobenzene. A solution of 2-fluoro-4-nitrophenol (50.0 g, 318 mmol), benzyl bromide (42 mL, 350 mmol) and potassium carbonate (66.0 g, 478 mmol) in DMF (200 mL) was heated to 40 °C overnight. The solution was cooled to room temperature, poured over ice and the resultant solid was filtered. This material was washed with water and dried to give 1-benzyloxy-2-fluoro-4-nitrobenzene (75.0 g, 95 %). $^1$H NMR (400 MHz, $d_6$-DMSO): δ 8.19-8.11 (m, 2H), 7.53-7.37 (m, 6H), 5.36 (s, 2H); $^{13}$C NMR (100 MHz, $d_6$-DMSO): δ 152.8, 152.4, 149.9, 140.9, 136.1, 129.3, 129.1, 128.7, 122.0, 115.2, 112.8, 112.6, 71.6; IR (cm$^{-1}$): 1499, 1346, 1279, 1211, 1142, 1072, 986, 885, 812, 789, 754, 742, 700, 648, 577.

**[0333]** 4-Benzyloxy-3-fluoroaniline. A mixture of iron powder (45.2 g, 0.809 g atoms), ammonium formate (53.6 g, 0.850 mol), 1-benzyloxy-2-fluoro-4-nitrobenzene (50.0 g, 0.200 mol), toluene (400 mL) and water (400 mL) was heated to reflux overnight. The mixture was filtered through Celite and washed with hot ethyl acetate. The combined organic layers were washed with water and brine, then dried over sodium sulfate and concentrated to afford 4-benzyloxy-3-fluoroaniline (44 g, 100 %). $^1$H NMR (400 MHz, $d_6$-DMSO): δ 7.43-7.26 (m, 5H), 6.90 (dd, 1H), 6.49 (dd, 1H), 6.34 (m, 1H), 4.99 (br s, 2H), 4.98 (s, 2H); $^{13}$C NMR (100 MHz, $d_6$-DMSO): δ 171.1, 155.1, 152.7, 144.9, 138.0, 137.2, 129.6, 129.0, 128.5, 118.9, 110.0, 102.9, 72.5; IR (cm$^{-1}$): 1510, 1454, 1277, 1215, 1126, 1007, 957, 843, 800, 789, 739, 694, 604; LC/MS (M+H = 218).

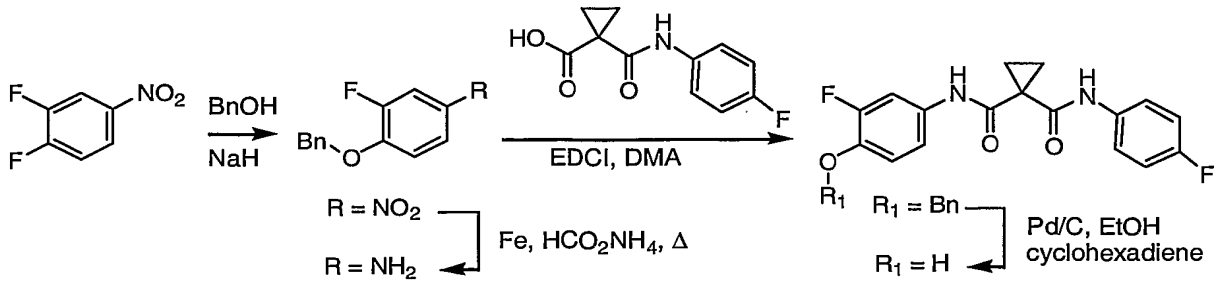
**[0334]** Ethyl [(4-benzyloxy-3-fluorophenyl)amino](oxo)acetate. Ethyl oxalyl chloride (44 mL, 390 mmol) was added to a solution of 4-benzyloxy-3-fluoroaniline (44 g, 180 mmol) in diisopropylethylamine (69 mL, 400 mmol) and stirred at room temperature for 15 min. The mixture was extracted with dichloromethane and washed with water and brine. The organic layer was dried over sodium sulfate and concentrated to afford ethyl [(4-

benzyloxy-3-fluorophenyl)amino](oxo)acetate (58.4 g, 100 %). $^1$H NMR (400 MHz, $d_6$-DMSO): δ 10.87 (s, 1H), 7.73 (d, 1H), 7.69 (d, 1H), 7.53 (d, 1H), 7.46-7.40 (m, 4H), 5.17 (s, 2H), 4.31 (q, 2H), 1.31(t, 3H); IR (cm$^{-1}$): 1732, 1705, 1558, 1541, 1508, 1456, 1273, 1186, 1167, 1101, 999, 858, 741, 694; LC/MS (M+H = 318).

**[0335]** *N*-(4-Benzyloxy-3-flourophenyl)-*N'*-(2-phenylethyl)ethanediamide. Phenethylamine (33 mL, 520 mmol) was added to ethyl [(4-benzyloxy-3-fluorophenyl)amino](oxo)acetate (81 g, 260 mmol) and the mixture was sonicated at room temperature for 30 min. The resulting solid was filtered, washed with water and dried to give *N*-(4-benzyloxy-3-flourophenyl)-*N'*-(2-phenylethyl)ethanediamide (100 g, 99 %). $^1$H NMR (400 MHz, $d_6$-DMSO): δ 10.72 (br s, 1H), 9.05 (m, 1H), 8.78 (m, 1H), 7.77 (m, 1H), 7.59 (m, 1H), 7.46-7.19 (m, 8H), 5.16 (m, 2H), 3.45 (m, 2H), 2.83 (m, 2H); IR (cm$^{-1}$): 2980, 2883, 1653, 1522, 1506, 1441, 1385, 1221, 1122, 951, 808, 746, 696, 584; LC/MS (M+H = 393).

**[0336]** *N*-(3-Fluoro-4-hydroxyphenyl)-*N'*-(2-phenylethyl)ethanediamide. A mixture of *N*-(4-benzyloxy-3-flourophenyl)-*N'*-(2-phenylethyl)ethanediamide (40 g, 100 mmol) and 38% hydrobromic acid in acetic acid (250 mL) was stirred at room temperature overnight. The resulting solid was filtered, washed with water and dried to give *N*-(3-fluoro-4-hydroxyphenyl)-*N'*-(2-phenylethyl)ethanediamide as a slightly yellow solid (30.6 g, 99 %yield). $^1$H NMR (400 MHz, $d_6$-DMSO): δ 10.60 (s, 1H), 9.02 (t, 1H), 7.70 (d, 1H), 7.47 (d, 1H), 7.32-7.20 (m, 3H), 6.91 (t, 1H), 3.43 (m, 2H), 2.81 (m, 2H); $^{13}$C NMR (100 MHz, $d_6$-DMSO): δ 160.5, 158.8, 152.0, 149.6, 142.2, 139.8, 130.3, 129.3, 129.0, 126.8, 118.1, 117.4, 109.6, 109.3 IR (cm$^{-1}$): 3279, 1653, 1518, 1456, 1279, 1190, 742, 696, 584; LC/MS (M+H = 303).

**Example 36**



[0337] 1-Benzyloxy-2-fluoro-4-nitro-benzene. To a slurry of sodium hydride (60% dispersion is oil, 693 mmol, 27.7 g) and dimethylacetamide (600 ml) was added benzyl alcohol (462 mmol, 48 ml) dropwise with stirring under $N_2$. The mixture was stirred for 1 hour at RT and then cooled to 0°C. 3,4-difluoronitrobenzene (508 mmol, 56.2 ml) was added to the cooled solution and stirred for 1 hour. Reaction mixture poured onto saturated ammonium chloride solution (800 ml) and stirred for 30 minutes, filtered and washed with water. The solid was stirred in ethyl acetate (500 mL), and filtered to give 54g of product. The ethyl acetate filtrate, after concentrated in vacuo, was triturated with diethyl ether (500 mL), sonicated for 2 hours, and filtered to give another 30g of product. The ether layer was concentrated and column purified using 5% EtOAc/hexanes as eluent to gave additional 15g of product. The total yield of 1-benzyloxy-2-fluoro-4-nitro-benzene was 95g (83%). (Note: the product contains ca. 5% of 3,4-Bis-benzyloxy-nitrobenzene, which is carried into the next step without further purification.) $^1$H NMR (400MHz, $CDCl_3$): δ 8.04 –8.00 (m, 2H), 7.43-7.37 (m, 5H), 7.08 (t, 1H), 5.26 (s, 2H).

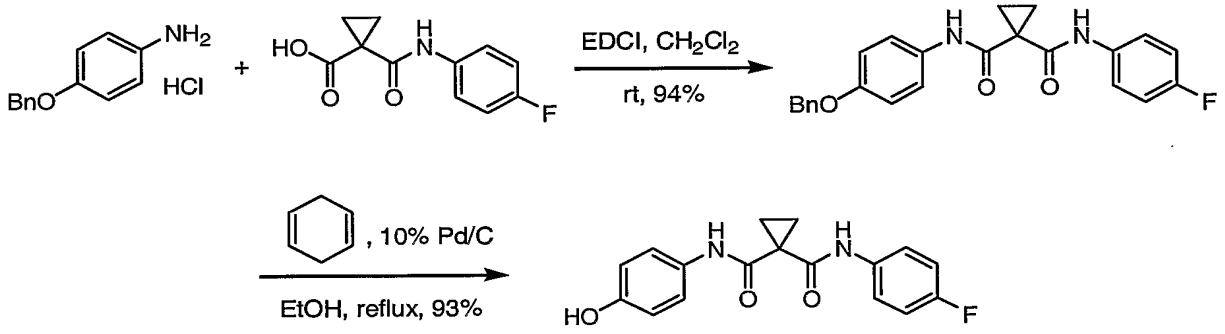
[0338] 4-Benzyloxy-3-fluoro-phenylamine. A mixture of 1-benzyloxy-2-fluoro-4-nitro-benzene (44g, 178 mmol), toluene (400 ml), ammonium formate (35 g), iron (30 g), and water (400 ml) was heated to reflux with stirring overnight. The reaction mixture was filtered through celite and washed with ethyl acetate (400ml). The organic layer was separated and washed with brine (300 ml), dried over sodium sulfate and concentrated to give 4-benzyloxy-3-fluoro-phenylamine as an oil (33.7 g, 87%). $^1$H NMR (400MHz, $CDCl_3$): δ 7.41-7.29 (m, 5H), 6.79 (t, 1H), 6.45 (dd, 1H), 6.14 (dd, 1H), 5.02 (s, 2H), 3.50 (s, 2H). LC/MS: (M+1) 218.

[0339] Cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-3-fluoro-phenyl)-amide (4-fluoro-phenyl)-amide. To a stirred mixture of 4-benzyloxy-3-fluoro-phenylamine (155.3 mmol, 33.7 g), 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (170.8 mmol, 38.13 g) and anhydrous dichloromethane (600 ml) was added EDCI (233.9 mmol, 44.7 g) in portions. After stirring at RT for 1 hr, the reaction mixture was diluted with saturated sodium bicarbonate (400 ml) and stirred for 30 minutes. The precipitate was filtered and air dried to give the 1$^{st}$ crop of product. The biphasic filtrate was separated, and the organic phase was washed with brine (300 ml), dried over sodium sulfate, and concentrated. The residue was taken up in DCM (100 ml), stirred for 15 minutes, and filtered to give a 2$^{nd}$ crop of product. The combined yield of cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-3-fluoro-phenyl)-amide (4-fluoro-phenyl)-amide was 64.5

g (98%). $^1$H NMR (400MHz, $CDCl_3$): δ 8.92 (br s, 1H), 8.88 (br s, 1H), 7.50-7.32 (m, 8H), 7.06-7.02 (m, 3H), 6.97-6.92 (t, 1H), 5.13 (s, 2H), 1.65 (s, 4H). LC/MS: ( M+1) 423.

**[0340]** Cyclopropane-1,1-dicarboxylic acid (3-fluoro-4-hydroxy-phenyl)-amide (4-fluoro-phenyl)-amide. A mixture of cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-3-fluoro-phenyl)-amide (4-fluoro-phenyl)-amide (152.8 mmol, 64.5), ethanol (800 ml), cyclohexadiene (764 mmol, 71 ml), and 10% Pd/C (2 g) was refluxed for 2 hours. Reaction mixture cooled and filtered through celite and washed with methanol. The combined filtrate was concentrated and stirred in 10% EtOAc/ether (350 ml). The resulting precipitate was filtered and washed with ether to give a 1st crop of product. The filtrate was concentrated and stirred in DCM (150 ml) to give another precipitate, which was then filtered to give a 2nd crop of product. The combined yield of cyclopropane-1,1-dicarboxylic acid (3-fluoro-4-hydroxy-phenyl)-amide (4-fluoro-phenyl)-amide was 43 g (85%) in 95% purity by HPLC (UV @ 254 nm). $^1$H NMR (400MHz, DMSO-D6): δ 10.07 (br s, 1H), 9.92 (br s, 1H), 9.64 (br s, 1H), 7.64-7.60 (m, 2H), 7.55-7.51 (m, 1H), 7.17-7.12 (m, 3H), 6.89-6.84 (t, 1H), 1.43 (s, 4H). LC/MS: (M+1) 333.

**Example 37**

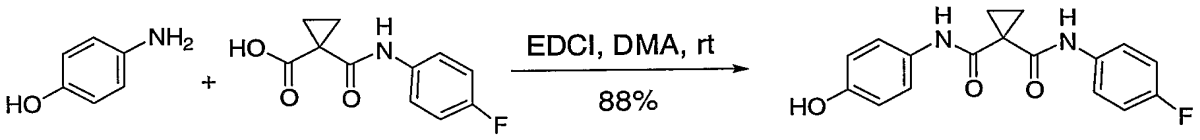



**[0341]** Cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-phenyl)-amide (4-fluoro-phenyl)-amide. To a 0 °C suspension of 4-benzyloxyaniline hydrochloride (47.0 g, 200 mmol) and 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (49.1 g, 220 mmol) in $CH_2Cl_2$ (400 mL) was added EDCI (38.2 g, 200 mmol). Stirring was continued at rt for 2-4 h until the reaction was complete. $CH_2Cl_2$ was removed under reduced pressure. $H_2O$ (300 mL) and MeOH (200 mL) were added, and the resulting mixture was stirred at rt for 30 min. After filtration and wash with $H_2O$, the solid was transferred to another flask containing 300 mL of sat. aqueous $NaHCO_3$ solution. The mixture was stirred for another 30 min. The solid was filtered, washed with water, and dried over night

on a lyophilizer, affording cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-phenyl)-amide (4-fluoro-phenyl)-amide (75.8g, 95% yield) as an off-white solid.

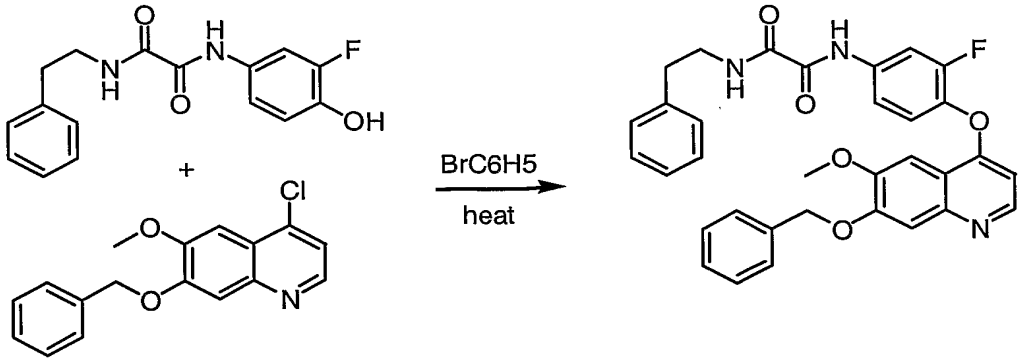
**[0342]** Cyclopropane-1,1-dicarboxylic acid (4-fluoro-phenyl)-amide (4-hydroxy-phenyl)-amide. To a refluxing mixture of cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-phenyl)-amide (4-fluoro-phenyl)-amide (46 g, 113 mmol), 10% Pd/C (2 g) in EtOH (400 mL) was added dropwise 1,4-cyclohexadiene (62.7 mL, 678 mmol). Stirring was continued for 2-5 h until the reaction was complete. The mixture was cooled to rt, filtered through celite, and washed with EtOH. The solution was then concentrated under reduced pressure. To the flask containing the crude product was added $CHCl_3$ (200 mL). The resulting suspension was stirred for 15 min at rt. The solid was filtered, and dried in the air to give cyclopropane-1,1-dicarboxylic acid (4-fluoro-phenyl)-amide (4-hydroxy-phenyl)-amide (34.4 g, 95%, yield).

**Example 38**



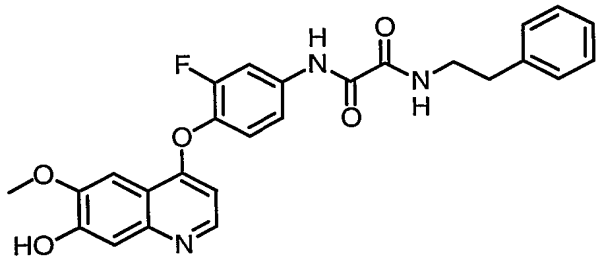

**[0343]** Alternate Synthesis of Cyclopropane-1,1-dicarboxylic acid (4-fluoro-phenyl)-amide (4-hydroxy-phenyl)-amide. To a solution of 4-aminophenol (2.93 g, 26.9 mmol) and 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (5.00 g, 22.4 mmol) in DMA (30 mL) was added EDCI (5.15 g, 26.9 mmol). The mixture was stirred vigorously until the reaction was complete (~ 3 h). With vigorous stirring, the reaction mixture was then poured into a flask containing sat. aqueous $NaHCO_3$ solution (200 mL). The stirring was continued for 1 h. The resulting suspension was then filtered. The solid was washed with water (50 mL), chloroform (50 mL) and dried under vacuum, affording 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (6.22g, 88% yield) as a powder (>95% purity by HPLC and $^1H$ NMR).

**Example 39**




**[0344]** *N*-{4-[(7-Benzyloxy-6-methoxyquinolin-4-yl)oxyl-3-fluorophenyl}-*N'*-(2-phenylethyl)ethanediamide. A mixture of 7-benzyloxy-4-chloro-6-methoxyquinoline (30 g, 100 mmol), *N*-(3-fluoro-4-hydroxyphenyl)-*N'*-(2-phenylethyl)ethanediamide (32 g, 106 mmol), DMAP (125 g, 1.02 mol) and bromobenzene (500 mL) was heated to reflux for 6 h. The mixture was cooled to room temperature and the bromobenzene was removed under reduced pressure. Methanol (500 mL) was added to the residue and the mixture was stirred at room temperature for 2 h. The resulting solid was filtered, washed with methanol and dried to give *N*-{4-[(7-benzyloxy-6-methoxyquinolin-4-yl)oxy]-3-fluorophenyl}-*N'*-(2-phenylethyl) ethanediamide (34 g, 61 %). $^1$H NMR (400 MHz, $d_6$-DMSO): δ 11.05 (s, 1H), 9.15 (s, 1H), 8.47 (d, 1H), 8.05 (d, 1H), 7.84 (d, 1H), 7.56-6.36 (m, 13H), 6.46 (d, 1H), 5.32 (s, 2H), 3.97 (s, 3H), 3.47 (q, 2H), 2.86 (t, 2H); $^{13}$C NMR (100 MHz, $d_6$-DMSO): δ 160.5, 160.2, 159.9, 159.5, 155.2, 152.7, 152.2, 150.3, 149.6, 146.9, 139.7, 137.4, 137.3, 137.2, 137.1, 129.3, 129.2, 129.1, 129.0, 128.9, 128.7, 128.6, 126.9, 124.8, 117.9, 115.3, 109.9, 102.8, 99.8, 70.6, 56.5, 41.3, 35.2; IR (cm$^{-1}$): 1657, 1510, 1481, 1433, 1416, 1352, 1310, 1252, 1215, 1609, 986, 891, 868, 850, 742, 696; LC/MS (M+H = 566).

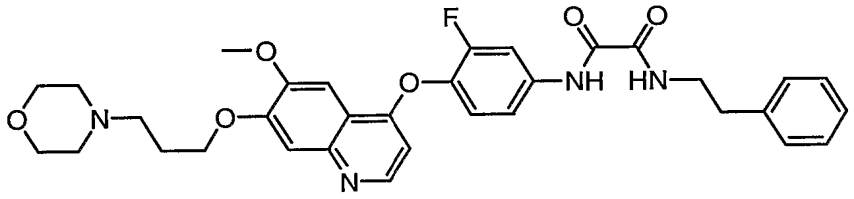
**Example 40**



**[0345]** *N*-{3-Fluoro-4-[(7-hydroxy-6-methoxyquinolin-4-yl)oxy]phenyl}-*N'*-(2-phenylethyl)ethanediamide. To a solution of *N*-{4-[(7-benzyloxy-6-methoxyquinolin-4-

yl)oxy]-3-fluorophenyl}-*N'*-(2-phenylethyl)ethanediamide (32 g, 56 mmol) in methanol (200 mL), DMF (100 mL), dichloromethane (100 mL), ethyl acetate (100 mL) and acetic acid (5 mL) was added palladium hydroxide (4.2 g) and the mixture was shaken on a Parr hydrogenator under a hydrogen pressure of 45 psi for 4 h. The resulting suspension was filtered through celite and the solid residue was washed with boiling dichloromethane (2 L) and acetone (2 L). The combined filtrates were evaporated to yield *N*-{3-fluoro-4-[(7-hydroxy-6-methoxyquinolin-4-yl)oxy]phenyl}-*N'*-(2-phenylethyl)ethanediamide as an off-white solid (25.6 g, 95 %). $^1$H NMR (400 MHz, $d_6$-DMSO): δ 11.06 (s, 1H), 10.25 (br s, 1H), 9.12 (t, 1H), 8.40 (d, 1H), 8.01 (dd, 1H), 7.50-7.44 (m, 2H), 7.31-7.23 (m, 6H), 6.39 (d, 1H), 3.95 (s, 3H), 2.85 (t, 2H), 2.50 (m, 2H); IR (cm-1): 1666, 1624, 1585, 1520, 1481, 1427, 1377, 1256, 1211, 1194, 1022, 880, 850, 839, 802, 750, 700; LC/MS (M+H = 476).

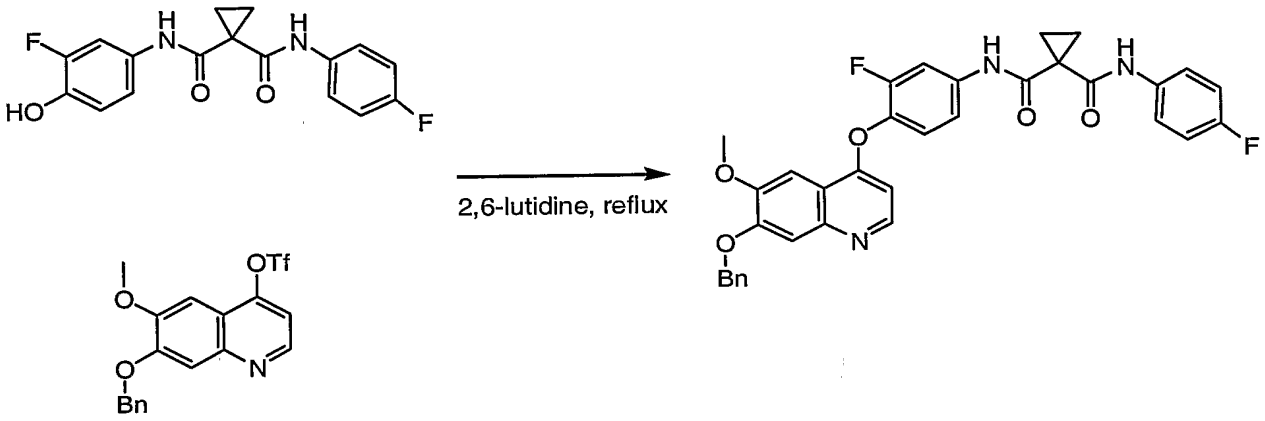
**Example 41**



**[0346]** *N*-(3-Fluoro-4-{[6-methoxy-7-(3-morpholin-4-ylpropoxy)quinolin-4-yl]oxy}phenyl)-*N'*-(2-phenylethyl)ethanediamide. A solution of *N*-{3-fluoro-4-[(7-hydroxy-6-methoxyquinolin-4-yl)oxy]phenyl}-*N'*-(2-phenylethyl)ethanediamide (25.6 g, 54 mmol), *N*-(3-chloropropyl)morpholine hydrochloride (11.7 g, 592 mmol) and potassium carbonate (16.6 g, 120 mmol) in DMF (300 mL) was heated to 80 °C overnight. Upon cooling, a majority of the DMF (250 mL) was removed on a rotary evaporator, 5% aqueous LiCl (300 mL) was added and the mixture was sonicated at room temperature. The solid was filtered, suspended in 1N HCl and washed with ethyl acetate (2 x 300 mL). The solution was adjusted to pH 14 using 2N sodium hydroxide and subsequently extracted with dichloromethane (3 x 200 mL). The organic layer was dried over sodium sulfate, filtered and evaporated to give *N*-(3-fluoro-4-{[6-methoxy-7-(3-morpholin-4-ylpropoxy)quinolin-4-yl]oxy}phenyl)-*N'*-(2-phenylethyl)ethanediamide as a yellow solid (24 g, 74 %). $^1$H NMR (400 MHz, $CDCl_3$): δ 9.37 (s, 1H), 8.46 (d, 1H), 7.81 (dd, 1H), 7.57 (t, 1H), 7.53 (s, 1H), 7.42 (s, 2H), 7.34-7.20 (m, 6H), 6.39 (d, 1H), 4.27 (t, 2H), 4.03 (s, 3H), 3.71 (m, 4H), 3.65 (q, 2H), 2.91 (t, 2H), 2.56 (br s, 4H), 2.13 (m, 2H); $^{13}$C NMR (100 MHz, $d_6$-DMSO): δ 160.1, 160.0, 159.5, 155.2, 152.7, 152.6, 150.2, 149.5, 147.1,

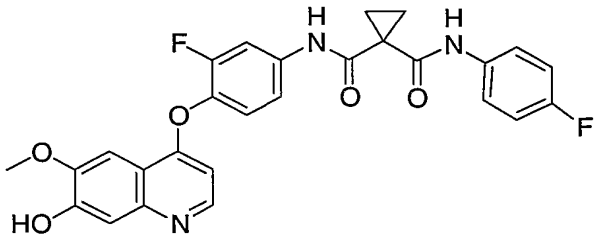
139.7, 137.3, 137.1, 129.3, 129.1, 126.9, 124.8, 117.9, 115.1, 109.2, 102.7, 99.6, 67.4, 66.9, 56.5, 55.5, 54.1, 41.3, 35.2, 26.4; IR ($cm^{-1}$): 1655, 1506, 1483, 1431, 1350, 1302, 1248, 1221, 1176, 1119, 864, 843, 804, 741, 700; LC/MS (M+H = 603).

**Example 42**



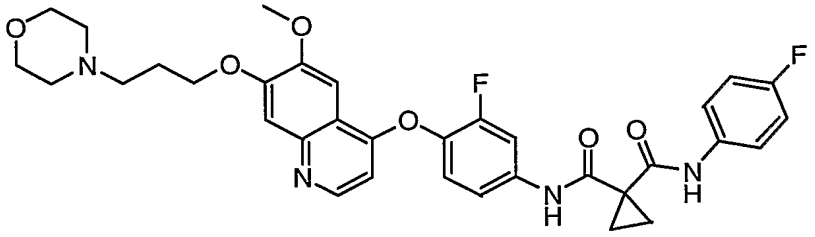

**[0347]** Cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide. To a flask containing cyclopropane-1,1-dicarboxylic acid (3-fluoro-4-hydroxy-phenyl)-amide (4-fluoro-phenyl)-amide (2.25 g, 6.7 mmol) and trifluoromethanesulfonic acid 7-benzyloxy-6-methoxy-quinolin-4-yl ester (1.87 g, 4.5 mmol) was added dry 2,6-lutidine (9 mL). The reaction mixture was heated to reflux (143°C) with vigorous stirring. The reaction progress was monitored by LC-MS. 2,6-Lutidine was removed under reduced pressure when the reaction was complete (about 6 h). The residue was treated with charcoal (1.5 g) in refluxing EtOAc (50 mL) for 15 min, and filtered through celite. The volume of the filtrate was reduced to about 20 mL and was added 20 mL of 1 N HCl. The crude product precipitated as the HCl salt, which was filtered and washed with EtOAc and $H_2O$ (88% purity by analytical HPLC). The HCl salt was free-based with saturated aqueous $NaHCO_3$ solution. Further purification by column chromatography (hexans:EtOAc = 1:4) gave cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide as an off-white solid (1.3 g, 48% yield. $^1H$ NMR (400 MHz, DMSO, $d_6$): 10.41 (s, 1H), 10.02 (s, 1H), 8.48 (d, 1H), 7.92 (dd, 1H), 7.65 (m, 2H), 7.54 (m, 5H), 7.41 (m, 4H), 7.17 (m, 2H), 6.43 (d, 1H), 5.32 (s, 2H), 3.97 (s, 3H), 1.48 (m, 4H). LC/MS Calcd for $[M+H]^+$ 596.2, found 596.3.

**Example 43**



**[0348]** Cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide. To a solution of the cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide (22.4 g, 37.6 mmol) in EtOH (340 mL) was added 1,4-cyclohexadiene (35 mL, 376 mmol) and 10% Pd/C (2.08 g). The reaction mixture was then heated at 65°C with stirring for 3 h (Caution: $H_2$ gas is released from the reaction). It was then allowed to cool to room temperature, and filtered through celite follwed by a MeOH wash. The solution was then concentrated under reduced pressure. The yellow residue was taken into EtOAc (1 L). The EtOAc solution was washed with water (1X), brine (2X), dried over $MgSO_4$ and concentrated *in vacuo*. Cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide was obtained as a yellow solid (17.3 g, 91.1% yield), which were carried on to the next reaction without further purification. $^1$H NMR (400 MHz, DMSO, d6): 10.39 (s, 1H), 10.15 (s, 1H), 10.00 (s, 1H), 8.38 (d, 1H), 7.88 (dd, 1H), 7.63 (m, 2H), 7.50 (m, 2H), 7.40 (t, 1H), 7.27 (s, 1H), 7.14 (m, 2H), 6.33 (d, 1H), 3.95 (s, 3H), 1.47 (m, 4H). LC/MS Calcd for $[M+H]^+$ 506.2, found 506.3. Anal. HPLC: 99.4% pure.

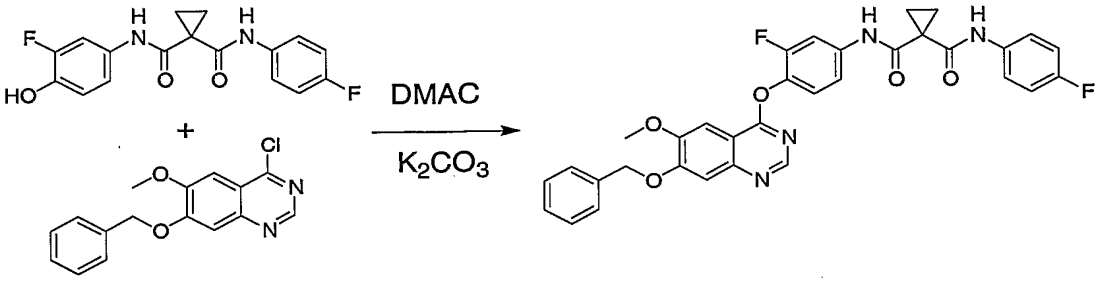
**Example 44**



**[0349]** *N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a mechanically stirred slurry of cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (16.6 g, 32.8 mmol) and

potassium carbonate (13.6 g, 98.6 mmol) in DMF (250 mL) was added 4-(3-chloropropyl)-morpholine hydrochloride (13, 7.92 g, 39.6 mmol). The resulting mixture was heated at 90°C for 5 hours (until phenol completely consumed). The reaction mixture was allowed to cool to room temperature, then dumped into water (900 mL), followed by extraction with EtOAc (3X). The combined extracts were washed with 5% LiCl (aq.) (3X) and brine (1X) followed by drying over MgSO4 and concentration in vacuo. The crude (18.8g) obtained as brown solid was further purified by flash chromatography [silica gel, 4-stage gradient system: 1) EtOAc; 2) EtOAc:MeOH:7N $NH_3$/MeOH (95:5:0.5); 3) DCM:MeOH:7N NH3/MeOH (95:5:0.5); 4) DCM:MeOH: 7N $NH_3$/MeOH (93:8:1)], affording N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide was obtained as an off white solid (15.0 g, 72% yield). 1H NMR (400 MHz, DMSO-d6): 10.41 (s, 1H), 10.02 (s, 1H), 8.47 (d, 1H), 7.91 (dd, 1H), 7.65 (m, 2H), 7.53 (m, 2H), 7.42 (t, 1H), 7.40 (s, 1H), 7.16 (m, 2H), 6.42 (d, 1H), 4.20 (t, 2H), 3.96 (s, 3H), 3.59 (t, 4H), 2.47 (t, 2H), 2.39 (br, s, 4H), 1.98 (m, 2H), 1.48 (m, 4H). LC/MS Calcd for [M+H]+ 633.3, found 633.0.

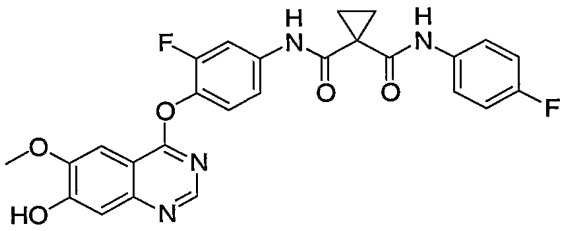
**Example 45**




**[0350]** Cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinazolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide: A mixture of 7-benzyloxy-4-chloro-6-methoxy-quinazoline (5 g, 16.67 mmol), cyclopropane-1,1-dicarboxylic acid (3-fluoro-4-hydroxy-phenyl)-amide (4-fluoro-phenyl)-amide (8.3 g, 25 mmol), potassium carbonate (125 mmol, 17.25 g), and dimethylacetamide (125 ml) was heated 50° C with stirring for 16h. Reaction mixture was poured onto ice/water (600 ml) and stirred for 30 minutes, and filtered. The solid was dissolved in ethyl acetate and washed with water (1x), brine, and concentrated. The crude was purified on silica get column eluting with 30% acetone in hexanes to yield cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-

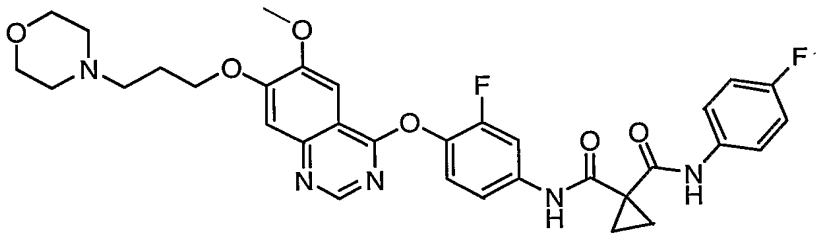
methoxy-quinazolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide (7.5 g, 76%). $^1$H NMR ($CDCl_3$): 8.64 (1H, br. s), 8.55 (1H, s), 8.33 (1H, br. s), 7.74-7.71 (1H, dd), 7.54 (1H, s), 7.48-7.33 (8H, m), 7.31-7.24 (2H, m), 7.06-7.02 (2H, m), 5.32 (2H, s), 4.06 (3H, s), 1.77-1.74 (2H, m), 1.63-1.61 (2H, m).

**Example 46**



**[0351]** Cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide. To a mixture of cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinazolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide (7.5 g, 12.6 mmol), acetic acid (few drops), dichloromethane (50 ml) and methanol (100 ml) was added 10% Pd/C (700 mg). The mixture was agitated in hydrogen gas (40 psi) until the reaction was complete (ca. 4 hr). The solution was filtered through celite and concentrated to give a crude product as a solid. The crude product was triturated with ether, and filtered. The filter cake was dried *in vacuo* to yield cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (6.1 g, 95% yield). $^1$H NMR (dmso-d6): 10.86 (1H, br. s), 10.34 (1H, br. s), 10.04 (1H, br. s), 8.46 (1H, s), 7.84-7.80 (1H, dd), 7.66-7.62 (2H, m), 7.55 (1H, s), 7.47-7.45 (1H, m), 7.41-7.37 (1H, m), 7.24 (1H, s), 7.18-7.13 (2H, t), 3.98 (3H, s), 1.46 (4H, s).

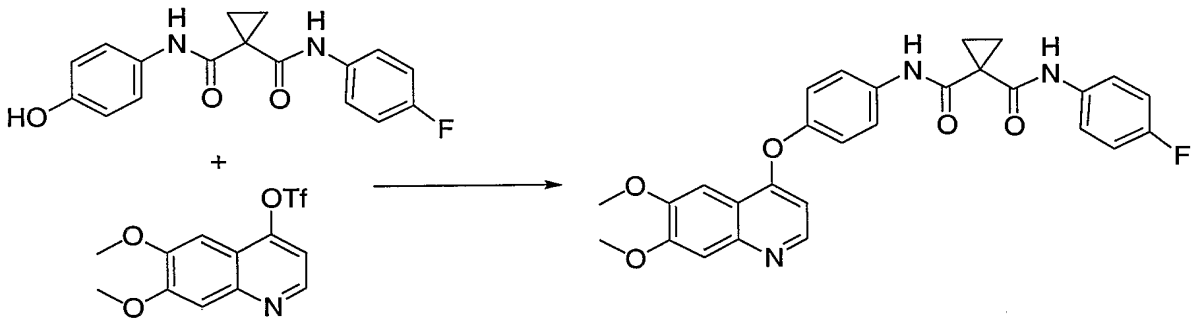
**Example 47**



**[0352]** N-[3-Fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a mixture of

cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (1.5 g, 2.96 mmol), 4-(3-hydroxypropyl)morpholine (0.623 mL, 4.5 mmol), triphenylphosphine (1.18 g, 4.5 mmol), and dichloromethane (50 mL) was added diisopropyl azodicarboxylate (0.886 mL, 4.5 mmol). The mixture was stirred at room temperature for 16 h, monitored by LCMS. After removal of solvent, the crude mixture was separated by flash column chromatography (silica), eluting with 5% methanol in dichloromethane to give N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarbox-amide (890 mg, 47% yield). 1HNMR (400MHz, DMSO-d6): d 10.36 (br s, 1H), 10.05 (br s, 1H), 8.55 (s, 1H), 7.83 (m, 1H), 7.64 (m, 2H), 7.57 (s, 1H), 7.44 (m, 3H), 7.18 (t, 2H), 4.27 (m, 2H), 3.99 (s, 3H), 3.61 (m, 6H), 2.40 (m, 4H), 2.01 (m, 2H), 1.47 (m, 4H). LC/MS Calcd for $[M+H]^+$ 634.2, found 634.3.

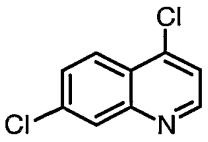
**Example 48**




**[0353]** N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a solution of cyclopropane-1,1-dicarboxylic acid (4-fluoro-phenyl)-amide (4-hydroxy-phenyl)-amide (6.98 g, 22.2 mmol) in anhydrous 2,6-lutidine (50 mL) was added trifluoromethanesulfonic acid 6, 7-dimethoxy-quinolin-4-yl ester (5 g, 14.8 mmol). The reaction mixture was heated at 165°C in a sealed pressure tube with stirring for 18 h. The reaction mixture was concentrated on high vacuum to completely remove lutidine. The resulting solid material was dissolved in DCM (250 mL), and washed several times with 1 N sodium hydroxide to remove the excess phenol. The crude mixture was loaded on a silica gel flash column and eluted with 75% EtOAc-hexanes, affording N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (3.2 g, 44%). $^1H$ NMR (400 MHz, $d_6$-DMSO): δ 10.2 (s, 1H), 10.05 (s, 1H), 8.4 (s, 1H), 7.8 (m, 2H), 7.65 (m, 2H), 7.5 (s, 1H),

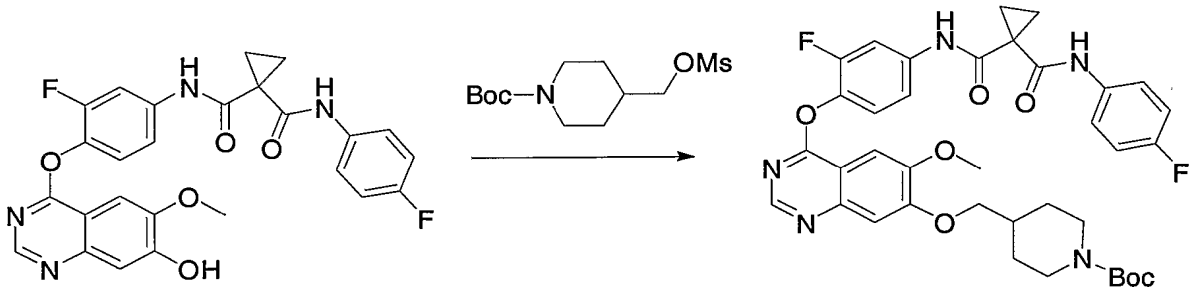
7.35 (s, 1H), 7.25 (m, 2H), 7.15(m, 2H), 6.4 (s, 1H), 4.0 (d, 6H), 1.5 (s, 4H). LC/MS: M+H= 502.

**Example 49**



**[0354]** 4,7-Dichloroquinoline. Phosphorus oxychloride (4mL, 429 mmol) was added to 7-chloro-4-hydroxyquinoline 2.86g, 15.9mmol) in a round bottom flask equipped with a reflux condenser. The mixture was heated to reflux for 2h, then allowed to cool to room temperature. The solution was concentrated *in vacuo* to a thick oil, then dumped over cracked ice. The resulting solution was neutralized with saturated $NaHCO_3$ (aq). The slurry was filtered and washed with water. The solids were dried under vacuum, afforded 4,7-dichloroquinoline as a white solid (2.79g, 88.5% yield).

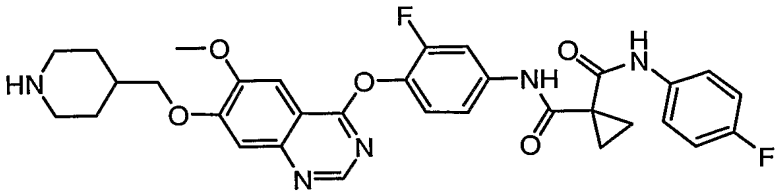
**Example 50**



**[0355]** 4-[4-(2-Fluoro-4-{[1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarbonyl]-amino}-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-piperidine-1-carboxylic acid tert-butyl ester. Cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (325 mg, 0.64 mmol), 4-methanesulfonyloxymethyl-piperidine-1-carboxylic acid tert-butyl ester (193 mg, 0.66 mmol), $K_2CO_3$ (181 mg, 1.31 mmol) were combined in DMF (5 ml) and heated to 80°C overnight. The reaction was not complete and more 4-methanesulfonyloxymethyl-piperidine-1-carboxylic acid tert-butyl ester (90 mg, 0.31 mmol) and $K_2CO_3$ (90 mg, 0.65 mmol) were added and heating at 80°C continued for another night. The reaction mixture

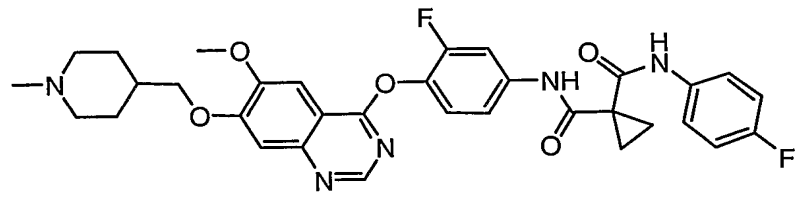
was allowed to cool to room temperature, then diluted with EtOAc and washed with $H_2O$ (3x), sat'd NaCl (1x), dried ($Na_2SO_4$) and concentrated *in vacuo*. The resulting crude material was purified by flash chromatography (1:1 hexanes:EtOAc, followed by 1:3 hexanes:EtOAc) to give 4-[4-(2-fluoro-4-{[1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarbonyl]-amino}-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-piperidine-1-carboxylic acid tert-butyl ester (273 mg, 60%). LC/MS Calcd for $[M+H]^+$ 704.3, found 704.4.

**Example 51**



**[0356]** Cyclopropane-1,1-dicarboxylic acid {3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinazolin-4-yloxyl-phenyl}-amide (4-fluoro-phenyl)-amide, TFA salt. 4-[4-(2-Fluoro-4-{[1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarbonyl]-amino}-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-piperidine-1-carboxylic acid tert-butyl ester (273 mg, 0.39 mmol) was dissolved in $CH_2Cl_2$ (8 ml) to which was added TFA (8 ml) and the mixture stirred at room temperature for 1hr. The reaction mixture was concentrated *in vacuo* and the resulting oil triturated with $Et_2O$. The resulting solids were filtered, washed with $Et_2O$ and dried under high vacuum to give cyclopropane-1,1-dicarboxylic acid {3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-amide (4-fluoro-phenyl)-amide, TFA salt (222 mg, 80%). LC/MS Calcd for $[M+H]^+$ 604.2, found 604.3.

**Example 52**



**[0357]** N-{3-Fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

Cyclopropane-1,1-dicarboxylic acid {3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-amide (4-fluoro-phenyl)-amide, TFA salt (222 mg, 0.31 mmol), $H_2O$ (3 ml), 37% formaldehyde in $H_2O$ (0.18 ml) and acetic acid (27 drops) were combined in acetonitrile (9 ml) to which was slowly added triacetoxyborohydride (561 mg, 2.65 mmol). The mixture was stirred at room temperature for 1-2 hr, then diluted with 1N NaOH and $H_2O$ and extracted with $CH_2Cl_2$ (3x). The combined $CH_2Cl_2$ extractions were washed with sat'd NaCl (1x), dried ($Na_2SO_4$) and concentrated *in vacuo*. The resulting residue was dissolved in a minimum of 1:1 dioxane:EtOAc to which was added 4M HCl in dioxane (1-2 ml). The resulting solids were filtered, washed with EtOAc and dried under high vacuum to give N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy] phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, HCl salt (167 mg, 83%). 1HNMR (400MHz, DMSO-$d_6$): δ 10.40 (s, 1H), 10.17 (br s, 1H) 10.07 (s, 1H), 8.61 (s, 1H), 7.85 (m, 1H), 7.65 (m, 2H), 7.48 (m, 2H), 7.42 (t, 1H), 7.16 (t, 2H), 4.12 (2, 2H), 4.00 (s, 3H), 3.46 (m, 2H), 2.99 (m, 2H), 2.73 (d, 3H), 2.13 (m, 1H), 2.01 (m, 2H), 1.63 (m, 2H), 1.47 (m, 4H). LC/MS Calcd for $[M+H]^+$ 618.2, found 618.3.

## Synthesis of Bridged Bicyclics

**[0358]** The following describes synthesis of bridged bicyclics with appended leaving groups for use as, for example, alkylating agents. In the context of this invention, these alkylating agents are used, for example, to alkylate the quinazoline or quinolines on the 6- or 7-oxygens to make compounds of the invention. The invention is not limited to alkylation chemistry to append such bridged bicyclics, but rather the aforementioned description is meant only to be illustrative of an aspect of the invention.

## Example 53

**[0359]** 1,4:3,6-dianhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-D-glucitol: To a solution of 1,4:3,6-dianhydro-2-*O*-methyl-D-glucitol (1.19g, 7.4 mmol) in dichloromethane was added pyridine (1mL, 12.36 mmol) followed by methanesulfonyl chloride (0.69mL, 8.92 mmol) and the mixture was allowed to stir at room temperature over 12 hours. The solvent was removed and the amorphous residue was partitioned with ethyl acetate and 0.1M aqueous hydrochloric acid. The aqueous phase was extracted once with additional

ethyl acetate and the combined organic layers were washed with saturated aqueous sodium chloride then dried over anhydrous magnesium sulfate. Filtration and concentration followed by drying *in vacuo* afforded 1,4:3,6-dianhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-D-glucitol (1.67g, 94% yield) as a colorless oil. GC/MS calculated for $C_8H_{14}SO_6$: 238 ($M^+$).

**Example 54**

**[0360]** 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-D-fructose ethylene glycol acetal: A solution of 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-D-fructose (2.00g, 8.06 mmol), ethylene glycol (5.00g, 80.6 mmol), and *p*-toluenesulfonic acid (1.53g, 8.06 mmol) in benzene (100mL) was refluxed for 90 min using a Dean-Stark Trap apparatus. The reaction mixture was diluted with ethyl acetate (100mL), washed with saturated aqueous sodium bicarbonate (2 x 50mL) then brine (50mL), and dried over anhydrous sodium sulfate. Filtration, concentration and column chromatography on silica (1:1 hexane/ethyl acetate) provided 1.44g (61% yield) of 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-D-fructose ethylene glycol acetal as a colorless solid. $^1$H NMR (400 MHz; $CDCl_3$): 8.08 (m, 2H), 7.58 (m, 1H), 7.54 (m, 2H), 5.38 (dd, 1H), 4.97 (t, 1H), 4.21-4.02 (m, 7H), 3.86 (d, 1H), 3.75 (d, 1H).

**Example 55**

**[0361]** 1,4:3,6-dianhydro-D-fructose ethylene glycol acetal: To a solution of 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-D-fructose ethylene glycol acetal (1.44g, 4.93 mmol) in methanol (40mL) was added 50% aqueous sodium hydroxide (0.38 g, 4.75 mmol) and the mixture was stirred at room temperature for 30 minutes. Neutralization with 1M HCl, followed by concentration and column chromatography on silica (1:2 hexane/ethyl acetate) provided 0.74g (80% yield) of 1,4:3,6-dianhydro-D-fructose ethylene glycol acetal as a colorless solid. $^1$H NMR (400 MHz; $CDCl_3$): 4.60 (t, 1H), 4.32 (m, 1H), 4.14 (d, 1H), 4.05-3.98 (m, 5H), 3.82 (s, 2H), 3.62 (dd, 1H), 2.65 (d, 1H).

**[0362]** 1,4:3,6-dianhydro-5-*O*-(methylsulfonyl)-D-fructose ethylene glycol acetal: To a solution of 1,4:3,6-dianhydro-D-fructose ethylene glycol acetal (0.74g, 3.93 mmol) and triethylamine (1.20g, 11.86 mmol) in dichloromethane (40mL) was added

methanesulfonyl chloride (0.90g, 7.88 mmol) at 0°C under nitrogen. The solution was warmed to room temperature and stirred for 13 h. Dichloromethane (50mL) was added, and the organic layer was washed with saturated aqueous sodium bicarbonate (30mL), water (30mL), and brine (30mL) then dried over anhydrous sodium sulfate. Filtration and concentration provided 1.02g (97%) of 1,4:3,6-dianhydro-5-*O*-(methylsulfonyl)-D-fructose ethylene glycol acetal as a yellow oil. $^1$H NMR (400 MHz; $CDCl_3$): 5.08 (m, 1H), 4.82 (t, 1H), 4.13 (dd, 1H), 4.04 (m, 4H), 3.93 (dd, 1H), 3.87 (d, 1H), 3.81 (d, 1H), 3.13 (s, 3H).

## Example 56

**[0363]** 1,4:3,6-dianhydro-2-deoxy-2-methylidene-D-*arabino*-hexitol: To a solution of 1,4:3,6-dianhydro-2-deoxy-2-methylidene-5-*O*-(phenylcarbonyl)-D-*arabino*-hexitol (329mg, 1.34 mmol) in methanol (10mL) was added 50% aqueous sodium hydroxide (95mg, 1.19 mmol) and the mixture was stirred at room temperature for 30 minutes. Neutralization with 4M hydrogen chloride in 1,4-dioxane followed by concentration and column chromatography on silica (1:1 hexane/ethyl acetate) provided 141mg (74%) of 1,4:3,6-dianhydro-2-deoxy-2-methylidene-D-*arabino*-hexitol as a colorless solid. $^1$H NMR (400 MHz; $CDCl_3$): 5.37 (m, 1H), 5.20 (m, 1H), 4.80 (m, 1H), 4.54 (m, 2H), 4.43 (m, 1H), 4.26 (m, 1H), 3.95 (dd, 1H), 3.54 (dd, 1H), 2.70 (d, 1H).

**[0364]** 1,4:3,6-dianhydro-2-deoxy-2-methylidene-5-*O*-(methylsulfonyl)-D-*arabino*-hexitol: To a solution of 1,4:3,6-dianhydro-2-deoxy-2-methylidene-D-*arabino*-hexitol (135mg, 0.95 mmol) and triethylamine (288mg, 2.85 mmol) in dichloromethane (10mL) was added methanesulfonyl chloride (222mg, 1.94 mmol) at 0°C under nitrogen. The solution was warmed to room temperature and stirred for 18 h. Dichloromethane (50mL) was added and the organic layer was washed with saturated aqueous sodium bicarbonate (2 x 25mL), water (25mL) and brine (25mL) then dried over anhydrous sodium sulfate. Filtration and concentration provided 213mg (72%) of 1,4:3,6-dianhydro-2-deoxy-2-methylidene-5-*O*-(methylsulfonyl)-D-*arabino*-hexitol as a yellow oil. $^1$H NMR (400 MHz; $CDCl_3$): 5.40 (m, 1H), 5.23 (m, 1H), 5.04 (m, 1H), 4.85 (m, 1H), 4.73 (t, 1H), 4.58 (m, 1H), 4.41 (m, 1H), 4.08 (dd, 1H), 3.86 (dd, 1H), 3.14 (s, 3H).

## Example 57

[0365] 1,4:3,6-dianhydro-2-deoxy-5-*O*-(phenylcarbonyl)-L-*arabino*-hex-1-enitol: To a mixture of 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-(D)-glycitol (4.32g, 17.3 mmol), triethylamine (4.91 mL, 35.3 mmol) and 4-dimethylaminopyridine (0.63g, 5.2 mmol) in dichloromethane (50 mL) at -10 ° to -15° was added trifluromethanesulfonic anhydride (3.48mL, 20.7 mmol) dropwise over ten minutes and the resulting mixture was stirred at this temperature for 3 hours. The mixture was poured into 100 mL of ice-water and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered then concentrated. The crude triflate was suspended in toluene (50 mL) followed by addition of 1,8-diazabicyclo[4,5,0]undec-7-ene (5.25 mL, 34.6 mmol) and the mixture was stirred at room temperature for 18 hours. The reaction mixture was poured into ice-water and partitioned then the aqueous portion was extracted with dichloromethane (3 x 50 mL). The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flashed chromatography (silica gel, 5-20% ethyl acetate-hexane) to give 1,4:3,6-dianhydro-2-deoxy-5-*O*-(phenylcarbonyl)-L-*arabino*-hex-1-enitol, as a white solid, 3.10g, 77% yield. $^1$H NMR (400MHz; $CDCl_3$): 8.08-8.06 (m, 2H), 7.61-7.57 (m, 1H), 7.56-7.43 (m, 2H), 6.62-6.61 (d, 1H), 5.48-5.46 (m,1H), 5.32-5.26 (m,1H), 5.13-5.10 (m, 2H), 4.18-4.14 (tr,1H), 3.61-3.56 (tr, 1H).

## Example 58

[0366] Methyl 3,6-anhydro-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside: To a solution of 1,4:3,6-dianhydro-2-deoxy-5-*O*-(phenylcarbonyl)-L-arabino-hex-1-enitol (1.00g, 4.3 mmol) in methanol (17 mL) at -4°C was added 3-chloroperoxybenzoic acid (85%, 1.35g, 8.6 mmol), and the resulting mixture was slowly warmed to room temperature and stirred for 18 hours. The reaction mixture was concentrated, diluted with dichloromethane (50 mL), washed with saturated aqueous sodium bicarbonate solution, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (silica gel, 25-60% ethyl acetate-hexane) to give methyl 3,6-anhydro-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside as a white solid, 1.03g, 83% yield. $^1$H NMR (400MHz; $CDCl_3$): 8.11-8.08 (d, 2H), 7.61-7.56 (tr, 1H), 7.48-7.44 (m, 2H), 5.24-5.17

(m, 2H), 4.96 (s, 1H), 4.57-4.56 (d, 1H), 4.27 (s, 1H), 4.22-4.18 (dd, 1H), 4.08-4.04 (dd, 1H) 3.36 (s, 3H).

**[0367]** Methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside: A mixture of methyl 3,6-anhydro-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside (1.03g, 3.7 mmol), silver (I) oxide (0.85g, 3.7 mmol) and methyl iodide (0.34 mL, 5.5 mmol) in DMF (2 mL) was heated at 60°C for 1 hour. After cooling to room temperature the reaction mixture was diluted with ethyl acetate (50 mL), filtered over celite, adsorbed on silica gel (10g) and purified by flash chromatography (silica gel, 5-30% ethyl acetate-hexane) to give methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside as a colorless oil, 0.82g, 76% yield. $^1$H NMR (400MHz; $CDCl_3$): 8.11-8.09 (d, 2H), 7.60-7.56 (m, 1H), 7.46-7.44 (m, 2H), 5.24-5.20 (m, 1H), 5.18-5.09 (tr, 1H), 4.99 (s, 1H), 4.61-4.60 (d, 1H), 4.21-4.17 (tr, 1H), 4.08-4.03 (tr, 1H), 3.81 (s, 1H), 3.40 (s, 3H), 3.57 (s, 3H).

**[0368]** Methyl 3,6-anhydro-2-*O*-methyl-α-D-idofuranoside: A solution of methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside (820mg, 3.1mmol) and 50% sodium hydroxide (248 mg, 3.1 mmol) in methanol (10mL) was stirred at room temperature for 30 minutes. The material was adsorbed on silica gel (5g) and passed through a short column (15% ethyl acetate in hexanes to 5% methanol in ethyl acetate) to give methyl 3,6-anhydro-2-*O*-methyl-α-D-idofuranoside as a colorless oil, 420 mg, 85% yield. $^1$H NMR (400MHz; $CDCl_3$): 5.04 (s, 1H), 5.84-5.81 (tr, 1H), 4.44-4.42 (tr, 1H), 4.25-4.19 (m, 1H), 3.85-3.75 (m, 1H), 3.49 (s, 3H), 3.43 (s, 3H), 2.75-2.72 (d, 1H).

**[0369]** Methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-β-L-glucofuranoside: Methyl 3,6-anhydro-2-*O*-methyl-α-D-idofuranoside (420 mg, 2.6 mmol) was dissolved in dichloromethane (10 mL) and pyridine (0.36 mL, 3.7 mmol) at 0°C. Methanesulfonyl chloride (0.14 mL, 3.1 mmol) was added and the resulting mixture was stirred at 0°C for 1 hour then at room temperature for 2 hours. The reaction mixture was washed with water and saturated aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, filtered and concentrated to give methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-β-L-glucofuranoside as a colorless oil, 669mg, 95% yield, which was used without further purification.

**Example 59**

[0370] 3,6-anhydro-5-*O*-(phenylcarbonyl)-α-L-glucofuranose: A mixture of osmium tetroxide (4% in water, 0.25 mL, 0.03 mmol) and N-methylmorpholine (505 mg, 4.3 mmol) in 3 mL of 50% acetone in water was warmed to 60°C. A solution of 1,4:3,6-dianhydro-2-deoxy-5-*O*-(phenylcarbonyl)-L-*arabino*-hex-1-enitol (2.00g, 8.6 mmol) in 6 mL of 50% acetone in water was added over 3 hours. During this time an additional amount of N-methylmorpholine (1.01g, 8.6 mmol) was added in small portions periodically. Upon completion of the addition process the reaction was stirred for another hour and cooled to room temperature. The crude mixture was applied to a column of silica gel and flashed (0-6% methanol in 1:1 ethyl acetate:hexane) to give 3,6-anhydro-5-*O*-(phenylcarbonyl)-α-L-glucofuranose as a white solid, 1.5g, 65% yield. $^1$H NMR (400MHz; DMSO-$d_6$): 8.01-7.95, (m, 2H), 7.68-7.66 (m, 1H), 7.57-7.53 (m, 2H), 5.18-5.11 (m, 2H), 4.85-4.81 (m, 1H, m), 4.37-4.35 (m, 1H), 4.05-3.96 (m, 2H), 3.85-3.83 (m, 1H).

[0371] 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-α-L-glucofuranoside: 3,6-Anhydro-5-*O*-(phenylcarbonyl)-α-L-glucofuranose (576 mg, 2.2 mmol) was added to a mixture of sodium hydride (60% oil dispersion, 346 mg, 8.7 mmol) and methyl iodide (0.54mL, 8.7 mmol) in 5 mL of DMF at 0°C and the resulting mixture was stirred for 1 hour. The reaction mixture was diluted with ethyl acetate and quenched with water (5 mL). The aqueous portion was extracted with ethyl acetate (3 x 5 mL). The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flashed chromatography (silica gel, 5-20% ethyl acetate in hexane) to give 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-α-L-glucofuranoside as a white solid, 270 mg, 42% yield. $^1$H NMR (400MHz; $CDCl_3$): 8.09-8.07 (m, 2H), 7.61-7.57 (m, 1H), 7.48-7.27 (m, 2H), 5.25-5.22 (m, 1H), 5.07-5.06 (d, 1H), 4.94-4.91 (m, 1H), 4.73-4.71 (m, 1H), 4.20-4.16 (m, 1H), 3.96-3.94 (m, 1H), 3.85-3.83 (tr, 1H), 3.50 (s, 3H), 3.42 (s, 3H).

[0372] Methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-α-L-glucofuranoside: A solution of methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-α-L-glucofuranoside (230mg, 0.92 mmol) and 50% sodium hydroxide (74 mg, 0.92 mmol) in methanol (5 mL) was stirred at room temperature for 30 minutes. The mixture was adsorbed on silica gel (2g) and passed through a short column (15% ethyl acetate in hexanes to 5% methanol in ethyl acetate) to afford a colorless oil which was employed directly in the next step, 140

mg, 0.72 mmol, 95% yield. The alcohol was dissolved in dichloromethane (5 mL) and pyridine (121 μL, 1.03 mmol) was added at 0°C. Methanesulfonyl chloride (27μL, 0.88 mmol) was added and the resulting mixture was stirred at 0°C for 1 hour then at room temperature for 2 hours. The reaction mixture was washed with water and saturated aqueous sodium bicarbonate solution, dried over sodium sulfate, filtered and concentrated to give methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-α-L-glucofuranoside as a colorless oil, 190 mg, 96% yield.

**Example 60**

**[0373]** 3,6-Anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(phenylcarbonyl)-α-L-glucofuranose: A mixture of 3,6-anhydro-5-*O*-(phenylcarbonyl)-α-L-glucofuranose (1.00g), 2,2-dimethoxy propane (0.63 mL), p-toluenesulfonic acid (20 mg) and benzene (10 mL) was heated at reflux for 3 hours. The reaction mixture was cooled then adsorbed on silica gel (10g) and purified by flash chromatography (silica gel, 5-35% ethyl acetate in hexanes) to give 3,6-anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(phenylcarbonyl)-α-L-glucofuranose as colorless oil, 0.85g, 74% yield. $^1$H NMR (400MHz; $CDCl_3$): 8.08-8.06 (d, 2H), 7.59-7.56 (tr, 1H), 7.46-7.42 (m, 2H), 5.99-5.98 (d, 1H), 5.35-5.31 (tr, 1H), 5.10-5.08 (d, 1H), 4.66-4.65 (d, 1H), 4.61-4.60 (d, 1H), 4.20-4.16 (dd, 1H), 3.91-3.74 (tr, 1H,), 1.50 (s, 3H), 1.34 (s, 3H).

**[0374]** 3,6-Anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(methylsulfonyl)-α-L-glucofuranose: A solution of 3,6-anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(phenylcarbonyl)-α-L-glucofuranose (850mg) and 50% sodium hydroxide (111 mg) in methanol (10mL) was stirred at room temperature for 30 minutes. The mixture was then adsorbed on silica gel (5g) and passed through a short column (15% ethyl acetate in hexanes to 5% methanol in ethyl acetate) and the alcohol intermediate, 390 mg, 70% yield, was used immediately in the next step. The alcohol was dissolved in dichloromethane (10 mL) and pyridine (0.32 mL) at 0°C. Methanesulfonyl chloride (0.12 mL) was added and the resulting mixture was stirred at 0°C for 1 hour then at room temperature for 2 hours. The reaction mixture was washed with water and saturated aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, filtered and concentrated to give 3,6-anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(methylsulfonyl)-α-L-glucofuranose as a colorless oil, 485 mg, 90% yield, which was immediately employed in the next step.

## Example 61

**[0375]** (3*S*,8a*S*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine: (*S*)-(+)-Prolinol (6.00 g, 59.3 mmol) was added to epichlorohydrin (47 mL, 600 mmol) at 0°C. The solution was stirred at 40°C for 0.5 h and then concentrated *in vacuo*. The residual oil was cooled in an ice bath and concentrated sulfuric acid (18 mL) was added dropwise with stirring. The mixture was heated at 170-180°C for 1.5 h, poured into ice (300 mL) and then basified with sodium carbonate to pH~8. The mixture was partitioned with ethyl acetate/hexanes and filtered. The filtrate was separated and the aqueous portion was extracted twice with ethyl acetate. The combined organic portion was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford oil that was purified by column chromatography (ethyl acetate for less polar product and then 30% methanol in ethyl acetate). (3*S*,8a*S*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine (less polar product) (1.87 g, 10.7 mmol, 18% yield): $^1$H NMR (400 MHz, $CDCl_3$): 4.06 (dd, 1H), 3.79-3.71 (m, 1H), 3.60-3.48 (m, 2H), 3.36 (dd, 1H), 3.15 (dd, 1H), 3.13-3.06 (m, 1H), 2.21-2.01 (m, 3H), 1.90-1.68 (m, 3H), 1.39-1.24 (m, 1H); MS (EI) for $C_8H_{14}NOCl$: 176 ($MH^+$). (3*R*,8a*S*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine (1.54 g, 8.77 mmol, 15% yield): $^1$H NMR (400 MHz, $CDCl_3$): 3.94-3.77 (m, 4H), 3.55 (dd, 1H), 3.02-2.93 (m, 2H), 2.45 (dd, 1H), 2.29-2.15 (m, 2H), 1.88-1.64 (m, 3H), 1.49-1.38 (m, 1H); MS (EI) for $C_8H_{14}NOCl$: 176 ($MH^+$).

**[0376]** Using the same or analogous synthetic techniques and/or substituting with alternative starting materials, the following were prepared:

**[0377]** (3*R*,8a*R*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine: $^1$H NMR (400 MHz, $CDCl_3$): 4.05 (dd, 1H), 3.79-3.70 (m, 1H), 3.61-3.48 (m, 2H), 3.35 (dd, 1H), 3.15 (dd, 1H), 3.13-3.07 (m, 1H), 2.21-2.01 (m, 3H), 1.89-1.67 (m, 3H), 1.39-1.25 (m, 1H); MS (EI) for $C_8H_{14}NOCl$: 176 ($MH^+$).

**[0378]** (3*S*,8a*R*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine: $^1$H NMR (400 MHz, $CDCl_3$): 3.93-3.77 (m, 4H), 3.55 (dd, 1H), 3.02-2.93 (m, 2H), 2.45 (dd, 1H), 2.30-2.15 (m, 2H), 1.88-1.64 (m, 3H), 1.49-1.37 (m, 1H); MS (EI) for $C_8H_{14}NOCl$: 176 ($MH^+$).

## Example 62

**[0379]** (3*S*,8a*S*)-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl acetate: (3*S*,8a*S*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine (2.30 g, 13.1 mmol) and potassium acetate (12.8 g, 131 mmol) were stirred in dimethylformamide (25 mL) at 140°C for 20 h. The mixture was partitioned between ethyl acetate and water. The organic portion was washed twice with water, then with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford (3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl acetate as a brown oil (2.53 g, 12.7 mmol, 97% yield). $^1$H NMR (400 MHz, $CDCl_3$): 4.14-4.02 (m, 3H), 3.81-3.72 (m, 1H), 3.37-3.31 (m, 1H), 3.09 (dt, 1H), 3.00 (dd, 1H), 2.21-2.00 (m, 3H), 2.10 (s, 3H), 1.90-1.67 (m, 3H), 1.39-1.24 (m, 1H); MS (EI) for $C_{10}H_{17}NO_3$: 200 ($MH^+$).

**[0380]** (3*S*,8a*S*)-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethanol: (3*S*,8a*S*)-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl acetate (2.36 g, 11.9 mmol) was treated with sodium methoxide (25 wt% solution in methanol; 2.7 mL) for 0.5 h. The mixture was cooled in an ice bath and a solution of 4M HCl in 1,4-dioxane (3 mL, 12.0 mmol) was added slowly. The mixture was stirred at room temperature for 5 minutes and then was concentrated *in vacuo* to afford a suspension which was diluted with dichloromethane, filtered and the filtrate was concentrated *in vacuo* to afford (3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethanol as a brown oil (1.93 g, >100% yield). $^1$H NMR (400 MHz, $CDCl_3$): 4.05 (dd, 1H), 3.73-3.65 (m, 2H), 3.62-3.56 (m, 1H), 3.39-3.34 (m, 1H), 3.10 (dt, 1H), 3.00-2.95 (m, 1H), 2.24-1.98 (m, 4H), 1.97-1.70 (m, 3H), 1.44-1.28 (m, 1H); MS (EI) for $C_8H_{15}NO_2$: 158 ($MH^+$).

**[0381]** (3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl methanesulfonate: (3*S*,8a*S*)-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethanol (1.00 g, 6.37 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (2.4 mL, 17.3 mmol) was added at 0°C followed by dropwise addition of methanesulfonyl chloride (0.93 mL, 12.0 mmol). The solution was warmed to room temperature and stirred for 1.25 h and then was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic portion was washed with saturated sodium bicarbonate solution. The combined aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford (3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-

ylmethyl methanesulfonate as an orange-brown oil (1.20 g, 5.1 mmol, 80% yield). MS (EI) for $C_9H_{17}NO_4S$: 236 ($MH^+$).

## Example 63

**[0382]** Octahydro-2*H*-quinolizin-3-ylmethanol: Ethyl octahydro-2*H*-quinolizine-3-carboxylate (2.35 g, 11.1 mmol) was added dropwise to a stirred suspension of lithium aluminum hydride (1 M solution in tetrahydrofuran, 33 mL, 33 mmol) in tetrahydrofuran (50 mL) at 0°C. The reaction was stirred at room temperature for 3 h. The mixture was cooled in an ice bath and ethyl acetate (6 mL) was added slowly, followed by water (1.25 mL), 15% aqueous sodium hydroxide solution (5 mL) and water (1.25 mL). The mixture was filtered through a pad of celite and washed with ether. The filtrate was concentrated *in vacuo* and dried rigorously to afford octahydro-2*H*-quinolizin-3-ylmethanol as a yellow oil (1.66 g, 9.82 mmol, 88% yield). MS (EI) for $C_{10}H_{19}NO$: 170 ($MH^+$).

**[0383]** Octahydro-2*H*-quinolizin-3-ylmethyl methanesulfonate: Octahydro-2*H*-quinolizin-3-ylmethanol (600 mg, 3.55 mmol) was dissolved in dichloromethane (8 mL) and triethylamine (1.5 mL, 10.8 mmol) was added at 0°C followed by dropwise addition of methanesulfonyl chloride (0.56 mL, 7.16 mmol). The solution was warmed to room temperature and stirred for 1.25 h and then was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford octahydro-2*H*-quinolizin-3-ylmethyl methanesulfonate as an orange oil (796 mg, 3.22 mmol, 91% yield). MS (EI) for $C_{11}H_{21}NO_3S$: 248 ($MH^+$).

## Example 64

**[0384]** (3*S*,8a*S*)-3-(Hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one: A solution of methyl 1-[(2*S*)-3-hydroxy-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]-L-prolinate (3.50 g, 10.4 mmol) in methanol was added to 5% palladium on carbon (50 wt.% in water) in methanol and treated with hydrogen at 40 psi for 1 h. The mixture was filtered and the filtrate was brought to reflux briefly and then cooled and concentrated *in vacuo* to afford (3*S*,8a*S*)-3-(hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as

a colorless solid (1.50 g, 8.83 mmol, 85% yield). $^1$H NMR (400 MHz, $CDCl_3$): 7.28-7.22 (m, 1H), 3.83-3.75 (m, 1H), 3.69 (dd, 1H), 3.56 (dd, 1H), 3.31 (t, 1H), 3.08 (dd, 1H), 2.92 (dt, 1H), 2.76-2.70 (m, 1H), 2.66 (dd, 1H), 2.28-2.16 (m, 1H), 2.02-1.73 (m, 3H); MS (EI) for $C_8H_{14}N_2O_2$: 171 ($MH^+$).

**[0385]** (3*S*,8a*S*)-3-({[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydro-pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one: To a solution of (3*S*,8a*S*)-3-(hydroxymethyl) hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (1.49 g, 8.82 mmol) in dimethylformamide (20 mL) was added triethylamine (2.45 mL, 17.6 mmol) and 4-dimethylaminopyridine (90 mg, 0.882 mmol). The solution was cooled in an ice bath and *tert*-butyldimethylsilyl chloride (2.66 g, 17.6 mmol) was added. The mixture was warmed to room temperature and stirred for 14 h. The mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and water. The aqueous portion was extracted twice with ethyl acetate. The combined organic portion was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a pale brown solid which was triturated with ethyl acetate to afford (3*S*,8a*S*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl) hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as an off-white solid (1.74 g, 5.84 mmol, 66% yield). $^1$H NMR (400 MHz, $CDCl_3$): 6.09-5.90 (m, 1H), 3.86-3.76 (m, 1H), 3.63 (dd, 1H), 3.44 (dd, 1H), 3.25 (t, 1H), 3.10 (ddd, 1H), 2.98-2.90 (m, 1H), 2.68-2.60 (m, 1H), 2.52 (dd, 1H), 2.28-2.18 (m, 1H), 2.06-1.95 (m, 1H), 1.93-1.74 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H); MS (EI) for $C_{14}H_{28}N_2O_2Si$: 285 ($MH^+$).

**[0386]** (3*S*,8a*S*)-3-({[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}methyl)-2-methylhexahydro pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one: (3*S*,8a*S*)-3-({[(1,1-Dimethylethyl)(dimethyl)silyl]oxy} methyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (1.51g, 5.32mmol) in dimethylformamide (8 mL) was added to an ice-cooled suspension of sodium hydride (60 wt.% dispersion in oil; 213 mg, 5.32 mmol) in dimethylformamide (8 mL). The mixture was stirred at 0°C for 0.25 h and then iodomethane (0.332 mL, 5.32 mmol) was added dropwise. The mixture was stirred at room temperature for 0.5 h and then was stirred at 70°C for 2 h. The mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and water. The aqueous portion was extracted with ethyl acetate. The combined organic portion was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford (3*S*,8a*S*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as a yellow oil (1.552 g, 5.21 mmol) which was dissolved in tetrahydrofuran (20 mL) and treated with tetrabutylammonium

fluoride (1.0M solution in tetrahydrofuran; 10.4 mL, 10.4 mmol) for 2 h at room temperature. The mixture was concentrated *in vacuo* and purified by column chromatography (10% methanol in dichloromethane) to afford (3*S*,8a*S*)-3-(hydroxymethyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as a yellow oil (496mg, 2.70mmol, 51% yield from (3*S*,8a*S*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy} methyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one). $^1$H NMR (400 MHz, $CDCl_3$): 3.98-3.93 (m, 1H), 3.86 (dd, 1H), 3.61-3.55 (m, 1H), 3.29-3.25 (m, 1H), 3.09-3.03 (m, 1H), 3.03-2.97 (m, 1H), 3.02 (s, 3H), 2.93 (dd, 1H), 2.87-2.79 (m, 1H), 2.32-2.21 (m, 1H), 2.00-1.86 (m, 2H), 1.83-1.64 (m, 1H); MS (EI) for $C_9H_{16}N_2O_2$: 185 ($MH^+$).

## Example 65

**[0387]** 1,2-Dideoxy-1-[(2*S*)-2-(methoxycarbonyl)-1-pyrrolidinyl]-2-[[(phenylmethoxy) carbonyl]amino]-D-*glycero*-hexitol: To a solution of 2-deoxy-2-{[(phenylmethyloxy) carbonyl]amino}-D-glycero-hexopyranose (5.0 g, 0.016 mol) in methanol (500 mL) was added L-proline methyl ester hydrochloride (2.8 g, 0.022 mol) and sodium cyanoborohydride (3.4 g, 0.054 mol). The solution was heated to 64 °C for 14 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* to afford 1,2-dideoxy-1-[(2*S*)-2-(methoxycarbonyl)-1-pyrrolidinyl]-2-[[(phenylmethoxy)carbonyl] amino]-D-*glycero*-hexitol (6.81 g, 100%) as a clear and colorless oil. MS (EI) for $C_{20}H_{31}N_2O_8$: 427 ($MH^+$).

## Example 66

**[0388]** Methyl 1-[(2*S*)-3-hydroxy-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]-L-prolinate: 1,2-dideoxy-1-[(2*S*)-2-(methoxycarbonyl)-1-pyrrolidinyl]-2-[[(phenylmethoxy) carbonyl]amino]-D-*glycero*-hexitol (6.81 g, 0.016 mol) was taken into water (100 mL) and the resulting solution was cooled to 0°C. Sodium periodiate (14.8 g, 0.069 mol) dissolved in water was added dropwise and the resulting mixture was stirred at 0°C for 2 h. The reaction mixture was partitioned with dichloromethane (3x100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was taken up in methanol (200 mL) and the resulting solution was cooled to 0°C. Sodium borohydride

(1.98 g, 0.052 mol) was added and the reaction mixture was stirred for 1 h at 0°C. The reaction mixture was concentrated *in vacuo* and partitioned with dichloromethane and saturated aqueous ammonium chloride. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude product was purified by column chromatography (5% methanol in dichloromethane) to yield methyl 1-[(2*S*)-3-hydroxy-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]-L-prolinate (4.9 g, 92%) as a white solid. MS (EI) for $C_{17}H_{25}N_2O_5$: 337 ($MH^+$).

**[0389]** Methyl 1-[(2*S*)-3-[(methylsulfonyl)oxy]-2-({[(phenylmethyl)oxy]carbonyl}amino) propyl]-L-prolinate: Methyl 1-[(2*S*)-3-hydroxy-2-({[(phenylmethyl)oxy]carbonyl}amino) propyl]-L-prolinate (200 mg, 0.594 mmol) was dissolved in dichloromethane (5 mL) followed by the addition of 4-(dimethylamino)pyridine (3.6 mg, 0.039 mmol) and triethylamine (0.125 mL, 0.891 mmol) and the resulting mixture was cooled to 0 °C. Methanesulfonyl chloride (0.060 mL, 0.773 mmol) was added dropwise and the reaction mixture was stirred for 1 h at 0°C. The mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford methyl 1-[(2*S*)-3-[(methylsulfonyl)oxy]-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]-L-prolinate (246 mg, 100%) as a clear and colorless oil. MS (EI) for $C_{18}H_{27}N_2O_7S$: 415 ($MH^+$).

## Example 67

**[0390]** 1,1-Dimethylethyl (3a*R*,6a*S*)-5-(hydroxymethyl)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate: Under a nitrogen atmosphere, borane tetrahydrofuran complex (1M in THF, 42 mL, 41.9 mmol) was diluted with tetrahydrofuran (42 mL) and cooled with an ice bath. Neat 2,3-dimethylbut-2-ene (5.0 mL, 41.9 mmol) was added in portions over 0.25 h and the solution was stirred at 0°C for 3 h. A solution of 1,1-dimethylethyl (3a*R*,6a*S*)-5-methylidenehexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate (1.98 g, 8.88 mmol) in tetrahydrofuran (10 mL) was added slowly, and the solution was warmed to room temperature and stirred 12 h. After cooling to 0°C, 10% aqueous sodium hydroxide (17 mL, 41.7 mmol) was added slowly, followed by 30% aqueous hydrogen peroxide (13 mL, 128 mmol) and the solution was warmed to room temperature. The solvent was removed *in vacuo* and the solution was partitioned between water and diethyl ether. The layers were separated and the aqueous layer was further extracted (3 x 50 mL diethyl ether). The

combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide 2.04 (95%) of 1,1-dimethylethyl (3a*R*,6a*S*)-5-(hydroxymethyl)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate, which was used without purification. $^1$H NMR (400 MHz, $CDCl_3$): 8.50 (broad s, 1H), 3.66-3.46 (m, 3H), 3.20-3.00 (m, 2H), 2.70-2.59 (m, 2H), 2.37-2.18 (m, 1H), 2.04 (m, 1H), 1.84 (broad s, 1H), 1.70-1.55 (m, 1H), 1.46 (s, 9H), 1.17 (m, 1H), 0.93 (m, 1H).

**[0391]** 1,1-Dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]methyl}hexahydrocyclopenta [*c*]pyrrole-2(1*H*)-carboxylate: Methanesulfonyl chloride (0.2mL, 2.48mmol), was added dropwise to a solution of 1,1-dimethylethyl (3a*R*,6a*S*)-5-(hydroxymethyl)hexahydro cyclopenta[*c*] pyrrole-2(1*H*)-carboxylate (0.40 g, 1.65 mmol) and triethylamine (0.69 mL, 4.95 mmol) in 20 mL dichloromethane at 0°C and the reaction mixture was stirred for 1 h at room temperature. The solvent was evaporated, the resulting crude mixture was diluted with 100 mL ethyl acetate and washed with water (30 mL), 1M aqueous sodium hydroxide, brine, 1M aqueous hydrochloric acid and brine again. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting 1,1-dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]methyl}hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate was used without further purification. MS (EI) for $C_{14}H_{25}NO_5S$: 320 ($MH^+$), 264 (M-tBu).

## Example 68

**[0392]** 1,1-Dimethylethyl (3a*R*,6a*S*)-5-(hydroxy)-hexahydrocyclopenta[*c*] pyrrole-2(1*H*)-carboxylate: Sodium borohydride (0.15 g, 4.00 mmol), was added to a solution of 1,1-dimethylethyl (3a*R*,6a*S*)-5-oxo-hexahydrocyclopenta[*c*] pyrrole-2(1*H*)-carboxylate (0.45 g, 2.00 mmol) in 10 mL methanol at 0°C and the reaction mixture was stirred for 1 h at this temperature. The solvent was evaporated, the crude mixture was diluted with 100 mL ethyl acetate and washed with water (30 mL), 1M aqueous hydrochloric acid and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give 1,1-dimethylethyl (3a*R*,6a*S*)-5-(hydroxy)-hexahydrocyclopenta[*c*] pyrrole-2(1*H*)-carboxylate (0.44g, 98%). $^1$H NMR (400 MHz, $d_6$-DMSO): 4.08 (m, 1H), 3.40 (m, 2H), 3.30 (m, 2H), 2.50 (m, 2H), 1.98 (m, 2H), 1.40 (s, 9H), 1.30 (m, 2H). MS (EI) for $C_{12}H_{21}NO_3$: 228 ($MH^+$).

**[0393]** 1,1-Dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]}hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate: Methanesulfonyl chloride (0.18 mL, 2.33 mmol), was added dropwise to a solution of 1,1-dimethylethyl (3a*R*,6a*S*)-5-(hydroxy)-hexahydrocyclopenta[*c*] pyrrole-2(1*H*)-carboxylate (0.44 g, 1.94 mmol) and triethylamine (0.81 mL, 5.81 mmol) in 10 mL dichloromethane at 0°C and the reaction mixture was stirred for 1 h at room temperature. The solvent was evaporated, the resulting crude mixture was diluted with 100 mL ethyl acetate and washed with water (30 mL), brine, 1M aqueous hydrochloric acid and brine again. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude 1,1-dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]}hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate was used without further purification. MS (EI) for $C_{13}H_{23}NO_5S$: 306 ($MH^+$).

## Example 69

**[0394]** 3-(Chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine: A solution of (3*R*)-morpholin-3-ylmethanol (4.21 g, 36.0 mmol) in 2-(chloromethyl)oxirane (28.2 mL, 0.360 mol) was heated to 40°C for 3 h and then the solution was concentrated *in vacuo*. The intermediate was cooled in an ice bath and treated with 30.0 mL of concentrated sulfuric acid. The mixture was heated to 170°C for 2 h and then allowed to cool to room temperature. The mixture was poured into ice-water and solid sodium bicarbonate was carefully added until the solution was basic. 10% methanol in ethyl acetate was added and the biphasic mixture was filtered. The layers were separated and the aqueous layer was extracted (3 x 100 mL 10% methanol in ethyl acetate). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography ($SiO_2$, 2:5 hexanes:ethyl acetate) provided 3-(chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine 2.44g (35%) as two separated diastereomers. (3*R*,9a*S*)-3-(chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine: (0.886 g, 13% yield): $^1H$ NMR (400 MHz, $CDCl_3$): 3.91 (m, 3H), 3.82 (m, 1H), 3.68 (dt, 1H), 3.61 (dd, 1H), 3.47 (dd, 1H), 3.35 (t, 1H), 3.19 (t, 1H), 2.80 (d, 1H), 2.54 (m, 2H), 2.40 (m, 2H); MS (EI) for $C_8H_{14}NO_2Cl$: 192 ($MH^+$). (3*S*,9a*S*)-3-(chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine: (1.55 g, 22% yield): $^1H$ NMR (400 MHz, $CDCl_3$): 3.85 (m, 2H), 3.73 (m, 3H), 3.50 (m, 2H), 3.29 (t, 1H), 3.18 (t, 1H), 2.85 (dd, 1H), 2.64 (dd, 1H), 2.40 (m, 2H), 2.17 (t, 1H); MS (EI) for $C_8H_{14}NO_2Cl$: 192 ($MH^+$).

**[0395]** Hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate: A suspension of (3*R*,9a*S*)-3-(chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine (1.97 g, 10.3 mmol) and potassium acetate (10.1 g, 102 mmol) in DMF (20.0 mL) was stirred at 140°C for 16 h, and then at 150°C for another 12 h. The reaction mixture was partitioned between water (250 mL) and ethyl acetate (250 mL), the organic layer was washed with 5% lithium chloride (2 x 100 mL) and brine (100 mL) then dried over anhydrous sodium sulfate and concentrated *in vacuo*. Column chromatography ($SiO_2$, 1:1 hexane:ethyl acetate, then 100% ethyl acetate) afforded 0.92 g (42%) of hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate as a yellow oil. Distinct diastereomers as described above were converted in this step to give: (3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate: $^1$H NMR (400 MHz, $CDCl_3$): 4.18 (dd, 1H), 4.00 (m, 1H), 3.80 (dd, 1H), 3.68 (dt, 1H), 3.60 (dd, 1H), 3.46 (m, 2H), 3.22 (t, 1H), 2.64 (dd, 1H), 2.53 (m, 2H), 2.43-2.35 (m, 2H), 2.10 (s, 3H), and (3*S*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate: $^1$H NMR (400 MHz, $CDCl_3$): 4.09 (d, 2H), 3.90-3.82 (m, 2H), 3.75-3.64 (m, 3H), 3.27 (t, 1H), 3.18 (t, 1H), 2.69 (dd, 1H), 2.63 (m, 1H), 2.46-2.33 (m, 2H), 2.16 (t, 1H), 2.10 (s, 3H).

**[0396]** (3*R*,9a*S*)-Hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl methanesulfonate: To a solution of (3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate (0.922 g, 4.28 mmol) in methanol (14.0 mL) was added 1.03 mL (4.50 mmol) of sodium methoxide (25% wt. in methanol) dropwise at room temperature. After 5 min., 1.6 mL (6.43 mmol) of 4.0M hydrogen chloride in dioxane was added and a pink precipitate formed. The solution was concentrated *in vacuo* and the pink solid was taken up in 30.0 mL dichloromethane. This slurry was cooled in an ice bath and triethylamine (3.0 mL, 21.5 mmol) was added, followed by methanesulfonyl chloride (0.37 mL, 4.71 mmol). The resultant yellow solution was stirred for 30 minutes at room temperature. The mixture was then partitioned between dichloromethane and saturated aqueous sodium bicarbonate then the aqueous layer was extracted (3 x 50 mL dichloromethane). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide crude (3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl methanesulfonate which was taken on to the following reaction without purification.

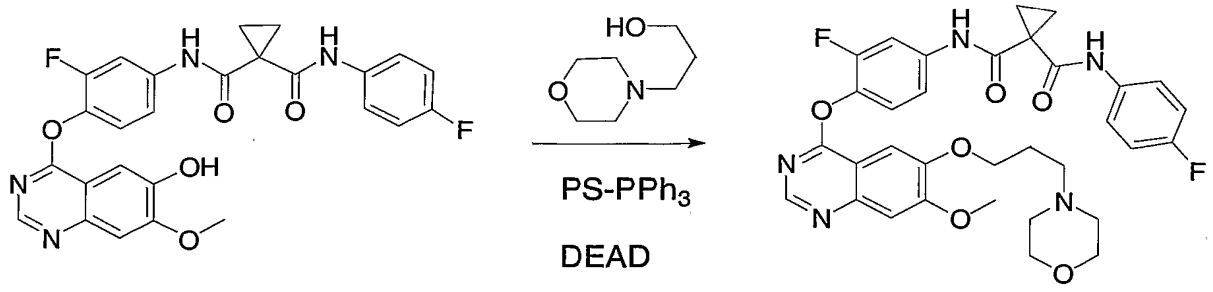
**Example 70**

**[0397]** (8a*R*)-6-(Chloromethyl)tetrahydro-1*H*-[1,3]thiazolo[4,3-*c*][1,4]oxazine: A solution of (4*R*)-1,3-thiazolidin-4-ylmethanol (0.300 g, 2.52 mmol) in 2-(chloromethyl)oxirane (2.0 mL, 25.5 mmol) was heated under nitrogen to 40°C for 12 h. The solution was then cooled to room temperature and 2-(chloromethyl)oxirane was removed *in vacuo*. The crude intermediate was cooled in ice, and was taken up in 2.0 mL of concentrated sulfuric acid. The resulting mixture was heated to 200°C for 0.5 h then poured carefully onto wet ice, which was allowed to melt. The aqueous solution was carefully made basic using solid sodium bicarbonate and the resulting mixture was filtered using water and 10% methanol in ethyl acetate as eluent. The layers were separated and the aqueous layer was extracted with 10% methanol in ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give 11.6 mg (2.4% yield) of crude (8a*R*)-6-(chloromethyl)tetrahydro-1*H*-[1,3]thiazolo[4,3-*c*][1,4]oxazine as a mixture of diastereomers which was directly taken on to the next step.

**Example 71**

**[0398]** 1,1-Dimethylethyl (3-*endo*)-3-{2-[(methylsulfonyl)oxy]ethyl}-8-azabicyclo[3.2.1]octane-8-carboxylate: To a solution of 1,1-dimethylethyl (3-*endo*)-3-(2-hydroxyethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (30.3 mg, 1.19 mmol) in dichloromethane (4.0 mL), was added triethylamine (0.5 mL, 3.56 mmol) and the solution was cooled to 0°C under nitrogen. Methanesulfonyl chloride (0.11 mL, 1.42 mmol) was added slowly and mixture was allowed to warm to room temperature and stirred for 1h. The reaction mixture was partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane (2 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide 35.1 mg (89%) of 1,1-dimethylethyl (3-*endo*)-3-{2-[(methylsulfonyl)oxy]ethyl}-8-azabicyclo[3.2.1]octane-8-carboxylate, which was carried forward for alkylation without purification.

**Example 72**



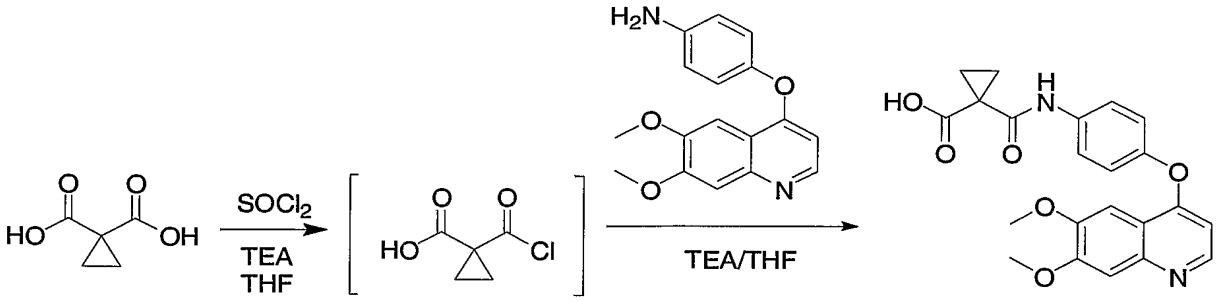

**[0399]** N-[3-Fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. Crude cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(6-hydroxy-7-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (333mg, 0.66mmol), PS-$PPh_3$ resin, (loading = 2.33mmol/g, 797mg, 1.86mmol), 3-morpholin-4-yl-propan-1-ol (0.26ml, 1.88mmol), and DEAD (0.31ml, 1.91mmol) were combined in $CH_2Cl_2$ (10ml) and stirred at room temperature for 1-2hrs. The reaction mixture was filtered and the resin thoroughly washed with $CH_2Cl_2$. The filtrate was concentrated *in vacuo* and the resulting residue was dissolved in EtOAc and washed with $H_2O$ (4x) and sat'd NaCl (1x) and then extracted with 1N HCl (3x). The combined 1N HCl extractions were washed with EtOAc (2x). The acidic aqueous phase was then basified with 1N NaOH and extracted with EtOAc (3x). The combined EtOAc extractions were washed with $H_2O$ (1x), sat'd NaCl (1x), dried ($Na_2SO_4$), and concentrated *in vacuo*. The resulting residue was purified by preparative reverse phase HPLC (25mM $NH_4OAc$/acetonitrile) and the pure fractions were lyophilized to give cyclopropane-1,1-dicarboxylic acid {3-fluoro-4-[7-methoxy-6-(3-morpholin-4-yl-propoxy)-quinazolin-4-yloxy]-phenyl}-amide (4-fluoro-phenyl)-amide (42.6mg, 10%). 1HNMR (400MHz, DMSO-d6): d 10.37 (br s, 1H), 10.05 (br s, 1H), 8.55 (s, 1H), 7.84 (m, 1H), 7.65 (m, 2H), 7.58 (s, 1H), 7.43 (m, 3H), 7.16 (t, 2H), 4.27 (m, 2H), 4.00 (s, 3H), 3.60 (m, 6H), 2.39 (m, 4H), 1.99 (m, 2H), 1.47 (m, 4H). LC/MS Calcd for $[M+H]^+$ 634.2, found 634.1.

**[0400]** Using the same or analogous synthetic techniques and/or substituting with alternative starting materials, the following were prepared:

**[0401]** N-{3-fluoro-4-[(7-(methyloxy)-6-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide: $^1H$ NMR (400MHz, $CDCl_3$): δ 9.67 (s, 1H), 8.59 (s, 1H), 8.43 (s, 1H), 7.75 (d, 1H), 7.52 (s, 1H),

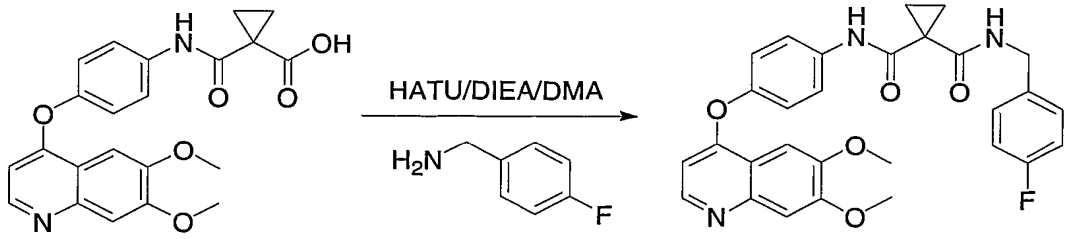
7.46 (m, 2H), 7.31 (s, 1H), 7.20 (m, 2H), 7.06 (t, 2H), 4.04 (d, 2H), 4.03 (s, 3H), 2.98 (d, 2H), 2.34 (s, 3H), 2.12-2.1.95 (m, 5H), 1.76 (m, 2H), 1.64 (m, 2H), 1.57 (m, 2H).

**Example 73**




**[0402]** Preparation of 1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropanecarboxylic acid. To the cyclopropyl di-carboxylic acid (449 mg, 3.45 mmol) in THF (3.5 mL) was added TEA (485 µL, 3.45 mmol). The resulting solution was stirred at room temperature under a nitrogen atmosphere for 40 minutes before adding thionyl chloride (250 µL, 3.44 mmol). The reaction was monitored by LCMS for the formation of mono acid chloride (quenched the sample with MeOH and looked for corresponding mono methyl ester). After 3 hours stirring at room temperature, 4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylamine (1.02 g, 3.44 mmol) was added as a solid, followed by more THF (1.5 mL). Continued to stir at room temperature for 16 hours. The resulting thick slurry was diluted with EtOAc (10 mL) and extracted with 1N NaOH. The biphasic slurry was filtered and the aqueous phase was acidified with conc. HCl to pH = 6 and filtered. Both solids were combined and washed with EtOAc, then dried under vacuum. The desired product, 1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropanecarboxylic acid, was obtained (962 mg, 68.7% yield, 97% pure) as a white solid. $^1$H NMR ($D_2O$/NaOH): 7.97 (d, 1H), 7.18 (d, 2H), 6.76 (m, 4H), 6.08 (d, 1H), 3.73 (s, 3H), 3.56 (s, 3H), 1.15 (d, 4H).

**Example 74**



**[0403]** 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[(4-fluorophenyl)methyl] cyclopropane-1,1-dicarboxamide. To a solution of 1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropanecarboxylic acid (74.3 mg, 0.182 mmol), 4-Fluoro benzylamine (25 μL, 0.219 mmol), DIEA (90.0 μL, 0.544 mmol) in DMA (1.0 mL) was added HATU (203 mg, 0.534 mmol). The resulting solution was stirred at room temperature for 1 hour before adding dropwise to water (10 mL) with stirring. The slurry was sonicated, filtered and the solids were washed with 1 N NaOH followed by water. After air drying, the solids were further purified by prep HPLC, affording 'N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[(4-fluorophenyl)methyl]cyclopropane-1,1-dicarboxamide (33 mg, 35% yield, 98% pure) as a white solid. $^1$H NMR (DMSO, $d_6$): 10.82 (s, 1H), 8.80 (d, 1H), 8.50 (t, 1H), 7.83 (d, 2H), 7.74 (s, 1H), 7.56 (s, 1H), 7.30-7.38 (m, 4H), 7.15 (t, 2H), 6.80 (d, 1H), 4.32 (d, 2H), 4.04 (s, 3H), 4.03 (s, 3H), 1.42 (s, 4H).

**[0404]** The following compounds were prepared, in a similar manner as above, from the coupling of 1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropane carboxylic acid with a corresponding alkylamine or arylamine.

**[0405]** N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. 1H NMR (DMSO-d6): 10.62 (s, 1H), 8.79 (d, 1H), 8.24 (t, 1H), 7.83 (d, 2H), 7.72 (s, 1H), 7.58 (s, 1H), 7.37 (d, 2H), 6.76 (d, 1H), 4.04 (s, 3H), 4.03 (s, 3H), 3.98 (m, 2H), 3.66 (m, 2H), 3.49 (m, 4H), 3.25 (t, 2H), 3.13 (br., 2H), 1.42 (d, 4H).

**[0406]** N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. 1H NMR (DMSO-d6): 10.78 (s, 1H), 10.53 (s, 1H), 8.43 (d, 1H), 8.12 (d, 1H), 7.82 (d, 2H), 7.49 (s, 1H), 7.37 (s, 1H), 7.20-7.28 (m, 3H), 7.15 (dd, 1H), 7.01 (td, 1H), 6.35 (d, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.47 (s, 2H), 2.17 (br., 4H), 1.49 (m, 4H), 1.41 (m, 4H), 1.32 (br., 2H).

**[0407]** 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. 1H NMR (DMSO-d6): 10.98 (s, 1H), 10.56 (s, 1H), 8.42 (d, 1H), 8.10 (dd, 1H), 7.81 (m, 2H), 7.49 (s, 1H), 7.37 (s, 1H), 7.17-7.27 (m, 4H), 7.01 (td, 1H), 6.35 (d, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.61 (s, 2H), 2.30 (br., 4H), 1.47 (br., 4H), 1.43 (m, 4H).

**[0408]** 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. 1H NMR (DMSO-d6): 10.12 (s, 1H),

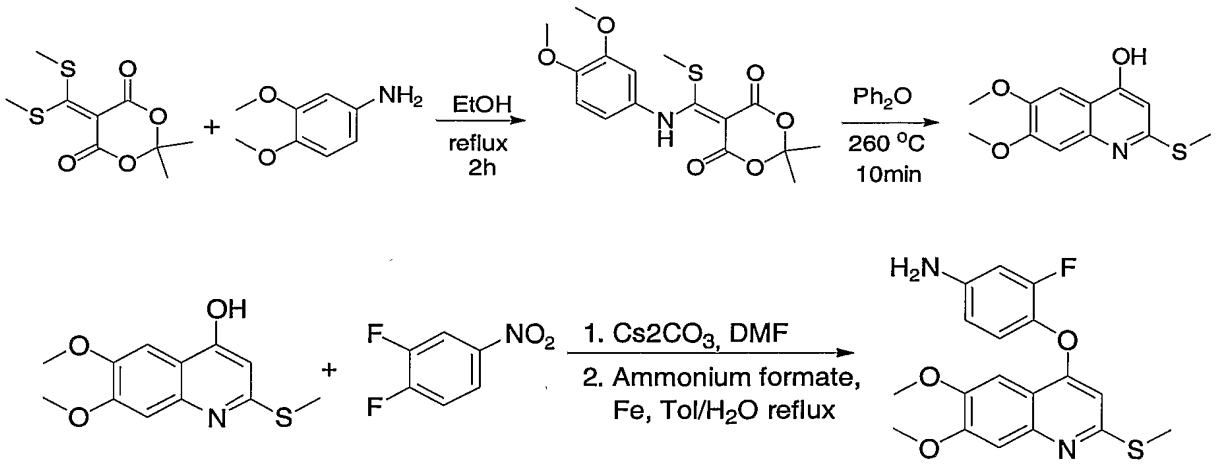
10.03 (s, 1H), 8.44 (d, 1H), 7.74 (d, 2H), 7.57 (s, 1H), 7.53 (d, 1H), 7.48 (s, 1H), 7.37 (s, 1H), 7.21 (m, 3H), 6.98 (d, 1H), 6.40 (d, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.56 (t, 4H), 3.41 (s, 2H), 2.34 (br., 4H), 1.48 (s, 4H).

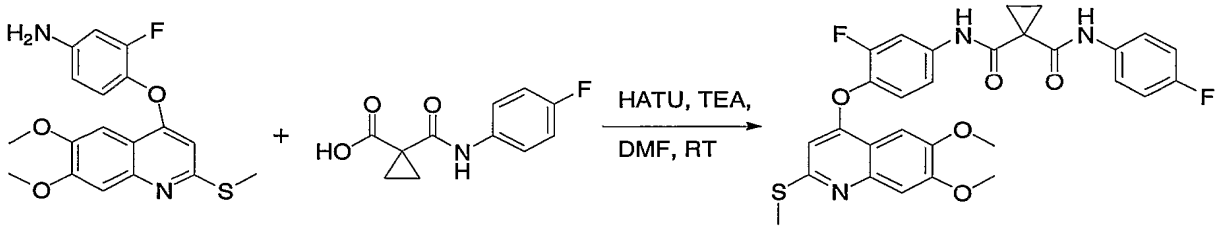
**[0409]** 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. 1H NMR (DMSO-d6): 10.54 (s, 1H), 10.47 (s, 1H), 8.43 (d, 1H), 8.08 (d, 1H), 7.78 (d, 2H), 7.49 (s, 1H), 7.37 (d, 1H), 7.18-7.30 (m, 4H), 7.03 (t, 1H), 6.37 (d, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.50 (s, 2H), 3.44 (br., 4H), 2.20 (br., 4H), 1.48 (d, 4H).

**[0410]** 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. 1H NMR (DMSO-d6): 10.0-10.2 (br., 2H), 8.46 (d, 1H), 7.76 (d, 2H), 7.53 (m, 3H), 7.39 (s, 1H), 7.24 (m, 3H), 6.98 (d, 1H), 6.43 (d, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.37 (s, 2H), 2.31 (br., 4H), 1.48 (m, 8H), 1.39 (br., 2H).

**[0411]** 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. 1H NMR (DMSO-d6): 10.0-10.2 (br., 2H), 8.46 (d, 1H), 7.77 (d, 2H), 7.59 (s, 1H), 7.53 (d, 1H), 7.51 (s, 1H), 7.39 (s, 1H), 7.23 (m, 3H), 6.99 (d, 1H), 6.43 (d, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.52 (s, 2H), 2.42 (br., 4H), 1.69 (br, 4H), 1.48 (s, 4H).

**Example 75**





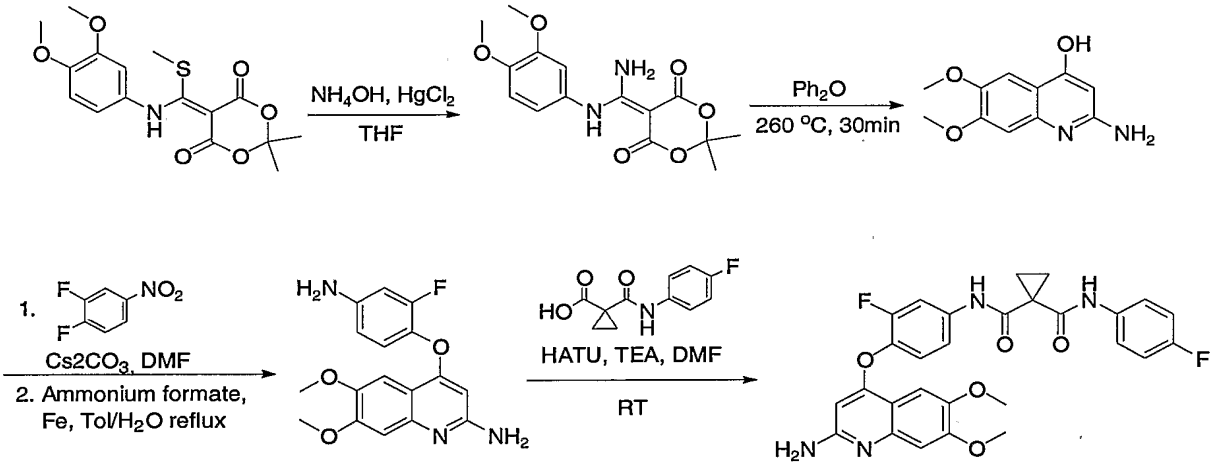

**[0412]** Synthesis of N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide Commercially available 5-(bis-methylsulfanyl-methylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione (3.5 g, 14 mmol) and 3,4-dimethoxyoaniline (2.2 g, 14 mmol) were reflux in EtOH (20 mL) for 2 hours. The EtOH was removed under reduced pressure and EtOAc was added to the residue. The product was filtered and washed with cold EtOAc (3X). 5-[(3,4-dimethoxy-phenylamino)-methylsulfanyl-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione was obtained as a white solid (1.7 g, 47% yield) and used without further purification. LCMS: m/z 352 $(M-H)^-$.

**[0413]** A mixture of 5-[(3,4-dimethoxy-phenylamino)-methylsulfanyl-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (1.7 g, 6.6 mmol) and diphenylether (3.5 g, 21 mmol) were heated at 260 $^0$C for 10 minutes. The mixture was cooled to room temperature and heptane was added. 6,7-Dimethoxy-2-methylsulfanyl-quinolin-4-ol was filtered and isolated as an orange solid and used without further purification (1.4 g, 83% yield). LCMS: m/z 352 $(M+H)^+$.

**[0414]** A mixture of 6,7-dimethoxy-2-methylsulfanyl-quinolin-4-ol (1.0 g, 4.0 mmol), 3,4-difluoronitrobenzene (0.48 mL, 4.3 mmol), cesium carbonate (2.6 g, 8.0 mmol), and DMF (15 mL) was stirred at room temperature for 12 hours, after which time, the mixture was filtered. The filtrate was extracted with DCM, washed with 10% $LiCl_{(aq.)}$, water, (1X) and brine (1X), followed by drying over $Na_2SO_4$ and concentration *in vacuo*. The crude solids were purified by flash chromatography (silica gel, 5% MeOH in DCM), affording the nitroquinoline (1.3 g, 85.8% yield) as an orange solid. LCMS: m/z 391 $(M+H)^+$. A mixture of nitroquinoline (0.33 g, 0.85 mmol), 5% Pt/S on carbon (0.050 g), ammonium formate (0.40 g, 6.3 mmol) in EtOH (5 mL) was heated at 80 $^0$C for 1 hour The mixture was cooled to room temperature and the solvent removed under reduced pressure. The residue was dissolved in DCM, the mixture filtered, and the precipitate discarded. Removal of the organic solvent afforded 4-(6,7-dimethoxy-2-methylsulfanyl-quinolin-4-yloxy)-3-fluoro-phenylamine as an orange oil (220 mg, 73% yield). LCMS: m/z 361 $(M+H)^+$.

**[0415]** To a mixture of 4-(6,7-dimethoxy-2-methylsulfanyl-quinolin-4-yloxy)-3-fluoro-phenylamine (0.22 g, 0.61 mmol) and 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (0.16 g, 0.73 mmol) in DMF (5 mL) was added TEA (0.25 mL, 1.8 mmol) followed by HATU (0.57 g, 1.5 mmol). The resulting solution was stirred overnight at room temperature. The reaction mixture was dumped into water and extracted with DCM (2X). The combined extracts were washed with 5% $LiCl_{(aq.)}$ (3X), water, (1X) and brine (1X), followed by drying over $Na_2SO_4$ and concentration *in vacuo*. The crude solids were purified by preparatory HPLC with ammonium acetate, affording N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (0.39 g, 11% yield) as a white solid. $^1H$ NMR (DMSO-$d_6$) δ 10.34 (s, 1H), 9.94 (s, 1H), 7.83 (d, 1H), 7.59 (m, 2H), 7.56 (m, 1H), 7.40 (m, 2H), 7.23 (s, 1H), 7.09 (t, 2H), 6.12 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.48 (s, 3H), 1.40 (m, 4H).

**Example 76**



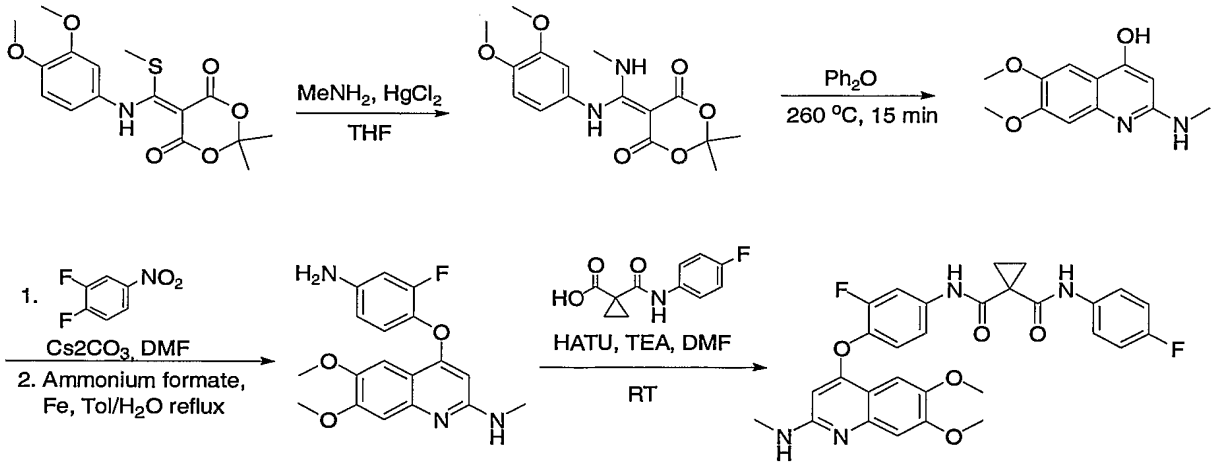

**[0416]** Synthesis of N-(4-{[2-amino-6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. A mixture of 5-[(3,4-dimethoxy-phenylamino)-methylsulfanyl-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (1.0 g, 2.8 mmol), 30% ammonium hydroxide (8.5 mL), $HgCl_2$ (0.76 g, 2.8 mmol) in THF (5 mL) was stirred at room temperature for 30 minutes. The mixture was extracted with DCM and water (3X) and dried with $Na_2SO_4$. Concentration *in vacuo* afforded 5-[amino-(3,4-dimethoxy-phenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione as a white solid (0.90 g, 97% yield) and this compound was used without further purification. LCMS: m/z 321 $(M-H)^-$.

**[0417]** A mixture of 5-[amino-(3,4-dimethoxy-phenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (0.90 g, 2.8 mmol) and diphenylether (3.0 g, 18 mmol) was heated at 260 $^0$C for 30 minutes. The mixture was cooled to room temperature and heptane was added. Product 2-amino-6,7-dimethoxy-quinolin-4-ol was filtered and isolated as an orange solid and used without further purification (0.31 g, 33% yield). LCMS: m/z 221 $(M+H)^+$.

**[0418]** 4-(4-Amino-2-fluoro-phenoxy)-6,7-dimethoxy-quinolin-2-ylamine was synthesized from 2-amino-6,7-dimethoxy-quinolin-4-ol in a similar manner as 4-(6,7-dimethoxy-2-methylsulfanyl-quinolin-4-yloxy)-3-fluoro-phenylamine, and obtained as a white solid (4.0% yield). LCMS: m/z 330 $(M+H)^+$.

**[0419]** N-(4-{[2-amino-6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide was synthesized from 4-(4-amino-2-fluoro-phenoxy)-6,7-dimethoxy-quinolin-2-ylamine in a similar manner as N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. It was purified by preparatory HPLC using ammonium acetate and isolated as a white solid (4.0% yield). $^1$H NMR (DMSO-$d_6$) δ 10.34 (s, 1H), 9.95 (s, 1H), 7.82 (d, 1H), 7.58 (m, 2H), 7.44 (d, 1H), 7.33 (t, 1H), 7.25 (s, 1H), 7.09 (t, 2H), 7.07 (s, 1H), 6.17 (br s, 2H), 5.66 (s, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 1.40 (d, 4H). LCMS: m/z 535 $(M+H)^+$.

**Example 77**




**[0420]** Synthesis of 'N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. A mixture of 5-

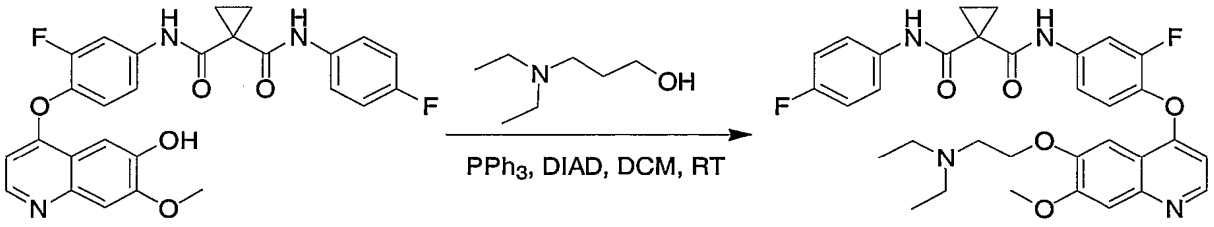
[(3,4-dimethoxy-phenylamino)-methylsulfanyl-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (0.50 g, 1.4 mmol), methylamine (2 M in THF, 0.75 mL, 1.5 mmol), $HgCl_2$ (0.38 g, 1.4 mmol) in THF (5 mL) was stirred at room temperature for 30 minutes. The mixture was extracted with DCM and water (3X) and dried with $Na_2SO_4$. Concentration *in vacuo* afforded 5-[(3,4-dimethoxy-phenylamino)-methylamino-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione as a yellow solid (0.48 g, 99% yield) and this compound was used without further purification. LCMS: m/z 335 $(M-H)^-$.

**[0421]** A mixture of 5-[(3,4-dimethoxy-phenylamino)-methylamino-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (0.40 g, 2.8 mmol) and diphenylether (3.0 g, 18 mmol) was heated at 260 $^0$C for 15 minutes. The mixture was cooled to room temperature and heptane was added. Product 6,7-dimethoxy-2-methylamino-quinolin-4-ol was filtered and isolated as a tan solid and used without further purification (0.30 g, quantitative yield). LCMS: m/z 235 $(M+H)^+$.

**[0422]** [4-(4-Amino-2-fluoro-phenoxy)-6,7-dimethoxy-quinolin-2-yl]-methyl-amine was synthesized from 6,7-dimethoxy-2-methylamino-quinolin-4-ol in a similar manner as 4-(4-Amino-2-fluoro-phenoxy)-6,7-dimethoxy-quinolin-2-ylamine, and isolated as a yellow oil (58% yield). LCMS: m/z 330 $(M+H)^+$.

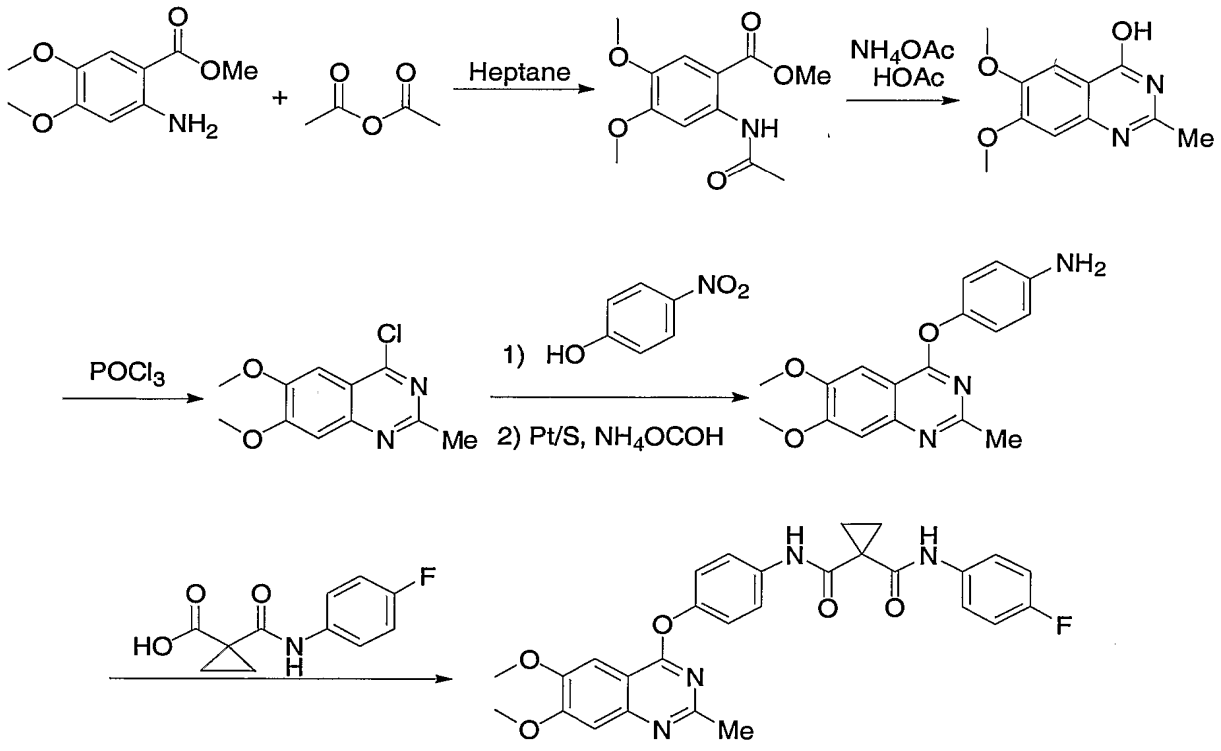
**[0423]** 'N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide was synthesized from [4-(4-amino-2-fluoro-phenoxy)-6,7-dimethoxy-quinolin-2-yl]-methyl-amine in a similar manner as N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluoro-phenyl)cyclopropane-1,1-dicarboxamide. It was purified by preparatory HPLC using ammonium acetate and isolated as a white solid (6.0 mg, 4.0% yield). $^1$H NMR (DMSO-$d_6$) δ 10.42 (s, 1H), 9.91 (s, 1H), 7.88 (dd, 1H), 7.56 (m, 2H), 7.44 (m, 4H), 7.09 (t, 2H), 5.90 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.39 (br s, 1H), 2.92 (s, 3H), 1.41 (dt, 4H). LCMS: m/z 535 $(M+H)^+$.

**Example 78**



**[0424]** 'N-(4-{[6-{[3-(diethylamino)propyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a slurry of cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(6-hydroxy-7-methoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (0.12 g, 0.23 mmol), hydroxypropyldiethylamine (0.090 mL, 0.61 mmol), triphenylphosphine (0.20 g, 0.76 mmol) in DCM (10 mL) was added DIAD (0.17 mL, 0.86 mmol). The resulting mixture was stirred at room temperature for 12 hours, after which time, the solvent was removed under reduced pressure. The residue was extracted with EtOAc and 1N HCl (6X) and brine (1X) followed by drying with $Na_2SO_4$. Concentration of the organic fraction *in vacuo* afforded 'N-(4-{[6-{[3-(diethylamino)propyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a yellow oil (0.18 g, wet, ca 95% purity by analytical HPLC). Further purification by preparatory HPLC using ammonium acetate afforded the product in 99% purity by analytical HPLC. LCMS: m/z 619 $(M+H)^+$. $^1H$ NMR (DMSO-$d_6$) δ 10.37 (br s, 1H), 10.00 (s, 1H), 8.44 (d, 1H), 7.87 (d, 1H), 7.62 (m, 2H), 7.49 (m, 2H), 7.41 (m, 2H), 7.13 (t, 2H), 6.40 (d, 1H), 4.17 (t, 2H), 3.93 (s, 3H), 2.59 (t, 2H), 2.49 (m, 6H), 1.91 (m, 4H), 0.94 (t, 6H).

**Example 79**



**[0425]** 'N-(4-fluorophenyl)-N'-(4-{[2-methyl-6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide. Commercially available 2-amino-4,5-dimethoxy-benzoic acid methyl ester (3g, 0.014 mol) and acetic anhydride (4.03 mL, 0.0426 mol) were heated in heptane at 100°C for 3 hours. After removal of heptane *in vaccuo*, the crude product of 2-acetylamino-4,5-dimethoxy-benzoic acid methyl ester was obtained and used without further purification. LC/MS: m/z 254 (M+H).

**[0426]** To the crude 2-acetylamino-4,5-dimethoxy-benzoic acid methyl ester obtained above was added ammonium acetate (7.98g, 0.104 mol) and acetic acid (10 mL). The mixture was heated at reflux in a pressure tube until the formation of the desired cyclization product, as indicated by LC/MS: m/z 221 (M+H). After cooling to RT, the reaction mixture was diluted with water, and extracted with EtOAc 3 times. The combined organic phase was basified with aq. NaOH solution, and washed 3 times with EtOAc. The aqueous layer was then acidified with aq. HCl and extracted three times with EtOAc. The combined organic extract was dired over $Na_2SO_4$ and concentrated in vacuo, affording 6,7-dimethoxy-2-methyl-quinazolin-4-ol (0.15g), which was used without further purification. LC/MS: m/z 221 (M+H).

**[0427]** A mixture of 6,7-dimethoxy-2-methyl-quinazolin-4-ol obtained from previous step (0.15g, 0.68 mmol) and POCl3 (1.59 mL, 17.04 mmol) was heated at reflux for 48 hours. The reaction mixture was poured into ice water, neutralized with $NaHCO_3$, and adjusted to basic with $K_2CO_3$. The mixture was cooled to 0°C with stirring. The resulting precipitate was filtered, giving 4-chloro-6,7-dimethoxy-2-methyl-quinazoline (0.094g), which was used without further purification.

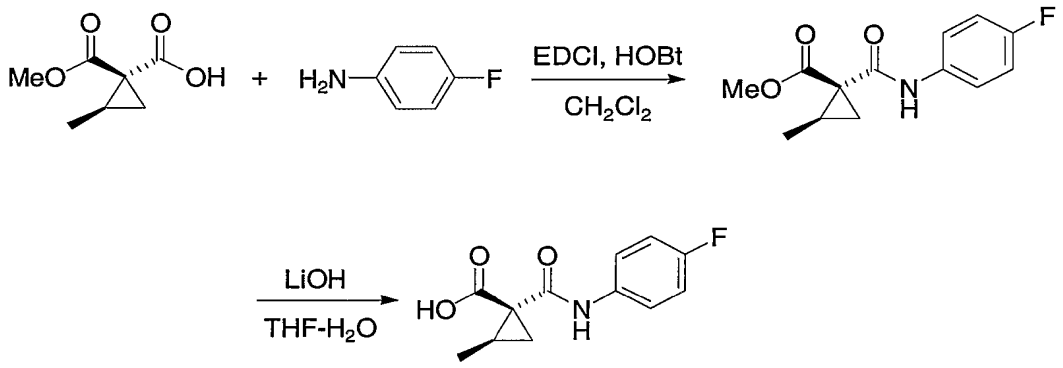
**[0428]** A mixture of the chloro quinazoline (0.094g, 0.397 mmol) obtained above, 4-nitrophenol (0.11g, 0.795 mmol) and bromobenzene (3mL) was heated at 160°C for 48 hours. The solvent was then removed and the reaction was taken up in MeOH. $Et_2O$ was added and the reaction stirred 30 min and the precipitate was filtered, affording 6,7-dimethoxy-2-methyl-4-(4-nitro-phenoxy)-quinazoline (0.081g) as a very light yellow solid. LC/MS: m/z 342 (M+H).

**[0429]** A mixture of 6,7-dimethoxy-2-methyl-4-(4-nitro-phenoxy)-quinazoline (0.081g, 0.236 mmole), Pt/S (0.008g, 15 mol%), ammounium formate (0.098g, 1.56 mmol) and EtOH (3mL) was heated with stirring at 70°C for 3 hours. The reaction mixture was then filtered while hot and washed with hot EtOH. The crude product of 4-(6,7-dimethoxy-2-

methyl-quinazolin-4-yloxy)-phenylamine (0.924g) was obtained as a yellow solid, which was used in the next reaction without further purification. LC/MS: m/z 312 (M+H).

**[0430]** To a mixture of 4-(6,7-dimethoxy-2-methyl-quinazolin-4-yloxy)-phenylamine (0.100g, 0.321 mmol) and 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (0.056g, 0.386 mmol) in DMF was added DIEA (0.168 mL, 0.963 mmol), followed by HATU (0.183g, 0.482 mmol). The reaction mixture was stirred at RT for 15 hours. The mixture was diluted with EtOAc, washed with 5% LiCl aq solution three times, dried over Na2SO4, and concentrated *in vacuo*. The crude product was purified on preparative HPLC to give 'N-(4-fluorophenyl)-N'-(4-{[2-methyl-6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide (3.2 mg) as a white solid. 1H NMR (DMSO-d6) 10.15 (bs, 1H), 10.01 (bs, 1H), 7.69-7.75 (m, 2H), 7.61-7.68 (m, 2H), 7.52 (s, 1H), 7.32 (s, 1H), 7.23-7.29 (m, 2H), 7.12-7.19 (m, 2H), 3.93 (d, 6H), 2.43 (s, 3H), 1.53 (s, 4H).

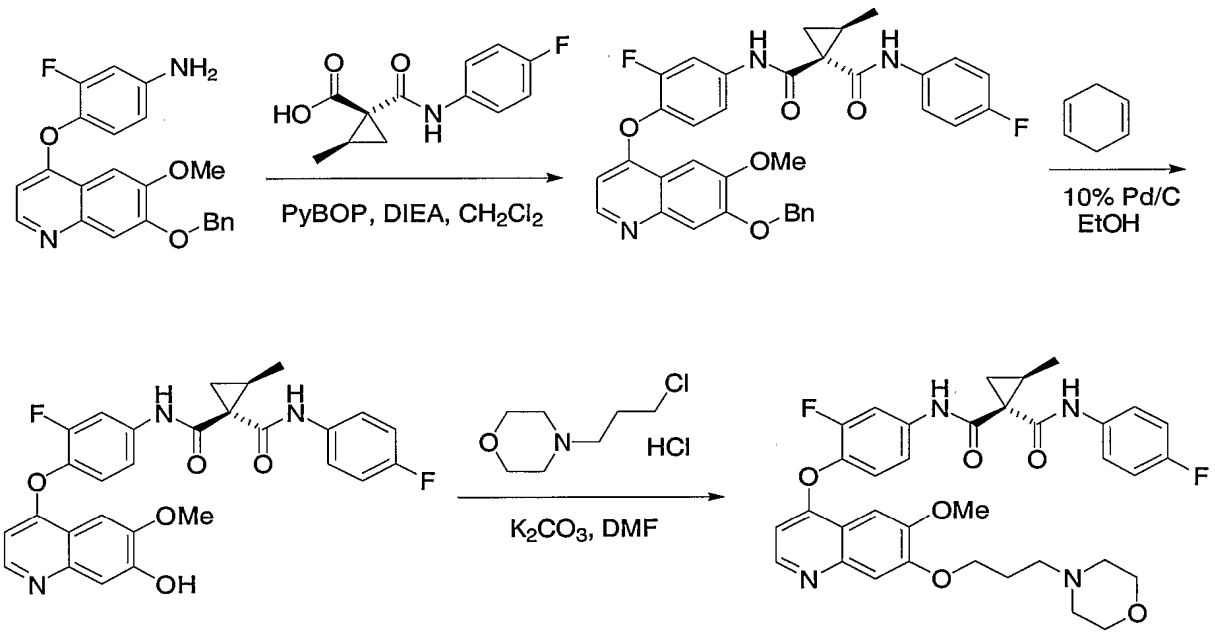
**Example 80**




**[0431]** Preparation of 1-(4-Fluoro-phenylcarbamoyl)-2-methyl-cyclopropanecarboxylic acid. 2-Methylcyclopropane-1,1-dicarboxylic acid methyl ester was prepared by following the literature procedure (Baldwin, J. E.; Adlington, R. M.; Rawlings, B. J. Tetrahedron Lett. 1985, 481.) The carboxylic acid (700 mg, 4.4 mmol) was dissolved in $CH_2Cl_2$ (10 mL). To the resulting solution was added 4-fluoroaniline (590 mg, 5.3 mmol), HOBt (890 mg, 6.6 mmol) and EDCI (2.5 g, 13.2 mmol). The stirring was continued for 3 h at rt. $CH_2Cl_2$ (30 mL) was added to the reaction mixture, and the resulting solution was washed with brine, and dried over $Na_2SO_4$. $CH_2Cl_2$ was removed under reduced pressure. Further purification by column chromatography gave 635 mg (57%) of the desired amide.

[0432] The methyl ester obtained above was then treated with $LiOH \cdot H_2O$ (116 mg, 2.78 mmol, 1.1 eqiv.) in THF (2 mL) and $H_2O$ (1 mL) for 3h at rt. THF was removed under reduced pressure. The aqueous solution was diluted with 20 mL of $H_2O$, washed with ether (10 mL), and acidified with 1 N HCl. The solid was filtered, dissolved in EtOAc, and dried over $Na_2SO_4$. Removal of EtOAc gave the crude product of 1-(4-fluoro-phenylcarbamoyl)-2-methyl-cyclopropane-carboxylic acid, which was used in the next reaction. $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 12.99 (br s, 1 H), 10.33 (br s, 1 H), 7.59 (dd, J = 9.0, 5.0 Hz, 2 H), 7.11 (dd, J = 9.0, 9.0 Hz, 2 H), 1.86-1.78 (m, 1 H), 1.43 (dd, J = 9.0, 4.2 Hz, 1 H), 1.30 (dd, J = 7.8, 4.3 Hz, 1 H), 1.19 (d, J = 6.3 Hz, 3 H).

**Example 81**



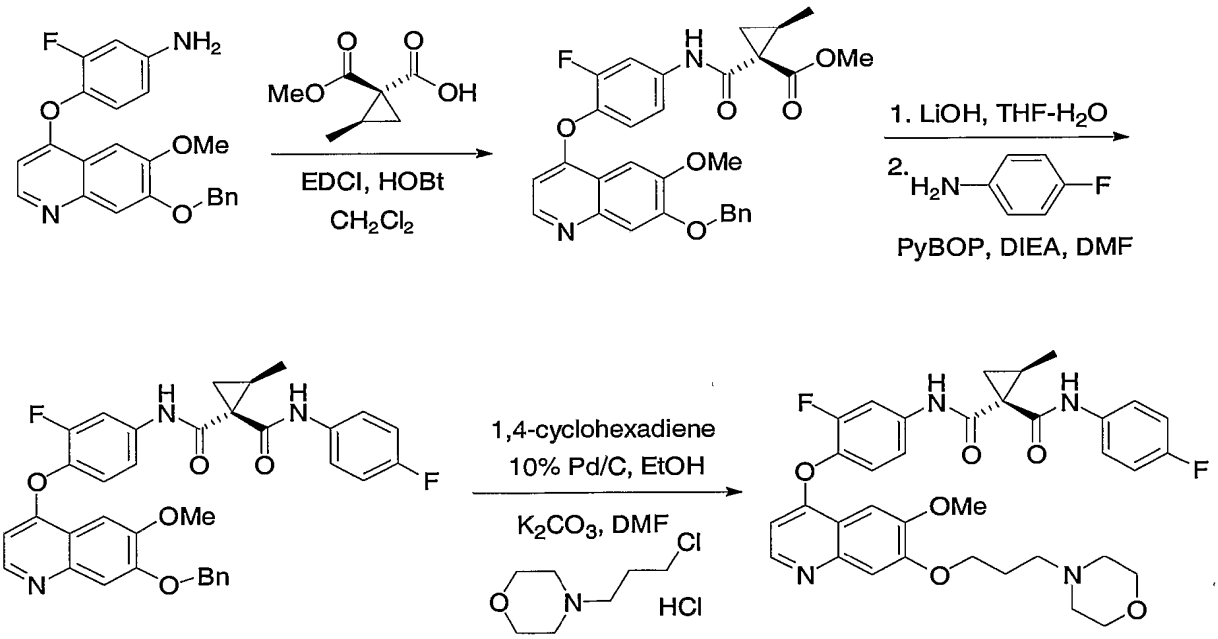

[0433] Synthesis of (1S,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl) oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide. To a solution of 4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenylamine (150 mg, 0.38 mmol) in $CH_2Cl_2$ (3 mL) was added DIEA (341 mg, 2.64 mmol), 1-(4-fluoro-phenylcarbamoyl)-2-methyl-cyclopropanecarboxylic acid (120 mg, 0.49 mmol) and PyBOP (686 mg, 1.32 mmol). The reaction mixture was stirred at rt for 6 h. After standard workup, the crude product was purified by column chromatography.

[0434] The coupling product (130 mg, 0.21 mmol) obtained above was dissolved in EtOH (2 mL). 1,4-cyclohexadiene (170 mg, 2.1 mmol) and 10% Pd/C (10 mg) were added. The

mixture was stirred for 2 h under reflux. After cooling, the mixture was filtered through Celite, and washed with MeOH. Removal of the solvents gave the crude product (136 mg), which was used in the next reaction.

**[0435]** To a solution of the 7-hydroxyquinoline (136 mg, 0.26 mmol) in DMF (2 mL) was added 4-(3-chloropropyl)morpholine hydrochloride (70 mg, 0.35 mmol) and $K_2CO_3$ (69 mg, 0.50 mmol). The reaction mixture was then stirred at 80 °C for 5 h. After cooling, EtOAc (20 mL) was added. The EtOAc solution was washed twice with brine, and dried over $Na_2SO_4$. Removal of EtOAc and purification by column chromatography ($CH_2Cl_2$ : MeOH = 10:1) gave '(1S,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide. The product was then dissolved in ethyl ether, and treated with 1.5 equiv. of 1 N HCl/ether. Filtration and lyophilization gave the HCl salt of '(1S,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide: $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.49 (br s, 1 H), 10.26 (br s, 1 H), 10.15 (br s, 1 H), 8.74 (br s, 1 H), 7.95 (br d, J = 13.2 Hz, 1 H), 7.8-7.5 (m, 6 H), 7.16 (t, J = 8.9 Hz, 2 H), 6.82 (br s, 1 H), 4.34 (t, J = 5.9 Hz, 2 H), 4.02 (s, 3 H), 3.99 (br s, 2 H), 3.77 (br t, J = 12.0 Hz, 2 H), 3.56-3.30 (m, 4 H), 3.17-3.07 (m, 2 H), 2.40-2.30 (m, 2 H), 2.04-1.95 (m, 1 H), 1.45 (dd, J = 7.2, 4.7 Hz, 1 H), 1.36 (dd, J = 8.5, 4.5 Hz, 1 H), 1.09 (d, J = 6.2 Hz, 3 H).

**Example 82**



[0436] Synthesis of (1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]-quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide. To a solution of 4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenylamine (322 mg, 0.82 mmol) and 2-Methyl-cyclopropane-1,1-dicarboxylic acid methyl ester (195 mg, 1.23 mmol) in $CH_2Cl_2$ (4 mL) was added HOBt (61 mg, 0.32 mmol) and EDCI (211 mg, 1.64 mmol). The stirring was continued for 12 h at rt. The reaction mixture was then diluted with EtOAc and washed with brine. Removal of organic solvents *in vacuo* and further purification by column chromatography gave the desired coupling product (153 mg).

[0437] The product (153 mg, 0.29 mmol) obtained above was treated with $LiOH \cdot H_2O$ (15 mg, 0.35 mmol) in THF (1 mL) and $H_2O$ (1 mL) for 2 h. THF was removed. 10 mL of $H_2O$ was added to the mixture. The aqueous solution was washed with ether, and acidified with 1 N HCl. The solid was then filtered and dried under vacuum.

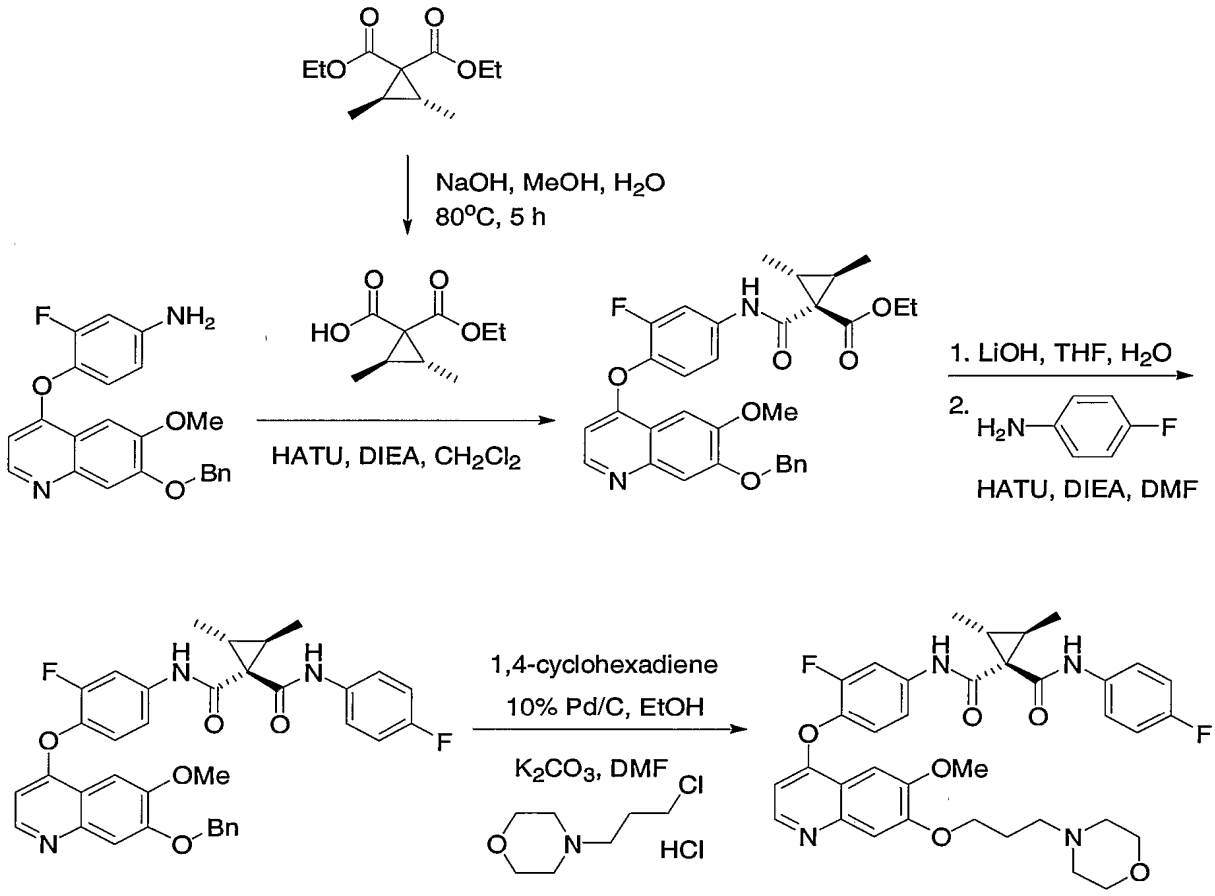
[0438] The crude carboxylic acid (118 mg, 0.23 mmol) and 4-fluoroaniline (111 mg, 0.27 mmol) were dissolved in DMF (2 mL). To this solution was added DIEA (178 mg, 1.38 mmol) and PyBOP (358 mg, 0.69 mmol). The mixture was stirred overnight at rt. It was then diluted with EtOAc, washed twice with brine. Removal of EtOAc and column chromatography gave the desired product.

[0439] The product (66 mg, 0.11 mmol) obtained above was dissolved in EtOH (2 mL). 1,4-cyclohexadiene (80 mg, 1.1 mmol) and 10% Pd/C (10 mg) were added. The mixture was stirred for 2 h under reflux. After cooling, the mixture was filtered through Celite, and washed with MeOH. Removal of the solvents gave the crude product (70 mg), which was used in the next reaction.

[0440] To a solution of the 7-hydroxyquinoline (80 mg, 0.15 mmol) in DMF (2 mL) was added 4-(3-chloropropyl)morpholine hydrochloride (62 mg, 0.31 mmol) and $K_2CO_3$ (64 mg, 0.46 mmol). The reaction mixture was then stirred at 80 °C for 5 h. After cooling, EtOAc (20 mL) was added. The EtOAc solution was washed twice with brine, and dried over $Na_2SO_4$. Removal of EtOAc and purification by column chromatography ($CH_2Cl_2$ : MeOH = 10:1) gave '(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide. The product was then dissolved in ethyl ether, and treated with 1.5 equiv. of 1 N HCl/ether. Filtration and lyophilization gave the HCl salt of '(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-

fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide: $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.65 (br s, 1 H), 10.54 (br s, 1 H), 9.74 (s, 1 H), 8.75 (br s, 1 H), 8.01 (br d, J = 12.9 Hz, 1 H), 7.80-7.50 (m, 6 H), 7.20-7.10 (m, 2 H), 6.84 (br s, 1 H), 4.34 (br t, J = 5 Hz, 2 H), 4.04 (s, 3 H), 4.05-3.95 (m, 2 H), 3.77 (br t, J = 11 Hz, 2 H), 3.52 (br d, J = 12.7 Hz, 4 H), 3.12 (br q, J = 9.0 Hz, 2 H), 2.40-2.30 (m, 2 H), 2.10-1.95 (m, 1 H), 1.40-1.30 (m, 2 H), 1.10 (d, J = 6.2 Hz, 3 H).

**Example 83**




**[0441]** Synthesis of '(2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]-quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide. 2,3-trans-Dimethyl-cyclopropane-1,1-dicarboxylic acid diethyl ester was prepared by following the literature procedure. (Ohishi, J. Synthesis, 1980, 690.) To a solution of 2,3-trans-dimethyl-cyclopropane-1,1-dicarboxylic acid diethyl ester (6.75 g, 31.5 mmol) in MeOH (30 mL) was added 33 mL of 1 N NaOH aqueous solution. The mixture was stirred at 85 °C for 5 h. MeOH was removed under reduced pressure; the residue was diluted with 40 mL of $H_2O$. The aqueous solution was washed with 20 mL of

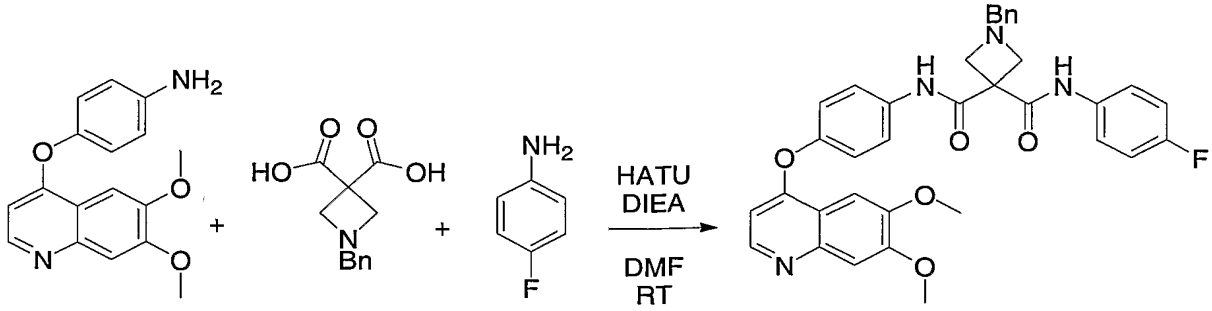
ether, and acidified with 1 N HCl. Filtration and drying under vacuum gave 4.72 g 80 %) of the desired carboxylic acid.

**[0442]** The aniline (1.08 g, 2.78 mmol) and the carboxylic acid (518 mg, 2.78 mmol) prepared above were dissolved in $CH_2Cl_2$ (15 mL). HATU (2.11 g, 5.56 mmol) and DIEA (1.8 mL, 11.1 mmol) were added. The reaction mixture was stirred at rt overnight. It was then concentrated and diluted with EtOAc. The EtOAc solution was then washed with 5% NaOH and brine. Removal of EtOAc gave the crude coupling product, which was hydrolyzed to the corresponding carboxylic acid by treatment with $LiOH•H_2O$ (175 mg, 4.17 mmol) in THF (100 mL) -$H_2O$ (50 mL) at 60 °C for 10 h.

**[0443]** The carboxylic acid (850 mg, 1.60 mmol) and 4-fluoroaniline (355 mg, 3.20 mmol) were dissolved in DMF (8 mL). HATU (3.89 g, 3.2 mmol) and DIEA (1.1 ml, 6.4 mmol) were added. The reaction mixture was stirred at rt overnight. $H_2O$ (10 mL) was added to the reaction, and a precipitate formed. The solid was filtered, washed with aqueous sat. $Na_2CO_3$ and ether. Further purification by column chromatography gave 596 mg (60%) of the desired product. Debenzylation was done by following the standard procedure.

**[0444]** To a solution of the 7-hydroxyquinoline (261 mg, 0.49 mmol) in DMF (5 mL) was added 4-(3-chloropropyl)morpholine hydrochloride (195 mg, 0.98 mmol) and $K_2CO_3$ (202 mg, 1.46 mmol). The reaction mixture was then stirred at 80 °C for 4 h. After cooling, EtOAc (20 mL) was added. The EtOAc solution was washed twice with brine, and dried over $Na_2SO_4$. Removal of EtOAc and purification by column chromatography ($CH_2Cl_2$ : MeOH = 10:1) gave 122 mg (37%) of '(2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethyl-cyclopropane-1,1-dicarboxamide. $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 5.1 Hz, 1 H), 8.11 (br s, 1 H), 7.77-7.70 (m, 2 H), 7.53 (s, 1 H), 7.50-7.44 (m, 2 H), 7.40 (s, 1 H), 7.22-7.16 (m, 2 H), 7.06-6.98 (m, 2 H), 6.36 (br d, J = 5.1 Hz, 1 H), 4.26 (t, J = 7.0 Hz, 2 H), 4.02 (s, 3 H), 3.72 (t, J = 4.4 Hz, 4 H), 2.57 (t, J = 7.3 Hz, 2 H), 2.50-2.42 (m, 4 H), 2.18-2.10 (m, 2 H), 1.80-1.66 (m, 2 H), 1.30-1.24 (m, 6 H).

**Example 84**

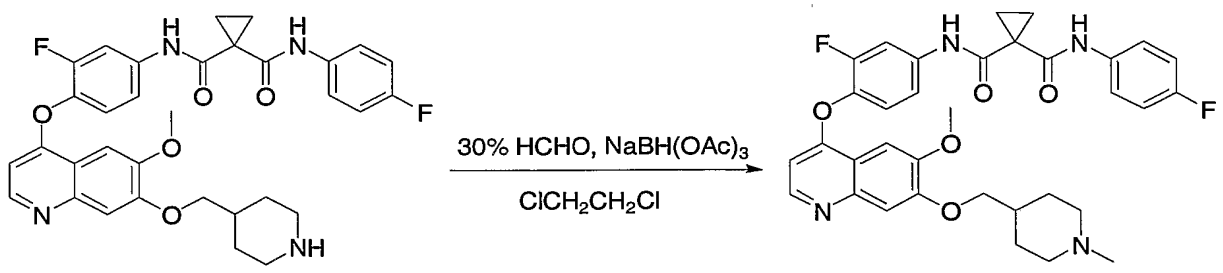



**[0445]** Synthesis of 'N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide. 1-Benzyl-azetidine-3,3-dicarboxylic acid was prepared by following the literature procedure (Miller, R. A.; et al. Syn. Comm. 2003, 33, 3347). To a solution of 4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylamine (4.2 mmol, 1 equiv.) and 4-fluoroaniline (4.2 mmol, 1 equiv.) in DMF (20 mL) was charged with DIEA (12.6 mmol, 3 equiv.) and a solution of 1-benzyl-azetidine-3,3-dicarboxylic acid ( 4.2 mmol, 1 equiv.) in DMF (10 mL). The reaction mixture was allowed to stir at RT and monitored by LCMS. The reaction was complete in 6 h. The reaction mixture was diluted with ethyl acetate and washed with 10% LiCl (3x), brine (3x), dried with sodium sulfate, filtered and the solvent was reduced *in vacuo*. The crude product was purified by silica gel chromatography eluting with 2% of MeOH in EtOAc. The fractions containing the desired product were further purified using preparative HPLC to give 'N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide (300 mg, 12% yield) as a white solid. $^1$HNMR (DMSO-d6): 10.0 (s, 1H), 9.90 (s, 1H), 8.45 (d, 1H), 7.80 (d, 2H), 7.70 (m, 2H), 7.50 (s, 1H), 7.40 (s, 1H), 7.48-7.15 (m, 9H), 3.95 (s, 6H), 3.70 (s, 4H), 3.60 (s, 2H). LCMS (POS): 607.2 (M+H).

**[0446]** N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) azetidine-3,3-dicarboxamide. To a solution of 'N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide (300 mg, 0.5 mmol) in MeOH (50 mL) was charged with Pd/C (50% wet, 10% mmol, 265 mg) and acetic acid (2 mL). The reaction mixture was subjected to hydrogenolysis condition under H2 (50 psi) on a Parr Hydrogenator for 16 hr. The reaction mixture was filtered through celite and washed with MeOH. After removal of solvent in vacuo, the crude product was purified using preparative HPLC (solvent system: MeCN/H2O/NH4OAc), affording N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)

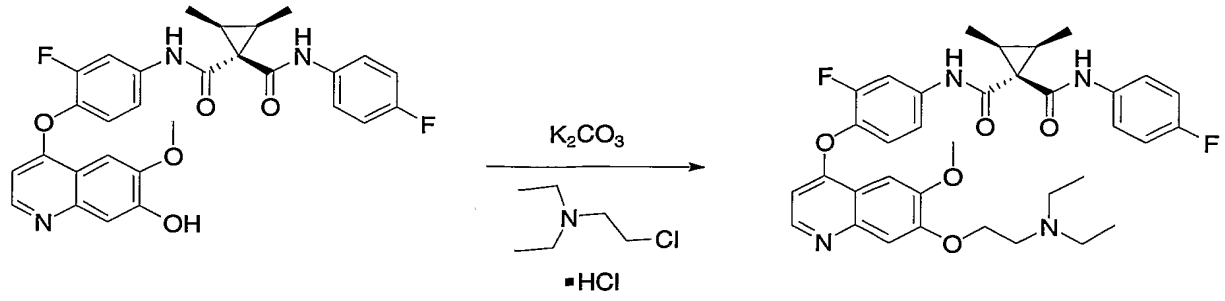
azetidine-3,3-dicarboxamide (82 mg, 32% yield) as a white solid. $^1$HNMR (DMSO-d6): 8.46 (d, 1H), 7.84 (d, 2H), 7.70 (m, 2H), 7.50 (s, 1H), 7.40 (s, 1H), 7.24 (d, 2H), 7.20 (t, 2H), 6.44 (d, 1H), 4.03 (s, 4H), 3.95 (s, 6H), 1.90 (s, 3H, acetate salt). LCMS (POS): 517.3 (M+H).

**Example 85**



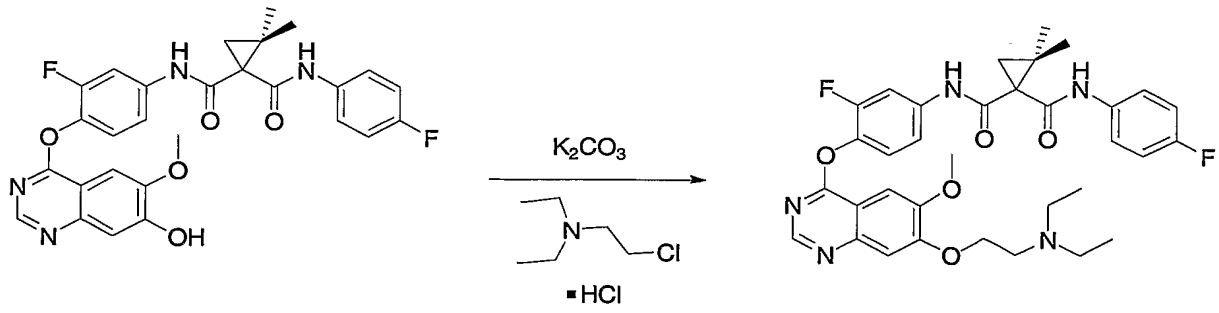

**[0447]** N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a solution of cyclopropane-1,1-dicarboxylic acid {3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-amide (4-fluoro-phenyl)-amide, TFA salt (~500 mg, 0.71 mmol) in $ClCH_2H_2Cl$ (8 mL) were added 30% formaldehyde (4 mL) and $NaBH(OAc)_3$ (752 mg, 3.55 mmol). The reaction mixture was stirred overnight. It was then quenched with aqueous sat. $NaHCO_3$, extracted with EtOAc. The organic phase was washed with brine and dried over $Na_2SO_4$. Drying salts were filtered, washed with EtOAc and the filtrate concentrated in vacuo to give 210mgs of crude product. The resulting residue was redissolved in EtOAc and any insoluble material filtered. To the filtrate was added 4M HCl in dioxane (200µl) and the mixture was stirred at room temperature for 1 hour. Solids were filtered, washed with EtOAc, dried under high vacuum, dissolved in 50% aqueous AcCN and lyophilized to give 'N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, HCl salt (113 mg, ~25% yield). $^1$HNMR (400MHz, DMSO-d6): δ 10.51 (s, 1H), 10.30 (br. s, 1H), 10.04 (s, 1H), 8.80 (d, 1H), 7.99 (dd, 1H), 7.55 (m, 2H), 7.67-7.53 (m, 4H), 7.16 (t, 2H), 6.89 (d, 1H), 4.13 (d, 2H), 4.05 (s, 3H), 3.47 (m, 2H), 3.00 (m, 2H), 2.74 (d, 3H), 2.17 (m, 1H), 2.03 (m, 2H), 1.68 (m, 2H), 1.49 (m, 4H). LC/MS Calcd for $[M+H]^+$ 617.3, found 617.4. Anal. HPLC (8 min gradient): 98% pure, 3.11 min.

**Example 86**



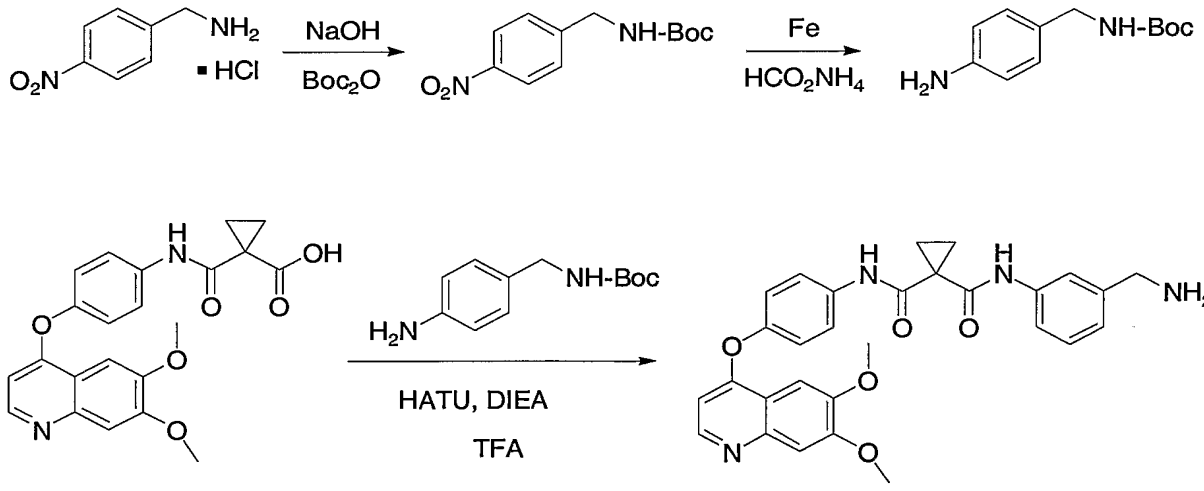

**[0448]** (1R,2R,3S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide. 2,3-Dimethyl-cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (210 mg, 0.39mmol), DMA (2mls), (2-chloro-ethyl)-diethyl-amine, HCl salt (73 mg, 0.42mmol) and $K_2CO_3$ (136 mg, 0.98mmol) were combined and heated at 80C overnight. The reaction mixture was then diluted with $H_2O$ and sonicated. The resulting solids were filtered, washed with $H_2O$ and dried under high vacuum. The crude product was then purified by preparative HPLC using an ammonium acetate buffer system and lyophilized to give '(1R,2R,3S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide (39 mg, 16% yield). $^1$HNMR (400MHz, DMSO-d6): δ 10.14 (s, 1H), 9.61 (s, 1H), 8.46 (d, 1H), 7.87 (dd, 1H), 7.67 (m, 2H), 7.57 (m, 1H), 7.51 (s, 1H), 7.42 (s, 1H), 7.39 (m, 1H), 7.15 (t, 2H), 6.41 (d, 1H), 4.20 (m, 2H), 3.94 (s, 3H), 2.87 (m, 2H), 2.60 (m, 4H), 1.80 (m, 2H), 1.18 (s, 3H), 1.17 (s, 3H), 1.01 (m, 6H). Note: 0.5eq of AcOH is present by NMR. LC/MS Calcd for $[M+H]^+$ 633.3, found 633.4. Anal. HPLC (25 min gradient): 96% pure, 18.52 min.

**Example 87**



**[0449]** N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide. 2,2-Dimethyl-cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (203 mg, 0.38mmol), DMA (2mls), (2-chloro-ethyl)-diethyl-amine, HCl salt (73 mg, 0.42mmol) and $K_2CO_3$ (146 mg, 1.05mmol) were combined and heated at 80C overnight. The reaction mixture was then diluted with $H_2O$ and extracted with $CH_2Cl_2$ (3x). The combined $CH_2Cl_2$ extractions were washed with sat'd $NaHCO_3$ (1x), sat'd NaCl (1x), dried ($Na_2SO_4$), and concentrated in vacuo. The resulting crude product was purified by flash chromatograghy (Silica Gel 60, 100% EtOAc, followed by 10% MeOH, 1% triethylamine in EtOAc), then dissolved in 50% aqueous AcCN and lyophilized to give 'N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethyl-cyclopropane-1,1-dicarboxamide (70 mg, 29% yield). $^1$HNMR (400MHz, DMSO): δ 10.24 (s, 1H), 10.00 (s, 1H), 8.54 (s, 1H), 7.84 (dd, 1H), 7.66 (m, 2H), 7.56 (s, 1H), 7.51 (m, 1H), 7.43 (m, 2H), 7.18 (t, 2H), 4.26 (m, 2H), 3.98 (s, 3H), 2.88 (m, 2H), 2.59 (m, 4H), 1.58 (m, 2H), 1.18 (s, 6H), 1.00 (t, 6H). LC/MS Calcd for $[M+H]^+$ 634.3, found 634.4. Anal. HPLC (25 min gradient): 94% pure, 24.08 min.

**Example 88**




**[0450]** Synthesis of 'N-[3-(aminomethyl)phenyl]-N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide. (4-Nitro-benzyl)-carbamic acid tert-butyl ester. 4-Nitro-benzylamine, HCl salt (5.19g, 27.5mmol) was dissolved in dioxane (100mls). NaOH (3.4g, 85.0mmol) in $H_2O$ (20mls) was added, followed by Boc

anhydride (7.6g, 34.8mmol). The mixture was stirred at room temperature. After 3hrs, the reaction mixture was diluted with EtOAc and washed with $H_2O$ (3x), sat'd NaCl (1x), dried ($Na_2SO_4$), and concentrated in vacuo. The resulting residue was triturated with hexanes, the resulting solids filtered, washed with hexanes and dried under vacuum to give (4-nitro-benzyl)-carbamic acid tert-butyl ester (6.34g, 91% yield). LC/MS Calcd for $[M+H]^+$ 253.1, found 197.0 (minus t-butyl).

**[0451]** (4-Amino-benzyl)-carbamic acid tert-butyl ester. (4-Nitro-benzyl)-carbamic acid tert-butyl ester (6.34g, 25.1mmol), iron powder (6.5g, 116mmol), ammonium formate (13.0g, 206mmol), $H_2O$ (75mls), and toluene (75mls) were combined and heated to reflux. After 3hrs the reaction mixture was allowed to cool and filtered through Celite with thorough washing with EtOAc. The filtrate was transferred to a separatory funnel and the phases separated. The organic phase was further washed with $H_2O$ (1x), sat'd NaCl (1x), dried ($Na_2SO_4$), and concentrated in vacuo to give (4-amino-benzyl)-carbamic acid tert-butyl ester (5.02g, 90% yield). LC/MS Calcd for $[M+H]^+$ 223.1, found 167.1 (minus t-butyl).

**[0452]** [3-({1-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropane-carbonyl}-amino)-benzyl]-carbamic acid tert-butyl ester. 1-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropanecarboxylic acid (254 mg, 0.62mmol), (4-amino-benzyl)-carbamic acid tert-butyl ester (164 mg, 0.74mmol), dry DMA (10mls), HATU (714 mg, 1.88mmol), and DIEA (325ml, 1.86mmol) were combined and stirred at room temperature. After 2hrs, the reaction mixture is diluted with $H_2O$ and the resulting solids are filtered, washed with $H_2O$, followed by sat'd $NaHCO_3$, and dried under high vacuum to give crude [3-({1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropanecarbonyl}-amino)-benzyl]-carbamic acid tert-butyl ester (301 mg, 79% yield) which was used in the next reaction without further purification. LC/MS Calcd for $[M+H]^+$ 613.3, found 613.1.

**[0453]** N-[3-(Aminomethyl)phenyl]-N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl) cyclopropane-1,1-dicarboxamide, TFA salt. [3-({1-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropanecarbonyl}-amino)-benzyl]-carbamic acid tert-butyl ester (50 mg, 0.081mmol) was dissolved in 50% TFA in $CH_2Cl_2$ (10mls) and stirred at room temperature. After 2hrs, the reaction mixture was concentrated in vacuo and the resulting residue was triturated with $Et_2O$. The resulting solids were filtered, washed with $Et_2O$ and dried under high vacuum to give 'N-[3-(aminomethyl)phenyl]-N'-(4-{[6,7-

bis(methyloxy)quinolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide as the TFA salt (54 mg, 100%). $^1$HNMR (400MHz, DMSO-d6): δ 10.28 (s, 1H), 10.19 (s, 1H), 8.77 (m, 1H), 8.21 (m, 3H), 7.84 (m, 2H), 7.76 (m, 1H), 7.71 (m, 1H), 7.58 (m, 2H), 7.38 (m, 3H), 7.19 (m, 1H), 6.76 (m, 1H), 4.03 (s, 6H), 3.39 (m, 2H), 1.53 (m, 4H). Note: all peaks are very broad and unresolved. LC/MS Calcd for $[M+H]^+$ 513.2, found 513.4. Anal. HPLC (25 min gradient): 88% pure, 12.39 min.

**[0454]** Table 3 contains $^1$H-NMR data for selected compounds of the invention.

**Table 3**

| Entry | Name | $^1$H-NMR |
|---|---|---|
| 1 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | 1H NMR (DMSO-d6): 10.52 (s, 1H), 10.02 (s, 1H), 9.38 (br., 3H), 8.79 (d, 1H), 7.98 (dd, 1H), 7.74 (s, 1H), 7.65 (m, 3H), 7.54 (m, 2H), 7.15 (t, 2H), 6.86 (d, 1H), 4.33 (t, 2H), 4.04 (s, 3H), 3.17-3.50 (m, 9H), 2.27 (br., 2H), 1.79 (m, 1H), 1.48 (m, 4H). Note: The peak at δ9.38 includes 2 TFA equivalents. |
| 2 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | 1H NMR (DMSO-d6): 10.41 (s, 1H), 10.03 (s, 1H), 8.47 (d, 1H), 7.90 (dd, 1H), 7.64 (m, 2H), 7.52 (s, 2H), 7.42 (t, 1H), 7.39 (s, 1H), 7.16 (t, 2H), 6.41 (d, 1H), 4.18 (t, 2H), 3.95 (s, 3H), 2.47 (t, 2H), 2.6-2.8 (br., 8H), 2.17 (s, 3H), 1.97 (m, 2H), 1.48 (s, 4H). |
| 3 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | 1H NMR (400MHz, DMSO-d6): d 10.51 (s, 1H), 10.30 (br. s, 1H), 10.04 (s, 1H), 8.80 (d, 1H), 7.99 (dd, 1H), 7.55 (m, 2H), 7.67-7.53 (m, 4H), 7.16 (t, 2H), 6.89 (d, 1H), 4.13 (d, 2H), 4.05 (s, 3H), 3.47 (m, 2H), 3.00 (m, 2H), 2.74 (d, 3H), 2.17 (m, 1H), 2.03 (m, 2H), 1.68 (m, 2H), 1.49 (m, 4H). |
| 4 | N-(4-fluorophenyl)-N'-[4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide | $^1$H NMR (400 MHz, DMSO-d6): 8.47 (d, 1H), 8.30 (m, 1H), 8.15 (m, 1H), 7.8 (m, 2H), 7.62 (s, 1H), 7.45 (m, 2H), 7.2 (m, 3H), 7.10 (m, 2H), 6.7 (d, 1H), 4.5 (m, 2H), 4.3 (m, 2H), 4.01(s, 3H), 3.5 (br, 2H), 3.3 (m, 2H), 3.1 (m, 2H), 2.51 (m, 2H), 1.9 (m, 2H) 1.6 (m, 4H). |
| 5 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | $^1$H NMR (400 MHz, DMSO-d6): 10.58 (s, 1H), 10.31 (bs, 1H), 10.04 (s, 1H), 8.75 (d, 1H), 7.99 (d, 1H), 7.74 (s, 1H), 7.63 (m, 4H), 7.19 (t, 2H), 6.91 (m, 1H), 4.39 (t, 2H), 4.19 (s, 3H), 3.21 (m, 7H), 2.29 (m, 2H), 1.46 (d, 4H), 1.15 (t, 6H). |

**Table 3**

| Entry | Name | $^1$H-NMR |
|---|---|---|
| 6 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | 1H NMR (DMSO-d6): 11.56 (s, 1H), 9.77 (s, 1H), 8.50 (d, 1H), 8.32 (d, 1H), 7.82 (d, 1H), 7.59 (m, 2H), 7.51 (s, 1H), 7.42 (s, 1H), 7.20 (t, 2H), 6.55 (d, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 1.73 (m, 2H), 3.65 (m, 2H). |
| 7 | N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | $^1$H NMR (DMSO-$d_6$) d 10.34 (s, 1H), 9.94 (s, 1H), 7.83 (d, 1H), 7.59 (m, 2H), 7.56 (m, 1H), 7.40 (m, 2H), 7.23 (s, 1H), 7.09 (t, 2H), 6.12 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.48 (s, 3H), 1.40 (m, 4H). |
| 8 | N-(4-fluorophenyl)-N'-(4-{[2-methyl-6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide | $^1$H NMR (DMSO-$d_6$) 10.15 (bs, 1H), 10.01 (bs, 1H), 7.69-7.75 (m, 2H), 7.61-7.68 (m, 2H), 7.52 (s, 1H), 7.32 (s, 1H), 7.23-7.29 (m, 2H), 7.12-7.19 (m, 2H), 3.93 (d, 6H), 2.43 (s, 3H), 1.53 (s, 4H). |
| 9 | N-(4-{[2-amino-6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | 1H NMR (DMSO-d6) d 10.34 (s, 1H), 9.95 (s, 1H), 7.82 (d, 1H), 7.58 (m, 2H), 7.44 (d, 1H), 7.33 (t, 1H), 7.25 (s, 1H), 7.09 (t, 2H), 7.07 (s, 1H), 6.17 (br s, 2H), 5.66 (s, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 1.40 (d, 4H). |
| 10 | N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | $^1$H NMR (DMSO-$d_6$) d 10.42 (s, 1H), 9.91 (s, 1H), 7.88 (dd, 1H), 7.56 (m, 2H), 7.44 (m, 4H), 7.09 (t, 2H), 5.90 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.39 (br s, 1H), 2.92 (s, 3H), 1.41 (dt, 4H). |
| 11 | (1S,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | $^1$H NMR (400 MHz, DMSO-$d_6$) d 10.49 (br s, 1 H), 10.26 (br s, 1 H), 10.15 (br s, 1 H), 8.74 (br s, 1 H), 7.95 (br d, J = 13.2 Hz, 1 H), 7.8-7.5 (m, 6 H), 7.16 (t, J = 8.9 Hz, 2 H), 6.82 (br s, 1 H), 4.34 (t, J = 5.9 Hz, 2 H), 4.02 (s, 3 H), 3.99 (br s, 2 H), 3.77 (br t, J = 12.0 Hz, 2 H), 3.56-3.30 (m, 4 H), 3.17-3.07 (m, 2 H), 2.40-2.30 (m, 2 H), 2.04-1.95 (m, 1 H), 1.45 (dd, J = 7.2, 4.7 Hz, 1 H), 1.36 (dd, J = 8.5, 4.5 Hz, 1 H), 1.09 (d, J = 6.2 Hz, 3 H). |

**Table 3**

| Entry | Name | $^1$H-NMR |
|---|---|---|
| 12 | (1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | $^1$H NMR (400 MHz, DMSO-$d_6$) d 10.65 (br s, 1 H), 10.54 (br s, 1 H), 9.74 (s, 1 H), 8.75 (br s, 1 H), 8.01 (br d, J = 12.9 Hz, 1 H), 7.80-7.50 (m, 6 H), 7.20-7.10 (m, 2 H), 6.84 (br s, 1 H), 4.34 (br t, J = 5 Hz, 2 H), 4.04 (s, 3 H), 4.05-3.95 (m, 2 H), 3.77 (br t, J = 11 Hz, 2 H), 3.52 (br d, J = 12.7 Hz, 4 H), 3.12 (br q, J = 9.0 Hz, 2 H), 2.40-2.30 (m, 2 H), 2.10-1.95 (m, 1 H), 1.40-1.30 (m, 2 H), 1.10 (d, J = 6.2 Hz, 3 H). |
| 13 | N-(4-{[6-{[3-(diethylamino)propyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | $^1$H NMR (DMSO-$d_6$) d 10.37 (br s, 1H), 10.00 (s, 1H), 8.44 (d, 1H), 7.87 (d, 1H), 7.62 (m, 2H), 7.49 (m, 2H), 7.41 (m, 2H), 7.13 (t, 2H), 6.40 (d, 1H), 4.17 (t, 2H), 3.93 (s, 3H), 2.59 (t, 2H), 2.49 (m, 6H), 1.91 (m, 4H), 0.94 (t, 6H). |
| 14 | N-(4-{[6-{[2-(diethylamino)ethyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | $^1$H NMR (DMSO-$d_6$) d 10.36 (br s, 1H), 9.99 (s, 1H), 8.44 (d, 1H), 7.88 (dd, 1H), 7.62 (m, 2H), 7.57 (m, 2H), 7.41 (m, 2H), 7.13 (t, 2H), 6.40 (d, 1H), 4.17 (t, 2H), 3.93 (s, 3H), 2.85 (t, 2H), 2.56 (q, 4H), 2.49 (m, 4H), 0.98 (t, 6H). |
| 15 | 1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[(1-{[(4-fluorophenyl)amino]carbonyl}cyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate | $^1$H NMR (400 MHz, $CDCl_3$): 10.05 (s, 1H), 8.49-8.27 (t, 1H), 7.79-7.76 (d, 1H), 7.57 (s, 1H), 7.47-7.43 (m, 3H), 7.27-7.20 (m, 1H), 7.09-7.04 (m, 2H), 6.40-6.39 (d, 1H), 4.28-4.25 (t, 2H), 3.50 (s, 3H), 3.47-3.44, (t, 4H), 2.62-2.59 (t, 2H), 2.46-2.44 (t, 4H), 2.18-2.11 (m, 2H), 2.09 (s, 1H), 1.83-1.81 (t, 2H), 1.64-1.61 (t, 2H), 1.47 (s, 9H). |
| 16 | (1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | $^1$H NMR (DMSO-$d_6$) d 10.40 (s, 1H), 9.65 (s, 1H), 8.45 (s, 1H), 7.79 (dd, 1H), 7.53 (m, 2H), 7.47 (s, 1H), 7.36 (m, 1H), 7.31 (m, 2H), 7.05 (t, 2H), 4.17 (t, 2H), 3.91 (s, 3H), 3.51 (t, 4H), 2.40 (t, 2H), 2.36 (m, 4H), 1.90 (m, 3H), 1.30 (m, 2H), 1.02 (d, 3H). |
| 17 | (1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | $^1$H NMR (DMSO-$d_6$) d 10.49 (s, 1H), 9.73 (s, 1H), 8.52 (s, 1H), 7.85 (dd, 1H), 7.61 (m, 2H), 7.54 (s, 1H), 7.41 (m, 3H), 7.12 (t, 2H), 7.23 (t, 2H), 3.96 (s, 3H), 2.86 (t, 2H), 2.56 (q, 4H), 1.98 (m, 1H), 1.34 (m, 2H), 1.07 (d, 3H), 0.97 (t, 6H). |

Table 3

| Entry | Name | $^1$H-NMR |
|---|---|---|
| 18 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | 1H NMR (DMSO-d6) 8.51 (s, 1H), 7.78-7.84 (m, 1H), 7.58-7.64 (m, 2H), 7.53 (s, 1H), 7.34-7.48 (m, 3H), 7.13 (t, 2H), 4.22 (t, 2H), 3.98 (s, 3H), 2.84 (t, 2H), 2.55 (q, 4H), 1.48 (s, 4H), 1.39 (t, 6H). |
| 19 | N-(4-{[7-{[3-(4-acetylpiperazin-1-yl)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | $^1$H NMR (400 MHz, $CDCl_3$): 10.04 (s, 1H), 8.48-8.47 (d, 1H), 8.21 (s, 1H), 7.79-7.76 (d, 1H), 7.57 (s, 1H), 7.52-7.44 (m, 3H), 7.28-7.20 (m, 2H), 7.09-7.05 (t, 2H), 6.40-6.39 (d, 1H), 4.30-4.26 (t, 2H), 4.04 (s, 3H), 3.64-3.62 (t, 2H), 3.49-3.47 (t, 2H), 2.62-2.58 (t, 2H), 2.50-2.44 (m, 4H), 2.17-2.12 (m, 2H), 2.10 (s, 3H), 1.84-1.81 (t, 2H), 1.64-1.61 (t, 2H). |
| 20 | 1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[((1R,2R)-1-{[(4-fluorophenyl)amino]carbonyl}-2-methylcyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate | $^1$H NMR (400 MHz, DMSO-$d_6$): 10.54 (s, 1H), 9.72 (s, 1H), 8.47-8.46 (d, 1H), 7.96-7.93 (dd, 1H), 7.63-7.61 (m, 2H), 7.52 (br s, 2H), 7.42-7.40 (d, 2H), 7.17-7.12 (t, 2H), 6.44-6.42 (d, 1H), 4.22-4.18 (t, 2H), 3.95 (s, 3H), 3.42-3.40 (m, 2H), 2.36-2.26 (m, 8H), 2.00-1.98 (m, 3H), 1.58-1.54 (m, 2H), 1.40 (s, 9H), 1.10-1.09 (d, 3H). |
| 21 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide | 1H NMR (DMSO-d6): 10.0 (s, 1H), 9.9 (s, 1H), 8.45 (d, 1H), 7.8 (d, 2H), 7.7 (m, 2H), 7.5 (s, 1H), 7.4 (s, 1H), 7.48-7.15 (m, 9H), 3.95 (s, 6H), 3.7 (s, 4H), 3.6 (s, 2H). |
| 22 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)azetidine-3,3-dicarboxamide | 1H NMR (DMSO-d6): 8.46 (d, 1H), 7.84 (d, 2H), 7.70 (m, 2H), 7.50 (s, 1H), 7.40 (s, 1H), 7.24 (d, 2H), 7.20 (t, 2H), 6.44 (d, 1H), 4.03 (s, 4H), 3.95 (s, 6H), 1.90 (s, 3H, acetate salt). |
| 23 | (1R,2S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | $^1$H NMR (400 MHz, DMSO-$d_6$): 10.26 (s, 1H), 9.75 (s, 1H), 8.47-8.46 (d, 1H), 7.91-7.87 (dd, 1H), 7.70-7.66 (m, 2H), 7.56-7.51 (m, 2H), 7.43-7.38 (m, 2H), 6.42-6.41 (d, 1H), 4.20-4.16 (t, 2H), 3.95 (s, 3H), 2.47-2.43 (m, 2H), 2.40-2.24 (m, 5H), 2.14 (s, 3H), 2.03-1.93 (m, 3H), 1.89 (s, 3H), 1.45-1.42 (m, 1H), 1.38-1.35 (m, 1H), 1.10-1.08 (d, 3H). |

**Table 3**

| Entry | Name | $^1$H-NMR |
|---|---|---|
| 24 | (1R,2R)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | $^1$H NMR (400 MHz, DMSO-$d_6$): 10.56 (s, 1H), 9.75 (s, 1H), 8.47-8.46 (d, 1H), 7.96-7.93 (d, 1H), 7.68-7.61 (m, 2H), 7.53-7.52 (m, 2H), 7.44-7.39 (m, 2H), 7.18-7.12 (m, 2H), 6.44-6.42 (d, 1H), 4.20-4.17 (t, 2H), 3.95 (s, 3H), 3.42-3.30 (m, 3H), 2.46-2.44 (m, 2H), 2.33 (br s, 2H), 2.15 (s, 3H), 2.05-1.94 (m, 2H), 1.89 (s, 5H), 1.40-1.35 (m, 1H), 1.10-1.09 (m, 3H). |
| 25 | (1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | $^1$H NMR (400 MHz, DMSO-$d_6$): 10.55 (s, 1H), 9.72 (s, 1H), 8.47-8.46 (d, 1H), 7.96-7.93 (d, 1H), 7.68-7.61 (m, 2H), 7.52 (br s, 2H), 7.44-7.40 (m, 2H), 7.17-7.12 (m, 2H), 6.44-6.43 (d, 1H), 4.21-4.18 (t, 2H), 3.95 (s, 3H), 2.79 (br s, 4H), 2.47-2.44 (t, 2H), 2.38 (br s, 3H), 2.04-1.95 (m, 3H), 1.40-1.35 (m, 2H), 1.11-1.09 (m, 5H). |
| 26 | N-(3-fluoro-4-{[7-({3-[4-(1-methylethyl)piperazin-1-yl]propyl}oxy)-6-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | $^1$H NMR (400 MHz, DMSO-$d_6$): 10.40 (s, 1H), 10.02 (s, 1H), 8.47-8.46 (d, 1H), 7.92-7.89 (d, 1H), 7.66-7.63 (m, 2H), 7.52-7.51 (d, 2H), 7.44-7.39 (m, 2H), 7.19-7.14 (m, 2H), 6.42-6.41 (d, 1H), 4.20-4.17 (t, 2H), 3.95 (s, 3H), 2.70-2.68 (m, 1H), 2.62-2.55 (m, 2H), 2.46-2.33 (m, 8H), 1.99-1.94 (m, 2H), 1.47 (s, 4H), 1.00-0.95 (m, 6H). |
| 27 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | $^1$H NMR (DMSO-$d_6$)10.34 (s, 1H), 10.01 (s, 1H), 8.50 (s, 1H), 7.81 (dd, 1H), 7.55-7.68 (m, 2H), 7.51-7.55 (m, 2H), 7.33-7.48 (m, 3H), 7.12 (t, 2H), 4.22 (t, 2H), 3.94 (s, 3H), 2.52-2.61 (m, 2H), 2.49-2.51 (m, 4H), 1.83-1.94 (m, 2H), 1.42 (s, 4H), 0.95 (t, 6H). |
| 28 | (1R,2R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | $^1$H NMR (DMSO-$d_6$) d 10.52 (s, 1H), 9.70 (s, 1H), 8.44 (d, 1H), 7.92 (dd, 1H), 7.61 (m, 2H), 7.50 (m, 2H), 7.43 (m, 2H), 7.12 (t, 2H), 6.41 (d, 1H), 4.17 (t, 2H), 3.93 (s, 3H), 2.55 (m, 2H), 2.31 (m, 4H), 1.98 (m, 1H), 1.88 (m, 2H), 1.35 (m, 2H), 1.07 (d, 3H), 0.94 (t, 6H). |
| 29 | (1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | $^1$H NMR (DMSO-$d_6$) d 10.52 (s, 1H), 9.70 (s, 1H), 8.44 (d, 1H), 7.78 (dd, 1H), 7.61 (m, 2H), 7.51 (m, 2H), 7.41 (m, 2H), 7.12 (t, 2H), 6.41 (d, 1H), 4.17 (t, 2H), 3.93 (s, 3H), 2.85 (t, 2H), 2.57 (q, 4H), 1.98 (m, 1H), 1.34 (m, 2H), 1.07 (d, 3H), 0.98 (t, 6H). |

**Table 3**

| Entry | Name | $^1$H-NMR |
|---|---|---|
| 30 | (1R,2S)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | $^1$H NMR (DMSO-$d_6$) d 10.17 (s, 1H), 9.97 (s, 1H), 8.39 (d, 1H), 7.80 (dd, 1H), 7.62 (m, 2H), 7.45 (m, 2H), 7.31 (m, 2H), 7.09 (t, 2H), 6.34 (d, 1H), 4.12 (t, 2H), 3.88 (s, 3H), 2.46 (m, 2H), 2.40 (m, 4H), 1.92 (m, 1H), 1.84 (m, 2H), 1.37 (m, 1H), 1.29 (m, 1H), 1.01 (d, 3H), 0.89 (t, 6H). |
| 31 | (1R,2S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | $^1$H NMR (DMSO-$d_6$) d 10.22 (s, 1H), 10.01 (s, 1H), 8.44 (d, 1H), 7.86 (dd, 1H), 7.66 (m, 2H), 7.49 (m, 2H), 7.39 (m, 2H), 7.14 (m, 2H), 6.39 (d, 1H), 4.18 (m, 2H), 3.92 (s, 3H), 2.85 (t, 2H), 2.57 (q, 4H), 1.97 (m, 1H), 1.42 (m, 1H), 1.35 (m, 1H), 1.06 (d, 3H), 0.98 (t, 6H). |
| 32 | N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide | $^1$H NMR ($CDCl_3$) 8.57 (s, 1H), 8.12 (s, 1H), 7.73-7.81 (m, 2H), 7.48-7.53 (m, 2H), 7.32 (s, 1H), 6.98-7.08 (m, 3H), 4.28 (t, 2H), 4.04 (s, 3H), 3.25 (t, 2H), 2.76 (q, 4H), 2.67 (q, 4H), 2.01-2.15 (m, 2H), 1.10 (t, 6H). |
| 33 | (1R,2S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | $^1$H NMR (400 MHz, DMSO-$d_6$): 10.28 (s, 1H), 9.80 (s, 1H) 8.47-8.46 (d, 1H), 7.90-7.88 (d, 1H), 7.70-7.62 (m, 2H), 7.56-7.52 (m, 2H), 7.44-7.39 (m, 2H), 7.18-7.12 (m, 2H), 6.44-6.41 (t, 1H), 4.20-4.17 (t, 2H), 3.95 (s, 3H), 2.74-2.72 (t, 3H), 2.46-2.42 (m, 1H), 2.35 (br s, 3H), 2.03-1.93 (m, 3H), 1.87 (s, 4H), 1.43-1.35 (m, 2H), 1.09-1.08 (m, 3H). |
| 34 | (1r,2R,3S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide | 1H NMR (DMSO-d6): 1H (10.12 ppm, s), 1H (9.6 ppm, s), 1H (8.46 ppm, d), 1H (7.88 ppm, dd), 2H (7.68 ppm, m), 1H (7.56 ppm, d), 1H (7.51 ppm, s), 2H(7.4 ppm, m), 2H (7.13 ppm, t), 1H (6.4 ppm, d), 2H (4.2 ppm, t), 3H (3.94 ppm, s), 4H ( 3.6 ppm, t), 2H (2.45 ppm, t), 4H (2.37 ppm, m), 2H (1.97 ppm, t), 2H (1.8 ppm, m), 6 H(1.28 ppm, d). |
| 35 | (1r,2R,3S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide | 1H NMR (DMSO-d6): 1H (10.12 ppm, s), 1H (9.6 ppm, s), 1H (8.46 ppm, d), 1H (7.88 ppm, dd), 2H (7.69 ppm, m), 1H (7.58 ppm, d), 1H (7.51 ppm, s), 2H (7.4 ppm, m), 2H (7.13 ppm, t), 1H (6.4 ppm, d), 2H (4.2 ppm, t), 3H (3.95 ppm, s), 10H (2.35 ppm, m), 3H (2.14 ppm, s), 2H (1.97 ppm, t), 2H (1.8 ppm, m), 6H (1.28 ppm, d). |

**Table 3**

| Entry | Name | $^1$H-NMR |
|---|---|---|
| 36 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide | $^1$H NMR (400 MHz, DMSO-d6): 8.45 (d, 2 H), 8.15 (d, 1H), 7.8 (d, 1H), 7.45 (m, 3H), 7.25 (m, 3H), 7.0 (m, 2H), 4.20 (t, 2H), 4.0 (s, 3H), 3.7 (m, 4H), 2.67 (m, 4H), 2.45 (m, 6H), 2.0 (m, 4H). |
| 37 | (2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide | $^1$H NMR (400 MHz, $CDCl_3$) d 8.44 (d, J = 5.1 Hz, 1 H), 8.11 (br s, 1 H), 7.77-7.70 (m, 2 H), 7.53 (s, 1 H), 7.50-7.44 (m, 2 H), 7.40 (s, 1 H), 7.22-7.16 (m, 2 H), 7.06-6.98 (m, 2 H), 6.36 (br d, J = 5.1 Hz, 1 H), 4.26 (t, J = 7.0 Hz, 2 H), 4.02 (s, 3 H), 3.72 (t, J = 4.4 Hz, 4 H), 2.57 (t, J = 7.3 Hz, 2 H), 2.50-2.42 (m, 4 H), 2.18-2.10 (m, 2 H), 1.80-1.66 (m, 2 H), 1.30-1.24 (m, 6 H). |
| 38 | (2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide | $^1$H NMR (400 MHz, DMSO-$d_6$) d 10.34 (s, 1 H), 10.05 (s, 1 H), 8.46 (br s, 1 H), 7.93 (br d, J = 4.7 Hz, 1 H), 7.54-7.52 (m, 2 H), 7.52-7.50 (m, 2 H), 7.50-7.30 (m, 2 H), 7.20-7.10 (m, 2 H), 6.47 (br s, 1 H), 4.30-4.20 (m, 2 H), 3.95 (s, 3 H), 3.40-3.10 (m, 6 H), 2.60-2.40 (m, 2 H), 1.90-1.80 (m, 2 H), 1.30-1.10 (m, 12 H). |
| 39 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide | 1H NMR (400MHz, DMSO-d6): d 10.47 (s, 1H), 10.16 (s, 1H), 8.43 (d, 1H), 7.92 (dd, 1H), 7.67 (m, 2H), 7.58 (m, 1H), 7.52 (s, 1H), 7.41 (m, 2H), 7.15 (t, 2H), 6.44 (d, 1H), 4.25 (t, 2H), 3.95 (s, 3H), 3.10 (m, 6H), 2.17 (m, 2H), 1.91 (s, 3H, acetate salt), 1.52 (m, 2H), 1.18 (m, 12H). |
| 40 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide | 1H NMR (400MHz, DMSO-d6): d 10.21 (s, 1H), 9.97 (s, 1H), 8.51 (s, 1H), 7.81 (dd, 1H), 7.64 (m, 2H), 7.54 (s, 1H), 7.48 (m, 1H), 7.41 (m, 1H), 7.38 (s, 1H), 7.15 (t, 2H), 4.24 (t, 2H), 3.97 (s, 3H), 3.58 (m, 4H), 2.45 (t, 2H), 2.38 (m, 4H), 1.97 (m, 2H), 1.58 (m, 2H), 1.18 (s, 3H), 1.17 (s, 3H). |
| 41 | (1R,2R,3S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide | 1H NMR (400MHz, DMSO-d6): d 10.14 (s, 1H), 9.61 (s, 1H), 8.46 (d, 1H), 7.87 (dd, 1H), 7.67 (m, 2H), 7.57 (m, 1H), 7.51 (s, 1H), 7.42 (s, 1H), 7.39 (m, 1H), 7.15 (t, 2H), 6.41 (d, 1H), 4.20 (m, 2H), 3.94 (s, 3H), 2.87 (m, 2H), 2.60 (m, 4H), 1.80 (m, 2H), 1.18 (s, 3H), 1.17 (s, 3H), 1.01 (m, 6H). Note: 0.5eq of AcOH is present by NMR. |

**Table 3**

| Entry | Name | $^1$H-NMR |
|---|---|---|
| 42 | N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide | 1H NMR (400MHz, DMSO): d 10.24 (s, 1H), 10.00 (s, 1H), 8.54 (s, 1H), 7.84 (dd, 1H), 7.66 (m, 2H), 7.56 (s, 1H), 7.51 (m, 1H), 7.43 (m, 2H), 7.18 (t, 2H), 4.26 (m, 2H), 3.98 (s, 3H), 2.88 (m, 2H), 2.59 (m, 4H), 1.58 (m, 2H), 1.18 (s, 6H), 1.00 (t, 6H). |
| 43 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide | 1H NMR (400MHz, DMSO-d6): d 10.21 (s, 1H), 9.97 (s, 1H), 8.51 (s, 1H), 7.82 (dd, 1H), 7.64 (m, 2H), 7.54 (s, 1H), 7.48 (m, 1H), 7.41 (m, 1H), 7.37 (s, 1H), 7.15 (t, 2H), 4.23 (t, 2H), 3.97 (s, 3H), 2.56 (m, 2H), 2.46 (m, 4H), 1.91 (m, 2H), 1.58 (m, 2H), 1.18 (s, 6H), 0.96 (t, 6H). |
| 44 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide | 1H NMR (CDCl3): 8.57 (s, 1H), 8.50 (s, 1H), 8.11 (s, 1H), 7.81 (dd, 1H), 7.53 (m, 3H), 7.28 (m, 4H), 7.04 (t, 2H), 4.24 (t, 2H), 4.04 (s, 3H), 2.95 (t, 2H), 2.84 (q, 4H), 2.75 (m, 4H), 2.21 (m, 2H), 2.02 (m, 2H), 1.18 (t, 6H). |
| 45 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide | 1H NMR (CDCL3): 8.57 (s, 1H), 8.49 (s, 1H), 8.10 (s, 1H), 7.80 (d, 1H), 7.70 (br., 1H), 7.52 (m, 3H), 7.31 (m, 3H), 7.04 (t, 2H), 4.26 (t, 2H), 4.04 (s, 3H), 2.62-2.77 (m, 14H), 2.40 (s, 3H), 2.13 (m, 2H), 2.01 (m, 2H). |
| 46 | (2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide | $^1$H NMR (400 MHz, $CDCl_3$) d 8.59 (s, 1 H), 8.11 (br s, 1 H), 7.80-7.76 (m, 2 H), 7.53 (s, 1 H), 7.50-7.46 (m, 2 H), 7.34 (s, 1 H), 7.26-7.24 (m, 2 H), 7.06-7.00 (m, 2 H), 4.28 (t, J = 6.6 Hz, 2 H), 4.05 (s, 3 H), 3.73 (br t, J = 4.4 Hz, 4 H), 2.57 (t, J = 7.0 Hz, 2 H), 2,52-2,45 (m, 4 H), 2.18-2.10 (m, 2 H), 1.80-1.68 (m, 2 H), 1.28-1.20 (m, 6 H). |
| 47 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide | $^1$H NMR (400 MHz, DMSO-$d_6$): 9.98 (s, 1H), 9.72 (s, 1H), 8.45-8.43 (d, 1H), 7.97-7.94 (dd, 1H), 7.73-7.69 (m, 2H), 7.65-7.52 (m, 3H), 7.44-7.39 (m, 1H), 7.18-7.14 (m, 2H), 6.43-6.42 (d, 1H), 4.20-4.19 (t, 2H), 3.95 (s, 3H), 2.70-2.66 (m, 6H), 2.45 (br s, 2H), 1.91-1.84 (m, 6H), 0.98 (br s, 6H). |

**Table 3**

| Entry | Name | $^1$H-NMR |
|---|---|---|
| 48 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide | $^1$H NMR (400 MHz, DMSO-$d_6$): 9.99 (s, 1H), 9.73 (s, 1H), 8.45-8.43 (d, 1H), 7.97-7.93 (dd, 1H), 7.73-7.69 (m, 2H), 7.65-7.52 (m, 2H), 7.44-7.38 (m, 2H), 7.18-7.14 (m, 2H), 6.43-6.42 (d, 1H), 4.19-4.16 (t, 3H), 3.95 (s, 3H), 2.70-2.66 (m, 4H), 2.47-2.33 (m, 8H), 2.15 (s, 3H), 1.98-1.94 (m, 2H), 1.90-1.84 (m, 4H). |
| 49 | (2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide | $^1$H NMR (400 MHz, $CDCl_3$) d 8.59 (br s, 1 H), 8.29 (br s, 1 H), 7.93 (s, 1 H), 7.77 (d, J = 10.8 Hz, 1 H), 7.53 (s, 1 H), 7.50-7.45 (m, 2 H), 7.32 (s, 1 H), 7.26-7.22 (m, 2 H), 7.05-6.99 (m, 2 H), 4.27 (t, J = 6.6 Hz, 2 H), 4.04 (s, 3 H), 3.03 (t, J = 6.5 Hz, 2 H), 2.67 (q, J = 7.0 Hz, 4 H), 1.80-1.70 (m, 2 H), 1.22 (br t, J = 5.3 Hz, 6 H), 1.09 (br t, J = 7.2 Hz, 6 H). |
| 50 | (2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide | $^1$H NMR (400 MHz, $CDCl_3$) d 8.58 (s, 1 H), 8.40-8.36 (m, 1 H), 8.02-7.96 (m, 1 H), 7.80-7.75 (m, 1 H), 7.53 (s, 1 H), 7.52-7.50 (m, 2 H), 7.31 (s, 1 H), 7.28-7.20 (m, 2 H), 7.02 (t, J = 8.5 Hz, 2 H), 4.25 (t, J = 6.3 Hz, 2 H), 4.04 (s, 3 H), 3.00-2.90 (m, 2 H), 2.88-2.80 (m, 4 H), 2.30-2.20 (m, 2 H), 1.76-1.68 (m, 2 H), 1.25-1.15 (m, 12 H). |
| 51 | (2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide | $^1$H NMR (400 MHz, $CDCl_3$) d 8.47 (d, J = 5.2 Hz, 1 H), 8.17 (br s, 1 H), 7.80-7.74 (m, 2 H), 7.55 (s, 1 H), 7.52-7.46 (m, 2 H), 7.42 (s, 1 H), 7.24-7.20 (m, 2 H), 7.05 (t, J = 8.6 Hz, 2 H), 6.38 (br d, J = 5.4 Hz, 1 H), 4.27 (t, J = 6.4 Hz, 2 H), 4.03 (s, 3 H), 3.04 (br t, J = 7.2 Hz, 2 H), 2.68 (q, J = 6.8 Hz, 4 H), 1.80-1.68 (m, 2 H), 1.26 (d, J = 6.4 Hz, 6 H), 1.09 (br t, J = 7.2 Hz, 6 H). |
| 52 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[(4-fluorophenyl)methyl]cyclopropane-1,1-dicarboxamide | 1H NMR (DMSO-d6): 10.82 (s, 1H), 8.80 (d, 1H), 8.50 (t, 1H), 7.83 (d, 2H), 7.74 (s, 1H), 7.56 (s, 1H), 7.30-7.38 (m, 4H), 7.15 (t, 2H), 6.80 (d, 1H), 4.32 (d, 2H), 4.04 (s, 3H), 4.03 (s, 3H), 1.42 (s, 4H). |
| 53 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(2-morpholin-4-ylethyl)cyclopropane-1,1-dicarboxamide | 1H NMR (DMSO-d6): 10.62 (s, 1H), 8.79 (d, 1H), 8.24 (t, 1H), 7.83 (d, 2H), 7.72 (s, 1H), 7.58 (s, 1H), 7.37 (d, 2H), 6.76 (d, 1H), 4.04 (s, 3H), 4.03 (s, 3H), 3.98 (m, 2H), 3.66 (m, 2H), 3.49 (m, 4H), 3.25 (t, 2H), 3.13 (br., 2H), 1.42 (d, 4H). |

**Table 3**

| Entry | Name | $^1$H-NMR |
|---|---|---|
| 54 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide | 1H NMR (DMSO-d6): 10.78 (s, 1H), 10.53 (s, 1H), 8.43 (d, 1H), 8.12 (d, 1H), 7.82 (d, 2H), 7.49 (s, 1H), 7.37 (s, 1H), 7.20-7.28 (m, 3H), 7.15 (dd, 1H), 7.01 (td, 1H), 6.35 (d, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.47 (s, 2H), 2.17 (br., 4H), 1.49 (m, 4H), 1.41 (m, 4H), 1.32 (br., 2H). |
| 55 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide | 1H NMR (DMSO-d6): 10.98 (s, 1H), 10.56 (s, 1H), 8.42 (d, 1H), 8.10 (dd, 1H), 7.81 (m, 2H), 7.49 (s, 1H), 7.37 (s, 1H), 7.17-7.27 (m, 4H), 7.01 (td, 1H), 6.35 (d, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.61 (s, 2H), 2.30 (br., 4H), 1.47 (br., 4H), 1.43 (m, 4H). |
| 56 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide | 1H NMR (DMSO-d6): 10.12 (s, 1H), 10.03 (s, 1H), 8.44 (d, 1H), 7.74 (d, 2H), 7.57 (s, 1H), 7.53 (d, 1H), 7.48 (s, 1H), 7.37 (s, 1H), 7.21 (m, 3H), 6.98 (d, 1H), 6.40 (d, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.56 (t, 4H), 3.41 (s, 2H), 2.34 (br., 4H), 1.48 (s, 4H). |
| 57 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide | 1H NMR (DMSO-d6): 10.54 (s, 1H), 10.47 (s, 1H), 8.43 (d, 1H), 8.08 (d, 1H), 7.78 (d, 2H), 7.49 (s, 1H), 7.37 (d, 1H), 7.18-7.30 (m, 4H), 7.03 (t, 1H), 6.37 (d, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.50 (s, 2H), 3.44 (br., 4H), 2.20 (br., 4H), 1.48 (d, 4H). |
| 58 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-phenylcyclopropane-1,1-dicarboxamide | 1H NMR (DMSO-d6): 10.14 (s, 1H), 10.03 (s, 1H), 8.44 (d, 1H), 7.74 (d, 2H), 7.62 (d, 2H), 7.48 (s, 1H), 7.37 (s, 1H), 7.27-7.31 (m, 2H), 7.19-7.23 (m, 2H), 7.05 (t, 1H), 6.41 (d, 1H), 3.93 (s, 6H), 3.92 (s, 3H), 1.48 (s, 4H). |
| 59 | N-[3-(aminomethyl)phenyl]-N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide | 1H NMR (400MHz, DMSO-d6): d 10.28 (s, 1H), 10.19 (s, 1H), 8.77 (m, 1H), 8.21 (m, 3H), 7.84 (m, 2H), 7.76 (m, 1H), 7.71 (m, 1H), 7.58 (m, 2H), 7.38 (m, 3H), 7.19 (m, 1H), 6.76 (m, 1H), 4.03 (s, 6H), 3.39 (m, 2H), 1.53 (m, 4H). Note: all peaks are very broad and unresolved. |
| 60 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide | 1H NMR (DMSO-d6): 10.0-10.2 (br., 2H), 8.46 (d, 1H), 7.76 (d, 2H), 7.53 (m, 3H), 7.39 (s, 1H), 7.24 (m, 3H), 6.98 (d, 1H), 6.43 (d, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.37 (s, 2H), 2.31 (br., 4H), 1.48 (m, 8H), 1.39 (br., 2H). |

**Table 3**

| Entry | Name | $^1$H-NMR |
|---|---|---|
| 61 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide | 1H NMR (DMSO-d6): 10.0-10.2 (br., 2H), 8.46 (d, 1H), 7.77 (d, 2H), 7.59 (s, 1H), 7.53 (d, 1H), 7.51 (s, 1H), 7.39 (s, 1H), 7.23 (m, 3H), 6.99 (d, 1H), 6.43 (d, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.52 (s, 2H), 2.42 (br., 4H), 1.69 (br, 4H), 1.48 (s, 4H). |

**Assays**

**[0455]** Kinase assays were performed by measurement of incorporation of $\gamma$-$^{33}$P ATP into immobilized myelin basic protein (MBP). High binding white 384 well plates (Greiner) were coated with MBP (Sigma #M-1891) by incubation of 60ul/well of 20μg/ml MBP in Tris-buffered saline (TBS; 50mM Tris pH 8.0, 138mM NaCl, 2.7mM KCl) for 24 hours at 4° C. Plates were washed 3X with 100μl TBS. Kinase reactions were carried out in a total volume of 34μl in kinase buffer (5mM Hepes pH 7.6, 15mM NaCl, 0.01% bovine gamma globulin (Sigma #I-5506), 10mM $MgCl_2$, 1mM DTT, 0.02% TritonX-100). Compound dilutions were performed in DMSO and added to assay wells to a final DMSO concentration of 1%. Each data point was measured in duplicate, and at least two duplicate assays were performed for each individual compound determination. Enzyme was added to final concentrations of 10nM or 20nM, for example. A mixture of unlabeled ATP and $\gamma$-$^{33}$P ATP was added to start the reaction ($2x10^6$ cpm of $\gamma$-$^{33}$P ATP per well (3000Ci/mmole) and either 10μM or 30μM unlabeled ATP, typically. The reactions were carried out for 1 hour at room temperature with shaking. Plates were washed 7x with TBS, followed by the addition of 50μl/well scintillation fluid (Wallac). Plates were read using a Wallac Trilux counter. This is only one format of such assays, various other formats are possible, as known to one skilled in the art.

**[0456]** The above assay procedure can be used to determine the $IC_{50}$ for inhibition and/or the inhibition constant, $K_i$. The $IC_{50}$ is defined as the concentration of compound required to reduce the enzyme activity by 50% under the conditions of the assay. Exemplary compositions have $IC_{50}$'s of, for example, less than about 100 μM, less than about 10 μM, less than about 1 μM, and further for example having $IC_{50}$'s of less than about 100 nM, and still further, for example, less than about 10 nM. The $K_i$ for a compound may be

determined from the $IC_{50}$ based on three assumptions. First, only one compound molecule binds to the enzyme and there is no cooperativity. Second, the concentrations of active enzyme and the compound tested are known (i.e., there are no significant amounts of impurities or inactive forms in the preparations). Third, the enzymatic rate of the enzyme-inhibitor complex is zero. The rate (i.e., compound concentration) data are fitted to the equation:

$$V = V_{max} E_0 \left[ I - \frac{(E_0 + I_0 + K_d) - \sqrt{(E_0 + I_0 + K_d)^2 - 4E_0 I_0}}{2E_0} \right]$$

where V is the observed rate, $V_{max}$, is the rate of the free enzyme, $I_0$ is the inhibitor concentration, $E_0$ is the enzyme concentration, and $K_d$ is the dissociation constant of the enzyme-inhibitor complex.

**Kinase specificity assays:**

**[0457]** Kinase activity and compound inhibition are investigated using one or more of the three assay formats described below. The ATP concentrations for each assay are selected to be close to the Michaelis-Menten constant ($K_M$) for each individual kinase. Dose-response experiments are performed at 10 different inhibitor concentrations in a 384-well plate format. The data are fitted to the following four-parameter equation:

$$Y = Min + (Max - Min) / (1 + (X/IC_{50})^{\wedge}H)$$

where Y is the observed signal, X is the inhibitor concentration, Min is the background signal in the absence of enzyme (0% enzyme activity), Max is the signal in the absence of inhibitor (100% enzyme activity), $IC_{50}$ is the inhibitor concentration at 50% enzyme inhibition and H represents the empirical Hill's slope to measure the cooperativity. Typically H is close to unity.

**c-Met Assay**

**[0458]** c-Met biochemical activity was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format as described above. Again, kinase activity was measured as the percent ATP remaining following the kinase reaction.

Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 1μM ATP, 1μM poly-EY and 10nM c-Met (baculovirus expressed human c-Met kinase domain P948-S1343) in a 20uL assay buffer (20mM Tris-HCL pH7.5, 10mM $MgCl_2$, 0.02% Triton X-100, 100mM DTT, 2mM $MnCl_2$). The mixture is incubated at ambient temperature for 2hours after which 20uL luciferase-luciferin mix is added and the chemiluminescent signal read using a Wallac Victor$^2$ reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5ug/mL oxalic acid (pH 7.8), 5 (or 50) mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 uM AMP, 28 ug/mL luciferin and 40,000 units of light/mL luciferase.

**KDR Assay**

**[0459]** KDR biochemical activity was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format. Kinase activity was measured as the percent ATP remaining following the kinase reaction. Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 3 μM ATP, 1.6 μM poly-EY and 5 nM KDR (baculovirus expressed human KDR kinase domain D807-V1356) in a 20uL assay buffer (20mM Tris-HCL pH7.5, 10mM $MgCl_2$, 0.01% Triton X-100, 1mM DTT, 3mM $MnCl_2$). The mixture is incubated at ambient temperature for 4 hours after which 20uL luciferase-luciferin mix is added and the chemiluminescent signal read using a Wallac Victor$^2$ reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5ug/mL oxalic acid (pH 7.8), 5 (or 50) mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 uM AMP, 28 ug/mL luciferin and 40,000 units of light/mL luciferase.

**flt-4 Assay**

**[0460]** Biochemical activity for flt-4 was assessed using an Alphascreen Tyrosine Kinase protocol. AlphaScreen™ (Perkin Elmer) technology is a proximity assay employing microparticles. Singlet oxygen derived from a donor bead following laser excitation results in chemiluminescence when in proximity (100 Å) to an acceptor bead due to biomolecular interactions. For the Flt-4 assay, donor beads coated with streptavidin and acceptor beads coated with PY100 anti-phosphotyrosine antibody were used (Perkin Elmer). Biotinylated poly(Glu,Tyr) 4:1 (Perkin Elmer) was used as the substrate.

Substrate phosphorylation was measured by addition of donor/acceptor beads by chemiluminescence following donor-acceptor bead complex formation. Test compounds, 5 μM ATP, 3 nM biotinylated poly(Glu, Tyr) and 1 nM Flt-4 (baculovirus expressed human Flt-4 kinase domain D725-R1298) were combined in a volume of 20 μL in a 384-well white, medium binding microtiter plate (Greiner). Reaction mixtures were incubated for 1 hr at ambient temperature. Reactions were quenched by addition of 10 uL of 15-30 mg/mL AlphaScreen bead suspension containing 75 mM Hepes, pH 7.4, 300 mM NaCl, 120 mM EDTA, 0.3% BSA and 0.03% Tween-20. After 2-16 hr incubation at ambient temperature plates were read using an AlphaQuest reader (Perkin Elmer). $IC_{50}$ values correlate well with those determined by radiometric assays.

**flt-3 Assay**

**[0461]** Biochemical activity for flt-3 was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format. Kinase activity was measured as the percent ATP remaining following the kinase reaction. Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 5 μM ATP, 3 μM poly-EY and 5 nM Flt-3 (baculovirus expressed human Flt-3 kinase domain R571-S993) in a 20uL assay buffer (20mM Tris-HCL pH7.5, 10mM $MgCl_2$, 0.01% Triton X-100, 1mM DTT, 2mM $MnCl_2$). The mixture is incubated at ambient temperature for 3 hours after which 20uL luciferase-luciferin mix is added and the chemiluminescent signal read using a Wallac Victor$^2$ reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5ug/mL oxalic acid (pH 7.8), 5 (or 50) mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 uM AMP, 28 ug/mL luciferin and 40,000 units of light/mL luciferase.

**c-Kit Assay**

**[0462]** c-Kit biochemical activity was assessed using AlphaScreen ™ (Perkin Elmer) technology, described above. Test compounds, ATP, biotinylated poly(Glu, Tyr) and c-Kit kinase were combined in a volume of 20 μL in a 384-well white, medium binding microtiter plate (Greiner). Reaction mixtures were incubated for 1 hr at ambient temperature. Reactions were quenched by addition of 10 uL of 15-30 mg/mL AlphaScreen bead suspension containing 75 mM Hepes, pH 7.4, 300 mM NaCl, 120 mM

EDTA, 0.3% BSA and 0.03% Tween-20. After 16 hr incubation at ambient temperature plates were read using an AlphaQuest reader (Perkin Elmer).

**Structure Activity Relationships**

**[0463]** Table 4 shows structure activity relationship data for selected compounds of the invention. Inhibition is indicated as $IC_{50}$ with the following key: A = $IC_{50}$ less than 50 nM, B = $IC_{50}$ greater than 50 nM, but less than 500 nM, C = $IC_{50}$ greater than 500 nM, but less than 5000 nM, and D = $IC_{50}$ greater than 5,000 nM. Depending upon the functionality about the quinazoline or quinoline, exemplary compounds of the invention exhibit selectivity for any of c-Met, KDR, c-Kit, flt-3, and flt-4. Abbreviations for enzymes listed in Tables 2-3 are defined as follows: c-Met refers to hepatocyte growth factor receptor kinase; KDR refers to kinase insert domain receptor tyrosine kinase; flt-4, fms-like tyrosine kinase-4, representative of the FLK family of receptor tyrosine kinases; c-Kit, also called stem cell factor receptor or steel factor receptor; and flt-3, fms-like tyrosine kinase-3. Empty cells in the tables indicate lack of data only.

**Table 4**

| Entry | Name | c-Met | KDR | c-Kit | flt3 | flt4 |
|---|---|---|---|---|---|---|
| 1 | N-[({3-fluoro-4-[(6-(methyloxy)-7-{[(3aR,6aS)-octahydrocyclopenta[c]pyrrol-5-ylmethyl]oxy}quinazolin-4-yl)oxy]phenyl}amino)carbonothioyl]-2-phenylacetamide | | A | | | A |
| 2 | N-{[(3-fluoro-4-{[7-({[(3aR,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide | A | A | A | | A |
| 3 | N-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)(methyl)amino]carbonothioyl}-2-phenylacetamide | C | | | | |
| 4 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)imidazolidin-2-one | C | | C | C | |
| 5 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)imidazolidin-2-one | C | | B | C | |
| 6 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylacetyl)imidazolidin-2-one | B | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 7 | ethyl [(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](oxo)acetate | B | B | C | | B |
| 8 | N-{[(4-{[6,7-bis(methyloxy)quinazolin-4-yl]amino}-3-fluorophenyl)amino]carbonothioyl}-2-phenylacetamide | A | B | C | | B |
| 9 | N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-methyl-N-(2-phenylethyl)sulfamide | C | | | | |
| 10 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)-1,2,4-oxadiazol-5-amine | C | | B | C | |
| 11 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)piperidin-2-one | C | | C | C | |
| 12 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(phenylmethyl)ethanediamide | B | B | B | C | B |
| 13 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-phenyl-1,3-thiazol-2-amine | C | | C | B | |
| 14 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylethyl)ethanediamide | A | A | A | C | A |
| 15 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-1-phenylmethanesulfonamide | C | | C | B | |
| 16 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-2-phenylethanesulfonamide | C | | C | C | |
| 17 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(phenylmethyl)benzenesulfonamide | C | | C | C | |
| 18 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(phenylmethyl)benzenesulfonamide | C | | C | C | |
| 19 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(2-phenylethyl)benzenesulfonamide | C | | C | C | |
| 20 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(2-phenylethyl)benzenesulfonamide | C | | C | C | |
| 21 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(3-phenylpropyl)benzenesulfonamide | C | | | | |
| 22 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)pyrrolidin-2-one | C | | C | B | |
| 23 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (phenylmethyl)carbamate | C | | | | |
| 24 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (2-phenylethyl)carbamate | C | | | | |
| 25 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(3-phenylpropyl)benzenesulfonamide | C | | | | |
| 26 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-phenylethanediamide | B | D | C | | C |
| 27 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]amino}-N-(3-phenylpropyl)benzamide | C | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 28 | N-{[(3-fluoro-4-{[7-{[(2-methyloctahydrocyclopenta[c]pyrrol-5-yl)methyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide | A | A | A | A | A |
| 29 | N-[(Z)-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](imino)methyl]-2-phenylacetamide | C | | | | |
| 30 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-[2-(phenyloxy)ethyl]benzenesulfonamide | C | | | | |
| 31 | This type of multiplicative nomenclature is not supported in current version! | C | | | | |
| 32 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-phenylpropane-1-sulfonamide | C | | | | |
| 33 | N~2~-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)sulfonyl]-N-phenylglycinamide | C | | | | |
| 34 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-2-phenylacetamide | C | | | | |
| 35 | N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide | A | C | D | | C |
| 36 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-amine | C | | C | C | |
| 37 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-amine | C | | C | C | |
| 38 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-phenylacetamide | B | C | D | | B |
| 39 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-morpholin-4-ylethyl)ethanediamide | C | | B | B | |
| 40 | 1,1-dimethylethyl {2-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino]-2-oxoethyl}(phenylmethyl)carbamate | C | | | | |
| 41 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-(phenylmethyl)glycinamide | B | | | | |
| 42 | N~2~-acetyl-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-(phenylmethyl)glycinamide | C | | | | |
| 43 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-yl)-2-phenylacetamide | B | | | | |
| 44 | 1,1-dimethylethyl {2-[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)amino]-2-oxoethyl}(phenylmethyl)carbamate | C | | | | |
| 45 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N~2~-(phenylmethyl)glycinamide | C | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 46 | N~2~-acetyl-N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N~2~-(phenylmethyl)glycinamide | C | | | | |
| 47 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-3-phenylpropanamide | C | | | | |
| 48 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-4-phenylbutanamide | C | | | | |
| 49 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N~2~-methyl-N~2~-(phenylmethyl)glycinamide | C | | | | |
| 50 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{2-[4-(methyloxy)phenyl]ethyl}ethanediamide | C | | C | C | |
| 51 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-methyl-N~2~-(phenylmethyl)glycinamide | B | A | B | B | A |
| 52 | N-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]amino}phenyl)amino]carbonothioyl}-2-phenylacetamide | A | B | B | C | A |
| 53 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-3-phenylpropanamide | C | | | | |
| 54 | N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide | A | B | C | | B |
| 55 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2,3-dihydro-1H-inden-1-yl)ethanediamide | A | B | B | | B |
| 56 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2,3-dihydro-1H-inden-2-yl)ethanediamide | C | | | | |
| 57 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydronaphthalen-1-yl)ethanediamide | B | B | C | | C |
| 58 | N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-(2-phenylethyl)-N-(phenylmethyl)sulfamide | 1470.06 | | | | |
| 59 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-(trifluoroacetyl)glycinamide | B | C | B | | B |
| 60 | N-{2-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino]-2-oxoethyl}benzamide | B | A | A | A | A |
| 61 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N'-(4-fluorophenyl)propanediamide | A | B | B | | B |
| 62 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2S)-1,2,3,4-tetrahydronaphthalen-2-yl]ethanediamide | C | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 63 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(4-methylphenyl)ethyl]ethanediamide | C | | C | C | |
| 64 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylpropyl)ethanediamide | B | A | B | B | B |
| 65 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(4-chlorophenyl)ethyl]ethanediamide | A | C | B | C | C |
| 66 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(phenylmethyl)sulfamide | C | | | | |
| 67 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(2-phenylethyl)sulfamide | C | | | | |
| 68 | ethyl [(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino](oxo)acetate | C | | | | |
| 69 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)ethanediamide | C | | | | |
| 70 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)propanediamide | A | B | B | | C |
| 71 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2R)-1,2,3,4-tetrahydronaphthalen-2-yl]ethanediamide | B | D | B | | C |
| 72 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(1-methylpyrrolidin-2-yl)ethyl]ethanediamide | C | | C | C | |
| 73 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(phenyloxy)ethyl]ethanediamide | B | B | B | | C |
| 74 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-hydroxy-1-(phenylmethyl)ethyl]urea | B | | | | |
| 75 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one | B | B | B | B | B |
| 76 | N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-methyl-N-(2-phenylethyl)ethanediamide | A | B | B | B | B |
| 77 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{[3-(trifluoromethyl)phenyl]methyl}ethanediamide | B | | B | B | |
| 78 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{2-[3-(trifluoromethyl)phenyl]ethyl}ethanediamide | C | | A | B | |
| 79 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-3-oxo-4-phenylbutanamide | C | | | | |

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| 80 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-2-[3-(trifluoromethyl)phenyl]acetamide | C | | | | |
| 81 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-[2-(phenyloxy)ethyl]-1,3-benzothiazol-2-amine | B | | | | |
| 82 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-piperidin-1-ylethyl)-1,3-benzothiazol-2-amine | C | | | | |
| 83 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-methyl-N-(2-phenylethyl)-1,3-benzothiazol-2-amine | C | | | | |
| 84 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-pyrrolidin-1-ylethyl)-1,3-benzothiazol-2-amine | C | | | | |
| 85 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-{[3-(trifluoromethyl)phenyl]methyl}-1,3-benzothiazol-2-amine | C | | | | |
| 86 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-{2-[3-(trifluoromethyl)phenyl]ethyl}-1,3-benzothiazol-2-amine | C | | | | |
| 87 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-[3-(trifluoromethyl)phenyl]propanediamide | C | | | | |
| 88 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3-(trifluoromethyl)phenyl]acetamide | C | A | B | B | B |
| 89 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-{[3-(trifluoromethyl)phenyl]methyl}glycinamide | B | A | B | B | A |
| 90 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-(2-phenylethyl)glycinamide | B | | | | |
| 91 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide | B | B | B | B | A |
| 92 | 1,1-dimethylethyl {2-[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino]-2-oxoethyl}(phenylmethyl)carbamate | C | | | | |
| 93 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N~2~-(phenylmethyl)glycinamide | C | | | | |
| 94 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3,5-bis(trifluoromethyl)phenyl]acetamide | C | B | B | D | C |
| 95 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[2-chloro-5-(trifluoromethyl)phenyl]acetamide | A | A | B | B | B |
| 96 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(2-phenylethyl)ethanediamide | A | A | A | A | A |

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| 97 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)ethanediamide | C | | | | |
| 98 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]ethanediamide | B | B | B | A | B |
| 99 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-methyl-N~2~-{[3-(trifluoromethyl)phenyl]methyl}glycinamide | C | | | | |
| 100 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-methyl-N~2~-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide | C | | | | |
| 101 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-methyl-N~2~-(2-phenylethyl)glycinamide | C | | | | |
| 102 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-(phenylmethyl)imidazolidin-2-one | B | B | B | B | C |
| 103 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridazin-3-yl)-N'-(4-fluorophenyl)propanediamide | A | C | B | A | C |
| 104 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-chlorophenyl)propanediamide | B | | | | |
| 105 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(3-chlorophenyl)propanediamide | C | | | | |
| 106 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N~2~-methyl-N~2~-(phenylmethyl)glycinamide | C | | | | |
| 107 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-chlorophenyl)propanediamide | B | | | | |
| 108 | (2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(methyloxy)imino]propanamide | B | B | | | |
| 109 | (2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(ethyloxy)imino]propanamide | B | A | | | |
| 110 | (2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-{[(phenylmethyl)oxy]imino}propanamide | B | B | | | |
| 111 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-1-(phenylmethyl)prolinamide | C | C | | | |
| 112 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one | B | C | B | C | C |
| 113 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)imidazolidin-2-one | C | C | | | |

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| 114 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)-4,5-dihydro-1,3-oxazol-2-amine | C | B | | | |
| 115 | 6,7-bis(methyloxy)-4-({4-[4-(phenylmethyl)piperazin-1-yl]phenyl}oxy)quinoline | C | C | | | |
| 116 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)piperazin-2-one | C | C | | | |
| 117 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N~2~-(phenylmethyl)alaninamide | C | C | | | |
| 118 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N~2~-methyl-N~2~-(phenylmethyl)alaninamide | C | C | | | |
| 119 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N~2~-(phenylmethyl)leucinamide | C | C | | | |
| 120 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N~2~-methyl-N~2~-(phenylmethyl)leucinamide | C | C | | | |
| 121 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N~2~-(phenylmethyl)valinamide | C | C | | | |
| 122 | N-[5-chloro-6-({6-(methyloxy)-4-[(piperidin-4-ylmethyl)oxy]quinolin-7-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)propanediamide | C | C | | | |
| 123 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)tetrahydropyrimidin-2(1H)-one | C | C | | | |
| 124 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-phenylethyl)ethanediamide | A | A | A | A | A |
| 125 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | B | A | B |
| 126 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide | C | C | | | |
| 127 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N~2~-methyl-N~2~-(phenylmethyl)valinamide | C | C | | | |
| 128 | (2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(phenyloxy)imino]propanamide | C | A | | | |
| 129 | (2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-phenyl-2-{[(phenylmethyl)oxy]imino}ethanamide | B | C | | | |
| 130 | 6,7-bis(methyloxy)-4-({4-[4-(phenylmethyl)piperidin-1-yl]phenyl}oxy)quinoline | C | C | | | |
| 131 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{[2-(1-methylethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]methyl}ethanediamide | B | B | | | |
| 132 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2-ethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]ethanediamide | B | C | | | |

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| 133 | 1,1-dimethylethyl 4-({[4-{[3-chloro-5-({3-[(4-fluorophenyl)amino]-3-oxopropanoyl}amino)pyridin-2-yl]oxy}-6-(methyloxy)quinolin-7-yl]oxy}methyl)piperidine-1-carboxylate | B | C | | | |
| 134 | N-[5-chloro-6-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)propanediamide | A | B | B | A | |
| 135 | N-{5-chloro-6-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]pyridin-3-yl}-N'-(4-fluorophenyl)propanediamide | A | B | B | A | |
| 136 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylethyl)ethanediamide | A | A | A | B | A |
| 137 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-phenylethyl)ethanediamide | A | A | A | B | A |
| 138 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-phenylethyl)ethanediamide | A | A | A | A | |
| 139 | N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylethyl)ethanediamide | A | A | A | A | A |
| 140 | N'-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N-methyl-N-(2-phenylethyl)ethanediamide | A | A | | | B |
| 141 | N-(3-fluoro-4-{[7-({[(3aR,5r,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(2-phenylethyl)ethanediamide | A | A | A | A | A |
| 142 | N-(3-fluoro-4-{[7-({[(3aR,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-yl]oxy}phenyl)-N'-(2-phenylethyl)ethanediamide | A | A | A | A | A |
| 143 | 2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-2-oxoacetamide | A | A | | | |
| 144 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-2-oxo-2-(3-phenylpyrrolidin-1-yl)acetamide | A | A | A | A | A |
| 145 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-2-oxo-2-(2-phenylmorpholin-4-yl)acetamide | A | B | B | B | |

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| 146 | N-[2-(dimethylamino)-2-phenylethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | B | A | |
| 147 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-oxo-2-phenylethyl)ethanediamide | A | B | B | B | B |
| 148 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-2,2-difluoro-N'-(4-fluorophenyl)propanediamide | C | C | | | |
| 149 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(phenylmethyl)ethanediamide | A | A | A | B | A |
| 150 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(2-fluorophenyl)ethyl]ethanediamide | A | A | A | A | A |
| 151 | N-[2-(3-chlorophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | A | A |
| 152 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{2-[2-(methyloxy)phenyl]ethyl}ethanediamide | A | A | A | A | A |
| 153 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-pyridin-3-ylethyl)ethanediamide | A | B | B | B | |
| 154 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(phenylmethyl)ethanediamide | A | A | A | B | A |
| 155 | N-{2-[2,5-bis(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | A | A |
| 156 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{2-[2-(trifluoromethyl)phenyl]ethyl}ethanediamide | A | A | A | A | C |
| 157 | N-{2-[2-(ethyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | A | A |
| 158 | N-[2-(2,4-dimethylphenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | B | B | A | B |
| 159 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1S)-2-(4-methylphenyl)-1-phenylethyl]ethanediamide | B | C | | | |
| 160 | N-[2-(4-chlorophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | A | B |

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| 161 | ({3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}amino)(oxo)acetic acid | B | C | | | |
| 162 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(3-fluorophenyl)ethyl]ethanediamide | A | A | | | A |
| 163 | N-[2-(2-chlorophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | B | A |
| 164 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{2-[3-(methyloxy)phenyl]ethyl}ethanediamide | A | A | A | A | A |
| 165 | N-(1,2-diphenylethyl)-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | B | B | C |
| 166 | N-[2-(2,4-dichlorophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | B | B | A | B |
| 167 | N-{2-[3,4-bis(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | B | B | B | |
| 168 | N-[2-(4-ethylphenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | B | B | B | C |
| 169 | N-{2-[4-(ethyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | B | C | B | B | |
| 170 | N-{2-[4-(ethyloxy)-3-(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | B | C | B | |
| 171 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{2-[4-(phenyloxy)phenyl]ethyl}ethanediamide | B | C | C | C | |
| 172 | N-{2-[3-(ethyloxy)-4-(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | C | B | B | |
| 173 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-pyridin-2-ylethyl)ethanediamide | A | A | A | B | B |
| 174 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-pyridin-4-ylethyl)ethanediamide | A | B | B | B | C |
| 175 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(4-fluorophenyl)ethyl]ethanediamide | A | A | A | A | A |

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| 176 | N-[2-(2-bromophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | A | A |
| 177 | N-[2-(2-chloro-6-fluorophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | B | A |
| 178 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(2R)-2-phenylpropyl]ethanediamide | A | A | A | B | A |
| 179 | N-(2,3-dihydro-1H-inden-1-yl)-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | A | A |
| 180 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(2-methylpropyl)ethanediamide | A | B | B | B | |
| 181 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(3-methylbutyl)ethanediamide | A | B | B | B | B |
| 182 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-[(2R)-2-phenylpropyl]ethanediamide | A | A | A | A | A |
| 183 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(2-phenylpropyl)ethanediamide | A | A | A | A | A |
| 184 | N-(2,3-dihydro-1H-inden-2-yl)-N'-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}ethanediamide | A | A | A | B | A |
| 185 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1R)-1-phenylethyl]ethanediamide | A | B | B | B | |
| 186 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1S)-1-phenylethyl]ethanediamide | A | B | A | B | C |
| 187 | N-[2-(3-bromophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | A | A |
| 188 | N-[2-(2,6-dichlorophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | A | A |
| 189 | N-[2-(1,3-benzodioxol-5-yl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | B | A | B |

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| 190 | N-{5-chloro-6-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]pyridin-3-yl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | B | A | A |
| 191 | N-{2-[3-bromo-4-(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | B | B | B |
| 192 | N-{2-[3,5-bis(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | B | B |
| 193 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(2-methylphenyl)ethyl]ethanediamide | A | A | A | B | A |
| 194 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(3-methylphenyl)ethyl]ethanediamide | A | A | A | A | A |
| 195 | N-{2-[3-(ethyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | B | B | B |
| 196 | N-[2-(3,4-dimethylphenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | B | B | B |
| 197 | N-[2-(2,5-dimethylphenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | A | A |
| 198 | N-{2-[3-chloro-4-(propyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | B | C | | | |
| 199 | N-{2-[4-(butyloxy)-3-chlorophenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | B | C | | | |
| 200 | N-{2-[4-(1,1-dimethylethyl)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | B | C | | | |
| 201 | N-{2-[4-(aminosulfonyl)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | B | B | B | B |
| 202 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{2-[4-hydroxy-3-(methyloxy)phenyl]ethyl}ethanediamide | A | B | B | A | B |
| 203 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{2-[3-hydroxy-4-(methyloxy)phenyl]ethyl}ethanediamide | A | B | B | B | B |
| 204 | N-[(2,4-dichlorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | A | B |

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| 205 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}ethanediamide | A | A | B | A | A |
| 206 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1R)-1-(4-methylphenyl)ethyl]ethanediamide | A | B | B | B | B |
| 207 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[3-fluoro-4-(trifluoromethyl)phenyl]methyl}ethanediamide | A | B | B | B | B |
| 208 | N-[(3-chloro-4-fluorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | A | B |
| 209 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{(1S)-1-[3-(methyloxy)phenyl]ethyl}ethanediamide | A | B | B | B | B |
| 210 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1R)-1-naphthalen-2-ylethyl]ethanediamide | A | B | B | B | |
| 211 | N-{[4-chloro-3-(trifluoromethyl)phenyl]methyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | A | A |
| 212 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1S)-1-(4-methylphenyl)ethyl]ethanediamide | A | B | C | B | |
| 213 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[6-(trifluoromethyl)pyridin-3-yl]methyl}ethanediamide | A | B | C | B | B |
| 214 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(2-methylphenyl)methyl]ethanediamide | A | A | A | A | B |
| 215 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(3-methylphenyl)methyl]ethanediamide | A | A | A | B | A |
| 216 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[4-fluoro-3-(trifluoromethyl)phenyl]methyl}ethanediamide | A | A | B | A | A |
| 217 | N-[(3,5-dichlorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | A | A |
| 218 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1R)-1,2,3,4-tetrahydronaphthalen-1-yl]ethanediamide | A | B | B | B | A |

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| 219 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1S)-1,2,3,4-tetrahydronaphthalen-1-yl]ethanediamide | A | A | A | A | A |
| 220 | N-cyclopentyl-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | B | B | B | B |
| 221 | N-[1-(4-bromophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | B | B | B | B |
| 222 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(2-fluorophenyl)methyl]ethanediamide | A | A | B | B | A |
| 223 | N-[2-(3,4-dichlorophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | A | |
| 224 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(4-fluorophenyl)methyl]ethanediamide | A | A | A | A | A |
| 225 | N-[(2,3-difluorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | B | B | A |
| 226 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(phenyloxy)ethyl]ethanediamide | A | A | A | A | A |
| 227 | N-(2,2-diphenylethyl)-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | B | B | A | B |
| 228 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{2-[4-(methyloxy)phenyl]ethyl}ethanediamide | A | B | B | B | B |
| 229 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-phenylpropyl)ethanediamide | A | A | A | A | A |
| 230 | N-[2-(4-bromophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | B | B | B |
| 231 | N-(4-{[7-{[(1-ethylpiperidin-4-yl)methyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-2-oxo-2-(2-phenylmorpholin-4-yl)acetamide | A | B | B | B | B |
| 232 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[3-fluoro-5-(trifluoromethyl)phenyl]methyl}ethanediamide | A | A | B | A | B |
| 233 | N-[(3,5-difluorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | B | A |

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| 234 | N-{[2-chloro-5-(trifluoromethyl)phenyl]methyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | B | A | B |
| 235 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(dimethylamino)-2-phenylethyl]ethanediamide | B | B | B | A | |
| 236 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[4-(methyloxy)phenyl]methyl}ethanediamide | A | A | A | B | B |
| 237 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[4-(trifluoromethyl)phenyl]methyl}ethanediamide | A | B | B | B | A |
| 238 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[3-(methyloxy)phenyl]methyl}ethanediamide | A | A | A | A | B |
| 239 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[3-(trifluoromethyl)phenyl]methyl}ethanediamide | A | A | A | A | B |
| 240 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-({3-[(trifluoromethyl)oxy]phenyl}methyl)ethanediamide | A | A | A | A | A |
| 241 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[2-(methyloxy)phenyl]methyl}ethanediamide | A | A | A | A | A |
| 242 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[2-(trifluoromethyl)phenyl]methyl}ethanediamide | A | A | A | A | A |
| 243 | N-[(3-chlorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | B | B |
| 244 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-({2-[(trifluoromethyl)oxy]phenyl}methyl)ethanediamide | A | A | A | A | A |
| 245 | N-[(2-chlorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | A | A |
| 246 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-({4-[(trifluoromethyl)oxy]phenyl}methyl)ethanediamide | A | B | B | B | B |
| 247 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-{[4-(methyloxy)phenyl]methyl}ethanediamide | A | B | A | B | |
| 248 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-{[4-(trifluoromethyl)phenyl]methyl}ethanediamide | A | B | B | B | B |

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| 249 | N-(4-{[7-[(azetidin-3-ylmethyl)oxy]-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylethyl)ethanediamide | A | A | | | |
| 250 | N-(3-fluoro-4-{[7-{[(1-methylazetidin-3-yl)methyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(2-phenylethyl)ethanediamide | A | A | A | A | A |
| 251 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-hydroxy-2-phenylethyl)ethanediamide | B | B | B | B | |
| 252 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2,4-difluorophenyl)propanediamide | A | C | | | |
| 253 | N'-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N-(4-fluorophenyl)-N-methylpropanediamide | B | C | | | |
| 254 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1R)-1-phenylpropyl]ethanediamide | A | B | B | B | B |
| 255 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1S)-1-phenylpropyl]ethanediamide | A | B | C | B | |
| 256 | N-[(3,4-difluorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | B | A |
| 257 | N-[(2,6-difluorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | B | A |
| 258 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-[2-(4-fluorophenyl)ethyl]ethanediamide | A | A | A | A | A |
| 259 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-phenylethanediamide | A | B | C | C | B |
| 260 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(3-fluorophenyl)ethanediamide | A | C | B | C | C |
| 261 | N-(3-chloro-4-fluorophenyl)-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | C | C | B | B |
| 262 | N-[3,4-bis(methyloxy)phenyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | C | C | B | B |
| 263 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(3-methylbutyl)ethanediamide | A | B | A | B | B |

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| 264 | N-(3,3-dimethylbutyl)-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | A | B |
| 265 | N-[5-chloro-6-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)propanediamide | A | B | B | A | B |
| 266 | N-[5-chloro-6-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)propanediamide | A | B | B | A | B |
| 267 | N-(5-chloro-6-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N'-(4-fluorophenyl)propanediamide | A | B | B | A | B |
| 268 | N-[(4-chlorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | | | |
| 269 | N-{[3,5-bis(methyloxy)phenyl]methyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | | A | |
| 270 | N-[(4-butylphenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | B | B | B | B |
| 271 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(4-methylphenyl)ethyl]ethanediamide | A | B | B | A | B |
| 272 | N-{[3,5-bis(trifluoromethyl)phenyl]methyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | C | B | |
| 273 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(pyrazin-2-ylmethyl)ethanediamide | B | C | C | B | |
| 274 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(pyridin-2-ylmethyl)ethanediamide | A | B | B | B | B |
| 275 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(2-phenylethyl)ethanediamide | A | A | A | A | A |
| 276 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(2-phenylethyl)ethanediamide | A | A | A | A | A |
| 277 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[2-fluoro-3-(trifluoromethyl)phenyl]methyl}ethanediamide | A | A | A | A | A |
| 278 | N-{2-[2-bromo-6-(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | A | A |

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| 279 | N-{2-[3,4-bis(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N-methylethanediamide | B | B | B | A | B |
| 280 | N-{2-[5-bromo-2-(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | A | A | A | A |
| 281 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[2-fluoro-5-(trifluoromethyl)phenyl]methyl}ethanediamide | A | A | B | A | B |
| 282 | N-[5-chloro-6-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | A | A | A |
| 283 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[1-(4-fluorophenyl)ethyl]ethanediamide | A | A | B | A | B |
| 284 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1S)-2-oxo-1-(phenylmethyl)-2-pyrrolidin-1-ylethyl]ethanediamide | A | C | B | B | C |
| 285 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[(3aR,6aS)-octahydrocyclopenta[c]pyrrol-5-ylmethyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(2-phenylethyl)ethanediamide | A | A | A | A | A |
| 286 | N-[2-(4-aminophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | B | B | B | B |
| 287 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-2-oxo-2-[4-(phenylmethyl)piperidin-1-yl]acetamide | A | A | B | A | B |
| 288 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)propanediamide | A | A | A | A | A |
| 289 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | A | A | 5.581 |
| 290 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(3-fluorophenyl)propanediamide | B | C | | | |
| 291 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-phenylpropanediamide | A | C | B | A | C |
| 292 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)-2,2-dimethylpropanediamide | B | B | B | A | B |
| 293 | N-ethyl-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | B | B | B | B |

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| 294 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(1-methylethyl)ethanediamide | A | B | B | B | C |
| 295 | N-butyl-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | B | B | B | B |
| 296 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(methyloxy)ethyl]ethanediamide | B | B | B | B | C |
| 297 | N-(cyclopropylmethyl)-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide | A | B | B | B | B |
| 298 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-morpholin-4-ylethyl)ethanediamide | B | A | B | A | B |
| 299 | N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-2-oxo-2-pyrrolidin-1-ylacetamide | A | B | B | B | B |
| 300 | N-ethyl-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N-methylethanediamide | A | B | C | B | B |
| 301 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(phenylmethyl)cyclopropane-1,1-dicarboxamide | A | C | B | B | B |
| 302 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)cyclopropane-1,1-dicarboxamide | C | C | | | |
| 303 | N-{4-[(7-chloroquinolin-4-yl)oxy]-3-fluorophenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | C | C | B |
| 304 | N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | A | A | A |
| 305 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-phenylcyclopropane-1,1-dicarboxamide | A | B | B | A | |
| 306 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | B | B | C | B |
| 307 | N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide | A | A | A | B | A |
| 308 | N-{4-[(7-chloroquinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | B | C | B |
| 309 | N-[5-chloro-6-({6-(methyloxy)-7-[(phenylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | C | C | B | C |

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| 310 | N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | A | A | A |
| 311 | N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | B | A | A |
| 312 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | A | A | A |
| 313 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | A | A | A |
| 314 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide | A | A | A | B | A |
| 315 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | A | A | A |
| 316 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | A | A | A |
| 317 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | A | C | A |
| 318 | N-(4-fluorophenyl)-N'-[2-methyl-6-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]cyclopropane-1,1-dicarboxamide | A | A | B | B | B |
| 319 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | A | A | A |
| 320 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloro-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | C | C | B | C |
| 321 | N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | B | A | A |
| 322 | N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | A | A | A |
| 323 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | B | A | A |
| 324 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | A | A | A |

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| 325 | N-{3-fluoro-4-[(7-(methyloxy)-6-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | B | A | A |
| 326 | N-[5-fluoro-2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | B | B | B |
| 327 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,3,5-trifluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | B | B | B |
| 328 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | B | B | C | C |
| 329 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | B | B | C | B |
| 330 | N-(3-fluoro-4-{[6-hydroxy-7-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | A | A | A |
| 331 | N-(4-fluorophenyl)-N'-[2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide | A | A | A | B | A |
| 332 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | A | A | A |
| 333 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | A | A | A |
| 334 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | A | A | A |
| 335 | N-(4-fluorophenyl)-N'-[4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide | A | A | A | A | A |
| 336 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | A | A | A |
| 337 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | B | B | C | C |
| 338 | N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | C | C | | | |

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| 339 | N-(4-fluorophenyl)-N'-(4-{[2-methyl-6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide | C | C | | | |
| 340 | N-(4-{[2-amino-6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | C | C | | | |
| 341 | N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | C | C | | | |
| 342 | (1S,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | A | A | B | A | A |
| 343 | (1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | A | A | A | A | A |
| 344 | N-(4-{[6-{[3-(diethylamino)propyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | | A | |
| 345 | N-(4-{[6-{[2-(diethylamino)ethyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | | A | |
| 346 | 1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[(1-{[(4-fluorophenyl)amino]carbonyl}cyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate | A | A | | B | |
| 347 | (1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | A | A | | | |
| 348 | (1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | A | A | | B | |
| 349 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | | A | |
| 350 | N-(4-{[7-{[3-(4-acetylpiperazin-1-yl)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | | A | |
| 351 | 1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[((1R,2R)-1-{[(4-fluorophenyl)amino]carbonyl}-2-methylcyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate | A | A | | B | |

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| 352 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide | A | C | | C | |
| 353 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)azetidine-3,3-dicarboxamide | B | C | | C | |
| 354 | (1R,2S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | A | A | | A | |
| 355 | (1R,2R)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | A | A | | A | |
| 356 | (1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | A | A | | A | |
| 357 | N-(3-fluoro-4-{[7-({3-[4-(1-methylethyl)piperazin-1-yl]propyl}oxy)-6-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | | A | |
| 358 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide | A | A | | A | |
| 359 | (1R,2R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | A | A | | A | |
| 360 | (1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | A | A | | A | |
| 361 | (1R,2S)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | A | A | | A | |
| 362 | (1R,2S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | A | A | | A | |
| 363 | N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide | A | A | | | |
| 364 | (1R,2S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | A | A | | A | |

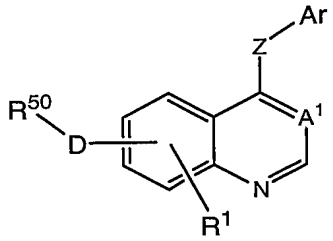
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| 365 | (1r,2R,3S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide | A | B | | B | |
| 366 | (1r,2R,3S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide | A | B | | B | |
| 367 | (1r,2R,3S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide | B | A | | B | |
| 368 | (1r,2R,3S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide | A | A | | B | |
| 369 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide | B | A | | B | |
| 370 | (2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide | A | A | | B | |
| 371 | (2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide | A | A | | B | |
| 372 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide | A | A | | B | |
| 373 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide | A | A | | C | |
| 374 | (1r,2R,3S)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide | A | B | | B | |
| 375 | N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide | A | A | | C | |
| 376 | (1r,2R,3S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide | A | B | | B | |

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| 377 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide | A | A | | B | |
| 378 | N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide | A | B | | C | |
| 379 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide | A | A | | C | |
| 380 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide | A | A | | B | |
| 381 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide | A | A | | B | |
| 382 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide | A | A | | B | |
| 383 | (2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide | A | A | | C | |
| 384 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide | A | A | | C | |
| 385 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide | A | A | | C | |
| 386 | (1R,2R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | A | A | | A | |
| 387 | (1R,2R)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | A | A | | A | |
| 388 | (2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide | B | A | | C | |

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| 389 | (2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide | A | A | | B | |
| 390 | (1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide | A | A | | A | |
| 391 | (2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide | A | A | | B | |
| 392 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[(4-fluorophenyl)methyl]cyclopropane-1,1-dicarboxamide | B | B | | A | |
| 393 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(2-morpholin-4-ylethyl)cyclopropane-1,1-dicarboxamide | C | D | | B | |
| 394 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide | B | D | | B | |
| 395 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide | B | C | | B | |
| 396 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide | B | A | | A | |
| 397 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide | B | C | | B | |
| 398 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-phenylcyclopropane-1,1-dicarboxamide | A | A | | A | |
| 399 | N-[3-(aminomethyl)phenyl]-N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide | B | A | | B | |
| 400 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide | B | A | | | |
| 401 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide | A | A | | | |

*What is claimed is:*

1. A compound for modulating kinase activity according to formula **I**,



**I**

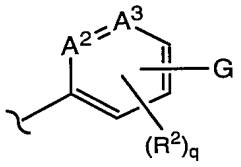
or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

$R^1$ is selected from -H, halogen, $-OR^3$, $-NO_2$, $-NH_2$, $-NR^3R^4$, and optionally substituted lower alkyl;

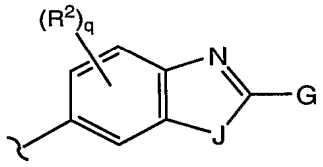
$A^1$ is selected from =N-, =C(H)-, and =C(CN)-;

Z is selected from $-S(O)_{0-2}-$, -O-, and $-NR^5-$;

Ar is either a group of formula **II**, or of formula **III**,



**II**



**III**

wherein,

$R^2$ is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

q is 0 to 4;

G is a group -B-L-T, wherein

B is selected from absent, $-N(R^{13})-$, $-N(SO_2R^{13})-$, -O-, $-S(O)_{0-2}-$, and -C(=O)-;

L is selected from absent, $-C(=S)N(R^{13})-$, $-C(=NR^{14})N(R^{13})-$, $-SO_2N(R^{13})-$, $-SO_2-$, $-C(=O)N(R^{13})-$, $-N(R^{13})-$, $-C(=O)C_{1-2}alkylN(R^{13})-$, $-N(R^{13})C_{1-2}alkylC(=O)-$, $-C(=O)C_{0-1}alkylC(=O)N(R^{13})-$, $-C_{0-4}alkylene-$, $-C(=O)C_{0-1}alkylC(=O)OR^3-$, $-C(=NR^{14})C_{0-1}alkylC(=O)-$, -C(=O)-, $-C(=O)C_{0-1}alkylC(=O)-$, and an optionally substituted four to six-membered heterocyclyl containing

between one and three annular heteroatoms including at least one nitrogen; and

T is selected from -H, -$R^{13}$, -$C_{0-4}$alkyl, -$C_{0-4}$alkylQ, -$OC_{0-4}$alkylQ, -$C_{0-4}$alkylOQ, -$N(R^{13})C_{0-4}$alkylQ, -$SO_2C_{0-4}$alkylQ, -$C(=O)C_{0-4}$alkylQ, -$C_{0-4}$alkyl$N(R^{13})$Q, and -$C(=O)N(R^{13})C_{0-4}$alkylQ, wherein each of the aforementioned $C_{0-4}$alkyl is optionally substituted;

J is selected from -$S(O)_{0-2}$-, -O-, and -$NR^{15}$-;

$R^3$ is -H or $R^4$;

$R^4$ is selected from optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, and optionally substituted lower heterocyclylalkyl; or

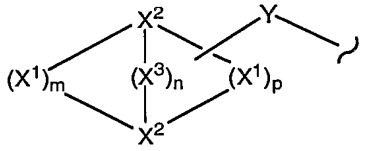
$R^3$ and $R^4$, when taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclyl, said optionally substituted five- to seven-membered heterocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

$A^2$ and $A^3$ are each independently selected from =N-, =$C(R^2)$-;

$R^5$ is -H or optionally substituted lower alkyl;

D is selected from -O-, -$S(O)_{0-2}$-, and -$NR^{15}$-;

$R^{50}$ is either $R^3$, or according to formula **IV**;




**IV**

wherein $X^1$, $X^2$, and optionally $X^3$, represent the atoms of a saturated bridged ring system, said saturated bridged ring system comprising up to four annular heteroatoms represented by any of $X^1$, $X^2$, and $X^3$; wherein,

each $X^1$ is independently selected from -$C(R^6)R^7$-, -O-, -$S(O)_{0-2}$-, and -$NR^8$-;

each $X^2$ is independently an optionally substituted bridgehead methine or a bridgehead nitrogen;

each $X^3$ is independently selected from -$C(R^6)R^7$-, -O-, -$S(O)_{0-2}$-, and -$NR^8$-;

Y is either:

an optionally substituted lower alkylene linker, between D and either 1) any annular atom of the saturated bridged ring system, except $X^2$ when $X^2$ is a bridgehead nitrogen, or 2) any heteroatom, represented by any of $R^6$ or $R^7$; provided there are at least two carbon atoms between D and any annular heteroatom of the saturated bridged ring system or any heteroatom represented by any of $R^6$ or $R^7$;

or Y is absent, when Y is absent, said saturated bridged ring system, is directly attached to D via an annular carbon of said saturated bridged ring system, unless D is $-SO_2-$, in which case said saturated bridged ring system, is directly attached to D via an any annular atom of said saturated bridged ring system;

m and p are each independently 1-4;

n is 0-2, when n = 0, then there is a single bond between the two bridgehead $X^2$'s;

$R^6$ and $R^7$ are each independently selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^4$, $-SO_2NR^3R^4$, $-CO_2R^3$, $-C(O)NR^3R^4$, $-N(R^3)SO_2R^4$, $-N(R^3)C(O)R^3$, $-NCO_2R^3$, $-C(O)R^3$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, optionally substituted lower heterocyclylalkyl, and a bond to either Y or D; or

$R^6$ and $R^7$, when taken together are oxo; or

$R^6$ and $R^7$, when taken together with a common carbon to which they are attached, form a optionally substituted three- to seven-membered spirocyclyl, said optionally substituted three- to seven-membered spirocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

$R^8$ is selected from $-R^3$, Y, $-SO_2NR^3R^4$, $-CO_2R^4$, $-C(O)NR^3R^3$, $-SO_2R^4$, and $-C(O)R^3$;

$R^{13}$ is selected from -H, $-C(=O)R^3$, $-C(=O)OR^3$, $-C(=O)SR^3$, $-SO_2R^4$, $-C(=O)N(R^3)R^3$, and optionally substituted lower alkyl,

two $R^{13}$, together with the atom or atoms to which they are attached, can combine to form a heteroalicyclic optionally substituted with between one and four of $R^{60}$, said heteroalicyclic can have up to four annular heteroatoms, and said heteroalicyclic can have

an aryl or heteroaryl fused thereto, in which case said aryl or heteroaryl is optionally substituted with an additional one to four of $R^{60}$;

$R^{14}$ is selected from -H, $-NO_2$, $-NH_2$, $-N(R^3)R^4$, -CN, $-OR^3$, optionally substituted lower alkyl, optionally substituted heteroalicyclylalkyl, optionally substituted aryl, optionally substituted arylalkyl and optionally substituted heteroalicyclic;

$R^{15}$ is a group $-M^1-M^2$, wherein $M^1$ is selected from absent, $-C(=S)N(R^{13})-$, $-C(=NR^{14})N(R^{13})-$, $-SO_2N(R^{13})-$, $-SO_2-$, $-C(=O)N(R^{13})-$, $-C(=O)C(=O)N(R^{13})-$, $-C_{0-4}$alkylene-, -C(=O)-, and an optionally substituted four to six-membered hetercyclyl annular containing between one and three heteratoms including at least one nitrogen; and $M^2$ is selected from -H, $-C_{0-6}$alkyl, alkoxy, $-C(=O)C_{0-4}$alkylQ, $-C_{0-4}$alkylQ, $-OC_{0-4}$alkylQ-, $-N(R^{13})C_{0-4}$alkylQ-, and $-C(=O)N(R^{13})C_{0-4}$alkylQ; and

Q is a five- to ten-membered ring system, optionally substituted with between zero and four of $R^{20}$;

$R^{20}$ is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

$R^{60}$ is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroarylalkyl, and optionally substituted arylalkyl;

two of $R^{60}$, when attached to a non-aromatic carbon, can be oxo;

with the proviso, only when Ar is according to formula **II**, if Y is a $C_{1-6}$ alkylene; Z is -NH- or $-N(CH_3)-$; $R^1$ is a $C_{1-6}$alkyl optionally substituted in the 2-position by -OH or a $C_{1-4}$alkoxy group; $R^2$ is -H or halogen; n = 0; and the atoms, $X^1$, of one bridge of the saturated bridged ring system, when combined with both bridgehead atoms, $X^2$, of the saturated bridged ring system, represent:

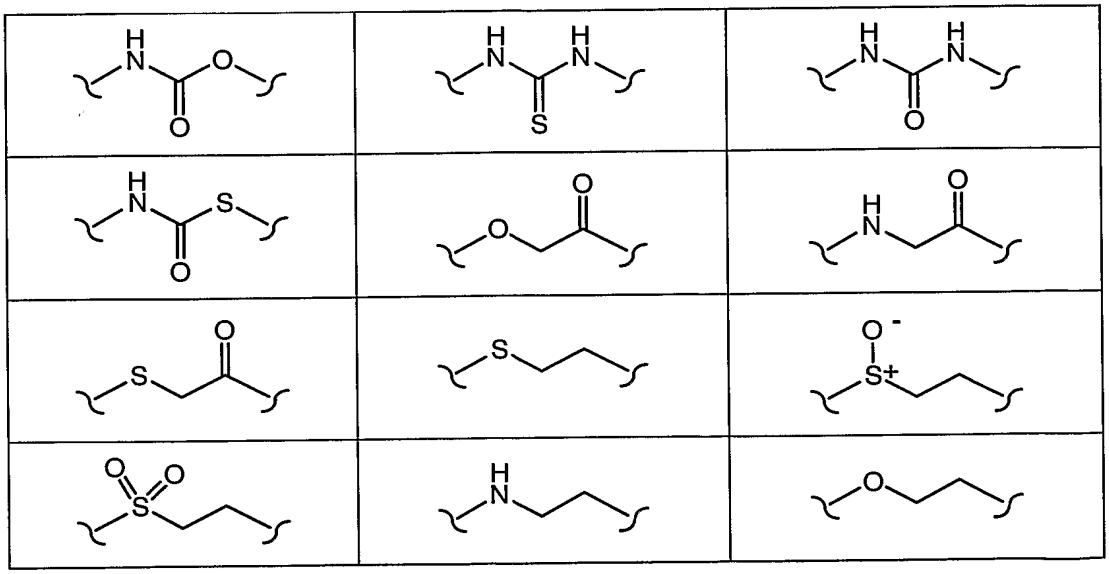
1) either a pyrrolidine or a piperidine, and any atom, $X^1$ or $X^2$, of either of said pyrrolidine or said piperidine is attached to Y, then the other bridge of said saturated bridged ring system cannot be any one of $-OC(O)CH_2-$, $-CH_2OC(O)-$, $-OC(O)CH_2CH_2-$, $-CH_2OC(O)CH_2-$, $-CH_2CH_2OC(O)-$, $-OC(O)CH_2NH-$, $-OC(O)CH_2N(C_{1-4}alkyl)-$, and $-OC(O)CH_2O-$; or

2) either a piperazine or a 4-($C_{1-4}$alkyl)-piperazine, and any atom, $X^1$ or $X^2$, of either of said piperazine or said 4-($C_{1-4}$alkyl)-piperazine is attached to Y, then the other bridge of said saturated bridged ring system, only when attached via the 2- and the 3-position of either of said piperazine or said 4-($C_{1-4}$alkyl)-piperazine, cannot be one of $-CH_2OC(O)CH_2-$, $-CH_2CH_2OC(O)-$, and either of the two aforementioned bridges optionally substituted by one or two $C_{1-2}$alkyl groups; or

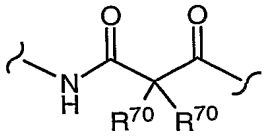
3) a piperazine, and any atom, $X^1$ or $X^2$, of said piperazine is attached to Y, then the other bridge of said saturated bridged ring system, only when attached via the 3- and the 4-position of said piperazine, cannot be one of $-C(O)OCH_2CH_2-$, $-CH_2OC(O)CH_2-$, and either of the two aforementioned bridges optionally substituted by one or two $C_{1-2}$alkyl groups, and only when either of the two aforementioned bridges are attached to the 3-position of said piperazine via their left-hand end as depicted above; or

4) a 2-oxomorpholine, said 2-oxomorpholine attached to Y via its 4-position, then the other bridge of said saturated bridged ring system, only when attached via the 5- and the 6-position of said 2-oxomorpholine, cannot be one of $-(CH_2)_g-$, $-CH_2WCH_2-$, $-CH_2WCH_2CH_2-$, and $-CH_2CH_2WCH_2-$, wherein W is -O-, $-S(O)_{0-2}-$, -NH-, or $-N(C_{1-4}$alkyl)- wherein g is 2, 3, or 4;

and with the proviso that when Z is-O-, Ar is according to formula **II**, and the portion of G directly attached to Ar is selected from:

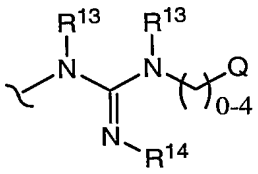
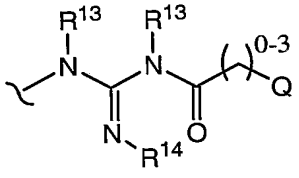
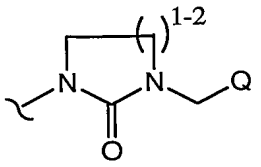
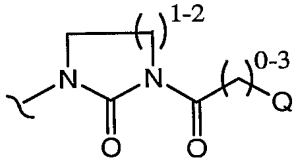
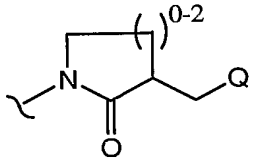
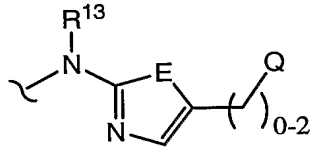
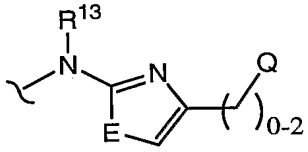
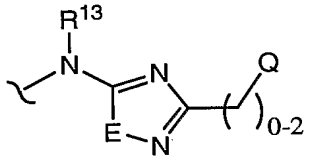
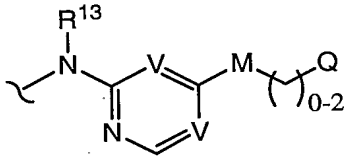
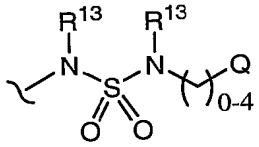
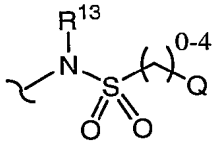
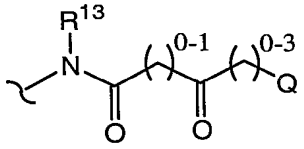
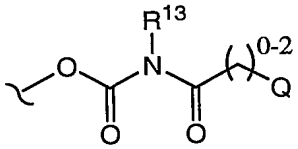
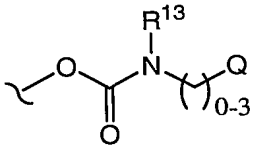
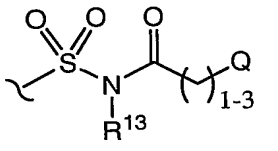
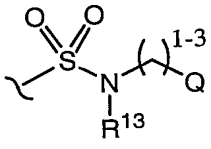
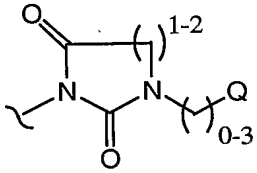
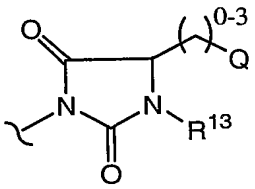


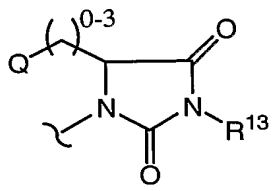
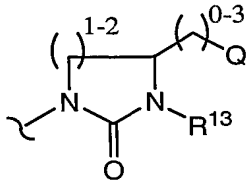
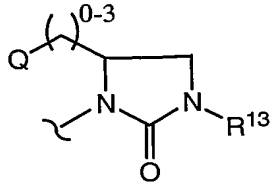
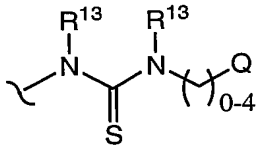
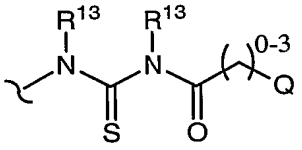
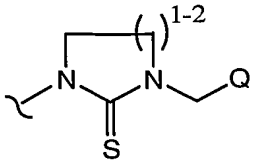
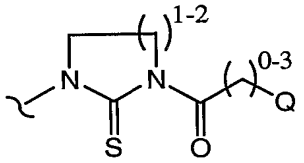
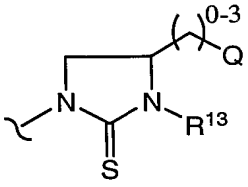
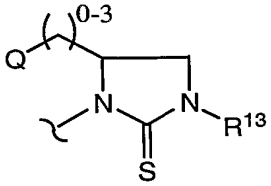
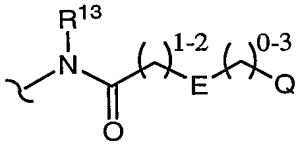
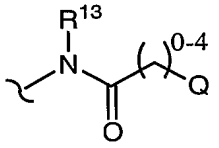
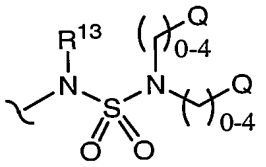
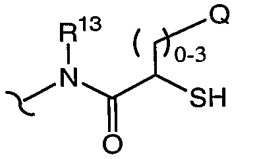
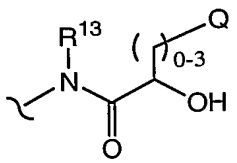
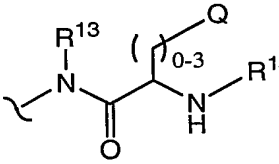
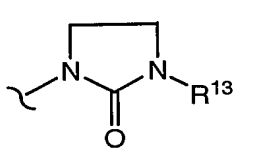
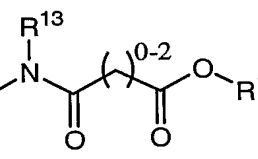
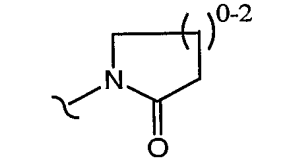
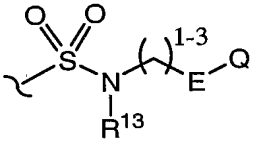
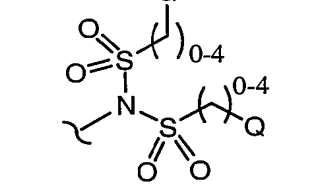
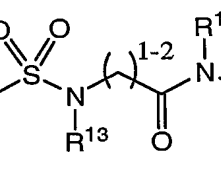
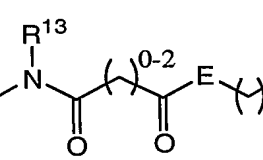
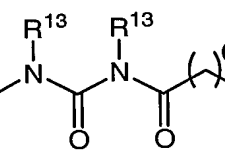
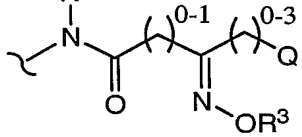
then $R^{50}$ must be of formula **IV**;

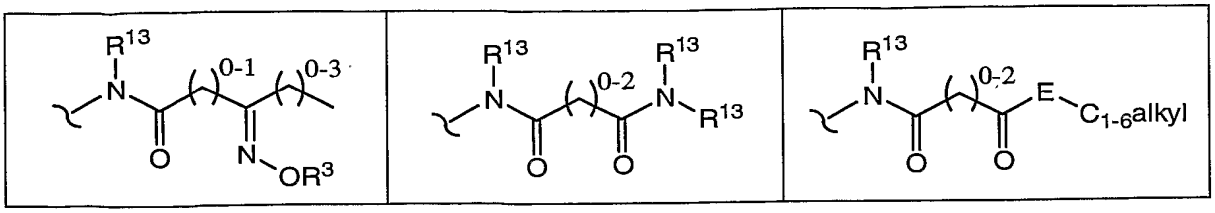
and with the proviso that when Ar is phenylene or substituted phenylene, Z is -S(O)$_{0-2}$- or -O-, then the portion of G directly attached to Ar cannot contain  , when $R^{70}$ is selected from -H, $C_{1-4}$alkyl, and $C_{1-4}$alkoxyl.

2. The compound according to claim 1, wherein In one example, the compound is according to paragraph [0033], wherein Z is either -O- or -$NR^5$-.

3. The compound according to claim 2, wherein G is selected from the following:

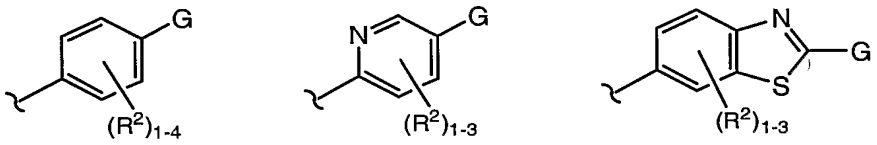
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wherein wherein Q, $R^{20}$, and $R^{13}$ are as defined above; each E is selected from -O-, $-N(R^{13})-$, $-CH_2-$, and $-S(O)_{0-2}-$; M is selected from -O-, $-N(R^{13})-$, $-CH_2-$, and $-C(=O)N(R^{13})-$; each V is independently either =N- or =C(H)-; each methylene in any of the above formulae is independently optionally substituted with $R^{25}$; and $R^{25}$ is selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; two of $R^{25}$, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic, two of $R^{25}$ on a single carbon can be oxo.

4. The compound according to claim 3, wherein Ar is according to one of formula **IIa**, **IIb**, and **IIIa**.



**IIa** **IIb** **IIIa**

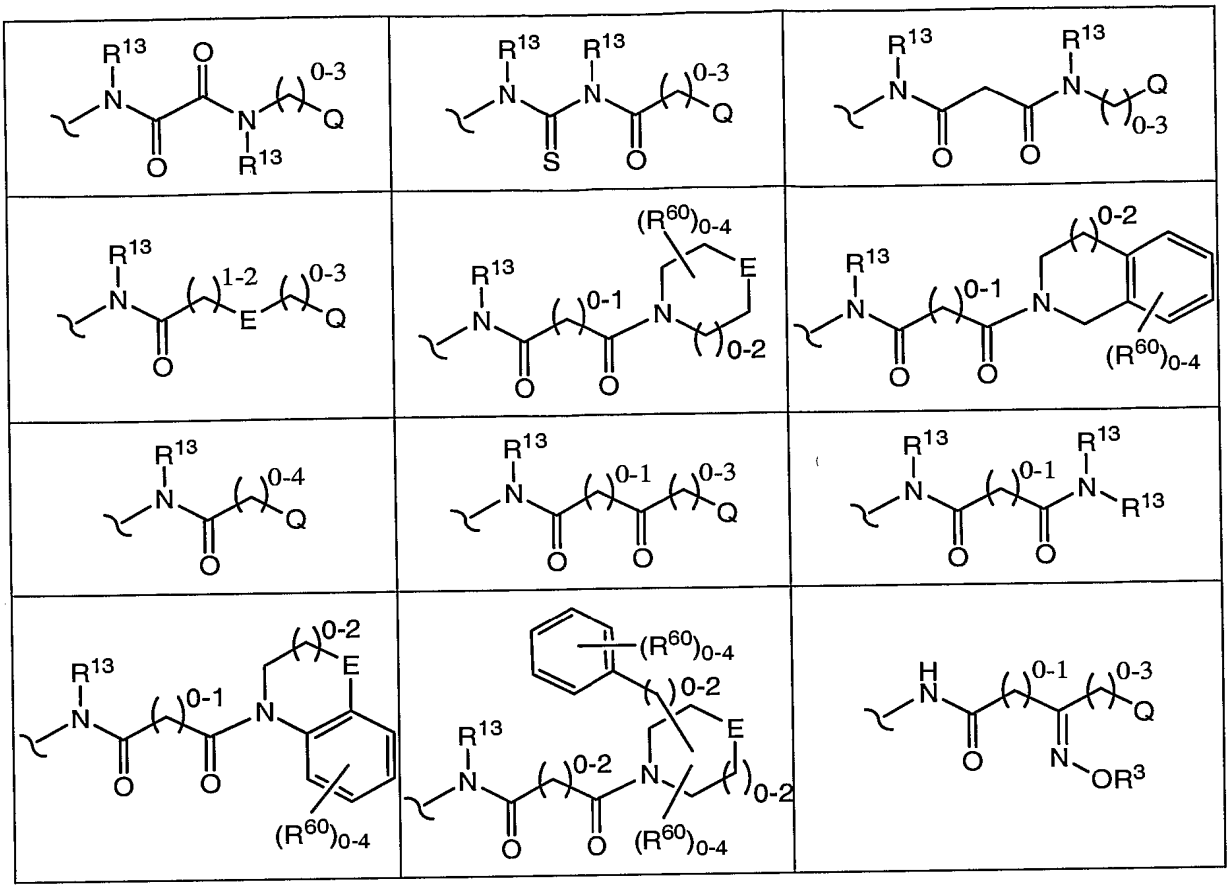
5. The compound according to claim 4, wherein D is -O- and $R^1$ is $-OR^3$.

6. The compound according to claim 5, wherein $-O-R^{50}$ and $R^1$ are interchangeably located at the 6-position and 7-position of the quinazoline or quinoline according to formula **I**.

7. The compound according to claim 6, wherein $R^1$ is -OH or $-OC_{1-6}$alkyl.

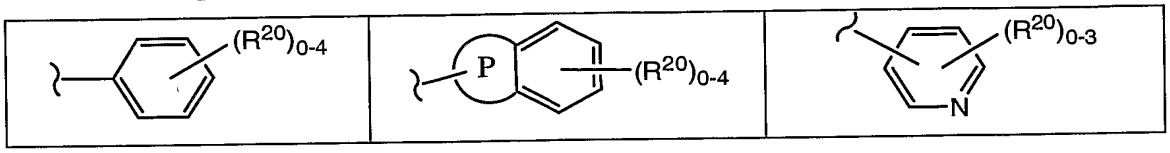
8. The compound according to claim 7, wherein $A^1$ is =N- or =C(H)-.

9. The compound according to claim 8, wherein G is selected from:



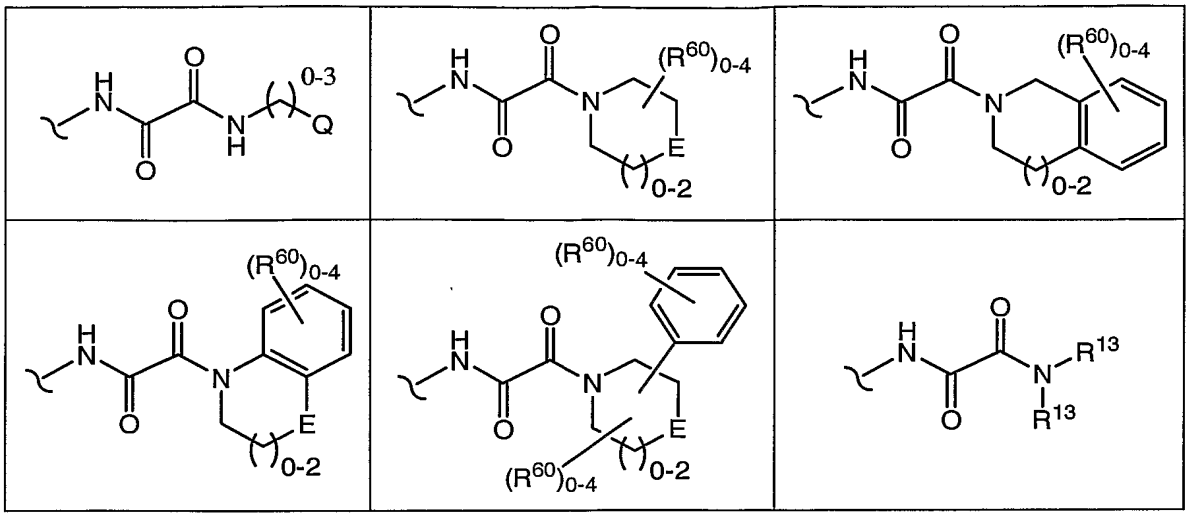
wherein Q, $R^{20}$, $R^{13}$, E, and $R^{60}$ are as defined above; each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with $R^{25}$; and $R^{25}$ is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; two of $R^{25}$, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic.

10. The compound according to claim 9, wherein Q is selected from:



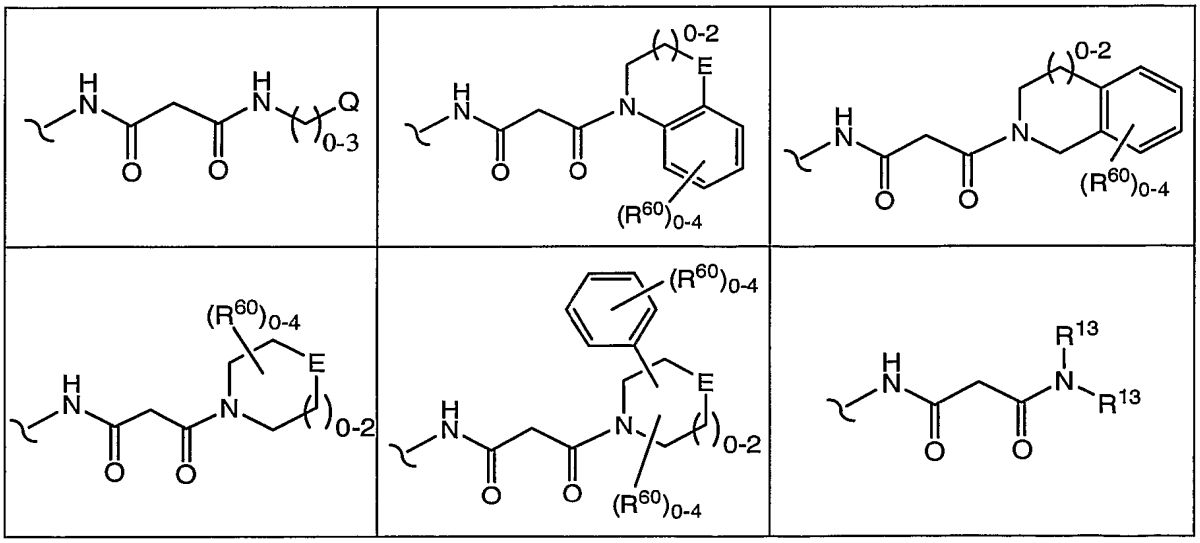
wherein $R^{20}$ is defined as above, and P is a five- to seven-membered ring, including the two shared carbons of the aromatic ring to which P is fused, P optionally containing between one and three heteroatoms.

11. The compound according to claim 10, wherein Ar is according to formula **IIa**, and G is selected from:



wherein Q, $R^{20}$, $R^{13}$, E, and $R^{60}$ are as defined above, and each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with $R^{25}$; and $R^{25}$ is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; two of $R^{25}$, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic.

12. The compound according to claim 10, wherein Ar is according to formula **IIb**, and G is selected from:



wherein Q, $R^{20}$, $R^{13}$, E, and $R^{60}$ are as defined above, and each methylene in any of the above formulae, other than those depicted in a ring, is independently optionally substituted with $R^{25}$; and $R^{25}$ is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; two of $R^{25}$, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic.

13. The compound according to claim 12, wherein the methylene between the two carbonyls of the depicted formulae is di-substituted with either optionally substituted lower alkyl, or an optionally substituted spirocycle.

14. The compound according to claim 11 or claim 12, wherein $R^{50}$ is a heteroalicylic or a $C_{1-6}$alkyl-heteroalicylic.

15. The compound according to claim 14, wherein at least one of $R^2$ is halogen.

16. The compound according to claim 14, wherein $R^{50}$ is according to formula **IV**.

17. The compound according to claim 16, wherein the saturated bridged ring system according to formula **IV** has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], [3.1.0], [3.3.3], [3.3.2], [3.3.1], [3.2.2], [3.2.1], [2.2.2], and [2.2.1].

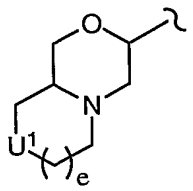
18. The compound according to claim 17, wherein Y is selected from $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2-$, $-CH_2-$, and absent.

19. The compound according to claim 18, wherein n is 0 and the saturated bridged ring system according to formula **IV** has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], and [3.1.0].

20. The compound according to claim 19, wherein said saturated bridged ring system contains at least one annular nitrogen or at least one annular oxygen.

21. The compound according to claim 20, wherein said saturated bridged ring system contains $-NR^8-$, wherein $R^8$ is selected from -H, optionally substituted lower alkyl, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.

22. The compound according to claim 20, wherein said saturated bridged ring system is of formula **V**,



**V**

wherein $U^1$ is selected from -O-, -$S(O)_{0-2}$-, -$NR^8$-, -$CR^6R^7$-, and absent; and e is 0 or 1.

23. The compound according to claim 22, wherein Y is -$CH_2$-.

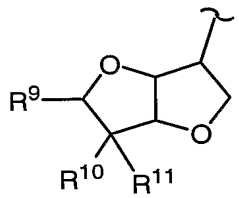
24. The compound according to claim 23, wherein $U^1$ is -$NR^8$-, wherein $R^8$ is selected from -H, optionally substituted lower alkyl, -$CO_2R^3$, -$C(O)NR^3R^3$, -$SO_2R^3$, and -$C(O)R^3$.

25. The compound according to claim 23, wherein $U^1$ is -O-.

26. The compound according to claim 23, wherein $U^1$ is absent.

27. The compound according to claim 20, wherein Y is selected from -$CH_2CH_2$-, -$CH_2$-, and absent.

28. The compound according to claim 27, wherein said saturated bridged ring system is of formula **VI**,



**VI**

wherein $R^9$, $R^{10}$, and $R^{11}$ are each independently selected from -H, and -$OR^{12}$; or

$R^9$ is selected from -H, and -$OR^{12}$, and $R^{10}$ and $R^{11}$, when taken together, are either an optionally substituted alkylidene or an oxo;

$R^{12}$ is selected from -H, -$C(O)R^3$, optionally substituted lower alkylidyne, optionally substituted lower arylalkylidyne, optionally substituted lower heterocyclylalkylidyne, optionally substituted lower alkylidene, optionally

substituted lower alkylidenearyl, optionally substituted lower alkylideneheterocyclyl, optionally substituted lower alkyl, optionally substituted lower alkylaryl, optionally substituted aryl, optionally substituted lower heterocyclylalkyl, and optionally substituted heterocyclyl;

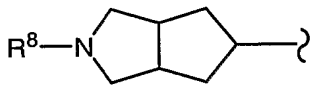
or two $R^{12}$'s, when taken together, form 1) a corresponding spirocyclic ketal when said two $R^{12}$'s stem from $R^{10}$ and $R^{11}$, or 2) a corresponding cyclic ketal when said two $R^{12}$'s stem from $R^9$ and one of $R^{10}$ and $R^{11}$.

29. The compound according to claim 28, wherein one of $R^{10}$ and $R^{11}$ is $-OR^{12}$, wherein $R^{12}$ is selected from -H, $-C(O)R^3$, and optionally substituted lower alkyl; and $R^9$ and the other of $R^{10}$ and $R^{11}$ are both -H.

30. The compound according to claim 29, wherein Y is either $-CH_2-$ or absent.

31. The compound according to claim 30, wherein $R^9$ is an alkyl group containing at least one fluorine substitution thereon.

32. The compound according to claim 21, wherein said saturated bridged ring system is of formula **VII**.

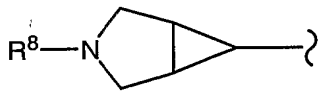


**VII**

33. The compound according to claim 32, wherein Y is either $-CH_2-$ or absent.

34. The compound according to claim 33, wherein $R^8$ is methyl or ethyl.

35. The compound according to claim 21, wherein said saturated bridged ring system is of formula **VIII**.

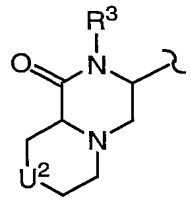


**VIII**

36. The compound according to claim 35, wherein Y is $-CH_2-$.

37. The compound according to claim 36, wherein $R^8$ is methyl or ethyl.

38. The compound according to claim 20, wherein said saturated bridged ring system is of formula **IX**



**IX**

wherein $U^2$ is selected from -O-, -S(O)$_{0-2}$-, -NR$^8$-, -CR$^6$R$^7$-, and absent.

39. The compound according to claim 38, wherein $R^3$ of formula **IX** is selected from -H and optionally substituted alkyl.

40. The compound according to claim 39, wherein $U^2$ is either -CR$^6$R$^7$- or absent.

41. The compound according to claim 40, wherein $U^2$ is either -$CH_2$- or absent.

42. The compound according to claim 41, wherein Y is -$CH_2$-.

43. The compound according to claim 21, wherein said saturated bridged ring system is according to formula **X**.



**X**

44. The compound according to claim 43, wherein $R^8$ is methyl or ethyl.

45. The compound according to claim 1, selected from Table 1.

**Table 1**

| Entry | Name | Structure |
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**Table 1**

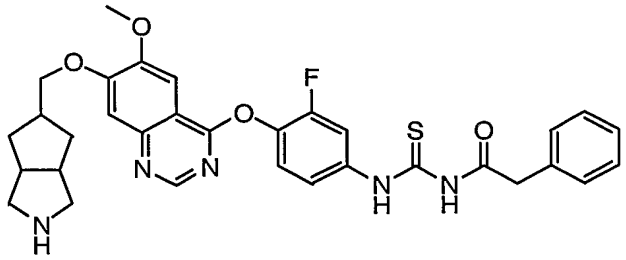
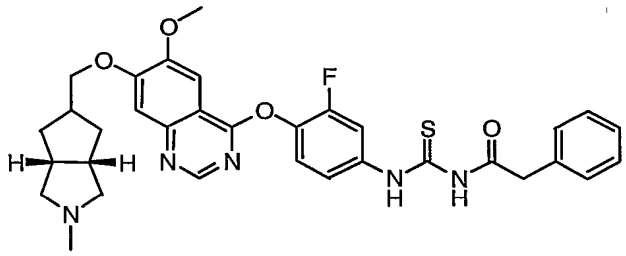
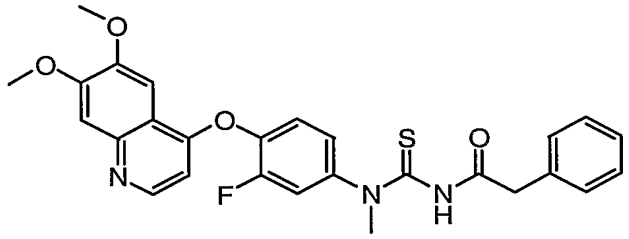
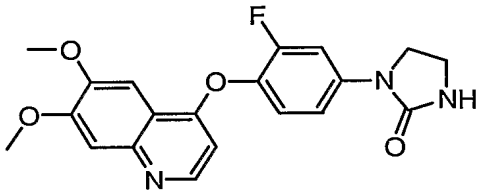
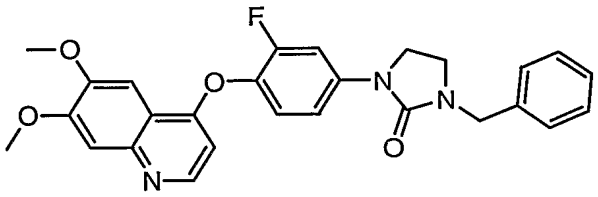
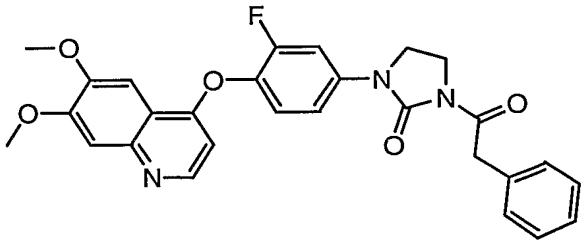
| Entry | Name | Structure |
|---|---|---|
| 1 | N-[({3-fluoro-4-[(6-(methyloxy)-7-{[(3aR,6aS)-octahydrocyclopenta[c]pyrrol-5-ylmethyl]oxy}quinazolin-4-yl)oxy]phenyl}amino)carbonothioyl]-2-phenylacetamide |  |
| 2 | N-{[(3-fluoro-4-{[7-({[(3aR,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide |  |
| 3 | N-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)(methyl)amino]carbonothioyl}-2-phenylacetamide |  |
| 4 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)imidazolidin-2-one |  |
| 5 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)imidazolidin-2-one |  |
| 6 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylacetyl)imidazolidin-2-one |  |

**Table 1**

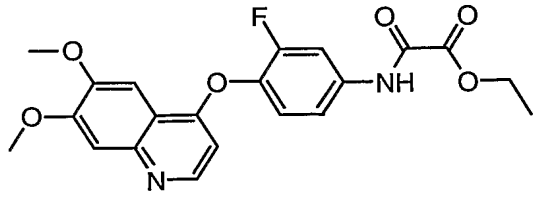
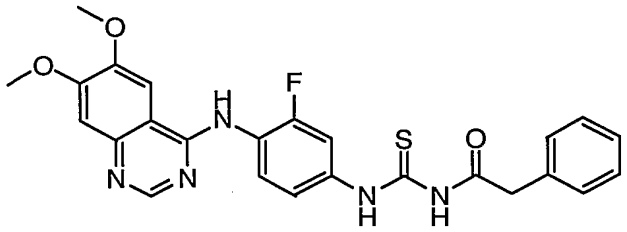
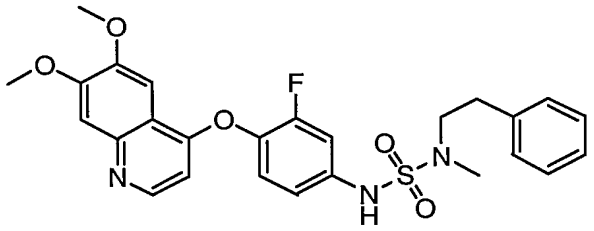
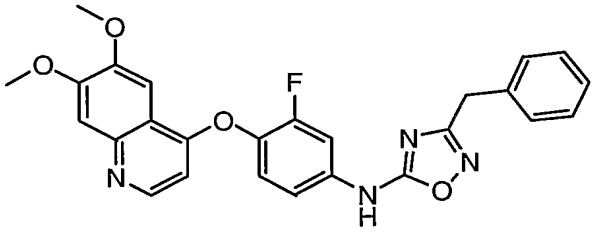
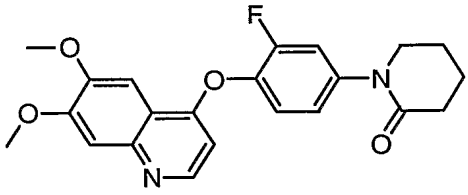
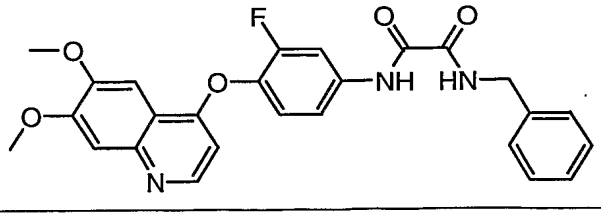
| Entry | Name | Structure |
|---|---|---|
| 7 | ethyl [(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](oxo)acetate |  |
| 8 | N-{[(4-{[6,7-bis(methyloxy)quinazolin-4-yl]amino}-3-fluorophenyl)amino]carbonothioyl}-2-phenylacetamide |  |
| 9 | N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-methyl-N-(2-phenylethyl)sulfamide |  |
| 10 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)-1,2,4-oxadiazol-5-amine |  |
| 11 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)piperidin-2-one |  |
| 12 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(phenylmethyl)ethanediamide |  |

**Table 1**

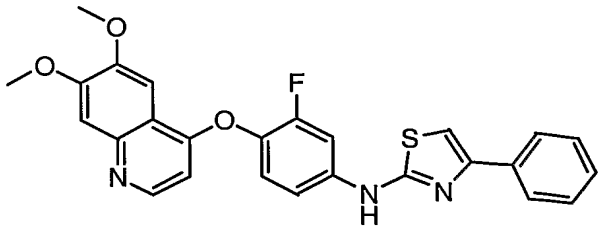
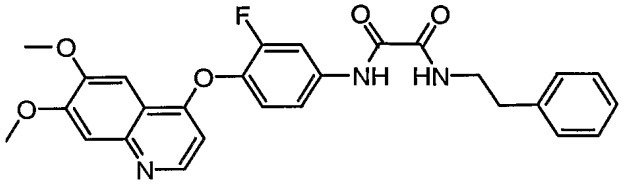
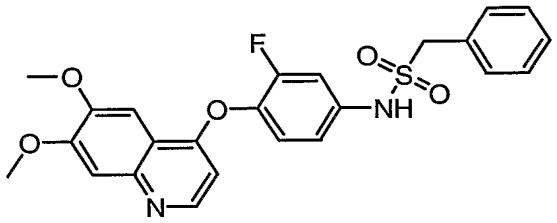
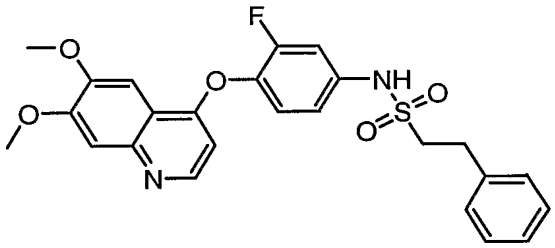
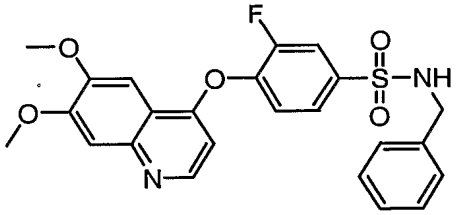
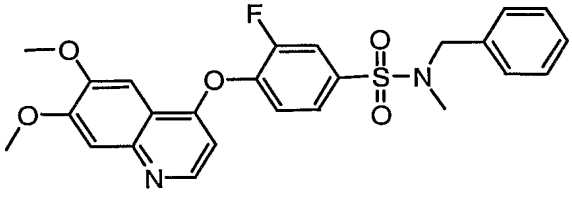
| Entry | Name | Structure |
|---|---|---|
| 13 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-phenyl-1,3-thiazol-2-amine |  |
| 14 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylethyl)ethanediamide |  |
| 15 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-1-phenylmethanesulfonamide |  |
| 16 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-2-phenylethanesulfonamide |  |
| 17 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(phenylmethyl)benzenesulfonamide |  |
| 18 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(phenylmethyl)benzenesulfonamide |  |

**Table 1**

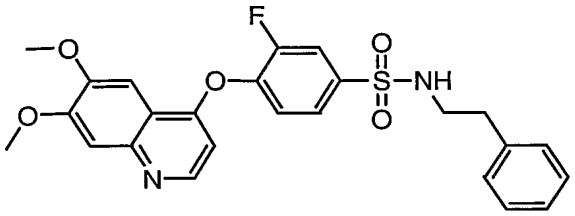
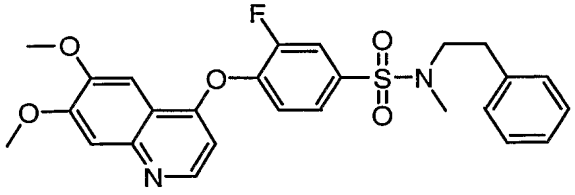
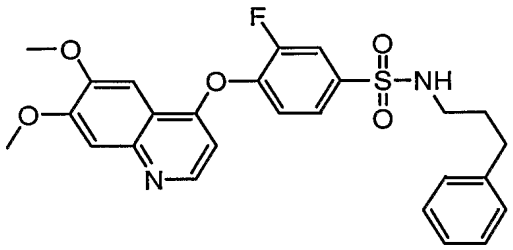
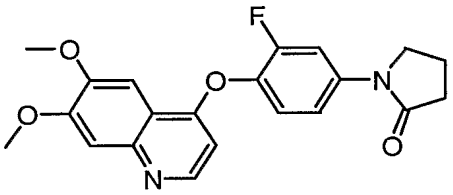
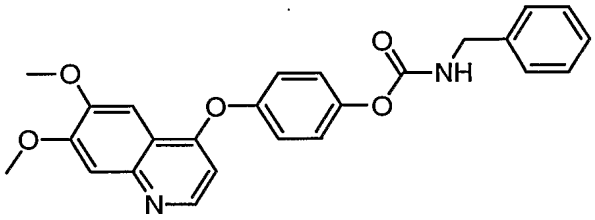
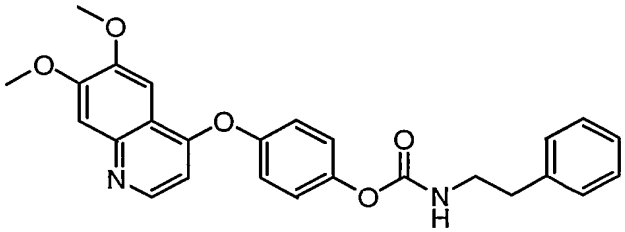
| Entry | Name | Structure |
|---|---|---|
| 19 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(2-phenylethyl)benzenesulfonamide |  |
| 20 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(2-phenylethyl)benzenesulfonamide |  |
| 21 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(3-phenylpropyl)benzenesulfonamide |  |
| 22 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)pyrrolidin-2-one |  |
| 23 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (phenylmethyl)carbamate |  |
| 24 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (2-phenylethyl)carbamate |  |

**Table 1**

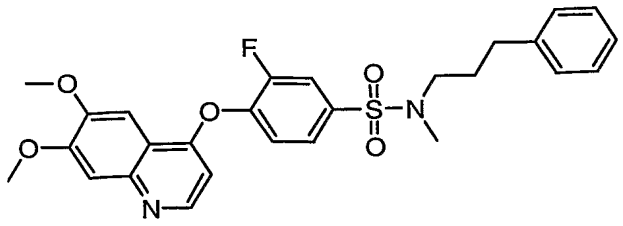
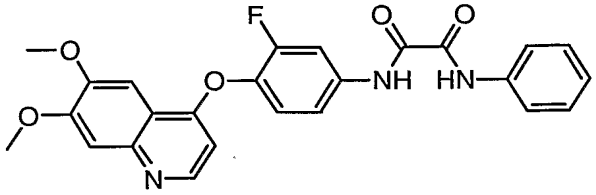
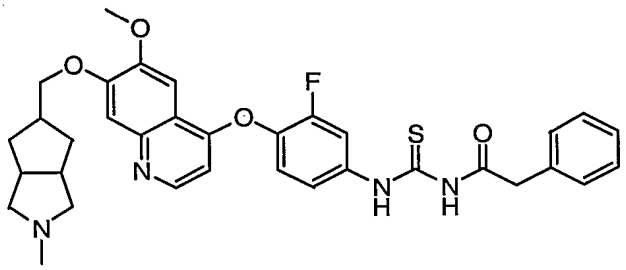
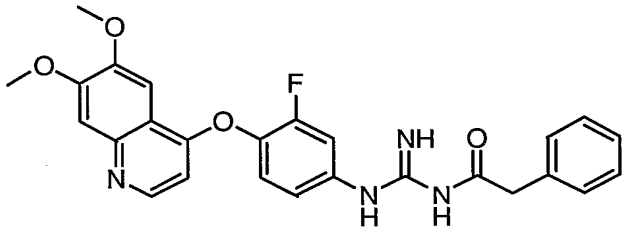
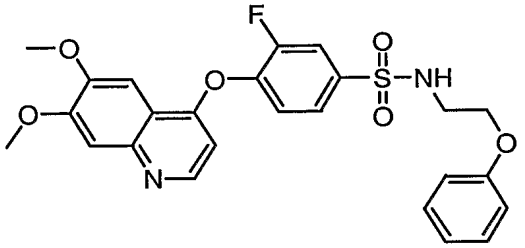
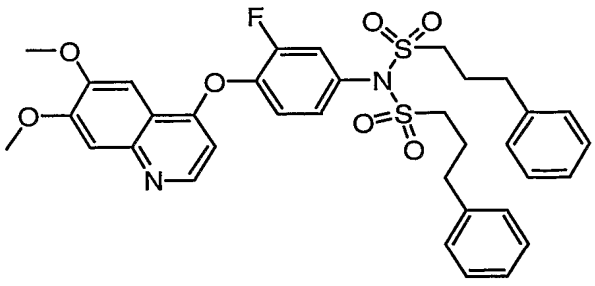
| Entry | Name | Structure |
|---|---|---|
| 25 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(3-phenylpropyl)benzenesulfonamide |  |
| 26 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-phenylethanediamide |  |
| 27 | N-{[(3-fluoro-4-{[7-{[(2-methyloctahydrocyclopenta[c]pyrrol-5-yl)methyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide |  |
| 28 | N-[(Z)-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](imino)methyl]-2-phenylacetamide |  |
| 29 | 4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-[2-(phenyloxy)ethyl]benzenesulfonamide |  |
| 30 | N,N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-bis-(3-phenylpropane-1-sulfonamide) |  |

**Table 1**

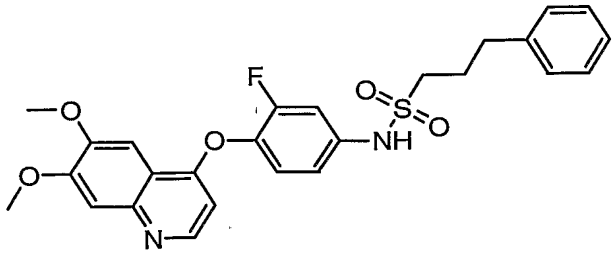
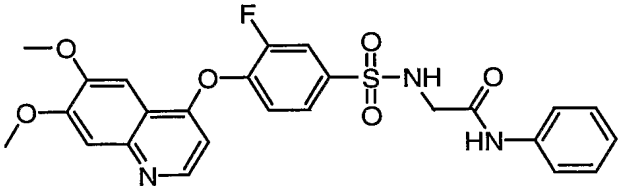
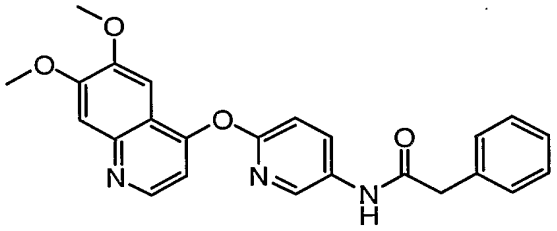
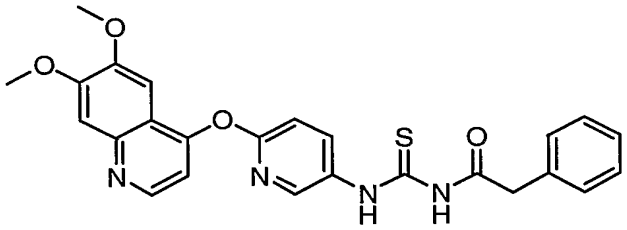
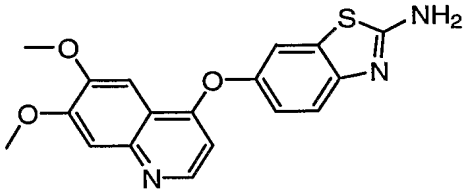
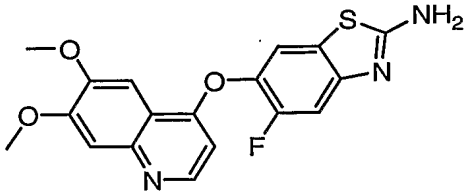
| Entry | Name | Structure |
|---|---|---|
| 31 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-phenylpropane-1-sulfonamide |  |
| 32 | N2-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)sulfonyl]-N1-phenylglycinamide |  |
| 33 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-2-phenylacetamide |  |
| 34 | N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide |  |
| 35 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-amine |  |
| 36 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-amine |  |

**Table 1**

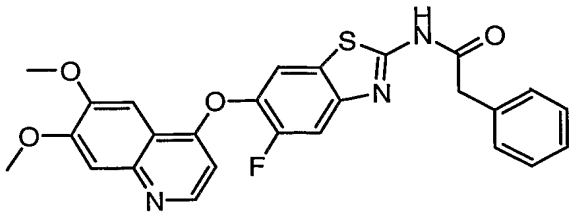
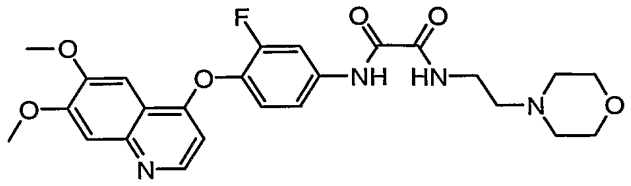
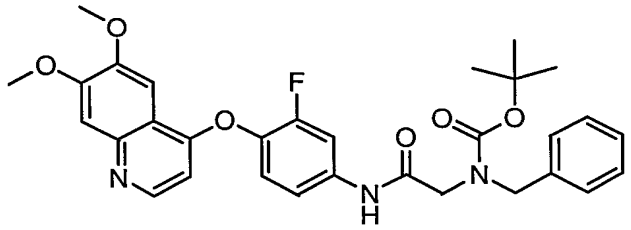
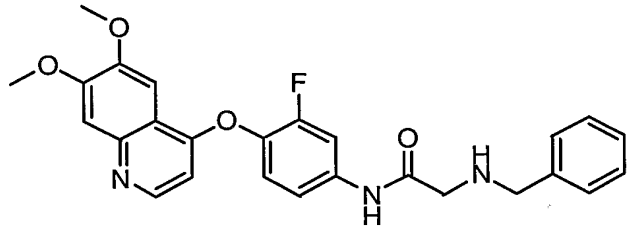
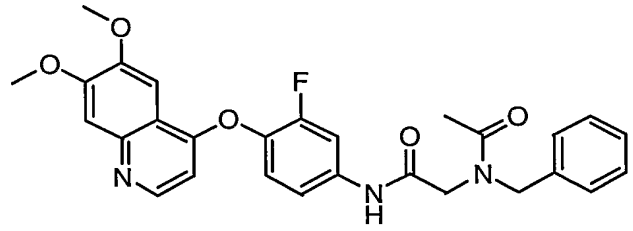
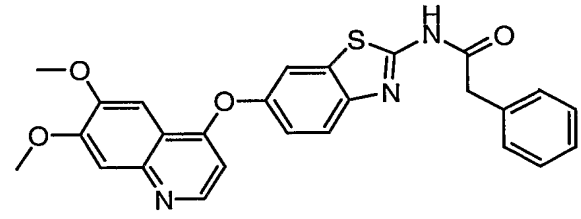
| Entry | Name | Structure |
|---|---|---|
| 37 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-phenylacetamide |  |
| 38 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-morpholin-4-ylethyl)ethanediamide |  |
| 39 | benzyl-{[4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylcarbamoyl]-methyl}-carbamic acid tert-butyl ester |  |
| 40 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(phenylmethyl)glycinamide |  |
| 41 | N2-acetyl-N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(phenylmethyl)glycinamide |  |
| 42 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-yl)-2-phenylacetamide |  |

**Table 1**

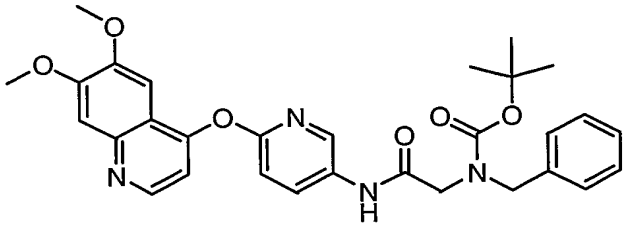
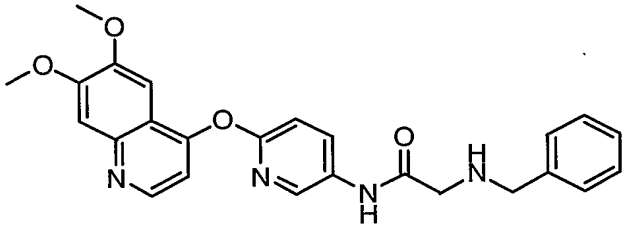
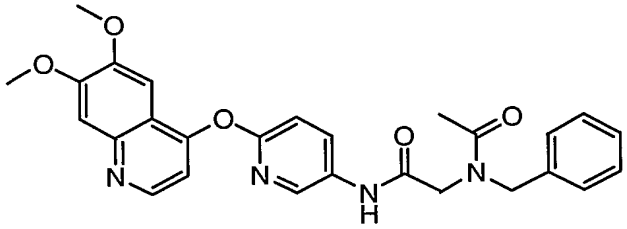
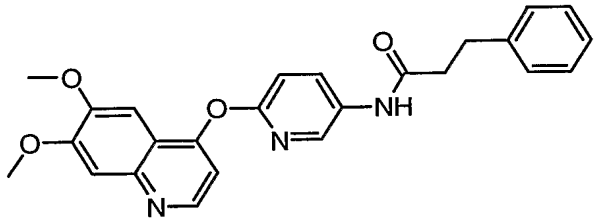
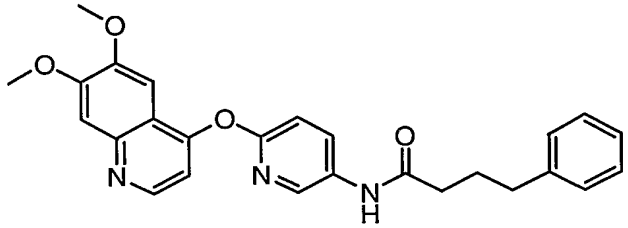
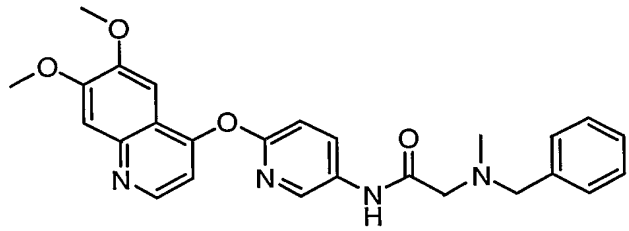
| Entry | Name | Structure |
|---|---|---|
| 43 | benzyl-{[6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylcarbamoyl]-methyl}-carbamic acid tert-butyl ester |  |
| 44 | N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-(phenylmethyl)glycinamide |  |
| 45 | N2-acetyl-N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-(phenylmethyl)glycinamide |  |
| 46 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-3-phenylpropanamide |  |
| 47 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-4-phenylbutanamide |  |
| 48 | N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-methyl-N2-(phenylmethyl)glycinamide |  |

**Table 1**

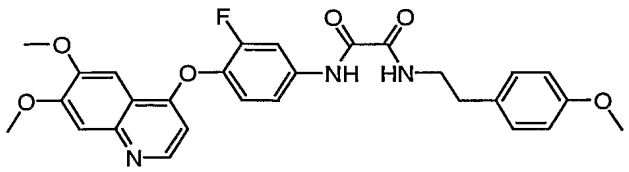
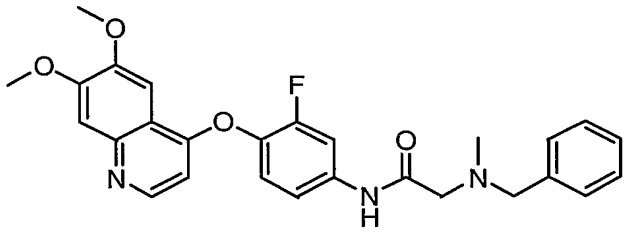
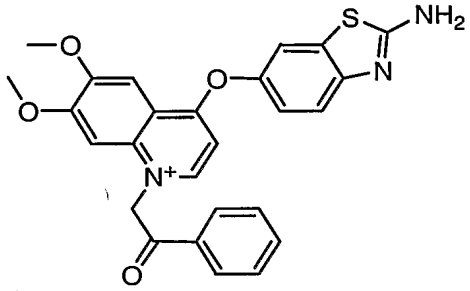
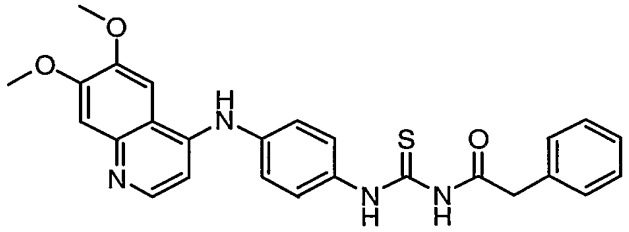
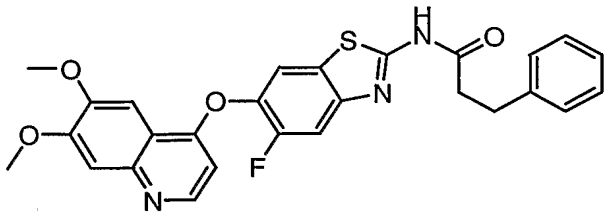
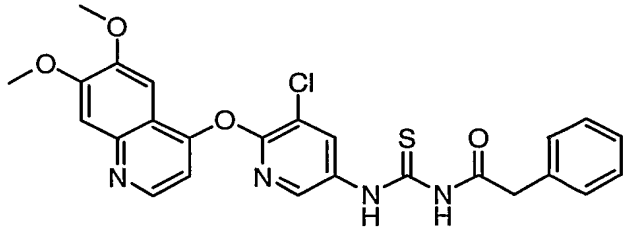
| Entry | Name | Structure |
|---|---|---|
| 49 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{2-[4-(methyloxy)phenyl]ethyl}ethanediamide |  |
| 50 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-(phenylmethyl)glycinamide |  |
| 51 | 4-[(2-amino-1,3-benzothiazol-6-yl)oxy]-6,7-bis(methyloxy)-1-(2-oxo-2-phenylethyl)quinolinium |  |
| 52 | N-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]amino}phenyl)amino]carbonothioyl}-2-phenylacetamide |  |
| 53 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-3-phenylpropanamide |  |
| 54 | N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide |  |

**Table 1**

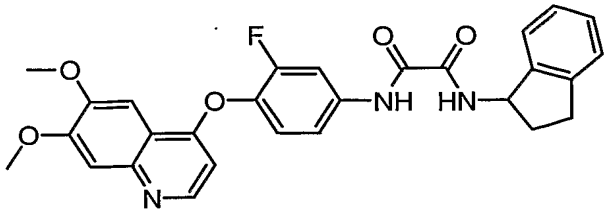
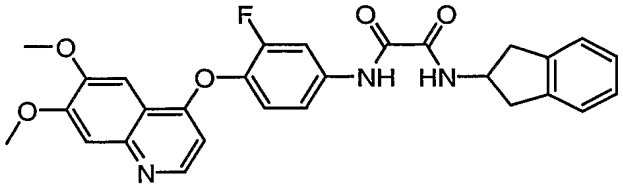
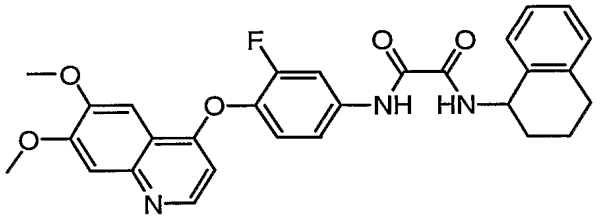
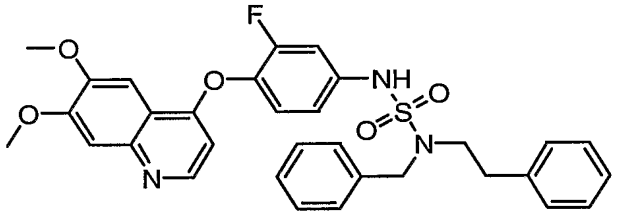
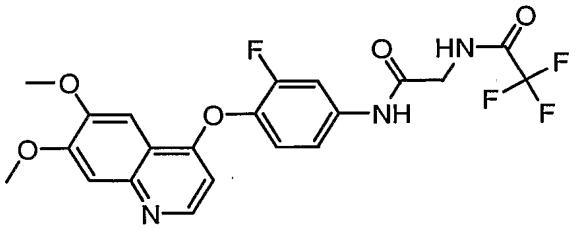
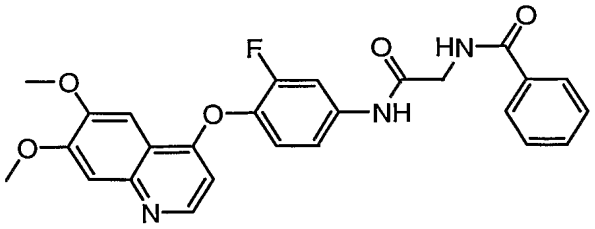
| Entry | Name | Structure |
|---|---|---|
| 55 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2,3-dihydro-1H-inden-1-yl)ethanediamide |  |
| 56 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2,3-dihydro-1H-inden-2-yl)ethanediamide |  |
| 57 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydronaphthalen-1-yl)ethanediamide |  |
| 58 | N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-(2-phenylethyl)-N-(phenylmethyl)sulfamide |  |
| 59 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(trifluoroacetyl)glycinamide |  |
| 60 | N-{[4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylcarbamoyl]-methyl}-benzamide |  |

**Table 1**

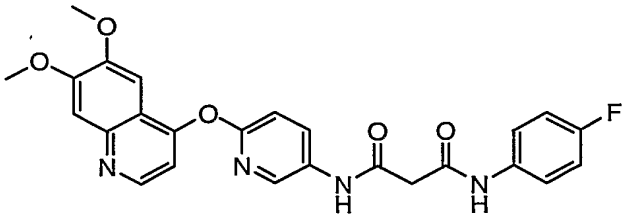
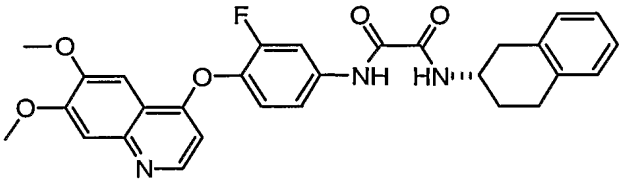
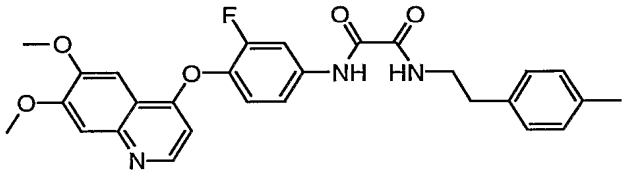
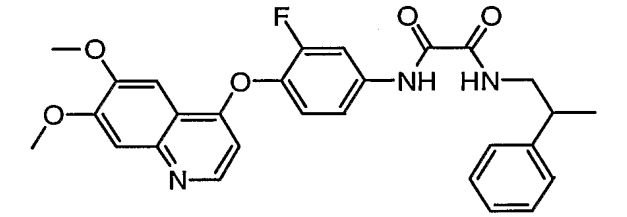
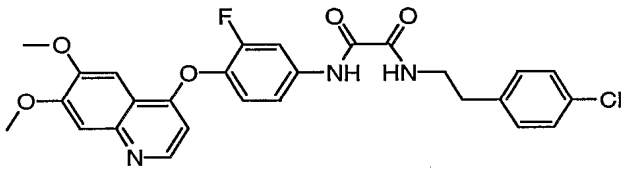
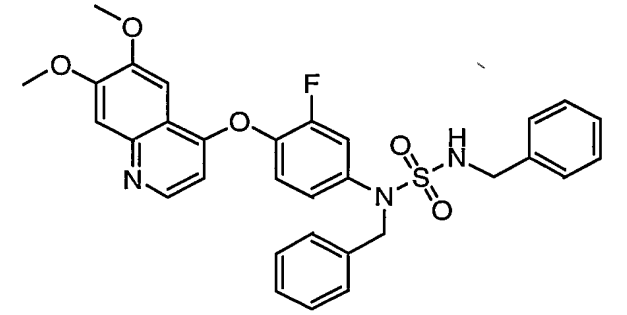
| Entry | Name | Structure |
|---|---|---|
| 61 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N'-(4-fluorophenyl)propanediamide |  |
| 62 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2S)-1,2,3,4-tetrahydronaphthalen-2-yl]ethanediamide |  |
| 63 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(4-methylphenyl)ethyl]ethanediamide |  |
| 64 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylpropyl)ethanediamide |  |
| 65 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(4-chlorophenyl)ethyl]ethanediamide |  |
| 66 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(phenylmethyl)sulfamide |  |

**Table 1**

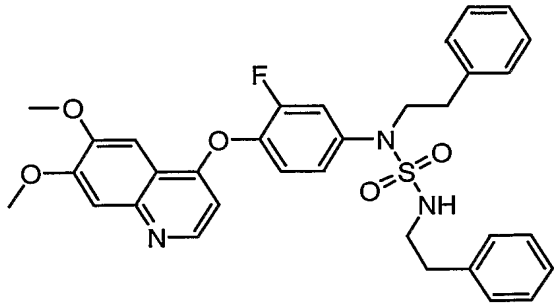
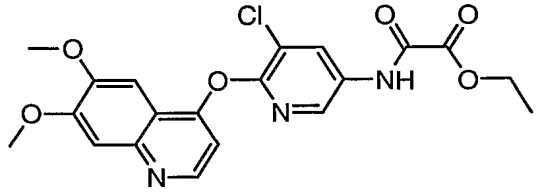
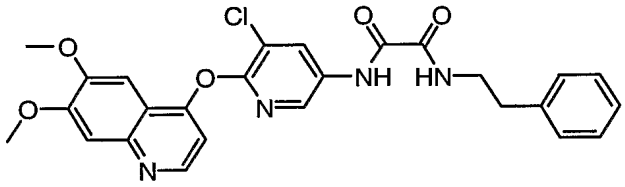
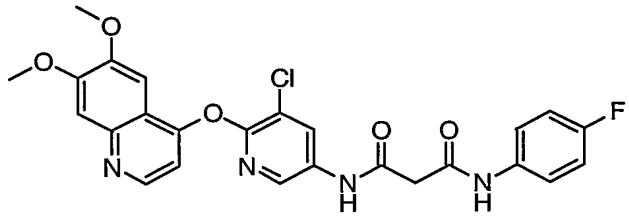
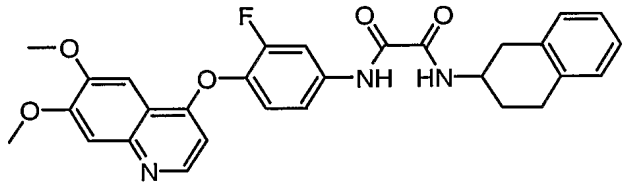
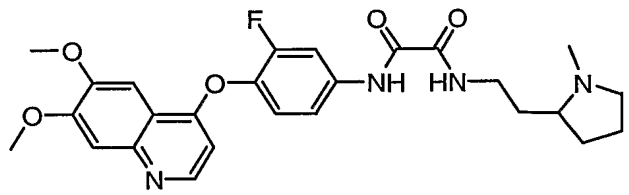
| Entry | Name | Structure |
|---|---|---|
| 67 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(2-phenylethyl)sulfamide |  |
| 68 | ethyl [(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino](oxo)acetate |  |
| 69 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)ethanediamide |  |
| 70 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)propanediamide |  |
| 71 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydronaphthalen-2-yl)ethanediamide |  |
| 72 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(1-methylpyrrolidin-2-yl)ethyl]ethanediamide |  |

**Table 1**

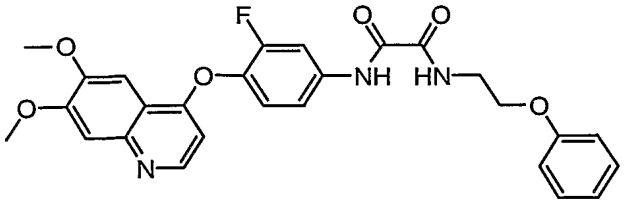
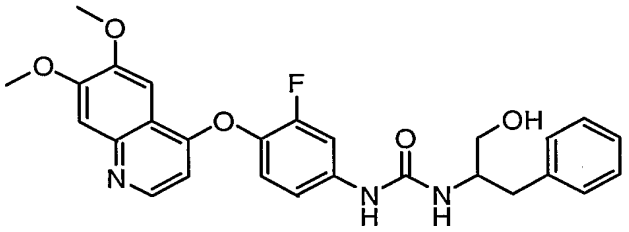
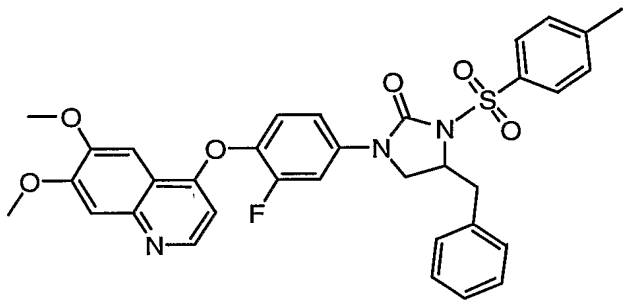
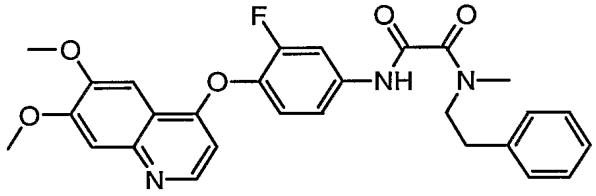
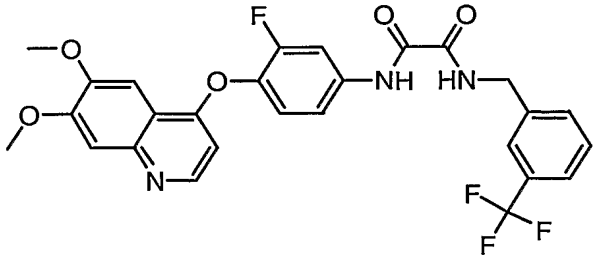
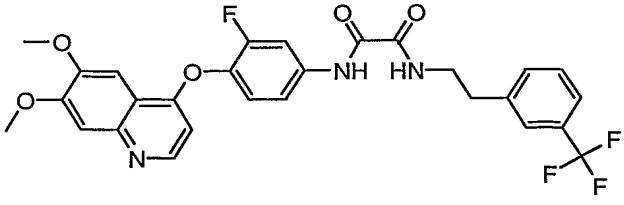
| Entry | Name | Structure |
|---|---|---|
| 73 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(phenyloxy)ethyl]ethanediamide |  |
| 74 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-hydroxy-1-(phenylmethyl)ethyl]urea |  |
| 75 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one |  |
| 76 | N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-methyl-N-(2-phenylethyl)ethanediamide |  |
| 77 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{[3-(trifluoromethyl)phenyl]methyl}ethanediamide |  |
| 78 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{2-[3-(trifluoromethyl)phenyl]ethyl}ethanediamide |  |

**Table 1**

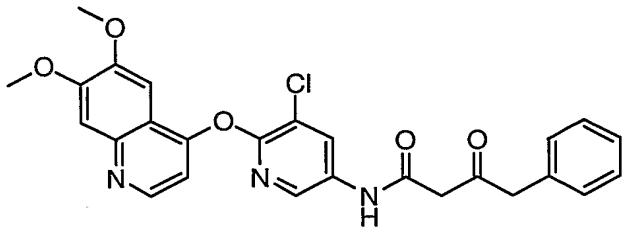
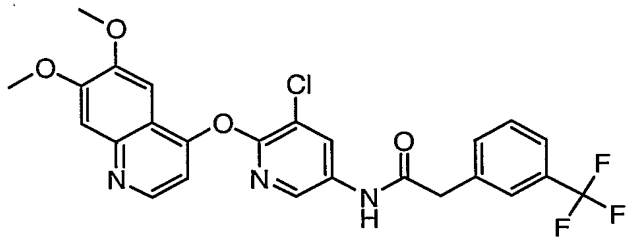
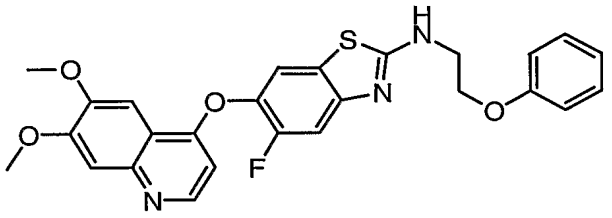
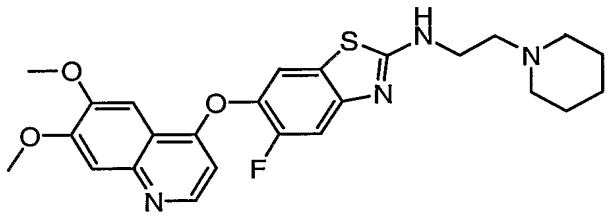
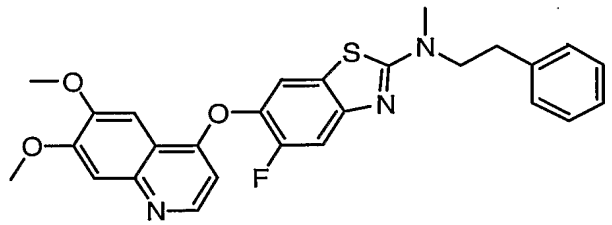
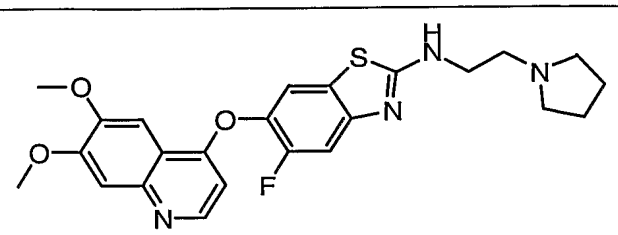
| Entry | Name | Structure |
|---|---|---|
| 79 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-3-oxo-4-phenylbutanamide |  |
| 80 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-2-[3-(trifluoromethyl)phenyl]acetamide |  |
| 81 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-[2-(phenyloxy)ethyl]-1,3-benzothiazol-2-amine |  |
| 82 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-piperidin-1-ylethyl)-1,3-benzothiazol-2-amine |  |
| 83 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-methyl-N-(2-phenylethyl)-1,3-benzothiazol-2-amine |  |
| 84 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-pyrrolidin-1-ylethyl)-1,3-benzothiazol-2-amine |  |

**Table 1**

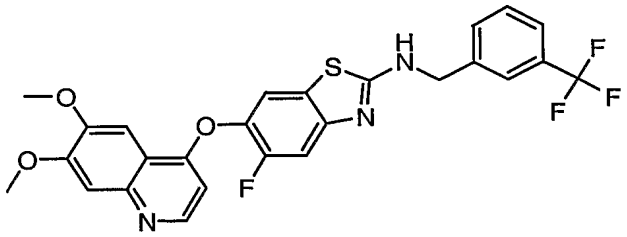
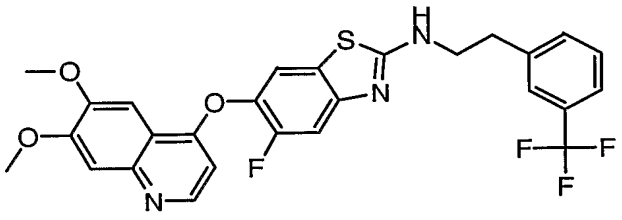
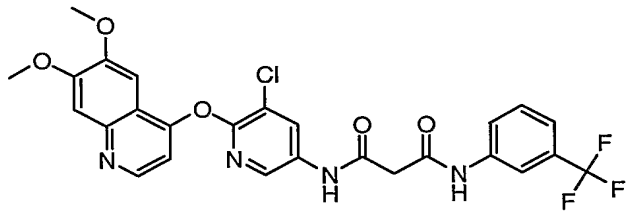
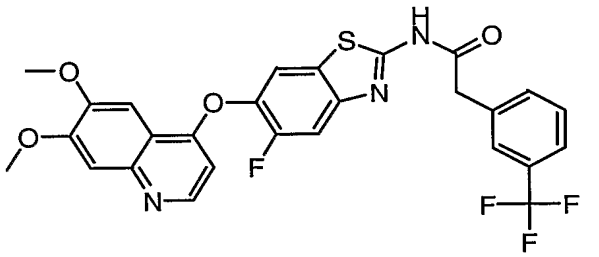
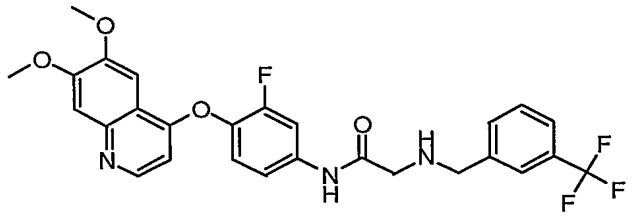
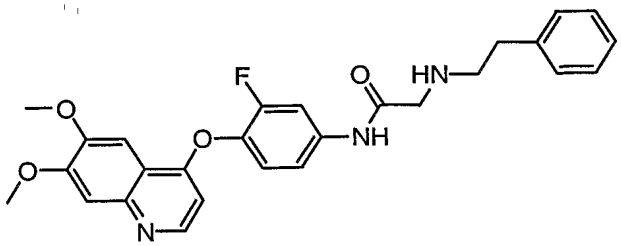
| Entry | Name | Structure |
|---|---|---|
| 85 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-{[3-(trifluoromethyl)phenyl]methyl}-1,3-benzothiazol-2-amine |  |
| 86 | 6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-{2-[3-(trifluoromethyl)phenyl]ethyl}-1,3-benzothiazol-2-amine |  |
| 87 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-[3-(trifluoromethyl)phenyl]propanediamide |  |
| 88 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3-(trifluoromethyl)phenyl]acetamide |  |
| 89 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-{[3-(trifluoromethyl)phenyl]methyl}glycinamide |  |
| 90 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(2-phenylethyl)glycinamide |  |

**Table 1**

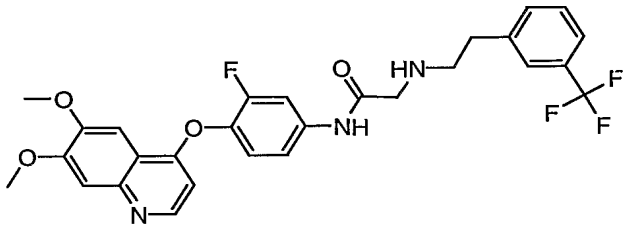
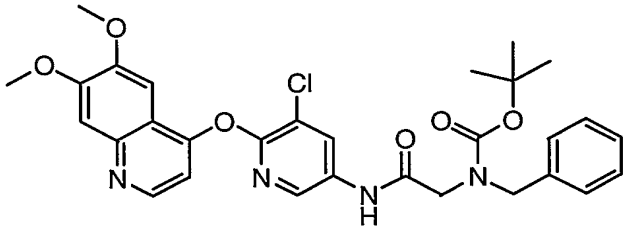
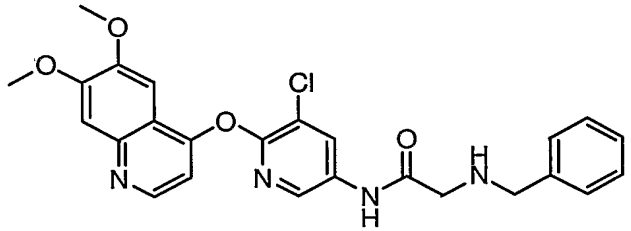
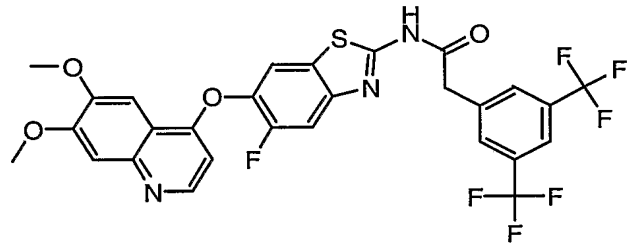
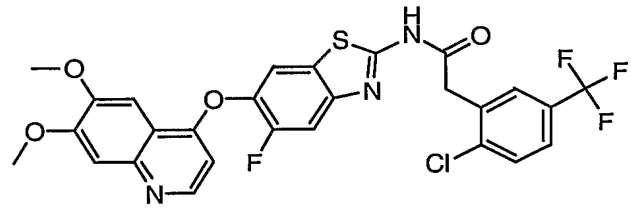
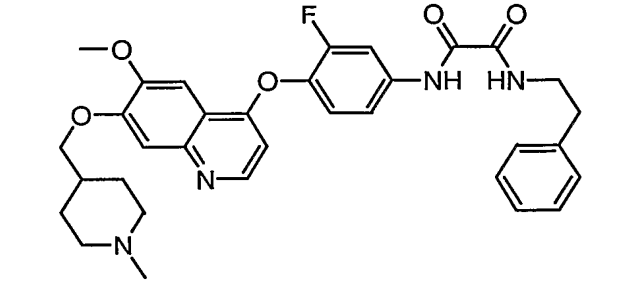
| Entry | Name | Structure |
|---|---|---|
| 91 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide |  |
| 92 | benzyl-{[5-chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylcarbamoyl]-methyl}-carbamic acid tert-butyl ester |  |
| 93 | N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N2-(phenylmethyl)glycinamide |  |
| 94 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3,5-bis(trifluoromethyl)phenyl]acetamide |  |
| 95 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[2-chloro-5-(trifluoromethyl)phenyl]acetamide |  |
| 96 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(2-phenylethyl)ethanediamide |  |

**Table 1**

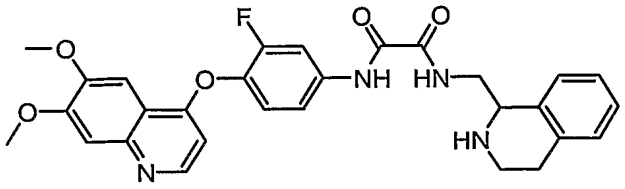
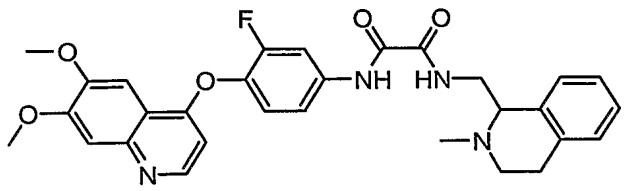
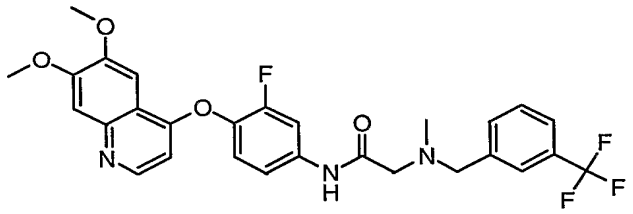
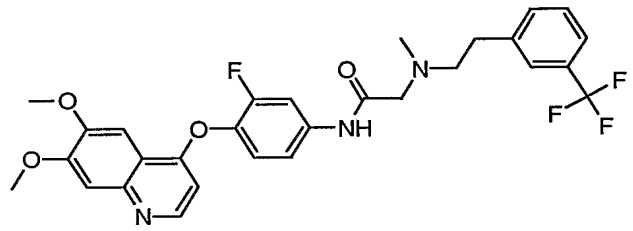
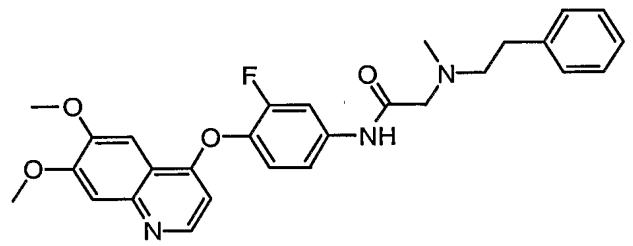
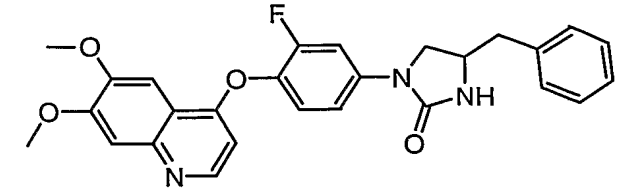
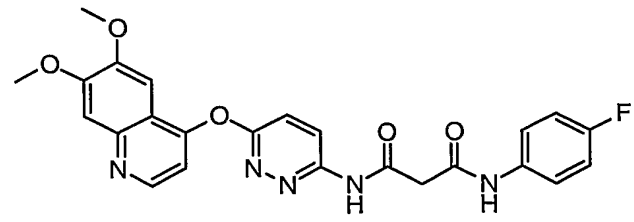
| Entry | Name | Structure |
|---|---|---|
| 97 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)ethanediamide |  |
| 98 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]ethanediamide |  |
| 99 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-{[3-(trifluoromethyl)phenyl]methyl}glycinamide |  |
| 100 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide |  |
| 101 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-(2-phenylethyl)glycinamide |  |
| 102 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-(phenylmethyl)imidazolidin-2-one |  |
| 103 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridazin-3-yl)-N'-(4-fluorophenyl)propanediamide |  |

**Table 1**

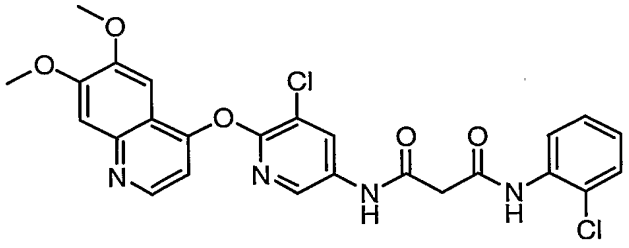
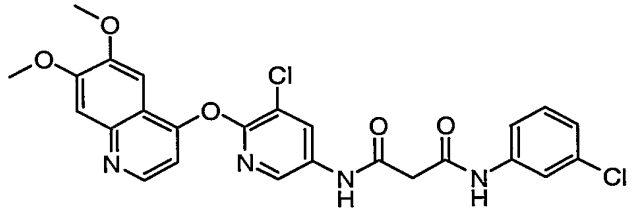
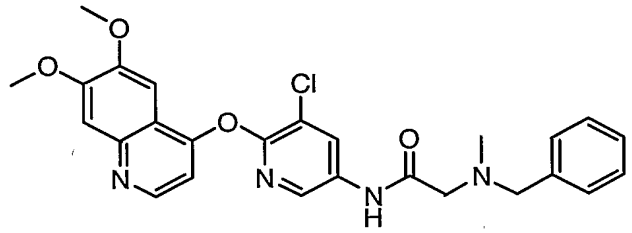
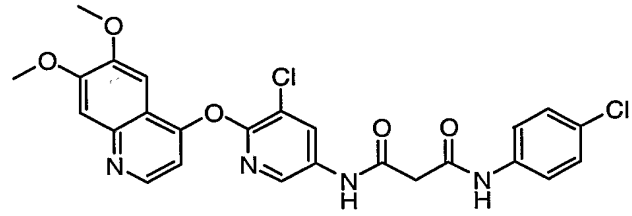
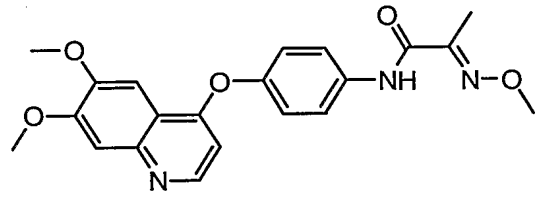
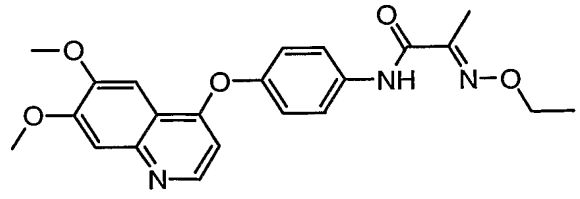
| Entry | Name | Structure |
|---|---|---|
| 104 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-chlorophenyl)propanediamide |  |
| 105 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(3-chlorophenyl)propanediamide |  |
| 106 | N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N2-methyl-N2-(phenylmethyl)glycinamide |  |
| 107 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-chlorophenyl)propanediamide |  |
| 108 | (2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(methyloxy)imino]propanamide |  |
| 109 | (2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(ethyloxy)imino]propanamide |  |

**Table 1**

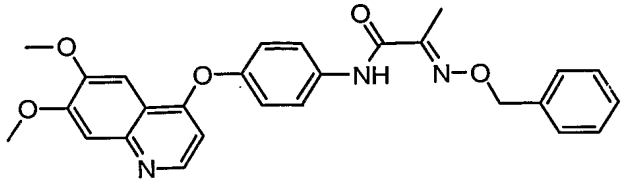
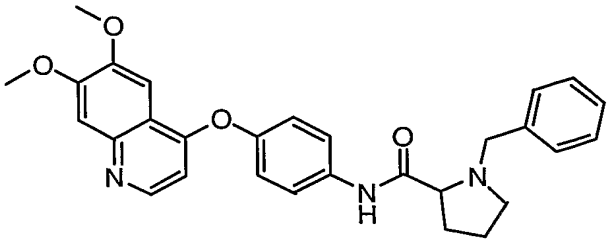
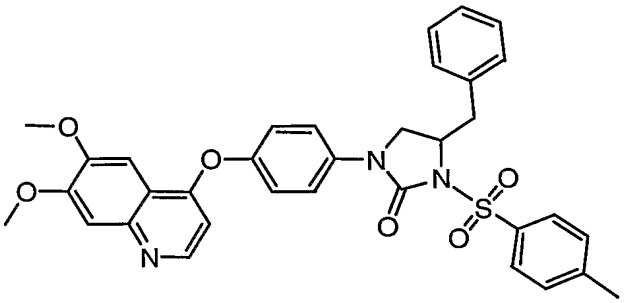
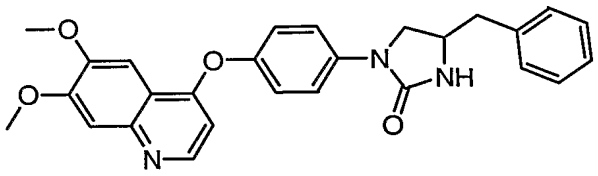
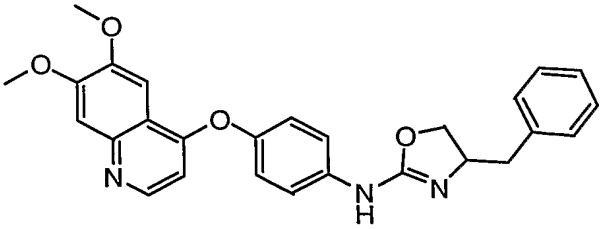
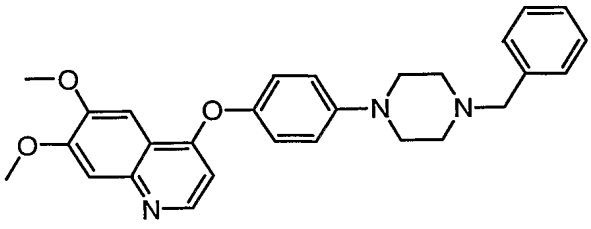
| Entry | Name | Structure |
|---|---|---|
| 110 | (2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-{[(phenylmethyl)oxy]imino}propanamide |  |
| 111 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-1-(phenylmethyl)prolinamide |  |
| 112 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one |  |
| 113 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)imidazolidin-2-one |  |
| 114 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)-4,5-dihydro-1,3-oxazol-2-amine |  |
| 115 | 6,7-bis(methyloxy)-4-({4-[4-(phenylmethyl)piperazin-1-yl]phenyl}oxy)quinoline |  |

**Table 1**

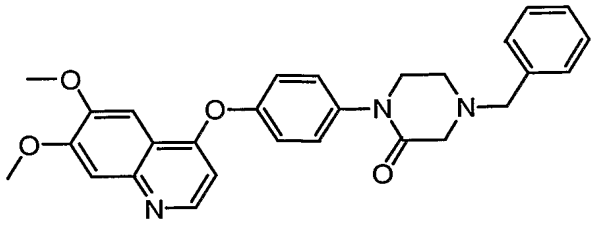
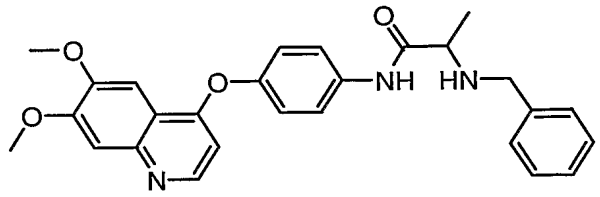
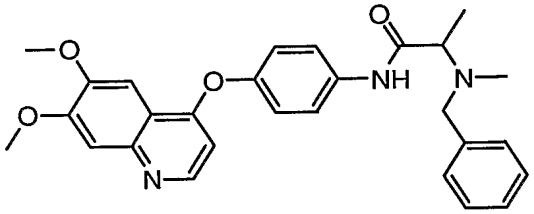
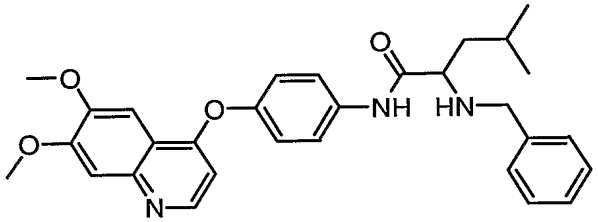
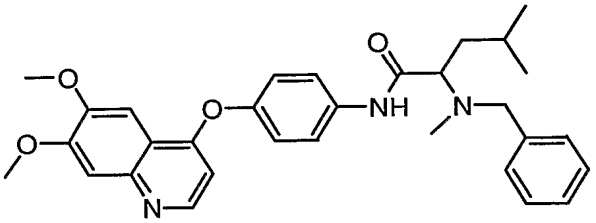
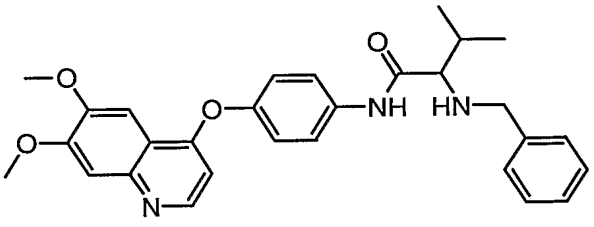
| Entry | Name | Structure |
|---|---|---|
| 116 | 1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)piperazin-2-one |  |
| 117 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)alaninamide |  |
| 118 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-methyl-N2-(phenylmethyl)alaninamide |  |
| 119 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)leucinamide |  |
| 120 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-methyl-N2-(phenylmethyl)leucinamide |  |
| 121 | N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)valinamide |  |

**Table 1**

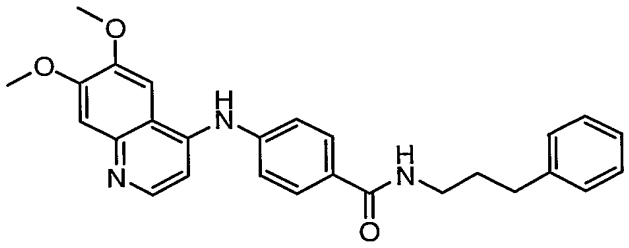
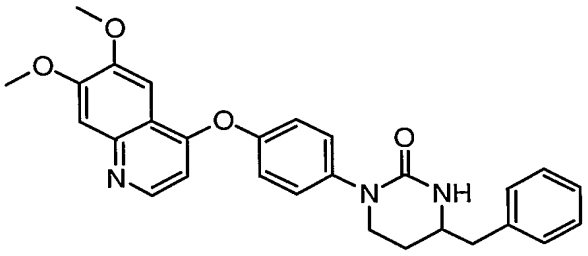
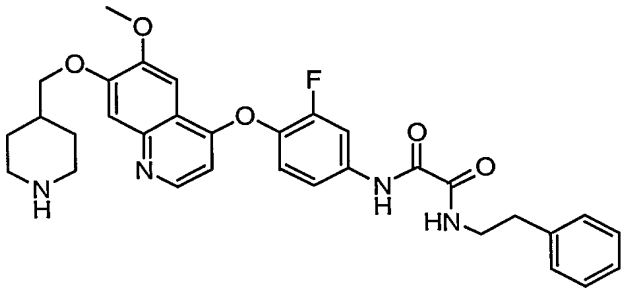
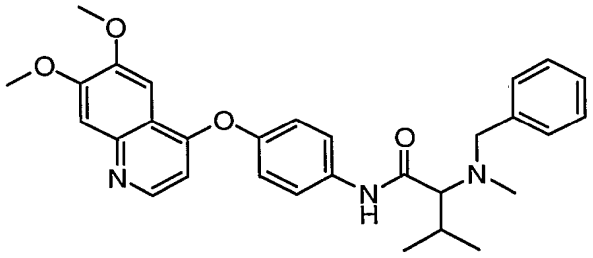
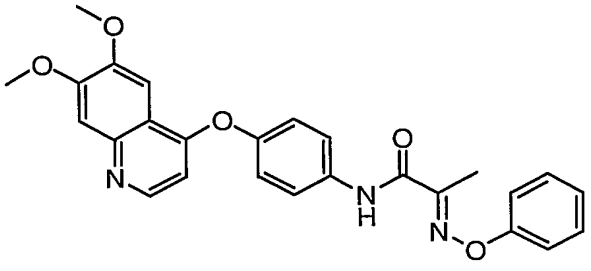
| Entry | Name | Structure |
|---|---|---|
| 122 | 4-(6,7-dimethoxy-quinolin-4-ylamino)-N-(3-phenyl-propyl)-benzamide |  |
| 123 | 4-benzyl-1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-tetrahydro-pyrimidin-2-one |  |
| 124 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide |  |
| 125 | 2-(Benzyl-methyl-amino)-N-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-3-methyl-butyramide (note: Alphabetic order of prefixes ignored while selecting parent chain) |  |
| 126 | N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenyl]-2-phenoxyimino-propionamide |  |

**Table 1**

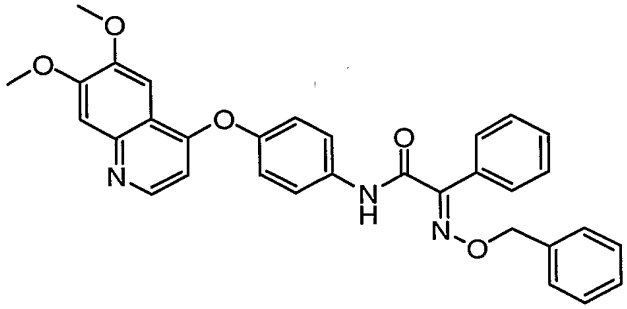
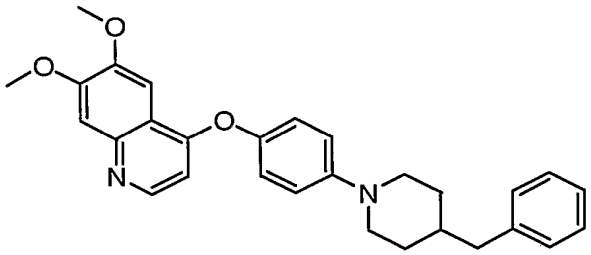
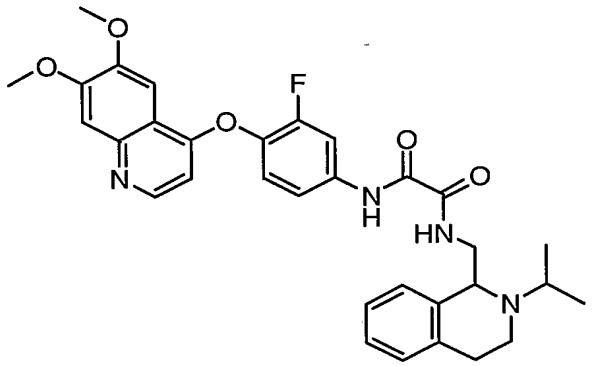
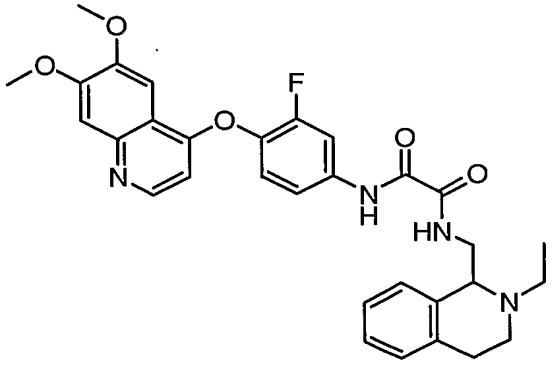
| Entry | Name | Structure |
|---|---|---|
| 127 | 2-Benzyloxyimino-N-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-2-phenyl-acetamide |  |
| 128 | 4-[4-(4-Benzyl-piperidin-1-yl)-phenoxy]-6,7-dimethoxy-quinoline |  |
| 129 | N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-oxalamide |  |
| 130 | N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-oxalamide |  |

**Table 1**

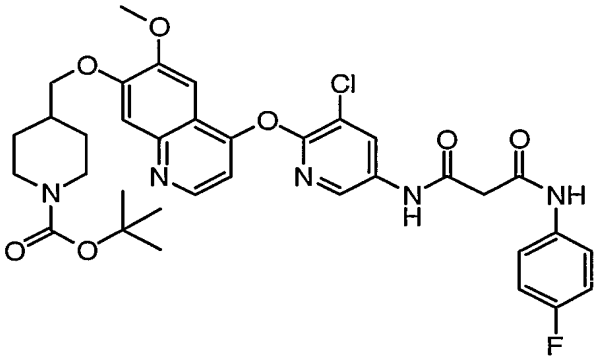
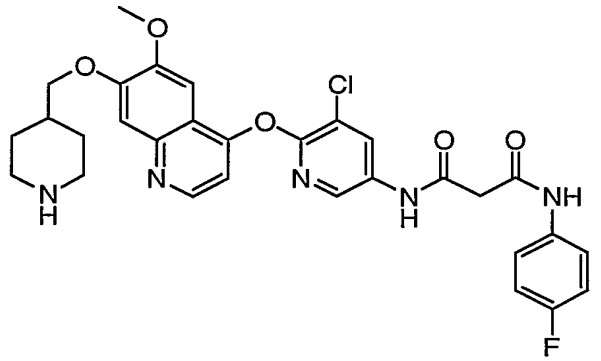
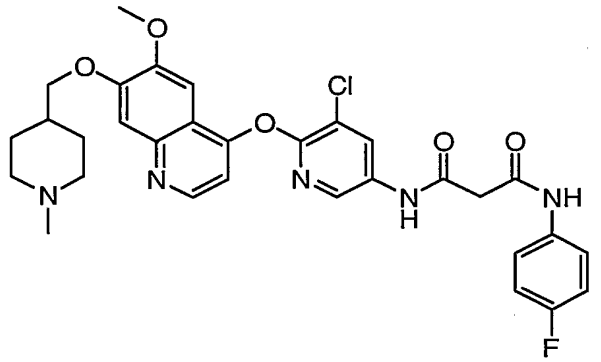
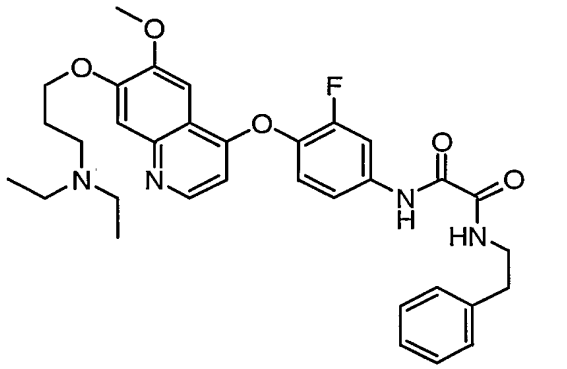
| Entry | Name | Structure |
|---|---|---|
| 131 | 4-(4-{3-Chloro-5-[2-(4-fluoro-phenylcarbamoyl)-acetylamino]-pyridin-2-yloxy}-6-methoxy-quinolin-7-yloxymethyl)-piperidine-1-carboxylic acid tert-butyl ester |  |
| 132 | N-{5-Chloro-6-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide |  |
| 133 | N-{5-Chloro-6-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide |  |
| 134 | N-{4-[7-(3-Diethylamino-propoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide |  |

**Table 1**

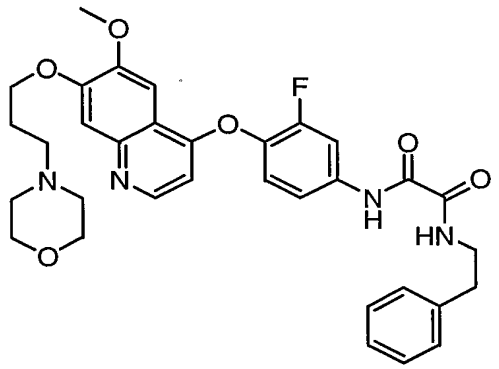
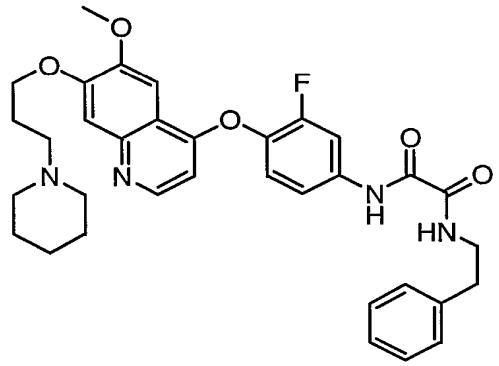
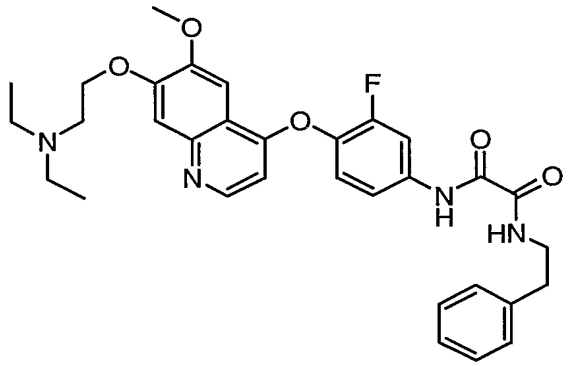
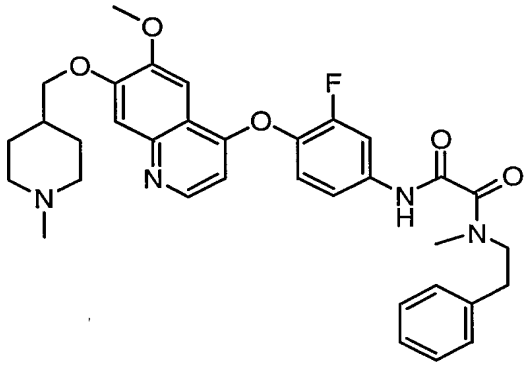
| Entry | Name | Structure |
|---|---|---|
| 135 | N-{3-Fluoro-4-[6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide |  |
| 136 | N-{3-Fluoro-4-[6-methoxy-7-(3-piperidin-1-yl-propoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide |  |
| 137 | N-{4-[7-(2-Diethylamino-ethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide |  |
| 138 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-methyl-N'-phenethyl-oxalamide |  |

**Table 1**

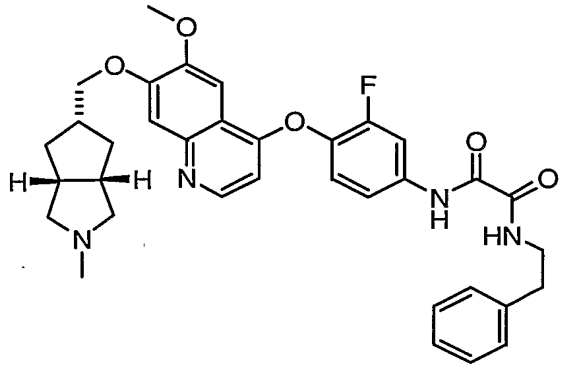
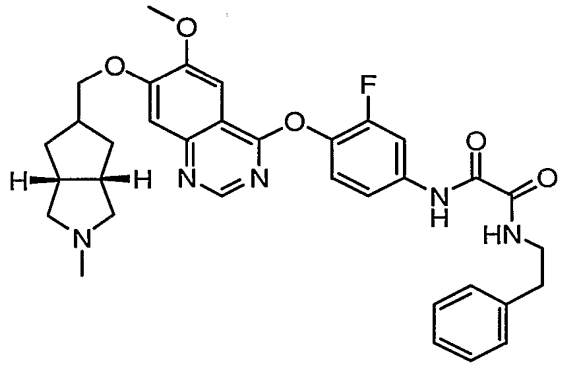
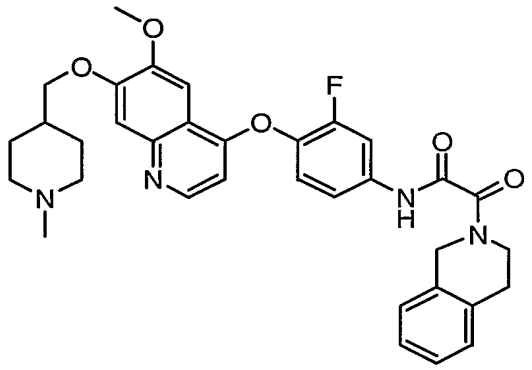
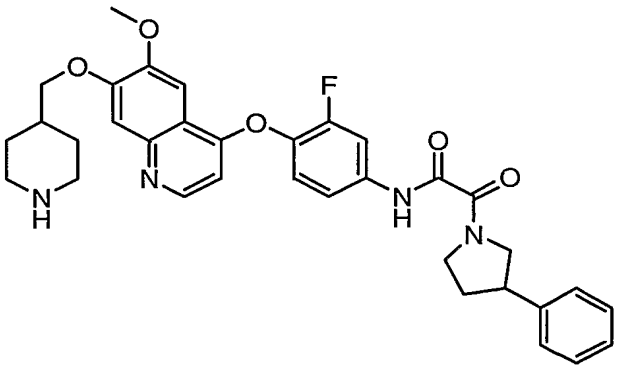
| Entry | Name | Structure |
|---|---|---|
| 139 | N-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide |  |
| 140 | N-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide |  |
| 141 | 2-(3,4-Dihydro-1H-isoquinolin-2-yl)-N-{3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-acetamide |  |
| 142 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-(3-phenyl-pyrrolidin-1-yl)-acetamide |  |

**Table 1**

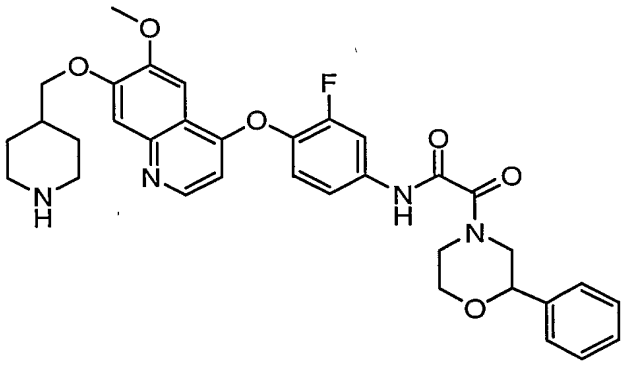
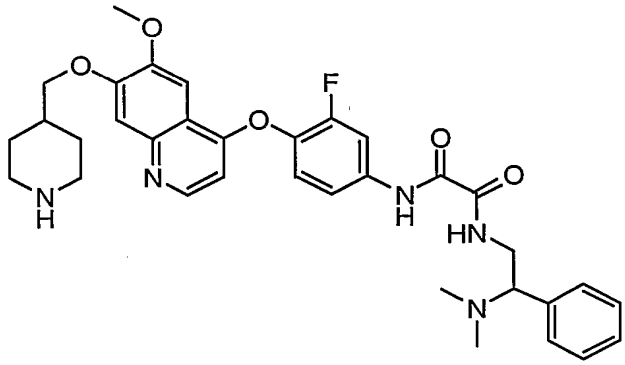
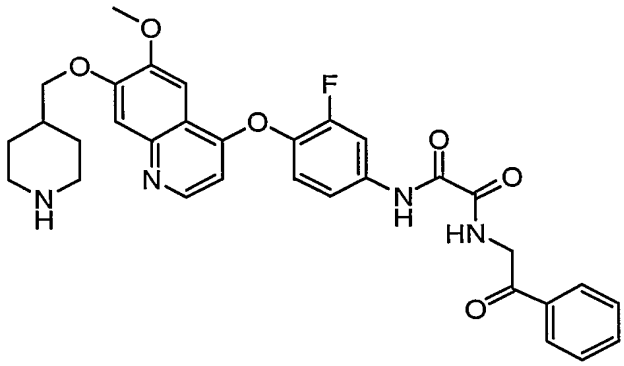
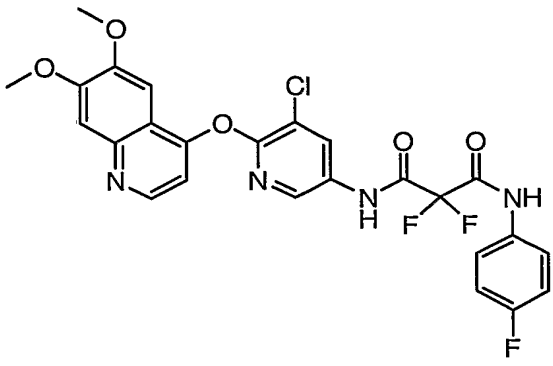
| Entry | Name | Structure |
|---|---|---|
| 143 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-(2-phenyl-morpholin-4-yl)-acetamide |  |
| 144 | N-(2-Dimethylamino-2-phenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 145 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-oxo-2-phenyl-ethyl)-oxalamide |  |
| 146 | N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-2,2-difluoro-N'-(4-fluoro-phenyl)-malonamide |  |

**Table 1**

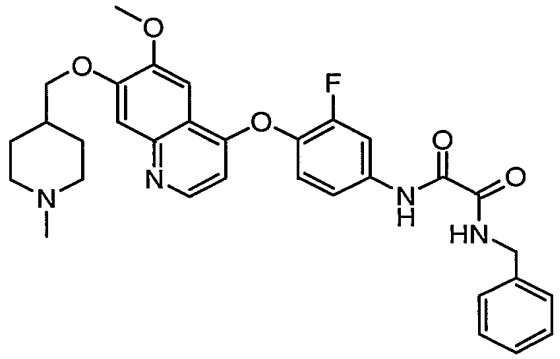
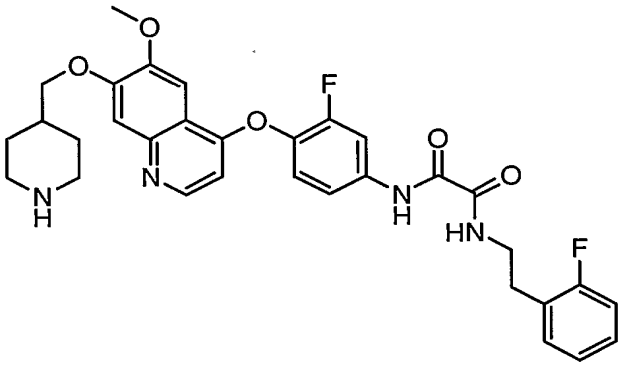
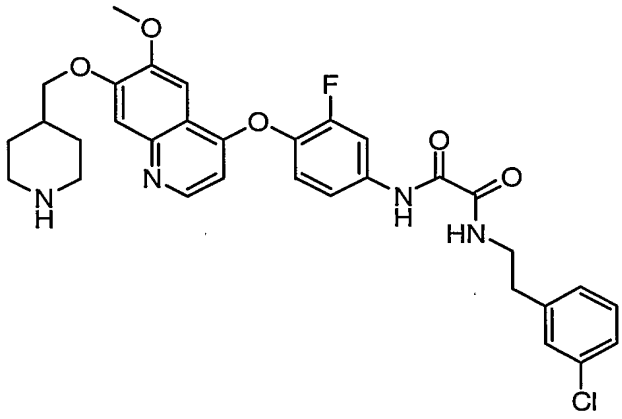
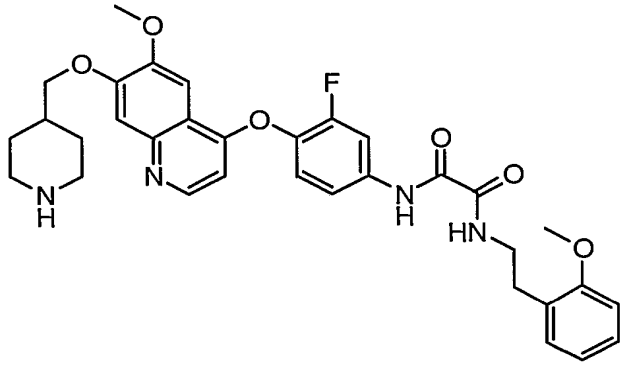
| Entry | Name | Structure |
|---|---|---|
| 147 | N-Benzyl-N'-{3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 148 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-fluoro-phenyl)-ethyl]-oxalamide |  |
| 149 | N-[2-(3-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 150 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-methoxy-phenyl)-ethyl]-oxalamide |  |

**Table 1**

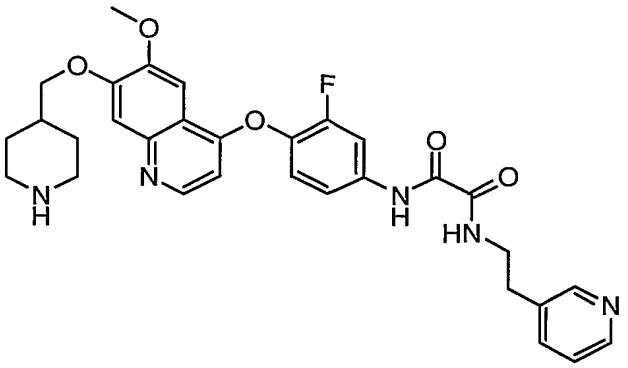
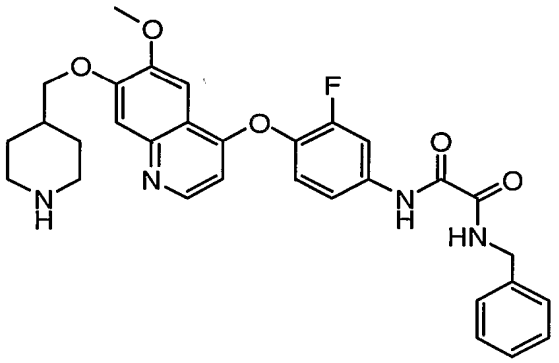
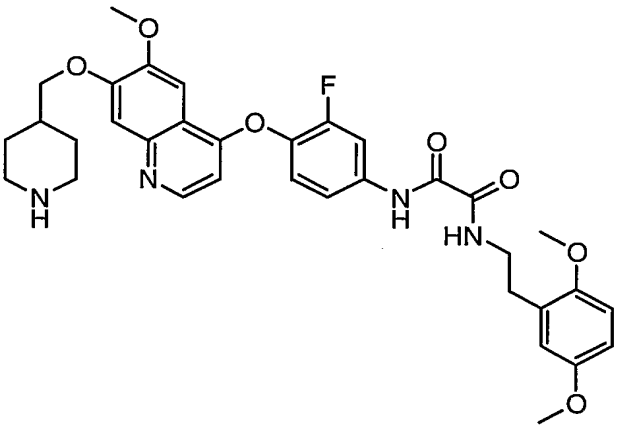
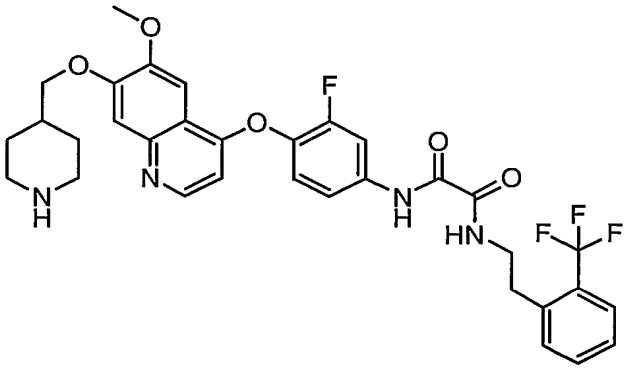
| Entry | Name | Structure |
|---|---|---|
| 151 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-3-yl-ethyl)-oxalamide |  |
| 152 | N-Benzyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 153 | N-[2-(2,5-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 154 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-trifluoromethyl-phenyl)-ethyl]-oxalamide |  |

**Table 1**

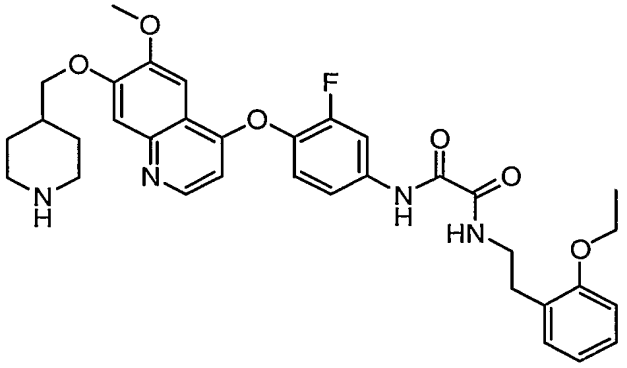
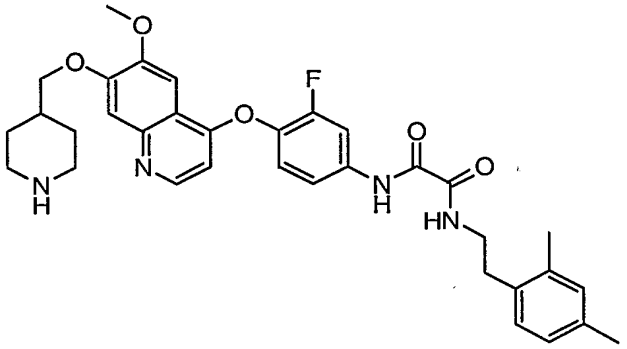
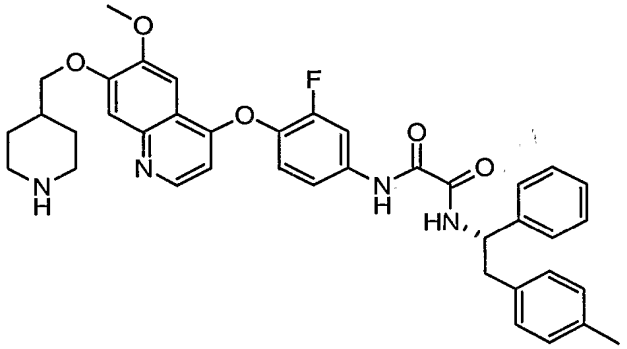
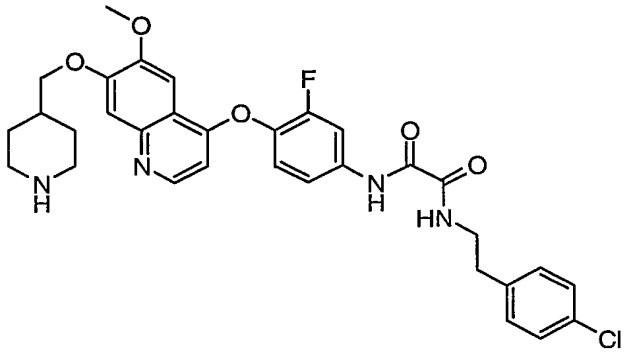
| Entry | Name | Structure |
|---|---|---|
| 155 | N-[2-(2-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 156 | N-[2-(2,4-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 157 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*S* -phenyl-2-p-tolyl-ethyl)-oxalamide |  |
| 158 | N-[2-(4-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

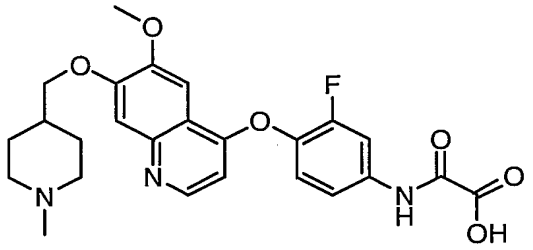
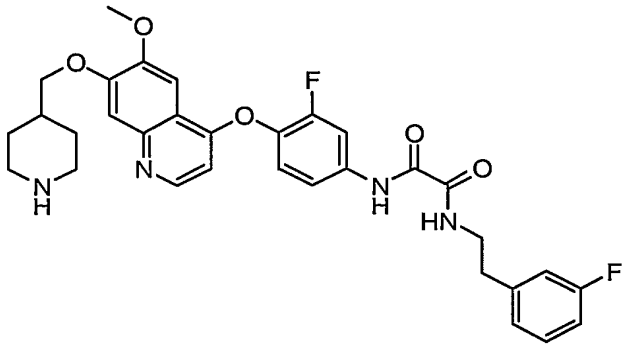
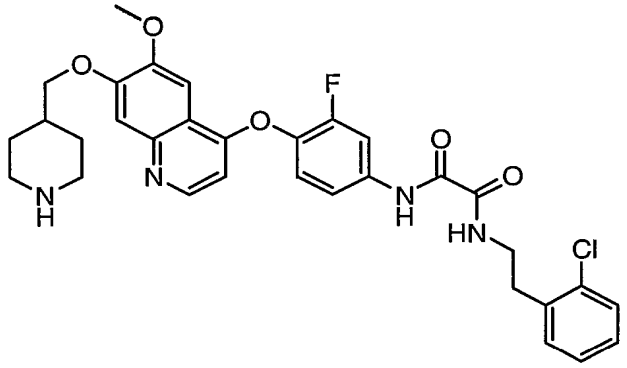
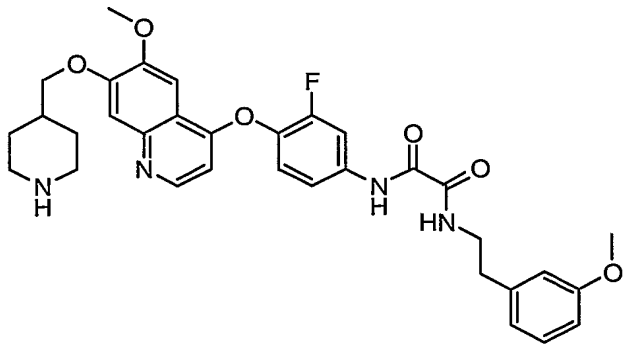
| Entry | Name | Structure |
|---|---|---|
| 159 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamic acid |  |
| 160 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-fluoro-phenyl)-ethyl]-oxalamide |  |
| 161 | N-[2-(2-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 162 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-methoxy-phenyl)-ethyl]-oxalamide |  |

**Table 1**

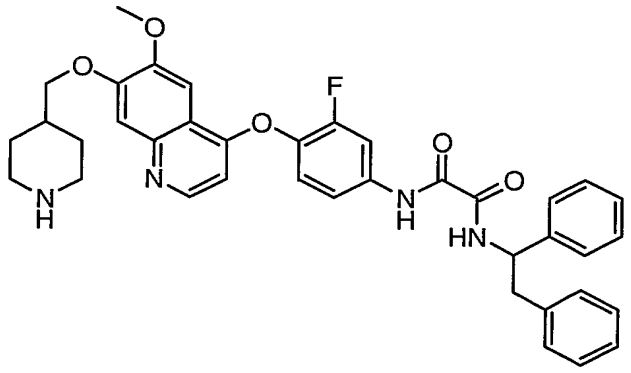
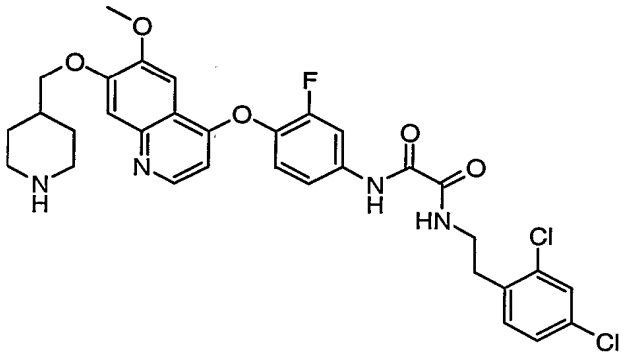
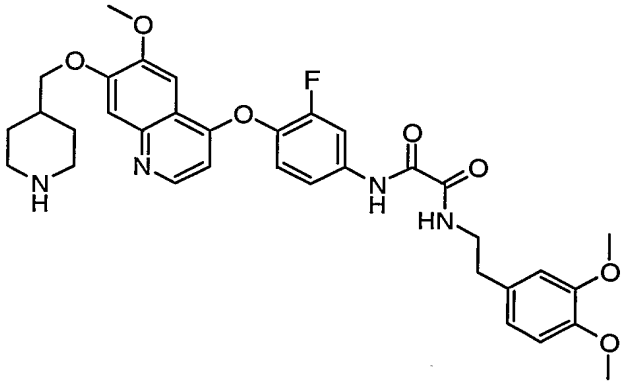
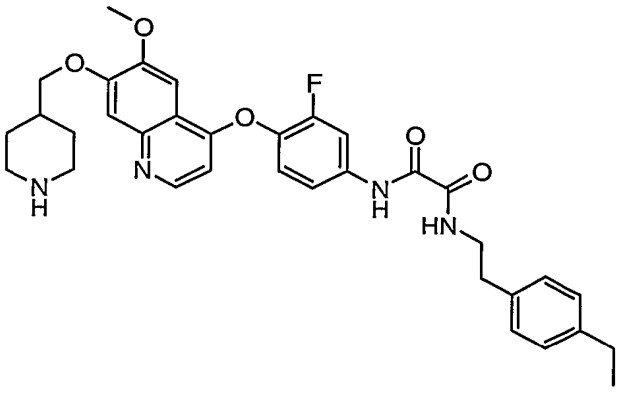
| Entry | Name | Structure |
|---|---|---|
| 163 | N-(1,2-Diphenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 164 | N-[2-(2,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 165 | N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 166 | N-[2-(4-Ethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

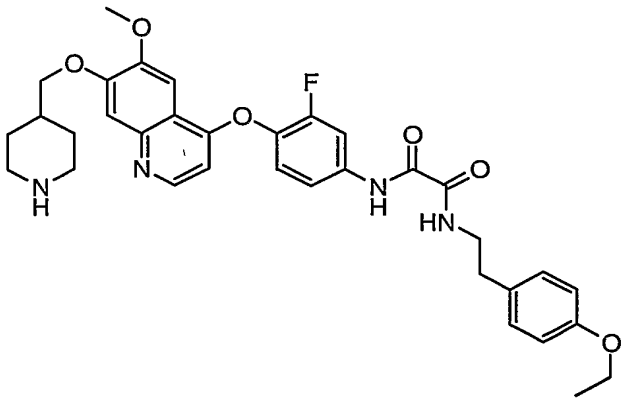
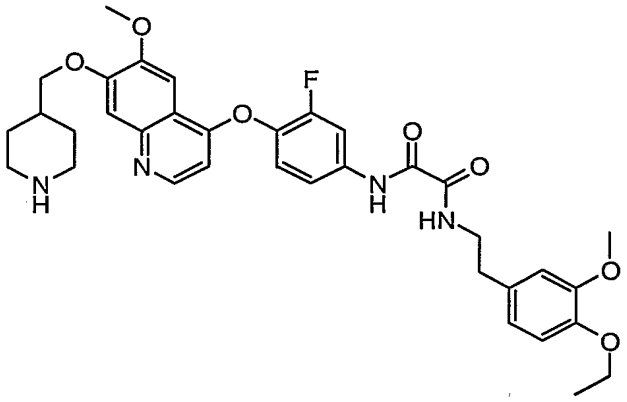
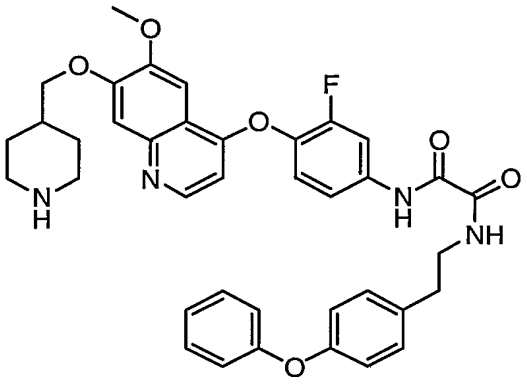
| Entry | Name | Structure |
|---|---|---|
| 167 | N-[2-(4-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 168 | N-[2-(4-Ethoxy-3-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 169 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-phenoxy-phenyl)-ethyl]-oxalamide |  |

**Table 1**

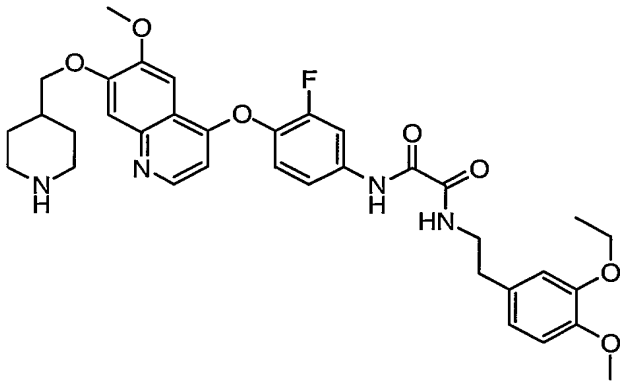
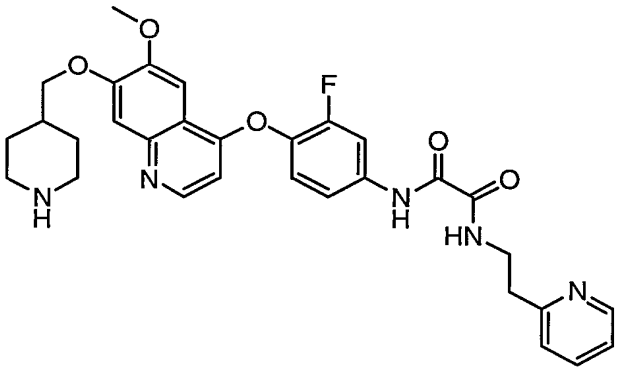
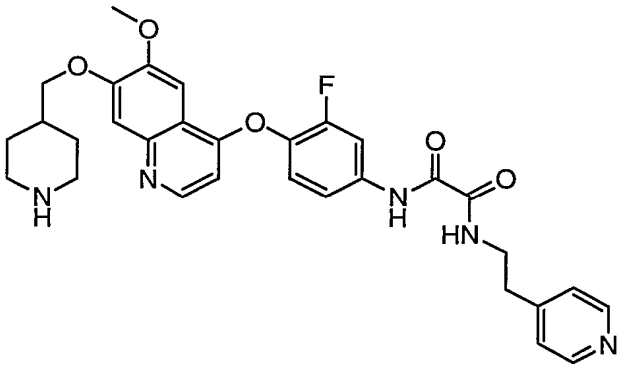
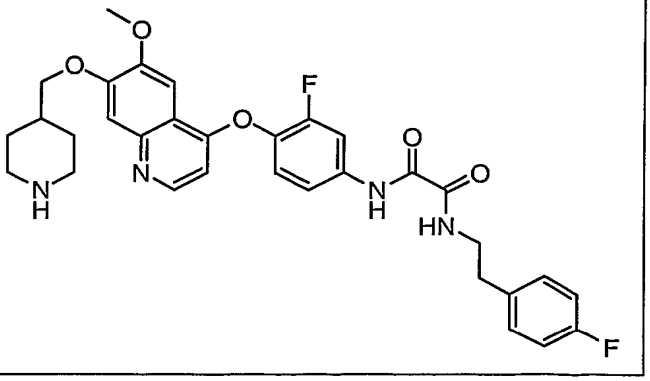
| Entry | Name | Structure |
|---|---|---|
| 170 | N-[2-(3-Ethoxy-4-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 171 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-2-yl-ethyl)-oxalamide |  |
| 172 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-4-yl-ethyl)-oxalamide |  |
| 173 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-fluoro-phenyl)-ethyl]-oxalamide |  |

**Table 1**

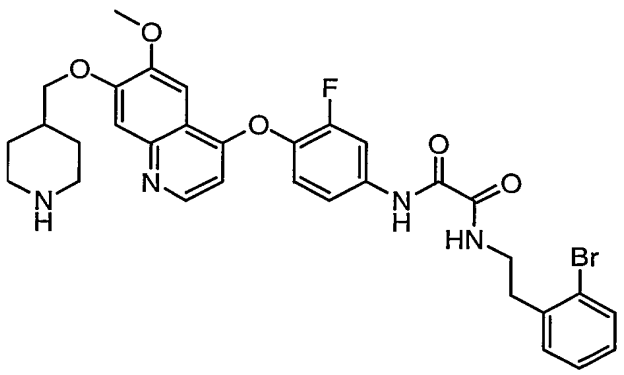
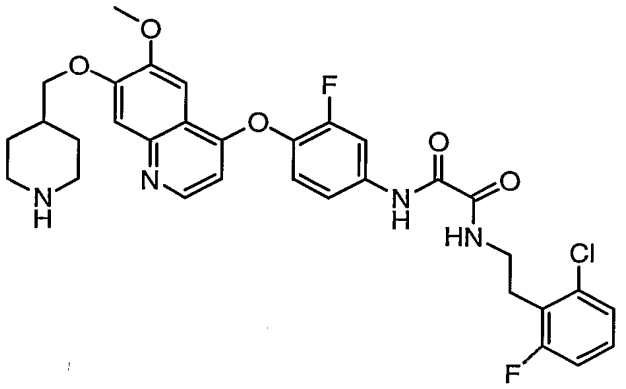
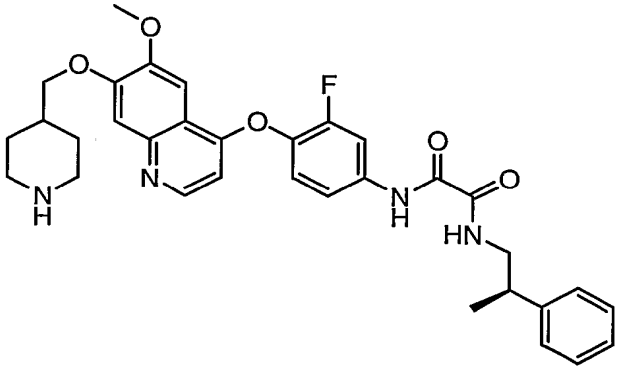
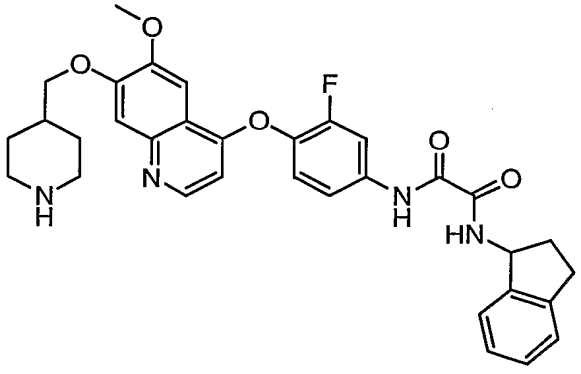
| Entry | Name | Structure |
|---|---|---|
| 174 | N-[2-(2-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 175 | N-[2-(2-Chloro-6-fluoro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 176 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2*R*-phenyl-propyl)-oxalamide |  |
| 177 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-indan-1-yl-oxalamide |  |

**Table 1**

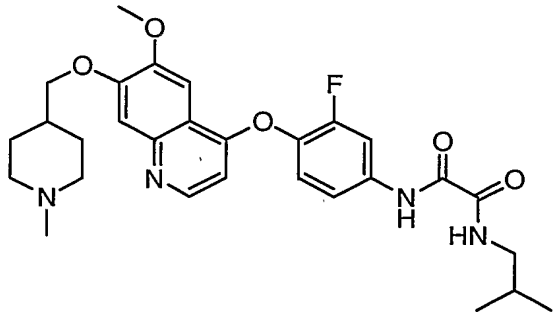
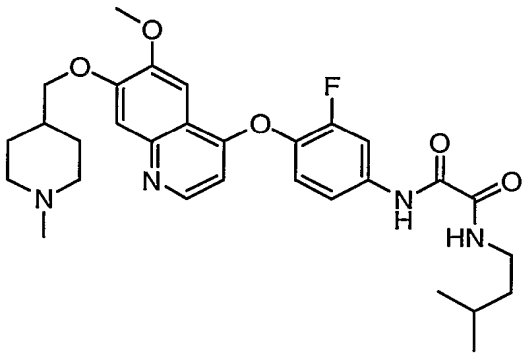
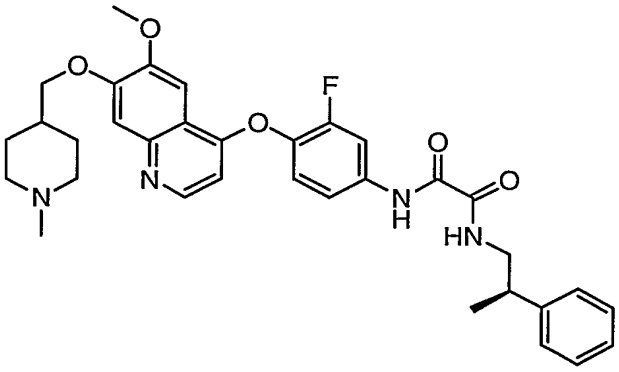
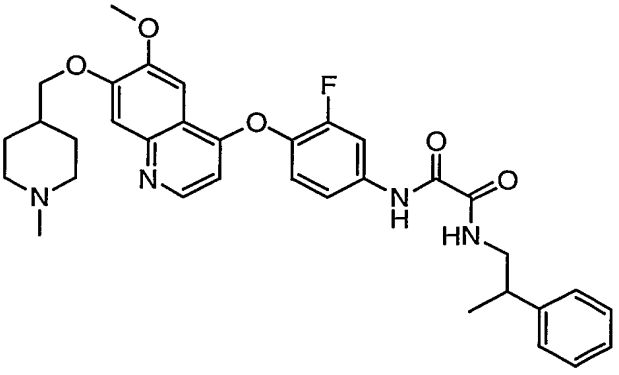
| Entry | Name | Structure |
|---|---|---|
| 178 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-isobutyl-oxalamide |  |
| 179 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-butyl)-oxalamide |  |
| 180 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2*R*-phenyl-propyl)-oxalamide |  |
| 181 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenyl-propyl)-oxalamide |  |

**Table 1**

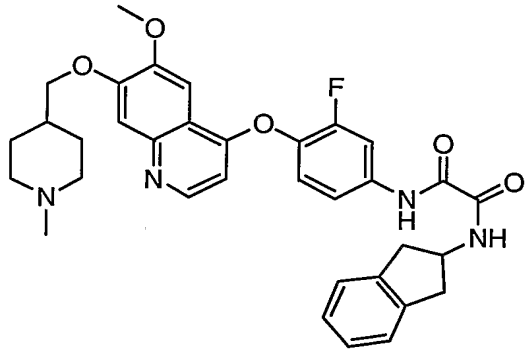
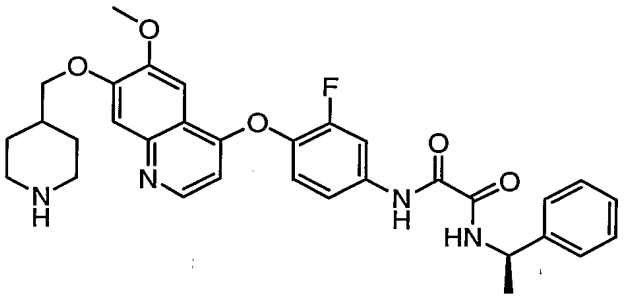
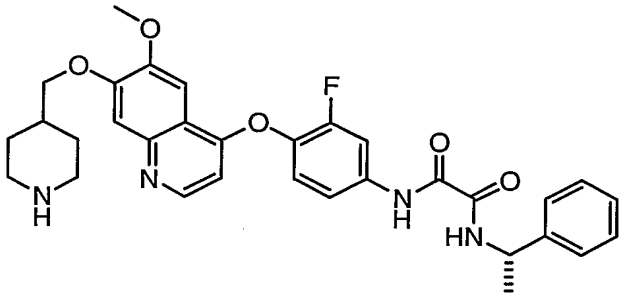
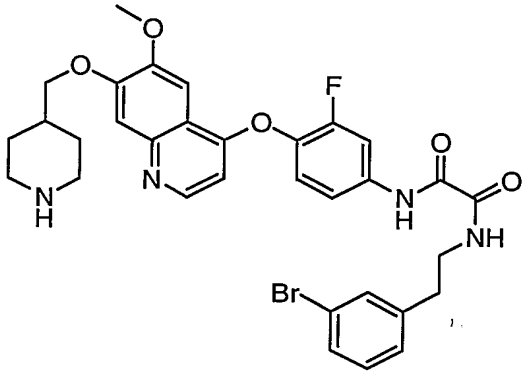
| Entry | Name | Structure |
|---|---|---|
| 182 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-indan-2-yl-oxalamide |  |
| 183 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*R*-phenyl-ethyl)-oxalamide |  |
| 184 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*S*-phenyl-ethyl)-oxalamide |  |
| 185 | N-[2-(3-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

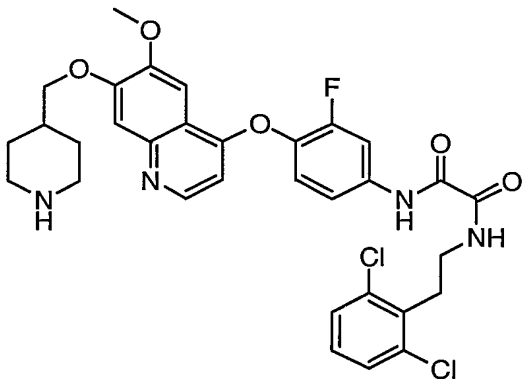
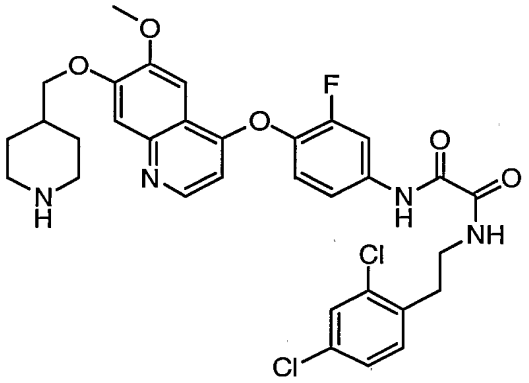
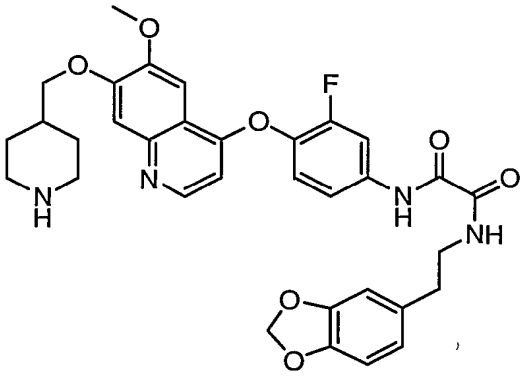
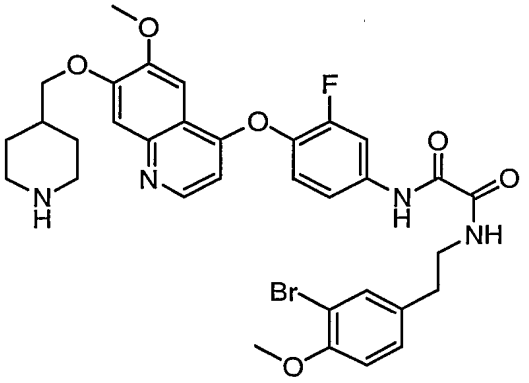
| Entry | Name | Structure |
|---|---|---|
| 186 | N-[2-(2,6-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 187 | N-[2-(2,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 188 | N-(2-Benzo[1,3]dioxol-5-yl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 189 | N-[2-(3-Bromo-4-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

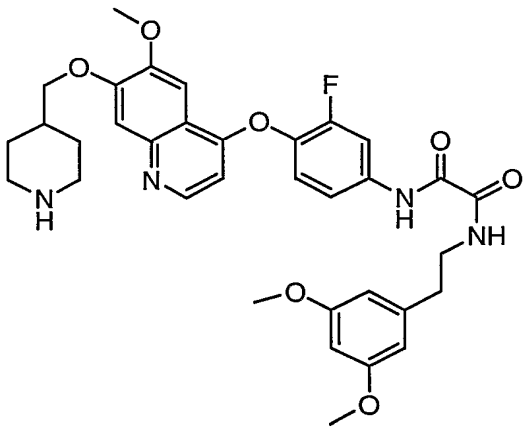
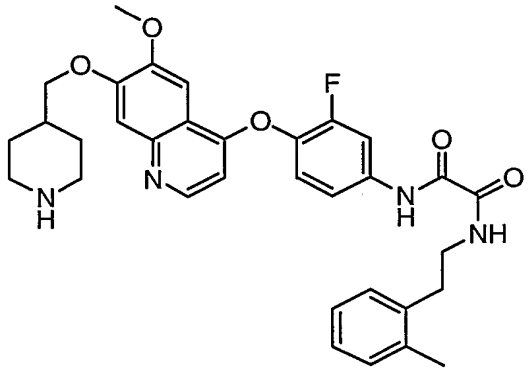
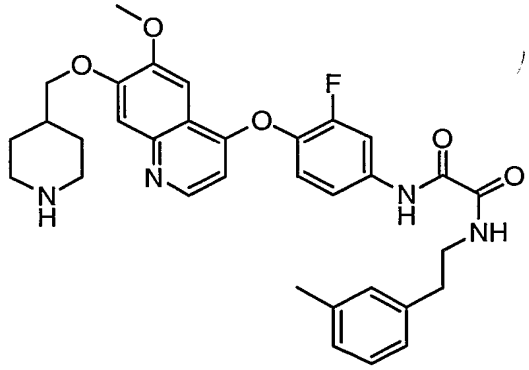
| Entry | Name | Structure |
|---|---|---|
| 190 | N-[2-(3,5-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 191 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-o-tolyl-ethyl)-oxalamide |  |
| 192 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-m-tolyl-ethyl)-oxalamide |  |

**Table 1**

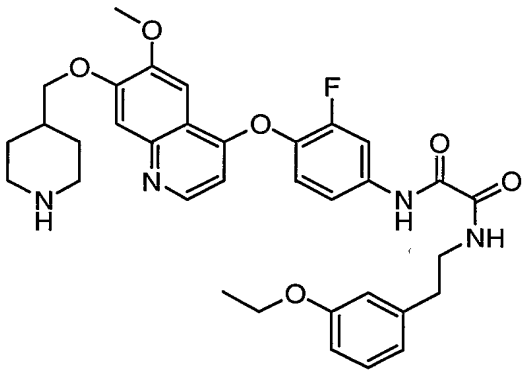
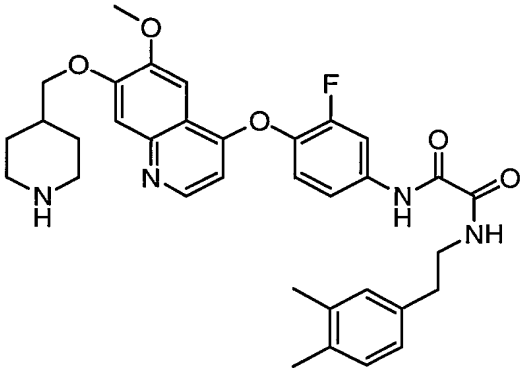
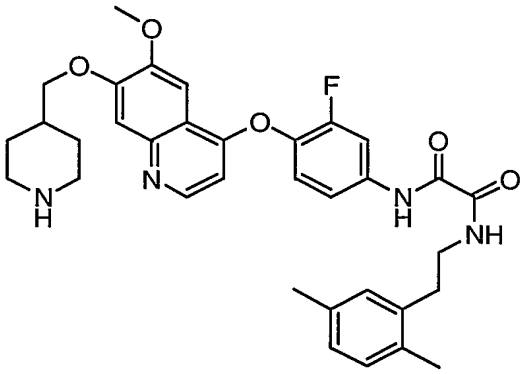
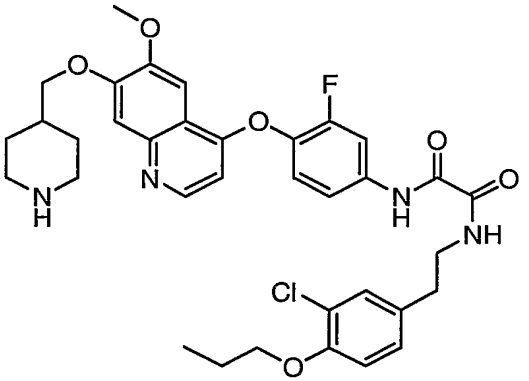
| Entry | Name | Structure |
|---|---|---|
| 193 | N-[2-(3-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 194 | N-[2-(3,4-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 195 | N-[2-(2,5-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 196 | N-[2-(3-Chloro-4-propoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

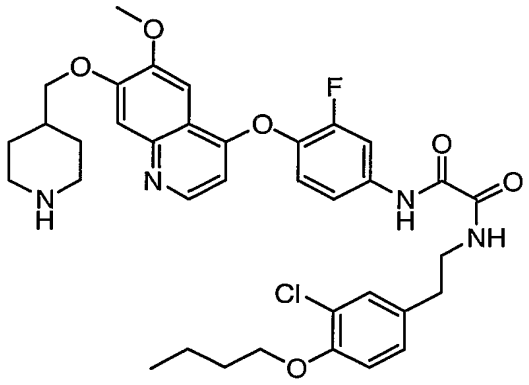
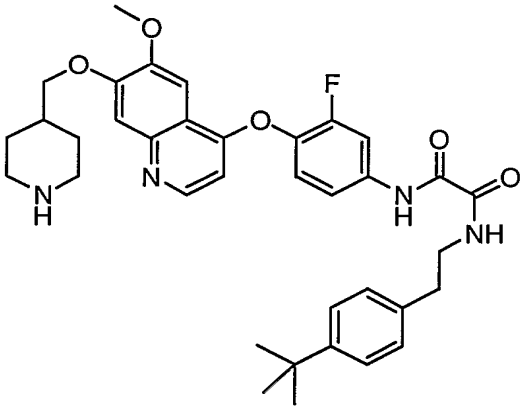
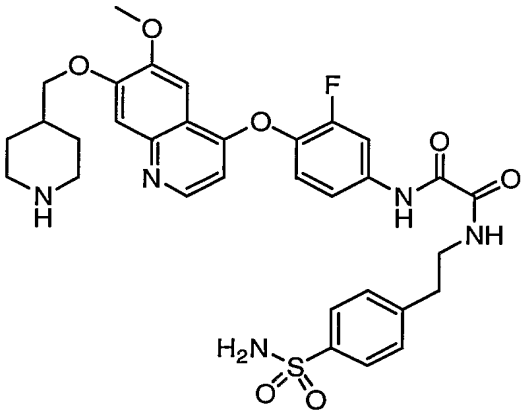
| Entry | Name | Structure |
|---|---|---|
| 197 | N-[2-(4-Butoxy-3-chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 198 | N-[2-(4-tert-Butyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 199 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-sulfamoyl-phenyl)-ethyl]-oxalamide |  |

**Table 1**

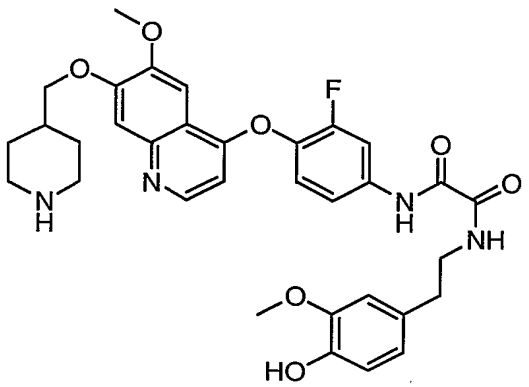
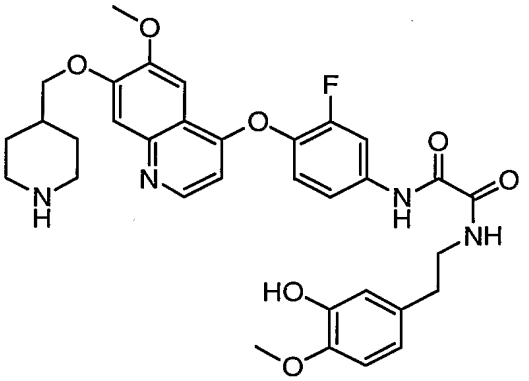
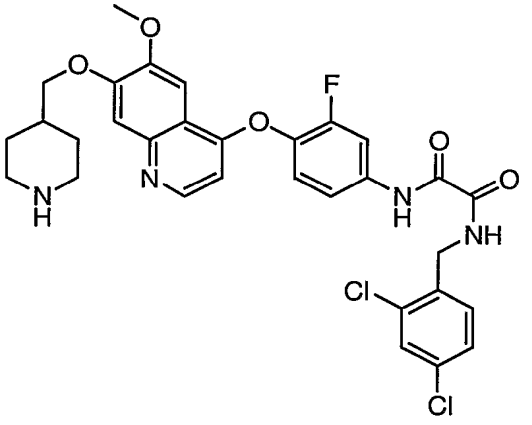
| Entry | Name | Structure |
|---|---|---|
| 200 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-hydroxy-3-methoxy-phenyl)-ethyl]-oxalamide |  |
| 201 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-hydroxy-4-methoxy-phenyl)-ethyl]-oxalamide |  |
| 202 | N-(2,4-Dichloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

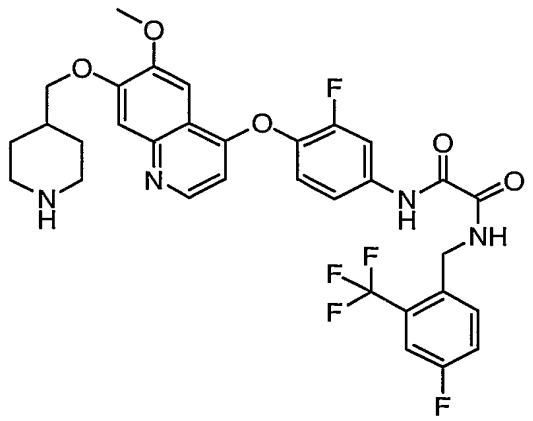
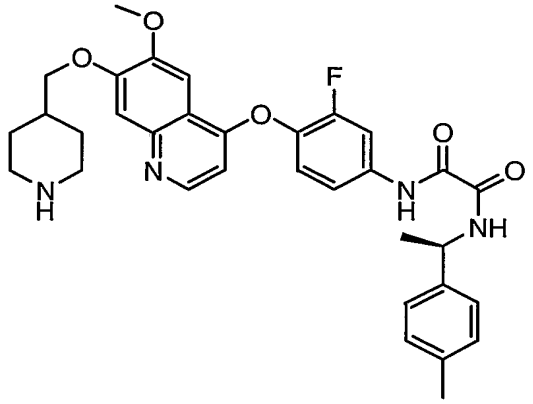
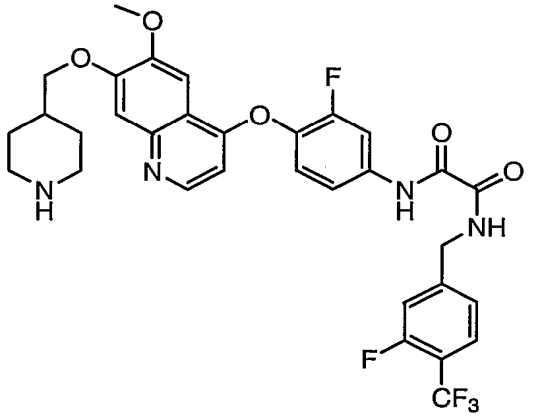
| Entry | Name | Structure |
|---|---|---|
| 203 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-fluoro-2-trifluoromethyl-benzyl)-oxalamide |  |
| 204 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-p-tolyl-ethyl)-oxalamide |  |
| 205 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-4-trifluoromethyl-benzyl)-oxalamide |  |

**Table 1**

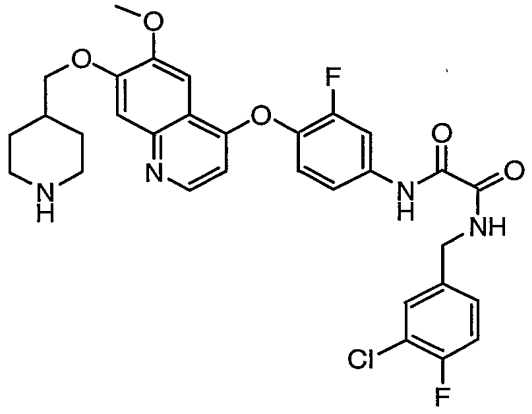
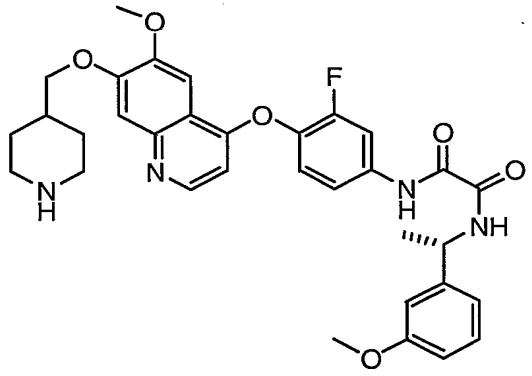
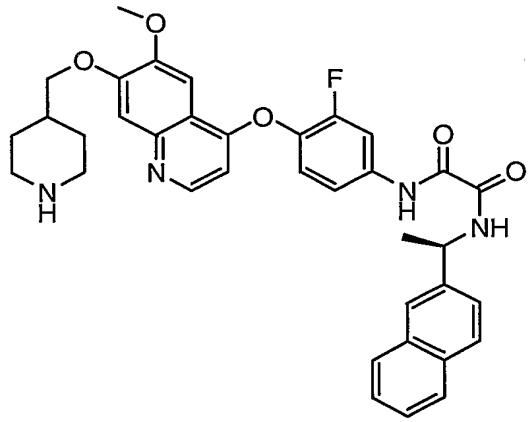
| Entry | Name | Structure |
|---|---|---|
| 206 | N-(3-Chloro-4-fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 207 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[1-(3-methoxy-phenyl)-ethyl]-oxalamide |  |
| 208 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-naphthalen-2-yl-ethyl)-oxalamide |  |

**Table 1**

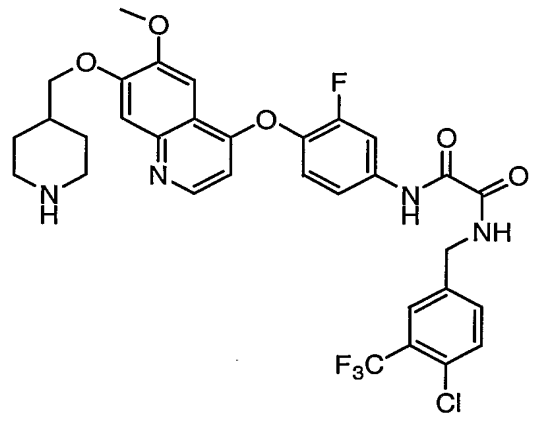
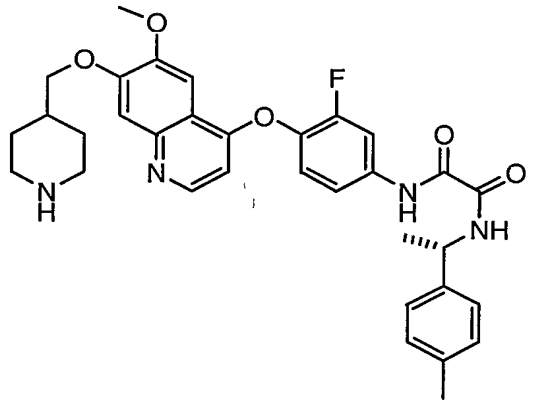
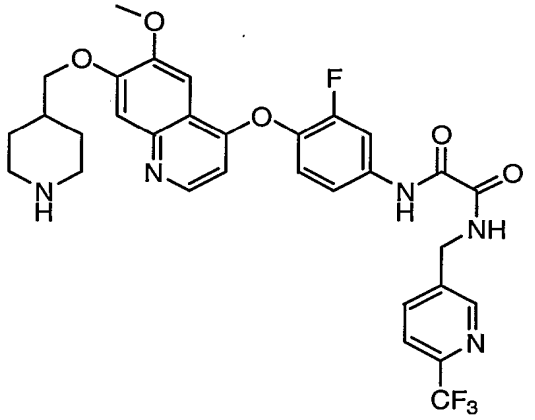
| Entry | Name | Structure |
|---|---|---|
| 209 | N-(4-Chloro-3-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 210 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-p-tolyl-ethyl)-oxalamide |  |
| 211 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(6-trifluoromethyl-pyridin-3-ylmethyl)-oxalamide |  |

**Table 1**

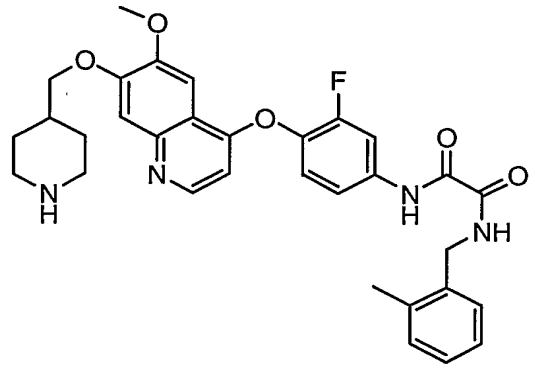
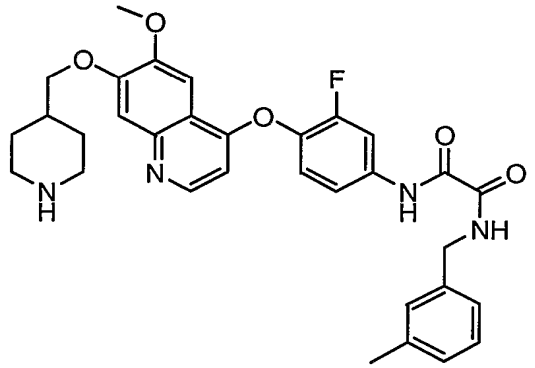
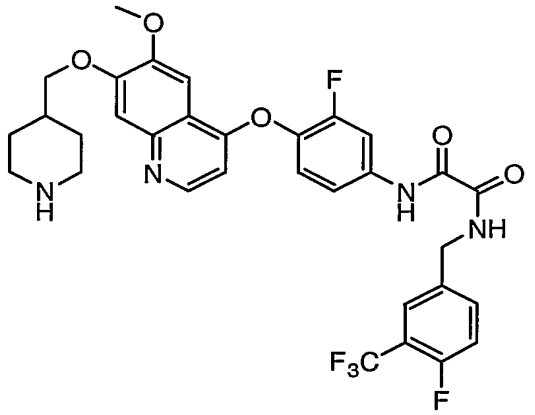
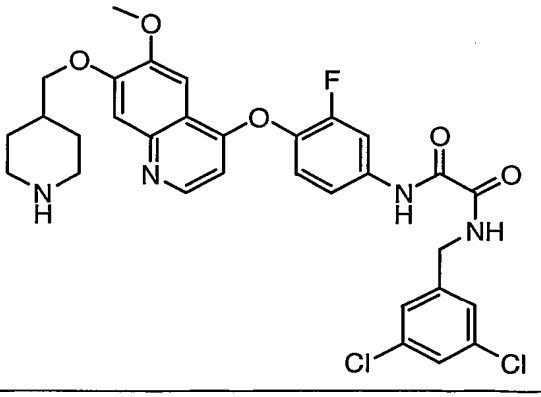
| Entry | Name | Structure |
|---|---|---|
| 212 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methyl-benzyl)-oxalamide |  |
| 213 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-benzyl)-oxalamide |  |
| 214 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-fluoro-3-trifluoromethyl-benzyl)-oxalamide |  |
| 215 | N-(3,5-Dichloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

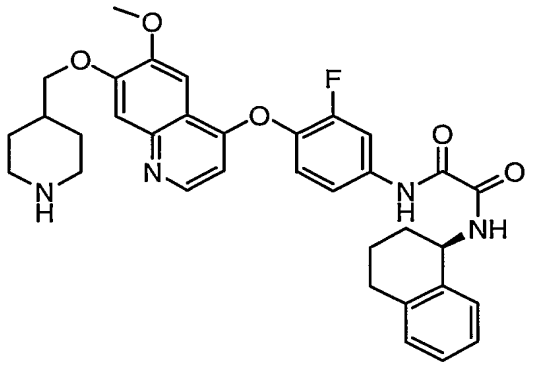
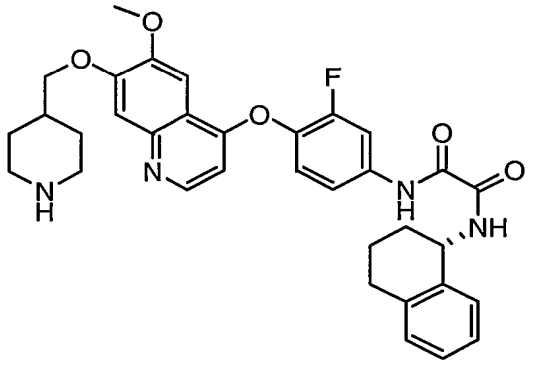
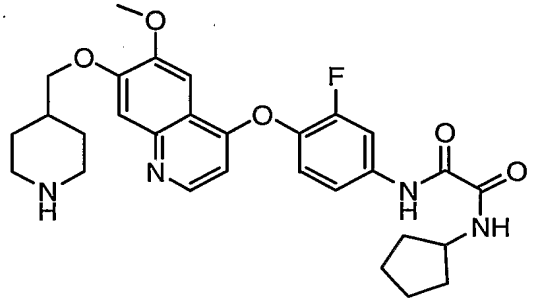
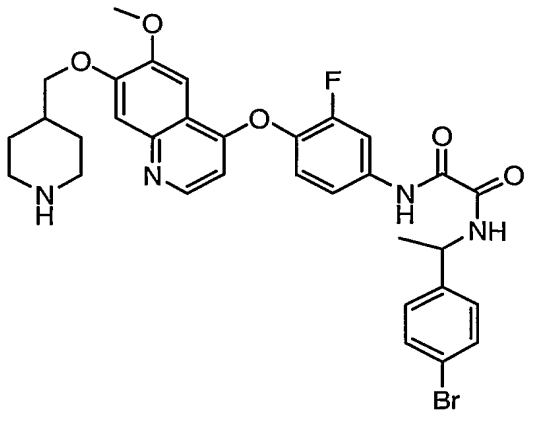
| Entry | Name | Structure |
|---|---|---|
| 216 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R,2,3,4-tetrahydro-naphthalen-1-yl)-oxalamide |  |
| 217 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1S,2,3,4-tetrahydro-naphthalen-1-yl)-oxalamide |  |
| 218 | N-Cyclopentyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 219 | N-[1-(4-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

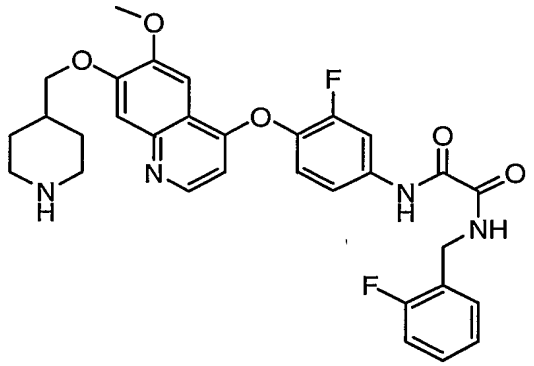
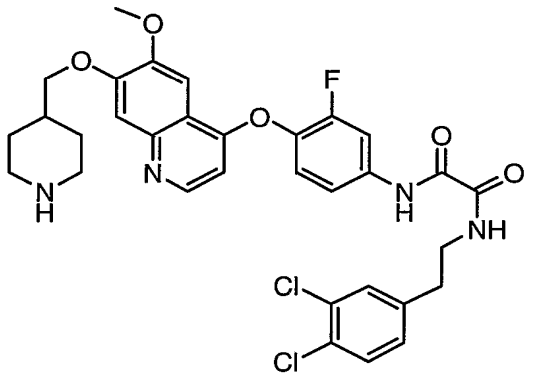
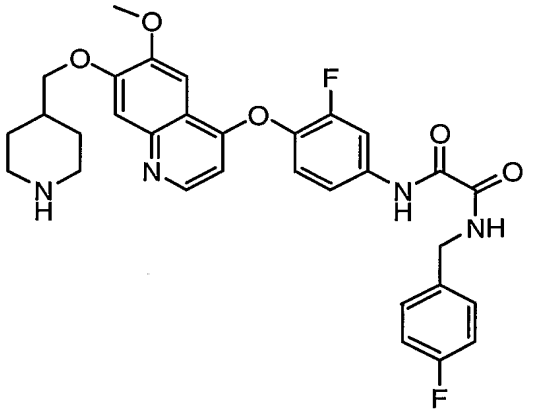
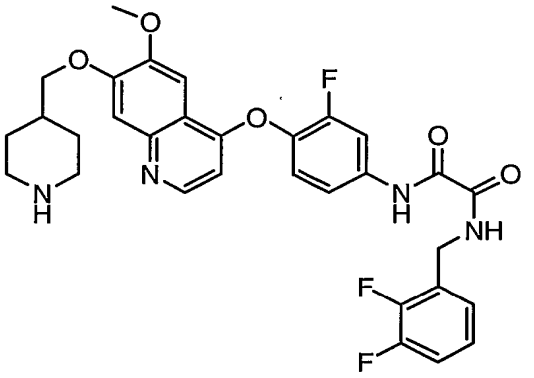
| Entry | Name | Structure |
|---|---|---|
| 220 | N-(2-Fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 221 | N-[2-(3,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 222 | N-(4-Fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 223 | N-(2,3-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

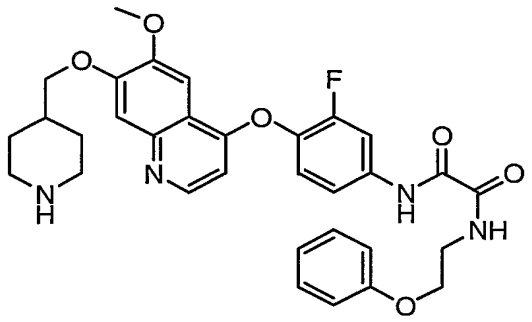
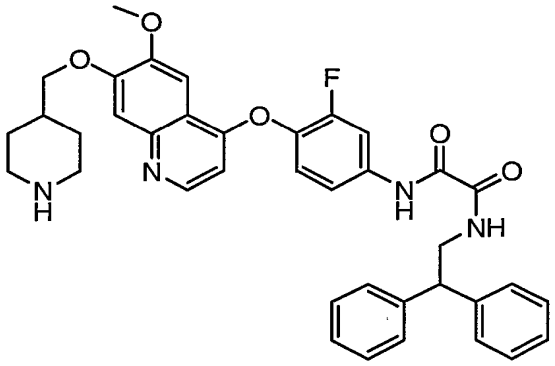
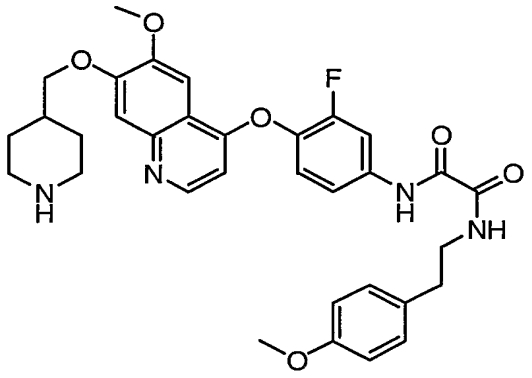
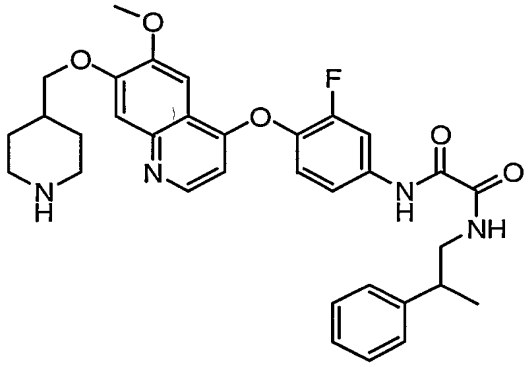
| Entry | Name | Structure |
|---|---|---|
| 224 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenoxy-ethyl)-oxalamide |  |
| 225 | N-(2,2-Diphenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 226 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-methoxy-phenyl)-ethyl]-oxalamide |  |
| 227 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenyl-propyl)-oxalamide |  |

**Table 1**

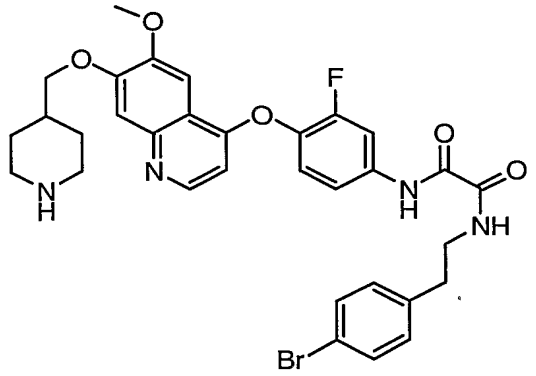
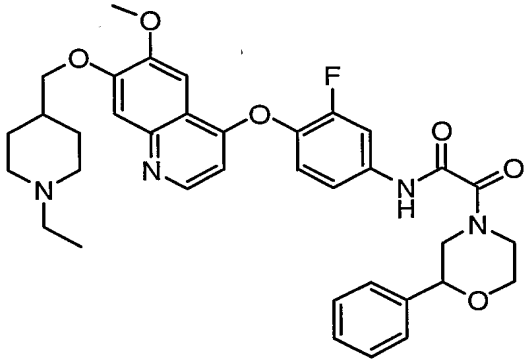
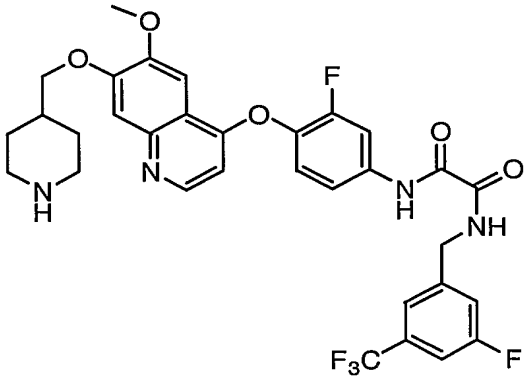
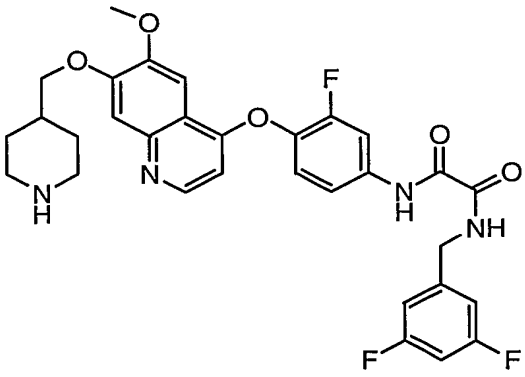
| Entry | Name | Structure |
|---|---|---|
| 228 | N-[2-(4-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 229 | N-{4-[7-(1-Ethyl-piperidin-4-ylmethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-2-oxo-2-(2-phenyl-morpholin-4-yl)-acetamide |  |
| 230 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-5-trifluoromethyl-benzyl)-oxalamide |  |
| 231 | N-(3,5-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

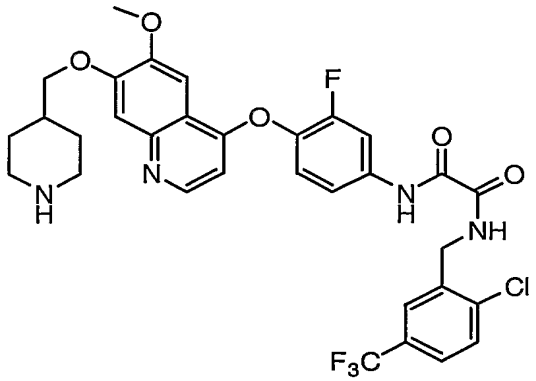
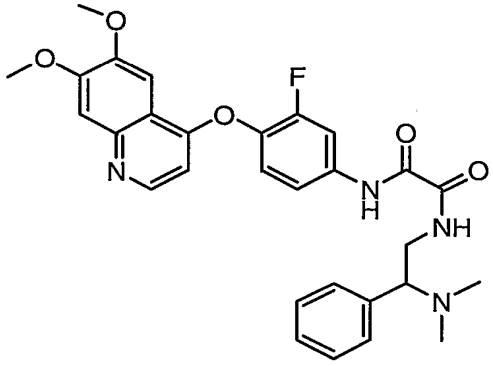
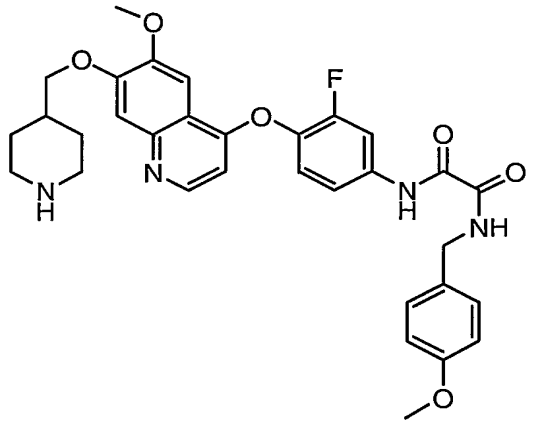
| Entry | Name | Structure |
|---|---|---|
| 232 | N-(2-Chloro-5-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 233 | N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-dimethylamino-2-phenyl-ethyl)-oxalamide |  |
| 234 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-methoxy-benzyl)-oxalamide |  |

**Table 1**

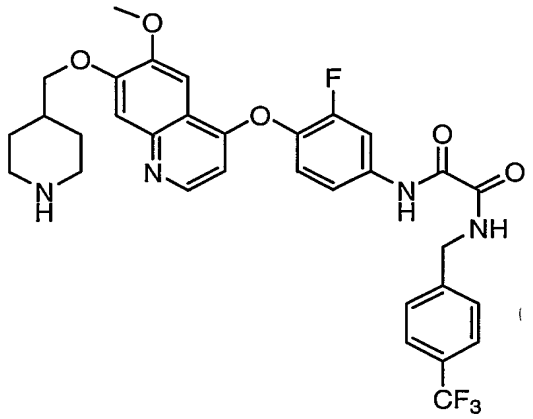
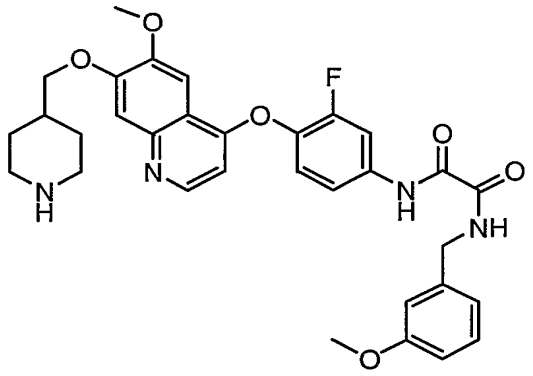
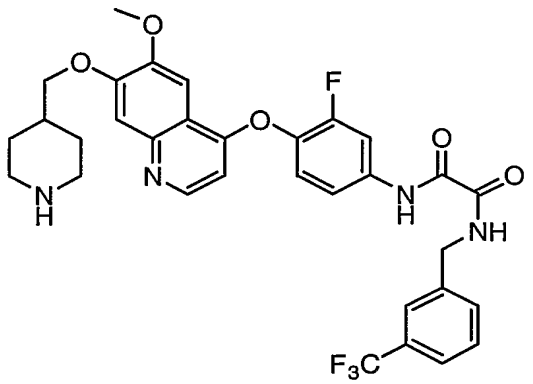
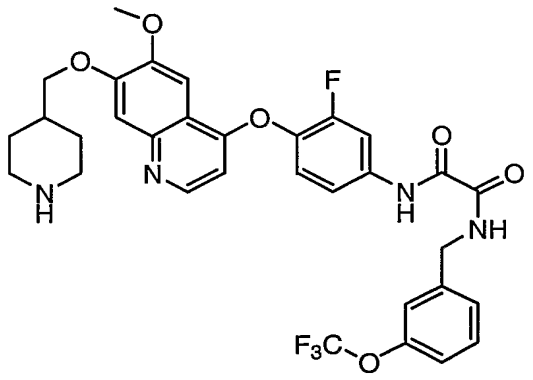
| Entry | Name | Structure |
|---|---|---|
| 235 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethyl-benzyl)-oxalamide |  |
| 236 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methoxy-benzyl)-oxalamide |  |
| 237 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-trifluoromethyl-benzyl)-oxalamide |  |
| 238 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-trifluoromethoxy-benzyl)-oxalamide |  |

**Table 1**

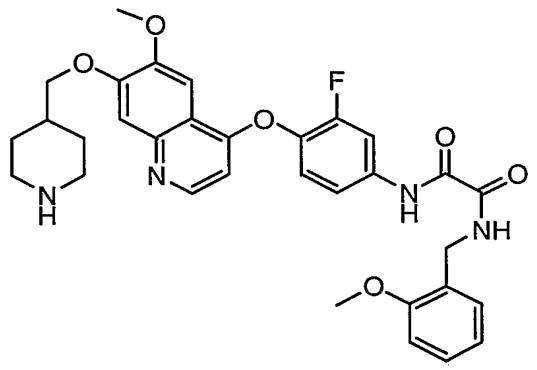
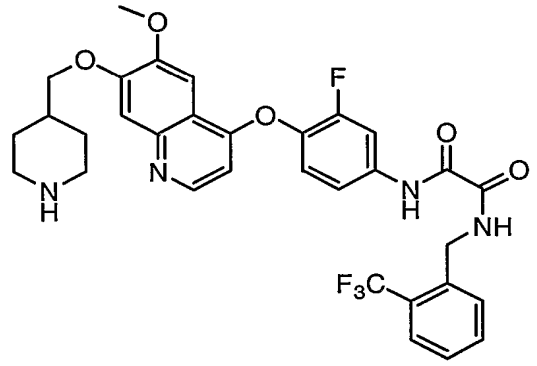
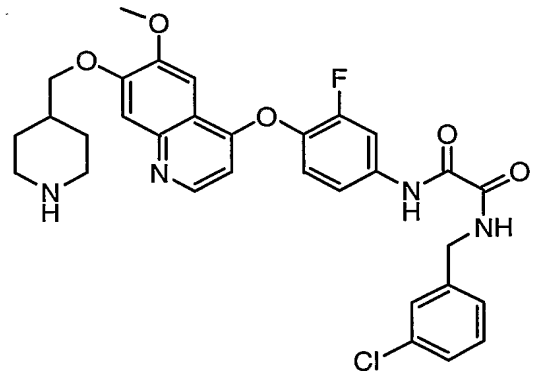
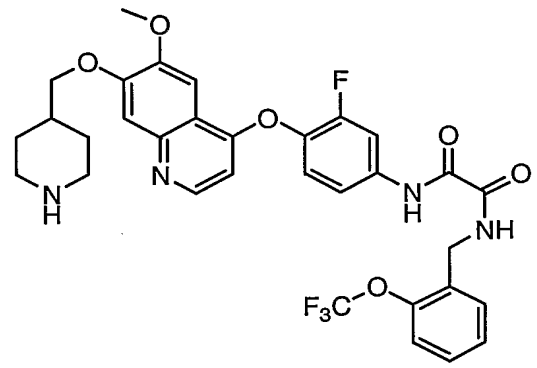
| Entry | Name | Structure |
|---|---|---|
| 239 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methoxy-benzyl)-oxalamide |  |
| 240 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-trifluoromethyl-benzyl)-oxalamide |  |
| 241 | N-(3-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 242 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-trifluoromethoxy-benzyl)-oxalamide |  |

**Table 1**

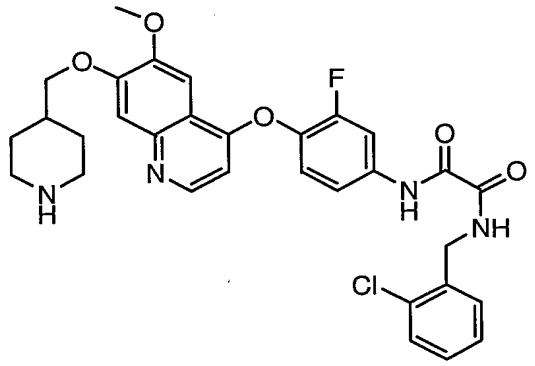
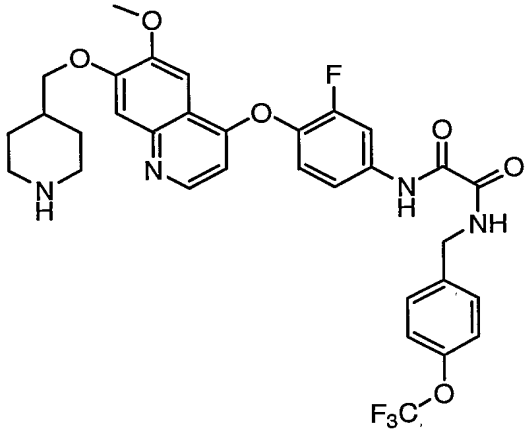
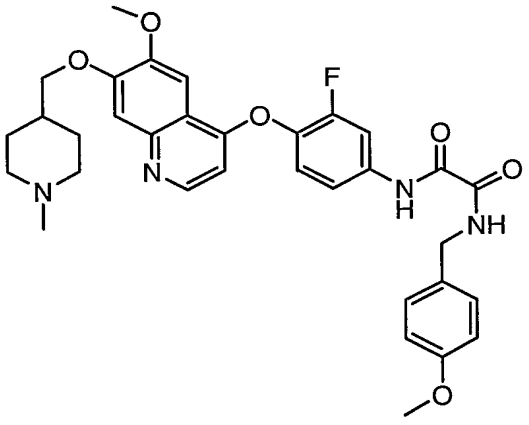
| Entry | Name | Structure |
|---|---|---|
| 243 | N-(2-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 244 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethoxy-benzyl)-oxalamide |  |
| 245 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-methoxy-benzyl)-oxalamide |  |

**Table 1**

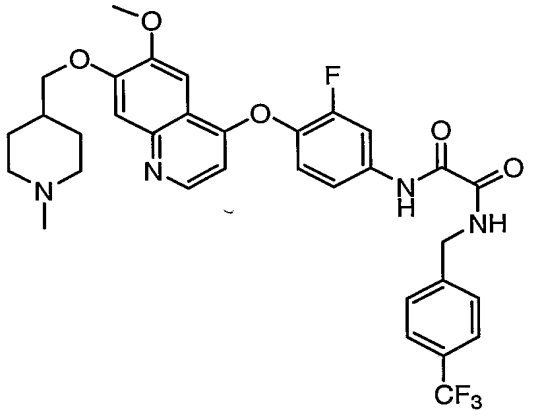
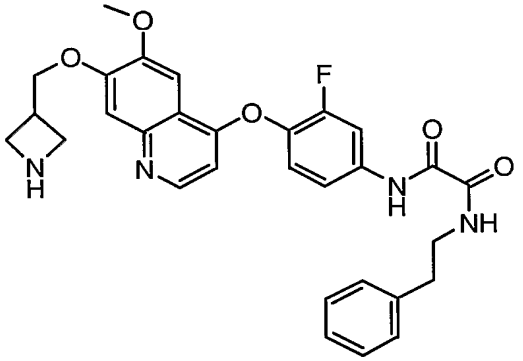
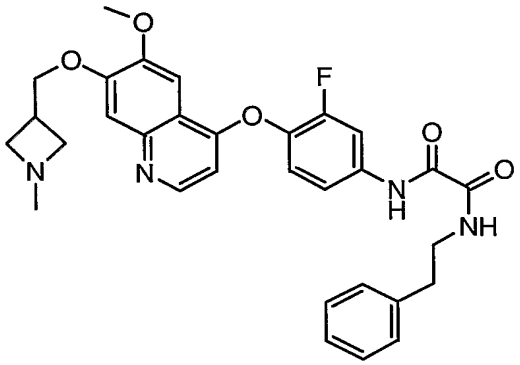
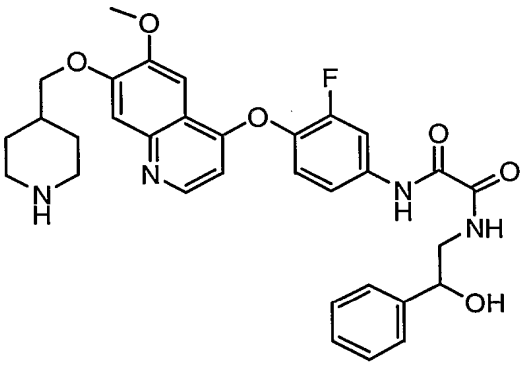
| Entry | Name | Structure |
|---|---|---|
| 246 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethyl-benzyl)-oxalamide |  |
| 247 | N-{4-[7-(Azetidin-3-ylmethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide |  |
| 248 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-azetidin-3-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide |  |
| 249 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-hydroxy-2-phenyl-ethyl)-oxalamide |  |

**Table 1**

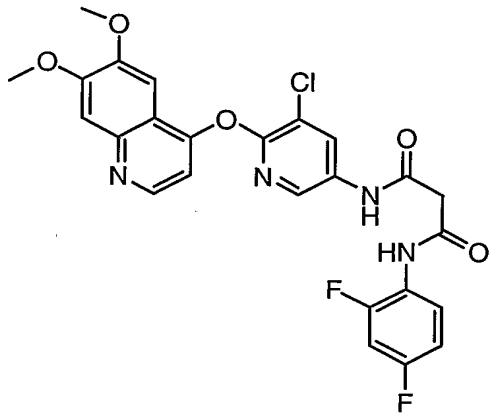
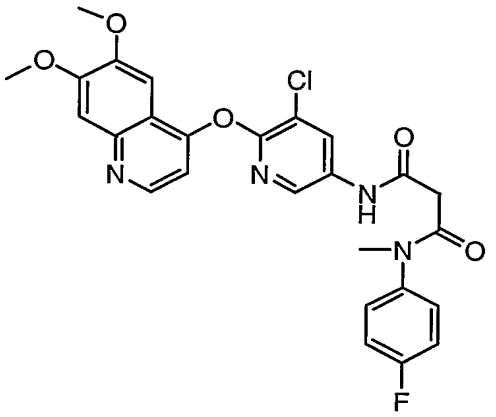
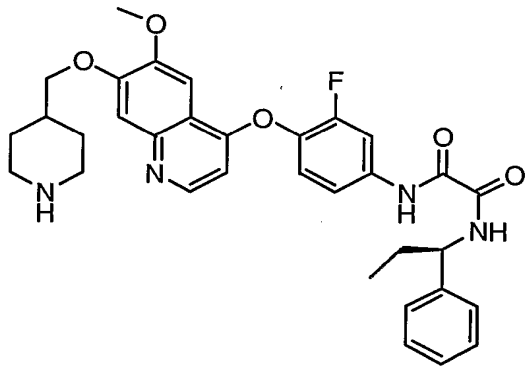
| Entry | Name | Structure |
|---|---|---|
| 250 | N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(2,4-difluoro-phenyl)-malonamide |  |
| 251 | N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(4-fluoro-phenyl)-N'-methyl-malonamide |  |
| 252 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R-phenyl-propyl)-oxalamide |  |

**Table 1**

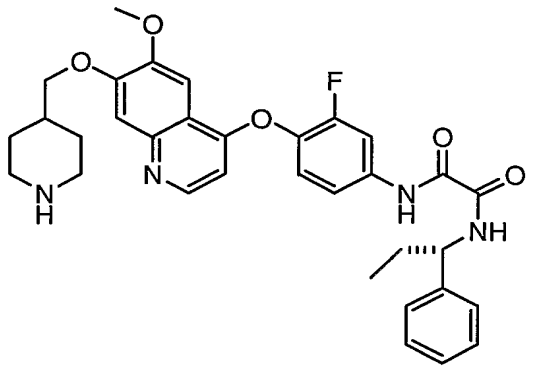
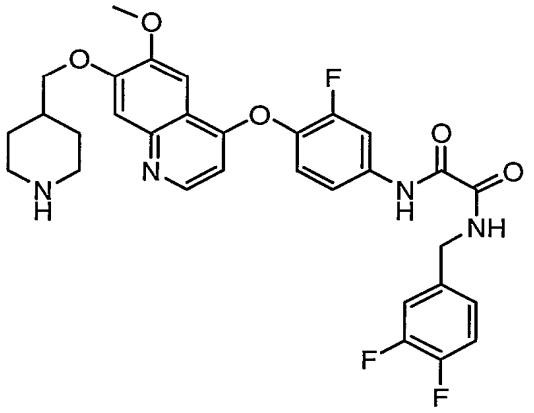
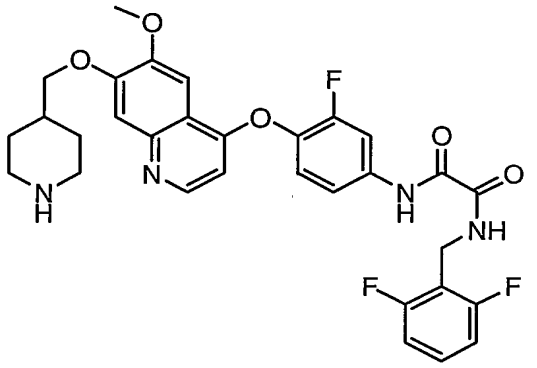
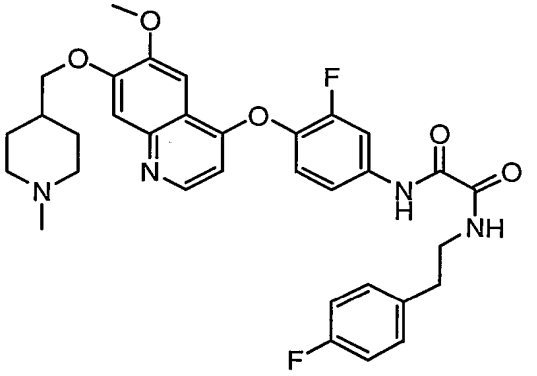
| Entry | Name | Structure |
|---|---|---|
| 253 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R-phenyl-propyl)-oxalamide |  |
| 254 | N-(3,4-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 255 | N-(2,6-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 256 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-fluoro-phenyl)-ethyl]-oxalamide |  |

**Table 1**

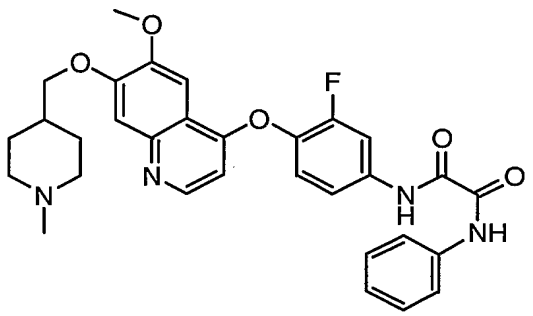
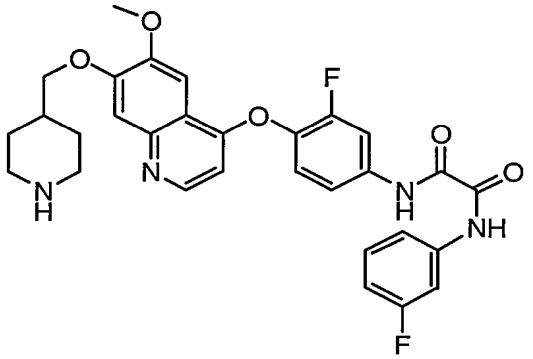
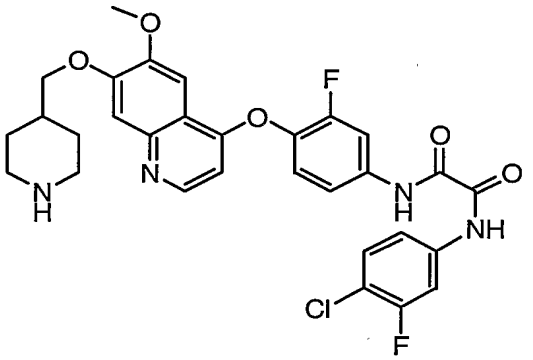
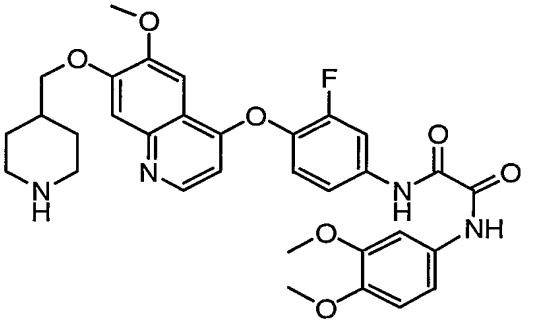
| Entry | Name | Structure |
|---|---|---|
| 257 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenyl-oxalamide |  |
| 258 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-phenyl)-oxalamide |  |
| 259 | N-(4-Chloro-3-fluoro-phenyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 260 | N-(3,4-Dimethoxy-phenyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

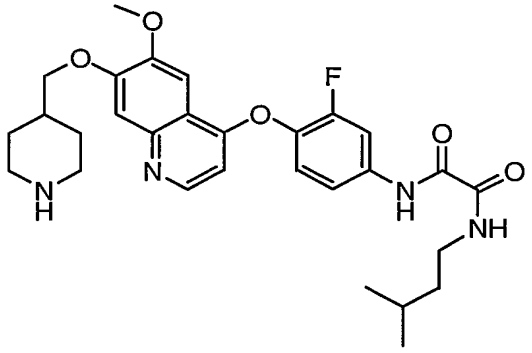
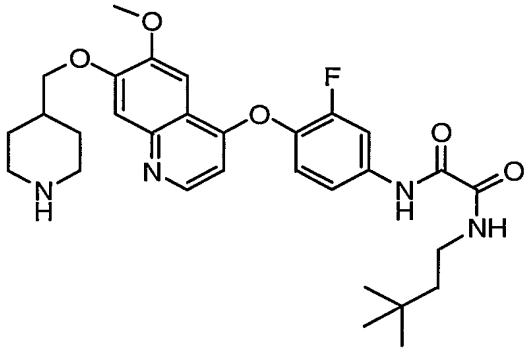
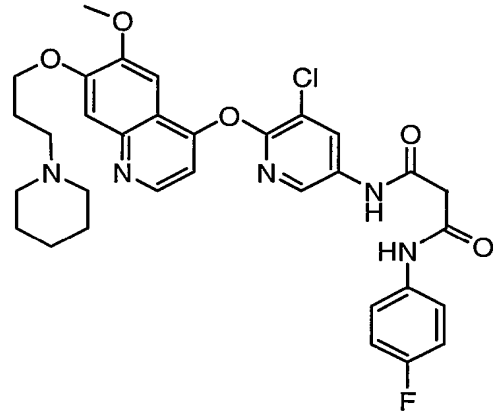
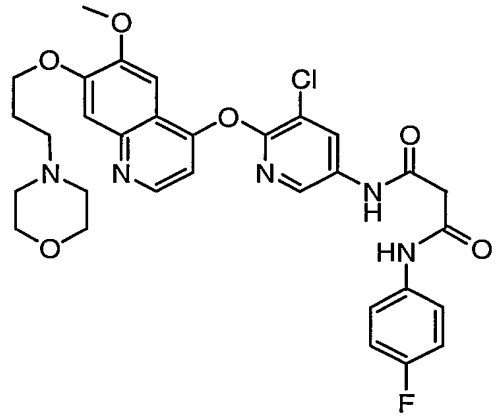
| Entry | Name | Structure |
|---|---|---|
| 261 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-butyl)-oxalamide |  |
| 262 | N-(3,3-Dimethyl-butyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 263 | N-{5-Chloro-6-[6-methoxy-7-(3-piperidin-1-yl-propoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide |  |
| 264 | N-{5-Chloro-6-[6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide |  |

**Table 1**

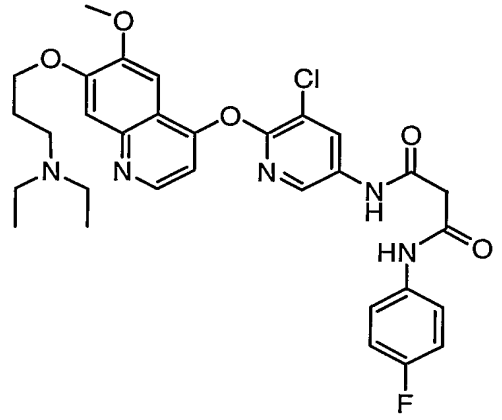
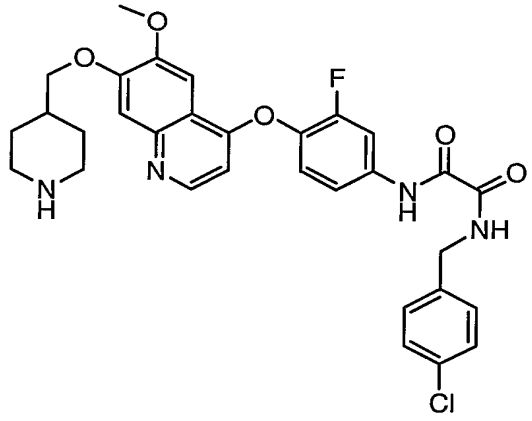
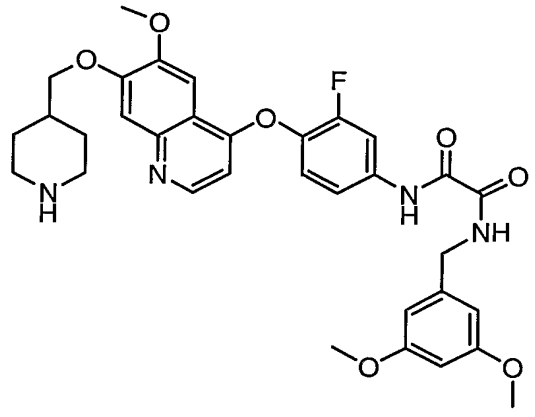
| Entry | Name | Structure |
|---|---|---|
| 265 | N-{5-Chloro-6-[7-(3-diethylamino-propoxy)-6-methoxy-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide |  |
| 266 | N-(4-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 267 | N-(3,5-Dimethoxy-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

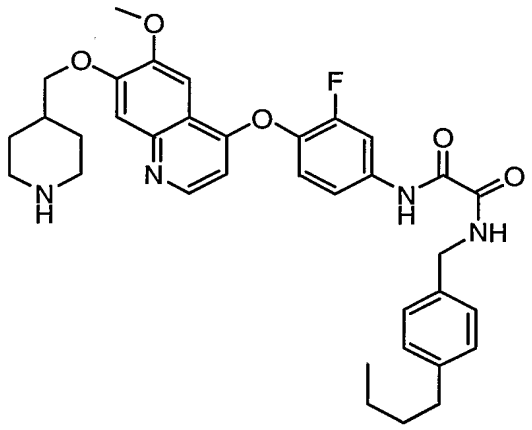
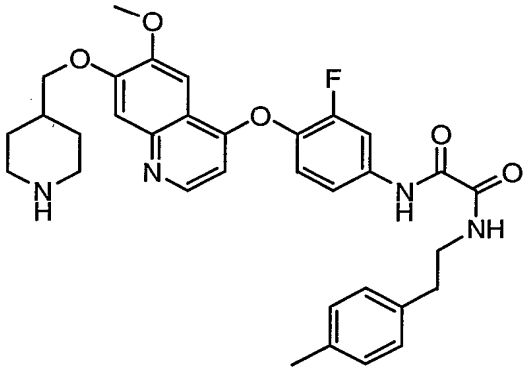
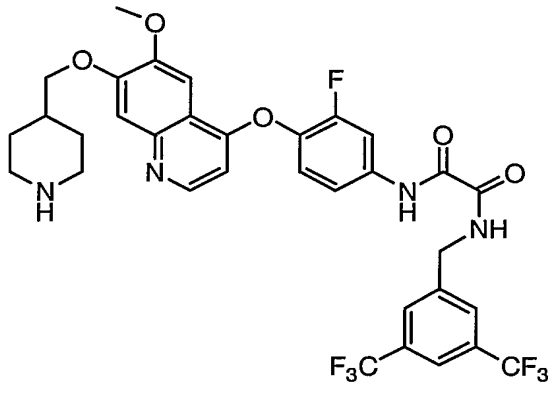
| Entry | Name | Structure |
|---|---|---|
| 268 | N-(4-Butyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 269 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-p-tolyl-ethyl)-oxalamide |  |
| 270 | N-(3,5-Bis-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

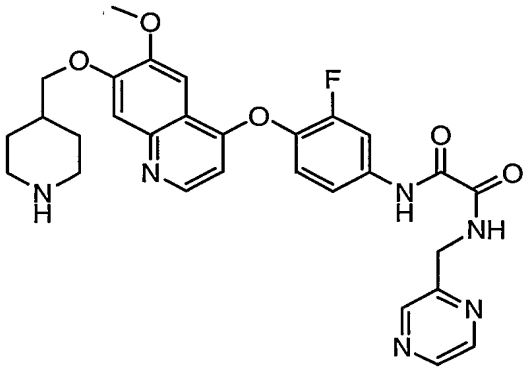
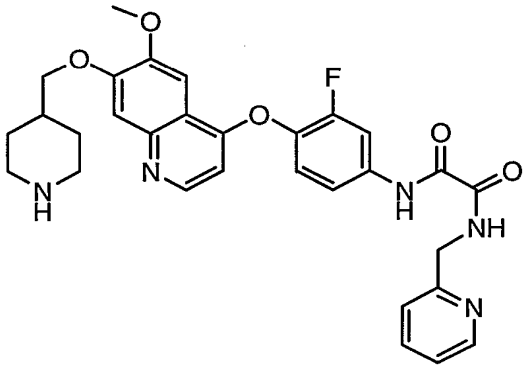
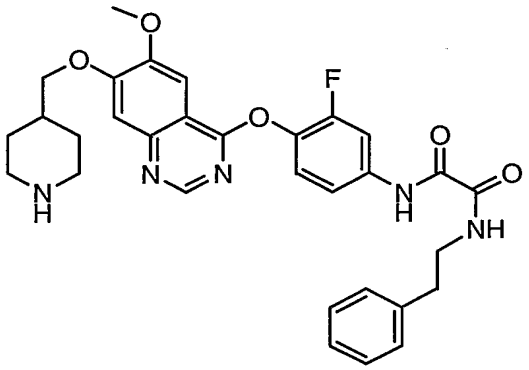
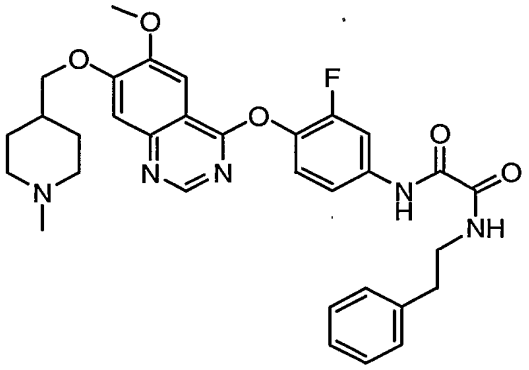
| Entry | Name | Structure |
|---|---|---|
| 271 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-pyrazin-2-ylmethyl-oxalamide |  |
| 272 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-pyridin-2-ylmethyl-oxalamide |  |
| 273 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide |  |
| 274 | N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide |  |

**Table 1**

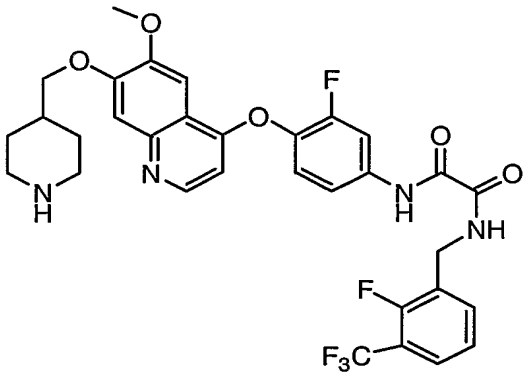
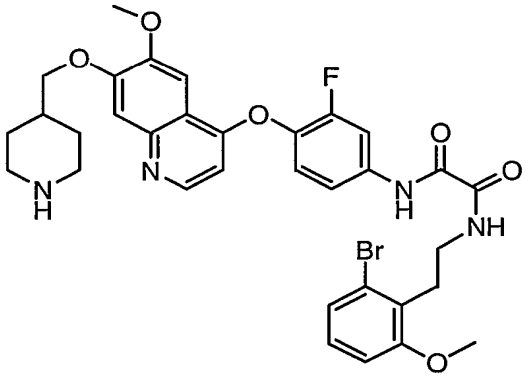
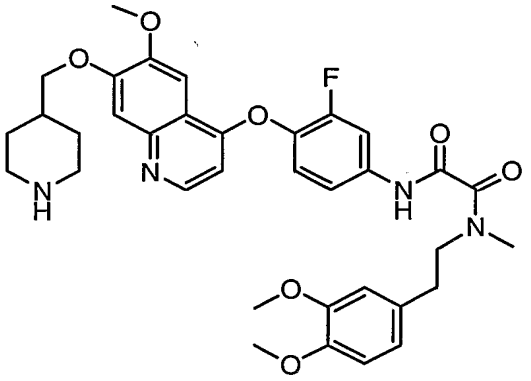
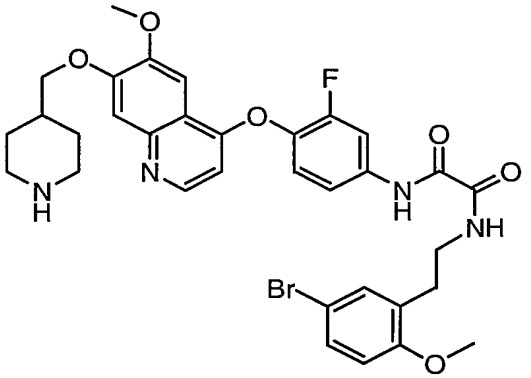
| Entry | Name | Structure |
|---|---|---|
| 275 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-fluoro-3-trifluoromethyl-benzyl)-oxalamide |  |
| 276 | N-[2-(2-Bromo-6-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 277 | N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N-methyl-oxalamide |  |
| 278 | N-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

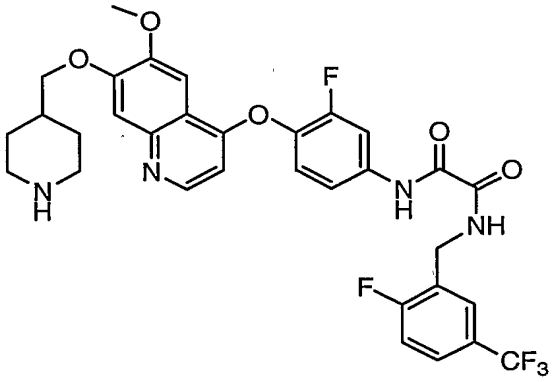
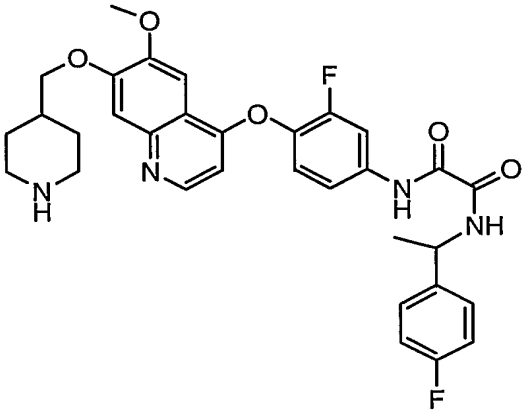
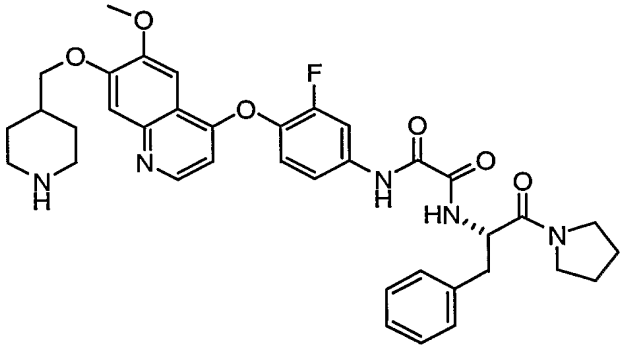
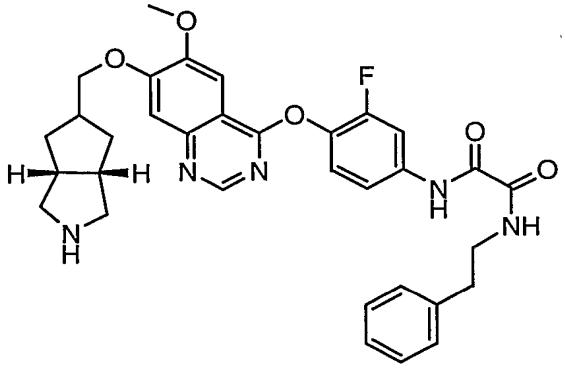
| Entry | Name | Structure |
|---|---|---|
| 279 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-fluoro-5-trifluoromethyl-benzyl)-oxalamide |  |
| 280 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[1-(4-fluoro-phenyl)-ethyl]-oxalamide |  |
| 281 | N-(1S-Benzyl-2-oxo-2-pyrrolidin-1-yl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 282 | N-{3-Fluoro-4-[6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide |  |

**Table 1**

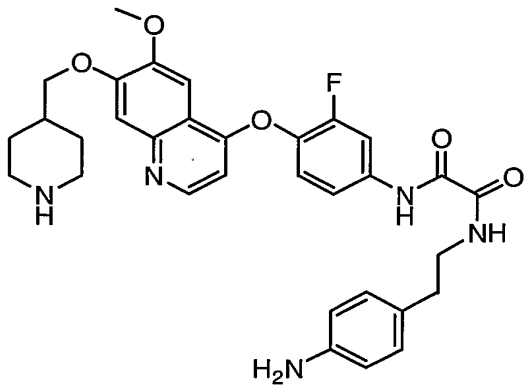
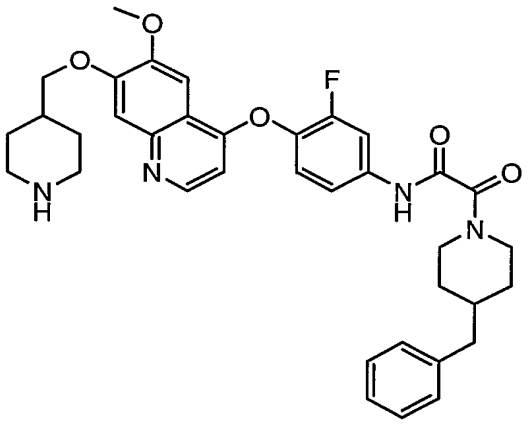
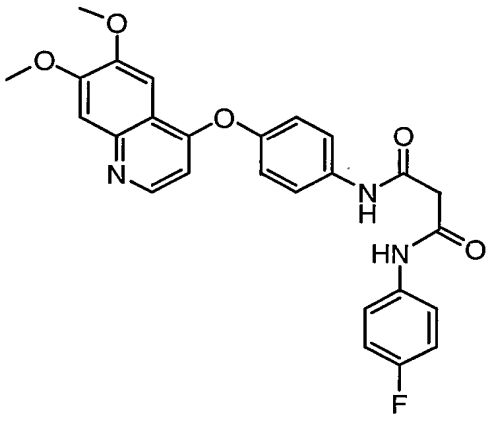
| Entry | Name | Structure |
|---|---|---|
| 283 | N-[2-(4-Amino-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 284 | 2-(4-Benzyl-piperidin-1-yl)-N-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-acetamide |  |
| 285 | N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenyl]-N'-(4-fluoro-phenyl)-malonamide |  |

**Table 1**

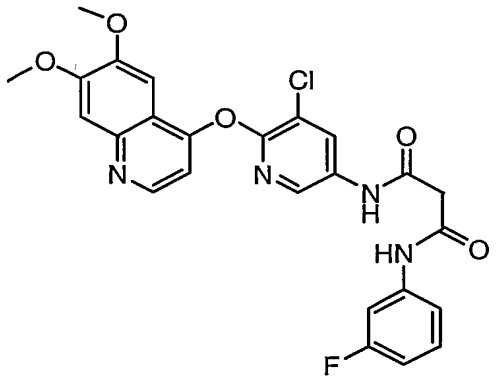
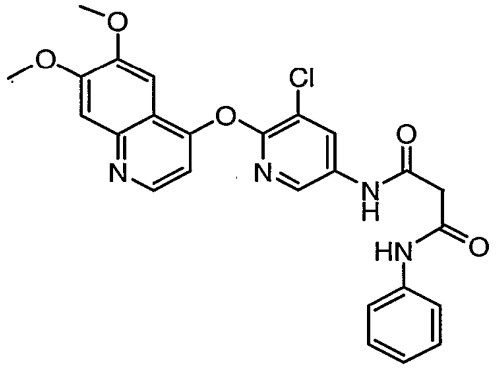
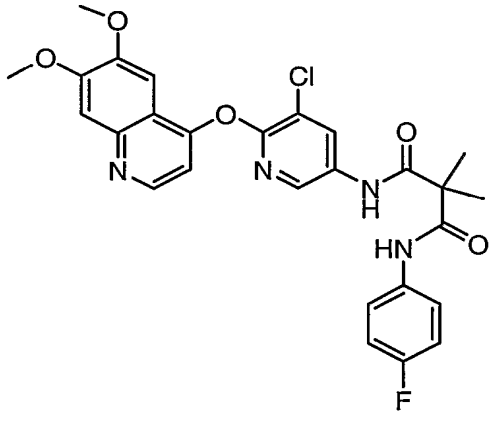
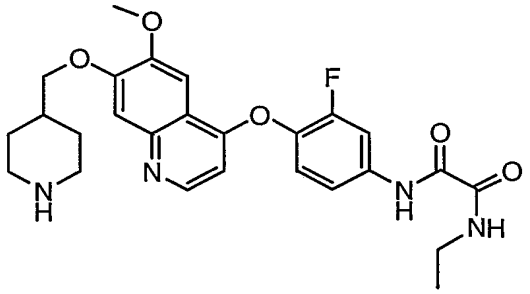
| Entry | Name | Structure |
|---|---|---|
| 286 | N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(3-fluoro-phenyl)-malonamide |  |
| 287 | N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-phenyl-malonamide |  |
| 288 | N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(4-fluoro-phenyl)-2,2-dimethyl-malonamide |  |
| 289 | N-Ethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |

**Table 1**

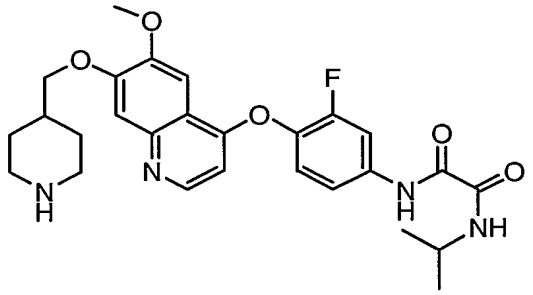
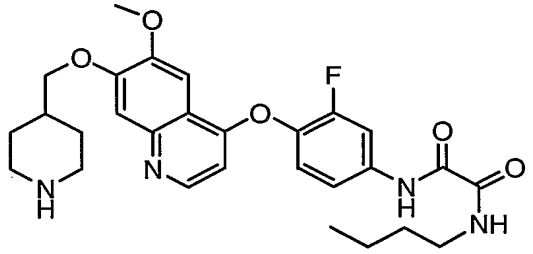
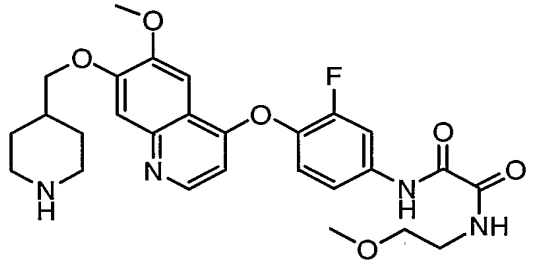
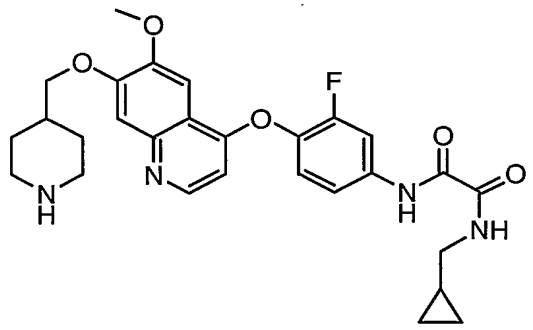
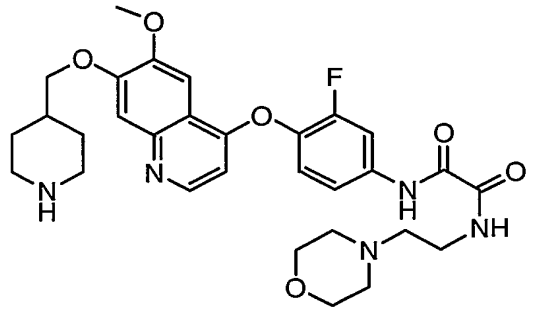
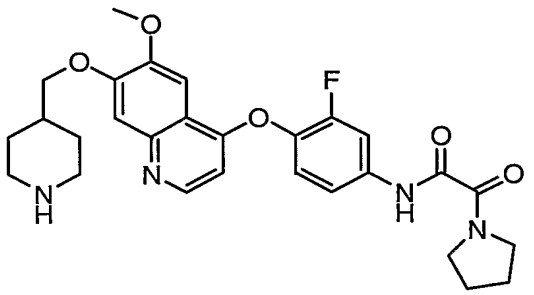
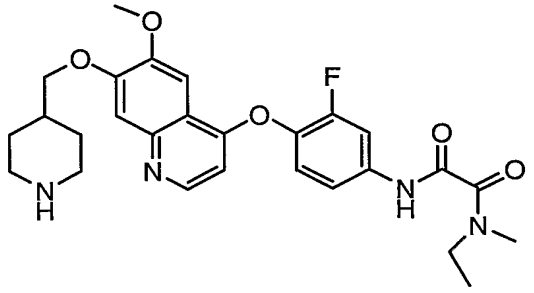
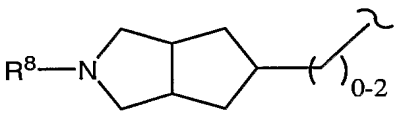
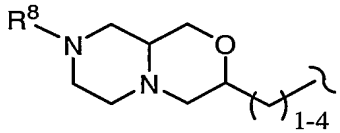
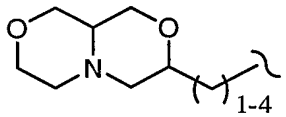
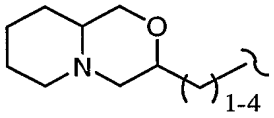
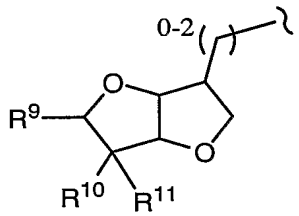
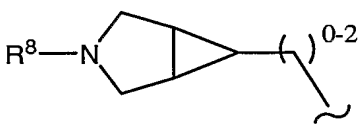
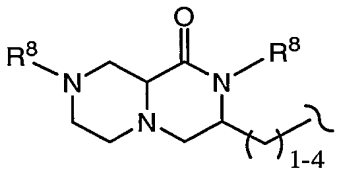
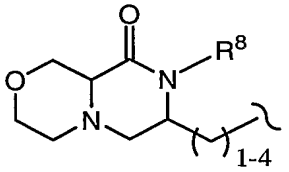
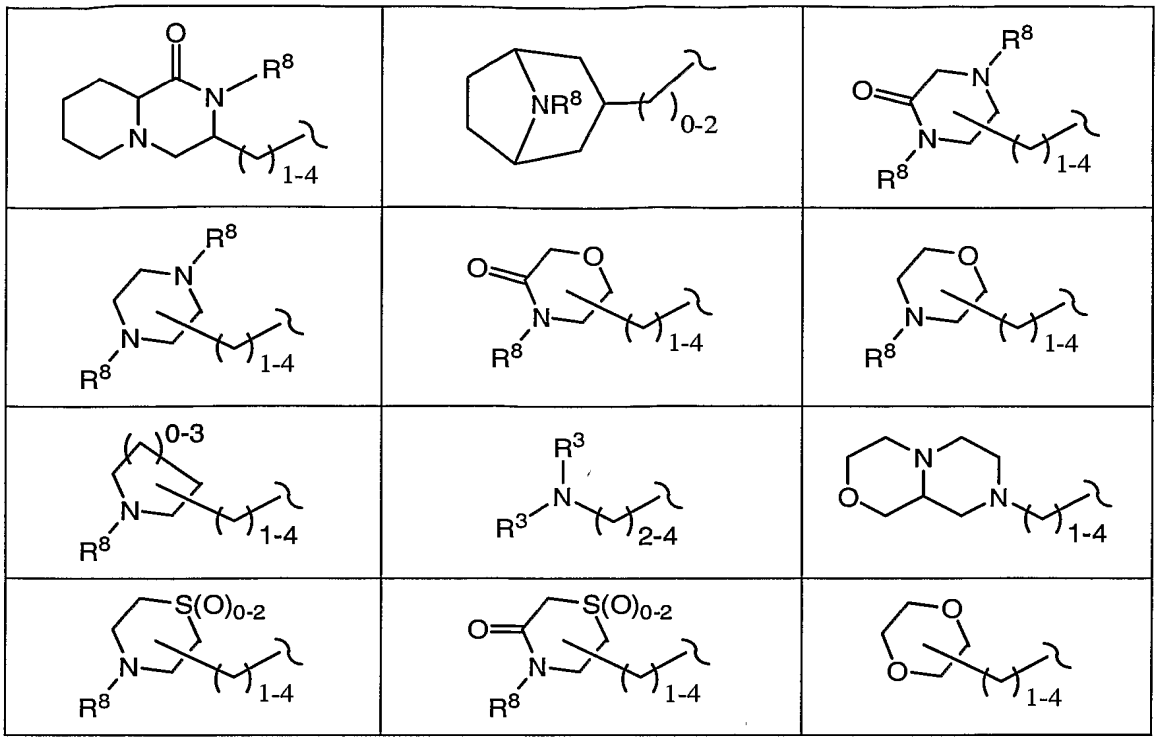
| Entry | Name | Structure |
|---|---|---|
| 290 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-isopropyl-oxalamide |  |
| 291 | N-Butyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 292 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methoxy-ethyl)-oxalamide |  |
| 293 | N-Cyclopropylmethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide |  |
| 294 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-morpholin-4-yl-ethyl)-oxalamide |  |

**Table 1**

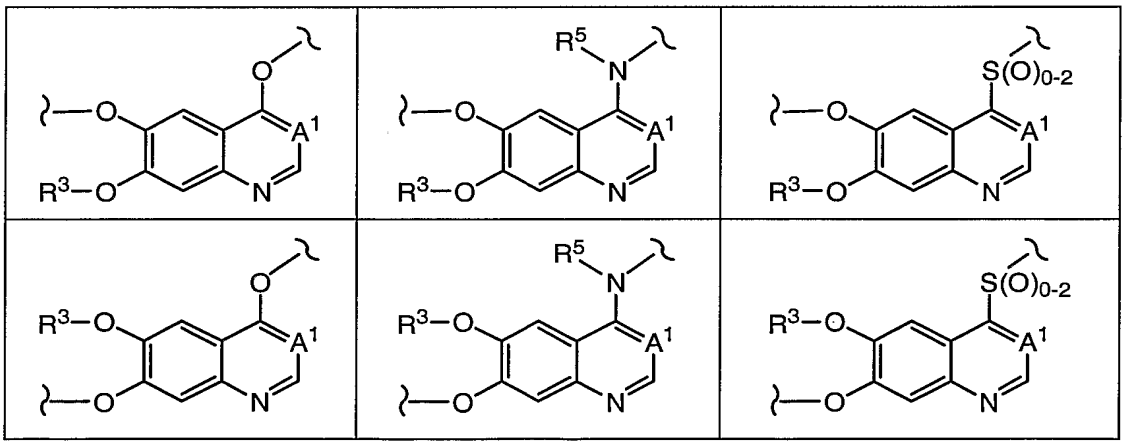
| Entry | Name | Structure |
|---|---|---|
| 295 | N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-pyrrolidin-1-yl-acetamide |  |
| 296 | N-Ethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N-methyl-oxalamide |  |

46. A compound for modulating kinase activity of formula A-B-C, or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein, A is selected from:

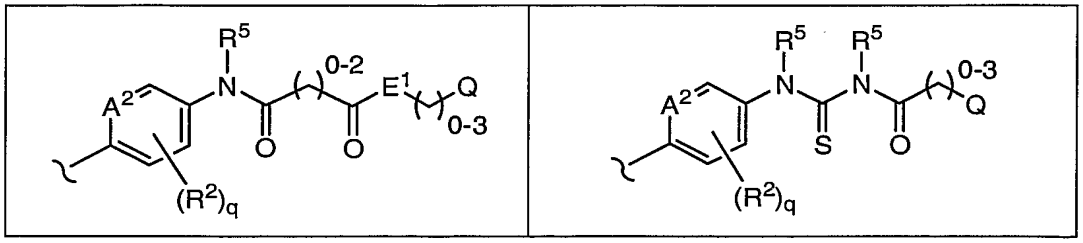
| | | |
|---|---|---|
| $-R^3$ |  |  |
|  |  |  |
|  |  |  |

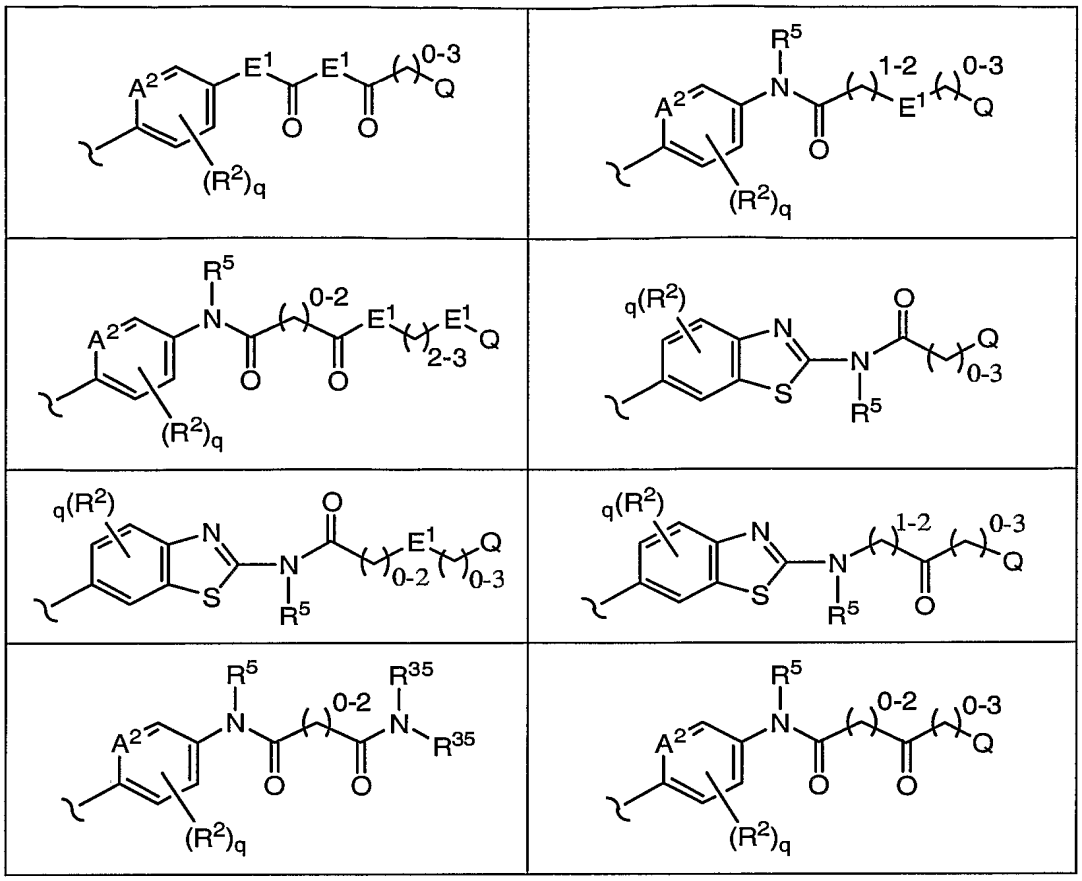


B is selected from:



and, C is selected from:





wherein $R^2$ is selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

q is 0 to 2;

each $R^3$ is independently selected from –H, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted arylalkyl, and optionally substituted heteroarylalkyl;

two $R^3$, together with the nitrogen to which they are attached, form a four- to seven-membered heteroalicyclic, said four- to seven-membered heteroalicyclic optionally containing one additional heteroatom; when one said additional heteroatom is a nitrogen, then said nitrogen is optionally substituted with a group selected from -H, trihalomethyl, $-SO_2R^5$, $-SO_2NR^5R^5$, $-CO_2R^5$, $-C(O)NR^5R^5$, $-C(O)R^5$, and optionally substituted lower alkyl;

each $R^{35}$ is independently selected from -H, $-C(=O)R^3$, $-C(=O)OR^3$, $-C(=O)SR^3$, $-SO_2R^3$, $-C(=O)N(R^3)R^3$, and optionally substituted lower alkyl;

two $R^{35}$, together with the nitrogen to which they are attached, can combine to form a heteroalicyclic optionally substituted with between one and four of $R^{60}$, said heteroalicyclic may have an additional annular heteroatom, and said heteroalicyclic may have an aryl fused thereto, said aryl optionally substituted with an additional one to four of $R^{60}$;

$A^1$ is selected from =N-, =C(H)-, and =C(CN)-;

$A^2$ is either =N- or =C(H)-;

$R^5$ is -H or optionally substituted lower alkyl;

$R^8$ is selected from $R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$;

$R^9$, $R^{10}$, and $R^{11}$ are each independently selected from -H, and $-OR^{12}$; or

$R^9$ is selected from -H, and $-OR^{12}$, and $R^{10}$ and $R^{11}$, when taken together, are either an optionally substituted alkylidene or an oxo; and

$R^{12}$ is selected from -H, $-C(O)R^3$, optionally substituted lower alkylidyne, optionally substituted lower arylalkylidyne, optionally substituted lower heterocyclylalkylidyne, optionally substituted lower alkylidene, optionally substituted lower alkylidenearyl, optionally substituted lower alkylideneheterocyclyl, optionally substituted lower alkyl, optionally substituted lower alkylaryl, optionally substituted aryl, optionally substituted lower heterocyclylalkyl, and optionally substituted heterocyclyl;

or two $R^{12}$'s, when taken together, form 1) a corresponding spirocyclic ketal when said two $R^{12}$'s stem from $R^{10}$ and $R^{11}$, or 2) a corresponding cyclic ketal when said two $R^{12}$'s stem from $R^9$ and one of $R^{10}$ and $R^{11}$;

$E^1$ is selected from -O-, $-CH_2-$, $-N(R^5)-$, and $-S(O)_{0-2}-$;

Q is a five- to ten-membered ring system, optionally substituted with between zero and four of $R^{20}$;

$R^{20}$ is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

$R^{60}$ is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$,

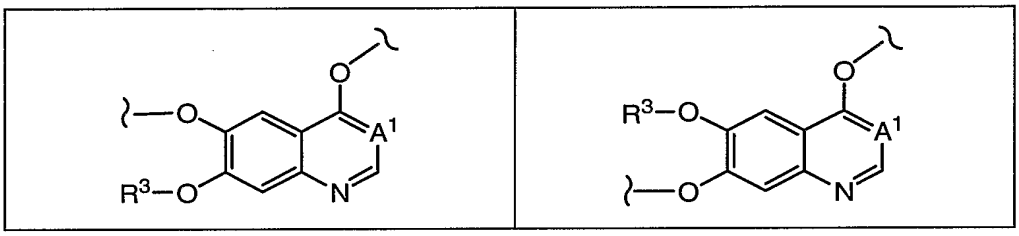
$-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroarylalkyl, and optionally substituted arylalkyl;

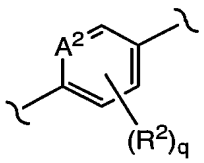
two of $R^{60}$, when attached to a non-aromatic carbon, can be oxo;

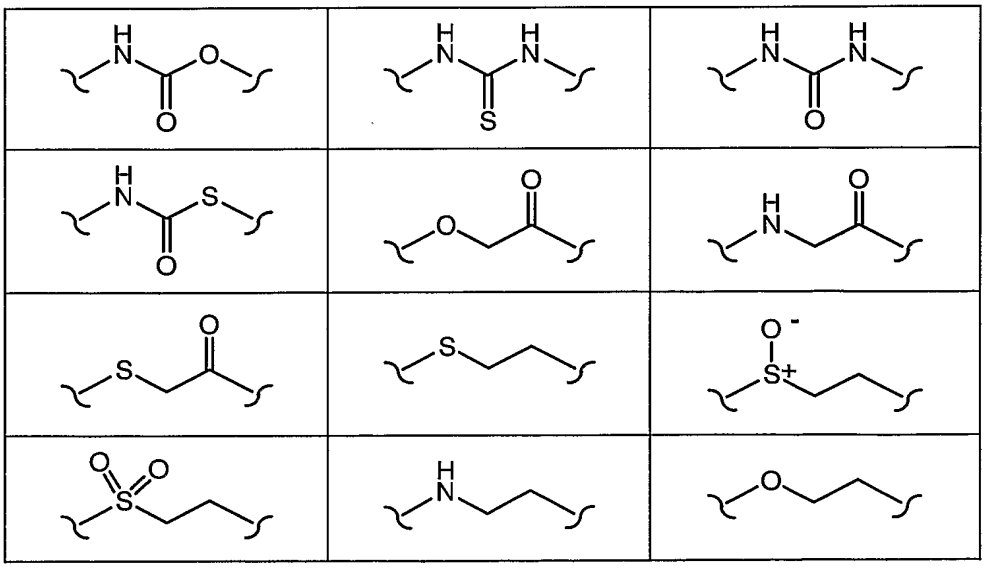
each methylene in any of the above formulae is independently optionally substituted with $R^{25}$;

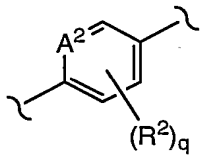
each $R^{25}$ is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; two of $R^{25}$, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic, two of $R^{25}$ on a single carbon can be oxo;

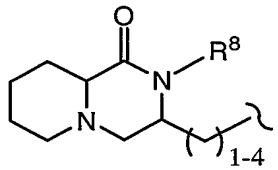
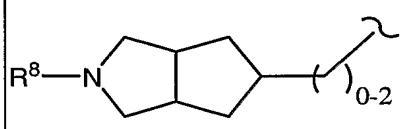
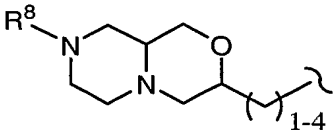
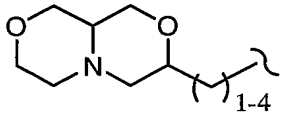
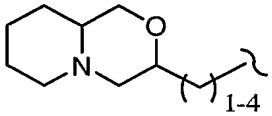
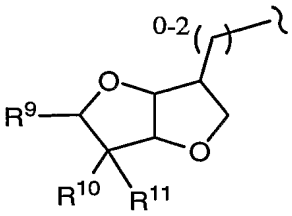
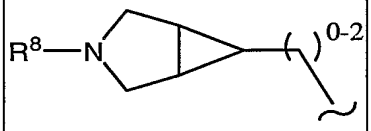
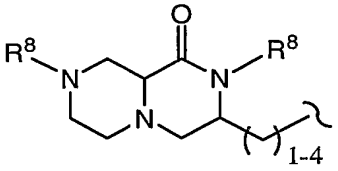
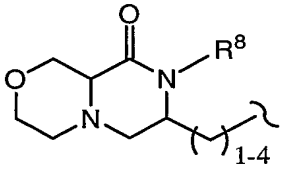
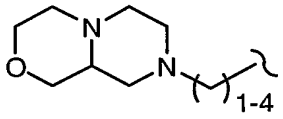
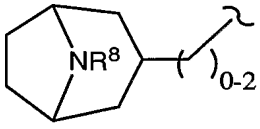
with the proviso that when B is selected from:

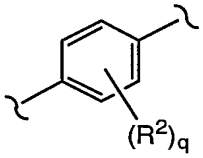


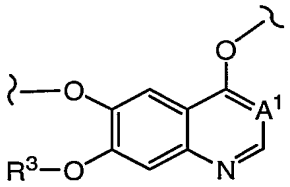
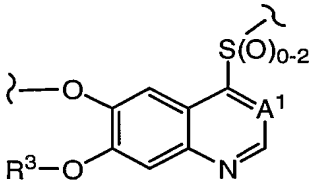
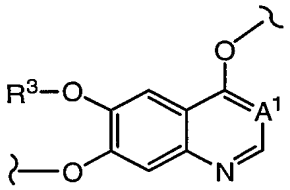
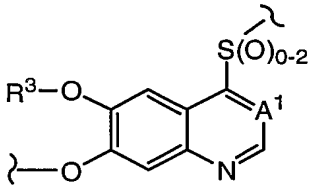
and C contains  , and the remaining portion of C contains one of:

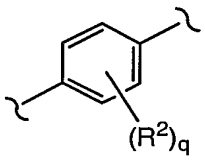
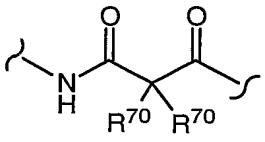


directly attached to  , then A must be one of:

| | | |
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|  |  |  |
|  |  | |

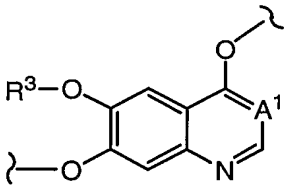
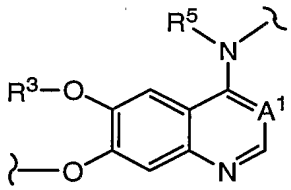
and with the proviso that when C contains  , and B is selected from:

| | |
|---|---|
|  |  |
|  |  |

then the portion of C directly attached to  cannot contain  , when $R^{70}$ is selected from -H, $C_{1-4}$alkyl, and $C_{1-4}$alkoxyl.

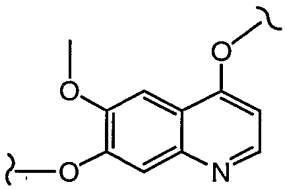
47. The compound according to claim 46, wherein Q is selected from phenyl, napthyl, 1,2,3,4-tetrahydronaphthyl, indanyl, benzodioxanyl, benzofuranyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroisoquinolyl, pyrrolyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, tetrahydropyridinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxazolidinyl, triazolyl, isoxazolyl, isoxazolidinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, benzothieliyl, and oxadiazolyl; each optionally substituted with between one and four of $R^{20}$; wherein each $R^{20}$ is independently selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl.

48. The compound according to claim 47, wherein B is either of the following:

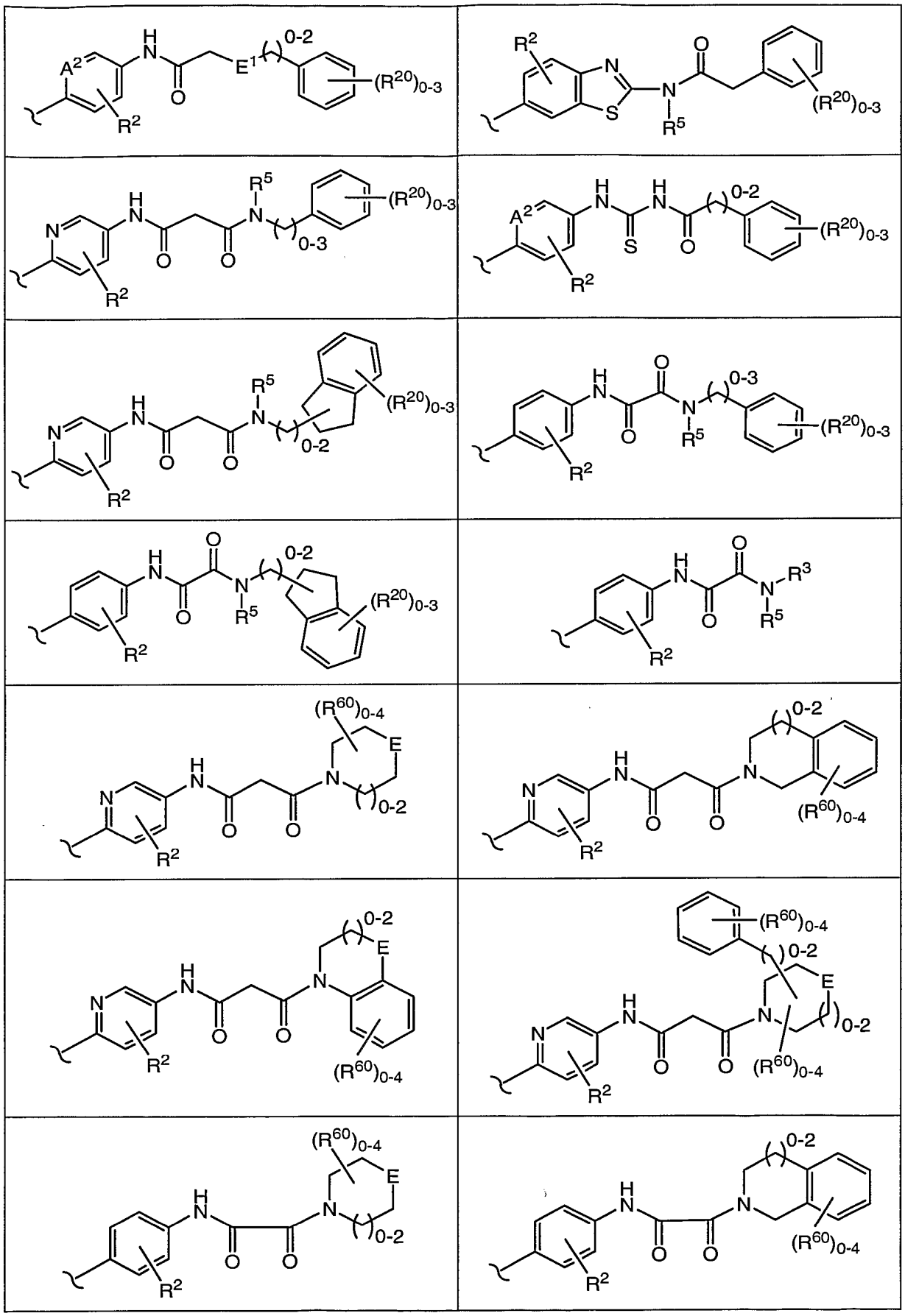



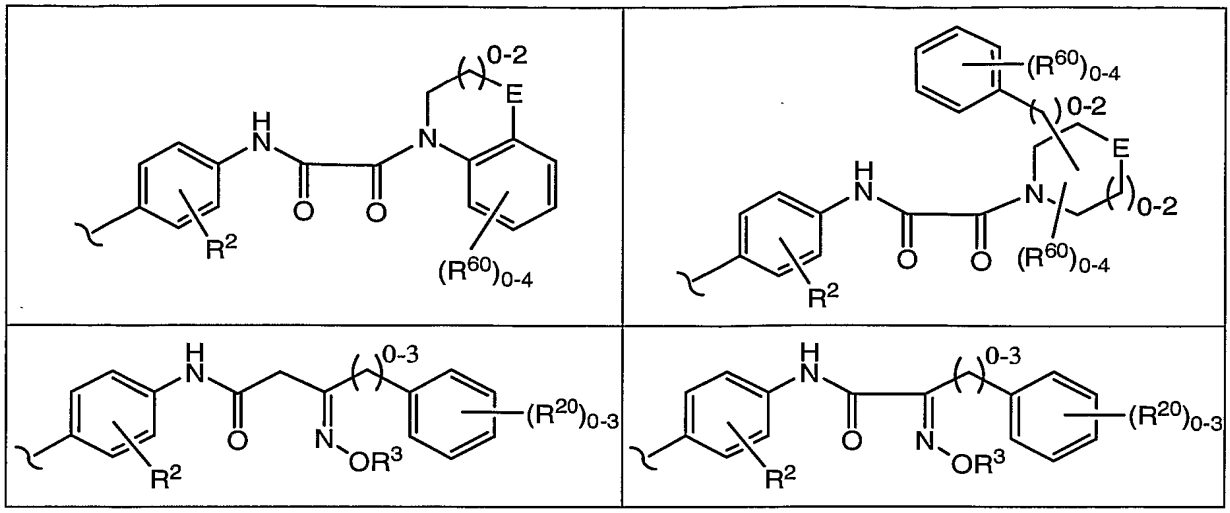
wherein $A^1$ is either =N- or =C(H)-.

49. The compound according to claim 48, wherein B is



50. The compound according to claim 49, wherein C is selected from:





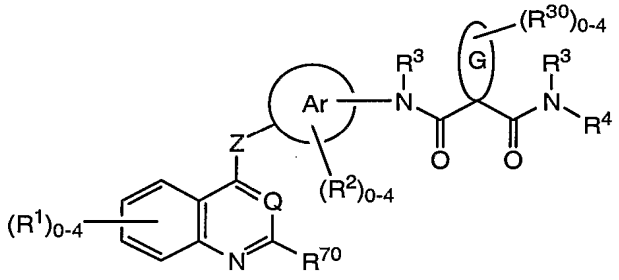
wherein $R^2$, $R^3$, $R^5$, $R^{20}$, $R^{25}$ and $R^{60}$ are as defined above.

51. The compound according to claim 50, $R^2$ is selected from halogen, trihalomethyl, -CN, -$NO_2$, -$OR^3$, -$NR^3R^3$, -$CO_2R^3$, -$C(O)NR^3R^3$, -$N(R^3)C(O)R^3$, -$N(R^3)CO_2R^3$, -$C(O)R^3$, and optionally substituted lower alkyl

52. The compound according to claim 51, wherein $R^2$ is halogen.

53. The compound according to claim 52, wherein $R^2$ is either fluorine or chlorine.

54. A compound for modulating kinase activity according to Formula **XI**,



**XI**

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

each $R^1$ is independently selected from halogen, -$OR^3$, -$NO_2$, -$NH_2$, -$NR^3R^4$, -D-$R^{50}$ and optionally substituted $C_{1\text{-}6}$alkyl;

$R^{70}$ is selected from -H, halogen, -$OR^3$, -$S(O)_{0\text{-}2}R^3$, -$NO_2$, -$NH_2$, -$NR^3R^4$, and optionally substituted $C_{1\text{-}6}$alkyl;

Q is selected from =N-, =C(H)-, and =C(CN)-;

Z is selected from -$S(O)_{0-2}$-, -O-, and -$NR^5$-;

Ar is either a five- or six-membered arylene or a five- or six-membered heteroarylene containing between one and three heteroatoms;

G is either an optionally substituted cycloalkyl or an optionally substituted heteroalicyclic;

each $R^2$ is independently selected from halogen, trihalomethyl, -CN, -$NO_2$, -$NH_2$, -$OR^3$, -$NR^3R^4$, -$S(O)_{0-2}R^3$, -$SO_2NR^3R^3$, -$CO_2R^3$, -$C(O)NR^3R^3$, -$N(R^3)SO_2R^3$, -$N(R^3)C(O)R^3$, -$N(R^3)CO_2R^3$, -$C(O)R^3$, and optionally substituted $C_{1-6}$alkyl;

each $R^3$ is independently -H or $R^4$;

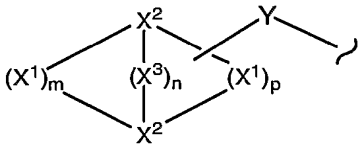
each $R^4$ is independently selected from optionally substituted $C_{1-6}$alkyl, optionally substituted aryl, optionally substituted aryl $C_{1-6}$alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl $C_{1-6}$alkyl; or

$R^3$ and $R^4$, when taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclyl, said optionally substituted five- to seven-membered heterocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

$R^5$ is -H or optionally substituted $C_{1-6}$alkyl;

each D is independently selected from -O-, -$S(O)_{0-2}$-, and -$NR^5$-;

each $R^{50}$ is independently either $R^3$, or according to formula **XII**;




**XII**

wherein $X^1$, $X^2$, and optionally $X^3$, represent the atoms of a saturated bridged ring system, said saturated bridged ring system comprising up to four annular heteroatoms represented by any of $X^1$, $X^2$, and $X^3$; wherein,

each $X^1$ is independently selected from -$C(R^6)R^7$-, -O-, -$S(O)_{0-2}$-, and -$NR^8$-;

each $X^2$ is independently an optionally substituted bridgehead methine or a bridgehead nitrogen;

each $X^3$ is independently selected from -$C(R^6)R^7$-, -O-, -$S(O)_{0-2}$-, and -$NR^8$-;

Y is either:

an optionally substituted lower alkylene linker, between D and either 1) any annular atom of the saturated bridged ring system, except $X^2$ when $X^2$ is a bridgehead nitrogen, or 2) any heteroatom, represented by any of $R^6$ or $R^7$; provided there are at least two carbon atoms between D and any annular heteroatom of the saturated bridged ring system or any heteroatom represented by any of $R^6$ or $R^7$;

or Y is absent, when Y is absent, said saturated bridged ring system, is directly attached to D via an annular carbon of said saturated bridged ring system, unless D is $-SO_2-$, in which case said saturated bridged ring system, is directly attached to D via an any annular atom of said saturated bridged ring system;

m and p are each independently one to four;

n is zero to two, when n equals zero, then there is a single bond between the two bridgehead $X^2$'s;

$R^6$ and $R^7$ are each independently selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^4$, $-SO_2NR^3R^4$, $-CO_2R^3$, $-C(O)NR^3R^4$, $-N(R^3)SO_2R^4$, $-N(R^3)C(O)R^3$, $-NCO_2R^3$, $-C(O)R^3$, optionally substituted $C_{1-6}$alkyl, optionally substituted aryl, optionally substituted aryl $C_{1-6}$alkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl $C_{1-6}$alkyl, and a bond to either Y or D; or

$R^6$ and $R^7$, when taken together are oxo; or

$R^6$ and $R^7$, when taken together with a common carbon to which they are attached, form a optionally substituted three- to seven-membered spirocyclyl, said optionally substituted three- to seven-membered spirocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

$R^8$ is selected from $-R^3$, Y, $-SO_2NR^3R^4$, $-CO_2R^4$, $-C(O)NR^3R^3$, $-SO_2R^4$, and $-C(O)R^3$; and

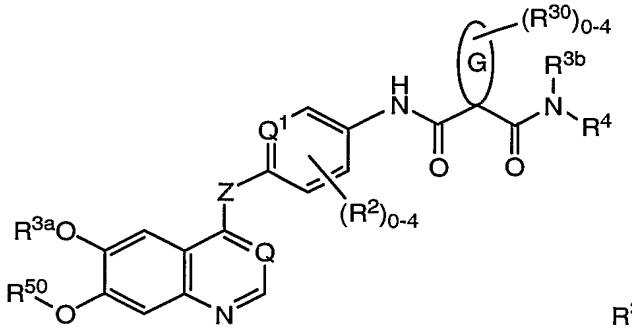
each $R^{30}$ is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted $C_{1-6}$alkyl.

55. The compound according to claim 54, wherein Z is either -O- or $-NR^5-$.

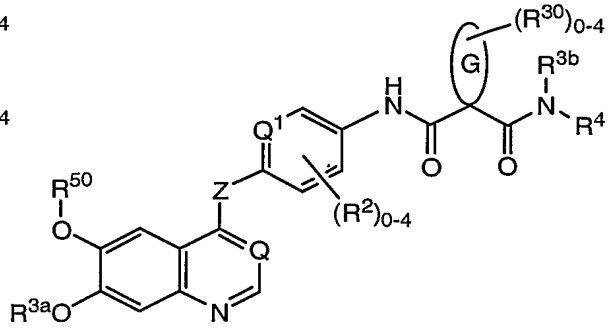
56. The compound according to claim 55, wherein at least one of $R^1$ is $-D-R^{50}$.

57. The compound according to claim 56, wherein D is -O- and at least one other $R^1$ is $-OR^3$.

58. The compound according to claim 57, of formula **XIIIa** or **XIIIb**:



**XIIIa**



**XIIIb**

wherein $Q^1$ is either =N- or =C(H)-.

59. The compound according to claim 58, wherein $R^{50}$ is selected from $C_{1-6}$alkyl optionally substituted with at least one of optionally substituted amino, optionally substituted $C_{1-6}$alkyl amino, optionally substituted $C_{1-6}$dialkyl amino, optionally substituted heteroalicylic, and a group of formula **XII**.

60. The compound according to claim 59, wherein $R^{3a}$ is $C_{1-6}$alkyl.

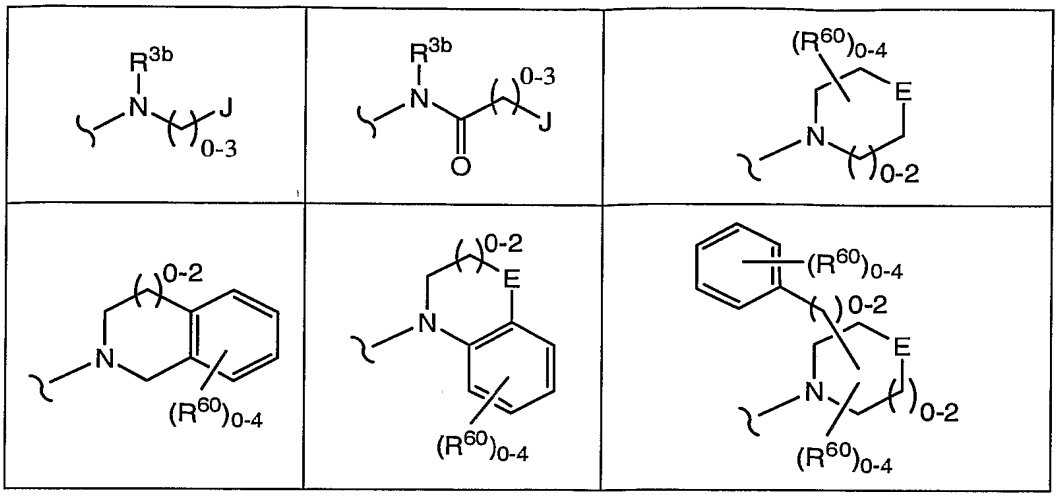
61. The compound according to claim 60, wherein Z is -O-.

62. The compound according to claim 61, wherein G is selected from cyclopropyl, aziradine, cyclobutyl, and azetidine, each optionally substituted with between zero and four of $R^{30}$.

63. The compound according to claim 62, wherein Q is either =N- or =C(H)-.

64. The compound according to claim 63, wherein $R^2$ is selected from -H, halogen, $C_{1-6}$ alkyl and perfluoro $C_{1-6}$ alkyl.

65. The compound according to claim 64, wherein $-N(R^{3b})R^4$ is selected from the following:



wherein J, is a five- to ten-membered ring, optionally substituted with between zero and five of $R^{20}$;

each $R^{20}$ is independently selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted $C_{1-6}$alkyl, optionally substituted aryl, optionally substituted aryl $C_{1-6}$alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl $C_{1-6}$alkyl;

two of $R^{20}$, together with the atom or atoms to which they are attached, combine to form an optionally substituted three- to seven-membered heteroalicyclic, said optionally substituted three- to seven-membered heteroalicyclic either spiro- to J or fused to J;

E is selected from -O-, $-N(R^5)$-, $-CH_2$-, and $-S(O)_{0-2}$-;

each $R^{60}$ is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted $C_{1-6}$alkyl, optionally substituted aryl, optionally substituted heteroaryl $C_{1-6}$alkyl, and optionally substituted aryl $C_{1-6}$alkyl;

each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with $R^{25}$; and

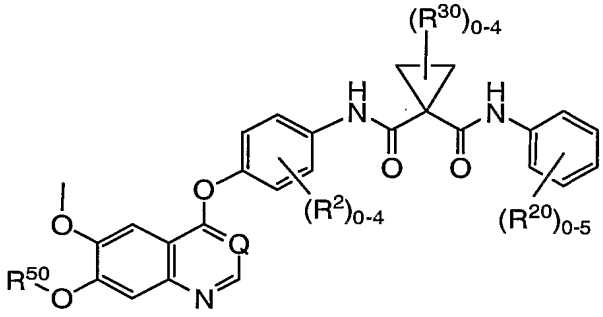
$R^{25}$ is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted aryl $C_{1-6}$alkyl, heteroaryl $C_{1-6}$alkyl, and optionally substituted $C_{1-6}$alkyl; or

two of $R^{25}$, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic;

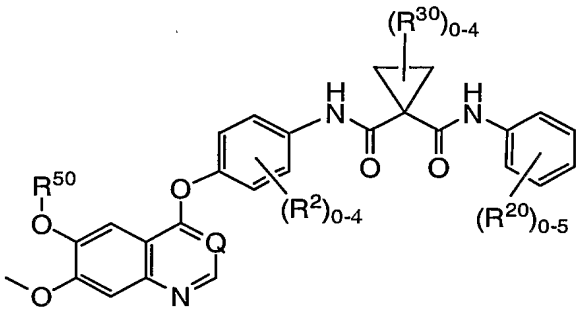
$R^{3b}$ is equivalent to $R^3$ as defined above; and

$R^4$ and $R^5$ are as defined above.

66. The compound according to claim 65, of formula **XIVa** or **XIVb**:



**XIVa**



**XIVb**

67. The compound according to claim 66, wherein $R^{50}$ is $C_{1\text{-}6}$alkyl optionally substituted with a group selected from optionally substituted amino, an optionally substituted alkylamino, optionally substituted dialkylamino, and optionally substituted heteroalicylic.

68. The compound according to claim 67, wherein the heteroalicyclic portion of said optionally substituted heteroalicyclic of $R^{50}$ is selected from the group consisting of piperidine, piperazine, morpholine, thiomorpholine, thiomorpholine 1-oxide, thiomorpholine 1,1-dioxide, 2-oxo-morpholine, pyrrolidine, and azepine.

69. The compound according to claim 67, wherein $R^{50}$ is according to formula **XII**.

70. The compound according to claim 69, wherein the saturated bridged ring system according to formula **XII** has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], [3.1.0], [3.3.3], [3.3.2], [3.3.1], [3.2.2], [3.2.1], [2.2.2], and [2.2.1].

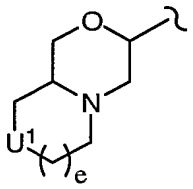
71. The compound according to claim 70, wherein Y is selected from $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2-$, $-CH_2-$, and absent.

72. The compound according to claim 71, wherein n is 0 and the saturated bridged ring system according to formula **XII** has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], and [3.1.0].

73. The compound according to claim 72, wherein said saturated bridged ring system contains at least one annular nitrogen or at least one annular oxygen.

74. The compound according to claim 73, wherein said saturated bridged ring system contains $-NR^8-$, wherein $R^8$ is selected from -H, optionally substituted $C_{1-6}$alkyl, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.

75. The compound according to claim 73, wherein said saturated bridged ring system is of formula **XV**,



**XV**

wherein $U^1$ is selected from $-O-$, $-S(O)_{0-2}-$, $-NR^8-$, $-CR^6R^7-$, and absent; and e is 0 or 1.

76. The compound according to claim 75, wherein Y is $-CH_2-$.

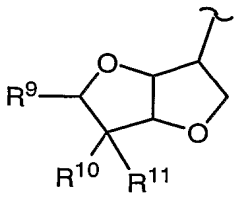
77. The compound according to claim 76, wherein $U^1$ is $-NR^8-$, wherein $R^8$ is selected from -H, optionally substituted lower alkyl, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.

78. The compound according to claim 76, wherein $U^1$ is -O-.

79. The compound according to claim 76, wherein $U^1$ is absent.

80. The compound according to claim 71, wherein Y is selected from $-CH_2CH_2-$, $-CH_2-$, and absent.

81. The compound according to claim 80, wherein said saturated bridged ring system is of formula **XVI**,



**XVI**

wherein $R^9$, $R^{10}$, and $R^{11}$ are each independently selected from -H, and -$OR^{12}$; or

$R^9$ is selected from -H, and -$OR^{12}$, and $R^{10}$ and $R^{11}$, when taken together, are either an optionally substituted alkylidene or an oxo;

$R^{12}$ is selected from -H, -$C(O)R^3$, optionally substituted lower alkylidyne, optionally substituted lower arylalkylidyne, optionally substituted lower heterocyclylalkylidyne, optionally substituted lower alkylidene, optionally substituted lower alkylidenearyl, optionally substituted lower alkylideneheterocyclyl, optionally substituted lower alkyl, optionally substituted lower alkylaryl, optionally substituted aryl, optionally substituted lower heterocyclylalkyl, and optionally substituted heterocyclyl;

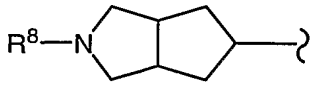
or two $R^{12}$'s, when taken together, form 1) a corresponding spirocyclic ketal when said two $R^{12}$'s stem from $R^{10}$ and $R^{11}$, or 2) a corresponding cyclic ketal when said two $R^{12}$'s stem from $R^9$ and one of $R^{10}$ and $R^{11}$.

82. The compound according to claim 81, wherein one of $R^{10}$ and $R^{11}$ is -$OR^{12}$, wherein $R^{12}$ is selected from -H, -$C(O)R^3$, and optionally substituted lower alkyl; and $R^9$ and the other of $R^{10}$ and $R^{11}$ are both -H.

83. The compound according to claim 82, wherein Y is either -$CH_2$- or absent.

84. The compound according to claim 81, wherein $R^9$ is an alkyl group containing at least one fluorine substitution thereon.

85. The compound according to claim 74, wherein said saturated bridged ring system is of formula **XVII**.



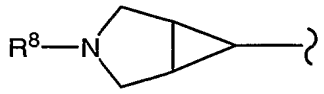
**XVII**

86. The compound according to claim 85, wherein Y is either -$CH_2$- or absent.

87. The compound according to claim 86, wherein $R^8$ is methyl or ethyl.

88. The compound according to claim 87, wherein at least one of $R^2$ is halogen.

89. The compound according to claim 74, wherein said saturated bridged ring system is of formula **XVIII**.

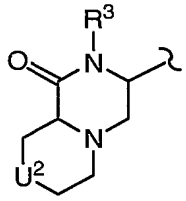


**XVIII**

90. The compound according to claim 89, wherein Y is $-CH_2-$.

91. The compound according to claim 90, wherein $R^8$ is methyl or ethyl.

92. The compound according to claim 73, wherein said saturated bridged ring system is of formula **XIX**



**XIX**

wherein $U^2$ is selected from -O-, $-S(O)_{0-2}-$, $-NR^8-$, $-CR^6R^7-$, and absent.

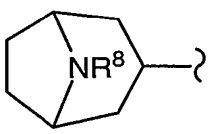
93. The compound according to claim 92, wherein $R^3$ of formula **XIX** is selected from -H and optionally substituted alkyl.

94. The compound according to claim 93, wherein $U^2$ is either $-CR^6R^7-$ or absent.

95. The compound according to claim 94, wherein $U^2$ is either $-CH_2-$ or absent.

96. The compound according to claim 95, wherein Y is $-CH_2-$.

97. The compound according to claim 74, wherein said saturated bridged ring system is according to formula **XX**.



98. The compound according to claim 97, wherein $R^8$ is methyl or ethyl.

99. The compound according to any of claims 67 through 98, wherein $R^2$ is selected from $C_{1-6}$ alkyl, perfluoro $C_{1-6}$ alkyl, and halogen.

100. The compound according to claim 99, wherein $R^2$ is selected from perfluoro $C_{1-3}$ alkyl and halogen.

101. The compound according to any of claims 67 through 98, wherein $R^{20}$ is selected from halogen, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, optionally substituted heterocyclyl, and optionally substituted heterocyclyl $C_{1-6}$alkyl, and (two of $R^{20}$) together with the atom or atoms to which they are attached, an optionally substituted three- to six-membered heteroalicyclic, said optionally substituted three- to six-membered heteroalicyclic fused to the phenyl as in **XIVa** or **XIVb**.

102. The compound according to claim 101, wherein $R^{20}$ is selected from halogen, $-NR^3R^4$, optionally substituted heterocyclyl, and optionally substituted heterocyclyl $C_{1-6}$alkyl, and (two of $R^{20}$) together with the atom or atoms to which they are attached, an optionally substituted five- to six-membered heteroalicyclic, said optionally substituted five- to six-membered heteroalicyclic fused to the phenyl as in **XIVa** or **XIVb**.

103. The compound according to claim 102, wherein $R^2$ is selected from $C_{1-6}$ alkyl, perfluoro $C_{1-6}$ alkyl, and halogen.

104. The compound according to claim 103, wherein $R^2$ is selected from perfluoro $C_{1-3}$ alkyl and halogen.

105. The compound according to claim 54, selected from Table 2.

**Table 2**

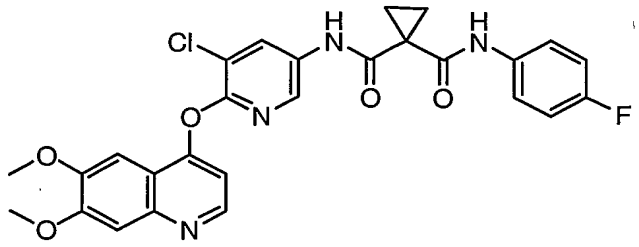
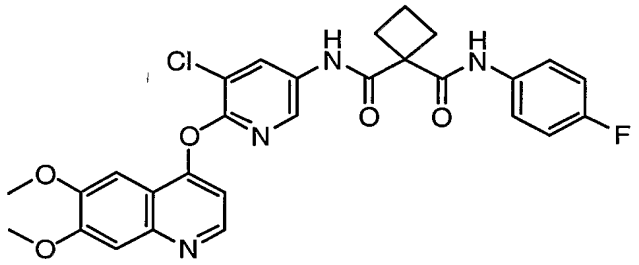
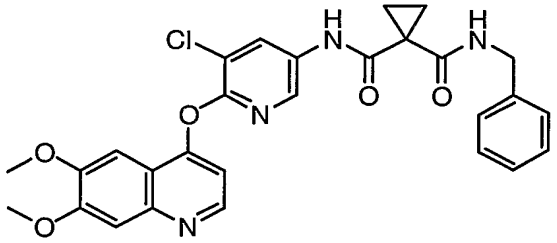
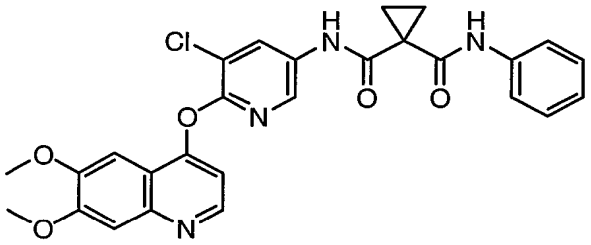
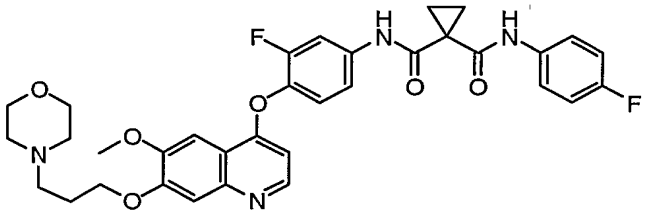
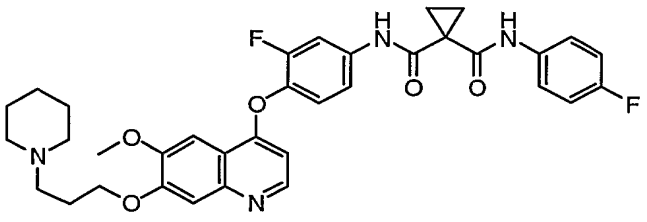
| Entry | Name | Structure |
|---|---|---|
| 1 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 2 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide |  |
| 3 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(phenylmethyl)cyclopropane-1,1-dicarboxamide |  |
| 4 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-phenylcyclopropane-1,1-dicarboxamide |  |
| 5 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 6 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |

**Table 2**

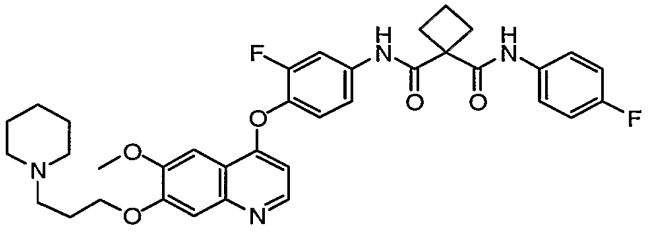
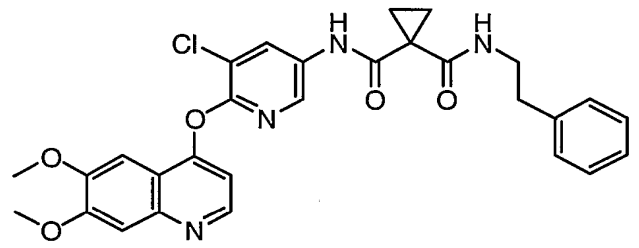
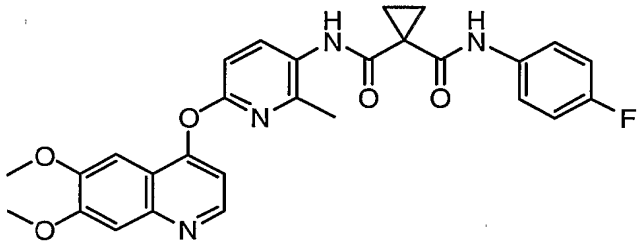
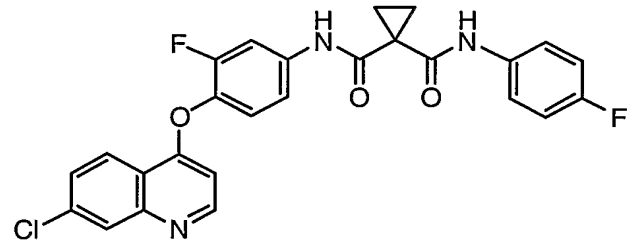
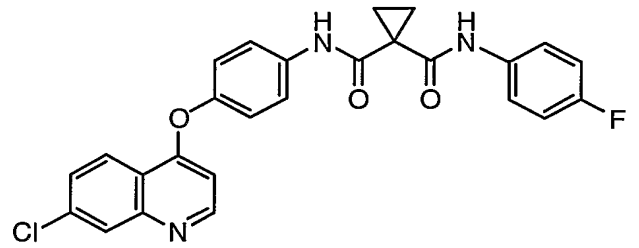
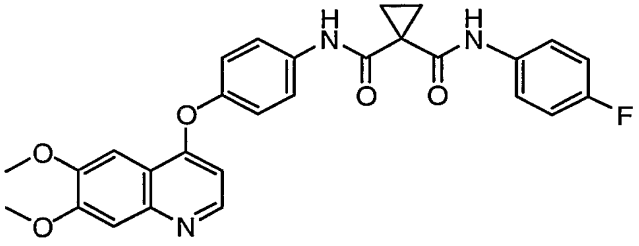
| Entry | Name | Structure |
|---|---|---|
| 7 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide |  |
| 8 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)cyclopropane-1,1-dicarboxamide |  |
| 9 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 10 | N-{4-[(7-chloroquinolin-4-yl)oxy]-3-fluorophenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 11 | N-{4-[(7-chloroquinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 12 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |

**Table 2**

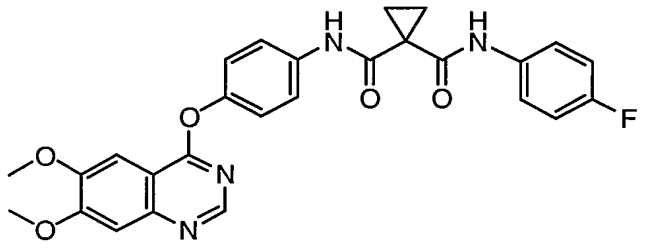
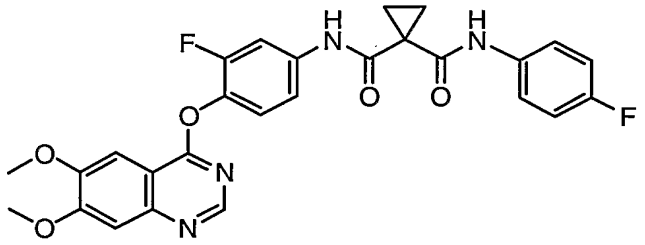
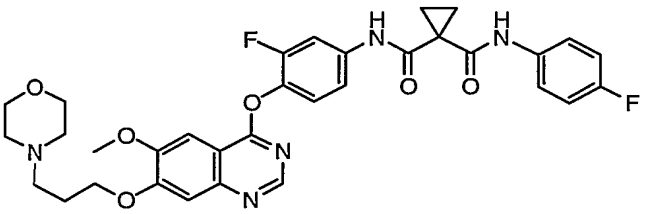
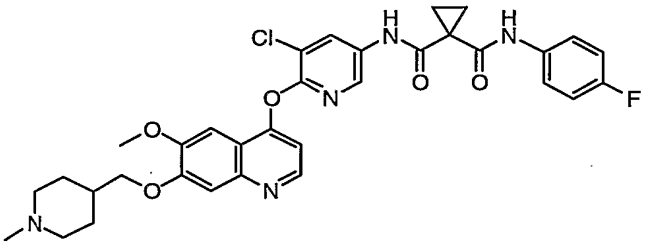
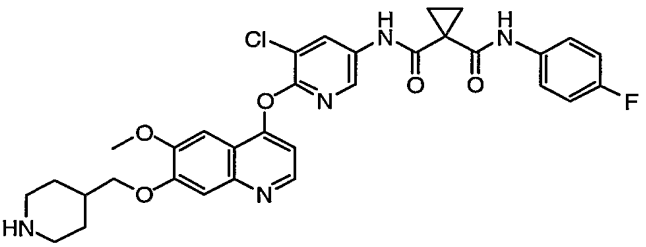
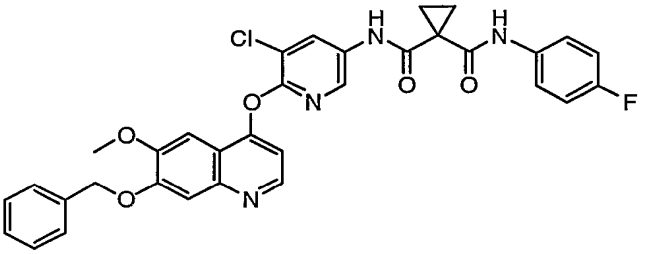
| Entry | Name | Structure |
|---|---|---|
| 13 | N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 14 | N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 15 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 16 | N-{5-chloro-6-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]pyridin-3-yl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 17 | N-[5-chloro-6-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 18 | N-[5-chloro-6-({6-(methyloxy)-7-[(phenylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |

**Table 2**

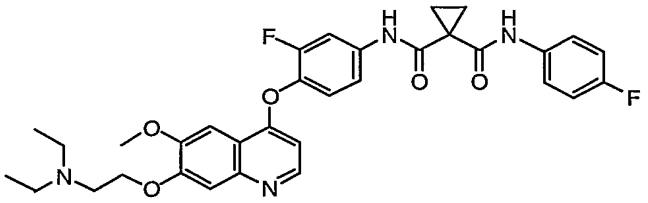
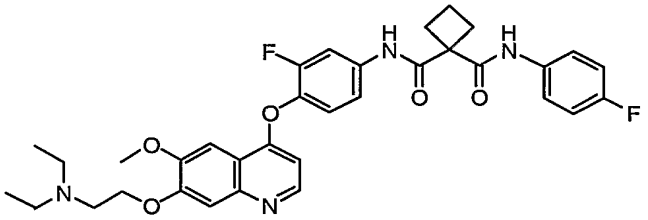
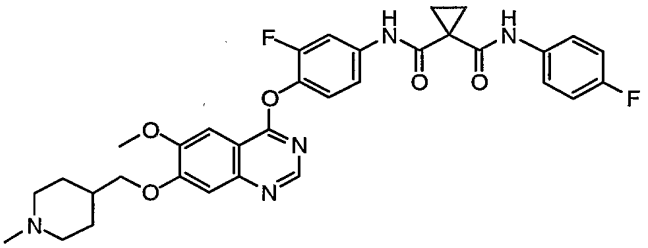
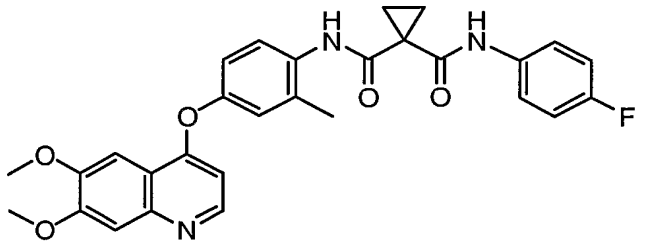
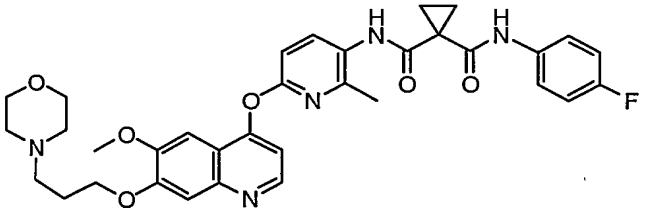
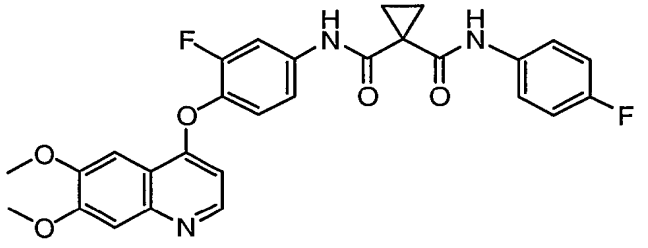
| Entry | Name | Structure |
|---|---|---|
| 19 | N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 20 | N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide |  |
| 21 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 22 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 23 | N-(4-fluorophenyl)-N'-[2-methyl-6-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]cyclopropane-1,1-dicarboxamide |  |
| 24 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |

**Table 2**

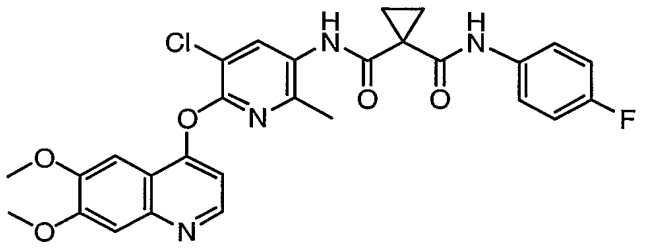
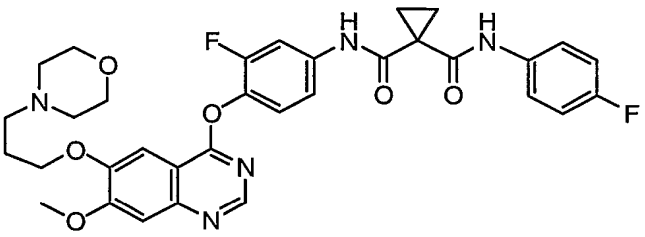
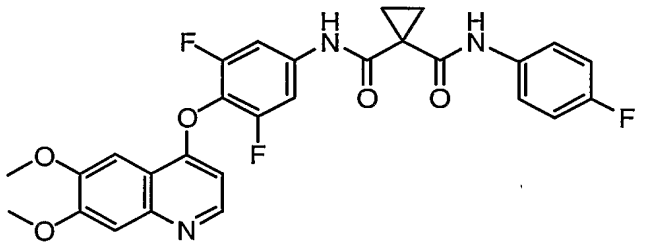
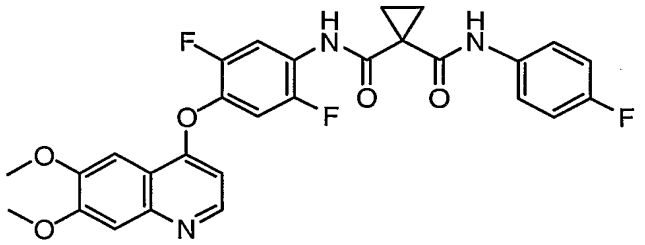
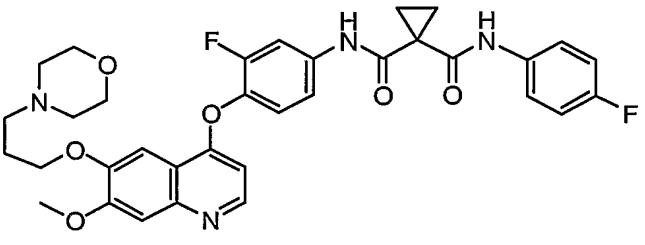
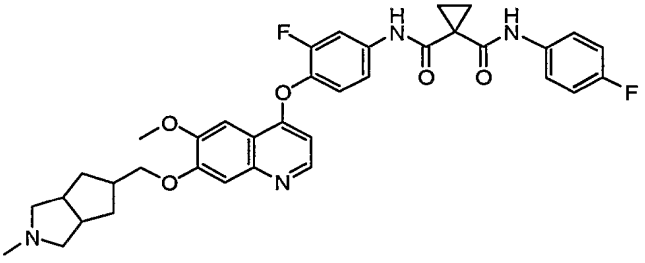
| Entry | Name | Structure |
|---|---|---|
| 25 | N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloro-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 26 | N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 27 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 28 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 29 | N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 30 | N-{3-fluoro-4-[(6-(methyloxy)-7-(2-methyl octahydrocyclo-penta[c]pyrrol-5-ylmethoxy)quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |

**Table 2**

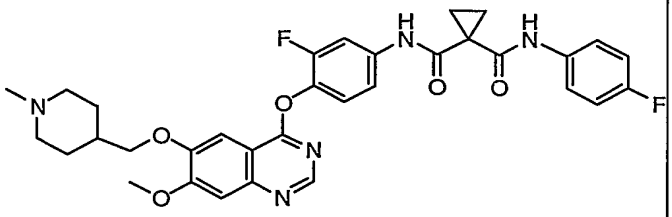
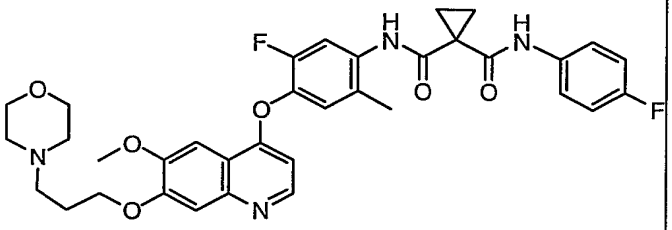
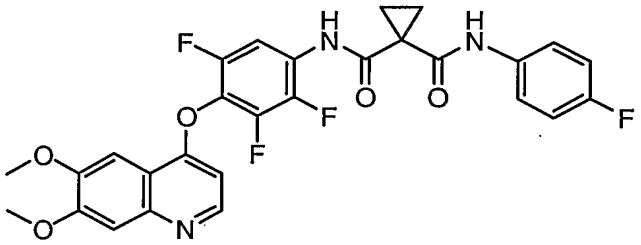
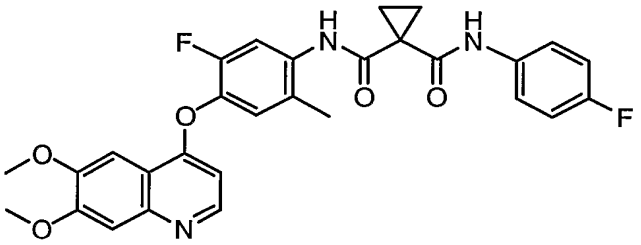
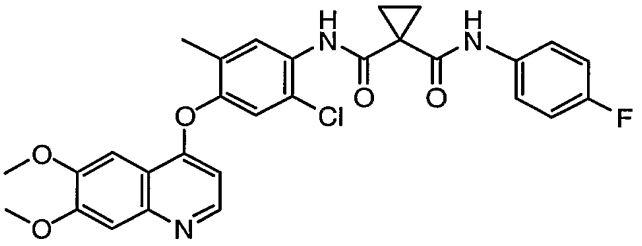
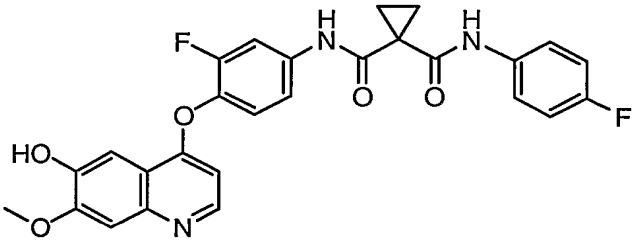
| Entry | Name | Structure |
|---|---|---|
| 31 | N-{3-fluoro-4-[(7-(methyloxy)-6-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 32 | N-[5-fluoro-2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 33 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,3,5-trifluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 34 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 35 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 36 | N-(3-fluoro-4-{[6-hydroxy-7-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |

**Table 2**

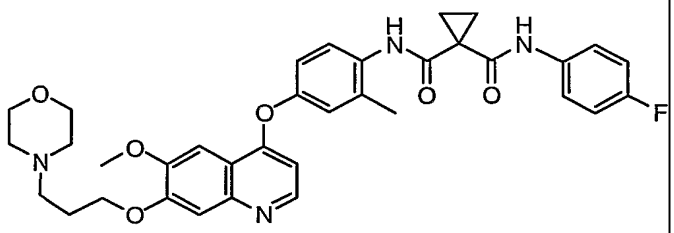
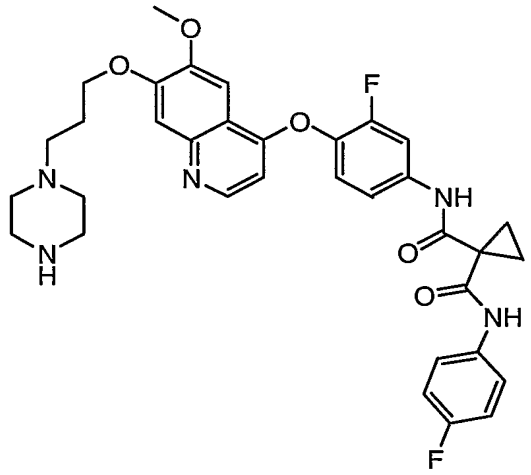
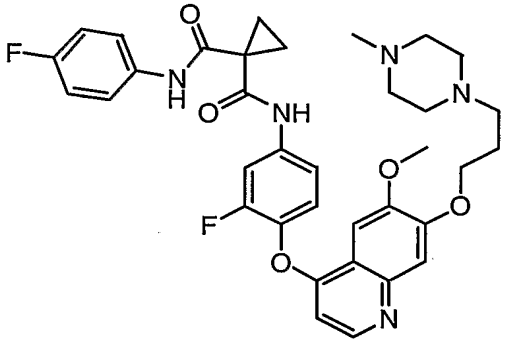
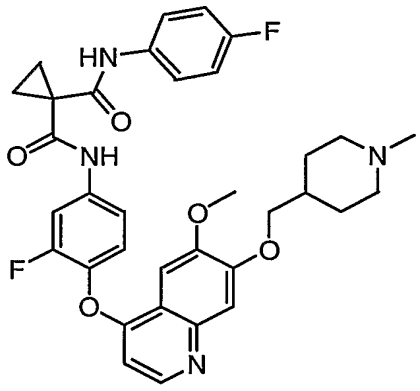
| Entry | Name | Structure |
|---|---|---|
| 37 | N-(4-fluorophenyl)-N'-[2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide |  |
| 38 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 39 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 40 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |

**Table 2**

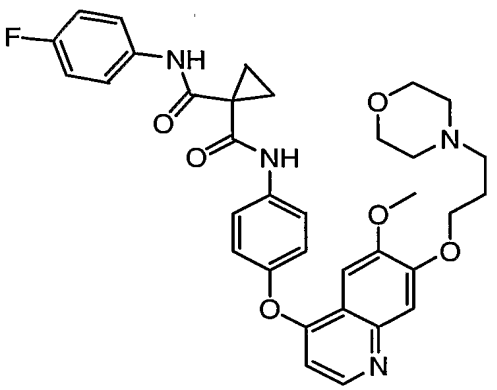
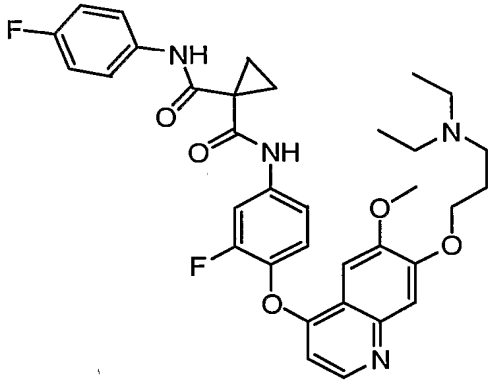
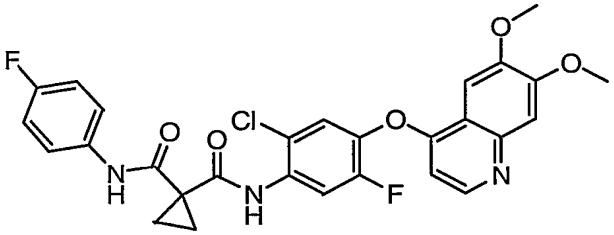
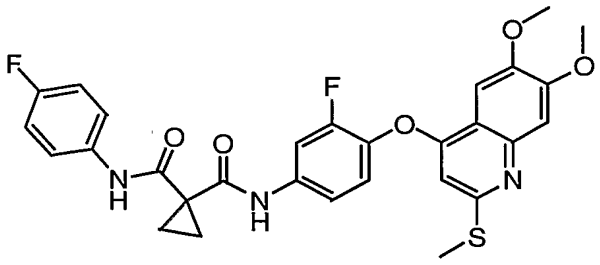
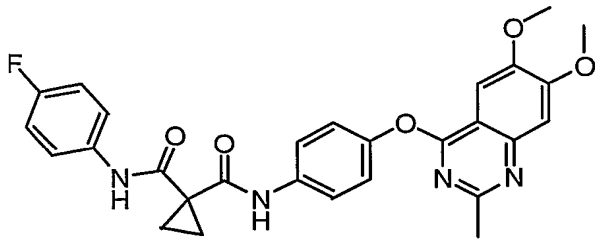
| Entry | Name | Structure |
|---|---|---|
| 41 | N-(4-fluorophenyl)-N'-[4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide |  |
| 42 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 43 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 44 | N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 45 | N-(4-fluorophenyl)-N'-(4-{[2-methyl-6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide |  |

**Table 2**

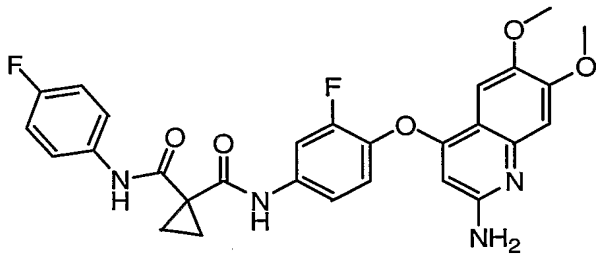
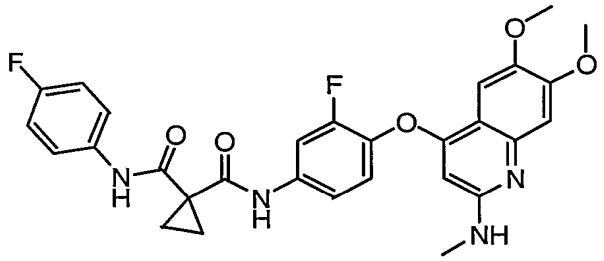
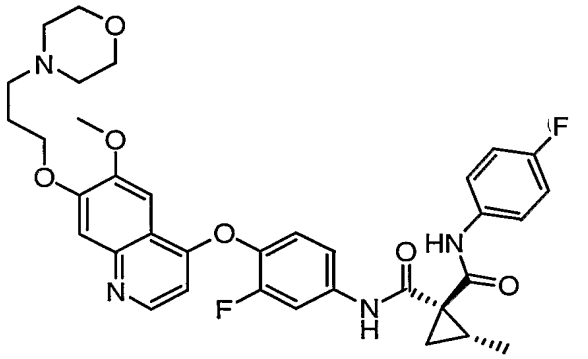
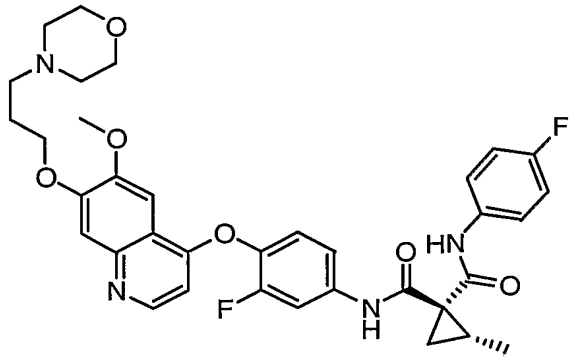
| Entry | Name | Structure |
|---|---|---|
| 46 | N-(4-{[2-amino-6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 47 | N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 48 | (1S,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |
| 49 | (1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |

**Table 2**

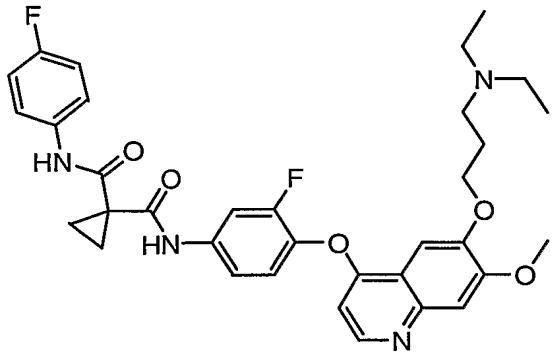
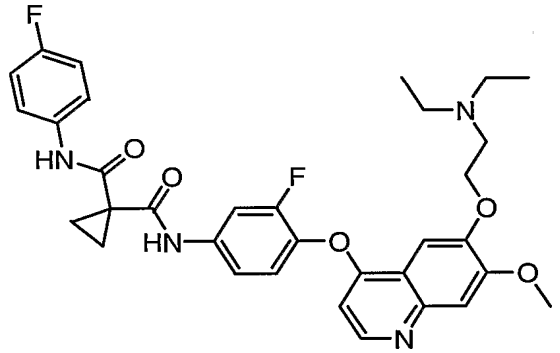
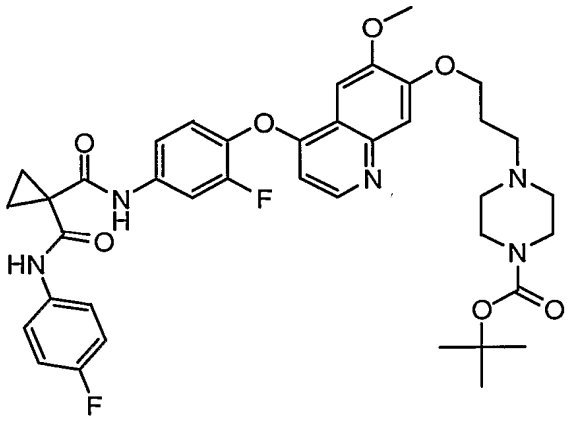
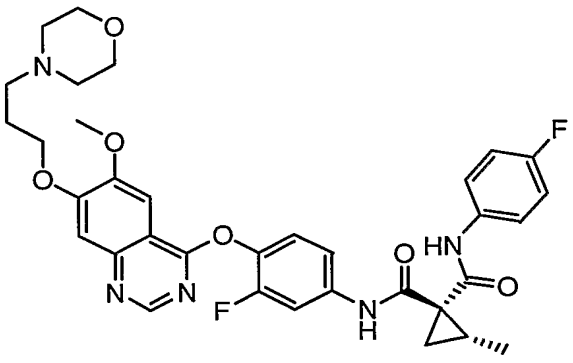
| Entry | Name | Structure |
|---|---|---|
| 50 | N-(4-{[6-{[3-(diethylamino)propyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 51 | N-(4-{[6-{[2-(diethylamino)ethyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 52 | 1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[(1-{[(4-fluorophenyl)amino]carbonyl}cyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate |  |
| 53 | (1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |

**Table 2**

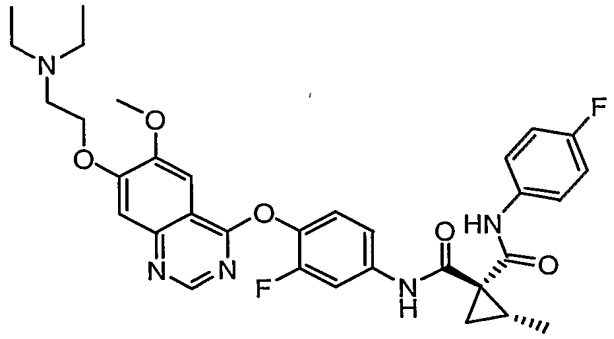
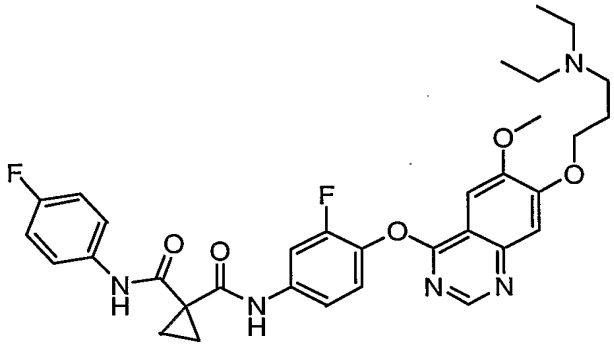
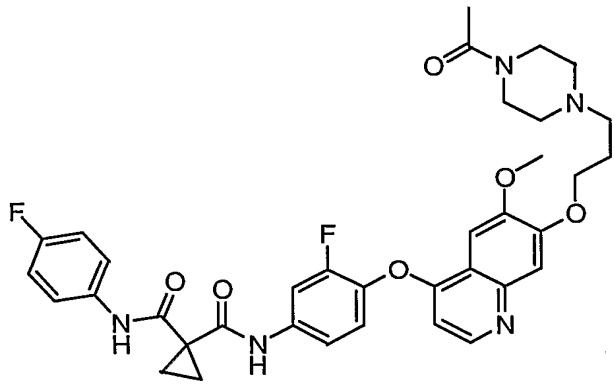
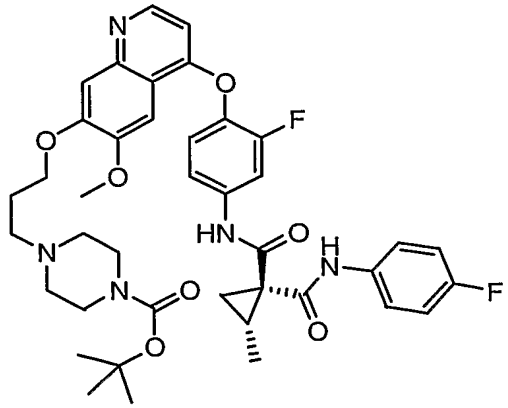
| Entry | Name | Structure |
|---|---|---|
| 54 | (1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |
| 55 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 56 | N-(4-{[7-{[3-(4-acetylpiperazin-1-yl)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 57 | 1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[((1R,2R)-1-{[(4-fluorophenyl)amino]carbonyl}-2-methylcyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate |  |

**Table 2**

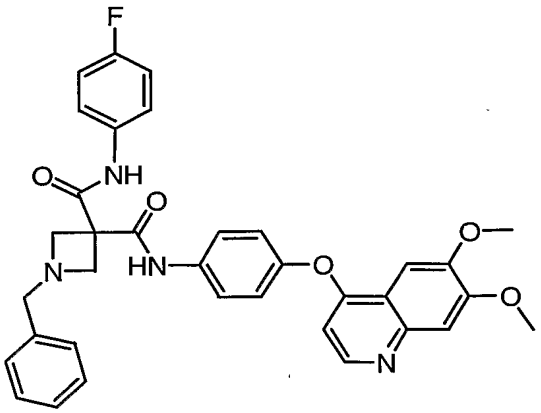
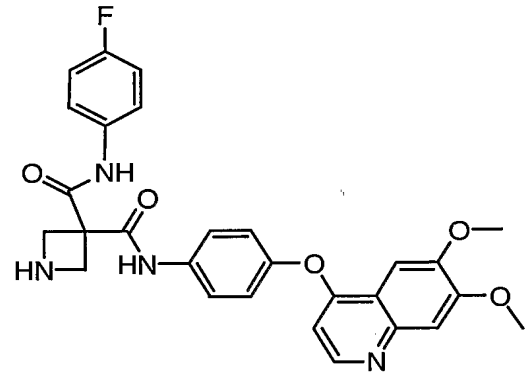
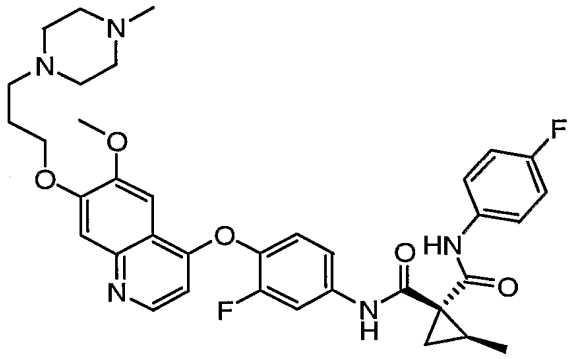
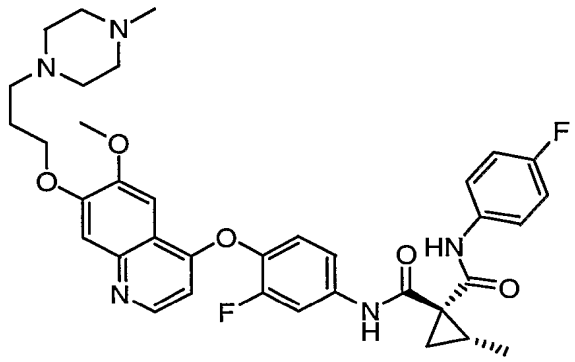
| Entry | Name | Structure |
|---|---|---|
| 58 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide |  |
| 59 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)azetidine-3,3-dicarboxamide |  |
| 60 | (1R,2S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |
| 61 | (1R,2R)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |

**Table 2**

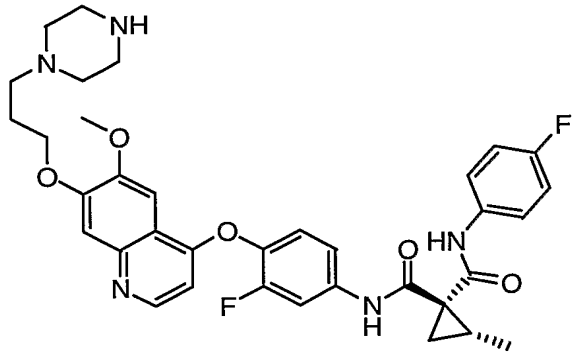
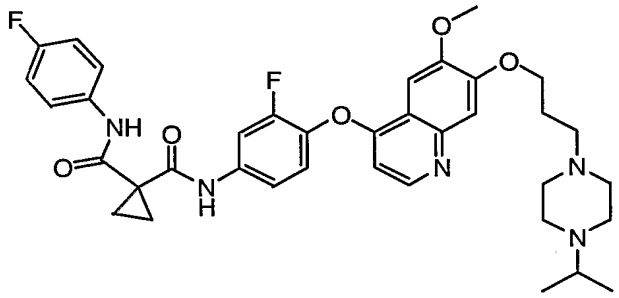
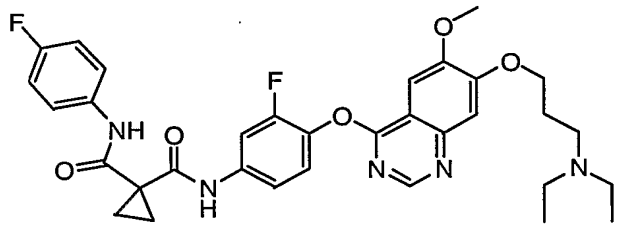
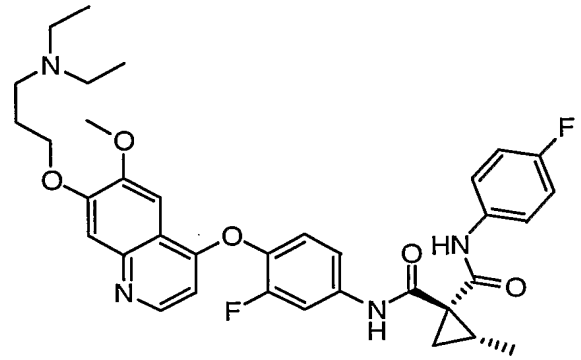
| Entry | Name | Structure |
|---|---|---|
| 62 | (1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |
| 63 | N-(3-fluoro-4-{[7-({3-[4-(1-methylethyl)piperazin-1-yl]propyl}oxy)-6-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 64 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide |  |
| 65 | (1R,2R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |

**Table 2**

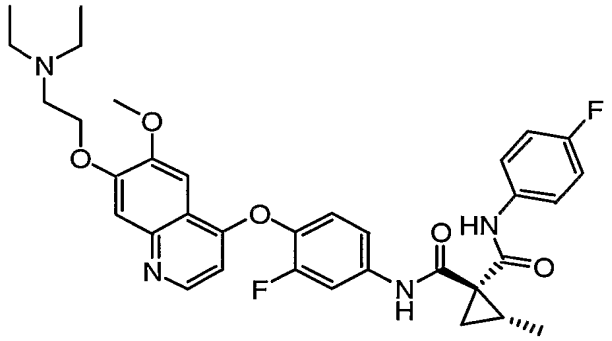
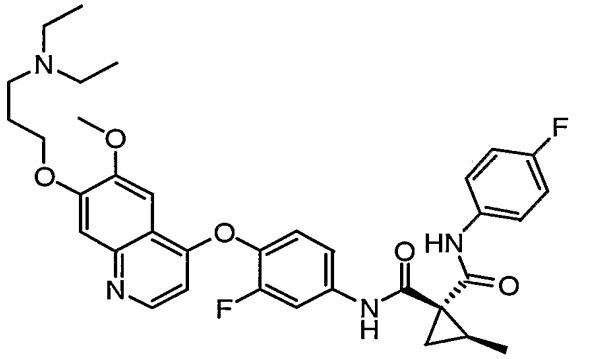
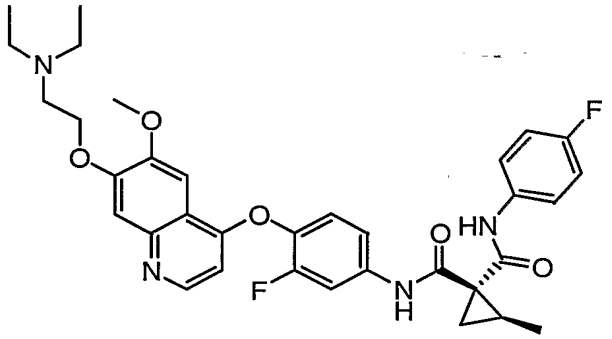
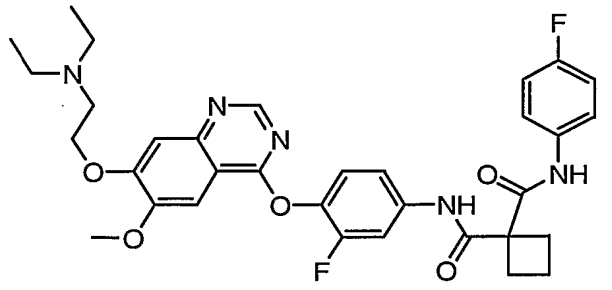
| Entry | Name | Structure |
|---|---|---|
| 66 | (1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |
| 67 | (1R,2S)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |
| 68 | (1R,2S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |
| 69 | N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide |  |

**Table 2**

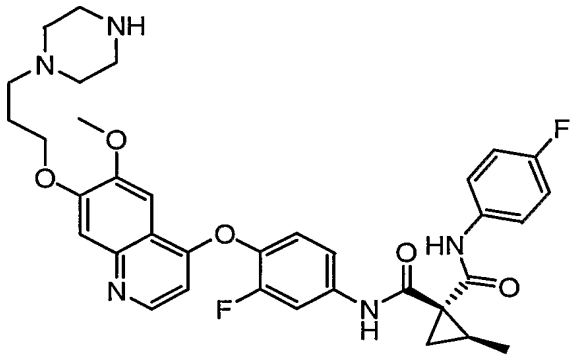
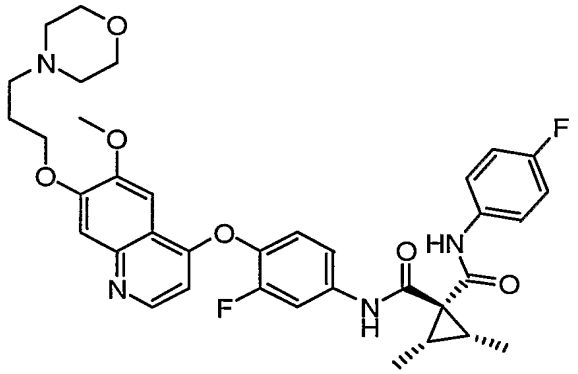
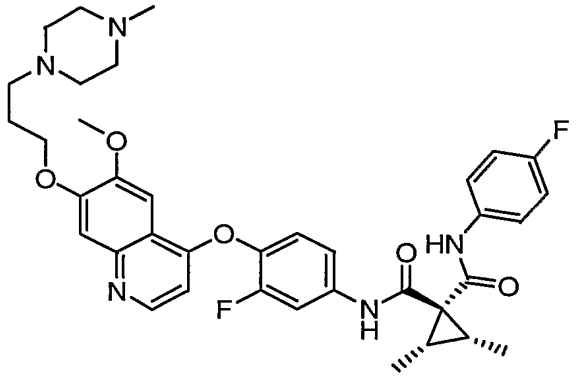
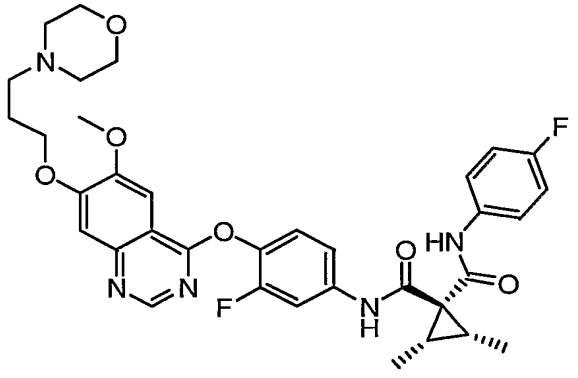
| Entry | Name | Structure |
|---|---|---|
| 70 | (1R,2S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |
| 71 | (1R,2R,3S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |
| 72 | (1R,2R,3S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |
| 73 | (1R,2R,3S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |

**Table 2**

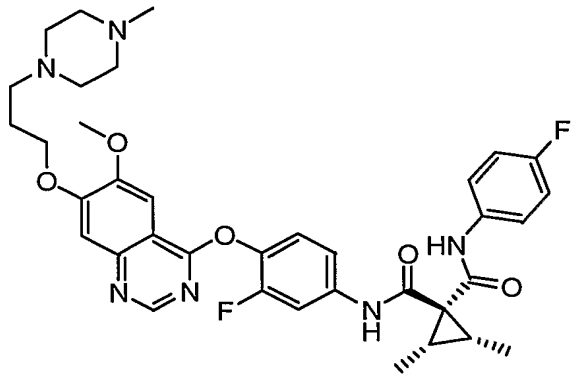
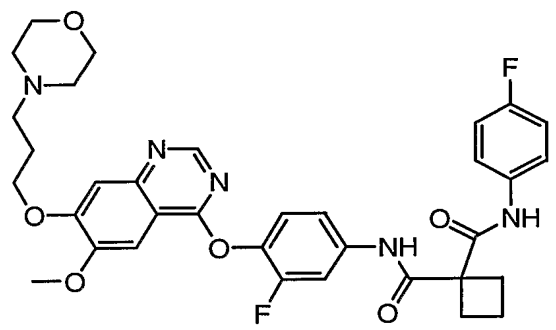
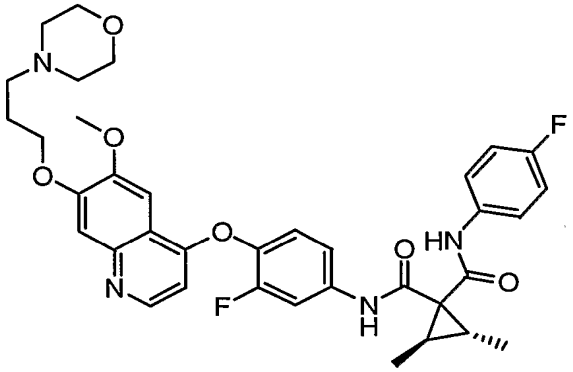
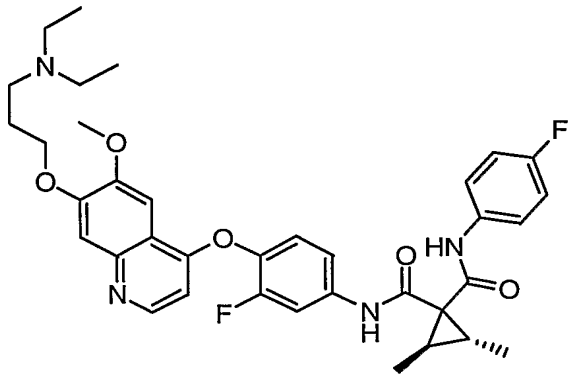
| Entry | Name | Structure |
|---|---|---|
| 74 | (1R,2R,3S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |
| 75 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide |  |
| 76 | (2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |
| 77 | (2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |

**Table 2**

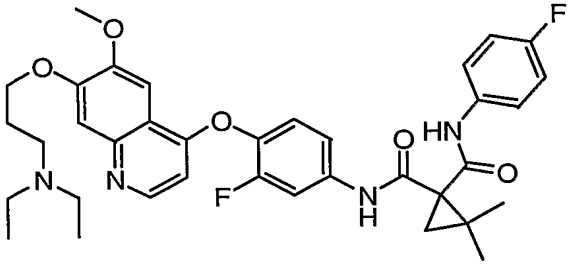
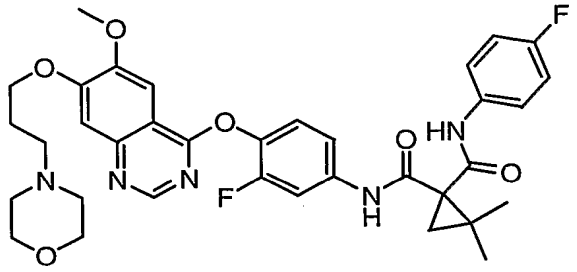
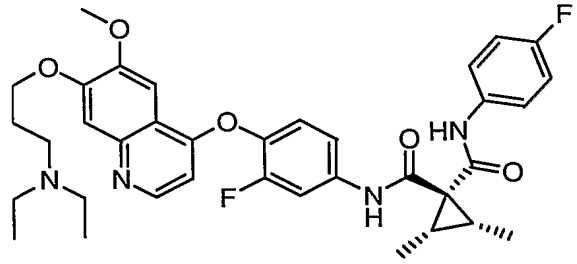
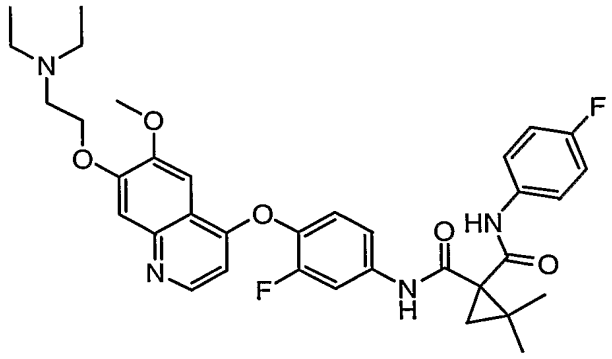
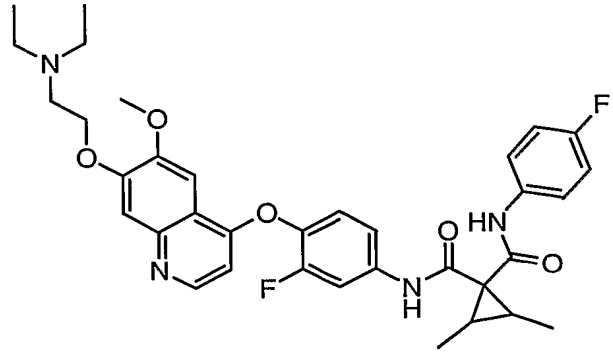
| Entry | Name | Structure |
|---|---|---|
| 78 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide |  |
| 79 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide |  |
| 80 | (1R,2R,3S)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |
| 81 | N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide |  |
| 82 | (1R,2R,3S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |

**Table 2**

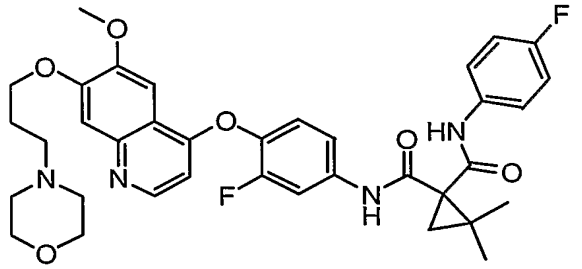
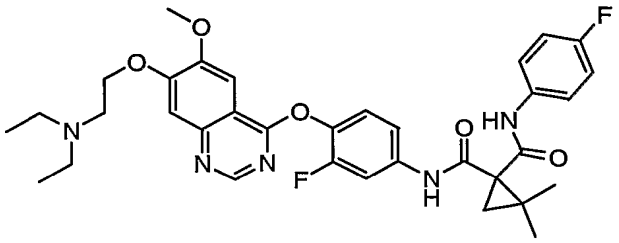
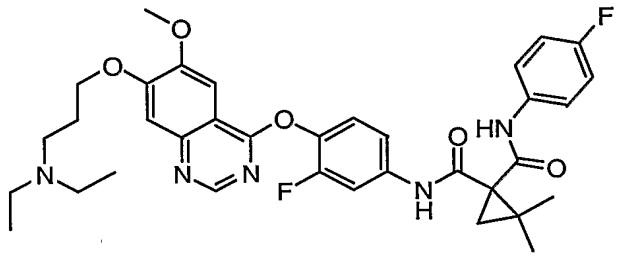
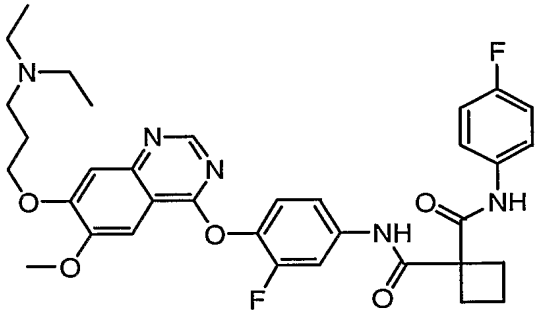
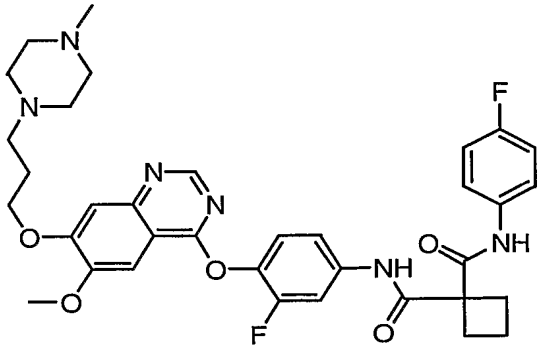
| Entry | Name | Structure |
|---|---|---|
| 83 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide |  |
| 84 | N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide |  |
| 85 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide |  |
| 86 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide |  |
| 87 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide |  |

**Table 2**

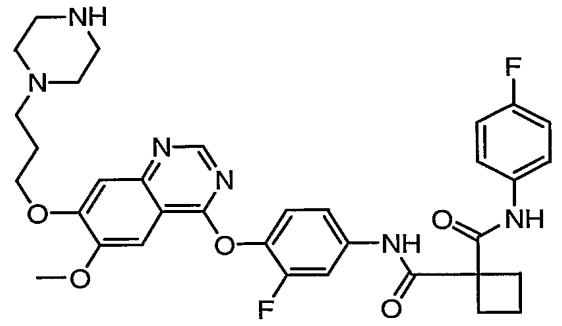
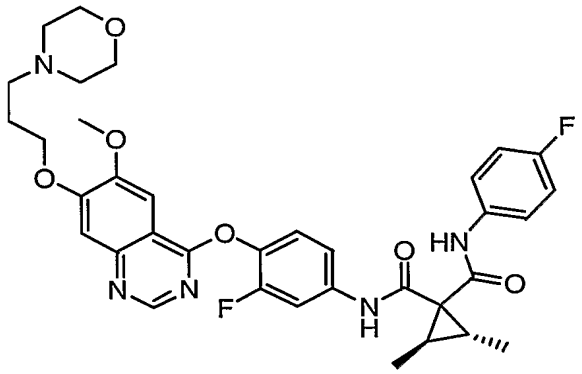
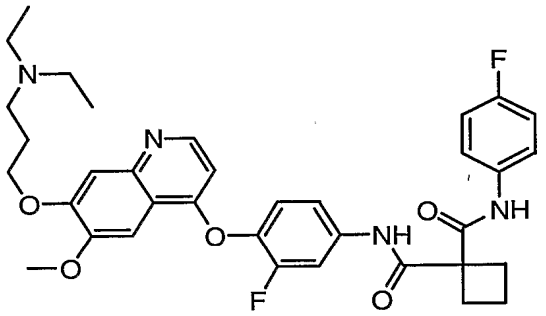
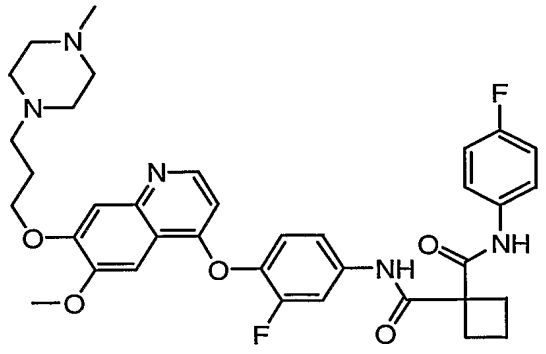
| Entry | Name | Structure |
|---|---|---|
| 88 | N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide |  |
| 89 | (2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |
| 90 | N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide |  |
| 91 | N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide |  |

**Table 2**

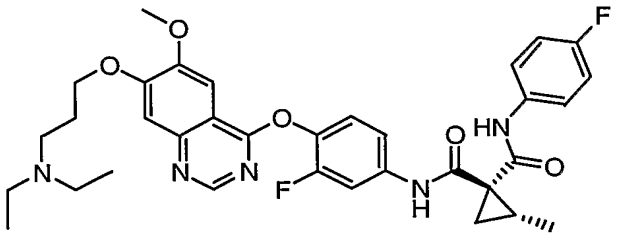
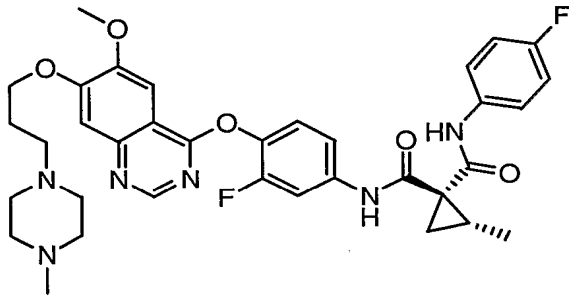
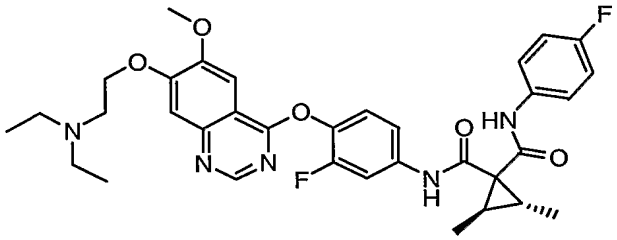
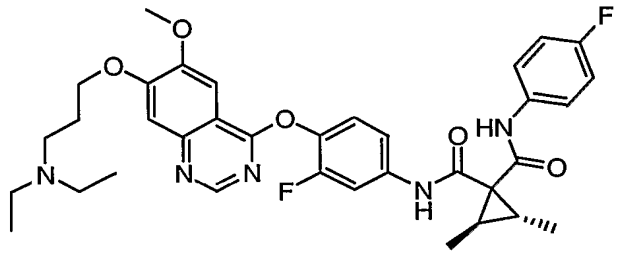
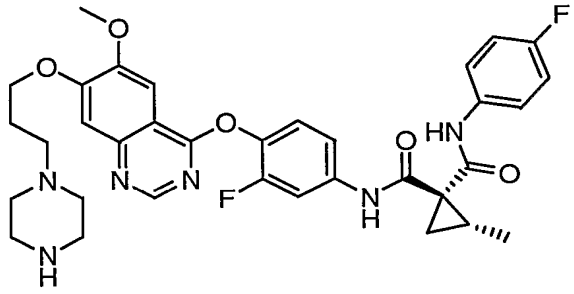
| Entry | Name | Structure |
|---|---|---|
| 92 | (1R,2R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |
| 93 | (1R,2R)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |
| 94 | (2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |
| 95 | (2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |
| 96 | (1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide |  |

**Table 2**

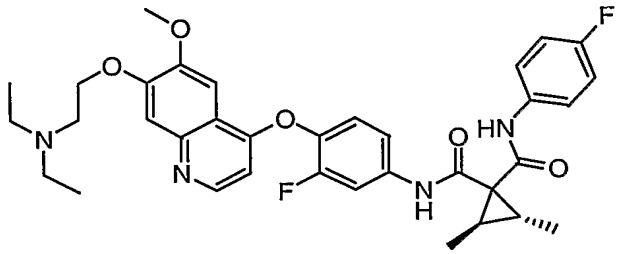
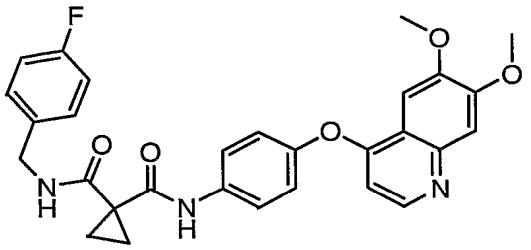
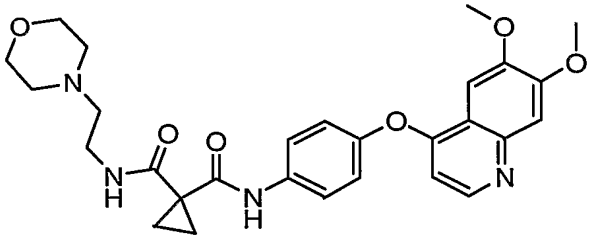
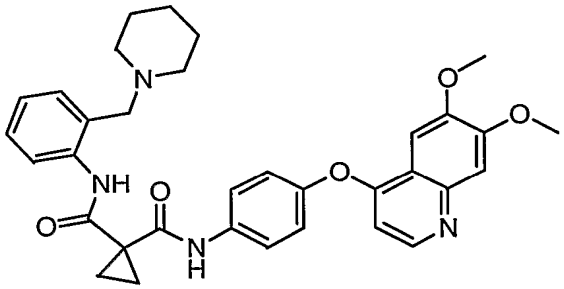
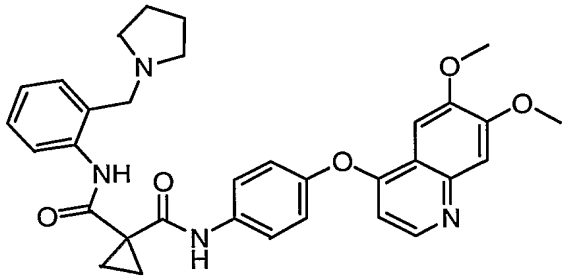
| Entry | Name | Structure |
|---|---|---|
| 97 | (2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide |  |
| 98 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[(4-fluorophenyl)methyl]cyclopropane-1,1-dicarboxamide |  |
| 99 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(2-morpholin-4-ylethyl)cyclopropane-1,1-dicarboxamide |  |
| 100 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide |  |
| 101 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide |  |

**Table 2**

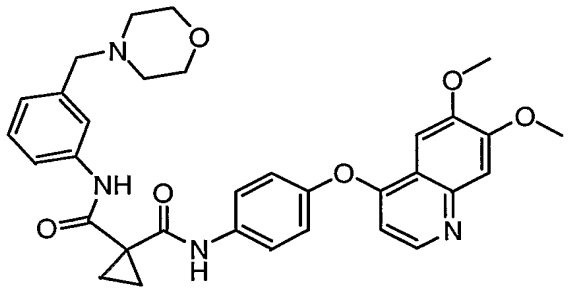
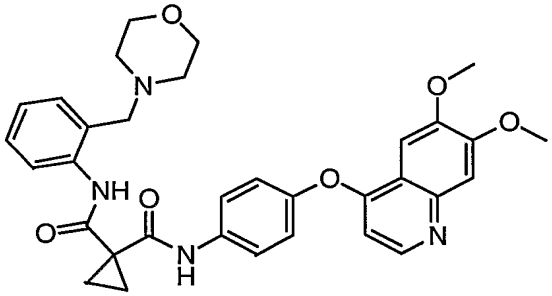
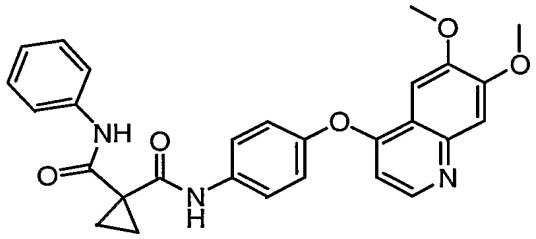
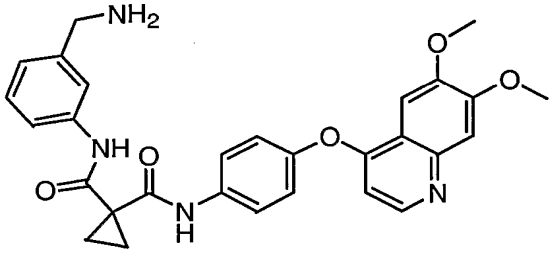
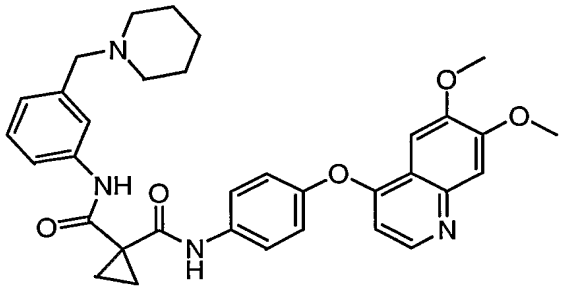
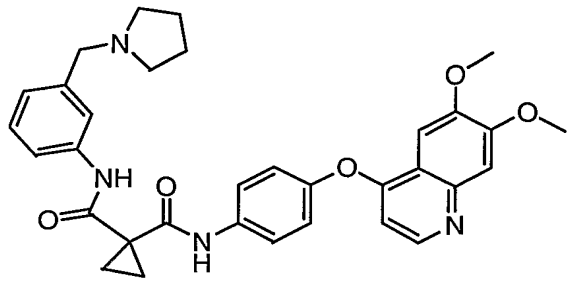
| Entry | Name | Structure |
|---|---|---|
| 102 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide |  |
| 103 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide |  |
| 104 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-phenylcyclopropane-1,1-dicarboxamide |  |
| 105 | N-[3-(aminomethyl)phenyl]-N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide |  |
| 106 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide |  |

**Table 2**

| Entry | Name | Structure |
|---|---|---|
| 107 | N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide |  |

106. A pharmaceutical composition comprising a compound according to any one of claims 1 - 105 and a pharmaceutically acceptable carrier.

107. A metabolite of the compound or the pharmaceutical composition according to any one of claims 1 - 106.

108. A method of modulating the *in vivo* activity of a kinase, the method comprising administering to a subject an effective amount of the compound or the pharmaceutical composition according to any of claims 1 - 105.

109. The method according to claim 108, wherein modulating the *in vivo* activity of the kinase comprises inhibition of said kinase.

110. The method according to claim 108, wherein the kinase is at least one of c-Met, KDR, c-Kit, flt-3, and flt-4.

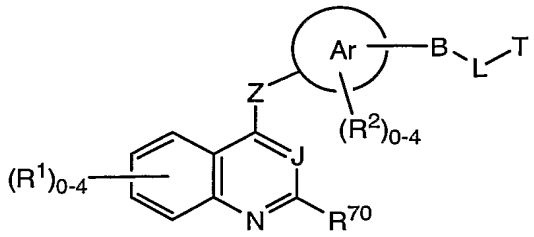
111. The method according to claim 110, wherein the kinase is c-Met.

112. A method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities, the method comprising administering, to a mammal in need thereof, a therapeutically effective amount of the compound or the pharmaceutical composition as described in any one of claims 1 - 106.

113. A method of screening for a modulator of a kinase, said kinase selected from c-Met, KDR, c-Kit, flt-3, and flt-4, the method comprising combining a compound according to any one of claims 1 - 105, and at least one candidate agent and determining the effect of the candidate agent on the activity of said kinase.

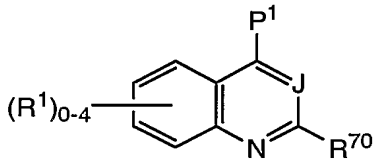
114. A method of inhibiting proliferative activity in a cell, the method comprising administering an effective amount of a composition comprising a compound according any one of claims 1 - 105 to a cell or a plurality of cells.

115. A process for preparing a compound of Formula **XXI**,

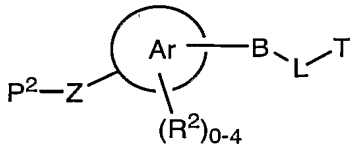


**XXI**

comprising reaction of a compound of Formula **XXII**, with a compound of Formula **XXIII**



**XXII**



**XXIII**

wherein,

each $R^1$ is independently selected from halogen, $-OR^3$, $-NO_2$, $-NH_2$, $-NR^3R^3$, $-D-R^{50}$ and optionally substituted $C_{1-6}$alkyl;

$R^{70}$ is selected from -H, halogen, $-OR^3$, $-S(O)_{0-2}R^3$, $-NO_2$, $-NH_2$, $-NR^3R^3$, and optionally substituted $C_{1-6}$alkyl;

J is selected from =N-, =C(H)-, =C(halogen)-, and =C(CN)-;

Z is selected from $-S(O)_{0-2}$-, -O-, and $-NR^5$-;

each $R^5$ is independently selected from -H, optionally substituted $C_{1-6}$alkyl, optionally substituted aryl, and optionally substituted aryl $C_{1-6}$alkyl;

Ar is either a five- to ten-membered arylene or a five- to ten-membered heteroarylene containing between one and three heteroatoms;

$R^2$ is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted $C_{1-6}$alkyl;

each $R^3$ is independently selected from -H, $-Si(R^5)(R^5)R^5$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted arylalkyl, and optionally substituted heteroarylalkyl;

two $R^3$, together with the nitrogen to which they are attached, form a four- to seven-membered heteroalicyclic, said four- to seven-membered heteroalicyclic optionally containing one additional heteroatom; when one said additional heteroatom is a nitrogen, then said nitrogen is optionally substituted with a group selected from -H, trihalomethyl, $-SO_2R^5$, $-SO_2NR^5R^5$, $-CO_2R^5$, $-C(O)NR^5R^5$, $-C(O)R^5$, and optionally substituted lower alkyl;

B is selected from absent, $-N(R^{13})-$, $-N(SO_2R^{13})-$, -O-, $-S(O)_{0-2}-$, and -C(=O)-;

L is selected from absent, $-C(=S)N(R^{13})-$, $-C(=NR^{14})N(R^{13})-$, $-SO_2N(R^{13})-$, $-SO_2-$, $-C(=O)N(R^{13})-$, $-N(R^{13})-$, $-C(=O)C_{1-2}alkylN(R^{13})-$, $-N(R^{13})C_{1-2}alkylC(=O)-$, $-C(=O)C_{0-1}alkylC(=O)N(R^{13})-$, -C(=O)-, $-C_{0-4}alkylene-$, $-C(=O)C_{0-1}alkylC(=O)OR^3-$, $-C(=NR^{14})C_{0-1}alkylC(=O)-$, $-C(=O)C_{0-1}alkylC(=O)-$, and an optionally substituted four- to six-membered heterocyclyl containing between one and three annular heteroatoms and comprising at least one nitrogen;

T is selected from -H, $-R^{13}$, $-C_{0-4}alkyl$, $-C_{0-4}alkylQ$, $-OC_{0-4}alkylQ$, $-C_{0-4}alkylOQ$, $-N(R^{13})C_{0-4}alkylQ$, $-SO_2C_{0-4}alkylQ$, $-C(=O)C_{0-4}alkylQ$, $-C_{0-4}alkylN(R^{13})Q$, and $-C(=O)N(R^{13})C_{0-4}alkylQ$, wherein each of the aforementioned $C_{0-4}alkyl$ is optionally substituted;

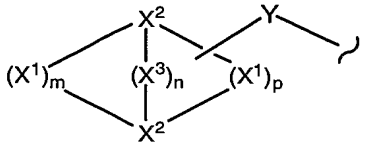
Q is a five- to ten-membered ring system, optionally substituted with between zero and four of $R^{20}$;

each $R^{20}$ is independently selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted $C_{1-6}alkyl$, optionally substituted aryl, optionally substituted aryl $C_{1-6}alkyl$, optionally substituted heterocyclyl, and optionally substituted heterocyclyl $C_{1-6}alkyl$;

two of $R^{20}$, together with the atom or atoms to which they are attached, combine to form an optionally substituted three- to seven-membered heteroalicyclic, said optionally substituted three- to seven-membered heteroalicyclic either spiro- to Q or fused to Q;

D is selected from -O-, $-S(O)_{0-2}-$, and $-NR^{15}-$;

$R^{50}$ is either $R^3$, or according to formula **XXIV**;



**XXIV**

wherein $X^1$, $X^2$, and optionally $X^3$, represent the atoms of a saturated bridged ring system, said saturated bridged ring system comprising up to four annular heteroatoms represented by any of $X^1$, $X^2$, and $X^3$; wherein,

each $X^1$ is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

each $X^2$ is independently an optionally substituted bridgehead methine or a bridgehead nitrogen;

each $X^3$ is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

Y is either:

an optionally substituted $C_{1-6}$alkylene linker, between D and either 1) any annular atom of the saturated bridged ring system, except $X^2$ when $X^2$ is a bridgehead nitrogen, or 2) any heteroatom, represented by any of $R^6$ or $R^7$; provided there are at least two carbon atoms between D and any annular heteroatom of the saturated bridged ring system or any heteroatom represented by any of $R^6$ or $R^7$;

or Y is absent, when Y is absent, said saturated bridged ring system, is directly attached to D via an annular carbon of said saturated bridged ring system, unless D is $-SO_2-$, in which case said saturated bridged ring system, is directly attached to D via an any annular atom of said saturated bridged ring system;

m and p are each independently one to four;

n is zero to two, when n is zero, then there is a single bond between the two bridgehead $X^2$'s;

$R^6$ and $R^7$ are each independently selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-NCO_2R^3$, $-C(O)R^3$, optionally substituted $C_{1-6}$alkyl, optionally substituted

aryl, optionally substituted aryl $C_{1-6}$alkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl a $C_{1-6}$lkyl, and a bond to either Y or D; or

$R^6$ and $R^7$, when taken together are oxo; or

$R^6$ and $R^7$, when taken together with a common carbon to which they are attached, form a optionally substituted three- to seven-membered spirocyclyl, said optionally substituted three- to seven-membered spirocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

$R^8$ is selected from $-R^3$, Y, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$;

$R^{13}$ is selected from -H, $-C(=O)R^3$, $-C(=O)OR^3$, $-C(=O)SR^3$, $-SO_2R^3$, $-C(=O)N(R^3)R^3$, and optionally substituted $C_{1-6}$alkyl;

two $R^{13}$, together with the atom or atoms to which they are attached, can combine to form a heteroalicyclic optionally substituted with between one and four of $R^{60}$, said heteroalicyclic comprising up to four annular heteroatoms, and said heteroalicyclic optionally comprising an aryl or heteroaryl fused thereto, in which case said aryl or heteroaryl is optionally substituted with an additional one to four of $R^{60}$;

$R^{14}$ is selected from -H, $-NO_2$, $-NH_2$, $-N(R^3)R^3$, -CN, $-OR^3$, optionally substituted $C_{1-6}$alkyl, optionally substituted heteroalicyclyl $C_{1-6}$alkyl, optionally substituted aryl, optionally substituted aryl $C_{1-6}$alkyl and optionally substituted heteroalicyclic;

$R^{15}$ is a group $-M^1-M^2$, wherein $M^1$ is selected from absent, $-C(=S)N(R^{13})-$, $-C(=NR^{14})N(R^{13})-$, $-SO_2N(R^{13})-$, $-SO_2-$, $-C(=O)N(R^{13})-$, $-C(=O)C(=O)N(R^{13})-$, $-C_{0-4}$alkylene-, -C(=O)-, and an optionally substituted four to six-membered heterocyclyl containing between one and three heteroatoms but comprising at least one nitrogen; and $M^2$ is selected from -H, $-C_{0-6}$alkyl, alkoxy, $-C(=O)C_{0-4}$alkylQ, $-C_{0-4}$alkylQ, $-OC_{0-4}$alkylQ-, $-N(R^{13})C_{0-4}$alkylQ-, and $-C(=O)N(R^{13})C_{0-4}$alkylQ;

$R^{60}$ is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted $C_{1-6}$alkyl, optionally substituted aryl, optionally substituted heteroaryl $C_{1-6}$alkyl, and optionally substituted aryl $C_{1-6}$alkyl;

two of $R^{60}$, when attached to a non-aromatic carbon, can be oxo;

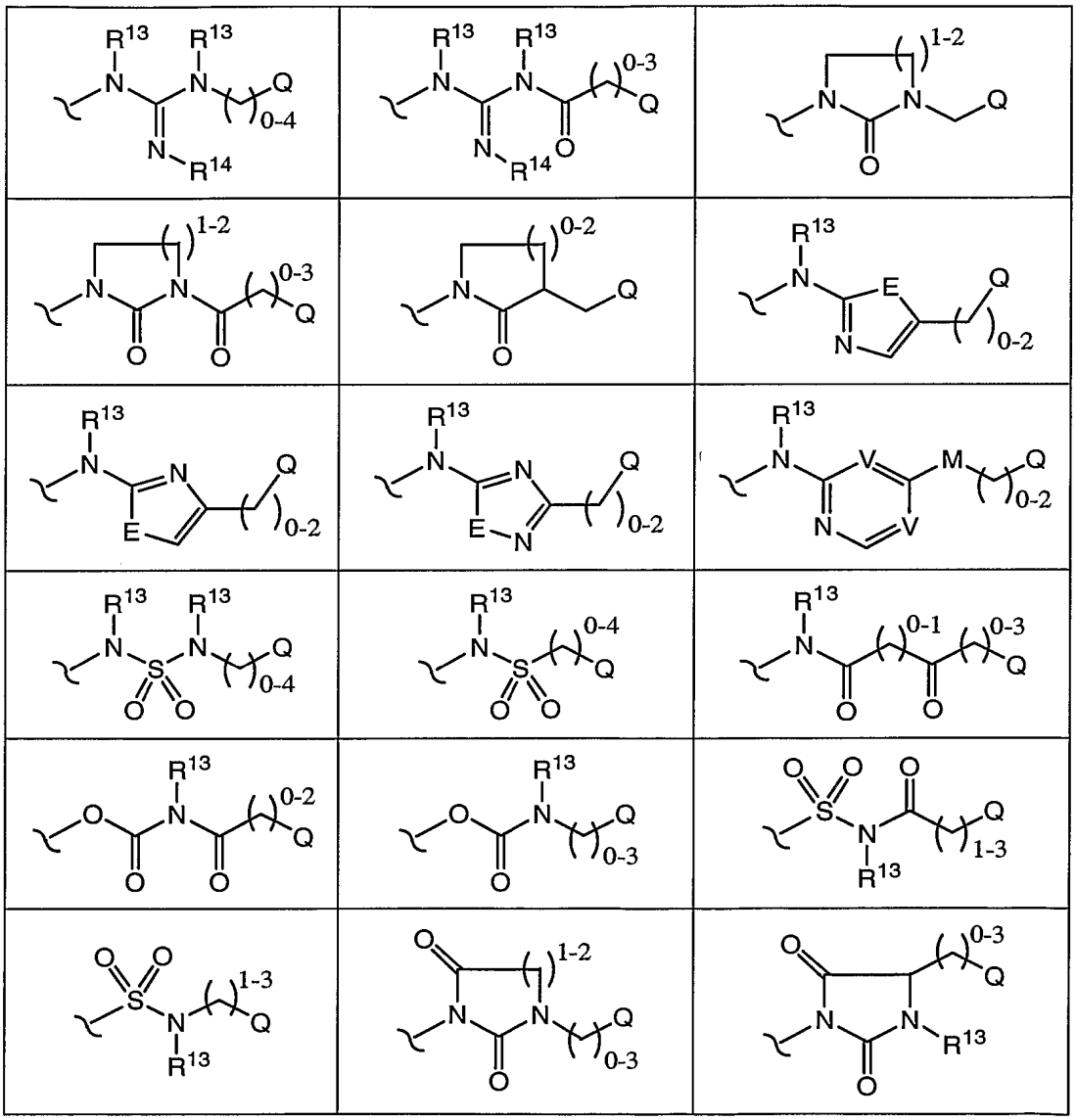
$P^1$ is a suitable leaving group; and

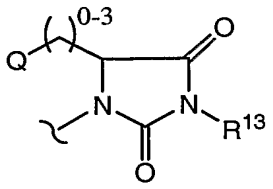
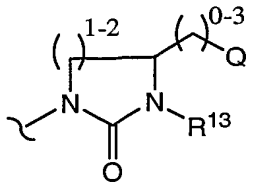
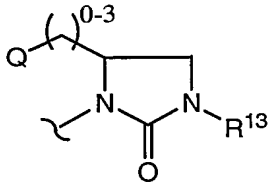
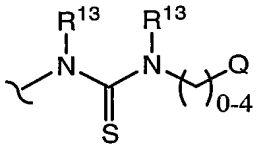
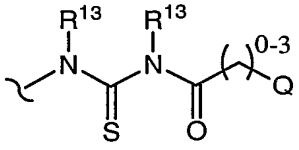
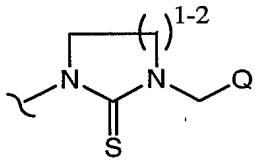
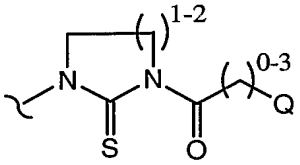
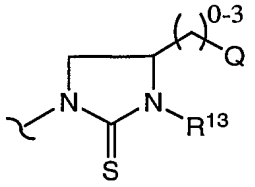
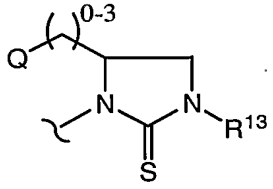
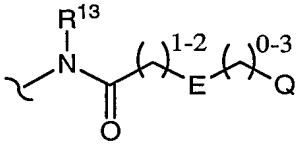
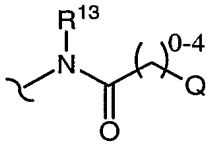
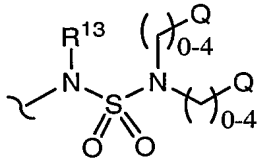
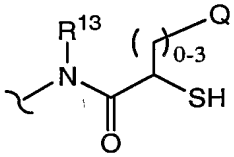
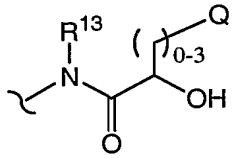
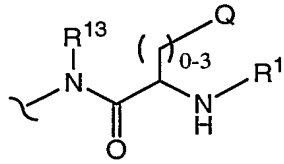
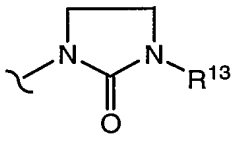
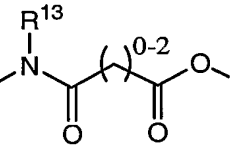
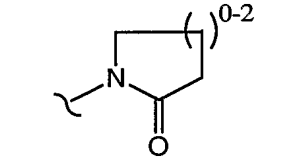
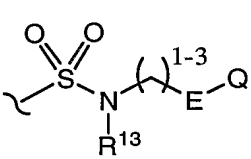
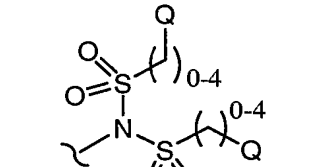
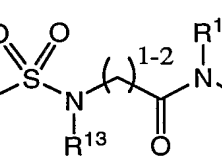
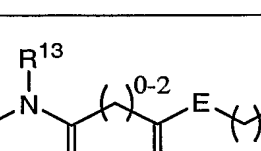
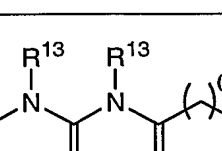
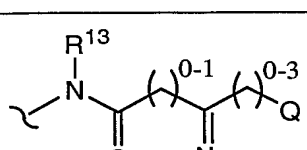
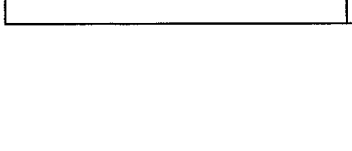
$P^2$ is selected from -H, a metal, and a group removed *in-situ* when combining **XXII** and **XXIII** to make **XXI**.

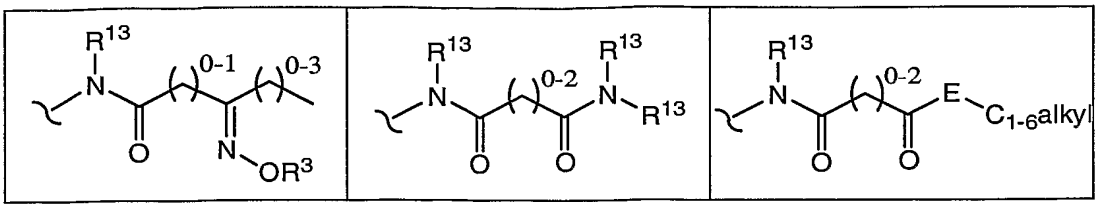
116. The process according to claim 115, wherein Ar is *para*-phenylene as defined by the substitution pattern of -Z- and -B-L-T about said phenylene.

117. The process according to claim 116, wherein Z is either -O- or $-NR^5-$.

118. The process according to claim 117, wherein -B-L-T is selected from the following:



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wherein Q, $R^{20}$, and $R^{13}$ are as defined above; each E is selected from -O-, -N($R^{13}$)-, -$CH_2$, and -S(O)$_{0-2}$-; M is selected from -O-, -N($R^{13}$)-, -$CH_2$-, and -C(=O)N($R^{13}$)-; each V is independently either =N- or =C(H)-; each methylene in any of the above formulae is independently optionally substituted with $R^{25}$; and $R^{25}$ is selected from halogen, trihalomethyl, -CN, -$NO_2$, -$NH_2$, -$OR^3$, -$NR^3R^3$, -S(O)$_{0-2}R^3$, -$SO_2NR^3R^3$, -$CO_2R^3$, -C(O)$NR^3R^3$, -N($R^3$)$SO_2R^3$, -N($R^3$)C(O)$R^3$, -N($R^3$)$CO_2R^3$, -C(O)$R^3$, optionally substituted aryl, optionally substituted aryl $C_{1-6}$alkyl, heteroaryl $C_{1-6}$alkyl, and optionally substituted $C_{1-6}$alkyl; two of $R^{25}$, together with the carbon or carbons to which they are attached, can combine to form an optionally substituted three- to seven-membered alicyclic or heteroalicyclic; two of $R^{25}$ on a single carbon can be oxo.

119. The process according to claim 118, wherein there is one of $R^1$ that is -D-$R^{50}$ and another of $R^1$ that is -$OR^{3a}$.

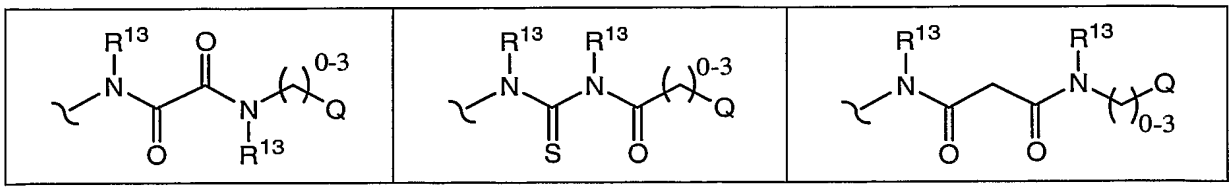
120. The process according to claim 119, wherein D is -O-.

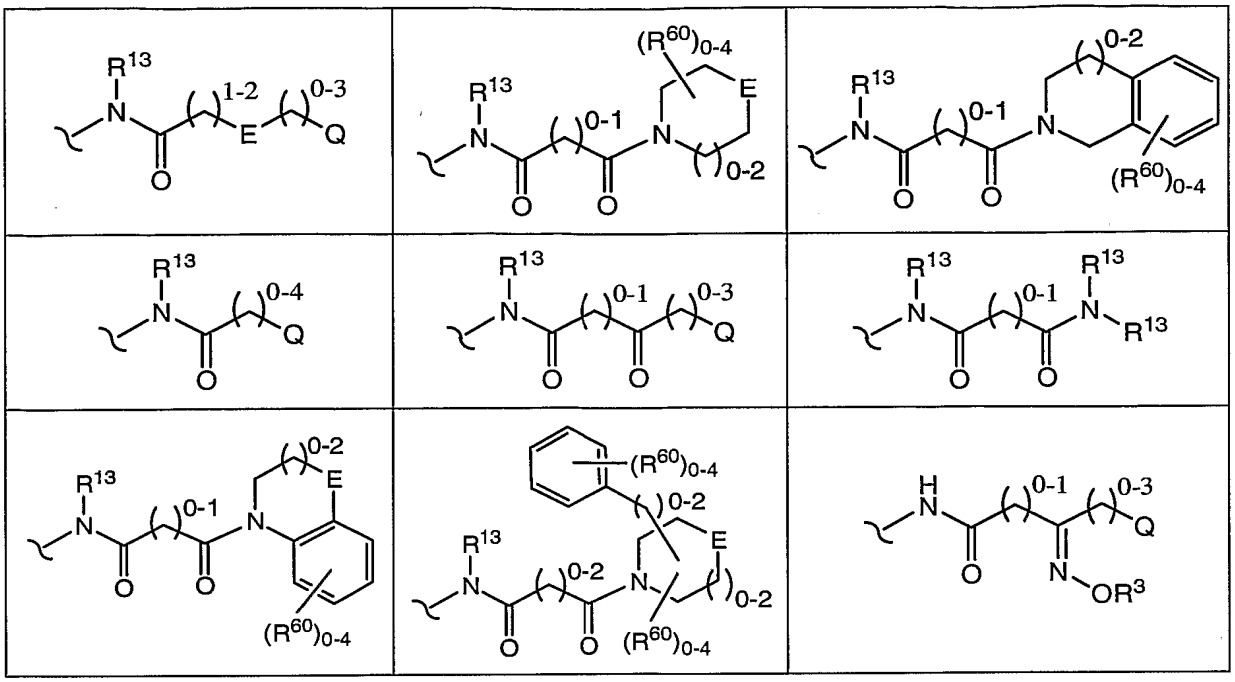
121. The process according to claim 120, wherein -O-$R^{50}$ and -$OR^{3a}$ are interchangeably located at the 6-position and 7-position of the quinazoline or quinoline according to Formula **XXI**.

122. The process according to claim 121, wherein -$OR^{3a}$ is selected from -OH, -OSi($R^5$)($R^5$)$R^5$, and optionally substituted -O$C_{1-6}$alkyl.

123. The process according to claim 122, wherein J is =N- or =C(H)-.

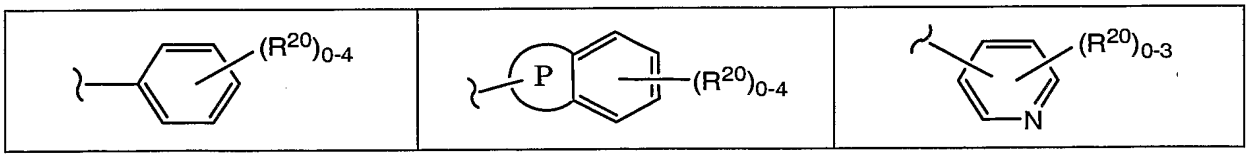
124. The process according to claim 123, wherein -B-L-T is selected from:





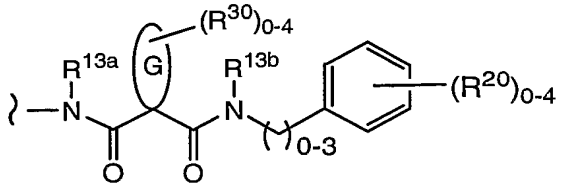
wherein Q, $R^{20}$, $R^{13}$, E, and $R^{60}$ are as defined above; each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with $R^{25}$; and $R^{25}$ is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted aryl $C_{1-6}$alkyl, heteroaryl $C_{1-6}$alkyl, and optionally substituted $C_{1-6}$alkyl; two of $R^{25}$, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered optionally substituted alicyclic or heteroalicyclic.

125. The process according to claim 124, wherein Q is selected from the following three formula:

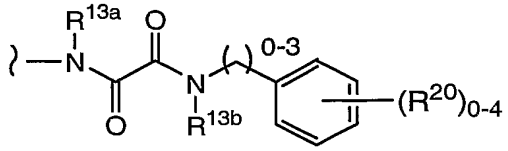


wherein $R^{20}$ is defined as above, and P is a five- to seven-membered ring, including the two shared carbons of the aromatic ring to which P is fused, P optionally containing between one and three heteroatoms.

126. The process according to claim 125, wherein -B-L-T is either of formula **XXV** or formula **XXVI**,



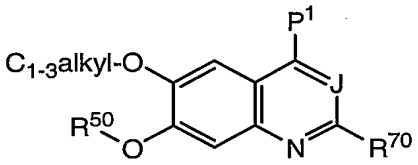
XXV



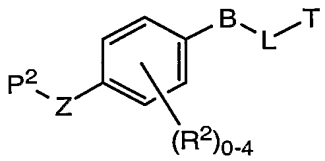
XXVI

wherein $R^{20}$ is defined as above; G is either an optionally substituted cycloalkyl or an optionally substituted heteroalicyclic; each $R^{30}$ is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted $C_{1-6}$alkyl; and $R^{3a}$ and $R^{3b}$ are each independently selected from -H and optionally substituted $C_{1-6}$alkyl.

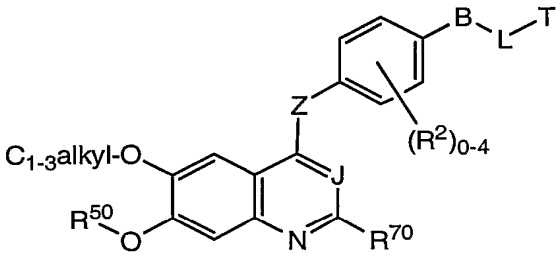
127. The process according to claim 126, wherein a compound of formula **XXIIa** is combined with a compound of formula **XXIIIa** to make a compound of formula **XXIa**,



XXIIa



XXIIIa



XXIa

wherein -B-L-T, Z, J, $R^{50}$, and $R^2$ are as defined above; $R^{70}$ is selected from -H, $-NO_2$, $-NH_2$, and $-NR^3R^3$; provided when Z is $-N(R^5)-$ that $R^5$ is selected from -H, $C_{1-3}$alkyl, and aryl $C_{1-3}$alkyl; $P^1$ is selected from halogen, optionally substituted alkyl-$S(O)_{0-2}$-, optionally substituted arylsulfonate, optionally substituted alkylsulfonate, a group containing boron, an azide, a group containing phosphorus, and a metal; and $P^2$ is selected from -H and a metal.

128. The process according to claim 127, wherein $P^2$ is selected from -H, lithium, sodium, potassium, cesium, copper, palladium, and titanium.

129. The process according to claim 128, wherein Z is -O-.

130. The process according to claim 129, wherein $P^1$ is selected from chlorine, bromine, a toluene sulfonate, and trifluoromethansulfonate.

131. The process according to claim 130, wherein $R^{70}$ is -H.

132. The process according to claim 131, wherein J is =C(H)-.

133. The process according to claim 132, wherein $R^2$ is selected from $C_{1-6}$ alkyl, perfluoro $C_{1-6}$ alkyl, and halogen.

134. The process according to claim 133, wherein **XXIIa** and **XXIIIa** are heated together, optionally with a base, optionally with microwave radiation, to form **XXIa**.

135. The process according to claim 134, wherein the base is selected from an organic base, an inorganic base, and a combination of an organic base and an inorganic base.

136. The process according to claim 135, wherein the base is selected from 2,6-lutidine, 4-N,N-dimethylaminopyridine, and a metal carbonate.

137. The process according to claim 136, wherein **XXIIa** and **XXIIIa** are heated together in a solvent with said base, at between about 40°C and 200°C for between about one hour and twenty-four hours to form **XXIa**.

138. The process according to claim 137, wherein the solvent is an organic solvent.

139. The process according to claim 138, wherein one molar equivalent of **XXIIa** is combined with between about one quarter and four molar equivalents of **XXIIIa**.

140. The process according to claim 139, wherein one molar equivalent of **XXIIa** is combined with more than one but less than two molar equivalents of **XXIIIa**.

141. The process according to claim 140, wherein **XXIIa** is combined with **XXIIIa** and said base in an aromatic solvent to form a mixture, and said mixture is heated to between about 100°C and 200°C for between about one and ten hours to form **Ia**.

142. The process according to claim 141, wherein the aromatic solvent is an optionally substituted benzene.

143. The process according to claim 142, wherein the aromatic solvent is bromobenzene.

144. The process according to claim 143, wherein the base is 4-N,N-dimethylaminopyridine.

145. The process according to claim 144, wherein said mixture is heated to reflux for between about three and seven hours.

146. The process according to claim 145, wherein said mixture is heated to reflux for between about four and six hours.

147. The process according to claim 140, wherein **XXIIa** is combined with **XXIIIa** and said base in a non-aromatic solvent to form a mixture, and said mixture is heated to between about 40°C and 100°C for between about one and twenty hours to form **XXIa**.

148. The process according to claim 147, wherein the non-aromatic solvent comprises a functional group selected from an amide, and ether, a nitrile, a halide, an ester, an amine, and a ketone.

149. The process according to claim 148, wherein the non-aromatic solvent is N,N-dimethylacetamide.

150. The process according to claim 149, wherein the base is potassium carbonate.

151. The process according to claim 150, wherein said mixture is heated to about 50°C between about ten and twenty hours.

152. The process according to claim 151, wherein the aromatic solvent is an optionally substituted pyridine.

153. The process according to claim 152, wherein the aromatic solvent is 2,6-lutidine.

154. The process according to claim 153, wherein the base is 2,6-lutidine.

155. The process according to claim 154, wherein said mixture is heated to reflux for between about three and seven hours.

156. The process according to claim 155, wherein said mixture is heated to reflux for between about four and six hours.

157. The process according to claim 139, wherein one molar equivalent of **XXIIIa** is combined with more than one but less than two molar equivalents of **XXIIa**.

158. The process according to claim 157, wherein **XXIIa** is combined with **XXIIIa** and said base in an aromatic solvent to form a mixture, and said mixture is heated to between about 100°C and 200°C for between about ten and twenty hours to form **XXIa**.

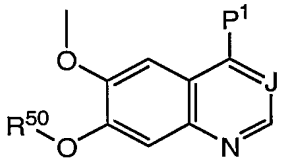
159. The process according to claim 158, wherein the aromatic solvent is an optionally substituted pyridine.

160. The process according to claim 159, wherein the aromatic solvent is 2,6-lutidine.

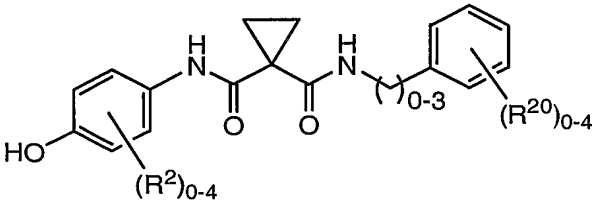
161. The process according to claim 160, wherein the base is 2,6-lutidine.

162. The process according to claim 161, wherein said mixture is heated to between about 150°C and 200°C for between about fifteen and twenty hours.

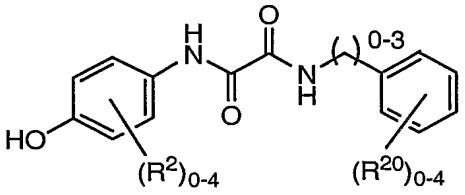
163. The process according to any of claims 134 - 162, wherein a compound of formula **XXIIb** is substituted for the compound of formula **XXIIa**, and either a compound of formula **XXIIIb** or a compound of formula **XXIIIc** is substituted for the compound of formula **XXIIIa**, in order to make a compound of formula **XXIb** or a compound of formula **XXIc**, respectively,



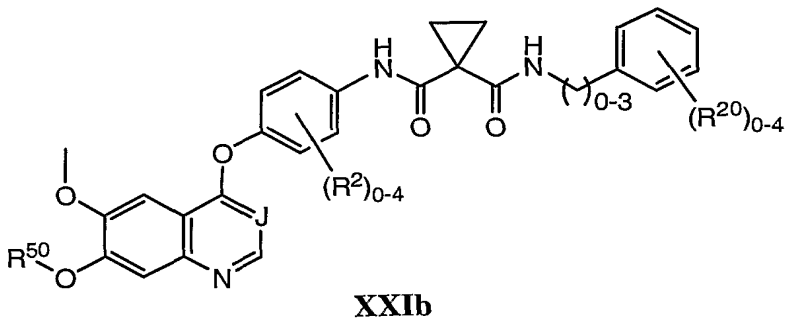

**XXIIb**



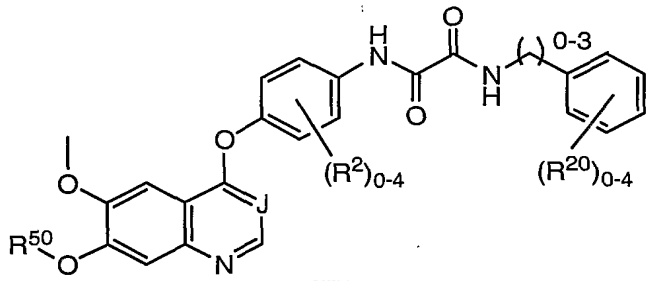

**XXIIIb**




**XXIIIc**



**XXIb**



**XXIc**

wherein J, $R^{50}$, $R^{20}$ and $R^2$ are as defined above.

164. The process according to claim 163, wherein $R^2$, if present, is halogen.

165. The process according to claim 164, wherein $R^2$, if present, is fluorine.

166. The process according to claim 165, wherein $R^2$, if present, is up to two fluorines *ortho* to the oxygen of the phenylene to which $R^2$ is attached.

167. The process according to claim 115, used to make a compound listed in either Table 1 or Table 2.

168. The process according to any of claims 115 - 167, further comprising converting said compound to a pharmaceutically acceptable salt, hydrate, or prodrug thereof.

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# BIB DATA SHEET

**CONFIRMATION NO. 6725**

| SERIAL NUMBER | FILING or 371(c) DATE<br>RULE | CLASS | GROUP ART UNIT | ATTORNEY DOCKET NO. |
|---|---|---|---|---|
| 13/984,559 | 03/20/2014 | 514 | 1625 | 224990/10-039C-US/343999 |

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**INVENTORS**

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**** CONTINUING DATA ***************************

This application is a 371 of PCT/US12/24591 02/10/2012
which claims benefit of 61/441,520 02/10/2011
and claims benefit of 61/441,527 02/10/2011

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **

| Foreign Priority claimed ☐ Yes ☑ No<br>35 USC 119(a-d) conditions met ☐ Yes ☐ No<br>Verified and Acknowledged /TIMOTHY R ROZOF/ Examiner's Signature | ☐ Met after Allowance<br>TRR Initials | STATE OR COUNTRY | SHEETS DRAWINGS | TOTAL CLAIMS | INDEPENDENT CLAIMS |
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**TITLE**

PROCESSES FOR PREPARING QUINOLINE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH COMPOUNDS

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**EAST Search History**

**EAST Search History (Prior Art)**

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | Time Stamp |
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| L4 | 494 | L3 and (protein near3 kinase) | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | ON | 2016/04/28 12:34 |
| L5 | 96 | L4 and ((c$met) or (Ret)) | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | ON | 2016/04/28 12:34 |
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| S31 | 96 | S30 and ((c$met) or (Ret)) | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | ON | 2016/01/07 13:23 |
| S32 | 2 | ("20070054928").PN. | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | OFF | 2016/01/07 13:23 |
| S33 | 755 | S29 and (compound near3 (IA or IB)) | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | ON | 2016/01/07 13:23 |
| S34 | 12 | S31 and (compound near3 (IA or IB)) | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | ON | 2016/01/07 13:23 |
| S35 | 0 | ((A61K31/47.cpc.) or (C07D215/233.cpc.)).CCLS. | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | OFF | 2016/01/07 13:33 |
| S36 | 5706 | A61K31/47.cpc. C07D215/233.cpc. | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | ON | 2016/01/07 13:33 |
| S37 | 4165 | S36 and @ad<="20110210" | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | ON | 2016/01/07 13:33 |
| S38 | 546 | S37 and (protein near3 kinase) | US-PGPUB; USPAT; USOCR; EPO; JPO; | OR | ON | 2016/01/07 13:34 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | DERWENT | | | |
| S39 | 81 | S38 and (compound near3 (IA or IB)) | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | ON | 2016/01/07 13:34 |

**EAST Search History (Interference)**

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | Time Stamp |
|---|---|---|---|---|---|---|
| S9 | 1 | ((546/153) or (514/312)).CCLS. | | OR | OFF | 2014/10/04 13:43 |
| S18 | 1 | ((546/153) or (514/312)).CCLS. | | OR | OFF | 2015/06/03 13:56 |
| S40 | 0 | ((546/153) or (514/312)).CCLS. | | OR | OFF | 2016/01/07 13:23 |
| S41 | 0 | ((546/153) or (514/312)).CCLS. | | OR | OFF | 2016/01/07 13:23 |

**4/ 28/ 2016 12:36:54 PM**
**C:\ Users\ trozof\ Documents\ EAST\ Workspaces\ 13984559.wsp**

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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# REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
## (Submitted Only via EFS-Web)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Application Number | 13/984,559 | Filing Date | 2014-03-20 | Docket Number (if applicable) | 224990/10-039C-US/343999 | Art Unit | 1625 |
| First Named Inventor | Jo Ann Wilson | | | Examiner Name | Timothy R. Rozof | | |

**This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.**
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

### SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

### MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

### FEES

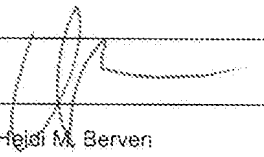
☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 503145

### SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature
☐ Applicant Signature

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| Signature of Registered U.S. Patent Practitioner | | | |
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| Signature |  | Date (YYYY-MM-DD) | 2016-04-20 |
| Name | Heidi M. Berven | Registration Number | 48951 |

This collection of information is required by 37 CFR 1.114. 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.

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**(Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13984559 |
| Filing Date | 2014-03-20 |
| First Named Inventor | Jo Ann Wilson |
| Art Unit | 1625 |
| Examiner Name | Timothy R. Rozof |
| Attorney Docket Number | 224990/10-039C-US/343999 |

## U.S.PATENTS

| 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 |
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| | 1 | 2009136663 | WO | | 2009-11-12 | TAKEDA PHARMACEUTICAL COMPANY LIMITED | | ☐ |

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| 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] |
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| INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13984559 |
| | Filing Date | 2014-03-20 |
| | First Named Inventor | Jo Ann Wilson |
| | Art Unit | 1625 |
| | Examiner Name | Timothy R. Rozof |
| | Attorney Docket Number | 224990/10-039C-US/343999 |

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| INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13984559 |
| | Filing Date | 2014-03-20 |
| | First Named Inventor | Jo Ann Wilson |
| | Art Unit | 1625 |
| | Examiner Name | Timothy R. Rozof |
| | Attorney Docket Number | 224990/10-039C-US/343999 |

**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 | | Date (YYYY-MM-DD) | 2016-04-20 |
| Name/Print | Heidi M Berven | Registration Number | 48951 |

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.**

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

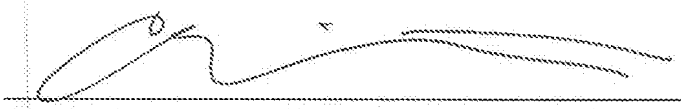
| | | | |
|---|---|---|---|
| Inventor: | Jo Ann Wilson | Art Unit: | 1625 |
| Application No.: | 13/984,559 | Examiner: | Timothy R. Rozof |
| Filing Date: | March 20, 2014 | Conf. No.: | 6725 |
| Atty. Docket No.: | 224990/10-039C-US/343999 | | |

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

**CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. § 1.8(a)**

The undersigned hereby certifies that the following documents are being electronically filed in accordance with 37 C.F.R. § 1.6(a)(4) on this 20th day of April, 2016:

1. Cover Letter to the Commissioner for Patents;
2. Request for Continued Examination under 37 C.F.R. § 1.114;
3. Request for Continued Examination Transmittal (PTO/SB/30);
4. Information Disclosure Statement (PTO/SB/08A);
5. Foreign Patent Document (1); and
6. This Certificate of Transmission under 37 C.F.R. § 1.8(a).



Charles Gregg-Geist (for Heidi M. Berven, Ph.D., Reg. No.: 48,951)

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(19) World Intellectual Property Organization
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*C07D 471/04* (2006.01) *A61K 31/437* (2006.01)
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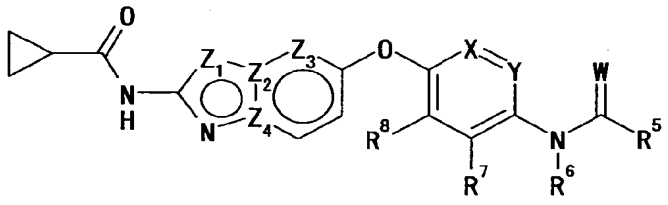
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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**Published**:
— *with international search report (Art. 21(3))*
— *with sequence listing part of description (Rule 5.2(a))*

(54) Title: FUSED HETEROCYCLIC DERIVATIVES AND USE THEREOF



(57) Abstract: The present invention provides a fused heterocyclic derivative having a strong kinase inhibitory activity and use thereof. The present invention relates to a compound represented by the formula wherein each symbol is as defined in the present specification, or a salt thereof.

WO 2009/136663 A1

# DESCRIPTION

# FUSED HETEROCYCLIC DERIVATIVES AND USE THEREOF

## Technical Field

The present invention relates to a fused heterocyclic derivative having a potent kinase inhibitory activity and useful for the prophylaxis or treatment of cancer and the like, and use thereof.

(Background of the Invention)

For a solid tumor to grow to a certain size or above, angiogenesis is essential for ensuring sufficient supply of nutrition and oxygen to cancer cell (see, for example, Non Patent Literature 1). One of the important factors causing angiogenesis toward tumor, a vascular endothelial growth factor (VEGF) is known. VEGF is bound to a vascular endothelial growth factor receptor (VEGFR) expressed on vascular endothelial cells and transmits signal for cell proliferation (see, for example, Non Patent Literature 2). Accordingly, inhibition of the VEGF-VEGFR signal transduction system is considered to enable suppression of angiogenesis and tumor growth (see, for example, Non Patent Literature 3). Moreover, since tumor blood vessels are involved in cancer hematogenous metastasis, inhibition of angiogenesis is considered to be effective for suppression of cancer metastasis.

Hepatocyte growth factor (HGF) is known to promote growth of vascular endothelial cell via its receptor (c-Met), and cause angiogenesis (see, for example, Non Patent Literature 4). It has been clarified that c-Met is highly expressed in various types of cancers (colorectal cancer, gastric cancer, lung cancer, kidney cancer, breast cancer, ovary cancer, prostate cancer and the like), and is deeply involved in the growth and survival of cancer cells (see, for example, Non Patent Literature 5). Therefore, cancer cell growth is expected to be suppressed by inhibiting c-Met. Moreover, activation of c-Met is also involved in the invasion

and metastasis of cancer cells (see, for example, Non Patent Literature 6), and inhibition of c-Met is considered to be effective for the prevention of invasion or metastasis of cancer.

Tyrosine Kinase with Immunoglobulin and Epidermal Growth homology domain 2 (TIE2) is a receptor of angiopoietin (angiopoietin 1 and angiopoietin 2), mainly expressed in vascular endothelial cells and is known to be indispensable for the development of blood vessels in the fetal stages (see, for example, Non Patent Literature 7). It has been reported that inhibition of binding of angiopoietin with solubilized form TIE2 etc. decreases tumor blood vessel density and suppresses tumor growth in non-clinical model (see, for example, Non Patent Literature 8). The system of angiopoietin TIE2 is suggested to play a key role in the tumor angiogenesis, along with the VEGF-VEGFR system. Therefore, inhibition of TIE2 is considered to suppress angiogenesis as well as tumor growth.

Fms Like Tyrosine Kinase 3 (FLT3) is mutated most frequently in acute myelocytic leukemia (AML), and is known to be constitutively activated even in the absence of a ligand, by length mutation (FLT3-ITD mutation) of transmembrane portion, which is called Internal Tandem Duplication (ITD), or activated mutation of tyrosine kinase portion (see, for example, Non Patent Literature 9). It is considered that signals from FLT3 activate downstream AKT, extracellular signal regulated kinase (ERK), signal transducer and activator of transcription (STAT5), and are involved in the growth of leukemia cells and suppression of differentiation (see, for example, Non Patent Literature 10). Particularly, the FLT3-ITD mutation observed in 20-30% of AML patients has been reported to correlate with poor life prognosis (see, for example, Non Patent Literature 11). Therefore, inhibition of FLT3 is considered to suppress growth of leukemia cells.

As compounds inhibiting kinase including VEGFR and c-Met, phthalazine derivatives (see, for example, Patent Literature 1), pyrrole-substituted 2-indolinone derivatives (see, for example, Patent Literature 2), quinazoline derivatives (see, for example, Patent Literature 3), ω-carboxyaryl-substituted diphenylurea derivatives (see, for example, Patent Literature 4), quinoline derivatives and quinazoline derivatives (see, for example, Patent Literature 5), nitrogen-containing aromatic ring derivatives (see, for example, Patent Literature 6), quinoline derivative and quinazoline derivative (see, for example, Patent Literature 7) and the like are known.

(Citation List)

Patent Literature

PTL 1: WO98/35958

PTL 2: WO01/60814

PTL 3: WO01/32651

PTL 4: WO00/42012

PTL 5: WO00/43366

PTL 6: WO02/32872

PTL 7: WO03/000660

Non Patent Literature

NPL 1: New England Journal of Medicine, 1971, vol. 285, No. 21, pages 1182-1186

NPL 2: Endocrine Reviews, 1997, vol. 18, No. 1, pages 4-25

NPL 3: Drug Discovery Today, 2001, vol. 6, No. 19, pages 1005-1024

NPL 4: EXS, 1997, vol. 79, pages 193-208

NPL 5: Cytokine & Growth Factor Reviews, 2002, vol. 13, No. 1, pages 41-59

NPL 6: Nature Reviews Molecular Cell Biology, 2003, vol. 4, No. 12, pages 915-925

NPL 7: Genes and Development, 1994, vol. 8, No. 16, pages 1897-1909

NPL 8: The Journal of Clinical investigation, 1997, No. 100,

No. 8, pages 2072-2078
NPL 9: Leukemia, 1996, vol. 10, No. 12, pages 1911-1918
NPL 10: Blood, 2000, vol. 96, No. 12, pages 3907-3914
NPL 11: Blood, 2001, vol. 98, No. 6, pages 1752-1759

## Summary of Invention

(Technical Problem)

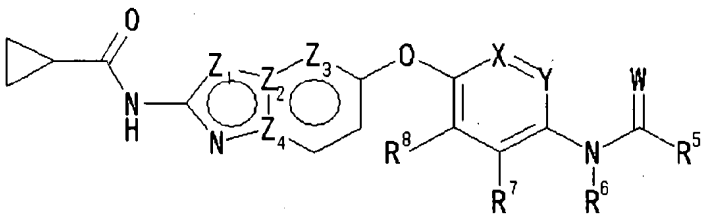
A kinase inhibitor superior in the affinity for kinase, efficacy expression, pharmacokinetics, solubility, interaction with other pharmaceutical products, safety and stability is expected to show a therapeutically superior effect. At present, however, such inhibitor superior in the affinity for kinase, and sufficiently satisfactory in the efficacy expression, pharmacokinetics, solubility, interaction with other pharmaceutical products, safety and stability has not been found. Thus, there is a demand for the development of a compound having a superior kinase inhibitory activity, and sufficiently satisfactory as a pharmaceutical product. Accordingly, an object of the present invention is to provide a compound having a superior kinase inhibitory activity, low toxic and sufficiently satisfactory as a pharmaceutical product.

(Solution to Problem)

The present inventors have conducted intensive studies in an attempt to solve the above-mentioned problems and found that a compound represented by the following formula or a salt thereof has a superior kinase inhibitory activity, which resulted in the completion of the present invention.

Accordingly, the present invention provides the following.

[1] A compound represented by the formula (I):



wherein $Z_1$, $Z_2$, $Z_3$ and $Z_4$ are in the following combination:
$(Z_1, Z_2, Z_3, Z_4) = (CR^1, N, CR^2, C)$,
$(N, N, CR^2, C)$,
$(N, C, CR^2, N)$,
$(S, C, CR^2, C)$, or
$(S, C, N, C)$;

$R^1$ and $R^2$ are the same or different and each is
(1) a hydrogen atom,
(2) a halogen atom,
(3) a group bonded via a carbon atom,
(4) a group bonded via a nitrogen atom,
(5) a group bonded via an oxygen atom, or
(6) a group bonded via a sulfur atom;

W is O or S;

X is $CR^3$ ($R^3$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl), or N;

Y is $CR^4$ ($R^4$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl), or N;

$R^5$ is
(1) $C_{3-6}$ cycloalkyl optionally having one $C_{6-10}$ aryl-aminocarbonyl optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl,
(2) $C_{1-6}$ alkyl-carbonylamino optionally having one $C_{6-10}$ aryl,
(3) $C_{1-6}$ alkoxy optionally having one $C_{6-10}$ aryl, or
(4) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from
(a) $C_{6-10}$ aryl optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl,
(b) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and
(c) oxo;

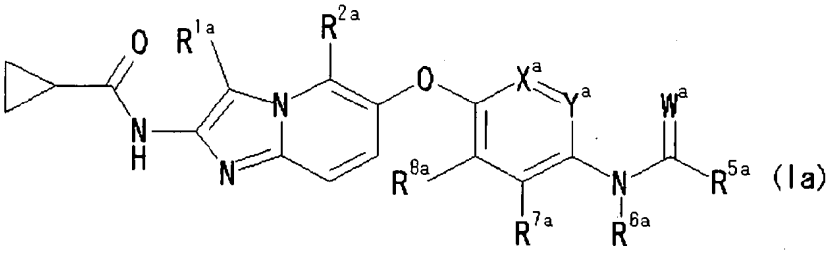
$R^6$ is a hydrogen atom;

$R^7$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl; and

$R^8$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl,

or a salt thereof (to be referred to as "compound (I)" in the present specification);

[2] a compound represented by the formula



(Ia)

wherein $R^{1a}$ and $R^{2a}$ are the same or different and each is

(1) a hydrogen atom,

(2) a halogen atom,

(3) a group bonded via a carbon atom,

(4) a group bonded via a nitrogen atom,

(5) a group bonded via an oxygen atom, or

(6) a group bonded via a sulfur atom;

$W^a$ is O or S;

$X^a$ is $CR^{3a}$ ($R^{3a}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl), or N;

$Y^a$ is $CR^{4a}$ ($R^{4a}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl), or N;

$R^{5a}$ is

(1) $C_{3-6}$ cycloalkyl optionally having one $C_{6-10}$ aryl-aminocarbonyl optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl,

(2) $C_{1-6}$ alkyl-carbonylamino optionally having one $C_{6-10}$ aryl,

(3) $C_{1-6}$ alkoxy optionally having one $C_{6-10}$ aryl, or

(4) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from

(a) $C_{6-10}$ aryl optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl,

(b) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and

(c) oxo;

$R^{6a}$ is a hydrogen atom;

$R^{7a}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl;
$R^{8a}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl,
or a salt thereof (to be referred to as "compound (Ia)" in the present specification);

[3] the compound of the above-mentioned [2] wherein
$R^{1a}$ is a hydrogen atom, a fluorine atom or methyl;
$R^{2a}$ is a hydrogen atom;
$W^a$ is O or S;
$X^a$ is CH, CF, CCl, $C(CH_3)$ or N;
$Y^a$ is CH, CF, CCl, $C(CH_3)$ or N;
$R^{5a}$ is
(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,
(2) acetylamino optionally having one phenyl,
(3) methoxy optionally having one phenyl,
(4) tert-butoxy, or
(5) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from
(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom, a chlorine atom, a bromine atom, methyl and isopropyl,
(b) methyl optionally having 1 to 3 fluorine atoms,
(c) ethyl optionally having 1 to 3 fluorine atoms,
(d) isopropyl, and
(e) oxo;
$R^{6a}$ is a hydrogen atom;
$R^{7a}$ is a hydrogen atom; and
$R^{8a}$ is a hydrogen atom;

[4] N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-N'-phenylcyclopropane-1,1-dicarboxamide or a salt thereof;

[5] N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-

1,2-dihydropyridine-3-carboxamide or a salt thereof;
[6] N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide or a salt thereof;
[7] N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)pyridin-2-yl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide or a salt thereof;
[8] a prodrug of the compound of the above-mentioned [1];
[9] a pharmaceutical agent comprising the compound of the above-mentioned [1] or a prodrug thereof;
[10] the pharmaceutical agent of the above-mentioned [9], which is a kinase inhibitor;
[11] the pharmaceutical agent of the above-mentioned [9], which is an agent for the prophylaxis or treatment of cancer;
[12] a method for the prophylaxis or treatment of cancer, which comprises administering an effective amount of the compound of the above-mentioned [1] or a prodrug thereof to the mammal;
[13] use of the compound of the above-mentioned [1] or a prodrug thereof for the production of an agent for the prophylaxis or treatment of cancer;
and the like.

(Advantageous Effects of Invention)

The compound (I) and a prodrug thereof have a strong inhibitory activity against kinases such as vascular endothelial growth factor receptor, hepatocyte growth factor receptor, angiopoietin receptor, Fms Like Tyrosine Kinase 3 (FLT3), platelet-derived growth factor receptor and the like, and have a strong angiogenesis inhibitory activity, cancer cell proliferation inhibitory action and the like. Therefore, they can provide clinically useful agents for the prophylaxis or treatment of cancer, cancer growth inhibitors or cancer invasion and/or metastasis suppressors. Moreover, compound (I) and a prodrug thereof can provide clinically useful agents for the

prophylaxis or treatment of applications to diseases other than cancer, such as chronic rheumatism, diabetic retinopathy and the like, and have excellent efficacy expression, pharmacokinetics, solubility, interaction with other pharmaceutical products, safety and stability.

(Detailed Description of the Invention)

The present invention is explained in detail in the following.

In the present specification, the term "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom or an iodine atom.

In the present specification, the term "$C_{1-6}$ alkyl" means, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl and the like.

In the present specification, the term "$C_{3-6}$ cycloalkyl" means, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

In the present specification, the term "$C_{6-10}$ aryl" means, for example, phenyl, naphthyl and the like.

In the present specification, the term "$C_{1-6}$ alkoxy" means methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like.

In the present specification, the term "$C_{1-6}$ alkyl-carbonylamino" means, for example, acetylamino, ethylcarbonylamino, propylcarbonylamino, isopropylcarbonylamino, butylcarbonylamino, isobutylcarbonylamino, sec-butylcarbonylamino, tert-butylcarbonylamino and the like.

In the present specification, the term "$C_{6-10}$ aryl-aminocarbonyl" means, for example, phenylaminocarbonyl, naphthylaminocarbonyl and the like.

In the present specification, the term "heterocyclic group" means, for example, a monocyclic aromatic heterocyclic group, a fused aromatic heterocyclic group or a nonaromatic

heterocyclic group.

The "monocyclic aromatic heterocyclic group" means, for example, a 5- to 7-membered (preferably 5- or 6-membered) monocyclic aromatic heterocyclic group containing, as a ring constituting atom besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (optionally oxidized) and a nitrogen atom, and the like. Examples thereof include furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), pyrazinyl (e.g., 2-pyrazinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (e.g., 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl), thiadiazolyl (e.g., 1,3,4-thiadiazol-2-yl), triazolyl (e.g., 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl), tetrazolyl (e.g., tetrazol-1-yl, tetrazol-5-yl), triazinyl (e.g., 1,3,5-triazin-2-yl) and the like.

The fused aromatic heterocyclic group includes a 9- to 12-membered fused aromatic heterocyclic group formed by fusion of a 5- to 7-membered monocyclic aromatic heterocyclic group containing, as ring-constituting atom besides carbon atom, 1 to 4 heteroatoms selected from an oxygen atom, a sulfur atom (optionally oxidized) and a nitrogen atom, and the like, and $C_{6-10}$ aryl and the like; a 8- to 12-membered fused aromatic heterocyclic group formed by fusion of 5- to 7-membered monocyclic aromatic heterocyclic groups, and the like. Examples thereof include quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-

quinolyl), isoquinolyl (e.g., 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl), quinazolyl (e.g., 2-quinazolyl, 4-quinazolyl), quinoxalyl (e.g., 2-quinoxalyl), benzofuryl (e.g., 2-benzofuryl, 3-benzofuryl), isobenzofuryl (e.g., 1-isobenzofuryl, 3-isobenzofuryl), benzothienyl (e.g., 2-benzothienyl, 3-benzothienyl), isobenzothienyl (e.g., 1-isobenzothienyl, 3-isobenzothienyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzothiazolyl (e.g., 2-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl), benzimidazolyl (e.g., benzimidazol-1-yl, benzimidazol-2-yl, benzimidazol-5-yl), indolyl (e.g., indol-1-yl, indol-2-yl, indol-3-yl, indol-4-yl, indol-5-yl, indol-6-yl), indazolyl (e.g., 1H-indazol-3-yl), pyrrolopyrazinyl (e.g., 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyrazin-6-yl), imidazopyridyl (e.g., 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl), imidazopyrazinyl (e.g., 1H-imidazo[4,5-b]pyrazin-2-yl), benzisoxazolyl (e.g., benzisoxazol-3-yl), benzotriazolyl (e.g., 1H-1,2,3-benzotriazol-5-yl), benzopyrazolyl (e.g., benzopyrazol-5-yl), pyrazolopyridyl (e.g., 1H-pyrazolo[4,3-c]pyridin-3-yl), pyrazolothienyl (e.g., 2H-pyrazolo[3,4-b]thiophen-2-yl), pyrazolotriazinyl (e.g., pyrazolo[5,1-c][1,2,4]triazin-3-yl) and the like.

Examples of the "nonaromatic heterocyclic group" include a 3- to 8-membered nonaromatic heterocyclic group containing, as a ring constituting atom besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (optionally oxidized) and a nitrogen atom, and the like. Examples thereof include oxiranyl (e.g., 2-oxiranyl), azetidinyl (e.g., 1-azetidinyl, 2-azetidinyl, 3-azetidinyl), oxetanyl (e.g., 2-oxetanyl, 3-oxetanyl), thietanyl (e.g., 2-thietanyl, 3-thietanyl), pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl), tetrahydrofuryl (e.g., 2-tetrahydrofuryl, 3-tetrahydrofuryl), thioranyl (e.g., 2-thioranyl, 3-thioranyl), piperidinyl (e.g., 1-piperidinyl, 2-piperidinyl, 3-piperidinyl,

4-piperidinyl), tetrahydropyranyl (e.g., 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl), thianyl (e.g., 2-thianyl, 3-thianyl), morpholinyl (e.g., 2-morpholinyl, 3-morpholinyl, 4-morpholinyl), thiomorpholinyl (e.g., 2-thiomorpholinyl, 3-thiomorpholinyl, 4-thiomorpholinyl), piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl), azepanyl (e.g., 1-azepanyl, 3-azepanyl), oxepanyl (e.g., 3-oxepanyl), thiepanyl (e.g., 3-thiepanyl), oxazepanyl (e.g., 1,4-oxazepan-4-yl, 1,4-oxazepan-5-yl), thiazepanyl (e.g., 1,4-thiazepan-4-yl, 1,4-thiazepan-5-yl), azocanyl (e.g., 1-azocanyl, 4-azocanyl), oxocanyl (e.g., 4-oxocanyl), thiocanyl (e.g., 4-thiocanyl), oxazocanyl (e.g., 1,4-oxazocan-5-yl), thioazocanyl (e.g., 1,4-thioazocan-5-yl), dioxinyl (e.g., 1,4-dioxin-2-yl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-1-yl, 2,3-dihydropyrazol-3-yl, 2,3-dihydropyrazol-4-yl, 2,3-dihydropyrazol-5-yl), hexahydropyrimidinyl (e.g., hexahydropyrimidin-1-yl, hexahydropyrimidin-2-yl, hexahydropyrimidin-4-yl, hexahydropyrimidin-5-yl), tetrahydropyrimidinyl (e.g., 1,2,3,4-tetrahydropyrimidin-1-yl, 1,2,3,4-tetrahydropyrimidin-2-yl, 1,2,5,6-tetrahydropyrimidin-1-yl, 1,2,5,6-tetrahydropyrimidin-2-yl), dihydropyrimidinyl (e.g., 1,2-dihydropyrimidin-1-yl, 1,2-dihydropyrimidin-2-yl), tetrahydropyridyl (e.g., 1,2,3,4-tetrahydropyridin-1-yl, 1,2,3,4-tetrahydropyridin-2-yl, 1,2,5,6-tetrahydropyridin-1-yl, 1,2,5,6-tetrahydropyridin-2-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl), tetrahydroimidazolyl (e.g., tetrahydroimidazol-1-yl, tetrahydroimidazol-2-yl, tetrahydroimidazol-4-yl), dihydroimidazolyl (e.g., 4,5-dihydroimidazol-1-yl, 4,5-dihydroimidazol-2-yl, 4,5-dihydroimidazol-4-yl, 4,5-dihydroimidazol-5-yl) and the like.

In the present specification, the term "group bonded via a carbon atom" means, for example, cyano, a hydrocarbon group

optionally having substituent(s), a heterocyclic group bonded via a carbon atom optionally having substituent(s) and the like.

Examples of the "hydrocarbon group optionally having substituent(s)" include alkyl optionally having substituent(s), alkenyl optionally having substituent(s), alkynyl optionally having substituent(s), cycloalkyl optionally having substituent(s), cycloalkenyl optionally having substituent(s), aryl optionally having substituent(s), cycloalkyl-alkyl optionally having substituent(s), cycloalkenyl-alkyl optionally having substituent(s), aryl-alkyl optionally having substituent(s), cycloalkanedienyl optionally having substituent(s) and the like.

In the present specification, the term "alkyl optionally having substituent(s)" means $C_{1-6}$ alkyl optionally having 1 to 3 substituents selected from the following substituent group (hereinafter to be abbreviated as substituent group A).

substituent group A:

(1) a halogen atom;

(2) cyano;

(3) nitro;

(4) hydroxy;

(5) $C_{1-6}$ alkoxy optionally having 1 to 3 halogen atoms;

(6) $C_{2-6}$ alkenyloxy (e.g., ethenyloxy, propenyloxy, butenyloxy, pentenyloxy, hexenyloxy etc.) optionally having 1 to 3 halogen atoms;

(7) $C_{2-6}$ alkynyloxy (e.g., ethynyloxy, propynyloxy, butynyloxy, pentynyloxy, hexynyloxy etc.) optionally having 1 to 3 halogen atoms;

(8) $C_{3-6}$ cycloalkyloxy (e.g., cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy etc.) optionally having 1 to 3 halogen atoms;

(9) $C_{3-6}$ cycloalkenyloxy (e.g., cyclopropenyloxy, cyclobutenyloxy, cyclopentenyloxy, cyclohexenyloxy etc.)

optionally having 1 to 3 halogen atoms;
(10) $C_{6-10}$ aryloxy (e.g., phenyloxy, 1-naphthyloxy, 2-naphthyloxy etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);
(11) $C_{3-6}$ cycloalkyl-$C_{1-6}$ alkoxy (e.g., cyclopropylmethyloxy, cyclopropylethyloxy, cyclobutylmethyloxy, cyclopentylmethyloxy, cyclohexylmethyloxy, cyclohexylethyloxy etc.) optionally having 1 to 3 halogen atoms;
(12) $C_{3-6}$ cycloalkenyl-$C_{1-6}$ alkoxy (e.g., cyclopentenylmethyloxy, cyclohexenylmethyloxy, cyclohexenylethyloxy, cyclohexenylpropyloxy etc.) optionally having 1 to 3 halogen atoms;
(13) $C_{6-10}$ aryl-$C_{1-6}$ alkoxy (e.g., phenylmethyloxy, phenylethyloxy etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);
(14) $C_{1-6}$ alkylsulfamoyl (e.g., methylsulfamoyl, ethylsulfamoyl, propylsulfamoyl etc.);
(15) di-$C_{1-6}$ alkylsulfamoyl (e.g., dimethylsulfamoyl, diethylsulfamoyl, dipropylsulfamoyl etc.);
(16) $C_{1-6}$ alkylamino-carbonyl (e.g., methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl etc.);
(17) di-$C_{1-6}$ alkylamino-carbonyl (e.g., dimethylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl etc.);
(18) formyl;
(19) $C_{1-6}$ alkyl-carbonyl (e.g., acetyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl etc.);
(20) $C_{2-6}$ alkenyl-carbonyl (e.g., ethenylcarbonyl, propenylcarbonyl, butenylcarbonyl, pentenylcarbonyl, hexenylcarbonyl etc.);
(21) $C_{2-6}$ alkynyl-carbonyl (e.g., ethynylcarbonyl, propynylcarbonyl, butynylcarbonyl, pentynylcarbonyl, hexynylcarbonyl etc.);

(22) $C_{3-6}$ cycloalkyl-carbonyl (e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl etc.);

(23) $C_{3-6}$ cycloalkenyl-carbonyl (e.g., cyclopropenylcarbonyl, cyclobutenylcarbonyl, cyclopentenylcarbonyl, cyclohexenylcarbonyl etc.);

(24) $C_{6-10}$ aryl-carbonyl (e.g., benzoyl, 1-naphthylcarbonyl, 2-naphthylcarbonyl etc.);

(25) $C_{3-6}$ cycloalkyl-$C_{1-6}$ alkyl-carbonyl (e.g., cyclopropylmethylcarbonyl, cyclopropylethylcarbonyl, cyclobutylmethylcarbonyl, cyclopentylmethylcarbonyl, cyclohexylmethylcarbonyl, cyclohexylethylcarbonyl etc.);

(26) $C_{3-6}$ cycloalkenyl-$C_{1-6}$ alkyl-carbonyl (e.g., cyclopentenylmethylcarbonyl, cyclohexenylmethylcarbonyl, cyclohexenylethylcarbonyl, cyclohexenylpropylcarbonyl etc.);

(27) $C_{6-10}$ aryl-$C_{1-6}$ alkyl-carbonyl (e.g., benzylcarbonyl, phenylethylcarbonyl etc.);

(28) 5- or 6-membered monocyclic aromatic heterocyclyl-carbonyl (e.g., furylcarbonyl, thienylcarbonyl, pyrrolylcarbonyl, oxazolylcarbonyl, isoxazolylcarbonyl, thiazolylcarbonyl, isothiazolylcarbonyl, imidazolylcarbonyl, pyridylcarbonyl, pyrazolylcarbonyl etc.);

(29) 8- to 12-membered fused aromatic heterocyclyl-carbonyl (e.g., benzofurylcarbonyl, isobenzofurylcarbonyl, benzothienylcarbonyl, isobenzothienylcarbonyl, indolylcarbonyl, isoindolylcarbonyl, 1H-indazolylcarbonyl, benzimidazolylcarbonyl, benzoxazolylcarbonyl etc.);

(30) 3- or 8-membered non-aromatic heterocyclyl-carbonyl (e.g., oxiranylcarbonyl, azetidinylcarbonyl, oxetanylcarbonyl, thietanylcarbonyl, pyrrolidinylcarbonyl, tetrahydrofurylcarbonyl, thiolanylcarbonyl, piperidinylcarbonyl etc.);

(31) $C_{1-6}$ alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl etc.);

(32) $C_{2-6}$ alkenylsulfonyl (e.g., ethenylsulfonyl,

propenylsulfonyl etc.);
(33) $C_{2-6}$ alkynylsulfonyl (e.g., ethynylsulfonyl, propynylsulfonyl, butynylsulfonyl, pentynylsulfonyl, hexynylsulfonyl etc.);
(34) $C_{3-6}$ cycloalkylsulfonyl (e.g., cyclopropylsulfonyl, cyclobutylsulfonyl etc.);
(35) $C_{3-6}$ cycloalkenylsulfonyl (e.g., cyclopropenylsulfonyl, cyclobutenylsulfonyl etc.);
(36) $C_{6-10}$ arylsulfonyl (e.g., phenylsulfonyl etc.);
(37) $C_{3-6}$ cycloalkyl-$C_{1-6}$ alkyl-sulfonyl (e.g., cyclopropylmethylsulfonyl etc.);
(38) $C_{3-6}$ cycloalkenyl-$C_{1-6}$ alkyl-sulfonyl (e.g., cyclopentenylmethylsulfonyl etc.);
(39) $C_{6-10}$ aryl-$C_{1-6}$ alkyl-sulfonyl (e.g., benzylsulfonyl etc.);
(40) 5- or 6-membered monocyclic aromatic heterocyclyl-sulfonyl (e.g., furylsulfonyl, thienylsulfonyl, pyridylsulfonyl etc.);
(41) 8- to 12-membered fused aromatic heterocyclyl-sulfonyl (e.g., benzofurylsulfonyl, isobenzofurylsulfonyl etc.);
(42) 3- to 8-membered non-aromatic heterocyclyl-sulfonyl (e.g., oxiranylsulfonyl, azetidinylsulfonyl etc.);
(43) amino;
(44) mono-$C_{1-6}$ alkylamino (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, tert-butylamino etc.) optionally having one substituent selected from

(a) $C_{6-10}$ aryl, and

(b) a 5- or 6-membered monocyclic aromatic heterocyclic group (e.g., furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyridyl, pyrazolyl etc.) optionally having one $C_{1-6}$ alkyl;

(45) di-$C_{1-6}$ alkylamino (e.g., dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, diisobutylamino, di-tert-butylamino etc.);
(46) $C_{1-6}$ alkyl-carbonylamino optionally having 1 to 3

substituents selected from

(a) a halogen atom, and

(b) a 5- or 6-membered monocyclic aromatic heterocyclic group (e.g., furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyridyl, pyrazolyl etc.);

(47) $C_{3-6}$ cycloalkyl-carbonylamino (e.g., cyclopropylcarbonylamino, cyclobutylcarbonylamino, cyclopentylcarbonylamino, cyclohexylcarbonylamino etc.);

(48) $C_{3-6}$ cycloalkenyl-carbonylamino (e.g., cyclopropenylcarbonylamino, cyclobutenylcarbonylamino, cyclopentenylcarbonylamino, cyclohexenylcarbonylamino etc.);

(49) $C_{6-10}$ aryl-carbonylamino (e.g., benzoylamino etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(50) mono(5- or 6-membered monocyclic aromatic heterocyclyl-carbonyl)amino (e.g., furylcarbonylamino, thienylcarbonylamino, pyrrolylcarbonylamino, oxazolylcarbonylamino, isoxazolylcarbonylamino, thiazolylcarbonylamino, isothiazolylcarbonylamino, imidazolylcarbonylamino, tetrazolylcarbonylamino, pyridylcarbonylamino, pyrazolylcarbonylamino etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(51) mono(8- to 12-membered fused aromatic heterocyclyl-carbonyl)amino (e.g., benzofurylcarbonylamino, isobenzofurylcarbonylamino, benzothienylcarbonylamino, isobenzothienylcarbonylamino, benzopyrazolylcarbonylamino etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(52) mono(3- to 8-membered non-aromatic heterocyclyl-carbonyl)amino (e.g., oxiranylcarbonylamino, azetidinylcarbonylamino, oxetanylcarbonylamino,

thietanylcarbonylamino, pyrrolidinylcarbonylamino, tetrahydrofurylcarbonylamino, thioranylcarbonylamino, piperidinylcarbonylamino etc.) optionally having 1 to 3 substituents selected from substituent group B and substituent group C (mentioned later);

(53) mono-$C_{1-6}$ alkoxy-carbonylamino (e.g., methoxycarbonylamino, ethoxycarbonylamino, tert-butoxycarbonylamino etc.);

(54) mercapto;

(55) $C_{1-6}$ alkylsulfanyl (e.g., methylsulfanyl, ethylsulfanyl etc.);

(56) $C_{2-6}$ alkenylsulfanyl (e.g., ethenylsulfanyl, propenylsulfanyl etc.);

(57) $C_{2-6}$ alkynylsulfanyl (e.g., ethynylsulfanyl, propynylsulfanyl, butynylsulfanyl, pentynylsulfanyl, hexynylsulfanyl etc.);

(58) $C_{3-6}$ cycloalkylsulfanyl (e.g., cyclopropylsulfanyl, cyclobutylsulfanyl etc.);

(59) $C_{3-6}$ cycloalkenylsulfanyl (e.g., cyclopropenylsulfanyl, cyclobutenylsulfanyl etc.);

(60) $C_{6-10}$ arylsulfanyl (e.g., phenylsulfanyl etc.);

(61) $C_{3-6}$ cycloalkyl-$C_{1-6}$ alkylsulfanyl (e.g., cyclopropylmethylsulfanyl etc.);

(62) $C_{3-6}$ cycloalkenyl-$C_{1-6}$ alkylsulfanyl (e.g., cyclopentenylmethylsulfanyl etc.);

(63) 5- or 6-membered monocyclic aromatic heterocyclic group (e.g., furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyridyl, pyrazolyl etc.);

(64) 8- to 12-membered fused aromatic heterocyclic group (e.g., benzofuryl, isobenzofuryl, benzothienyl, isobenzothienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl etc.);

(65) 3- to 8-membered non-aromatic heterocyclic group (e.g., oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidinyl etc.);

(66) 5- or 6-membered monocyclic aromatic heterocyclyl-oxy (e.g., furyloxy, thienyloxy, pyrrolyloxy, oxazolyloxy, isoxazolyloxy, thiazolyloxy, isothiazolyloxy, imidazolyloxy, pyridyloxy, pyrazolyloxy etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(67) 8- to 12-membered fused aromatic heterocyclyl-oxy (e.g., benzofuryloxy, isobenzofuryloxy, benzothienyloxy, isobenzothienyloxy, indolyloxy, isoindolyloxy, 1H-indazolyloxy, benzimidazolyloxy, benzoxazolyloxy etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(68) 3- to 8-membered non-aromatic heterocyclyl-oxy (e.g., oxiranyloxy, azetidinyloxy, oxetanyloxy, thietanyloxy, pyrrolidinyloxy, tetrahydrofuryloxy, thiolanyloxy, piperidinyloxy etc.) optionally having 1 to 3 substituents selected from substituent group B and substituent group C (mentioned later);

(69) oxo;

(70) $C_{1-6}$ alkylsulfinyl (e.g., methylsulfinyl, ethylsulfinyl etc.);

(71) $C_{2-6}$ alkenylsulfinyl (e.g., ethenylsulfinyl, propenylsulfinyl etc.);

(72) $C_{2-6}$ alkynylsulfinyl (e.g., ethynylsulfinyl, propynylsulfinyl, butynylsulfinyl, pentynylsulfinyl, hexynylsulfinyl etc.);

(73) $C_{3-6}$ cycloalkylsulfinyl (e.g., cyclopropylsulfinyl, cyclobutylsulfinyl etc.);

(74) $C_{3-6}$ cycloalkenylsulfinyl (e.g., cyclopropenylsulfinyl, cyclobutenylsulfinyl etc.);

(75) $C_{6-10}$ arylsulfinyl (e.g., phenylsulfinyl etc.);

(76) $C_{3-6}$ cycloalkyl-$C_{1-6}$ alkyl-sulfinyl (e.g., cyclopropylmethylsulfinyl etc.);

(77) $C_{3-6}$ cycloalkenyl-$C_{1-6}$ alkyl-sulfinyl (e.g.,

cyclopentenylmethylsulfinyl etc.);
(78) $C_{1-6}$ alkylamino-thiocarbonyl (e.g., methylaminothiocarbonyl, ethylaminothiocarbonyl, propylaminothiocarbonyl etc.);
(79) di-$C_{1-6}$ alkyl-aminothiocarbonyl (e.g., dimethylaminothiocarbonyl, diethylaminothiocarbonyl, dipropylaminothiocarbonyl etc.);
(80) carboxy;
(81) $C_{1-6}$ alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl etc.);
(82) $C_{2-6}$ alkenyloxy-carbonyl (e.g., ethenyloxycarbonyl, propenyloxycarbonyl, butenyloxycarbonyl, pentenyloxycarbonyl, hexenyloxycarbonyl etc.);
(83) $C_{2-6}$ alkynyloxy-carbonyl (e.g., ethynyloxycarbonyl, propynyloxycarbonyl, butynyloxycarbonyl, pentynyloxycarbonyl, hexynyloxycarbonyl etc.);
(84) $C_{3-6}$ cycloalkyl-oxy-carbonyl (e.g., cyclopropyloxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl etc.);
(85) $C_{3-6}$ cycloalkenyloxy-carbonyl (e.g., cyclopropenyloxycarbonyl, cyclobutenyloxycarbonyl, cyclopentenyloxycarbonyl, cyclohexenyloxycarbonyl etc.);
(86) $C_{6-10}$ aryloxy-carbonyl (e.g., phenyloxycarbonyl, 1-naphthyloxycarbonyl, 2-naphthyloxycarbonyl etc.);
(87) $C_{3-6}$ cycloalkyl-$C_{1-6}$ alkoxy-carbonyl (e.g., cyclopropylmethyloxycarbonyl, cyclopropylethyloxycarbonyl, cyclobutylmethyloxycarbonyl, cyclopentylmethyloxycarbonyl, cyclohexylmethyloxycarbonyl, cyclohexylethyloxycarbonyl etc.);
(88) $C_{3-6}$ cycloalkenyl-$C_{1-6}$ alkoxy-carbonyl (e.g., cyclopentenylmethyloxycarbonyl, cyclohexenylmethyloxycarbonyl, cyclohexenylethyloxycarbonyl, cyclohexenylpropyloxycarbonyl etc.);
(89) $C_{6-10}$ aryl-$C_{1-6}$ alkoxy-carbonyl (e.g.,

phenylmethyloxycarbonyl, phenylethyloxycarbonyl etc.);
(90) sulfamoyl;
(91) carbamoyl;
(92) mono($C_{6-10}$ aryl-$C_{1-6}$ alkyl-carbonyl)amino (e.g., phenylmethylcarbonylamino etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);
(93) mono(5- or 6-membered monocyclic aromatic heterocyclyl-$C_{1-6}$ alkyl-carbonyl)amino (e.g., furylmethylcarbonylamino, thienylmethylcarbonylamino, pyrrolylmethylcarbonylamino, oxazolylmethylcarbonylamino, isoxazolylmethylcarbonylamino, thiazolylmethylcarbonylamino, isothiazolylmethylcarbonylamino, imidazolylmethylcarbonylamino, tetrazolylmethylcarbonylamino, pyridylmethylcarbonylamino, pyrazolylmethylcarbonylamino etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);
(94) mono(8- to 12-membered fused aromatic heterocyclyl-$C_{1-6}$ alkyl-carbonyl)amino (e.g., benzofurylmethylcarbonylamino, isobenzofurylmethylcarbonylamino, benzothienylmethylcarbonylamino, isobenzothienylmethylcarbonylamino, benzopyrazolylmethylcarbonylamino etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);
(95) mono(3- to 8-membered non-aromatic heterocyclyl-$C_{1-6}$ alkyl-carbonyl)amino (e.g., oxiranylmethylcarbonylamino, azetidinylmethylcarbonylamino, oxetanylmethylcarbonylamino, thietanylmethylcarbonylamino, pyrrolidinylmethylcarbonylamino, tetrahydrofurylmethylcarbonylamino, thioranylmethylcarbonylamino, piperidinylmethylcarbonylamino etc.) optionally having 1 to 3 substituents selected from substituent group B and substituent group C (mentioned later);
(96) mono-$C_{6-10}$ aryl-ureido (e.g., phenylureido etc.)

optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(97) mono-5- or 6-membered monocyclic aromatic heterocyclyl-ureido (e.g., furylureido, thienylureido, pyrrolylureido, oxazolylureido, isoxazolylureido, thiazolylureido, isothiazolylureido, imidazolylureido, tetrazolylureido, pyridylureido, pyrazolylureido etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(98) mono-8- to 12-membered fused aromatic heterocyclyl-ureido (e.g., benzofurylureido, isobenzofurylureido, benzothienylureido, isobenzothienylureido, benzopyrazolylureido etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(99) mono-3- to 8-membered non-aromatic heterocyclyl-ureido (e.g., oxiranylureido, azetidinylureido, oxetanylureido, thietanylureido, pyrrolidinylureido, tetrahydrofurylureido, thioranylureido, piperidinylureido etc.) optionally having 1 to 3 substituents selected from substituent group B and substituent group C (mentioned later);

(100) mono($C_{6-10}$ aryl-$C_{1-6}$ alkyl)ureido (e.g., phenylmethylureido etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(101) mono(5- or 6-membered monocyclic aromatic heterocyclyl-$C_{1-6}$ alkyl)ureido (e.g., furylmethylureido, thienylmethylureido, pyrrolylmethylureido, oxazolylmethylureido, isoxazolylmethylureido, thiazolylmethylureido, isothiazolylmethylureido, imidazolylmethylureido, tetrazolylmethylureido, pyridylmethylureido, pyrazolylmethylureido etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B

and substituent group C (mentioned later);
(102) mono(8- to 12-membered fused aromatic heterocyclyl-$C_{1-6}$ alkyl)ureido (e.g., benzofurylmethylureido, isobenzofurylmethylureido, benzothienylmethylureido, isobenzothienylmethylureido, benzopyrazolylmethylureido etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);
(103) mono(3- to 8-membered non-aromatic heterocyclyl-$C_{1-6}$ alkyl)ureido (e.g., oxiranylmethylureido, azetidinylmethylureido, oxetanylmethylureido, thietanylmethylureido, pyrrolidinylmethylureido, tetrahydrofurylmethylureido, thioranylmethylureido, piperidinylmethylureido etc.) optionally having 1 to 3 substituents selected from substituent group B and substituent group C (mentioned later);
(104) mono-$C_{6-10}$ aryl-aminocarbonyl optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);
(105) mono-5- or 6-membered monocyclic aromatic heterocyclyl-aminocarbonyl (e.g., furylaminocarbonyl, thienylaminocarbonyl, pyrrolylaminocarbonyl, oxazolylaminocarbonyl, isoxazolylaminocarbonyl, thiazolylaminocarbonyl, isothiazolylaminocarbonyl, imidazolylaminocarbonyl, tetrazolylaminocarbonyl, pyridylaminocarbonyl, pyrazolylaminocarbonyl etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);
(106) mono-8- to 12-membered fused aromatic heterocyclyl-aminocarbonyl (e.g., benzofurylaminocarbonyl, isobenzofurylaminocarbonyl, benzothienylaminocarbonyl, isobenzothienylaminocarbonyl, benzopyrazolylaminocarbonyl etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C

(mentioned later);

(107) mono-3- to 8-membered non-aromatic heterocyclyl-aminocarbonyl (e.g., oxiranylaminocarbonyl, azetidinylaminocarbonyl, oxetanylaminocarbonyl, thietanylaminocarbonyl, pyrrolidinylaminocarbonyl, tetrahydrofurylaminocarbonyl, thioranylaminocarbonyl, piperidinylaminocarbonyl etc.) optionally having 1 to 3 substituents selected from substituent group B and substituent group C (mentioned later);

(108) mono($C_{6-10}$ aryl-$C_{1-6}$ alkyl)aminocarbonyl (e.g., phenylmethylaminocarbonyl etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(109) mono(5- or 6-membered monocyclic aromatic heterocyclyl-$C_{1-6}$ alkyl)aminocarbonyl (e.g., furylmethylaminocarbonyl, thienylmethylaminocarbonyl, pyrrolylmethylaminocarbonyl, oxazolylmethylaminocarbonyl, isoxazolylmethylaminocarbonyl, thiazolylmethylaminocarbonyl, isothiazolylmethylaminocarbonyl, imidazolylmethylaminocarbonyl, tetrazolylmethylaminocarbonyl, pyridylmethylaminocarbonyl, pyrazolylmethylaminocarbonyl etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(110) mono(8- to 12-membered fused aromatic heterocyclyl-$C_{1-6}$ alkyl)aminocarbonyl (e.g., benzofurylmethylaminocarbonyl, isobenzofurylmethylaminocarbonyl, benzothienylmethylaminocarbonyl, isobenzothienylmethylaminocarbonyl, benzopyrazolylmethylaminocarbonyl etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(111) mono(3- to 8-membered non-aromatic heterocyclyl-$C_{1-6}$ alkyl)aminocarbonyl (e.g., oxiranylmethylaminocarbonyl, azetidinylmethylaminocarbonyl, oxetanylmethylaminocarbonyl,

thietanylmethylaminocarbonyl, pyrrolidinylmethylaminocarbonyl, tetrahydrofurylmethylaminocarbonyl, thioranylmethylaminocarbonyl, piperidinylmethylaminocarbonyl etc.) optionally having 1 to 3 substituents selected from substituent group B and substituent group C (mentioned later);

(112) mono-5- or 6-membered monocyclic aromatic heterocyclyl-amino (e.g., furylamino, thienylamino, pyrrolylamino, oxazolylamino, isoxazolylamino, thiazolylamino, isothiazolylamino, imidazolylamino, tetrazolylamino, pyridylamino, pyrazolylamino etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(113) cyclic amino (e.g., pyrrolidino, piperidino, piperazino, morpholino, thiomorpholino etc.) fused with a benzene ring and optionally having one oxo;

(114) $C_{2-6}$ alkynyl-carbonylamino (e.g., ethynylcarbonylamino, propynylcarbonylamino, butynylcarbonylamino, pentynylcarbonylamino, hexynylcarbonylamino etc.) optionally having one $C_{6-10}$ aryl (e.g., phenyl etc.);

(115) $C_{6-10}$ aryl-sulfonylamino (e.g., phenylsulfonylamino, naphthylsulfonylamino etc.) optionally having one substituent selected from

(a) a halogen atom,

(b) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and

(c) $C_{1-6}$ alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl etc.);

(116) 5- or 6-membered monocyclic aromatic heterocyclyl-sulfonylamino (e.g., furylsulfonylamino, thienylsulfonylamino, pyrrolylsulfonylamino, oxazolylsulfonylamino, isoxazolylsulfonylamino, thiazolylsulfonylamino, isothiazolylsulfonylamino, imidazolylsulfonylamino, tetrazolylsulfonylamino, pyridylsulfonylamino, pyrazolylsulfonylamino etc.) optionally having one $C_{1-6}$ alkyl;

(117) ureido; and

(118) $C_{1-6}$ alkyl-ureido (e.g., methylureido, ethylureido, propylureido etc.).

substituent group B:

(1) a halogen atom;

(2) cyano;

(3) hydroxy;

(4) 3- to 8-membered non-aromatic heterocyclyl-oxy (e.g., oxiranyloxy, azetidinyloxy, oxetanyloxy, thietanyloxy, pyrrolidinyloxy, tetrahydrofuryloxy, thioranyloxy, piperidinyloxy etc.);

(5) amino;

(6) mono-$C_{1-6}$ alkyl-amino (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, tert-butylamino etc.);

(7) di-$C_{1-6}$ alkyl-amino (e.g., dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, diisobutylamino, di-tert-butylamino, N-ethyl-N-methylamino, N-methyl-N-propylamino, N-ethyl-N-propylamino etc.);

(8) mono-$C_{3-6}$ cycloalkyl-amino (e.g., cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino etc.);

(9) mono($C_{1-6}$ alkyl-carbonyl)amino (e.g., acetylamino, ethylcarbonylamino, propylcarbonylamino, isobutylcarbonylamino, tert-butylcarbonylamino etc.);

(10) mono($C_{3-6}$ cycloalkyl-carbonyl)amino (e.g., cyclopropylcarbonylamino, cyclobutylcarbonylamino, cyclopentylcarbonylamino, cyclohexylcarbonylamino etc.);

(11) mercapto;

(12) $C_{1-6}$ alkyl-sulfanyl (e.g., methylsulfanyl, ethylsulfanyl etc.);

(13) $C_{3-6}$ cycloalkyl-sulfanyl (e.g., cyclopropylsulfanyl, cyclobutylsulfanyl etc.);

(14) 3- to 8-membered non-aromatic heterocyclyl-sulfanyl (e.g., oxiranylsulfanyl, azetidinylsulfanyl etc.);

(15) $C_{1-6}$ alkyl-sulfinyl (e.g., methylsulfinyl, ethylsulfinyl etc.);

(16) $C_{3-6}$ cycloalkyl-sulfinyl (e.g., cyclopropylsulfinyl, cyclobutylsulfinyl etc.);

(17) 3- to 8-membered non-aromatic heterocyclyl-sulfinyl (e.g., oxiranylsulfinyl, azetidinylsulfinyl etc.);

(18) $C_{1-6}$ alkyl-sulfonyl (e.g., methylsulfonyl, ethylsulfonyl etc.);

(19) $C_{3-6}$ cycloalkyl-sulfonyl (e.g., cyclopropylsulfonyl, cyclobutylsulfonyl etc.);

(20) 3- to 8-membered non-aromatic heterocyclyl-sulfonyl (e.g., oxiranylsulfonyl, azetidinylsulfonyl etc.);

(21) oxo;

(22) formyl;

(23) $C_{1-6}$ alkyl-carbonyl (e.g., acetyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl etc.);

(24) $C_{3-6}$ cycloalkyl-carbonyl (e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl etc.);

(25) 3- to 8-membered non-aromatic heterocyclyl-carbonyl (e.g., oxiranylcarbonyl, azetidinylcarbonyl, oxetanylcarbonyl, thietanylcarbonyl, pyrrolidinylcarbonyl, tetrahydrofurylcarbonyl, thioranylcarbonyl, piperidinylcarbonyl etc.);

(26) carboxy;

(27) carbamoyl;

(28) mono($C_{1-6}$ alkyl-amino)carbonyl (e.g., methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl etc.);

(29) di-($C_{1-6}$ alkyl-amino)carbonyl (e.g., dimethylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl etc.);

(30) sulfo;

(31) sulfamoyl;

(32) mono-$C_{1-6}$ alkylsulfamoyl (e.g., methylsulfamoyl, ethylsulfamoyl, propylsulfamoyl etc.);

(33) di-$C_{1-6}$ alkylsulfamoyl (e.g., dimethylsulfamoyl, diethylsulfamoyl, dipropylsulfamoyl etc.);
(34) a 3- to 8-membered nonaromatic heterocyclic group (e.g., oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thioranyl, piperidinyl etc.);
(35) $C_{1-4}$ alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, trimethylendioxy etc.); and
(36) $C_{1-6}$ alkylsulfanyl (e.g., methylsulfanyl, ethylsulfanyl, propylsulfanyl etc.).

substituent group C:
(1) $C_{1-6}$ alkyl optionally having 1 to 3 substituents selected from substituent group B;
(2) $C_{1-6}$ alkoxy optionally having 1 to 3 substituents selected from substituent group B;
(3) $C_{3-6}$ cycloalkyl optionally having 1 to 3 substituents selected from substituent group B;
(4) $C_{3-6}$ cycloalkyloxy (e.g., cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy etc.) optionally having 1 to 3 substituents selected from substituent group B;
(5) $C_{3-6}$ cycloalkyl-$C_{1-6}$ alkyl (e.g., cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclohexylethyl etc.) optionally having 1 to 3 substituents selected from substituent group B;
(6) $C_{3-6}$ cycloalkyl-$C_{1-6}$ alkoxy (e.g., cyclopropylmethyloxy, cyclopropylethyloxy, cyclobutylmethyloxy, cyclopentylmethyloxy, cyclohexylmethyloxy, cyclohexylethyloxy etc.) optionally having 1 to 3 substituents selected from substituent group B;
(7) $C_{6-10}$ aryl optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B;
(8) $C_{6-10}$ aryloxy (e.g., phenyloxy, 1-naphthyloxy, 2-naphthyloxy etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B;
(9) $C_{6-10}$ aryl-$C_{1-6}$ alkyl (e.g., benzyl, phenylethyl etc.) optionally having 1 to 3 substituents (excluding oxo) selected

from substituent group B;
(10) $C_{6-10}$ aryl-$C_{1-6}$ alkoxy (e.g., phenylmethyloxy, phenylethyloxy etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B;
(11) 5- or 6-membered monocyclic aromatic heterocyclic group (e.g., furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyridyl, pyrazolyl etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B;
(12) 5- or 6-membered monocyclic aromatic heterocyclyl-oxy (e.g., furyloxy, thienyloxy, pyrrolyloxy, oxazolyloxy, isoxazolyloxy, thiazolyloxy, isothiazolyloxy, imidazolyloxy, pyridyloxy, pyrazolyloxy etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B;
(13) 5- or 6-membered monocyclic aromatic heterocyclyl-$C_{1-6}$ alkyl (e.g., furylmethyl, thienylmethyl, pyrrolylmethyl, oxazolylmethyl, isoxazolylmethyl, thiazolylmethyl, isothiazolylmethyl, imidazolylmethyl, pyridylmethyl, pyrazolylmethyl etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B; and
(14) 5- or 6-membered monocyclic aromatic heterocyclyl-$C_{1-6}$ alkoxy (e.g., furylmethyloxy, thienylmethyloxy, pyrrolylmethyloxy, oxazolylmethyloxy, isoxazolylmethyloxy, thiazolylmethyloxy, isothiazolylmethyloxy, imidazolylmethyloxy, pyridylmethyloxy, pyrazolylmethyloxy etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B.

In the present specification, the term "alkenyl optionally having substituent(s)" means $C_{2-6}$ alkenyl (e.g., ethenyl, propenyl, butenyl, pentenyl, hexenyl, butadienyl etc.) optionally having 1 to 3 substituents selected from substituent group A.

In the present specification, the term "alkynyl

optionally having substituent(s)" means $C_{2-6}$ alkynyl (e.g., ethynyl, propynyl, butynyl, pentynyl, hexynyl etc.) optionally having 1 to 3 substituents selected from substituent group A.

In the present specification, the term "cycloalkyl optionally having substituent(s)" means $C_{3-6}$ cycloalkyl optionally having 1 to 3 substituents selected from

(1) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and

(2) substituent group A.

In the present specification, the term "cycloalkenyl optionally having substituent(s)" means $C_{3-6}$ cycloalkenyl (e.g., cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl etc.) optionally having 1 to 3 substituents selected from

(1) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and

(2) substituent group A.

In the present specification, the term "aryl optionally having substituent(s)" means $C_{6-10}$ aryl optionally having 1 to 3 substituents selected from

(1) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and

(2) substituent group A (excluding oxo).

In the present specification, the term "cycloalkyl-alkyl optionally having substituent(s)" means $C_{3-6}$ cycloalkyl-$C_{1-4}$ alkyl (e.g., cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclohexylethyl etc.) optionally having 1 to 3 substituents selected from

(1) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and

(2) substituent group A.

In the present specification, the term "cycloalkenyl-alkyl optionally having substituent(s)" means $C_{3-6}$ cycloalkenyl-$C_{1-4}$ alkyl (e.g., cyclopentenylmethyl, cyclohexenylmethyl, cyclohexenylethyl, cyclohexenylpropyl etc.) optionally having 1 to 3 substituents selected from

(1) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and

(2) substituent group A.

In the present specification, the term "aryl-alkyl optionally having substituent(s)" means $C_{6-10}$ aryl-$C_{1-4}$ alkyl (e.g., benzyl, phenylethyl etc.) optionally having 1 to 3 substituents selected from
(1) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and
(2) substituent group A (excluding oxo).

In the present specification, the term "cycloalkanedienyl optionally having substituent(s)" means $C_{4-6}$ cycloalkanedienyl (e.g., 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl etc.) optionally having 1 to 3 substituents selected from
(1) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and
(2) substituent group A.

In the present specification, the term "heterocyclic group bonded via a carbon atom and optionally having substituent(s)" means
(A) a monocyclic aromatic heterocyclic group or fused aromatic heterocyclic group bonded via a carbon atom and optionally having 1 to 3 substituents selected from (1) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and
(2) substituent group A (excluding oxo), or
(B) a nonaromatic heterocyclic group bonded via a carbon atom and optionally having 1 to 3 substituents selected from (1) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and
(2) substituent group A.

The "bonded via a carbon atom monocyclic aromatic heterocyclic group" is, for example, a 5- to 7-membered (preferably, 5- or 6-membered) monocyclic aromatic heterocyclic group (having a bond at carbon atom) containing, as a ring constituting atom besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (optionally oxidized) and a nitrogen atom, and the like. Examples thereof include furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-

pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), pyrazinyl (e.g., 2-pyrazinyl), pyrrolyl (e.g., 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), pyrazolyl (e.g., 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (e.g., 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl), thiadiazolyl (e.g., 1,3,4-thiadiazol-2-yl), triazolyl (e.g., 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl), tetrazolyl (e.g., tetrazol-5-yl), triazinyl (e.g., 1,3,5-triazin-2-yl) and the like.

The "fused aromatic heterocyclic group bonded via a carbon atom" is, for example, a 8- to 12-membered fused aromatic heterocyclic group (having a bond at carbon atom) wherein a 5- to 7-membered monocyclic aromatic heterocyclic group containing, as a ring constituting atom besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (optionally oxidized) and a nitrogen atom, etc. and $C_{6-10}$ aryl and the like are fused; a 8- to 12-membered fused aromatic heterocyclic group (having a bond at carbon atom) wherein 5- to 7-membered monocyclic aromatic heterocyclic groups are fused, and the like. Examples thereof include quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl), isoquinolyl (e.g., 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl), quinazolyl (e.g., 2-quinazolyl, 4-quinazolyl), quinoxalyl (e.g., 2-quinoxalyl), benzofuryl (e.g., 2-benzofuryl, 3-benzofuryl), isobenzofuryl (e.g., 1-isobenzofuryl, 3-isobenzofuryl), benzothienyl (e.g., 2-benzothienyl, 3-benzothienyl), isobenzothienyl (e.g., 1-isobenzothienyl, 3-isobenzothienyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzothiazolyl (e.g., 2-benzothiazolyl, 5-

benzothiazolyl, 6-benzothiazolyl), benzimidazolyl (e.g., benzimidazol-2-yl, benzimidazol-5-yl), indolyl (e.g., indol-2-yl, indol-3-yl, indol-4-yl, indol-5-yl, indol-6-yl), indazolyl (e.g., 1H-indazol-3-yl), pyrrolopyrazinyl (e.g., 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyrazin-6-yl), imidazopyridyl (e.g., 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl), imidazopyrazinyl (e.g., 1H-imidazo[4,5-b]pyrazin-2-yl), benzisoxazolyl (e.g., benzisoxazol-3-yl), benzotriazolyl (e.g., 1H-1,2,3-benzotriazol-5-yl), benzopyrazolyl (e.g., benzopyrazol-5-yl), pyrazolopyridyl (e.g., 1H-pyrazolo[4,3-c]pyridin-3-yl), pyrazolothienyl (e.g., 2H-pyrazolo[3,4-b]thiophen-2-yl), pyrazolotriazinyl (e.g., pyrazolo[5,1-c][1,2,4]triazin-3-yl) and the like.

Examples of the "nonaromatic heterocyclic group bonded via a carbon atom" include a 3- to 8-membered nonaromatic heterocyclic group (having a bond at carbon atom) containing, as a ring constituting atom besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (optionally oxidized) and a nitrogen atom, and the like. Examples thereof include oxiranyl (e.g., 2-oxiranyl), azetidinyl (e.g., 2-azetidinyl, 3-azetidinyl), oxetanyl (e.g., 2-oxetanyl, 3-oxetanyl), thietanyl (e.g., 2-thietanyl, 3-thietanyl), pyrrolidinyl (e.g., 2-pyrrolidinyl, 3-pyrrolidinyl), tetrahydrofuryl (e.g., 2-tetrahydrofuryl, 3-tetrahydrofuryl), thioranyl (e.g., 2-thioranyl, 3-thioranyl), piperidinyl (e.g., 2-piperidinyl, 3-piperidinyl, 4-piperidinyl), tetrahydropyranyl (e.g., 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl), thianyl (e.g., 2-thianyl, 3-thianyl), morpholinyl (e.g., 2-morpholinyl, 3-morpholinyl), thiomorpholinyl (e.g., 2-thiomorpholinyl, 3-thiomorpholinyl), piperazinyl (e.g., 2-piperazinyl), azepanyl (e.g., 3-azepanyl), oxepanyl (e.g., 3-oxepanyl), thiepanyl (e.g., 3-thiepanyl), oxazepanyl (e.g., 1,4-oxazepane-5-yl),

thiazepanyl (e.g., 1,4-thiazepane-5-yl), azocanyl (e.g., 4-azocanyl), oxocanyl (e.g., 4-oxocanyl), thiocanyl (e.g., 4-thiocanyl), oxazocanyl (e.g., 1,4-oxazocan-5-yl), thioazocanyl (e.g., 1,4-thioazocan5-yl), dioxinyl (e.g., 1,4-dioxin-2-yl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-3-yl, 2,3-dihydropyrazol-4-yl, 2,3-dihydropyrazol-5-yl), hexahydropyrimidinyl (e.g., hexahydropyrimidin-2-yl, hexahydropyrimidin-4-yl, hexahydropyrimidin-5-yl), tetrahydropyrimidinyl (e.g., 1,2,3,4-tetrahydropyrimidin-2-yl, 1,2,5,6-tetrahydropyrimidin-2-yl), dihydropyrimidinyl (e.g., 1,2-dihydropyrimidin-2-yl), tetrahydropyridyl (e.g., 1,2,3,4-tetrahydropyridin-2-yl, 1,2,5,6-tetrahydropyridin-2-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl), tetrahydroimidazolyl (e.g., tetrahydroimidazol-2-yl, tetrahydroimidazol-4-yl), dihydroimidazolyl (e.g., 4,5-dihydroimidazol-2-yl, 4,5-dihydroimidazol-4-yl, 4,5-dihydroimidazol-5-yl) and the like.

In the present specification, the term "a group bonded via a nitrogen atom" means, for example,

(1) nitro,

(2) amino optionally having substituent(s),

(3) a heterocyclic group bonded via a nitrogen atom and optionally having substituent(s),

and the like.

In the present specification, the substituent of amino of the term "amino optionally having substituent(s)" includes, for example, a group bonded via a carbon atom, and the formula $-SO_2R^a$ ($R^a$ is a group bonded via a carbon atom) and the like, wherein the amino is optionally mono- or di-substituted. When it is di-substituted, the substituents may be the same or different.

The "heterocyclic group bonded via a nitrogen atom and optionally having substituent(s)" includes, for example,

(A) a monocyclic aromatic heterocyclic group or fused aromatic heterocyclic group, which is bonded via a nitrogen atom and optionally has 1 to 3 substituents selected from
(1) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and
(2) substituent group A (excluding oxo), or
(B) a nonaromatic heterocyclic group, which is bonded via a nitrogen atom and optionally has 1 to 3 substituents selected from
(1) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and
(2) substituent group A.

The "monocyclic aromatic heterocyclic group bonded via a nitrogen atom" includes, for example, a 5- to 7-membered (preferably, 5- or 6-membered) monocyclic aromatic heterocyclic group (having a bond at nitrogen atom) optionally containing, as ring constituting atom besides carbon atom and one nitrogen atom, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (optionally oxidized), and a nitrogen atom, and the like. Examples thereof include pyrrolyl (e.g., 1-pyrrolyl), imidazolyl (e.g., 1-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl), triazolyl (e.g., 1,2,4-triazol-1-yl), tetrazolyl (e.g., tetrazol-1-yl)) and the like.

The "fused aromatic heterocyclic group bonded via a nitrogen atom" is, for example, a 8- to 12-membered fused aromatic heterocyclic group (having a bond at nitrogen atom), wherein a 5- to 7-membered monocyclic aromatic heterocyclic group optionally containing, as ring constituting atom besides carbon atom and one nitrogen atom, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (optionally oxidized), and a nitrogen atom, etc. and $C_{6-10}$ aryl and the like are fused; a 8- to 12-membered fused aromatic heterocyclic group (having a bond at nitrogen atom) wherein 5- to 7-membered monocyclic aromatic heterocyclic groups are fused, and the like. Examples thereof include benzimidazolyl (e.g., benzimidazol-1-yl), indolyl (e.g., indol-1-yl) and the

like.

Examples of the "nonaromatic heterocyclic group bonded via a nitrogen atom" include a 3- to 8-membered nonaromatic heterocyclic group (having a bond at nitrogen atom) optionally containing, as ring constituting atom besides carbon atom and one nitrogen atom, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (optionally oxidized), and a nitrogen atom, and the like. Examples thereof include azetidinyl (e.g., 1-azetidinyl), pyrrolidinyl (e.g., 1-pyrrolidinyl), piperidinyl (e.g., 1-piperidinyl), morpholinyl (e.g., 4-morpholinyl), thiomorpholinyl (e.g., 4-thiomorpholinyl), piperazinyl (e.g., 1-piperazinyl), azepanyl (e.g., 1-azepanyl), oxazepanyl (e.g., 1,4-oxazepan-4-yl), thiazepanyl (e.g., 1,4-thiazepane-4-yl), azocanyl (e.g., 1-azocanyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-1-yl), hexahydropyrimidinyl (e.g., hexahydropyrimidin-1-yl), tetrahydropyrimidinyl (e.g., 1,2,3,4-tetrahydropyrimidin-1-yl), 1,2,5,6-tetrahydropyrimidin-1-yl), dihydropyrimidinyl (e.g., 1,2-dihydropyrimidin-1-yl), tetrahydropyridyl (e.g., 1,2,3,4-tetrahydropyridin-1-yl, 1,2,5,6-tetrahydropyridin-1-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-1-yl), tetrahydroimidazolyl (e.g., tetrahydroimidazol-1-yl), dihydroimidazolyl (e.g., 4,5-dihydroimidazol-1-yl) and the like.

In the present specification, the "nitrogen-containing heterocyclic group" is a heterocyclic group containing one or more nitrogen atoms as ring constituting atom. Specific preferable examples include

(1) 5- to 7-membered (preferably, 5- or 6-membered) monocyclic nitrogen-containing aromatic heterocycle containing one or more nitrogen atoms as ring constituting atom, specifically, pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), pyrazinyl

(e.g., 2-pyrazinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl), triazolyl (e.g., 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl), tetrazolyl (e.g., tetrazol-1-yl, tetrazol-5-yl) and the like;
(2) a 3- to 8-membered nitrogen-containing nonaromatic heterocyclic group containing one or more nitrogen atoms as ring constituting atom, specifically, azetidinyl (e.g., 1-azetidinyl, 2-azetidinyl, 3-azetidinyl), pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl), piperidinyl (e.g., 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl), morpholinyl (e.g., 2-morpholinyl, 3-morpholinyl, 4-morpholinyl), thiomorpholinyl (e.g., 2-thiomorpholinyl, 3-thiomorpholinyl, 4-thiomorpholinyl), piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl), azepanyl (e.g., 1-azepanyl, 3-azepanyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-1-yl, 2,3-dihydropyrazol-3-yl, 2,3-dihydropyrazol-4-yl, 2,3-dihydropyrazol-5-yl), hexahydropyrimidinyl (e.g., hexahydropyrimidin-1-yl, hexahydropyrimidin-2-yl, hexahydropyrimidin-4-yl, hexahydropyrimidin-5-yl), tetrahydropyrimidinyl (e.g., 1,2,3,4-tetrahydropyrimidin-1-yl, 1,2,3,4-tetrahydropyrimidin-2-yl, 1,2,5,6-tetrahydropyrimidin-1-yl, 1,2,5,6-tetrahydropyrimidin-2-yl), dihydropyrimidinyl (e.g., 1,2-dihydropyrimidin-1-yl, 1,2-dihydropyrimidin-2-yl), tetrahydropyridyl (e.g., 1,2,3,4-tetrahydropyridin-1-yl, 1,2,3,4-tetrahydropyridin-2-yl, 1,2,5,6-tetrahydropyridin-1-yl, 1,2,5,6-tetrahydropyridin-2-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl), tetrahydroimidazolyl (e.g., tetrahydroimidazol-1-yl, tetrahydroimidazol-2-yl, tetrahydroimidazol-4-yl), dihydroimidazolyl (e.g., 4,5-dihydroimidazol-1-yl, 4,5-dihydroimidazol-2-yl, 4,5-dihydroimidazol-4-yl, 4,5-

dihydroimidazol-5-yl) and the like;
and the like.

In the present specification, "N-oxide of the nitrogen-containing heterocyclic group" is the above-mentioned nitrogen-containing heterocyclic group wherein an oxygen atom is bonded to the nitrogen atom of the ring and, for example, N-oxidepyridyl (e.g., N-oxidepyridin-2-yl, N-oxidepyridin-3-yl, N-oxidepyridin-4-yl), N-oxidepyrazinyl (e.g., N-oxidepyrazin-2-yl), N-oxidepyrimidinyl (e.g., N-oxidepyrimidin-2-yl, N-oxidepyrimidin-4-yl, N-oxidepyrimidin-5-yl), N-oxidepyridazinyl (e.g., N-oxidepyridazin-3-yl, N-oxidepyridazin-4-yl) and the like can be mentioned.

In the present specification, the term "a group bonded via an oxygen atom" means, for example, hydroxy optionally having substituent(s). The substituent of the "hydroxy optionally having substituent(s)" is a group bonded via a carbon atom and the like.

In the present specification, the term "a group bonded via a sulfur atom" means, for example, mercapto, a group represented by the formula $-S(O)_nR^b$ wherein n is an integer of 0 to 2 and $R^b$ is a group bonded via a carbon atom or a group bonded via a nitrogen atom, and the like.

The compound (I) is explained in the following.

$R^1$ is

(1) a hydrogen atom,
(2) a halogen atom,
(3) a group bonded via a carbon atom,
(4) a group bonded via a nitrogen atom,
(5) a group bonded via an oxygen atom, or
(6) a group bonded via a sulfur atom.

$R^1$ is a hydrogen atom, a halogen atom (particularly, a fluorine atom), or a $C_{1-6}$ alkyl group (particularly, methyl) is preferable, and a hydrogen atom is more preferable.

$R^2$ is

(1) a hydrogen atom,
(2) a halogen atom,
(3) a group bonded via a carbon atom,
(4) a group bonded via a nitrogen atom,
(5) a group bonded via an oxygen atom, or
(6) a group bonded via a sulfur atom.

$R^2$ is preferably a hydrogen atom.

W is O or S.

As W, O is preferable.

X is $CR^3$ ($R^3$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl) or N.

X is preferably $CR^{3'}$ wherein $R^{3'}$ is a hydrogen atom, a halogen atom or methyl, or N. Particularly, CH, CF, CCl, $C(CH_3)$ or N is preferable, and CH, CF or N is more preferable.

Y is $CR^4$ ($R^4$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl) or N.

Y is preferably $CR^{4'}$ wherein $R^{4'}$ is a hydrogen atom, a halogen atom or methyl, or N. Particularly, CH, CF, CCl, $C(CH_3)$ or N is preferable, and CH, CF or N is more preferable.

$R^5$ is

(1) $C_{3-6}$ cycloalkyl optionally having one $C_{6-10}$ aryl-aminocarbonyl optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl,
(2) $C_{1-6}$ alkyl-carbonylamino optionally having one $C_{6-10}$ aryl,
(3) $C_{1-6}$ alkoxy optionally having one $C_{6-10}$ aryl, or
(4) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from

(a) $C_{6-10}$ aryl optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl,

(b) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and

(c) oxo.

$R^5$ is preferably

(1) cyclopropyl optionally having one phenylaminocarbonyl

optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or,

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-4-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl), hexahydropyrimidinyl (e.g., hexahydropyrimidin-1-yl), tetrahydroimidazolyl (e.g., tetrahydroimidazol-1-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom, a chlorine atom, a bromine atom, methyl and isopropyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms,

(d) isopropyl, and

(e) oxo.

$R^6$ is a hydrogen atom.

$R^7$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl.

$R^7$ is preferably a hydrogen atom.

$R^8$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl.

$R^8$ is preferably a hydrogen atom.

As compound (I), the compounds described in Examples 1 - 38 are preferable, and the compounds described in Examples 1, 3 - 38 are more preferable.

As compound (I), the compounds described in Examples 39 - 85 are also preferable.

In compound (I), $Z_1$, $Z_2$, $Z_3$ and $Z_4$ are in the following combination.

$(Z_1, Z_2, Z_3, Z_4) = (CR^1, N, CR^2, C)$,

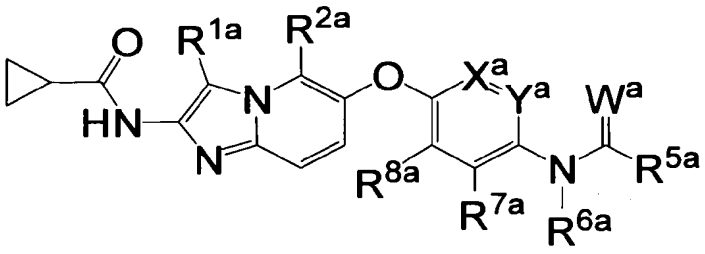
$(N, N, CR^2, C)$,

(N,C,$CR^2$,N),

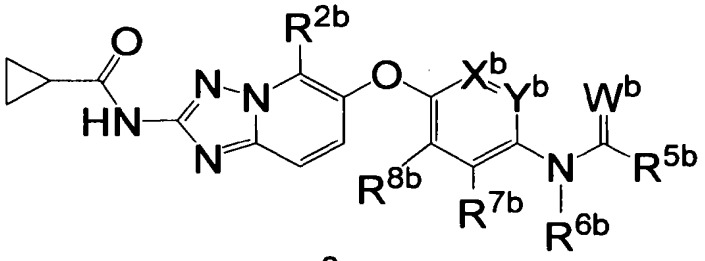
(S,C,$CR^2$,C) or

(S,C,N,C).

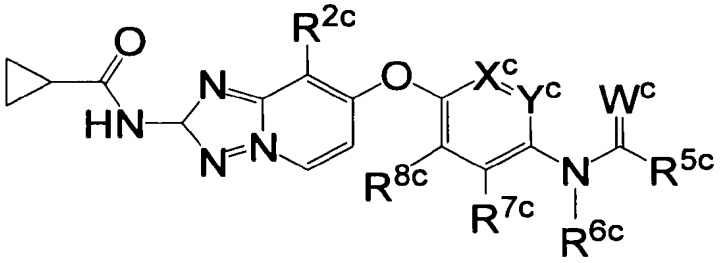
That is, compound (I) can be subdivided into the compounds represented by following formulas (Ia) - (Ie) (hereinafter sometimes to be abbreviated as compounds (Ia) - (Ie)).



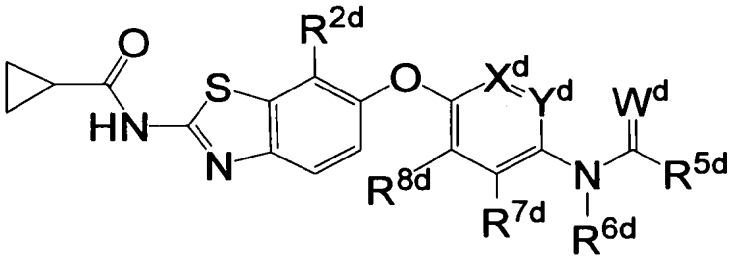
(Ia)



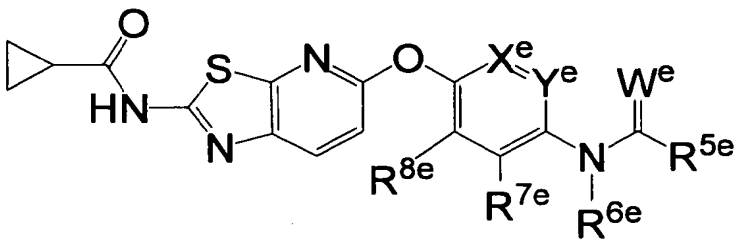
(Ib)



(Ic)



(Id)

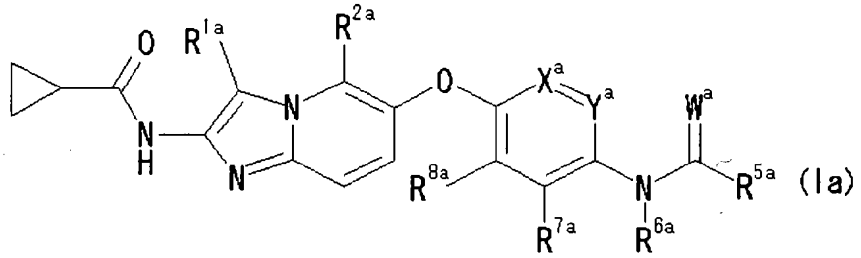


(Ie)

The compounds (Ia) - (Ie) are explained in the following.

[Compound (Ia)]

imidazo[1,2-a]pyridine derivative: a compound represented by the formula



(Ia)

wherein $R^{1a}$ and $R^{2a}$ are the same or different and each is

(1) a hydrogen atom,

(2) a halogen atom,

(3) a group bonded via a carbon atom,

(4) a group bonded via a nitrogen atom,

(5) a group bonded via an oxygen atom, or

(6) a group bonded via a sulfur atom;

$W^a$ is O or S;

$X^a$ is $CR^{3a}$ ($R^{3a}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl), or N;

$Y^a$ is $CR^{4a}$ ($R^{4a}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl), or N;

$R^{5a}$ is

(1) $C_{3-6}$ cycloalkyl optionally having one $C_{6-10}$ aryl-aminocarbonyl optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl,

(2) $C_{1-6}$ alkyl-carbonylamino optionally having one $C_{6-10}$ aryl,

(3) $C_{1-6}$ alkoxy optionally having one $C_{6-10}$ aryl, or

(4) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from

(a) $C_{6-10}$ aryl optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl,

(b) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and

(c) oxo;

$R^{6a}$ is a hydrogen atom;

$R^{7a}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl; and

$R^{8a}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl,

or a salt thereof (compound (Ia)).

$R^{1a}$ is preferably a hydrogen atom, a halogen atom (particularly, a fluorine atom), or a $C_{1-6}$ alkyl group (particularly, methyl), and a hydrogen atom is more preferable.

$R^{2a}$ is preferably a hydrogen atom.

$W^a$ is preferably O.

$X^a$ is preferably $CR^{3a'}$ wherein $R^{3a'}$ is a hydrogen atom, a halogen atom or methyl, or N. Particularly, CH, CF, CCl, $C(CH_3)$ or N is preferable, and CH, CF or N is more preferable.

$Y^a$ is preferably $CR^{4a'}$ wherein $R^{4a'}$ is a hydrogen atom, a halogen atom or methyl, or N. Particularly, CH, CF, CCl, $C(CH_3)$ or N is preferable, and CH, CF or N is more preferable.

$R^{5a}$ is preferably

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-4-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl), hexahydropyrimidinyl (e.g., hexahydropyrimidin-1-yl), tetrahydroimidazolyl (e.g., tetrahydroimidazol-1-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom, a chlorine atom, a bromine atom, methyl and isopropyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms,

(d) isopropyl, and

(e) oxo.

$R^{7a}$ is preferably a hydrogen atom.

$R^{8a}$ is preferably a hydrogen atom.

Preferable specific examples of compound (Ia) include the following.

[Compound (Ia-A)]

In compound (Ia), a compound wherein

$R^{1a}$ is a hydrogen atom;

$R^{2a}$ is a hydrogen atom;

$W^a$ is O or S;

$X^a$ is $CR^{3a'}$ wherein $R^{3a'}$ is a hydrogen atom or a halogen atom;

$Y^a$ is $CR^{4a'}$ wherein $R^{4a'}$ is a hydrogen atom or a halogen atom;

$R^{5a}$ is

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-4-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms, and

(d) oxo;

$R^{6a}$ is a hydrogen atom;

$R^{7a}$ is a hydrogen atom; and

$R^{8a}$ is a hydrogen atom is preferable.

[Compound (Ia-A1)]

In compound (Ia-A), a compound wherein

$R^{1a}$ is a hydrogen atom;

$R^{2a}$ is a hydrogen atom;

$W^a$ is O;

$X^a$ is CH or CF;

$Y^a$ is CH or CF;

$R^{5a}$ is

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-4-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms, and

(d) oxo;

$R^{6a}$ is a hydrogen atom;

$R^{7a}$ is a hydrogen atom; and

$R^{8a}$ is a hydrogen atom is preferable.

[Compound (Ia-A2)]

The compounds of Examples 1 - 17, Examples 22 - 33 and Examples 35 - 38, particularly Examples 1, 3 - 17, Examples 22 - 33 and Examples 35 - 38.

[Compound (Ia-B)]

In compound (Ia), a compound wherein

$R^{1a}$ is a hydrogen atom, a halogen atom (particularly, a fluorine atom), or a $C_{1-6}$ alkyl group (particularly, methyl);

$R^{2a}$ is a hydrogen atom;

$W^a$ is O or S (particularly, O);

$X^a$ is $CR^{3a'}$ wherein $R^{3a'}$ is a hydrogen atom, a halogen atom or methyl, or N;

$Y^a$ is $CR^{4a'}$ wherein $R^{4a'}$ is a hydrogen atom, a halogen atom or methyl, or N;

$R^{5a}$ is

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-4-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl), hexahydropyrimidinyl (e.g., hexahydropyrimidin-1-yl), tetrahydroimidazolyl (e.g., tetrahydroimidazol-1-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom, a chlorine atom, a bromine atom, methyl and isopropyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms,

(d) isopropyl, and

(e) oxo;

$R^{6a}$ is a hydrogen atom;

$R^{7a}$ is a hydrogen atom; and

$R^{8a}$ is a hydrogen atom is preferable.

[Compound (Ia-B1)]

In compound (Ia-B), a compound wherein

$R^{1a}$ is a hydrogen atom, a fluorine atom or methyl;

$R^{2a}$ is a hydrogen atom;

$W^a$ is O;

$X^a$ is CH, CF, CCl, $C(CH_3)$ or N;

$Y^a$ is CH, CF, CCl, $C(CH_3)$ or N;

$R^{5a}$ is

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-4-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl), hexahydropyrimidinyl (e.g., hexahydropyrimidin-1-yl), tetrahydroimidazolyl (e.g., tetrahydroimidazol-1-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom, a chlorine atom, a bromine atom, methyl and isopropyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms,

(d) isopropyl, and

(e) oxo;

$R^{6a}$ is a hydrogen atom;

$R^{7a}$ is a hydrogen atom; and

$R^{8a}$ is a hydrogen atom is preferable.

[Compound (Ia-B2)]

The compounds of Examples 1 - 17, Examples 22 - 33,

Examples 35 - 75 and Examples 77 - 85, particularly Examples 1, 3 - 17, Examples 22 - 33, Examples 35 - 75 and Examples 77 - 85.

[Compound (Ia-B3)]

The compounds of Examples 1 - 17, Examples 22 - 33, Examples 35 - 75 and Examples 77 - 94, particularly Examples 1, 3 - 17, Examples 22 - 33, Examples 35 - 75 and Examples 77 - 94.

[Compound (Ia-C)]

N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-N'-phenylcyclopropane-1,1-dicarboxamide or a salt thereof;

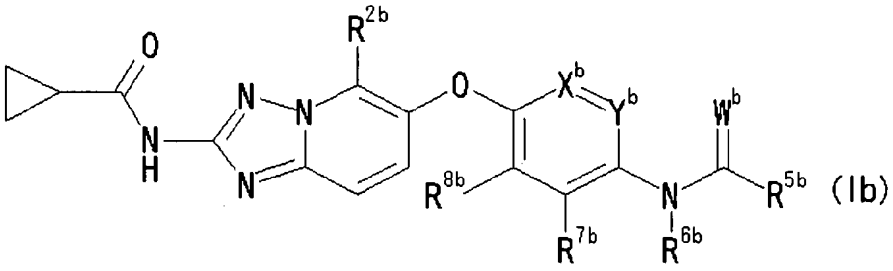
N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide or a salt thereof;

N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide or a salt thereof; or

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)pyridin-2-yl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide or a salt thereof.

[Compound (Ib)]

1,2,4-triazolo[1,5-a]pyridine derivative: a compound represented by the formula



(Ib)

wherein $R^{2b}$ is

(1) a hydrogen atom,

(2) a halogen atom,

(3) a group bonded via a carbon atom,
(4) a group bonded via a nitrogen atom,
(5) a group bonded via an oxygen atom, or
(6) a group bonded via a sulfur atom;
$W^b$ is O or S;
$X^b$ is $CR^{3b}$ ($R^{3b}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl), or N;
$Y^b$ is $CR^{4b}$ ($R^{4b}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl), or N;
$R^{5b}$ is
(1) $C_{3-6}$ cycloalkyl optionally having one $C_{6-10}$ aryl-aminocarbonyl optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl,
(2) $C_{1-6}$ alkyl-carbonylamino optionally having one $C_{6-10}$ aryl,
(3) $C_{1-6}$ alkoxy optionally having one $C_{6-10}$ aryl, or
(4) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from
(a) $C_{6-10}$ aryl optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl,
(b) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and
(c) oxo;
$R^{6b}$ is a hydrogen atom;
$R^{7b}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl; and
$R^{8b}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl,
or a salt thereof (compound (Ib)).

$R^{2b}$ is preferably a hydrogen atom.

$W^b$ is preferably O.

$X^b$ is preferably $CR^{3b'}$ wherein $R^{3b'}$ is a hydrogen atom or a halogen atom, and particularly, CF is preferable.

$Y^b$ is preferably $CR^{4b'}$ wherein $R^{4b'}$ is a hydrogen atom or a halogen atom, and particularly, CH is preferable.

$R^{5b}$ is preferably
(1) cyclopropyl optionally having one phenylaminocarbonyl

optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-4-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms, and

(d) oxo,

more preferably,

cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl.

$R^{7b}$ is preferably a hydrogen atom.

$R^{8b}$ is preferably a hydrogen atom.

Preferable specific examples of compound (Ib) include the following.

[Compound (Ib-A)]

In compound (Ib), a compound wherein

$R^{2b}$ is a hydrogen atom;

$W^b$ is O;

$X^b$ is $CR^{3b'}$ wherein $R^{3b'}$ is a hydrogen atom or a halogen atom;

$Y^b$ is $CR^{4b'}$ wherein $R^{4b'}$ is a hydrogen atom or a halogen atom;

$R^{5b}$ is

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,
(3) methoxy optionally having one phenyl,
(4) tert-butoxy, or
(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (pyrazolyl, dihydropyrazolyl, dihydropyridyl, N-oxidepyridyl) optionally having 1 to 4 substituents selected from
(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,
(b) methyl optionally having 1 to 3 fluorine atoms,
(c) ethyl optionally having 1 to 3 fluorine atoms, and
(d) oxo;

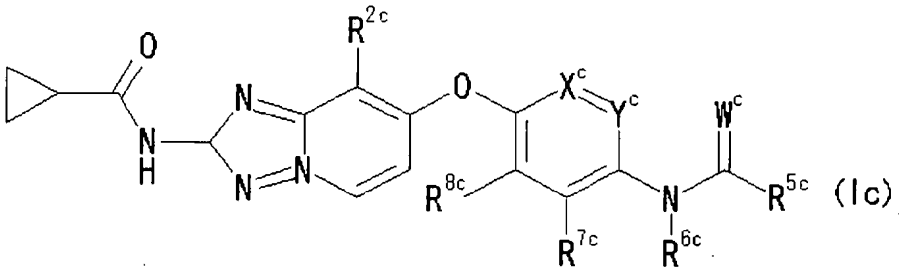
$R^{6b}$ is a hydrogen atom;
$R^{7b}$ is a hydrogen atom; and
$R^{8b}$ is a hydrogen atom is preferable.

Particularly, compound (Ib-A) wherein
$R^{2b}$ is a hydrogen atom;
$W^b$ is O;
$X^b$ is CF;
$Y^b$ is CH;
$R^{5b}$ is a cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl;
$R^{6b}$ is a hydrogen atom;
$R^{7b}$ is a hydrogen atom; and
$R^{8b}$ is a hydrogen atom is preferable.

Specifically, compound (Ib-A) is preferably the compound of Example 34.

[Compound (Ic)]

1,2,4-triazolo[1,5-a]pyridine derivative: a compound represented by the formula



(Ic)

wherein $R^{2c}$ is

(1) a hydrogen atom,

(2) a halogen atom,

(3) a group bonded via a carbon atom,

(4) a group bonded via a nitrogen atom,

(5) a group bonded via an oxygen atom, or

(6) a group bonded via a sulfur atom;

$W^c$ is O or S;

$X^c$ is $CR^{3c}$ ($R^{3c}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl), or N;

$Y^c$ is $CR^{4c}$ ($R^{4c}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl), or N;

$R^{5c}$ is

(1) $C_{3-6}$ cycloalkyl optionally having one $C_{6-10}$ aryl-aminocarbonyl optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl,

(2) $C_{1-6}$ alkyl-carbonylamino optionally having one $C_{6-10}$ aryl,

(3) $C_{1-6}$ alkoxy optionally having one $C_{6-10}$ aryl, or

(4) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from

(a) $C_{6-10}$ aryl optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl,

(b) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and

(c) oxo;

$R^{6c}$ is a hydrogen atom;

$R^{7c}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl; and

$R^{8c}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl,

or a salt thereof (compound (Ic)).

$R^{2c}$ is preferably a hydrogen atom.

$W^c$ is preferably O.

$X^c$ is preferably $CR^{3c'}$ wherein $R^{3c'}$ is a hydrogen atom or a halogen atom, and particularly preferably CF.

$Y^c$ is preferably $CR^{4c'}$ wherein $R^{4c'}$ is a hydrogen atom or a halogen atom is preferable, and particularly preferably CH.

$R^{5c}$ is preferably

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-4-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms, and

(d) oxo,

and more preferably

a nitrogen-containing heterocyclic group (particularly, dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms, and

(d) oxo.

$R^{7c}$ is preferably a hydrogen atom.

$R^{8c}$ is preferably a hydrogen atom.

Preferable specific examples of compound (Ic) include the following.

[Compound (Ic-A)]

In compound (Ic), a compound wherein

$R^{2c}$ is a hydrogen atom;

$W^c$ is O;

$X^c$ is $CR^{3c'}$ wherein $R^{3c'}$ is a hydrogen atom or a halogen atom;

$Y^c$ is $CR^{4c'}$ wherein $R^{3c'}$ is a hydrogen atom or a halogen atom;

$R^{5c}$ is

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-4-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms, and

(d) oxo;

$R^{6c}$ is a hydrogen atom;

$R^{7c}$ is a hydrogen atom; and

$R^{8c}$ is a hydrogen atom, is preferable.

Particularly, compound (Ic-A) wherein

$R^{2c}$ is a hydrogen atom;

$W^c$ is O;

$X^c$ is CF;

$Y^c$ is CH;

$R^{5c}$ is

a nitrogen-containing heterocyclic group (particularly, dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms, and

(d) oxo;

$R^{6c}$ is a hydrogen atom;

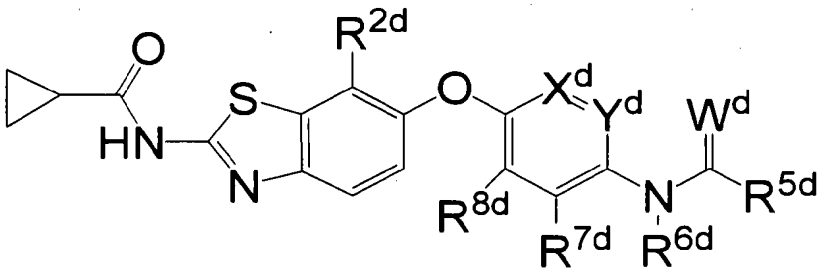
$R^{7c}$ is a hydrogen atom; and

$R^{8c}$ is a hydrogen atom is preferable.

Specifically, compound (Ic-A) is preferably the compound of Example 76.

[Compound (Id)]

1,3-benzothiazole derivative: a compound represented by the formula




(Id)

wherein $R^{2d}$ is

(1) a hydrogen atom,

(2) a halogen atom,

(3) a group bonded via a carbon atom,

(4) a group bonded via a nitrogen atom,

(5) a group bonded via an oxygen atom, or

(6) a group bonded via a sulfur atom;

$W^d$ is O or S;

$X^d$ is $CR^{3d}$ ($R^{3d}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl),

or N;

$Y^d$ is $CR^{4d}$ ($R^{4d}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl), or N;

$R^{5d}$ is

(1) $C_{3-6}$ cycloalkyl optionally having one $C_{6-10}$ aryl-aminocarbonyl optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl,

(2) $C_{1-6}$ alkyl-carbonylamino optionally having one $C_{6-10}$ aryl,

(3) $C_{1-6}$ alkoxy optionally having one $C_{6-10}$ aryl, or

(4) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from

(a) $C_{6-10}$ aryl optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl,

(b) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and

(c) oxo;

$R^{6d}$ is a hydrogen atom;

$R^{7d}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl; and

$R^{8d}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl,

or a salt thereof (compound (Id)).

$R^{2d}$ is preferably a hydrogen atom.

$W^d$ is preferably O.

$X^d$ is preferably $CR^{3d'}$ wherein $R^{3d'}$ is a hydrogen atom or a halogen atom, and particularly preferably CF.

$Y^d$ is preferably $CR^{4d'}$ wherein $R^{4d'}$ is a hydrogen atom or a halogen atom, and particularly preferably CH.

$R^{5d}$ is preferably

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide

thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-4-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms, and

(d) oxo,

and more preferably

cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl.

$R^{7d}$ is preferably a hydrogen atom.

$R^{8d}$ is preferably a hydrogen atom.

Preferable specific examples of compound (Id) include the following.

[Compound (Id-A)]

In compound (Id), a compound wherein

$R^{2d}$ is a hydrogen atom;

$W^d$ is O;

$X^d$ is $CR^{3d'}$ wherein $R^{3d'}$ is a hydrogen atom or a halogen atom;

$Y^d$ is $CR^{4d'}$ wherein $R^{4d'}$ is a hydrogen atom or a halogen atom;

$R^{5d}$ is

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-

oxidepyridyl (e.g., N-oxidepyridin-2-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms, and

(d) oxo;

$R^{6d}$ is a hydrogen atom;

$R^{7d}$ is a hydrogen atom; and

$R^{8d}$ is a hydrogen atom is preferable.

Particularly, in compound (Id-A), a compound wherein

$R^{2d}$ is a hydrogen atom;

$W^d$ is O;

$X^d$ is CF;

$Y^d$ is CH;

$R^{5d}$ is a cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl;

$R^{6d}$ is a hydrogen atom;

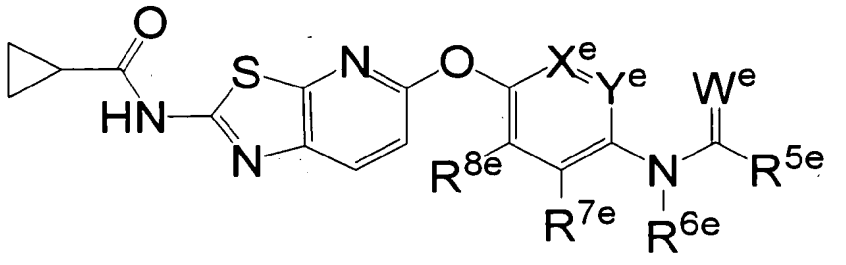
$R^{7d}$ is a hydrogen atom; and

$R^{8d}$ is a hydrogen atom is preferable.

Specifically, as compound (Id-A), the compound of Example 18 is preferable.

[Compound (Ie)]

1,3-thiazolo[5,4-b]pyridine derivative: a compound represented by the formula



(Ie)

wherein

$W^e$ is O or S;

$X^e$ is $CR^{3e}$ ($R^{3e}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl), or N;

$Y^e$ is $CR^{4e}$ ($R^{4e}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl), or N;

$R^{5e}$ is

(1) $C_{3-6}$ cycloalkyl optionally having one $C_{6-10}$ aryl-aminocarbonyl optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl,

(2) $C_{1-6}$ alkyl-carbonylamino optionally having one $C_{6-10}$ aryl,

(3) $C_{1-6}$ alkoxy optionally having one $C_{6-10}$ aryl, or

(4) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from

(a) $C_{6-10}$ aryl optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl,

(b) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and

(c) oxo;

$R^{6e}$ is a hydrogen atom;

$R^{7e}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl; and

$R^{8e}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl,

or a salt thereof (compound (Ie)).

$W^e$ is preferably O.

$X^e$ is preferably $CR^{3e'}$ wherein $R^{3e'}$ is a hydrogen atom or a halogen atom, and particularly preferably CF.

$Y^e$ is preferably $CR^{4e'}$ wherein $R^{4e'}$ is a hydrogen atom or a halogen atom, and particularly preferably CH.

$R^{5e}$ is preferably

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 fluorine atoms,

(2) acetylamino optionally having one phenyl,

(3) methoxy or tert-butoxy optionally having one phenyl, or

(4) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-

oxidepyridyl (e.g., N-oxidepyridin-2-yl)) optionally having 1 to 3 substituents selected from

(a) phenyl optionally having 1 to 3 fluorine atoms,

(b) methyl,

(c) ethyl, and

(d) oxo,

and more preferably, a nitrogen-containing heterocyclic group (particularly, dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl)) optionally having 1 to 3 substituents selected from

(a) phenyl optionally having 1 to 3 fluorine atoms,

(b) methyl,

(c) ethyl, and

(d) oxo.

$R^{6e}$ is a hydrogen atom.

$R^{7e}$ is preferably a hydrogen atom.

$R^{8e}$ is preferably a hydrogen atom.

Preferable specific examples of compound (Ie) include the following.

[Compound (Ie-A)]

In compound (Ie), a compound wherein

$W^e$ is O;

$X^e$ is $CR^{3e'}$ wherein $R^{3e'}$ is a hydrogen atom or a halogen atom;

$Y^e$ is $CR^{4e'}$ wherein $R^{4e'}$ is a hydrogen atom or a halogen atom;

$R^{5e}$ is

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 fluorine atoms,

(2) acetylamino optionally having one phenyl,

(3) methoxy or tert-butoxy optionally having one phenyl, or

(4) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl)) optionally having 1 to 3 substituents selected from

(a) phenyl optionally having 1 to 3 fluorine atoms,

(b) methyl,

(c) ethyl, and

(d) oxo;

$R^{6e}$ is a hydrogen atom;

$R^{7e}$ is a hydrogen atom; and

$R^{8e}$ is a hydrogen atom is preferable.

Particularly, compound (Ie-A) wherein

$W^e$ is O;

$X^e$ is CF;

$Y^e$ is CH;

$R^{5e}$ is

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 fluorine atoms,

(2) tert-butoxy optionally having one phenyl, or

(3) a nitrogen-containing heterocyclic group (particularly, dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl)) optionally having 1 to 3 substituents selected from

(a) phenyl optionally having 1 to 3 fluorine atoms,

(b) methyl,

(c) ethyl, and

(d) oxo;

$R^{6e}$ is a hydrogen atom;

$R^{7e}$ is a hydrogen atom; and

$R^{8e}$ is a hydrogen atom is preferable.

Specifically, as compound (Ie-A), compounds of Examples 19 - 21 are preferable.

When compound (I) is a salt, examples of the salt include a metal salt, an ammonium salt, a salt with organic base, a salt with inorganic acid, a salt with organic acid, a salt with basic or acidic amino acid and the like. Preferable examples of the metal salt include alkali metal salt such as sodium salt, potassium salt and the like; alkaline earth metal salt such as calcium salt, magnesium salt, barium salt and the like; aluminum salt and the like. Preferable examples of the salt with the

organic base include a salt with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and the like. Preferable examples of the salt with the inorganic acid include a salt with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like. Preferable examples of the salt with the organic acid include a salt with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like. Preferable examples of the salt with the basic amino acid include a salt with arginine, lysine, ornithine and the like. Preferable examples of the salt with the acidic amino acid include a salt with aspartic acid, glutamic acid and the like.

Of these, pharmaceutically acceptable salt is preferable. For example, where the compound has an acidic functional group, inorganic salt such as alkali metal salt (e.g., sodium salt, potassium salt etc.), alkaline earth metal salt (e.g., calcium salt, magnesium salt etc.) and the like, ammonium salt and the like can be mentioned. Alternatively, where the compound has a basic functional group, for example, a salt with inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like, or a salt with organic acid such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like can be mentioned.

Hereinafter, the production methods of compound (I) of the present invention are explained.

The compound (I) of the present invention can be obtained, for example, according to the methods shown in the following Schemes or a method analogous thereto and the like.

Each compound in the following Schemes includes salts, and as such salts, for example, those similar to the salts of the compound (I) and the like can be used.

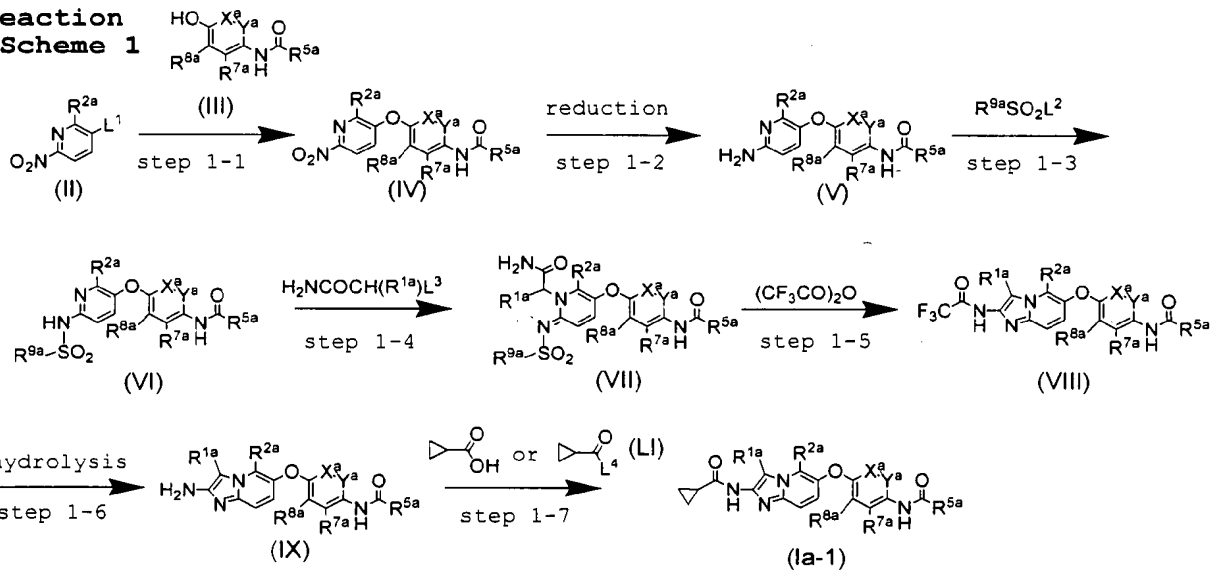
The compound obtained in each step can be used in the form of a reaction mixture or a crude product for the next reaction. In addition, the compound can be isolated from a reaction mixture according to a conventional method, and can be easily purified by a separation means such as recrystallization, distillation, chromatography and the like.

Schematic reaction formulas are shown in the following, wherein each symbol in the compounds is as defined above.

[Production method 1]

In compound (Ia), compound (Ia-1) wherein $W^a$ is an oxygen atom can be produced, for example, by a method shown in Reaction scheme 1. The compound (Ia-1) is encompassed in compound (Ia).

**Reaction Scheme 1**




wherein $L^1$ - $L^4$ are each a leaving group; $R^{9a}$ is (1) $C_{1-6}$ alkyl (e.g., methyl, ethyl) optionally having 1 to 3 substituents selected from (a) a halogen atom and (b) nitro, or (2) $C_{6-10}$ aryl (e.g., phenyl) optionally having 1 to 3 substituents selected from (a) a halogen atom, (b) nitro, and (c) $C_{1-6}$ alkyl

(e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms; and other symbols are as defined above.

Examples of the leaving group for $L^1$ include (1) a halogen atom, (2) $C_{1-6}$ alkylsulfonyloxy (e.g., methylsulfonyloxy, ethylsulfonyloxy) optionally having 1 to 3 substituents selected from (a) a halogen atom, (b) nitro, and (c) $C_{1-6}$ alkyl (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms, (3) $C_{6-10}$ arylsulfonyloxy (e.g., phenylsulfonyloxy) optionally having 1 to 3 substituents selected from (a) a halogen atom, (b) nitro, and (c) $C_{1-6}$ alkyl (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms, and the like.

Examples of the leaving group for $L^2$ include a halogen atom and the like.

Examples of the leaving group for $L^3$ include those similar to the leaving group for $L^1$.

Examples of the leaving group for $L^4$ include a halogen atom and the like.

(step 1-1):

Compound (IV) can be produced by reacting compound (II) with compound (III).

Compound (III) is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (II).

In this reaction, a base may be added as necessary. As the base, an inorganic base, an organic base and the like are used. Specific examples include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium hydride, sodium amide, lithiumdiisopropylamide and the like. The base

is used in a proportion of about 1 mol to about 30 mol, preferably about 1 mol to about 10 mol, per 1 mol of compound (II).

This reaction is advantageously carried out using a solvent inert to the reaction. While the solvent is not particularly limited as long as the reaction proceeds, for example, alcohols such as methanol, ethanol, 2-propanol, 2-methyl-2-propanol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like; esters such as ethyl acetate and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, chlorobenzene, trifluoromethylbenzene and the like; nitriles such as acetonitrile and the like; sulfoxides such as dimethyl sulfoxide and the like; pyridine; acetic acid; water; and the like can be used alone or in a mixture.

While the reaction time varies depending on the kind of reagent and solvent to be used, it is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

(step 1-2):

Compound (V) can be produced by reducing nitro of compound (IV). Nitro can be reduced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock), the fourth series of experimental chemistry, vol. 20, 279-280 and the like, or a method analogous thereto.

(step 1-3):

Compound (VI) can be produced by reacting compound (V)

with a compound represented by the formula $R^{9a}SO_2L^2$ in the presence of a base.

$R^{9a}SO_2L^2$ is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (V).

As the base, those similar to the bases of step 1-1 are used. The base is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (V).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 1-1 are used. Alternatively, an excess amount of a base may be used as a solvent.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

$R^{9a}SO_2L^2$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

(step 1-4):

Compound (VII) can be produced by reacting compound (VI) with a compound represented by the formula $H_2NCOCH(R^{1a})L^3$ in the presence of a base.

$H_2NCOCH(R^{1a})L^3$ is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (VI).

As the base, those similar to the bases of step 1-1 are used. The base is used in a proportion of about 0.1 mol to 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (VI).

This reaction is advantageously carried out using a

solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 1-1 are used. Alternatively, an excess amount of a base may be used as a solvent.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

$H_2NCOCH(R^{1a})L^3$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

(step 1-5):

Compound (VIII) can be produced by reacting compound (VII) with trifluoroacetic acid anhydride.

Trifluoroacetic acid anhydride is used in a solvent amount for compound (VII).

This reaction is advantageously performed using an additional solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 1-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

(step 1-6):

Compound (IX) can be produced by alkalihydrolysis of compound (VIII). This reaction is performed in a water-containing solvent in the presence of a base.

Examples of the base include sodium hydroxide, potassium hydroxide, lithium hydroxide, barium hydroxide, calcium hydroxide, potassium carbonate, sodium carbonate, cesium carbonate, sodium methoxide and the like. The base is used in a proportion of about 1 mol to about 50 mol, preferably about

1 mol to about 10 mol, per 1 mol of compound (VIII).

Examples of the water-containing solvent include mixed solvent of one or more kinds of solvents selected from methanol, ethanol, tetrahydrofuran, 1,4-dioxane and the like and water, and the like.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 100°C.

(step 1-7):

Compound (Ia-1) can be produced by reacting compound (IX) with cyclopropanecarboxylic acid in the presence of a condensation agent, or compound (IX) with compound (LI).

When compound (IX) is reacted with cyclopropanecarboxylic acid in the presence of a condensation agent, cyclopropanecarboxylic acid is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 3 mol, per 1 mol of compound (IX).

Examples of the condensation agent include 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and the like. The condensation agent is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 5 mol, per 1 mol of compound (IX).

Where necessary, a suitable condensation promoter (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide and the like) can be used in this reaction.

Such condensation promoter is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (IX).

This reaction may proceed more smoothly by addition of a base (e.g., triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, 4-(dimethylamino)pyridine and the like). The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (IX).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 1-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

When compound (IX) is reacted with compound (LI), compound (LI) is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (IX).

Generally, this reaction is preferably performed in the presence of a base. However, the presence of a base is not always essential. Examples of the base to be used include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline and the like. The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (IX).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 1-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

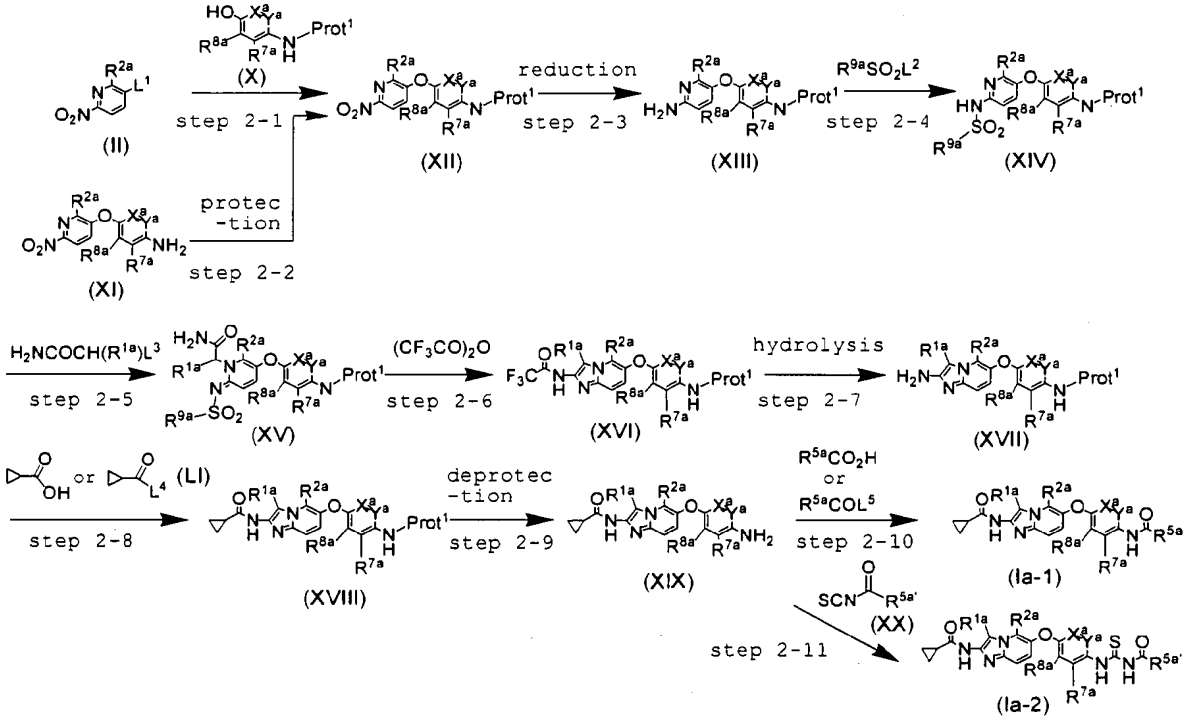
The reaction temperature is generally about -78°C to

about 200°C, preferably about -20°C to about 150°C.

[Production method 2]

In compound (Ia), compound (Ia-2) wherein $W^a$ is a sulfur atom and $R^{5a}$ is $C_{1-6}$ alkyl-carbonylamino optionally having one $C_{6-10}$ aryl can be produced, for example, by a method shown in Reaction scheme 2. The compound (Ia-2) is encompassed in compound (Ia). In addition, compound (Ia-1) can also be produced by a method shown in Reaction scheme 2.

**Reaction Scheme 2**




wherein $Prot^1$ is an amino-protecting group; $L^5$ is a leaving group; $R^{5a'}$ is $C_{1-6}$ alkyl optionally having one $C_{6-10}$ aryl; and other symbols are as defined above.

Examples of the amino-protecting group for $Prot^1$ include benzyloxycarbonyl, tert-butoxycarbonyl and the like.

Examples of the leaving group for $L^5$ include a halogen atom and the like.

The "$C_{1-6}$ alkyl optionally having one $C_{6-10}$ aryl" for $R^{5a'}$ means a group bonded to carbonylamino to form "$C_{1-6}$ alkyl-

carbonylamino optionally having one $C_{6-10}$ aryl" for the above-mentioned $R^5$.

(step 2-1):

Compound (XII) can be produced by reacting compound (II) with compound (X) in the presence of a base.

Compound (X) is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (II).

As the base, those similar to the bases of step 1-1 are used. The base is used in a proportion of about 1 mol to about 30 mol, preferably about 1 mol to about 10 mol, per 1 mol of compound (II).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 1-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

(step 2-2):

Compound (XII) can also be produced by protecting amino of compound (XI). Amino can be protected according to a method known *per se*, for example, the methods described in "Protective Groups in Organic Synthesis, 3rd Ed." (Theodora W. Greene) and the like, or a method analogous thereto.

(steps 2-3 - 2-8):

Compound (XIII), compound (XIV), compound (XV), compound (XVI), compound (XVII) and compound (XVIII) can be synthesized from compound (XII) in the same manner as in steps 1-2 to 1-7, respectively.

(step 2-9):

Compound (XIX) can be produced by removing the amino-protecting group of compound (XVIII). The amino-protecting group can be removed according to a method known *per se*, for

example, the methods described in "Protective Groups in Organic Synthesis, 3rd Ed." (Theodora W. Greene) and the like, or a method analogous thereto.

(step 2-10):

Compound (Ia-1) can be produced by reacting compound (XIX) with carboxylic acid ($R^{5a}CO_2H$) in the presence of a condensation agent.

Carboxylic acid ($R^{5a}CO_2H$) is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 3 mol, per 1 mol of compound (XIX).

Examples of the condensation agent include 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N,N-tetramethyluronium hexafluorophosphate and the like. The condensation agent is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 5 mol, per 1 mol of compound (XIX).

Where necessary, a suitable condensation promoter (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide etc.) can be used in this reaction. Such condensation promoter is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XIX).

This reaction may proceed more smoothly by addition of a base. As the base, those similar to the bases of step 1-1 are used. The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XIX).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 1-1 are used.

The reaction time is generally about 1 min to about 200 hr, preferably about 10 min to about 100 hr.

The reaction temperature is generally about -100°C to about 250°C, preferably about -78°C to about 200°C.

$R^{5a}CO_2H$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

Compound (Ia-1) can also be produced by reacting compound (XIX) with a reactive derivative ($R^{5a}COL^5$) of carboxylic acid in the presence of a base.

The reactive derivative ($R^{5a}COL^5$) of carboxylic acid is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 3 mol, per 1 mol of compound (XIX).

The base may be used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XIX). As the base, those similar to the bases of step 1-1 are used.

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 1-1 are used.

The reaction time is generally about 1 min to about 200 hr, preferably about 10 min to about 100 hr.

The reaction temperature is generally about -100°C to about 250°C, preferably about -78°C to about 200°C.

$R^{5a}COL^5$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

(step 2-11):

Compound (Ia-2) can be produced by reacting compound (XIX) with acylthiocyanate derivative (XX).

The acylthiocyanate derivative (XX) is used in a proportion of about 0.1 mol to 10 mol, preferably about 0.5 mol to about 5 mol, per 1 mol of compound (XIX).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 1-1 are used.

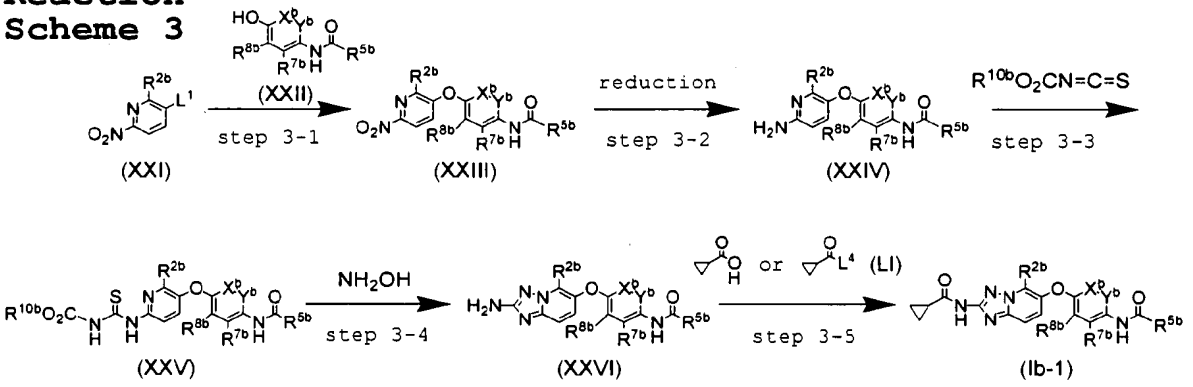
The reaction time is generally about 1 min to about 200 hr, preferably about 10 min to about 100 hr.

The reaction temperature is generally about -100°C to about 250°C, preferably about -78°C to about 200°C.

[Production method 3]

In compound (Ib), compound (Ib-1) wherein $W^b$ is an oxygen atom can be produced, for example, by the method shown in Reaction scheme 3. The compound (Ib-1) is encompassed in compound (Ib).

**Reaction Scheme 3**




wherein $R^{10b}$ is $C_{1-6}$ alkyl optionally having 1 to 3 substituents selected from (a) a halogen atom and (b) nitro; and other symbols are as defined above.

(step 3-1):

Compound (XXIII) can be produced by reacting compound (XXI) with compound (XXII).

Compound (XXII) is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XXI).

In this reaction, a base may be added as necessary. As the base, an inorganic base, an organic base and the like are used. Specific examples include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium hydride, sodium amide, lithiumdiisopropylamide and the like. The base is used in a proportion of about 1 mol to about 30 mol, preferably about 1 mol to about 10 mol, per 1 mol of compound (XXI).

This reaction is advantageously carried out using a solvent inert to the reaction. The solvent is not particularly limited as long as the reaction proceeds and, for example, alcohols such as methanol, ethanol, 2-propanol, 2-methyl-2-propanol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like; esters such as ethyl acetate and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; nitriles such as acetonitrile and the like; sulfoxides such as dimethyl sulfoxide and the like; pyridine; acetic acid; water; and the like can be used alone or in a mixture.

While the reaction time varies depending on the kind of reagent and solvent to be used, it is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

(step 3-2):

Compound (XXIV) can be produced by reducing nitro of compound (XXIII).

Nitro can be reduced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock), the fourth series of experimental chemistry, vol. 20, 279-280 and the like, or a method analogous thereto.

(step 3-3):

Compound (XXV) can be produced by reacting compound (XXIV) with a compound represented by the formula $R^{10b}O_2C-N=C=S$.

$R^{10b}O_2C-N=C=S$ is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XXIV).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 3-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

$R^{10b}O_2C-N=C=S$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

(step 3-4):

Compound (XXVI) can be produced by reacting compound (XXV) with hydroxylamine in the presence of a base.

Hydroxylamine is used in a proportion of about 0.1 mol to about 100 mol, preferably about 0.3 mol to about 30 mol, per 1 mol of compound (XXV).

As the base, those similar to the bases exemplified in step 3-1 are used. The base is used in a proportion of about 0.1 mol to about 100 mol, preferably about 0.3 mol to about 30 mol, per 1 mol of compound (XXV).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 3-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

(step 3-5):

Compound (Ib-1) can be produced by reacting compound (XXVI) with cyclopropanecarboxylic acid in the presence of a condensation agent or compound (XXVI) with compound (LI).

When compound (XXVI) is reacted with cyclopropanecarboxylic acid in the presence of a condensation agent, cyclopropanecarboxylic acid is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 3 mol, per 1 mol of compound (XXVI).

Examples of the condensation agent include 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and the like. The condensation agent is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 5 mol, per 1 mol of compound (XXVI).

Where necessary, a suitable condensation promoter (e.g.,

1-hydroxybenzotriazole, N-hydroxysuccinimide and the like) can be used in this reaction. Such condensation promoter is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XXVI).

This reaction may proceed more smoothly by addition of a base (e.g., triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like). The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XXVI).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 3-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

When compound (XXVI) is reacted with compound (LI), compound (LI) is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XXVI).

Generally, this reaction is preferably performed in the presence of a base. However, the presence of a base is not always essential. Examples of the base include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline and the like. The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XXVI).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to

the solvents exemplified in step 3-1 are used.

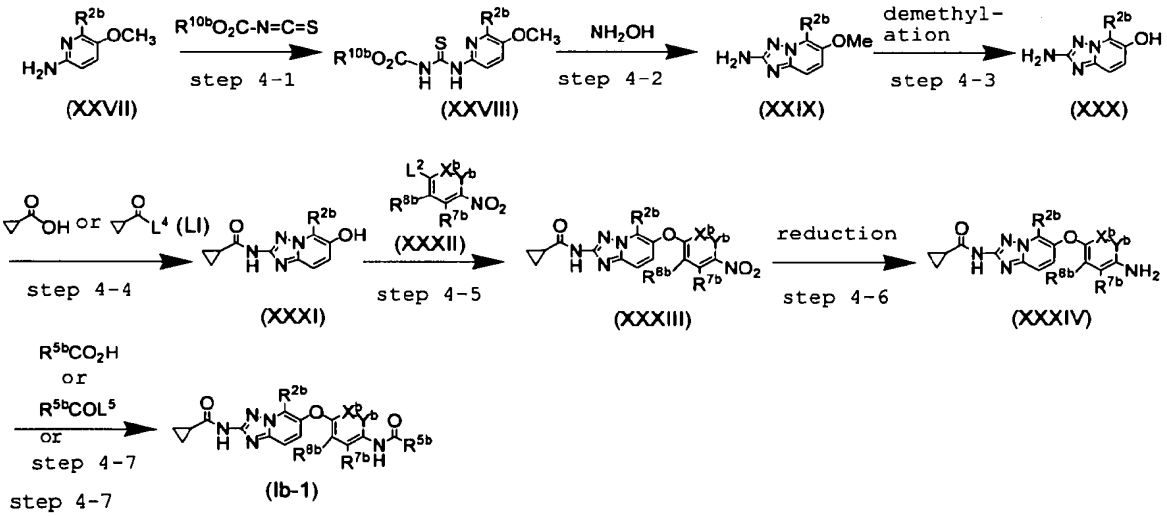
The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

[Production method 4]

Compound (Ib-1) can also be produced, for example, by a method shown in Reaction scheme 4.

**Reaction Scheme 4**




wherein the symbols are as defined above.

(steps 4-1 and 4-2):

Compound (XXVIII) and compound (XXIX) can be synthesized from compound (XXVII) in the same manner as in steps 3-3 and 3-4, respectively.

(step 4-3):

Compound (XXX) can be produced by demethylation of compound (XXIX).

Demethylation can be performed according to a method known *per se*, for example, the method described in "Protective Groups in Organic Synthesis, 3rd Ed." (Theodora W. Greene) and the like, or a method analogous thereto.

(step 4-4):

Compound (XXXI) can be produced by reacting compound (XXX) with cyclopropanecarboxylic acid in the presence of a condensation agent, or by reacting compound (XXX) with compound (LI) in the same manner as in step 3-5.

(step 4-5):

Compound (XXXIII) can be produced by reacting compound (XXXI) with compound (XXXII) in the presence of a base.

Compound (XXXII) is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XXXI).

As the base, those similar to the bases exemplified in step 3-1 are used. The base is used in a proportion of about 1 mol to about 30 mol, preferably about 1 mol to about 10 mol, per 1 mol of compound (XXXI).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 3-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

(step 4-6):

Compound (XXXIV) can be produced by reducing nitro of compound (XXXIII) in the same manner as in step 3-2.

(step 4-7):

Compound (Ib-1) can be produced by reacting compound (XXXIV) with carboxylic acid ($R^{5b}CO_2H$) in the presence of a condensation agent.

Carboxylic acid ($R^{5b}CO_2H$) is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 3 mol, per 1 mol of compound (XXXIV).

Examples of the condensation agent include 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate,

diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N,N-tetramethyluronium hexafluorophosphate and the like. The condensation agent is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 5 mol, per 1 mol of compound (XXXIV).

Where necessary, a suitable condensation promoter (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide etc.) can be used in this reaction. Such condensation promoter is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XXXIV).

This reaction may proceed more smoothly by the addition of a base. As the base, those similar to the bases exemplified in step 3-1 are used. The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XXXIV).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 3-1 are used.

The reaction time is generally about 1 min to about 200 hr, preferably about 10 min to about 100 hr.

The reaction temperature is generally about -100°C to about 250°C, preferably about -78°C to about 200°C.

$R^{5b}CO_2H$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

Compound (Ib-1) can also be produced by reacting compound (XXXIV) with a reactive derivative ($R^{5b}COL^5$) of carboxylic acid.

The reactive derivative ($R^{5b}COL^5$) of carboxylic acid is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 3 mol, per 1 mol of compound (XXXIV).

This reaction may be performed in the presence of a base. As the base, those similar to the bases exemplified in step 3-1 are used. The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XXXIV).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 3-1 are used.

The reaction time is generally about 1 min to about 200 hr, preferably about 10 min to about 100 hr.

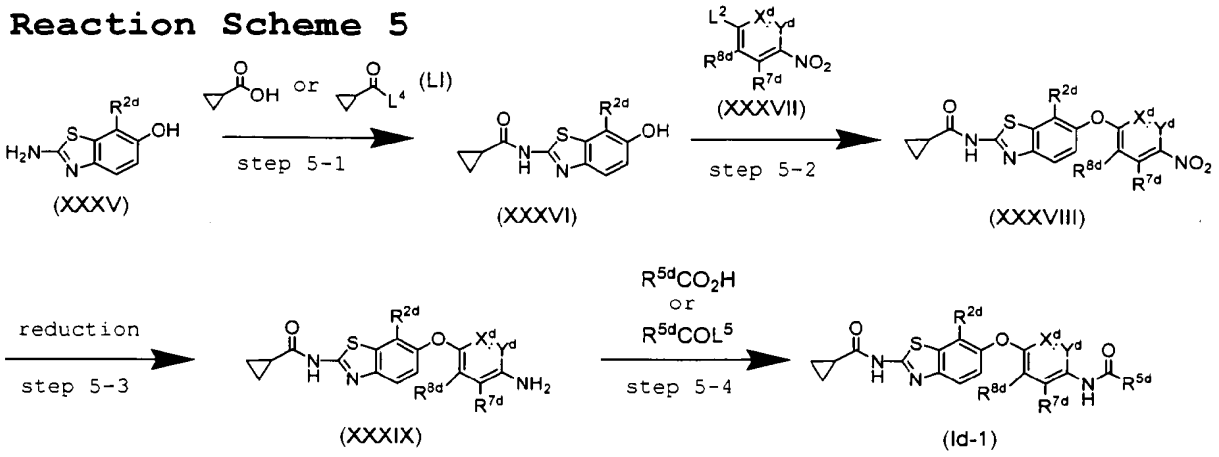
The reaction temperature is generally about -100°C to about 250°C, preferably about -78°C to about 200°C.

$R^{5b}COL^5$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

[Production method 5]

In compound (Id), compound (Id-1) wherein $W^d$ is an oxygen atom can also be produced, for example, by a method shown in Reaction scheme 5. The compound (Id-1) is encompassed in compound (Id).

**Reaction Scheme 5**




wherein the symbols are as defined above.

(step 5-1):

Compound (XXXVI) can be produced by reacting compound (XXXV) with cyclopropanecarboxylic acid in the presence of a condensation agent, or by reacting compound (XXXV) with compound (LI).

When compound (XXXV) is reacted with cyclopropanecarboxylic acid in the presence of a condensation agent, cyclopropanecarboxylic acid is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 3 mol, per 1 mol of compound (XXXV).

Examples of the condensation agent include 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and the like. The condensation agent is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 5 mol, per 1 mol of compound (XXXV).

Where necessary, a suitable condensation promoter (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide and the like) can be used in this reaction. Such condensation promoter is used

in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XXXV).

This reaction may proceed more smoothly by the addition of a base (e.g., triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like). The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XXXV).

This reaction is advantageously carried out using a solvent inert to the reaction. While the solvent is not particularly limited as long as the reaction proceeds, for example, alcohols such as methanol, ethanol, 2-propanol, 2-methyl-2-propanol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like; esters such as ethyl acetate and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; nitriles such as acetonitrile and the like; sulfoxides such as dimethyl sulfoxide and the like; pyridine; acetic acid; water; and the like can be used alone or in a mixture.

While the reaction time varies depending on the kind of reagent and solvent to be used, it is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

When compound (XXXV) is reacted with compound (LI), compound (LI) is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XXXV).

Generally, this reaction is preferably performed in the

presence of a base. However, the presence of a base is not always essential. Examples of the base include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline and the like. The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XXXV).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the aforementioned solvents are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

(step 5-2):

Compound (XXXVIII) can be produced by reacting compound (XXXVI) with compound (XXXVII).

Compound (XXXVII) is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XXXVI).

In this reaction, a base may be added as necessary. As the base, an inorganic base, an organic base and the like are used. Specific examples include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium hydride, sodium amide, lithiumdiisopropylamide and the like. The base

is used in a proportion of about 1 mol to about 30 mol, preferably about 1 mol to about 10 mol, per 1 mol of compound (XXXVI).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 5-1 are used.

While the reaction time varies depending on the reagent and solvent to be used, it is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

(step 5-3):

Compound (XXXIX) can be produced by reducing nitro of compound (XXXVIII).

Nitro can be reduced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock), the fourth series of experimental chemistry, vol. 20, 279-280 and the like, or a method analogous thereto.

(step 5-4):

Compound (Id-1) can be produced by reacting compound (XXXIX) with carboxylic acid ($R^{5d}CO_2H$) in the presence of a condensation agent, or by reacting compound (XXXIX) with a reactive derivative of carboxylic acid ($R^{5d}COL^5$).

When compound (XXXIX) is reacted with carboxylic acid ($R^{5d}CO_2H$) in the presence of a condensation agent, carboxylic acid is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 3 mol, per 1 mol of compound (XXXIX).

Examples of the condensation agent include 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate,

diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and the like. The condensation agent is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 5 mol, per 1 mol of compound (XXXIX).

Where necessary, a suitable condensation promoter (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide and the like) can be used in this reaction. Such condensation promoter is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XXXIX).

This reaction may proceed more smoothly by the addition of a base (e.g., triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like). The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XXXIX).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 5-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

$R^{5d}CO_2H$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

When compound (XXXIX) is reacted with a reactive derivative of carboxylic acid ($R^{5d}COL^5$), the reactive derivative of carboxylic acid ($R^{5d}COL^5$) is used in a proportion

of about 1 mol to about 10 mol, preferably about 1 mol to about 3 mol, per 1 mol of compound (XXXIX).

Generally, this reaction is preferably performed in the presence of a base. However, the presence of a base is not always essential. Examples of the base include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline and the like. The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XXXIX).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 5-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

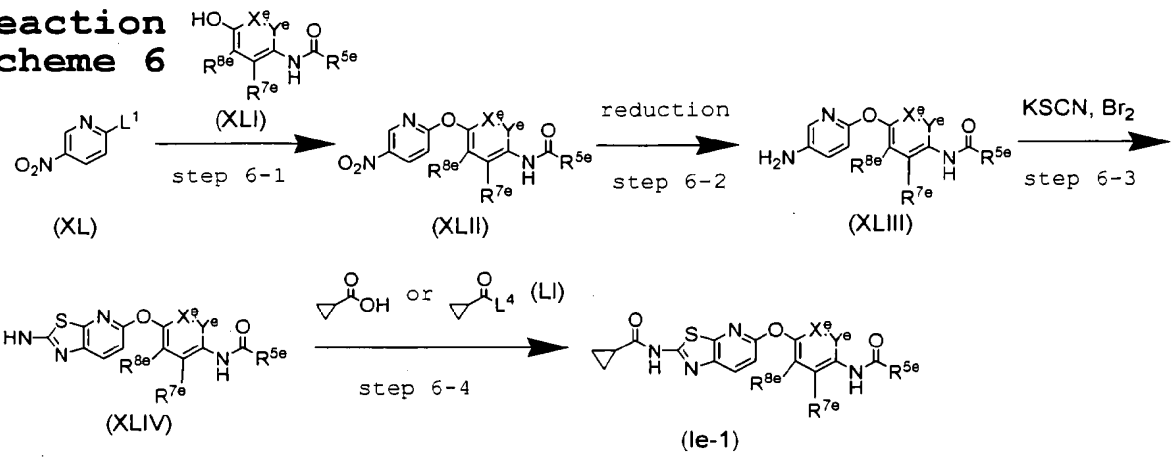
The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

$R^{5d}COL^5$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

[Production method 6]

In compound (Ie), compound (Ie-1) wherein $W^e$ is an oxygen atom can be produced, for example, by the method shown in Reaction scheme 6. The compound (Ie-1) is encompassed in compound (Ie).

**Reaction Scheme 6**




wherein the symbols are as defined above.

(step 6-1):

Compound (XLII) can be produced by reacting compound (XL) with compound (XLI).

Compound (XLI) is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XL).

Where necessary, a base may be added in this reaction. As the base, an inorganic base, an organic base and the like are used. Specific examples include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium hydride, sodium amide, lithiumdiisopropylamide and the like. The base is used in a proportion of about 1 mol to about 30 mol, preferably about 1 mol to about 10 mol, per 1 mol of compound (XL).

This reaction is advantageously carried out using a solvent inert to the reaction. The solvent is not particularly limited as long as the reaction proceeds, and, for example, alcohols such as methanol, ethanol, 2-propanol, 2-methyl-2-

propanol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like; esters such as ethyl acetate and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; nitriles such as acetonitrile and the like; sulfoxides such as dimethyl sulfoxide and the like; pyridine; acetic acid; water; and the like can be used alone or in a mixture.

While the reaction time varies depending on the kind of reagent and solvent to be used, it is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

(step 6-2):

Compound (XLIII) can be produced by reducing nitro of compound (XLII).

Nitro can be reduced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock), the fourth series of experimental chemistry, vol. 20, 279-280 and the like, or a method analogous thereto.

(step 6-3):

Compound (XLIV) can be produced by reacting compound (XLIII) with potassium thiocyanate and bromine.

Potassium thiocyanate is used in a proportion of about 1 mol to about 100 mol, preferably about 1 mol to about 30 mol, per 1 mol of compound (XLIII).

Bromine is used in a proportion of about 1 mol to about 30 mol, preferably about 1 mol to about 10 mol, per 1 mol of

compound (XLIII).

This reaction is advantageously carried out using a solvent inert to the reaction. Examples of the solvent include acetic acid and the like.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

(step 6-4):

Compound (Ie-1) can be produced by reacting compound (XLIV) with cyclopropanecarboxylic acid in the presence of a condensation agent, or by reacting compound (XLIV) with compound (LI).

When compound (XLIV) is reacted with cyclopropanecarboxylic acid in the presence of a condensation agent, cyclopropanecarboxylic acid is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 3 mol, per 1 mol of compound (XLIV).

Examples of the condensation agent include 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and the like. The condensation agent is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 5 mol, per 1 mol of compound (XLIV).

Where necessary, a suitable condensation promoter (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide and the like) can be used in this reaction. Such condensation promoter is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XLIV).

This reaction may proceed more smoothly by the addition

of a base (e.g., triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like). The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XLIV).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 6-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

when compound (XLIV) is reacted with compound (LI), compound (LI) is used in a proportion of about 1 to about 10 mol, preferably about 1 to about 3 mol, per 1 mol of compound (XLIV).

Generally, this reaction is preferably performed in the presence of a base. However, the presence of a base is not always essential. Examples of the base include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline and the like. The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XLIV).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 6-1 are used.

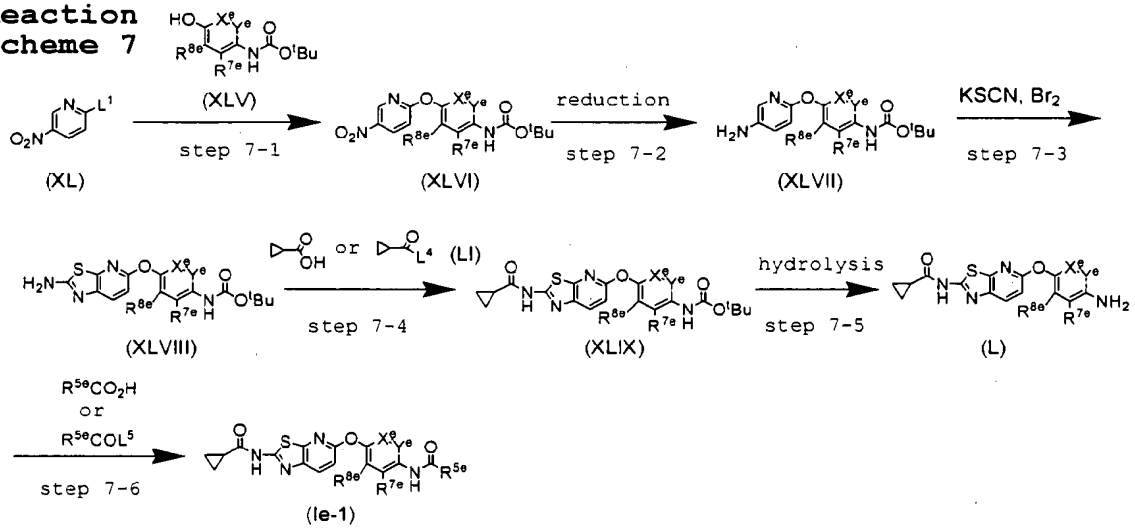
The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

[Production method 7]

Compound (Ie-1) can also be produced, for example, by the method shown in Reaction scheme 7.

**Reaction Scheme 7**




wherein the symbols are as defined above.

(steps 7-1 to 7-4):

compound (XLVI), compound (XLVII), compound (XLVIII) and compound (XLIX) can be synthesized from compound (XL) and compound (XLV) in the same manner as in steps 6-1 to 6-4, respectively.

(step 7-5):

Compound (L) can be produced by removing the amino-protecting group from compound (XLIX).

The amino-protecting group can be removed according to a method known *per se*, for example, the methods described in "Protective Groups in Organic Synthesis, 3rd Ed." (Theodora W. Greene) and the like, or a method analogous thereto.

(step 7-6):

Compound (Ie-1) can be produced by reacting compound (L) with carboxylic acid ($R^{5e}CO_2H$) in the presence of a condensation agent in the same manner as in step 6-4, or by reacting compound (L) with a reactive derivative ($R^{5e}COL^5$) of carboxylic acid.

$R^{5e}CO_2H$ may be commercially available, or can be produced

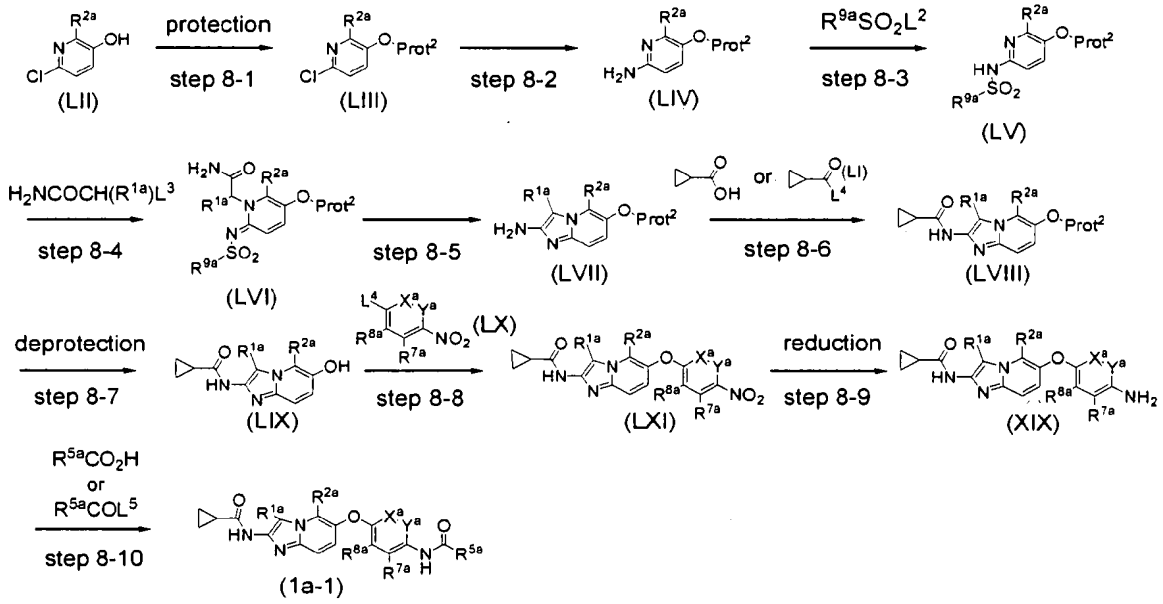
according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

$R^{5e}COL^5$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

[Production method 8]

Compound (Ia-1) can also be produced, for example, by the method shown in Reaction scheme 8.

**Reaction Scheme 8**




wherein $Prot^2$ is a phenolic hydroxyl-protecting group; and other symbols are as defined above.

As the phenolic hydroxyl-protecting group for $Prot^2$, benzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl and the like are used.

(step 8-1):

Compound (LIII) can be produced by protecting the phenolic hydroxyl group of compound (LII).

The phenolic hydroxyl group can be protected according to a method known *per se*, for example, the methods described in "Protective Groups in Organic Synthesis, 3rd Ed." (Theodora W. Greene) and the like, or a method analogous thereto.

(step 8-2):

Compound (LIV) can be produced using compound (LIII) according to the method described in "ORGANIC LETTERS, 2001, Vol. 3, No. 21, 3417-3419" (Xiaohua Huang), or a method analogous thereto a method.

(steps 8-3 to 8-4):

Compound (LV) and compound (LVI) can be produced from compound (LIV) by steps 8-3 and 8-4 in the same manner as in steps 2-4 and 2-5, respectively.

(step 8-5):

Compound (LVII) can be produced by reacting compound (LVI) with trifluoroacetic acid anhydride and then subjecting the obtained compound to alkalihydrolysis in the presence of a base.

Trifluoroacetic acid anhydride is used in a proportion of about 1 mol to about 30 mol, preferably about 1 mol to about 10 mol, per 1 mol of compound (LVI).

This reaction is advantageously performed by further using a solvent inert to the reaction. The solvent is not particularly limited as long as the reaction proceeds and, for example, alcohols such as methanol, ethanol, 2-propanol, 2-methyl-2-propanol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like; esters such as ethyl acetate and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and the like; nitriles such as acetonitrile and the

like; sulfoxides such as dimethyl sulfoxide and the like; and the like can be used alone or in a mixture.

While the reaction time varies depending on the reagent and solvent to be used, it is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

Examples of the base to be used for the subsequent alkalihydrolysis include aqueous sodium hydroxide solution, aqueous potassium hydroxide solution, aqueous barium hydroxide solution, aqueous calcium hydroxide solution, aqueous potassium carbonate solution, aqueous sodium carbonate solution, aqueous cesium carbonate solution and the like.

While the reaction time varies depending on the reagent and solvent to be used, it is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

(step 8-6):

Compound (LVIII) can be produced from compound (LVII) in the same manner as in step 2-8.

(step 8-7):

Compound (LIX) can be produced by removing the phenolic hydroxyl-protecting group of compound (LVIII).

The phenolic hydroxyl-protecting group can be removed according to a method known *per se*, for example, the methods described in "Protective Groups in Organic Synthesis, 3rd Ed." (Theodora W. Greene) and the like, or a method analogous thereto.

(step 8-8):

Compound (LXI) can be produced by reacting compound (LIX) with compound (LX) in the presence of a base.

Compound (LX) is used in a proportion of about 0.1 mol to about 30 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (LIX).

As the base, inorganic base or organic base and the like are used. Specifically, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium hydride, sodium amide, lithium diisopropylamide and the like can be mentioned. The base is used in a proportion of about 1 mol to about 30 mol, preferably about 1 mol to about 10 mol, per 1 mol of compound (LIX).

This reaction is advantageously carried out using a solvent inert to the reaction. The solvent is not particularly limited as long as the reaction proceeds and, for example, ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like; esters such as ethyl acetate and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, chlorobenzene, trifluoromethylbenzene and the like; nitriles such as acetonitrile and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like can be used alone or in a mixture.

While the reaction time varies depending on the reagent and solvent to be used, it is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

(step 8-9):

Compound (XIX) can be produced by reducing nitro of compound (LXI). Nitro can be reduced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock), the fourth series of experimental chemistry, vol. 20, 279-280 and the like, or a method analogous thereto.

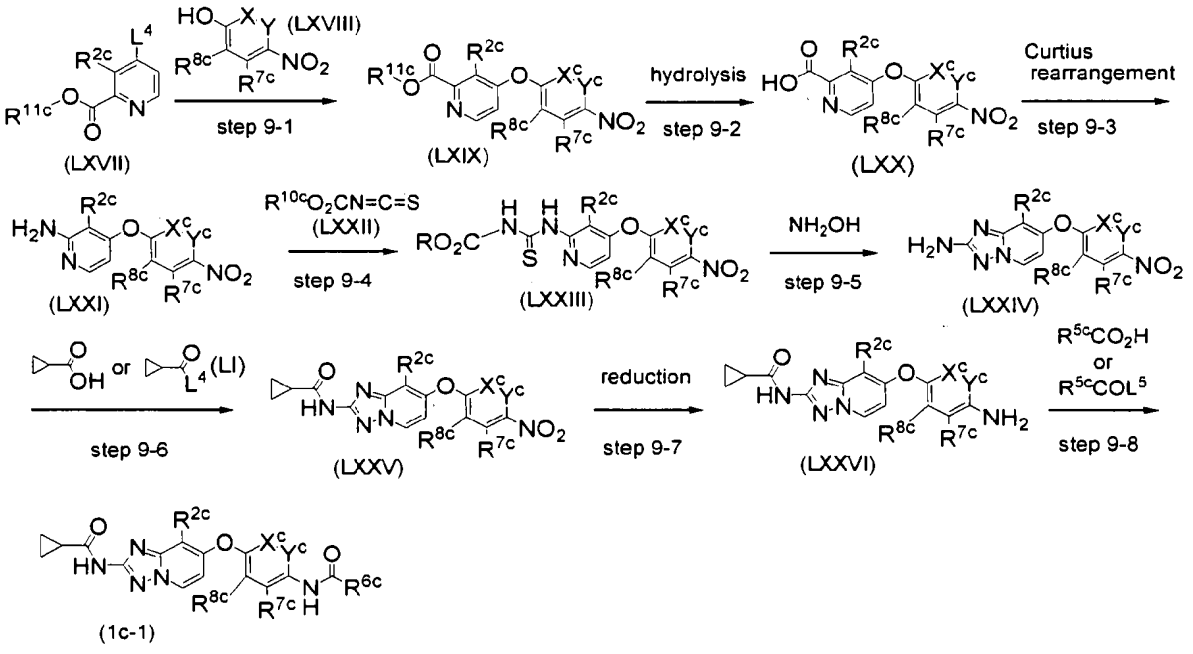
(step 8-10):

Compound (Ia-1) can be synthesized from compound (XIX) in the same manner as in step 2-10.

[Production method 9]

In compound (Ic), compound (Ic-1) wherein $W^c$ is an oxygen atom can be produced, for example, by the method shown in Reaction scheme 9. The compound (Ic-1) is encompassed in compound (Ic).

**Reaction Scheme 9**




wherein $R^{10c}$ is $C_{1-6}$ alkyl optionally having 1 to 3 substituents selected from (a) a halogen atom and (b) nitro; and other symbols are as defined above.

(step 9-1):

Compound (LXIX) can be produced by reacting compound (LXVII) with compound (LXVIII).

Compound (LXVIII) is used in a proportion of about 0.1 mol to about 30 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (LXVII).

This reaction is advantageously carried out using a solvent inert to the reaction. The solvent is not particularly limited as long as the reaction proceeds and, for example, ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like; esters such as ethyl acetate and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, chlorobenzene, trifluoromethylbenzene and the like; nitriles such as acetonitrile and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like can be used alone or in a mixture.

Where necessary, a base may be used in this reaction. Examples of the base include triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline, potassium tert-butoxide, sodium hydride and the like. The base is used in a proportion of about 1 mol to about 30 mol, preferably about 1 mol to about 20 mol, per 1 mol of compound (LXVII).

While the reaction time varies depending on the reagent and solvent to be used, it is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

(step 9-2):

Compound (LXX) can be produced by alkalihydrolysis of

compound (LXIX).

This reaction is performed in a water-containing solvent in the presence of a base. Examples of the base include sodium hydroxide, potassium hydroxide, lithium hydroxide, barium hydroxide, calcium hydroxide, potassium carbonate, sodium carbonate, cesium carbonate, sodium methoxide and the like. The base is used in a proportion of about 1 mol to about 50 mol, preferably about 1 mol to about 10 mol, per 1 mol of compound (LXIX). Examples of the water-containing solvent include a mixed solvent of one or more kinds of solvents selected from methanol, ethanol, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like, and water, and the like.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about 0°C to about 150°C.

(step 9-3):

Compound (LXXI) can be produced by converting carboxyl of compound (LXX) to amino by a method such as Curtius rearrangement and the like.

Carboxyl can be converted to amino according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

(step 9-4):

Compound (LXXIII) can be produced by reacting compound (LXXI) with compound (LXXII).

Compound (LXXII) is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (LXXI).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to

the solvents exemplified in step 9-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

(step 9-5):

Compound (LXXIV) can be produced by reacting compound (LXXIII) with hydroxylamine in the presence of a base.

Hydroxylamine is used in a proportion of about 0.1 mol to about 100 mol, preferably about 0.3 mol to about 30 mol, per 1 mol of compound (LXXIII).

Examples of the base include triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline and the like. The base is used in a proportion of about 0.1 mol to about 100 mol, preferably about 0.3 mol to about 30 mol, per 1 mol of compound (LXXIII).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 9-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

(step 9-6):

Compound (LXXV) can be produced by reacting compound (LXXIV) with cyclopropanecarboxylic acid in the presence of a condensation agent, or reacting compound (LXXIV) with compound (LI) in the same manner as in step 2-8.

(step 9-7):

Compound (LXXVI) can be produced by reducing nitro of compound (LXXV).

Nitro can be reduced according to a method known *per se*,

for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock), the fourth series of experimental chemistry, vol. 20, 279-280 and the like, or a method analogous thereto.

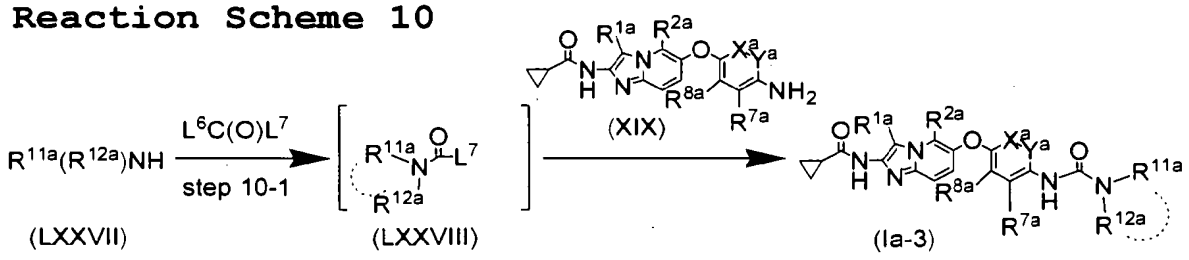
(step 9-8):

Compound (1c-1) can be produced by reacting compound (LXXVI) with $R^{5c}CO_2H$ in the presence of a condensation agent, or reacting compound (LXXVI) with $R^{5c}COL^5$ in the same manner as in step 2-10.

[Production method 10]

In compound (Ia), compound (Ia-3) wherein $W^a$ is an oxygen atom; and $R^{5a}$ is (1) $C_{1-6}$ alkyl-carbonylamino optionally having one $C_{6-10}$ aryl, or (2) a nitrogen-containing heterocyclic group (having a bond on nitrogen atom) optionally having 1 to 4 substituents selected from (a) $C_{6-10}$ aryl optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl, (b) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and (c) oxo can also be produced, for example, by the method shown in Reaction scheme 10. The compound (Ia-3) is encompassed in compound (Ia).

**Reaction Scheme 10**




wherein $R^{11a}$ is a hydrogen atom, $R^{12a}$ is $C_{1-6}$ alkyl-carbonyl optionally having one $C_{6-10}$ aryl, or $R^{11a}$ and $R^{12a}$ may form, together with the adjacent nitrogen atom, a nitrogen-containing heterocyclic group (having a bond on nitrogen atom) optionally having 1 to 4 substituents selected from (a) $C_{6-10}$ aryl optionally having 1 to 3 substituents selected from a

halogen atom and $C_{1-6}$ alkyl, (b) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and (c)oxo; $L^6$ and $L^7$ are each a leaving group; and other symbols are as defined above.

The leaving groups for $L^6$ and $L^7$ are the same or different and each is, for example, (1) a halogen atom, (2) alkoxy optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl, (3) aryloxy optionally having 1 to 3 substituents selected from a halogen atom, $C_{1-6}$ alkyl and nitro, and the like.

(step 10-1):

Compound (1a-3) can be produced by first reacting compound (LXXVII) with a compound represented by the formula $L^6C(O)L^7$ to give compound (LXXVIII), and then reacting compound (LXXVIII) with compound (XIX).

$L^6C(O)L^7$ is used in a proportion of 0.1 to 10 mol, preferably 0.3 to 3 mol, per 1 mol of compound (LXXVII).

The reaction may be performed in the presence of a base. As the base, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline and the like can be mentioned. The base is used in a proportion of about 0.1 mol to about 30 mol, preferably about 0.3 mol to about 10 mol, per 1 mol of compound (LXXVII).

This reaction is advantageously carried out using a solvent inert to the reaction. The solvent is not particularly limited as long as the reaction proceeds and, for example, ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like; esters such as ethyl acetate and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, chlorobenzene, trifluoromethylbenzene and the like; nitriles such as

acetonitrile and the like; sulfoxides such as dimethyl sulfoxide and the like; pyridine; and the like can be used alone or in a mixture.

While the reaction time varies depending on the reagent and solvent to be used, it is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

A compound represented by the formula $L^6C(O)L^7$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

The obtained $R^{11a}(R^{12a})NC(O)L^7$ [compound (LXXVIII)] can be used for the next reaction in the form of a reaction mixture or a crude product. It may be isolated and purified from the reaction mixture according to a conventional method and used for the next reaction.

Compound (XIX) is used in a proportion of 0.1 to 10 mol, preferably 0.3 to 3 mol, per 1 mol of compound (LXXVIII).

This reaction may be performed in the presence of a base. As the base, those similar to the bases exemplified above can be used. The base is used in a proportion of 0.1 to 10 mol, preferably 0.3 to 3 mol, per 1 mol of compound (LXXVIII).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified above are used.

The reaction time is generally about 1 min to about 200 hr, preferably about 10 min to about 100 hr.

The reaction temperature is generally about -100°C to about 250°C, preferably about -78°C to about 200°C.

In the aforementioned reactions, compounds (II), (III),

(X), (XI), (XX), (XXI), (XXII), (XXVII), (XXXII), (XXXV), (XXXVII), (XL), (XLI), (XLV), (LI), (LII), (LX), (LXVII), (LXVIII), (LXXII) and (LXXVII) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

In each of the above-mentioned reactions, when a starting material compound has amino, carboxyl or hydroxyl as a substituent, these groups may be protected by a protecting group generally used for peptide chemistry and the like. In this case, the object compound can be obtained by removing the protecting group after reaction, as necessary. The introduction and removal of these protecting groups can be performed according to a method known *per se*, for example, the methods described in Wiley-Interscience, 1999, "Protective Groups in Organic Synthesis, 3rd Ed." (Theodora W. Greene, Peter G. M. Wuts) and the like.

Examples of the amino-protecting group include formyl group, $C_{1-6}$ alkyl-carbonyl group, $C_{1-6}$ alkoxy-carbonyl group, benzoyl group, $C_{7-10}$ aralkyl-carbonyl group (e.g., benzylcarbonyl), $C_{7-14}$ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl), trityl group, phthaloyl group, N,N-dimethylaminomethylene group, substituted silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl), $C_{2-6}$ alkenyl group (e.g., 1-allyl) and the like. These groups are optionally substituted by 1 to 3 substituents selected from a halogen atom, a $C_{1-6}$ alkoxy group and a nitro group.

Examples of the carboxyl-protecting group include $C_{1-6}$ alkyl group, $C_{7-11}$ aralkyl group (e.g., benzyl), phenyl group, trityl group, substituted silyl group (e.g., trimethylsilyl,

triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl), $C_{2-6}$ alkenyl group (e.g., 1-allyl) and the like.

Examples of the hydroxyl-protecting group include $C_{1-6}$ alkyl group, phenyl group, trityl group, $C_{7-10}$ aralkyl group (e.g., benzyl), formyl group, $C_{1-6}$ alkyl-carbonyl group, benzoyl group, $C_{7-10}$ aralkyl-carbonyl group (e.g., benzylcarbonyl), 2-tetrahydropyranyl group, 2-tetrahydrofuranyl group, substituted silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl), $C_{2-6}$ alkenyl group (e.g., 1-allyl) and the like. These groups are optionally substituted by 1 to 3 substituents selected from a halogen atom, a $C_{1-6}$ alkyl group, a $C_{1-6}$ alkoxy group and a nitro group.

When desired, the above-mentioned reaction may be combined with any one or two or more of known hydrolysis, deprotection, acylation reaction, alkylation reaction, oxidation reaction, cyclization reaction, carbon chain extension reaction, and substituent change reaction, whereby compound (I) can also be produced.

Compound (I) can be isolated and purified by a means known *per se*, such as phase transfer, concentration, solvent extraction, fractionation, liquid conversion, crystallization, recrystallization, chromatography and the like. When compound (I) is obtained as free compounds, they can be converted to desired salts by a method known *per se* or a modification thereof; conversely, when the compounds are obtained as salts, they can be converted to free forms or other desired salts by a method known *per se* or a modification thereof.

Compound (I) may be used as a prodrug. A prodrug of compound (I) and the like means a compound which is converted to compound (I) and the like by a reaction due to an enzyme, a gastric acid, etc. under the physiological condition in the living body, that is, a compound which is converted to

compound (I) and the like by oxidation, reduction, hydrolysis, etc. due to an enzyme; a compound which is converted to compound (I) and the like by hydrolysis etc. due to gastric acid, and the like.

A prodrug of compound (I) may be a compound obtained by subjecting an amino in compound (I) to an acylation, alkylation or phosphorylation (e.g., a compound obtained by subjecting an amino in compound (I) to an eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, pyrrolidylmethylation, pivaloyloxymethylation or tert-butylation, etc.); a compound obtained by subjecting a hydroxy in compound (I) to an acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting an hydroxy in compound (I) to an acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation or dimethylaminomethylcarbonylation, etc.); a compound obtained by subjecting a carboxy in compound (I) to an esterification or amidation (e.g., a compound obtained by subjecting a carboxy in compound (I) to an ethyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification, pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonylethyl esterification or methylamidation, etc.); and the like. Any one of these compounds can be produced from compound (I) by a method known *per se*.

A prodrug of compound (I) may also be one which is converted into compound (I) under a physiological condition, such as those described in *IYAKUHIN no KAIHATSU* (Development of Pharmaceuticals), Vol. 7, Design of Molecules, p.163-198, Published by HIROKAWA SHOTEN (1990).

When compound (I) has isomers such as optical isomer,

stereoisomer, positional isomer, rotational isomer and the like, any isomers and mixtures are encompassed in compound (I). For example, when compound (I) has an optical isomer, an optical isomer separated from a racemate is also encompassed in compound (I). These isomers can be obtained as independent products by a synthesis means or a separation means (concentration, solvent extraction, column chromatography, recrystallization and the like) known *per se*.

The compound (I) may be a crystal, and both a single crystal and crystal mixtures are encompassed in compound (I). Crystals can be produced by crystallization according to crystallization methods known *per se*.

Compound (I) encompasses hydrate, non-hydrate, solvate and non-solvate within the scope thereof.

A compound labeled with an isotope (e.g., $^{3}H$, $^{14}C$, $^{35}S$, $^{125}I$ etc.) and the like is also encompassed in compound (I).

Furthermore, compound (I) may be a deuterated compound wherein $^{1}H$ is converted to $^{2}H(D)$.

Compound (I) of the present invention and a prodrug thereof (hereinafter sometimes to be abbreviated as the compound of the present invention) have, for example, phosphorylation-inhibitory activity against a kinase having such phosphorylating action. As used herein, kinase encompasses not only a substance having a phosphorylating action by itself as a whole, but also a substance a part of which has a phosphorylating action. The phosphorylating action possessed by kinases encompasses both a phosphorylating action on its own and that on other substances.

Examples of kinase include vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), Raf, hepatocyte growth factor receptor (c-Met), angiopoietin receptor, FLT3 and the like.

Examples of vascular endothelial growth factor receptor (VEGFR) include vascular endothelial growth factor receptor 1 (VEGFR1, Flt-1), vascular endothelial growth factor receptor 2

(VEGFR2, KDR, Flk-1), vascular endothelial growth factor receptor 3 (VEGFR3, Flt-4) and the like. Of these, vascular endothelial growth factor receptor 2 (VEGFR2) is preferable.

Examples of platelet-derived growth factor receptor (PDGFR) include platelet-derived growth factor receptor α (PDGFRα), platelet-derived growth factor receptor β (PDGFRβ) and the like.

Examples of Raf include A-Raf, B-Raf, C-Raf and the like.

Examples of angiopoietin receptor include Tyrosine Kinase with Immunoglobulin and Epidermal Growth homology domain 1 (TIE1), TIE2 and the like.

Particularly, as kinase, vascular endothelial growth factor receptor 2 (VEGFR2), platelet-derived growth factor receptor (PDGFR), Raf, hepatocyte growth factor receptor (c-Met), TIE2 and FLT3 are preferable.

Besides these, as kinase, fibroblast growth factor receptor 1 (FGFR1), fibroblast growth factor receptor 2 (FGFR2), fibroblast growth factor receptor 3 (FGFR3), fibroblast growth factor receptor 4 (FGFR4), stem cell factor receptor (c-Kit), Aurora A, Aurora B, Axl, CDK, MEK1, MEK2, Akt, ERK, MAPK, Src, epithelial cell growth factor receptor (EGFR), human epithelial growth factor receptor 2 (HER2), human epithelial growth factor receptor 4 (HER4), Abl, Fgr, Fms, Ron, Ret, Eph, TrkA and the like can also be used.

For example, the vascular endothelial growth factor receptor 2 (VEGFR2) inhibitory activity of the compound of the present invention can be determined according to Test Example 1, the vascular endothelial cell proliferation inhibitory activity can be determined according to Test Example 2, the hepatocyte growth factor receptor (c-Met) inhibitory activity can be determined according to Test Example 3, the human gastric cancer cell line MKN-45 growth inhibitory activity can be determined according to Test Example 4, the human gastric cancer cell line MKN-45 antitumor activity and human blood

cell cancer cell line MV-4-11 antitumor activity can be determined according to Test Example 5, the FLT3 inhibitory activity can be determined according to Test Example 6, the TIE2 inhibitory activity can be determined according to Test Example 7, and the human blood cell cancer cell line MV-4-11 growth inhibitory activity can be determined according to Test Example 8.

The compound of the present invention particularly shows potent inhibitory activity for vascular endothelial growth factor receptor (VEGFR), and specifically high selectivity for vascular endothelial growth factor receptor 2 (VEGFR2, KDR, Flk-1) and potent kinase inhibitory activity for VEGFR1 and PDGFR. In addition, the compound of the present invention shows potent inhibitory action on hepatocyte growth factor receptor (c-Met). The compound of the present invention also shows potent inhibitory action on TIE2. Moreover, the compound of the present invention shows potent inhibitory action on FLT3. Furthermore, since the compound of the present invention is also superior in the efficacy, pharmacokinetics (absorption, distribution, metabolism, excretion etc.), solubility (water-solubility etc.), interaction with other pharmaceutical products, safety (acute toxicity, chronic toxicity, genetic toxicity, reproductive toxicity, cardiotoxicity, carcinogenicity etc.) and stability (chemical stability, stability to enzyme etc.), it is useful as a pharmaceutical agent.

The compound of the present invention is useful as a kinase inhibitor, preferably a vascular endothelial growth factor receptor (VEGFR) inhibitor [preferably a vascular endothelial growth factor receptor 2 (VEGFR2, KDR, Flk-1) inhibitor], a platelet-derived growth factor receptor (PDGFR) inhibitor, hepatocyte growth factor receptor (c-Met) inhibitor, TIE2 inhibitor, FLT3 inhibitor for a mammal (e.g., mouse, rat, hamster, rabbit, cat, dog, bovine, sheep, monkey, human etc.).

Therefore, the compound of the present invention is useful

as an angiogenesis inhibitor, a vascular endothelial cell proliferation inhibitor, cancer cell proliferation inhibitor and the like.

The compound of the present invention is used as a pharmaceutical agent such as an agent for the prophylaxis or treatment of diseases possibly affected by a vascular endothelial growth factor, platelet-derived growth factor, hepatocyte growth factor, angiopoietin, for example, cancer [e.g., colorectal cancer (e.g., familial colorectal cancer, hereditary nonpolyposis colorectal cancer, gastrointestinal stromal tumor etc.), lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, malignant mesothelioma, etc.), mesothelioma, pancreatic cancer (e.g., pancreatic duct cancer, etc.), gastric cancer (e.g., scirrhous gastric cancer, papillary glandular cancer, mucinous glandular cancer, adenosquamous cancer, etc.), breast cancer (e.g., invasive ductal carcinoma, ductal cancer in situ, inflammatory breast cancer, etc.), ovary cancer (e.g., ovarian epithelial cancer, extragonadal germ cell tumor, ovarian germ cell tumor, ovarian low malignant potential tumor etc.), prostate cancer (e.g., hormone-dependent prostate cancer, non-hormone dependent prostate cancer, etc.), liver cancer (e.g., primary liver cancer, extrahepatic bile duct cancer, etc.), thyroid cancer (e.g., medullary thyroid cancer, etc.), head and neck cancer (laryngeal cancer), kidney cancer (e.g., renal cell carcinoma, renal pelvis and ureter transitional cell cancer, etc.), esophagus cancer, testis cancer, uterus cancer, pancreatic endocrine tumor, brain tumor (e.g., pineal astrocytoma, pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, etc.), melanoma, sarcoma, urinary bladder cancer, blood cancer including multiple myeloma (e.g., acute myelocytic leukemia, myelodysplastic syndrome) etc.], diabetic retinopathy, rheumatoid arthritis, psoriasis, atherosclerosis, Kaposi's sarcoma, COPD, pain, asthma, endometriosis, nephritis,

osteoarthritis, inflammation such as age-related macular degeneration and the like and hypertension; the above-mentioned cancer growth inhibitor; the above-mentioned cancer metastasis suppressor; an apoptosis promoter; and the like.

Of these, it is effective as an agent for the prophylaxis or treatment of colorectal cancer, lung cancer, pancreatic cancer, gastric cancer, breast cancer, ovary cancer, prostate cancer, liver cancer, thyroid cancer, kidney cancer, brain tumor melanoma, urinary bladder cancer and blood cancer. Particularly, the compound of the present invention is effective as an agent for the prophylaxis or treatment of lung cancer, gastric cancer, colorectal cancer, ovary cancer, prostate cancer, kidney cancer or blood cancer.

In addition, based on the strong hepatocyte growth factor receptor (c-Met) inhibitory action, the compound of the present invention is useful as an agent for suppressing invasion and/or metastasis of cancer (e.g., colorectal cancer, gastric cancer, lung cancer, kidney cancer, breast cancer, ovary cancer, prostate cancer, brain tumor). Based on the strong Fms Like Tyrosine Kinase 3 (FLT3) inhibitory action, moreover, the compound of the present invention is effective as an agent for the prophylaxis or treatment of leukemia (e.g., acute myelocytic leukemia, acute lymphatic leukemia).

The compound of the present invention can be administered orally or parenterally as it is or in a mixture with a pharmacologically acceptable carrier.

The dosage form of the compound of the present invention for oral administration is, for example, tablet (including sugar-coated tablet, film-coated tablet), pill, granule, powder, capsule (including soft capsule, microcapsule), syrup, emulsion, suspension and the like, and the dosage form for parenteral administration is, for example, injection, injecting agent, instillation, suppository and the like. In addition, it is effective to make a sustained release preparation by combining

the compound with a suitable base (e.g., polymer of butyric acid, polymer of glycolic acid, copolymer of butyric acid-glycolic acid, a mixture of a polymer of butyric acid and a polymer of glycolic acid, polyglycerol fatty acid ester etc.).

As a method to produce the compound of the present invention in the above-mentioned dosage form, a known production method generally used in the pertinent field can be employed. When the above-mentioned dosage form is produced, suitable amounts of additives such as excipient, binder, disintegrant, lubricant, sweetening agent, surfactant, suspending agent, emulsifier and the like, generally used in the pertinent field, are appropriately added as necessary for production.

When the compound of the present invention is prepared into a tablet, for example, it can be produced by adding an excipient, a binder, a disintegrant, a lubricant and the like, and when a pill or a granule is to be prepared, it can be produced by adding an excipient, a binder, a disintegrant and the like. When a powder or a capsule is to be prepared, it can be produced by adding an excipient and the like, when a syrup is to be prepared, it can be produced by adding a sweetener and the like, and when an emulsion or a suspension is to be prepared, it can be produced by adding a suspending agent, a surfactant, an emulsifier and the like.

Examples of the excipient include lactose, sucrose, glucose, starch, sucrose, crystalline cellulose, powdered glycyrrhiza, mannitol, sodium hydrogen carbonate, calcium phosphate, calcium sulfate and the like.

Examples of the binder include 5 - 10 wt% starch liquid paste, 10 - 20 wt% gum arabic solution or gelatin solution, 1 - 5 wt% tragacanth solution, carboxymethyl cellulose solution, sodium alginate solution, glycerin and the like.

Examples of the disintegrant include starch, calcium carbonate and the like.

Examples of the lubricant include magnesium stearate,

stearic acid, calcium stearate, purified talc and the like.

Examples of the sweetener include glucose, fructose, invert sugar, sorbitol, xylitol, glycerin, simple syrup and the like.

Examples of the surfactant include sodium lauryl sulfate, polysorbate 80, sorbitan monofatty acid ester, polyoxyl 40 stearate and the like.

Examples of the suspending agent include gum arabic, sodium alginate, sodium carboxymethyl cellulose, methyl cellulose, bentonite and the like.

Examples of the emulsifier include gum arabic, tragacanth, gelatin, polysorbate 80 and the like.

Furthermore, when the compound of the present invention is produced in the above-mentioned dosage form, a suitable amount of a colorant, a preservative, an aromatic, a corrigent, a stabilizer, a thickening agent and the like typically used in the field of preparation can be added on demand.

As the injection, intravenous injection as well as subcutaneous injection, intracutaneous injection, intramuscular injection, instillation and the like are mentioned, and as the sustained release preparation, an iontophoresis transdermal agent and the like are mentioned.

Such injections are prepared by methods known *per se*, or by dissolving, suspending or emulsifying the compound of the present invention in a sterilized aqueous or oily liquid. As an aqueous liquid for injection, physiological saline, isotonic solutions containing glucose or other auxiliary drugs (e.g., D-sorbitol, D-mannitol, sodium chloride and the like) and the like can be mentioned, and they can be used in combination with suitable solubilizing agents, such as alcohols (e.g., ethanol), polyalcohols (e.g., propylene glycol, polyethylene glycol), nonionic surfactants (e.g., polysorbate 80, HCO-50) and the like. As an oily liquid, sesame oil, soybean oil and the like can be mentioned, which may be used in combination with solubilizing

agents such as benzyl benzoate, benzyl alcohol and the like. In addition, buffers (e.g., phosphate buffer, sodium acetate buffer), soothing agents (e.g., benzalkonium chloride, procaine hydrochloride and the like), stabilizers (e.g., human serum albumin, polyethylene glycol and the like), preservatives (e.g., benzyl alcohol, phenol and the like) and the like can be mentioned. A prepared injection is generally filled in an ampoule.

While the content of the compound of the present invention in the pharmaceutical agent of the present invention varies depending on the form of the pharmaceutical preparation, it is generally about 0.01 to 100 wt%, preferably about 2 to 85 wt%, more preferably about 5 to 70 wt%, relative to the entire preparation.

While the content of the additive in the pharmaceutical agent of the present invention varies depending on the form of the pharmaceutical preparation, it is generally about 1 to 99.9 wt%, preferably about 10 to 90 wt%, relative to the entire preparation.

The compound of the present invention is stable and low toxic, and can be used safely. While the daily dose varies depending on the condition and body weight of patients, the kind of compound, administration route and the like, in the case of, for example, oral administration to patients for the treatment of cancer, the daily dose to an adult (body weight about 60 kg) is about 0.1 to 1000 mg, preferably about 0.3 to 300 mg, more preferably about 1 to 200 mg, as an active ingredient (the compound of the present invention), which can be given in a single administration or administered in 2 or 3 portions a day.

When the compound of the present invention is administered parenterally, it is generally administered in the form of a liquid (e.g., injection). While the dose varies depending on the subject of administration, target organ, symptom, administration method and the like, it is, for example, about

0.01 mg to about 100 mg, preferably about 0.01 to about 50 mg, more preferably about 0.01 to about 20 mg, in the form of an injection, relative to 1 kg body weight, which is preferably given by intravenous injection.

The compound of the present invention can be used concurrently with other drugs. To be specific, the compound of the present invention can be used together with medicaments such as hormonal therapeutic agents, chemotherapeutic agents, immunotherapeutic agents, pharmaceutical agents inhibiting the action of cell growth factors or cell growth factor receptors and the like. In the following, the drugs that can be used in combination with the compound of the present invention are abbreviated as concomitant drugs.

Examples of the "hormonal therapeutic agents" include fosfestrol, diethylstylbestrol, chlorotrianisene, medroxyprogesterone acetate, megestrol acetate, chlormadinone acetate, cyproterone acetate, danazol, allylestrenol, gestrinone, mepartricin, raloxifene, ormeloxifene, levormeloxifene, anti-estrogens (e.g., tamoxifen citrate, toremifene citrate, and the like), pill preparations, mepitiostane, testrolactone, aminoglutethimide, LH-RH agonists (e.g., goserelin acetate, buserelin, leuprorelin, and the like), droloxifene, epitiostanol, ethinylestradiol sulfonate, aromatase inhibitors (e.g., fadrozole hydrochloride, anastrozole, retrozole, exemestane, vorozole, formestane, and the like), anti-androgens (e.g., flutamide, bicartamide, nilutamide, and the like), 5$\alpha$-reductase inhibitors (e.g., finasteride, epristeride, and the like), aderenal cortex hormone drugs (e.g., dexamethasone, prednisolone, betamethasone, triamcinolone, and the like), androgen synthesis inhibitors (e.g., abiraterone, and the like), retinoid and drugs that retard retinoid metabolism (e.g., liarozole, and the like), thyroid gland hormone, and DDS (Drug Delivery System) preparations therefor and the like.

Examples of the "chemotherapeutic agents" include alkylating agents, antimetabolites, anticancer antibiotics, plant-derived anticancer agents, and the like.

Examples of the "alkylating agents" include nitrogen mustard, nitrogen mustard-N-oxide hydrochloride, chlorambutyl, cyclophosphamide, ifosfamide, thiotepa, carboquone, improsulfan tosylate, busulfan, nimustine hydrochloride, mitobronitol, melphalan, dacarbazine, ranimustine, sodium estramustine phosphate, triethylenemelamine, carmustine, lomustine, streptozocin, pipobroman, etoglucid, carboplatin, cisplatin, miboplatin, nedaplatin, oxaliplatin, altretamine, ambamustine, dibrospidium hydrochloride, fotemustine, prednimustine, pumitepa, ribomustin, temozolomide, treosulphan, trophosphamide, zinostatin stimalamer, adozelesin, cystemustine, bizelesin, DDS (Drug Delivery System) preparations thereof, and the like.

Examples of the "antimetabolites" include mercaptopurine, 6-mercaptopurine riboside, thioinosine, methotrexate, pemetrexed, enocitabine, cytarabine, cytarabine ocfosfate, ancitabine hydrochloride, 5-FU drugs (e.g., fluorouracil, tegafur, UFT, doxifluridine, carmofur, gallocitabine, emmitefur, capecitabine, and the like), aminopterine, nelzarabine, leucovorin calcium, tabloid, butocine, folinate calcium, levofolinate calcium, cladribine, emitefur, fludarabine, gemcitabine, hydroxycarbamide, pentostatin, piritrexim, idoxuridine, mitoguazone, thiazophrine, ambamustine, bendamustine, DDS preparations thereof, and the like.

Examples of the "anticancer antibiotics" include actinomycin-D, actinomycin-C, mitomycin-C, chromomycin-A3, bleomycin hydrochloride, bleomycin sulfate, peplomycin sulfate, daunorubicin hydrochloride, doxorubicin hydrochloride, aclarubicin hydrochloride, pirarubicin hydrochloride, epirubicin hydrochloride, neocarzinostatin, mithramycin,

sarcomycin, carzinophilin, mitotane, zorubicin hydrochloride, mitoxantrone hydrochloride, idarubicin hydrochloride, DDS preparations thereof, and the like.

Examples of the "plant-derived anticancer agents" include etoposide, etoposide phosphate, vinblastine sulfate, vincristine sulfate, vindesine sulfate, teniposide, paclitaxel, docetaxel, vinorelbine, DDS preparations thereof, and the like.

Examples of the "immunotherapeutic agents (BRM)" include picibanil, krestin, sizofiran, lentinan, ubenimex, interferons, interleukins, macrophage colony-stimulating factor, granulocyte colony-stimulating factor, erythropoietin, lymphotoxin, BCG vaccine, corynebacterium parvum, levamisole, polysaccharide K, procodazole, anti-CTLA4 antibody, and the like.

Example of the "cell growth factor" in the "pharmaceutical agents inhibiting the action of cell growth factors or cell growth factor receptors" include any substances that promote cell proliferation, which are normally peptides having not more than 20,000 molecular weight that are capable of exhibiting their activity at low concentrations by binding to a receptor including (1) EGF (epidermal growth factor) or substances possessing substantially the same activity as EGF [e.g., TGF$\alpha$, and the like], (2) insulin or substances possessing substantially the same activity as insulin [e.g., insulin, IGF (insulin-like growth factor)-1, IGF-2, and the like], (3) FGF (fibroblast growth factor) or substances possessing substantially the same activity as FGF [e.g., acidic FGF, basic FGF, KGF (keratinocyte growth factor), FGF-10, and the like], (4) other cell growth factors [e.g., CSF (colony stimulating factor), EPO (erythropoietin), IL-2 (interleukin-2), NGF (nerve growth factor), PDGF (platelet-derived growth factor), TGF$\beta$ (transforming growth factor $\beta$), HGF (hepatocyte growth factor), VEGF (vascular endothelial growth factor), heregulin, angiopoietin, and the like].

Examples of the "cell growth factor receptors" include any receptors capable of binding to the aforementioned growth factors, including EGF receptor heregulin receptor (HER3, etc.), insulin receptor IGF receptor-1, IGF receptor-2, FGF receptor-1 or FGF receptor-2, VEGF receptor angiopoietin receptor (Tie2 etc.), PDGF receptor HGF receptor (c-Met), NGF receptor (TrkA) and the like.

As the "pharmaceutical agents inhibiting the action of cell growth factors or cell growth factor receptors", EGF inhibitor, TGFα inhibitor, haregulin inhibitor, insulin inhibitor, IGF inhibitor, FGF inhibitor, KGF inhibitor, CSF inhibitor, EPO inhibitor, IL-2 inhibitor, NGF inhibitor, PDGF inhibitor, TGFβ inhibitor, HGF inhibitor, VEGF inhibitor, angiopoietin inhibitor, EGF receptor inhibitor, HER2 inhibitor, HER4 inhibitor, insulin receptor inhibitor, IGF-1 receptor inhibitor, IGF-2 receptor inhibitor, FGF receptor-1 inhibitor, FGF receptor-2 inhibitor, FGF receptor-3 inhibitor, FGF receptor-4 inhibitor, VEGF receptor inhibitor, Tie-2 inhibitor, PDGF receptor inhibitor, Abl inhibitor, Raf inhibitor, FLT3 inhibitor, c-Kit inhibitor, Src inhibitor, PKC inhibitor, Trk inhibitor, Ret inhibitor, mTOR inhibitor, Aurora inhibitor, PLK inhibitor, MEK (MEK1/2) inhibitor, c-MET inhibitor, CDK inhibitor, Akt inhibitor, ERK inhibitor, TrkA inhibitor and the like are used. More specifically, anti-VEGF antibody (Bevacizumab etc.), anti-HER2 antibody (Trastuzumab, Pertuzumab etc.), anti-EGFR antibody (Cetuximab, Panitumumab, Matuzumab, Nimotuzumab etc.), anti-VEGFR antibody, anti-HGF antibody, Imatinib, Erlotinib, Gefitinib, Sorafenib, Sunitinib, Dasatinib, Lapatinib, Vatalanib, 4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-7-[3-(1-pyrrolidinyl)propoxy]quinazoline (AZD-2171), Lestaurtinib, Pazopanib, Canertinib, Tandutinib, 3-(4-bromo-2,6-difluorobenzyloxy)-5-[3-[4-(1-pyrrolidinyl)butyl]ureido]isothiazole-4-carboxamide (CP-547632), Axitinib, N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(pyridin-

4-ylmethylamino)pyridine-3-carboxamide (AMG-706), Nilotinib, 6-[4-(4-ethylpiperazin-1-ylmethyl)phenyl]-N-[1(R)-phenylethyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (AEE-788), Vandetanib, Temsirolimus, Everolimus, Enzastaurin, N-[4-[4-(4-methylpiperazin-1-yl)-6-(3-methyl-1H-pyrazol-5-ylamino)pyrimidin-2-ylsulfanyl]phenyl]cyclopropanecarboxamide (VX-680), phosphoric acid 2-[N-[3-[4-[5-[N-(3-fluorophenyl)carbamoylmethyl]-1H-pyrazol-3-ylamino]quinazolin-7-yloxy]propyl]-N-ethylamino]ethyl ester (AZD-1152), 4-[9-chloro-7-(2,6-difluorophenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-ylamino]benzoic acid (MLN-8054), N-[2-methoxy-5-[(E)-2-(2,4,6-trimethoxyphenyl)vinylsulfonylmethyl]phenyl]glycine sodium salt (ON-1910Na), 4-[8-cyclopentyl-7(R)-ethyl-5-methyl-6-oxo-5,6,7,8-tetrahydropteridin-2-ylamino]-3-methoxy-N-(1-methylpiperidin-4-yl)benzamide (BI-2536), 5-(4-bromo-2-chlorophenylamino)-4-fluoro-1-methyl-1H-benzimidazole-6-carbohydroxamic acid 2-hydroxyethyl ester (AZD-6244), N-[2(R),3-dihydroxypropoxy]-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzamide (PD-0325901) and the like are used.

In addition to the aforementioned drugs, L-asparaginase, aceglatone, procarbazine hydrochloride, protoporphyrin-cobalt complex salt, mercuric hematoporphyrin-sodium, topoisomerase I inhibitors (e.g., irinotecan, topotecan, and the like), topoisomerase II inhibitors (e.g., sobuzoxane, and the like), differentiation inducers (e.g., retinoid, vitamin D, and the like), other angiogenesis inhibitors (e.g., humagillin, shark extract, COX-2 inhibitor and the like), α-blockers (e.g., tamsulosin hydrochloride, and the like), bisphosphonic acids (e.g., pamidronate, zoledronate), thalidomide, 5 azacytidine, decitabine, proteasome inhibitor (e.g., bortezomib), antitumor antibody such as anti-CD20 antibody and the like, toxin labeled antibody and the like can also be used.

By combining the compound of the present invention and a concomitant drug, a superior effect such as

(1) the dose can be reduced as compared to single administration of the compound of the present invention or a concomitant drug,
(2) the drug to be combined with the compound of the present invention can be selected according to the condition of patients (mild case, severe case and the like),
(3) the period of treatment can be set longer,
(4) a sustained treatment effect can be designed,
(5) a synergistic effect can be afforded by a combined use of the compound of the present invention and a concomitant drug, and the like, can be achieved.

In the present specification, the compound of the present invention and a concomitant drug used in combination are referred to as the "combination agent of the present invention".

For use of the combination agent of the present invention, the administration time of the compound of the present invention and the concomitant drug is not restricted, and the compound of the present invention and the concomitant drug can be administered to an administration subject simultaneously, or may be administered at different times. The dosage of the concomitant drug may be determined according to the dose clinically set, and can be appropriately selected depending on the administration subject, administration route, disease, combination and the like.

Examples of the administration mode of the combined use of the compound of the present invention and the concomitant drug include the following methods:
(1) The compound of the present invention and the concomitant drug are simultaneously produced to give a single preparation, which is then administered. (2) The compound of the present invention and the concomitant drug are separately produced to give two kinds of preparations which are administered simultaneously by the same administration route. (3) The compound of the present invention and the concomitant drug are separately produced to give two kinds of preparations which are

administered by the same administration route at different times. (4) The compound of the present invention and the concomitant drug are separately produced to give two kinds of preparations which are administered simultaneously by different administration routes. (5) The compound of the present invention and the concomitant drug are separately produced to give two kinds of preparations which are administered by different administration routes at different times (e.g., the compound of the present invention and the concomitant drug are administered in this order, or in the reverse order). The dose of the concomitant drug is determined in accordance with its clinical dose, and the ratio of the compound of the present invention and the concomitant drug is determined depending on the subject, administration route, disease, symptom, combination, and the like. For example, when the subject is human, the concomitant drug is used in 0.01 to 100 (w/w), relative to the compound of the present invention.

The combination agent of the present invention has low toxicity and, for example, the compound of the present invention and/or the above-mentioned concomitant drug can be mixed, according to a method known *per se*, with a pharmacologically acceptable carrier to give pharmaceutical compositions, such as tablets (including sugar-coated tablet, film-coated tablet), powders, granules, capsules (including soft capsule), solutions, injections, suppositories, sustained release agents and the like, which can be safely administered orally or parenterally (e.g., local, rectum, venous, and the like). An injection can be administered directly to the lesion or administered by intravenous, intramuscular, subcutaneous or intra-tissue administration.

As a pharmacologically acceptable carrier which may be used for preparing a preparation of the combination agent of the present invention, those similar to the aforementioned pharmacologically acceptable carriers, that can be used for the

production of the pharmaceutical agent of the present invention, can be mentioned. Where necessary, the aforementioned additives that can be used for the production of the pharmaceutical agent of the present invention, such as preservatives, antioxidants, colorants, sweetening agents, adsorbents, wetting agents and the like can also be used in appropriate amounts.

The compounding ratio of the compound of the present invention to the concomitant drug in the combination agent of the present invention can be appropriately set depending on the administration subject, administration route, diseases and the like.

For example, the content of the compound of the present invention in the combination agent of the present invention varies depending on the dosage form, and is usually from about 0.01 to 100% by weight, preferably from about 0.1 to 50% by weight, further preferably from about 0.5 to 20% by weight, based on the preparation.

The content of the concomitant drug in the combination agent of the present invention varies depending on the dosage form, and is usually from about 0.01 to 90% by weight, preferably from about 0.1 to 50% by weight, further preferably from about 0.5 to 20% by weight, based on the preparation.

The content of additives in the combination agent of the present invention varies depending on the dosage form, and is usually from about 1 to 99.99% by weight, preferably from about 10 to 90% by weight, based on the preparation.

When the compound of the present invention and the concomitant drug are separately prepared, the same content may be adopted.

These preparations can be produced by a method known *per se*, which is generally employed in the preparation process.

For example, the compound of the present invention and the concomitant drug can be made into an aqueous injection together with a dispersing agent (e.g., Tween 80 (manufactured by Atlas

Powder, US), HCO 60 (manufactured by Nikko Chemicals), polyethylene glycol, carboxymethylcellulose, sodium alginate, hydroxypropylmethylcellulose, dextrin and the like), a stabilizer (e.g., ascorbic acid, sodium pyrosulfite, and the like), a surfactant (e.g., Polysorbate 80, macrogol and the like), a solubilizer (e.g., glycerin, ethanol and the like), a buffer (e.g., phosphoric acid and alkali metal salt thereof, citric acid and alkali metal salt thereof, and the like), an isotonizing agent (e.g., sodium chloride, potassium chloride, mannitol, sorbitol, glucose and the like), a pH adjuster (e.g., hydrochloric acid, sodium hydroxide and the like), a preservative (e.g., ethyl parahydroxybenzoate, benzoic acid, methylparaben, propylparaben, benzyl alcohol and the like), a dissolving agent (e.g., conc. glycerin, meglumine and the like), a solubilizing agent (e.g., propylene glycol, sucrose and the like), a soothing agent (e.g., glucose, benzyl alcohol and the like), and the like, or can be dissolved, suspended or emulsified in a vegetable oil such as olive oil, sesame oil, cotton seed oil, corn oil and the like or a solubilizing agent such as propylene glycol and the like and prepared into an oily injection, whereby an injection is afforded.

In addition, an excipient (e.g., lactose, sucrose, starch and the like), a disintegrating agent (e.g., starch, calcium carbonate and the like), a binder (e.g., starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose and the like), a lubricant (e.g., talc, magnesium stearate, polyethylene glycol 6000 and the like) and the like may be added to the compound of the present invention or the concomitant drug according to a method known *per se*, and the mixture can be compression-molded, then if desirable, the molded product can be coated by a method known *per se* for the purpose of masking of taste, enteric property or durability, to give a preparation for oral administration. As the coating agent, for example, hydroxypropylmethylcellulose, ethylcellulose,

hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethylene glycol, Tween 80, Pluronic F68, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudoragit (methacrylic acid·acrylic acid copolymer, manufactured by Rohm, Germany), pigment (e.g., iron oxide red, titanium dioxide, etc.) and the like can be used. The preparation for oral administration may be any of an immediate-release preparation and a sustained release preparation.

Moreover, the compound of the present invention and the concomitant drug can be made into an oily or aqueous solid, semisolid or liquid suppository according to a method known *per se*, by mixing them with an oily substrate, aqueous substrate or aqueous gel substrate. As the above-mentioned oily substrate, for example, glycerides of higher fatty acids [e.g., cacao butter, Witepsols (manufactured by Dynamit Nobel, Germany), etc.], glycerides of medium chain fatty acid [e.g., Miglyols (manufactured by Dynamit Nobel, Germany), etc.], or vegetable oils (e.g., sesame oil, soybean oil, cotton seed oil and the like), and the like are mentioned. Furthermore, as the aqueous substrate, for example, polyethylene glycol, propylene glycol and the like are mentioned, and as the aqueous gel substrate, for example, natural gums, cellulose derivatives, vinyl polymers, acrylic acid polymers and the like are mentioned.

As the above-mentioned sustained release preparation, sustained release microcapsules and the like are mentioned. The sustained release microcapsule can be produced by a method known *per se*.

The compound of the present invention is preferably molded into a preparation for oral administration such as a solid preparation (e.g., powder, granule, tablet, capsule) and the like, or molded into a preparation for rectal administration such as a suppository and the like. Particularly, a preparation for oral administration is preferable.

The concomitant drug can be made into the above-mentioned drug form depending on the kind of the drug.

The dosage of a combination agent of the present invention differs depending on the kind of a compound of the present invention, age, body weight, condition, drug form, administration method, administration period and the like, and for example, for one cancer patient (adult, body weight: about 60 kg), the combination agent is administered intravenously, at a dose of about 0.01 to about 1000 mg/kg/day, preferably about 0.01 to about 100 mg/kg/day, more preferably about 0.1 to about 100 mg/kg/day, particularly about 0.1 to about 50 mg/kg/day, especially about 1.5 to about 30 mg/kg/day, in terms of the compound of the present invention or the concomitant drug, respectively, once or several times in division a day. Of course, since the dose as described above varies depending on various conditions, amounts smaller than the above-mentioned dosage may sometimes be sufficient, further, amounts over that range sometimes have to be administered.

The amount of the concomitant drug can be set at any value unless side effects are problematical. The daily dosage in terms of the concomitant drug differs depending on the severity of the symptom, age, sex, body weight, sensitivity difference of the subject, administration period, interval, and nature, pharmacy, kind of the pharmaceutical preparation, kind of effective ingredient, and the like, and not particularly restricted, and the amount of a drug is, in the case of oral administration for example, usually from about 0.001 to 2000 mg, preferably from about 0.01 to 500 mg, further preferably from about 0.1 to 100 mg, per 1 kg of a mammal and this is usually administered once to 4-times in division a day.

In administration of a combination agent of the present invention, the compound of the present invention may be administered after administration of the concomitant drug or the concomitant drug may be administered after administration of the

compound of the present invention, though they may be administered simultaneously. When administered at a time interval, the interval differs depending on the effective ingredient to be administered, drug form and administration method, and for example, when the concomitant drug is administered first, a method in which the compound of the present invention is administered within time range of from 1 min to 3 days, preferably from 10 min to 1 day, more preferably from 15 min to 1 hr after administration of the concomitant drug is exemplified. When the compound of the present invention is administered first, a method in which the concomitant drug is administered within time range of from 1 min to 1 day, preferably from 10 min to 6 hrs, more preferably from 15 min to 1 hr after administration of the compound of the present invention is exemplified.

In a preferable administration method, for example, the concomitant drug which has been molded into an oral administration preparation is administered orally at a daily dose of about 0.001 to 200 mg/kg, and about 15 min later, the compound of the present invention which has been molded into an oral administration preparation is administered orally at a daily dose of about 0.005 to 100 mg/kg.

Furthermore, the compound of the present invention or the combination agent of the present invention can be used concurrently with a non-drug therapy. To be precise, the compound of the present invention and the combination agent of the present invention can be combined with a non-drug therapy such as (1) surgery, (2) hypertensive chemotherapy using angiotensin II etc., (3) gene therapy, (4) thermotherapy, (5) cryotherapy, (6) laser cauterization, (7) radiotherapy, and the like.

For example, by using the compound of the present invention or the combination agent of the present invention before or after an surgery and the like, or before or after a

combined treatment of two or three kinds thereof, effects such as prevention of emergence of resistance, prolongation of Disease-Free Survival, suppression of cancer metastasis or recurrence, prolongation of life and the like can be afforded.

In addition, it is possible to combine a treatment with the compound of the present invention or the combination agent of the present invention with a supportive therapy [(i) administration of antibiotic (e.g., β-lactam type such as pansporin and the like, macrolide type such as clarithromycin and the like etc.) for the complication with various infectious diseases, (ii) administration of total parenteral nutrition, amino acid preparation or general vitamin preparation for the improvement of malnutrition, (iii) administration of morphine for pain mitigation, (iv) administration of a pharmaceutical agent for ameliorating side effects such as nausea, vomiting, anorexia, diarrhea, leucopenia, thrombocytopenia, decreased hemoglobin concentration, hair loss, hepatopathy, renopathy, DIC, fever and the like and (v) administration of a pharmaceutical agent for suppressing multiple drug resistance of cancer and the like].

Preferably, the compound of the present invention or the combination agent of the present invention is administered orally (including sustained-release preparations), intravenously (including boluses, infusions and clathrates), subcutaneously and intramuscularly (including boluses, infusions and sustained-release preparations), transdermally, intratumorally or proximally before or after the above-described treatment is conducted.

As a period for administering the compound of the present invention or the combination agent of the present invention before the surgery, etc., for example, it can be administrated 1-time about 30 min to 24 hrs before the surgery, etc., or in 1 to 3 cycles about 3 months to 6 months before the surgery, etc. In this way, the surgery, etc. can be conducted easily because,

for example, a cancer tissue would be reduced by administering the compound of the present invention or the combination agent of the present invention before the surgery, and the like.

As a period for administering the compound of the present invention or the combination agent of the present invention after the surgery, etc., for example, it can be administrated repeatedly per a few weeks to 3 months, about 30 min to 24 hrs after the surgery, and the like. In this way, it enhances the effect of the surgery, etc. by administering the compound of the present invention or the combination agent of the present invention after the surgery, and the like.

**Examples**

The present invention is specifically explained in the following by way of Reference Examples, Examples, Formulation Examples, Experimental Examples and Test Examples, which are not to be construed as limitative.

In the Examples, preparative HPLC was performed as in the following.

Preparative HPLC tools: Gilson, Inc. High-Throughput purification system

column: YMC Combiprep ODS-A S-5 5 μm, 12 nM. 50 X 20 mm

detection method: UV 220 nm

Unless otherwise specified, the elution by column chromatography was performed under observation by TLC (thin layer chromatography) in Reference Examples and Examples. For TLC observation, 60F254 manufactured by Merck, or NH TLC plate manufactured by Fuji Silysia Chemical Ltd. was used as a TLC plate, and the solvent used as an elution solvent in column chromatography was used as a eluent. For detection, moreover, a UV detector was employed. As the silica gel for column chromatography, silica gel 60 (70-230 mesh) manufactured by Merck, silica gel manufactured by Fuji Silysia Chemical Ltd. or NH silica gel manufactured by Fuji Silysia Chemical Ltd. and the like were used. The room temperature generally means from

about 10°C to 35°C. For drying the extract, anhydrous sodium sulfate or anhydrous magnesium sulfate was used.

In Formulation Examples, the Japanese Pharmacopoeia 15th Edition (hereinafter to be referred to as The Japanese Pharmacopoeia) or Japanese Pharmaceutical Excipients 2003 compatible products were used as the preparation additives (e.g., lactose, cornstarch, magnesium stearate, crystalline cellulose).

Abbreviations in the Examples and Reference Examples mean the following.

NMR: nuclear magnetic resonance spectra

Hz: hertz

J: coupling constant

m: multiplet

q: quartet

t: triplet

d: doublet

s: singlet

br: broad

dt: double triplet

brs: broad singlet

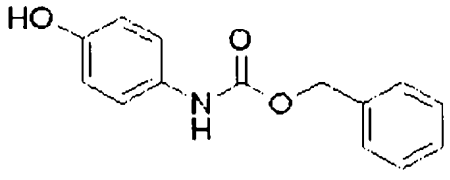
wt%: weight percent

DMSO: dimethyl sulfoxide

HATU: O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

Reference Example 1

Production of benzyl (4-hydroxyphenyl)carbamate



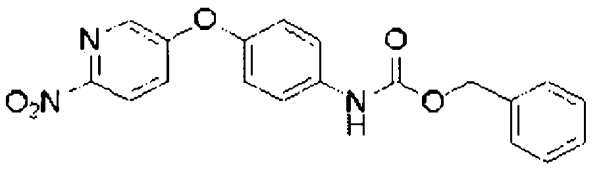

To a suspension of p-aminophenol (7.0 g, 63.9 mmol) in tetrahydrofuran (105 mL) was added saturated aqueous sodium hydrogen carbonate (70 mL), and benzyl chloroformate (12.0 g, 70.3 mmol) was added dropwise at 0°C. After stirring at room

temperature for 16 hr, the reaction mixture was extracted with ethyl acetate (200 mL). The organic layer was washed with saturated brine (100 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was washed with hexane/ethyl acetate (=4/1) and collected by filtration to give the title compound (8.2 g, 53%).

$^1$H-NMR ($CDCl_3$, 300MHz) δ 4.78 (1H, s), 5.19 (2H, s), 6.52 (1H, br s), 6.77 (2H, d, J = 9.2 Hz), 7.22 - 7.26 (2H, d, J = 8.1 Hz), 7.30 - 7.42 (5H, m).

Reference Example 2

Production of benzyl {4-[(6-nitropyridin-3-yl)oxy]phenyl}carbamate



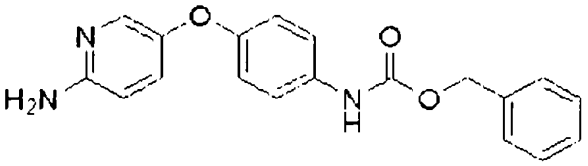
To a solution of benzyl (4-hydroxyphenyl)carbamate (1.44 g, 5.91 mmol) in N,N-dimethylformamide (10 mL) were added cesium carbonate (2.41 g, 7.39 mmol) and 5-bromo-2-nitropyridine (1.0 g, 4.93 mmol), and the mixture was stirred at room temperature for 16 hr. Water (40 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran (=2/1, 120 mL). The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (NH silica gel, hexane/ethyl acetate=3/1→1/3) to give the title compound (1.01 g, 56%).

$^1$H-NMR ($CDCl_3$, 300MHz) δ 5.22 (2H, s), 6.90 (1H, s), 7.07 (2H, d, J = 8.9 Hz), 7.34 - 7.43 (6H, m), 7.50 (2H, d, J = 8.9 Hz), 8.22 (1H, d, J = 8.7 Hz), 8.31 (1H, d, J = 2.7 Hz).

Reference Example 3

Production of benzyl {4-[(6-aminopyridin-3-

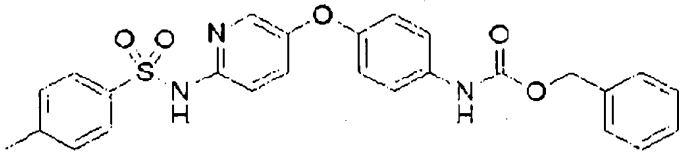
yl)oxy]phenyl}carbamate



To a solution of benzyl {4-[(6-nitropyridin-3-yl)oxy]phenyl}carbamate (5.99 g, 16.4 mmol) in ethanol (80 mL)/water (16 mL) were added reduced iron (5.8 g, 98.4 mmol) and calcium chloride (1.42 g, 11.5 mmol), and the mixture was heated under reflux for 16 hr. The reaction mixture was cooled to room temperature, filtered through celite, and washed with ethanol. The solvent was evaporated under reduced pressure, saturated aqueous sodium hydrogen carbonate (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (150 mL). The organic layer was washed with water and saturated brine in this order, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, a solid was precipitated with hexane/ethyl acetate (=2/1, 30 mL) and collected by filtration to give the title compound (4.43 g, 81%). The solvent of the filtrate was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (NH silica, hexane/ethyl acetate=3/1→1/3) to give the title compound (0.43 mg, 8%). $^1$H-NMR (DMSO-$d_6$, 300MHz) δ 5.13 (2H, s), 5.82 (2H, s), 6.47 (1H, d, J = 8.9 Hz), 6.85 (2H, ddd, J = 10.3, 3.4, 2.2 Hz), 7.15 (1H, dd, J = 8.9, 2.8 Hz), 7.27 - 7.50 (7H, m), 7.71 (1H, d, J = 2.8 Hz), 9.67 (1H, br s).

Reference Example 4

Production of benzyl {4-[(6-{[(4-methylphenyl)sulfonyl]amino}pyridin-3-yl)oxy]phenyl}carbamate

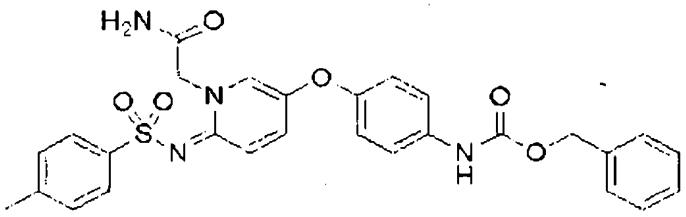


To a solution of benzyl {4-[(6-aminopyridin-3-

yl)oxy]phenyl}carbamate (20.0 g, 59.6 mmol) in pyridine (100 mL) was added p-toluenesulfonyl chloride (13.6 g, 71.6 mmol), and the mixture was stirred at room temperature for 16 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with 0.5N hydrochloric acid, water and saturated brine in this order, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/ethyl acetate and collected by filtration to give the title compound (23.8 g, 82%).
$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 2.35 (3H, s), 5.14 (2H, s), 6.94 (2H, d, J = 9.0 Hz), 7.09 (1H, d, J = 9.0 Hz), 7.32 - 7.47 (10H, m), 7.76 (2H, d, J = 8.4 Hz), 7.91 (1H, d, J = 2.4 Hz), 9.76 (1H, s), 10.96 (1H, br s).

Reference Example 5

Production of benzyl (4-{[1-(2-amino-2-oxoethyl)-6-{[(4-methylphenyl)sulfonyl]imino}-1,6-dihydropyridin-3-yl]oxy}phenyl)carbamate



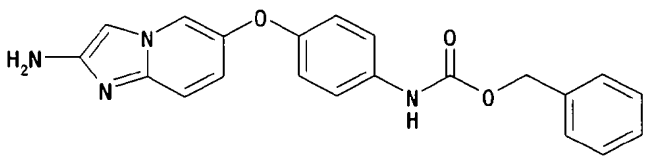
To a solution of benzyl {4-[(6-{[(4-methylphenyl)sulfonyl]amino}pyridin-3-yl)oxy]phenyl}carbamate (23.8 g, 48.6 mmol) in N,N-dimethylformamide (238 mL) were added N,N-diisopropylethylamine (11.0 mL, 63.2 mmol) and iodoacetamide (11.7 g, 63.2 mmol), and the mixture was stirred at room temperature for 24 hr. Water was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate/tetrahydrofuran. The combined organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with

hexane/ethyl acetate and collected by filtration to give the title compound (20.6 g, 78%).

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 2.34 (3H, s), 4.81 (2H, s), 5.14 (2H, s), 6.97 (2H, d, J = 9.0 Hz), 7.27 (2H, d, J = 8.1 Hz), 7.31 - 7.48 (9H, m), 7.63 - 7.68 (3H, m), 7.74 (1H, br s), 7.99 (1H, d, J = 3.0 Hz), 9.76 (1H, br s).

Reference Example 6

Production of benzyl {4-[(2-aminoimidazo[1,2-a]pyridin-6-yl)oxy]phenyl}carbamate

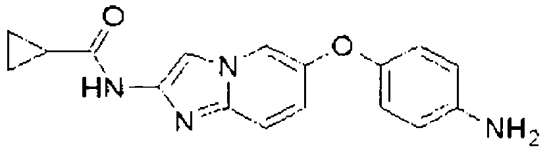


To a solution of benzyl (4-{[1-(2-amino-2-oxoethyl)-6-{[(4-methylphenyl)sulfonyl]imino}-1,6-dihydropyridin-3-yl]oxy}phenyl)carbamate (20.6 g, 37.7 mmol) in tetrahydrofuran (206 mL) was added trifluoroacetic acid anhydride (144 mL), and the mixture was stirred at room temperature for 48 hr. The solvent was evaporated under reduced pressure, ethyl acetate/tetrahydrofuran was added to the residue, washed with saturated aqueous sodium hydrogen carbonate and saturated brine in this order, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, ethanol (200 mL) and 4N aqueous sodium hydroxide solution (50 mL) were added to the residue, and the mixture was stirred at 45°C for 10 hr. The solvent was concentrated to about half under reduced pressure, water was added to the residue, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate→ethyl acetate/methanol=10/1) to give the title compound (9.0 g, 64%).

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 5.14 (2H, s), 5.28 (2H, br s), 6.84 (1H, dd, J = 9.5, 2.3 Hz), 6.93 - 7.01 (3H, m), 7.19 (1H, d, J = 9.5 Hz), 7.30 - 7.49 (7H, m), 8.19 (1H, d, J = 2.3 Hz), 9.73 (1H, s).

Reference Example 7

Production of N-[6-(4-aminophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide

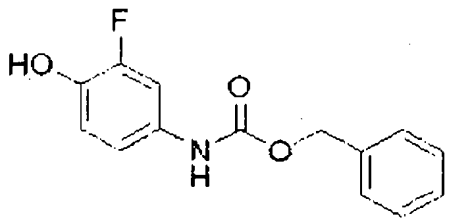


To a solution of benzyl [4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]carbamate (500 mg, 1.13 mmol) in 1,2-dimethoxyethane (15 mL) was added 0.15 mol/L aqueous barium hydroxide solution (10 mL), and the mixture was stirred at 90°C for 36 hr. After cooling to room temperature, the reaction mixture was adjusted to pH about 5 with citric acid, and to pH about 10 with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate/tetrahydrofuran, and the organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=50/50→0/100) to give the title compound (223 g, 64%).

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.76 - 0.82 (4H, m), 1.85 - 1.96 (1H, m), 4.95 (2H, m), 6.57 (2H, d, J = 8.7 Hz), 6.79 (2H, d, J = 8.7 Hz), 6.96 - 7.11 (1H, m), 7.38 (1H, d, J = 9.6 Hz), 7.99 (1H, s), 8.25 (1H, d, J = 1.8 Hz), 10.89 (1H, s).

Reference Example 8

Production of benzyl (3-fluoro-4-hydroxyphenyl)carbamate

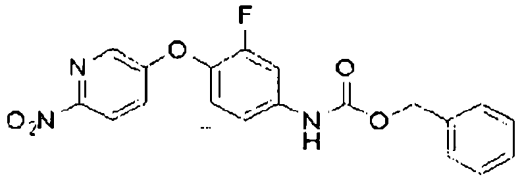


To a suspension of 4-amino-2-fluorophenol (60 g, 472 mmol) in tetrahydrofuran/water (=1/1, 600 mL) was added sodium hydrogen carbonate (43.6 g, 519 mmol), and benzyl chloroformate (74.1 mL, 519 mmol) was added dropwise at 0°C. The mixture was stirred at room temperature for 16 hr, 2N hydrochloric acid (150 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, the residue was washed with hexane/diethyl ether(=1/1) and collected by filtration to give the title compound (82.5 g, 67%). The solvent of the filtrate was evaporated under reduced pressure, and the residue was washed with hexane/diethyl ether(=1/1) and collected by filtration to give the title compound (17.7 g, 14%).

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 5.12 (2H, s), 6.85 (1H, t, J = 9.3 Hz), 6.97 - 7.04 (1H, m), 7.25 - 7.45 (6H, m), 9.48 (1H, br s), 9.64 (1H, br s).

Reference Example 9

Production of benzyl {3-fluoro-4-[(6-nitropyridin-3-yl)oxy]phenyl}carbamate



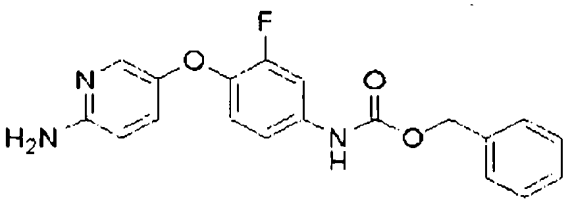
To a solution of benzyl (3-fluoro-4-hydroxyphenyl)carbamate (80 g, 252 mmol) in dimethyl sulfoxide (600 mL) were added cesium carbonate (123 g, 378 mmol) and 5-chloro-2-nitropyridine (40 g, 252 mmol), and the mixture was

stirred at room temperature for 3 hr. Saturated aqueous sodium hydrogen carbonate (1000 mL) and water (1000 mL) were added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/ethyl acetate(=3/1) and collected by filtration to give the title compound (79.8 g, 83%).

$^1$H-NMR ($CDCl_3$, 300MHz) δ 5.23 (2H, S), 6.82 (1H, s), 7.05 - 7.19 (2H, m), 7.31 - 7.44 (6H, m), 7.59 (1H, dd, J = 12.3, 2.4 Hz), 8.24 (1H, d, J = 9.0 Hz), 8.32 (1H, d, J = 2.7 Hz).

Reference Example 10

Production of benzyl {4-[(6-aminopyridin-3-yl)oxy]-3-fluorophenyl}carbamate



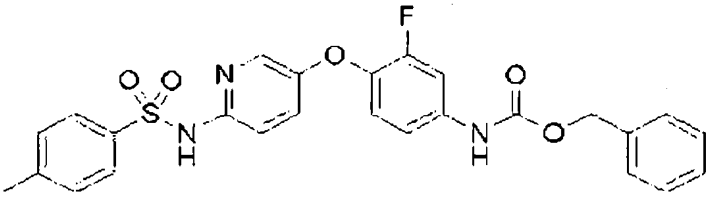

To a solution of benzyl {4-[(6-nitropyridin-3-yl)oxy]phenyl}carbamate (40 g, 104 mmol) in ethanol (1020 mL)/water (180 mL) were added reduced iron (29.1 g, 522 mmol) and calcium chloride (5.8 g, 52 mmol), and the mixture was heated under reflux for 8 hr. The reaction mixture was cooled to room temperature, filtered through celite, and washed with ethanol. The solvent was evaporated under reduced pressure, water (200 mL) was added to the residue, and the mixture was extracted with ethyl acetate (800 mL). The organic layer was washed with water and saturated brine in this order, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and a solid was precipitated with hexane/ethyl acetate (=3/1) and collected by filtration to give the title compound (28.2 g, 76%).

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 5.15 (2H, s), 5.82 (2H, s), 6.45 (1H,

d, J = 8.7 Hz), 6.96 (1H, t, J = 9.0 Hz), 7.11 - 7.19 (2H, m), 7.30 - 7.53 (6H, m), 7.70 (1H, d, J = 2.7 Hz), 9.94 (1H, s).

Reference Example 11

Production of benzyl {3-fluoro-4-[(6-{[(4-methylphenyl)sulfonyl]amino}pyridin-3-yl)oxy]phenyl}carbamate

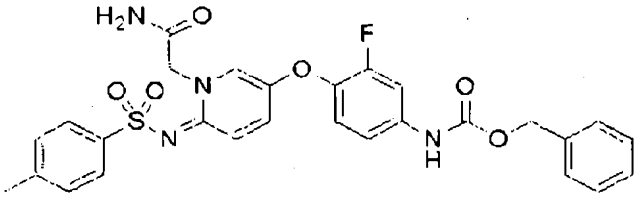


To a solution of benzyl {4-[(6-aminopyridin-3-yl)oxy]-3-fluorophenyl}carbamate (28.2 g, 79.8 mmol) in pyridine (141 mL) was added p-toluenesulfonyl chloride (18.3 g, 98.5 mmol), and the mixture was stirred at room temperature for 16 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with 0.5N hydrochloric acid, water and saturated brine in this order, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/ethyl acetate and collected by filtration to give the title compound (29.2 g, 72%).

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 2.35 (3H, s), 5.16 (2H, s), 7.05 - 7.24 (2H, m), 7.28 - 7.46 (9H, m), 7.50 - 7.58 (1H, m), 7.75 (2H, d, J = 8.4 Hz), 7.91 (1H, d, J = 2.7 Hz), 10.03 (1H, s), 10.95 (1H, br s).

Reference Example 12

Production of benzyl (4-{[(6Z)-1-(2-amino-2-oxoethyl)-6-{[(4-methylphenyl)sulfonyl]imino}-1,6-dihydropyridin-3-yl]oxy}-3-fluorophenyl)carbamate



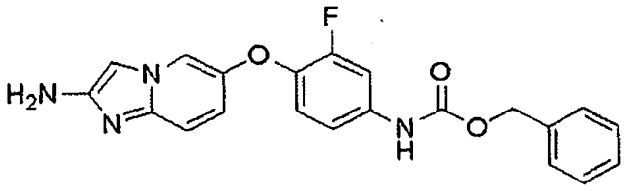
To a solution of benzyl {3-fluoro-4-[(6-{[(4-methylphenyl)sulfonyl]amino}pyridin-3-yl)oxy]phenyl}carbamate

(35.0 g, 69.0 mmol) in N,N-dimethylformamide (350 mL) were added N,N-diisopropylethylamine (15.6 mL, 89.6mmol) and iodoacetamide (16.6 g, 89.6 mmol), and the mixture was stirred at room temperature for 24 hr. Water was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate/tetrahydrofuran. The combined organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/ethyl acetate and collected by filtration to give the title compound (28.0 g, 72%).

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 2.34 (3H, s), 4.80 (2H, s), 5.16 (2H, s), 7.08 - 7.46 (12H, m), 7.50 - 7.58 (1H, m), 7.64 - 7.74 (3H, m), 7.95 (1H, d, J = 3.0 Hz), 10.03 (1H, s).

Reference Example 13

Production of benzyl {4-[(2-aminoimidazo[1,2-a]pyridin-6-yl)oxy]-3-fluorophenyl}carbamate



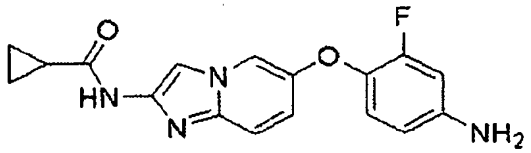

To a solution of benzyl (4-{[1-(2-amino-2-oxoethyl)-6-{[(4-methylphenyl)sulfonyl]imino}-1,6-dihydropyridin-3-yl]oxy}-3-fluorophenyl)carbamate (28.0 g, 49.6 mmol) in tetrahydrofuran (280 mL) was added trifluoroacetic acid anhydride (196 mL), and the mixture was stirred at room temperature for 3 hr. The solvent was evaporated under reduced pressure, ethyl acetate/tetrahydrofuran was added to the residue, and the mixture was washed with saturated aqueous sodium hydrogen carbonate and saturated brine in this order, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, ethanol(140 mL) and 4N aqueous sodium hydroxide solution (40 mL) were added to

the residue, and the mixture was stirred at room temperature for 4 hr. The solvent was concentrated under reduced pressure to about 1/3, water was added to the residue, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol=10/0→9/1) to give the title compound (10.0 g, 51%).

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 5.03 (2H, s), 5.16 (2H, s), 6.85 (1H, dd, J = 9.5, 2.3 Hz), 6.97 (1H, s), 7.08 - 7.23 (3H, m), 7.32 - 7.45 (5H, m), 7.54 (1H, dd, J = 13.5, 2.4 Hz), 8.14 (1H, d, J = 1.8 Hz), 9.99 (1H, s).

Reference Example 14

Production of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide



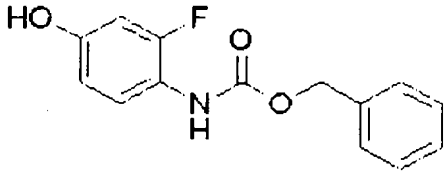
To a suspension of benzyl [4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]carbamate (18.0 g, 39.1 mmol) in 1,2-dimethoxyethane (360 mL) was added 0.15 mol/L aqueous barium hydroxide solution (240 mL), and the mixture was stirred at 90°C for 16 hr. After cooling to room temperature, the reaction mixture was adjusted to about pH 8 with 2N hydrochloric acid, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate and collected by filtration to give the title compound (9.1 g, 71%).

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.74 - 0.81 (4H, m), 1.85 - 1.94 (1H,

m), 5.34 (2H, s), 6.38 (1H, dd, J = 8.7 1.2 Hz), 6.49 (1H, dd, J = 13.5, 2.4 Hz), 6.90 - 7.05 (2H, m), 7.38 (1H, d, J = 9.6 Hz), 8.00 (1H, s), 8.22 (1H, d, J = 2.1 Hz), 10.88 (1H, s).

Reference Example 15

Production of benzyl (2-fluoro-4-hydroxyphenyl)carbamate

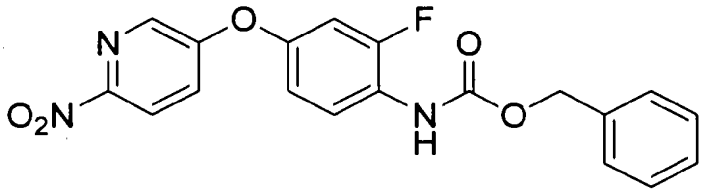


To a suspension of 4-amino-3-fluorophenol (50 g, 39.3 mmol) in tetrahydrofuran/water (=1/1, 500 mL) was added sodium hydrogen carbonate (36.3 g, 39.3 mmol), and benzyl chloroformate (62 mL, 43.3 mmol) was added dropwise at room temperature. The mixture was stirred at room temperature for 16 hr, and extracted with ethyl acetate (1000 mL). The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/diethyl ether(=1/1) and collected by filtration to give the title compound (94.5 g, 92%).

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 5.10 (2H, s), 6.53 - 6.64 (2H, m), 7.10 - 7.26 (1H, m), 7.30 - 7.43 (5H, m), 9.02 (1H, br s), 9.76 (1H, s).

Reference Example 16

Production of benzyl {2-fluoro-4-[(6-nitropyridin-3-yl)oxy]phenyl}carbamate



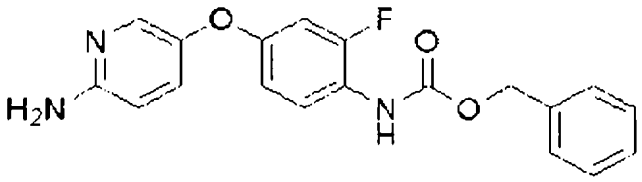
To a solution of benzyl (2-fluoro-4-hydroxyphenyl)carbamate (79 g, 303 mmol) in dimethyl sulfoxide (480 mL) were added cesium carbonate (123 g, 378 mmol) and 5-chloro-2-nitropyridine (40 g, 252 mmol), and the mixture was

stirred at room temperature for 6 hr. Water (1000 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/ethyl acetate(=3/1) and collected by filtration to give the title compound (74 g, 77%).

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 5.17 (2H, s), 7.05 - 7.12 (1H, m), 7.27 - 7.46 (6H, m), 7.66 - 7.78 (2H, m), 8.34 (1H, d, J = 8.6 Hz), 8.46 (1H, d, J = 2.9 Hz), 9.57 (1H, s).

Reference Example 17

Production of benzyl {4-[(6-aminopyridin-3-yl)oxy]-2-fluorophenyl}carbamate



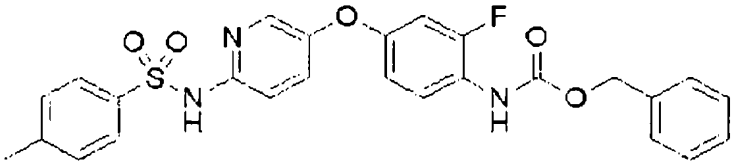
To a solution of benzyl {2-fluoro-4-[(6-nitropyridin-3-yl)oxy]phenyl}carbamate (40 g, 104.3 mmol) in ethanol (1020 mL)/water (180 mL) were added reduced iron (29.1 g, 521.7 mmol) and calcium chloride (5.8 g, 52.2 mmol), and the mixture was heated under reflux for 8 hr. The reaction mixture was cooled to room temperature, filtered through celite, and washed with ethanol. The solvent was evaporated under reduced pressure, water (200 mL) was added to the residue, and the mixture was extracted with ethyl acetate (800 mL). The organic layer was washed with water and saturated brine in this order, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, hexane/ethyl acetate (=3/1) was added, and the precipitate was collected by filtration to give the title compound (28.2 g, 76%).

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 5.13 (2H, s), 5.92 (2H, s), 6.49 (1H, d, J = 9.0 Hz), 6.63 - 6.68 (1H, m), 6.81 (1H, dd, J = 11.9,

2.9 Hz), 7.22 (1H, dd, J = 8.7, 2.9 Hz), 7.30 - 7.48 (6H, m), 7.76 (1H, d, J = 2.9 Hz), 9.28 (1H, br s).

Reference Example 18

Production of benzyl {2-fluoro-4-[(6-{[(4-methylphenyl)sulfonyl]amino}pyridin-3-yl)oxy]phenyl}carbamate

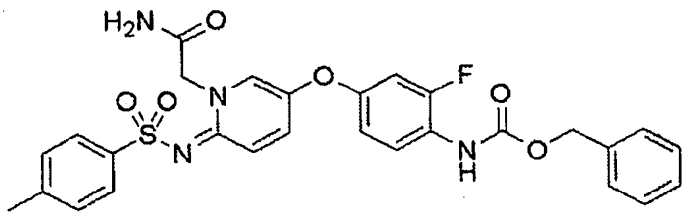


To a solution of benzyl {4-[(6-aminopyridin-3-yl)oxy]-2-fluorophenyl}carbamate (32 g, 90.6 mmol) in pyridine (141 mL) was added p-toluenesulfonyl chloride (18.3 g, 108.7 mmol), and the mixture was stirred at 80°C for 3 hr. After cooling to room temperature, pyridine was evaporated under reduced pressure, water was added to the residue, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/ethyl acetate and collected by filtration to give the title compound (32.0 g, 70%).

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 2.36 (3H, s), 5.13 (2H, s), 6.73 - 6.79 (1H, m), 6.95 (1H, dd, J = 11.6, 2.9 Hz), 7.12 (1H, d, J = 9.0 Hz), 7.30 - 7.56 (9H, m), 7.78 (2H, d, J = 8.4 Hz), 8.00 (1H, d, J = 2.7 Hz), 9.37 (1H, s), 11.04 (1H, br s).

Reference Example 19

Production of benzyl (4-{[(6Z)-1-(2-amino-2-oxoethyl)-6-{[(4-methylphenyl)sulfonyl]imino}-1,6-dihydropyridin-3-yl]oxy}-2-fluorophenyl)carbamate

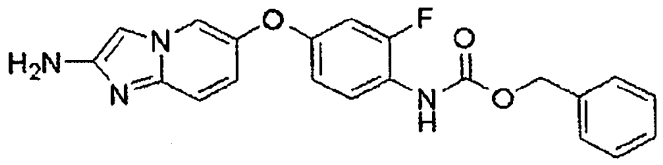


To a solution of benzyl {2-fluoro-4-[(6-{[(4-methylphenyl)sulfonyl]amino}pyridin-3-yl)oxy]phenyl}carbamate (32.0 g, 63.1 mmol) in N,N-dimethylformamide (320 mL) were added N,N-diisopropylethylamine (14.3 mL, 82.0 mmol) and iodoacetamide (15.2 g, 82.0 mmol), and the mixture was stirred at room temperature for 24 hr. Water was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate/tetrahydrofuran. The combined organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/ethyl acetate and collected by filtration to give the title compound (34.2 g, 96%).

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 2.34 (3H, s), 4.81 (2H, s), 5.13 (2H, s), 6.79 - 6.87 (1H, m), 7.02 (1H, dd, J = 11.7, 2.9 Hz), 7.28 (1H, d, J = 7.8 Hz), 7.30 - 7.43 (8H, m), 7.53 - 7.59 (1H, m), 7.65 - 7.75 (4H, m), 8.12 (1H, d, J = 3.0 Hz), 9.38 (1H, br s).

Reference Example 20

Production of benzyl {4-[(2-aminoimidazo[1,2-a]pyridin-6-yl)oxy]-2-fluorophenyl}carbamate



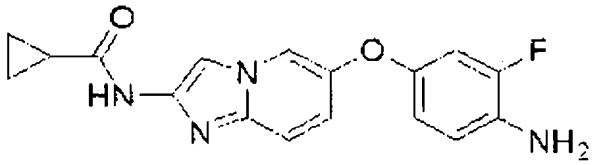
To a solution of benzyl (4-{[1-(2-amino-2-oxoethyl)-6-{[(4-methylphenyl)sulfonyl]imino}-1,6-dihydropyridin-3-yl]oxy}-2-fluorophenyl)carbamate (28.0 g) in tetrahydrofuran (280 mL) was added trifluoroacetic acid anhydride (196 mL), and the mixture was stirred at room temperature for 3 hr. The solvent was evaporated under reduced pressure, ethyl acetate/tetrahydrofuran was added to the residue, and the mixture was washed with saturated aqueous sodium hydrogen carbonate and saturated brine in this order, dried over

anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, ethanol (140 mL) and 4N aqueous sodium hydroxide solution (40 mL) were added to the residue, and the mixture was stirred at room temperature for 4 hr. The solvent was concentrated under reduced pressure to 1/3, water was added to the residue, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol=10/1→9/1) to give the title compound (12.1 g, 51%).

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 5.13 (4H, s), 6.76 - 6.82 (1H, m), 6.87 (1H, dd, J = 9.5, 2.3 Hz), 6.91 - 6.96 (1H, m), 7.00 (1H, s), 7.20 (1H, d, J = 9.3 Hz), 7.33 - 7.44 (6H, m), 7.46 - 7.55 (1H, m), 8.32 (1H, d, J = 1.8 Hz), 9.34 (1H, br s).

Reference Example 21

Production of N-[6-(4-amino-3-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide



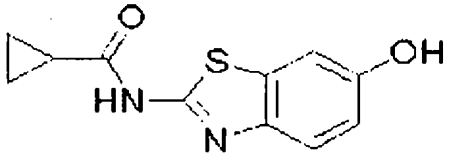

To a suspension of benzyl [4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-2-fluorophenyl]carbamate (9.7 g, 21.1 mmol) in 1,2-dimethoxyethane (291 mL) was added 0.15 mol/L aqueous barium hydroxide solution (194 mL), and the mixture was stirred at 90°C for 16 hr. After cooling to room temperature, the reaction mixture was adjusted to about pH 8 with 2N hydrochloric acid, and extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure,

and the residue was washed with ethyl acetate and collected by filtration to give the title compound (4.3 g, 63%).

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.78 - 0.82 (4H, m), 1.86 - 1.94 (1H, m), 4.98 (2H, s), 6.64 - 6.90 (3H, m), 7.02 (1H, dd, J = 9.6, 2.4 Hz), 7.40 (1H, d, J = 9.9 Hz), 8.01 (1H, s), 8.34 (1H, d, J = 1.5 Hz), 10.92 (1H, s).

Reference Example 22

Production of N-(6-hydroxy-1,3-benzothiazol-2-yl)cyclopropanecarboxamide

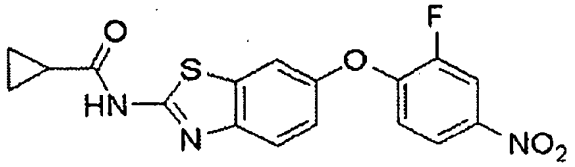



To a solution of 2-amino-1,3-benzothiazol-6-ol (4.99 g, 30.0 mmol) in N,N-dimethylacetamide (20 mL) was added cyclopropanecarbonyl chloride (4.08 mL, 45.0 mmol) at 0°C, and the mixture was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed 3 times with water, dried over anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate/diisopropyl ether and collected by filtration to give the title compound (3.22 g, 13.7 mmol) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.87 - 0.97 (4H, m), 1.92 - 2.01 (1H, m), 6.87 (1H, dd, J = 8.7, 2.3 Hz), 7.25 (1H, d, J = 2.3 Hz), 7.52 (1H, d, J = 8.7 Hz), 9.53 (1H, br s), 12.41 (1H, br s).

Reference Example 23

Production of N-[6-(2-fluoro-4-nitrophenoxy)-1,3-benzothiazol-2-yl]cyclopropanecarboxamide

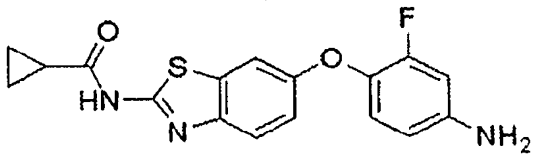


A suspension of N-(6-hydroxy-1,3-benzothiazol-2-yl)cyclopropanecarboxamide (1.17 g, 5.00 mmol), 1,2-difluoro-4-nitrobenzene (0.96 g, 6.00 mmol) and cesium carbonate (3.26 g, 10.0 mmol) in dimethyl sulfoxide (10 mL) was stirred at 50°C for 5 hr. After cooling to room temperature, water was added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate/tetrahydrofuran. The organic layer was washed with water, dried over anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate and collected by filtration to give the title compound (1.22 g, 65%) as a pale-yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.92 - 0.99 (4H, m), 1.96 - 2.03 (1H, m), 7.10 - 7.17 (1H, m), 7.30 (1H, dd, J = 8.9, 2.6 Hz), 7.82 (1H, d, J = 8.9 Hz), 7.90 (1H, d, J = 2.6 Hz), 8.04 - 8.09 (1H, m), 8.36 (1H, dd, J = 10.8, 2.7 Hz), 12.71 (1H, br s).

Reference Example 24

Production of N-[6-(4-amino-2-fluorophenoxy)-1,3-benzothiazol-2-yl]cyclopropanecarboxamide



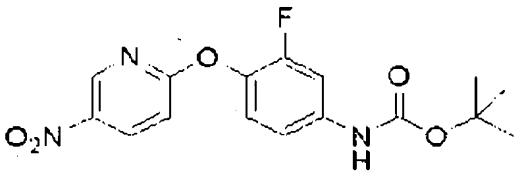

To a suspension of N-[6-(2-fluoro-4-nitrophenoxy)-1,3-benzothiazol-2-yl]cyclopropanecarboxamide (1.15 g, 3.07 mmol) in ethanol (50 mL)/water (10 mL) were added ammonium chloride (1.64 g, 30.7 mmol) and reduced iron (856 g, 15.3 mmol), and the mixture was heated under reflux for 4 hr. The reaction mixture was cooled to room temperature, filtered through celite, and washed with a mixed solution of ethanol/water. The solvent was evaporated under reduced pressure, 1N aqueous sodium hydroxide solution was added to the residue, and the mixture was extracted 3 times with ethyl acetate/tetrahydrofuran. The combined organic layer was dried

over anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate/diisopropyl ether and collected by filtration to give the title compound (644 mg, 61%) as a pale-yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.89 - 0.95 (4H, m), 1.92 - 2.02 (1H, m), 5.35 (2H, s), 6.35 - 6.43 (1H, m), 6.49 (1H, dd, J = 13.2, 2.7 Hz), 6.90 - 7.02 (2H, m), 7.40 (1H, d, J = 2.6 Hz), 7.65 (1H, d, J = 8.7 Hz), 12.54 (1H, br s).

Reference Example 25

Production of tert-butyl {3-fluoro-4-[(5-nitropyridin-2-yl)oxy]phenyl}carbamate

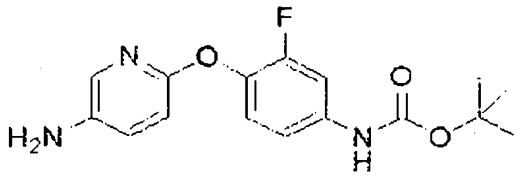


To a solution of tert-butyl (3-fluoro-4-hydroxyphenyl)carbamate (17.2 g, 75.7 mmol) in dimethyl sulfoxide (100 mL) were added 2-chloro-5-nitropyridine (10 g, 63.1 mmol) and cesium carbonate (30.8 g, 94.6 mmol), and the mixture was stirred at room temperature for 4 hr. Water was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/ethyl acetate(=5/1) and collected by filtration to give the title compound (17.0 g, 77%).

$^1$H-NMR ($CDCl_3$, 300MHz) δ 1.53 (9H, s), 6.57 (1H, s), 7.00 - 7.16 (3H, m), 7.52 (1H, dd, J = 12.3, 2.1 Hz), 8.49 (1H, dd, J = 9.0, 2.9 Hz), 9.00 (1H, d, J = 2.9 Hz).

Reference Example 26

Production of tert-butyl {4-[(5-aminopyridin-2-yl)oxy]-3-fluorophenyl}carbamate

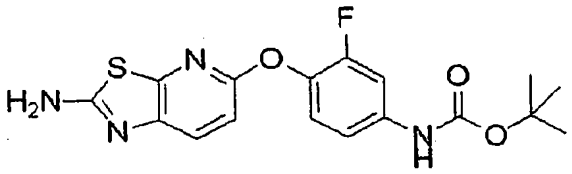


To a suspension of tert-butyl {3-fluoro-4-[(5-nitropyridin-2-yl)oxy]phenyl}carbamate (15 g, 42.9 mmol) in methanol (300 mL) was added 5 wt% palladium/carbon (3.0 g), and the mixture was stirred at room temperature for 8 hr under a hydrogen atmosphere. After nitrogen substitution, insoluble material was collected by filtration and washed with methanol. The solvent of the filtrate was evaporated under reduced pressure, water was added to the residue, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure to give the title compound (12.3 g, 90%).

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 1.48 (9H, s), 4.98 (2H, s), 6.76 (1H, d, J = 9.0 Hz), 7.04 - 7.10 (2H, m), 7.13 - 7.19 (1H, m), 7.40 - 7.47 (2H, m), 9.51 (1H, s).

Reference Example 27

Production of tert-butyl {4-[(2-amino[1,3]thiazolo[5,4-b]pyridin-5-yl)oxy]-3-fluorophenyl}carbamate



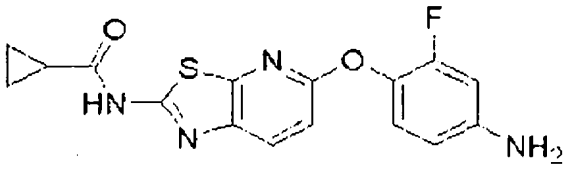
To a solution of potassium thiocyanate (6.1 g, 62.6 mmol) in acetic acid (60 mL) was added a solution of tert-butyl {4-[(5-aminopyridin-2-yl)oxy]-3-fluorophenyl}carbamate (5.0 g, 15.7 mmol) in acetic acid (40 mL) at 0°C. A solution of bromine (3.25 g, 20.4 mmol) in acetic acid (20 mL) was added at 0°C, and the mixture was stirred at room temperature

for 6 hr. Acetic acid was evaporated under reduced pressure, saturated aqueous sodium hydrogen carbonate was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate alone) to give the title compound (2.07 g, 35%).

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 1.49 (9H, s), 6.92 (1H, d, J = 8.7 Hz), 7.17 - 7.23 (2H, m), 7.46 - 7.53 (1H, m), 7.57 (2H, s), 7.70 (1H, d, J = 8.7 Hz), 9.59 (1H, s).

Reference Example 28

Production of N-[5-(4-amino-2-fluorophenoxy)[1,3]thiazolo[5,4-b]pyridin-2-yl]cyclopropanecarboxamide



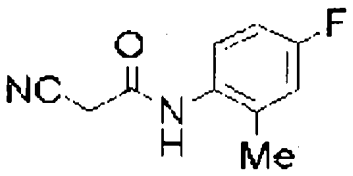
To a solution of tert-butyl [4-({2-[(cyclopropylcarbonyl)amino][1,3]thiazolo[5,4-b]pyridin-5-yl}oxy)-3-fluorophenyl]carbamate (0.50 g, 1.12 mmol) in trifluoroacetic acid (10 mL) was added anisole (0.5 mL), and the mixture was stirred at 0°C for 2 hr. Trifluoroacetic acid was evaporated under reduced pressure, ethyl acetate was added to the residue, and the mixture was washed with saturated aqueous sodium hydrogen carbonate and saturated brine in this order, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=1/1→1/9) to give the title compound (294 mg, 76%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.90 - 0.99 (4H, m), 1.95 - 2.05 (1H, m), 5.34 (2H, s), 6.36 - 6.51 (2H, m), 6.97 (1H, t, J = 8.7 Hz), 7.06 (1H, d, J = 8.7 Hz), 8.11 (1H, d, J = 8.7 Hz), 12.64

(1H, br s).

Reference Example 29

Production of 2-cyano-N-(4-fluoro-2-methylphenyl)acetamide

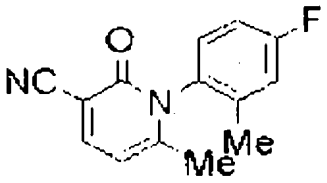


4-Fluoro-2-methylaniline (3.9 g, 31 mmol) was added to ethyl cyanoacetate (5.3 g, 46 mmol) and the mixture was stirred at 150°C for 4 hr. After cooling to room temperature, hexane-ethyl acetate was added to the reaction mixture, and the precipitate was collected by filtration to give the title compound (4.0 g, 67%) as a pale-yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.20 (3H, s), 3.91 (2H, d, J = 10.2 Hz), 7.02 (1H, td, J=8.6, 2.9 Hz), 7.11 (1H, dd, J=9.7, 2.9 Hz), 7.36 (1H, dd, J = 8.8, 5.6 Hz), 9.69 (1H, s).

Reference Example 30

Production of 1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile



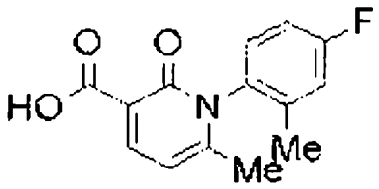
2-Cyano-N-(4-fluoro-2-methylphenyl)acetamide (2.0 g, 10 mmol) and 4-methoxybut-3-en-2-one (1.4 mL, 13 mmol) were suspended in 2-(2-methoxyethoxy)ethanol (20 mL), and 1,4-diazabicyclo[2.2.2]octane (1.2 g, 10 mmol) was added. The mixture was stirred at 120°C for 6 hr, and cooled to room temperature. The mixture was diluted with ethyl acetate (40 mL), and washed with saturated aqueous sodium hydrogen carbonate solution. Then the organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. Hexane-ethyl acetate was added to the residue, and the resulting precipitate was collected by

filtration to give the title compound (630 mg, 25%) as a yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.97 (3H, s), 1.98 (3H, s), 6.53 (1H, d, J=7.6 Hz), 7.17 - 7.28 (1H, m), 7.29 - 7.40 (2H, m), 8.19 (1H, d, J=7.4 Hz).

Reference Example 31

Production of 1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

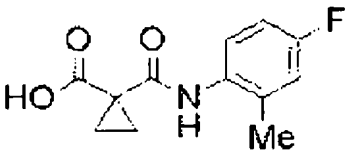



1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (590 mg, 2.9 mmol) was suspended in water (3.0 mL), conc. sulfuric acid (3.0 mL) was slowly added dropwise. The mixture was stirred overnight at 100°C, and allowed to cool to room temperature. The reaction system was basified with aqueous sodium hydroxide solution (8N) and washed with ethyl acetate. The aqueous layer was acidified with hydrochloric acid (1N), and extracted twice with ethyl acetate. The mixed organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. Hexane-ethyl acetate was added to the residue, and the resulting precipitate was collected by filtration to give the title compound (480 mg, 75%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.99 (3H, s), 2.06 (3H, s), 6.84 (1H, d, J=7.6 Hz), 7.22 - 7.32 (1H, m), 7.38 (1H, dd, J=9.6, 3.0 Hz), 7.44 (1H, dd, J=8.7, 5.5 Hz), 8.44 (1H, d, J=7.6 Hz), 14.14 (1H, s).

Reference Example 32

Production of 1-[(4-fluoro-2-methylphenyl)carbamoyl]cyclopropanecarboxylic acid

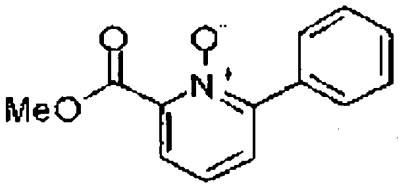


Cyclopropane-1,1-dicarboxylic acid (1.0 g, 8.0 mmol) was suspended in tetrahydrofuran (20 mL), and triethylamine (1.1 mL, 8.0 mmol) was added. After stirring at room temperature for 1 hr, the mixture was cooled in an ice bath. Under ice-cooling, thionyl chloride (0.58 mL, 8.0 mmol) was added dropwise, and the mixture was stirred as it was for 30 min. To this mixture was dropwise added a solution of 4-fluoro-2-methylaniline (3.9 g, 31 mmol) in tetrahydrofuran (2.0 mL) under ice-cooling, and the reaction mixture was warmed to room temperature and stirred overnight. An aqueous sodium hydroxide solution (1N, 50 mL) was added, and the mixture was washed twice with ethyl acetate. The aqueous layer was acidified with hydrochloric acid (1N), and the mixture was extracted twice with ethyl acetate. The mixed organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. Hexane-ethyl acetate was added to the residue, and the precipitate was collected by filtration to give the title compound (1.1 g, 60%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) $\delta$ 1.52 (4H, s), 2.27 (3H, s), 6.99 (1H, td, J=8.7, 3.0 Hz), 7.10 (1H, dd, J=9.7, 2.9 Hz), 7.77 (1H, dd, J=8.9, 5.7 Hz), 10.66 (1H, s), 13.35 (1H, br s).

Reference Example 33

Production of methyl 6-phenylpyridine-2-carboxylate 1-oxide



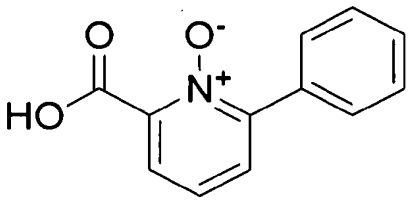
To a solution of methyl 6-phenylpyridine-2-carboxylate (509 mg, 6.24 mmol) in dichloromethane (5 mL) was added m-chloroperbenzoic acid (purity: 69-75%, 2.87 g, 12.5 mmol), and

the mixture was stirred at room temperature for 3 days. Saturated sodium thiosulfate aqueous solution was added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=1/2→1/1) to give the title compound (142 mg, 10%) as a colorless oil.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 3.88 (3H, s), 7.45 - 7.55 (4H, m), 7.69 (1H, dd, J = 7.8, 2.1 Hz), 7.76 (1H, dd, J = 7.8, 2.1 Hz), 7.78 - 7.84 (2H, m).

Reference Example 34

Production of 6-phenylpyridine-2-carboxylic acid 1-oxide

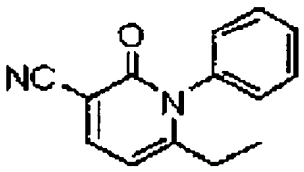


To a solution of methyl 6-phenylpyridine-2-carboxylate 1-oxide in methanol (2 mL) was added 1N aqueous sodium hydroxide solution (1 mL), and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated, 1N hydrochloric acid was added, the precipitate was collected by filtration, and washed with water to give the title compound (120 mg, 90%) as white crystals.

$^1$H-NMR (300 MHz, DMSO-$d_6$) δ 7.52 - 7.63 (3H, m), 7.76 - 7.85 (2H, m), 7.91 - 8.09 (2H, m), 8.35 (1H, dd, J = 7.7, 2.3 Hz).

Reference Example 35

Production of 6-ethyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carbonitrile

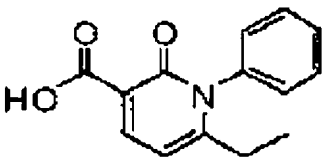


A solution of 2-cyano-N-phenylacetamide (1.08 g, 6.73 mmol), (1E)-1-methoxypent-1-en-3-one (1.0 g, 8.76 mmol) and 1,4-diazabicyclo[2.2.2]octane (755 mg, 6.73 mmol) in 2-(2-methoxyethoxy)ethanol (10 mL) was stirred with heating at 120°C for 7 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=2/1→4/1) to give the title compound (412 mg, 27%) as a pale-brown solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.00 (3H, t, J = 7.5 Hz), 2.24 (2H, q, J = 7.5 Hz), 6.44 (1H, d, J = 7.7 Hz), 7.31 - 7.39 (2H, m), 7.43 - 7.62 (3H, m), 8.20 (1H, d, J = 7.7 Hz).

Reference Example 36

Production of 6-ethyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid

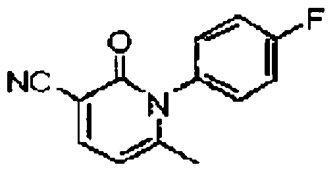


6-Ethyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carbonitrile (395 mg, 1.76 mmol) was dissolved in conc. sulfuric acid (0.4 mL) and water (0.4 mL), and the mixture was stirred with heating at 120°C for 7 hr. 1N Aqueous sodium hydroxide solution was added to the reaction solution, and the mixture was washed with ethyl acetate. 1N Hydrochloric acid was added to the aqueous layer, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was

washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The residue was washed with ethyl acetate to give the title compound (310 mg, 72%) as a colorless solid.
$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.04 (3H, t, J = 7.5 Hz), 2.32 (2H, q, J = 7.5 Hz), 6.77 (1H, d, J = 7.7 Hz), 7.38 - 7.49 (2H, m), 7.51 - 7.67 (3H, m), 8.46 (1H, d, J = 7.7 Hz), 14.28 (1H, s).

Reference Example 37

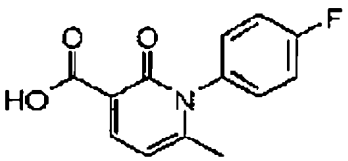
Production of 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile




A solution of 2-cyano-N-(4-fluorophenyl)acetamide (15 g, 84.2 mmol), 4-methoxybut-3-en-2-one (12.6 g, 125.9 mmol) and 1,4-diazabicyclo[2.2.2]octane (9.4 g, 84.2 mmol) in 2-(2-methoxyethoxy)ethanol (150 mL) was stirred with heating at 120°C for 5 hr. (3E)-4-Methoxybut-3-en-2-one (4.2 g, 41.9 mmol) and 1,4-diazabicyclo[2,2,2]octane (4.7 g, 41.9 mmol) were further added to the reaction mixture, and the mixture was stirred with heating at 120°C for 1 hr. 2N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained solid was washed with ethyl acetate to give the title compound (6 g, 31%) as a pale-brown solid.
$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.01 (3H, s), 6.45 - 6.52 (1H, m), 7.35 - 7.48 (4H, m), 8.15 (1H, d, J = 7.4 Hz).

Reference Example 38

Production of 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

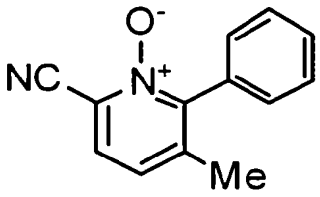


1-(4-Fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (3 g, 13.1 mmol) was dissolved in conc. sulfuric acid (6.0 mL) and water (6.0 mL), and the mixture was stirred with heating at 120°C for 20 hr. 8N Aqueous sodium hydroxide solution was added to the reaction solution, and the mixture was washed with ethyl acetate. 2N hydrochloric acid was added to the aqueous layer, and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The residue was washed with diethyl ether and collected by filtration to give the title compound (2.41 g, 74%) as a pale-brown solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.10 (3H, s), 6.80 (1H, d, J = 7.9 Hz), 7.37 - 7.58 (4H, m), 8.41 (1H, d, J = 7.9 Hz), 14.21 (1H, s).

Reference Example 39

Production of 5-methyl-6-phenylpyridine-2-carbonitrile 1-oxide



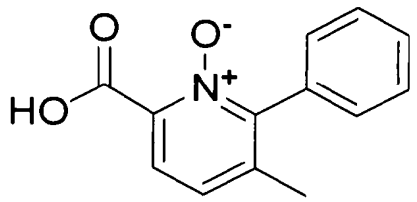
A solution of 6-(4-fluorophenyl)-5-methylpyridine-2-carbonitrile (750 mg, 3.86 mmol) and m-chloroperbenzoic acid (purity 69%, 2.4 g, 96.5 mmol) in tetrahydrofuran (8 mL) was stirred with heating at 50°C for 3 days. Saturated aqueous sodium thiosulfate solution was added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent

was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=1/3→1/2) to give the title compound (74.8 mg, 9%) as white crystals.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.10 (3H, s), 7.32 - 7.41 (2H, m), 7.45 - 7.59 (4H, m), 8.03 (1H, d, J = 8.3 Hz).

Reference Example 40

Production of 5-methyl-6-phenylpyridine-2-carboxylic acid 1-oxide

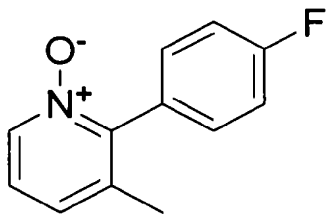


In the same manner as in Reference Example 38 and using 5-methyl-6-phenylpyridine-2-carbonitrile 1-oxide (74.8 mg, 0.356 mmol), conc. sulfuric acid (0.3 mL) and water (0.3 mL), the title compound (83.1 mg, 99%) was obtained as colorless crystals.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.16 (3H, s), 7.43 - 7.49 (2H, m), 7.51 - 7.62 (3H, m), 7.92 (1H, d, J = 8.5 Hz), 8.28 (1H, d, J = 8.5 Hz).

Reference Example 41

Production of 2-(4-fluorophenyl)-3-methylpyridine 1-oxide



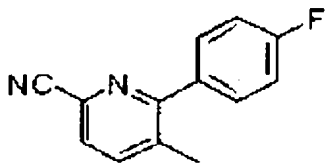
A solution of 2-(4-fluorophenyl)-3-methylpyridine (26.8 g, 0.143 mol) and m-chloroperbenzoic acid (purity 69%, 39 g, 0.157 mol) in tetrahydrofuran (100 mL) was stirred with heating at 50°C for 5 hr. The solvent was evaporated under reduced pressure, and the obtained residue was purified 3

times by silica gel column chromatography (NH silica gel, ethyl acetate) to give a white solid. The obtained solid was washed with ethyl acetate to give the title compound (24.7 g, 85%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.04 (3H, s), 7.21 - 7.46 (6H, m), 8.16 - 8.24 (1H, m).

Reference Example 42

Production of 6-(4-fluorophenyl)-5-methylpyridine-2-carbonitrile



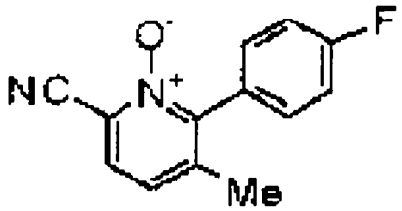

To a solution of 2-(4-fluorophenyl)-3-methylpyridine 1-oxide (24 g, 0.118 mol) in tetrahydrofuran (200 mL) were added trimethylsilyl cyanide (19.2 mL, 0.153 mol) and dimethylcarbamoyl chloride (14.1 mL, 0.153 mmol), and the mixture was heated under reflux for 2 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with diethyl ether and collected by filtration to give the title compound (16.7 g, 67%) as a white solid. Under reduced pressure, the filtrate was concentrated, and the obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=1/9) to give the title compound (3.0 g, 12%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.41 (3H, s), 7.07 - 7.43 (2H, m), 7.53 - 7.76 (2H, m), 7.90 - 8.07 (2H, m).

Reference Example 43

Production of 6-(4-fluorophenyl)-5-methylpyridine-2-

carbonitrile 1-oxide

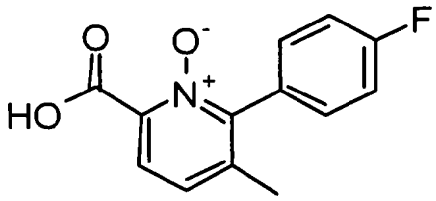


To a solution of 6-(4-fluorophenyl)-5-methylpyridine-2-carbonitrile (16.76 g, 79 mmol) and sodium percarbonate (24.8 g, 158 mmol) in acetonitrile (200 mL) was added dropwise trifluoromethanesulfonic acid anhydride (66.8 g, 237 mmol) at 0°C, and the mixture was stirred at 0°C for 1 hr and further at room temperature overnight. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane=1/2→1/1) to give the title compound (6.2 g, 40%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.11 (3H, s), 7.30 - 7.42 (2H, m), 7.42 - 7.53 (3H, m), 8.03 (1H, d, J = 8.3 Hz).

Reference Example 44

Production of 6-(4-fluorophenyl)-5-methylpyridine-2-carboxylic acid 1-oxide



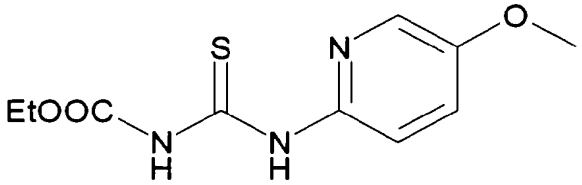
In the same manner as in Reference Example 38 and using 6-(4-fluorophenyl)-5-methylpyridine-2-carbonitrile 1-oxide (6.07 g, 26.6 mmol), conc. sulfuric acid (18 mL) and water (18 mL), the title compound (5.72 g, 87%) was obtained as a white

solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.18 (3H, s), 7.35 - 7.47 (2H, m), 7.50 - 7.62 (2H, m), 7.93 (1H, d, J = 8.9 Hz), 8.30 (1H, d, J = 8.1 Hz).

Reference Example 45

Production of ethyl [(5-methoxypyridin-2-yl)carbamothioyl]carbamate

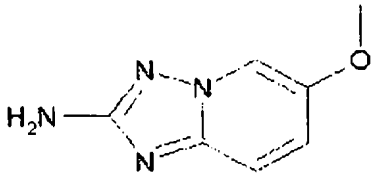



To a solution of 5-methoxypyridin-2-amine (1.05 g, 8.43 mmol) in dimethyl sulfoxide (5 mL) was added ethyl isothiocyanatoformate (1.44 g, 11.0 mmol), and the mixture was stirred for 15 hr. The reaction mixture was diluted with water, and extracted with ethyl acetate (×3). The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was dried to give the title compound (1.34 g, 62%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.26 (3H, t, J = 7.2 Hz), 3.84 (3H, s), 4.22 (2H, q, J = 7.2 Hz), 7.51 (1H, dd, J = 9.0, 3.0 Hz), 8.12 (1H, d, J = 3.0 Hz), 8.54 (1H, br s), 11.38 (1H, br s), 12.04 (1H, br s).

Reference Example 46

Production of 6-methoxy[1,2,4]triazolo[1,5-a]pyridin-2-amine



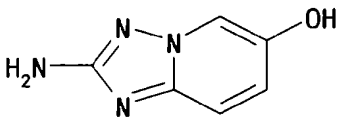

A mixture of ethyl [(5-methoxypyridin-2-yl)carbamothioyl]carbamate (1.34 g, 5.25 mmol), hydroxylammonium chloride (2.55 g, 36.7 mmol), N,N-diisopropylethylamine (4.57 mL, 26.2 mmol), ethanol (15 mL)

and methanol (15 mL) was stirred at 80°C for 8 hr. The reaction mixture was diluted with water, and extracted with ethyl acetate (×3). The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was collected by filtration, and washed with ethyl acetate-hexane to give the title compound (790 mg, 92%) as a yellow oil.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 3.78 (3H, s), 5.79 (2H, br s), 7.18 (1H, dd, J = 9.6, 2.4 Hz), 7.27 (1H, d, J = 9.6 Hz), 8.28 (1H, d, J = 2.4 Hz).

Reference Example 47

Production of 2-amino[1,2,4]triazolo[1,5-a]pyridin-6-ol hydrobromide



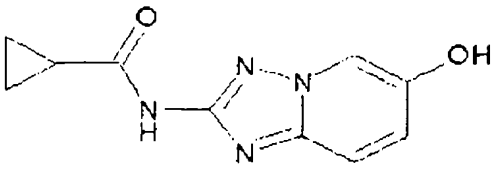

HBr

A mixture of 6-methoxy[1,2,4]triazolo[1,5-a]pyridin-2-amine (780 mg, 4.75 mmol), 48% hydrobromic acid (3 mL) was stirred under refluxing conditions for 7 hr. 48% Hydrobromic acid (2 mL) was further added and the mixture was stirred under refluxing conditions for 3 hr. The mixture was concentrated under reduced pressure, and diisopropyl ether (2 mL) and ethanol (1 mL) were added to the residue. The precipitate was collected by filtration, and washed with diisopropyl ether to give the title compound (984 mg, 89%) as a brown solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 7.53 - 7.61 (2H, m), 8.34 (1H, dd, J = 1.8, 0.9 Hz), 10.57 (1H, br s).

Reference Example 48

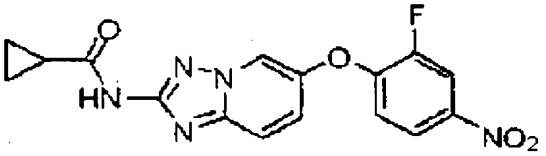
Production of N-(6-hydroxy[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide



To a solution of 2-amino[1,2,4]triazolo[1,5-a]pyridin-6-ol hydrobromide (1.50 g, 4.22 mmol) in N,N-dimethylacetamide (5 mL) was added cyclopropanecarbonyl chloride (1.15 mL, 12.7 mmol) with stirring under ice-cooling, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with water, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was collected by filtration, and washed with ethyl acetate-hexane to give the title compound (1.59 g, 89%) as a white solid.
$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.79 - 0.82 (4H, m), 1.96 - 2.05 (1H, m), 7.28 (1H, dd, J = 9.4, 2.4 Hz), 7.52 (1H, d, J = 9.4 Hz), 8.20 (1H, d, J = 2.4 Hz), 10.01 (1H, br s), 10.82 (1H, s).

Reference Example 49

Production of N-[6-(2-fluoro-4-nitrophenoxy)[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide



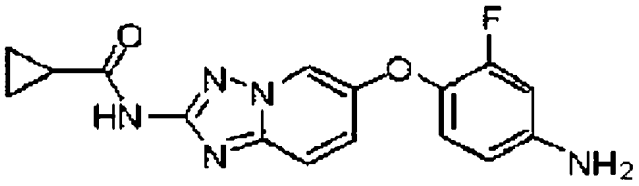
To a solution of N-(6-hydroxy[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide (2 g, 9.16 mmol) and 1,2-difluoro-4-nitrobenzene (1.46 g, 9.16 mmol) in dimethyl sulfoxide (20 mL) was added cesium carbonate (4.48 g, 13.7 mmol), and the mixture was stirred at room temperature for 17 hr. The reaction mixture was filtered through celite, and the filtrate was diluted with water and ethyl acetate, and extracted twice with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous

magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate to give the title compound (1.5 g, 46%) as a white solid.

$^1$H-NMR (300 MHz, DMSO-$d_6$) δ 0.77 - 0.87 (4H, m), 2.04 (1H, br s), 7.23 - 7.35 (1H, m), 7.64 - 7.73 (1H, m), 7.78 - 7.84 (1H, m), 8.05 (1H, dd, J = 9.1, 1.1 Hz),8.35 (1H, d, J = 10.8 Hz), 9.17 (1H, s), 11.10 (1H, br s).

Reference Example 50

Production of N-[6-(4-amino-2-fluorophenoxy)[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide



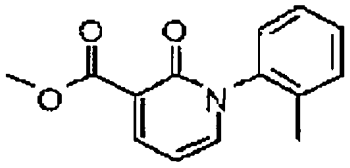
A solution of N-[6-(2-fluoro-4-nitrophenoxy)[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide (400 mg, 1.12 mmol), reduced iron (312 mg, 5.59 mmol) and ammonium chloride (600 mg, 11.2 mmol) in ethanol (8 mL) and water (2 mL) was heated under reflux for 1.5 hr. The reaction mixture was filtered through celite, and the filtrate was diluted with water and ethyl acetate and extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane=1/2→ethyl acetate/methanol=9/1) to give the title compound (125 mg, 34%) as a white solid.

$^1$H-NMR (300 MHz, DMSO-$d_6$) δ 0.72 - 0.90 (4H, m), 1.93 - 2.13 (1H, m), 5.41 (2H, s), 6.33 - 6.44 (1H, m), 6.50 (1H, dd, J = 13.4, 2.5 Hz), 6.92 - 7.05 (1H, m), 7.44 (1H, dd, J = 9.6, 2.5 Hz), 7.66 (1H, dd, J = 9.6, 0.8 Hz), 8.45 (1H, d, J = 1.9 Hz),

10.98 (1H, s).

Reference Example 51

Production of methyl 1-(2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

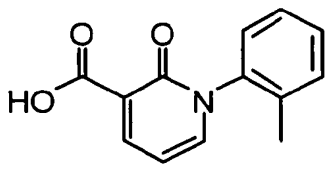


To a solution of methyl 2-oxo-2H-pyran-3-carboxylate (3 g, 19.5 mmol) in tetrahydrofuran (30 mL) and N,N-dimethylformamide (10 mL) was added 2-methylaniline (2.09 g, 19.5 mmol), and the mixture was stirred at room temperature for 7 hr. 4-Dimethylaminopyridine (119 mg, 0.974 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.48 g, 23.4 mmol) were added to the reaction mixture, and the mixture was further stirred at room temperature for 17 hr. 1N Hydrochloric acid was added to the reaction solution, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=1/1) to give the title compound (882 mg, 19%) as yellow crystals.

$^1$H-NMR (300 MHz, DMSO-$d_6$) $\delta$ 2.04 (3H, s), 3.75 (3H, s), 6.36 - 6.47 (1H, m), 7.17 - 7.45 (4H, m), 7.86 (1H, dd, J = 6.6, 2.3 Hz), 8.16 (1H, dd, J = 7.2, 2.3 Hz).

Reference Example 52

Production of 1-(2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid

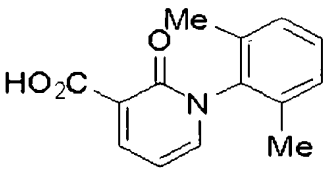


To a solution (9 mL) of methyl 1-(2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (880 mg, 3.62 mmol) in methanol was added 1N aqueous sodium hydroxide solution (5 mL), and the mixture was stirred at room temperature for 4 hr. The reaction mixture was adjusted to pH<7 with 1N hydrochloric acid and concentrated under reduced pressure. The precipitate was collected by filtration and washed with water to give the title compound (704 mg, 85%) as yellow crystals.

$^1$H-NMR (300 MHz, DMSO-$d_6$) δ 2.07 (3H, s), 6.74 - 6.88 (1H, m), 7.35 - 7.51 (4H, m), 8.14 (1H, dd, J = 6.6, 2.1 Hz), 8.52 (1H, dd, J = 7.4, 2.1 Hz), 14.25 (1H, br s).

Reference Example 53

Production of 1-(2,6-dimethylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid

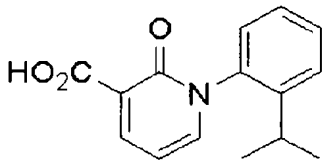



Dimethyl [(3-methoxyprop-2-en-1-ylidene)propanedionate (1.1 g, 5.6 mmol) and 2,6-dimethylaniline (0.69 mL, 5.6 mmol) were dissolved in N,N-dimethylacetamide (1.2 mL), and the mixture was stirred at 130°C overnight. After cooling to room temperature, the reaction system was diluted with ethyl acetate and washed with saturated sodium hydrogen carbonate. The organic layer was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (15 mL), 60% sodium hydride (1.1 g, 28 mmol) was slowly added with stirring, and the mixture was further stirred at room temperature for 3 hr. Distilled water (10 mL) was added, and the mixture was further stirred at room temperature for 1 hr. 1N Aqueous sodium hydroxide solution (10 mL) was added to the reaction system and the mixture was washed with ethyl acetate. The aqueous layer was acidified with 1N hydrochloric acid (20 mL) and extracted twice with

ethyl acetate. The collected organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. Hexane/ethyl acetate (=2/1) was added, and the resulting precipitate was collected by filtration to give the title compound (220 mg, 16%) as a white solid.
$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.00 (6H, s), 6.88 (1H, d, J = 7.2 Hz), 7.26-7.41 (3H, m), 8.10 (1H, dd, J = 6.6, 2.1 Hz), 8.56 (1H, dd, J = 7.2, 2.1 Hz), 14.20 (1H, s).

Reference Example 54

Production of 1-[2-(1-methylethyl)phenyl]-2-oxo-1,2-dihydropyridine-3-carboxylic acid



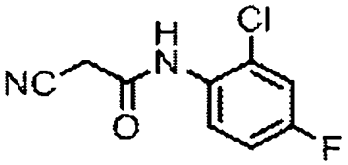
Methyl 2-oxo-2H-pyran-3-carboxylate (3.0 g, 19 mmol) was dissolved in a mixed solvent of tetrahydrofuran (40 mL) and N,N-dimethylformamide (10 mL), and 2-(1-methylethyl)aniline (2.7 mL, 19 mmol) was added. After stirring overnight at room temperature, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.5 g, 23 mmol) and 4-(N,N-dimethylamino)pyridine (120 mg, 1.0 mmol) were added, and the mixture was further stirred overnight at room temperature. The reaction system was diluted with ethyl acetate and washed with saturated aqueous sodium hydrogen carbonate solution, and the organic layer was dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=40/60→60/40) to give methyl 1-[2-(1-methylethyl)phenyl]-2-oxo-1,2-dihydropyridine-3-carboxylate (800 mg). Methyl 1-[2-(1-methylethyl)phenyl]-2-oxo-1,2-dihydropyridine-3-carboxylate (800 mg) was dissolved in a mixed solvent of tetrahydrofuran (5 mL) and methanol (5 mL), 1N aqueous sodium hydroxide solution (5 mL) was added, and the

mixture was stirred at room temperature for 2 hr. The mixture was diluted with distilled water (20 mL) and washed with ethyl acetate. The aqueous layer was acidified with 1N hydrochloric acid (7 mL) and extracted twice with ethyl acetate. The collected organic layer was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. A small amount of hexane/ethyl acetate was added to the residue, and the resulting precipitate was collected by filtration to give 1-[2-(1-methylethyl)phenyl]-2-oxo-1,2-dihydropyridine-3-carboxylic acid (760 mg, 15%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.07 - 1.18 (6H, m), 2.51 - 2.57 (1H, m), 6.76 - 6.87 (1H, m), 7.32 - 7.43 (2H, m), 7.50 - 7.62 (2H, m), 8.19 (1H, dd, J = 6.6, 2.1 Hz), 8.53 (1H, dd, J = 7.2, 2.1 Hz), 14.25 (1H, s).

Reference Example 55

Production of N-(2-chloro-4-fluorophenyl)-2-cyanoacetamide

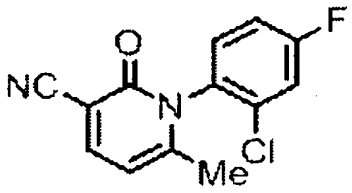



A mixture of 2-chloro-4-fluoroaniline (3.55 g, 24.3 mmol), cyanoacetic acid (2.48 g, 29.2 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide·hydrochloride (7.01 g, 36.5 mmol), 1H-1,2,3-benzotriazol-1-ol (4.94 g, 36.5 mmol), triethylamine (5.10 mL, 36.5 mmol) and N,N-dimethylformamide (50 mL) was stirred at room temperature for 16 hr. The mixture was diluted with ethyl acetate, washed with water, saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and filtered through a basic silica gel pad. The solvent was evaporated under reduced pressure, and the obtained residue was washed with hexane and collected by filtration to give the title compound (2.84 g, 54%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 3.98 (2H, s), 7.21 - 7.30 (1H, m), 7.49 - 7.58 (1H, m), 7.61 - 7.71 (1H, m), 10.00 (1H, s).

Reference Example 56

Production of 1-(2-chloro-4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile

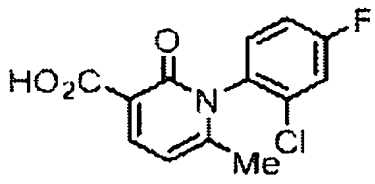


A mixture of N-(2-chloro-4-fluorophenyl)-2-cyanoacetamide (2.00 g, 9.40 mmol), (3E)-4-methoxybut-3-en-2-one (1.13 g, 11.2 mmol), 1,4-diazabicyclo[2.2.2]octane (1.05 g, 9.40 mmol) and 2-(2-methoxyethoxy)ethanol (20 mL) was stirred at 130°C for 3 hr. After cooling to room temperature, the mixture was diluted with ethyl acetate, washed with 1N hydrochloric acid, water (×2) and saturated brine, dried over anhydrous magnesium sulfate, and filtered through a silica gel pad. The solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (100 g, ethyl acetate/hexane=2/98→50/50). The obtained residue was washed with ethyl acetate/hexane and collected by filtration to give the title compound (0.75 g, 30%) as a pale-yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.01 (3H, s), 6.51 - 6.61 (1H, m), 7.42 - 7.55 (1H, m), 7.63 - 7.73 (1H, m), 7.77 - 7.85 (1H, m), 8.18 - 8.27 (1H, m).

Reference Example 57

Production of 1-(2-chloro-4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid



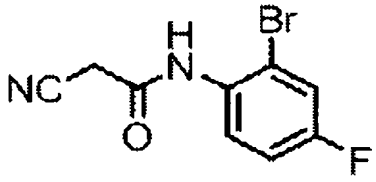
To a mixture of 1-(2-chloro-4-fluorophenyl)-6-methyl-2-

oxo-1,2-dihydropyridine-3-carbonitrile, 1-(2-chloro-4-fluorophenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (0.75 g, 3.80 mmol) and water (5 mL) was added conc. sulfuric acid (5 mL) at 0°C, and the mixture was stirred at 100°C for 18 hr. After cooling to 0°C, the mixture was basified (pH 11) with 8N aqueous sodium hydroxide solution and washed with ethyl acetate. The aqueous layer was acidified (pH 4) with 5N hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with diethyl ether and collected by filtration to give the title compound (588 mg, 55%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.09 (3H, s), 6.85 (1H, d, J = 7.5 Hz), 7.48 - 7.57 (1H, m), 7.72 - 7.89 (2H, m), 8.46 (1H, d, J = 7.5 Hz), 13.84 (1H, br s).

Reference Example 58

Production of N-(2-bromo-4-fluorophenyl)-2-cyanoacetamide



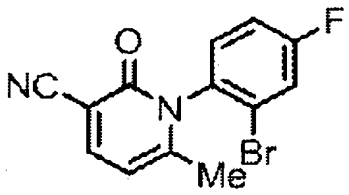

A mixture of 2-bromo-4-fluoroaniline (10.0 g, 52.6 mmol), cyanoacetic acid (5.36 g, 63.1 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide·hydrochloride (15.1 g, 78.9 mmol), 1H-1,2,3-benzotriazol-1-ol (10.6 g, 78.9 mmol), triethylamine (10.9 mL, 78.9 mmol) and N,N-dimethylformamide (150 mL) was stirred at room temperature for 16 hr. The mixture was diluted with ethyl acetate, washed with water, saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and filtered through a pad packed with NH silica gel. The solvent was evaporated under reduced pressure, and the obtained residue was washed with hexane and collected by

filtration to give the title compound (8.04 g, 59%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 3.96 (2H, s), 7.26 - 7.34 (1H, m), 7.54 - 7.61 (1H, m), 7.64 - 7.70 (1H, m), 9.97 (1H, s).

Reference Example 59

Production of 1-(2-bromo-4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile

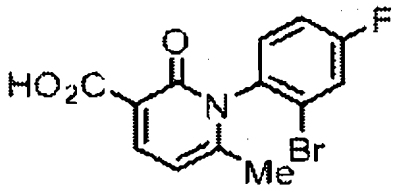



A mixture of N-(2-bromo-4-fluorophenyl)-2-cyanoacetamide (5.00 g, 19.4 mmol), (3E)-4-methoxybut-3-en-2-one (2.33 g, 23.3 mmol), 1,4-diazabicyclo[2.2.2]octane (2.18 g, 19.4 mmol) and 2-(2-methoxyethoxy)ethanol (50 mL) was stirred at 130°C for 5 hr. After cooling to room temperature, the mixture was diluted with ethyl acetate, washed with 1N hydrochloric acid, water (×2) and saturated brine, dried over anhydrous magnesium sulfate, and filtered through a silica gel pad. The solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (100 g, ethyl acetate/hexane=2/98→50/50), washed with ethyl acetate-hexane and collected by filtration to give the title compound (1.78 g, 29%) as a pale-brown powder.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.99 (3H, s), 6.51 - 6.59 (1H, m), 7.46 - 7.56 (1H, m), 7.63 - 7.70 (1H, m), 7.87 - 7.95 (1H, m), 8.21 - 8.26 (1H, m).

Reference Example 60

Production of 1-(2-bromo-4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

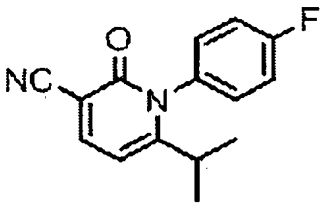


To a mixture of 1-(2-bromo-4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile, 1-(2-bromo-4-fluorophenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (2.00 g, 6.51 mmol) and water (10 mL) was added conc. sulfuric acid (10 mL) at 0°C, and the mixture was stirred at 100°C for 16 hr. After cooling to 0°C, the mixture was basified (pH 11) with 8N aqueous sodium hydroxide solution and washed with ethyl acetate. The aqueous layer was acidified (pH 4) with 5N hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with diethyl ether and collected by filtration to give the title compound (1.12 g, 53%) as a white powder.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.08 (3H, s), 6.85 (1H, d, J = 7.6 Hz), 7.52 - 7.60 (1H, m), 7.71 - 7.78 (1H, m), 7.91 - 7.98 (1H, m), 8.46 (1H, d, J = 7.6 Hz), 13.87 (1H, br s).

Reference Example 61

Production of 1-(4-fluorophenyl)-6-(1-methylethyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile



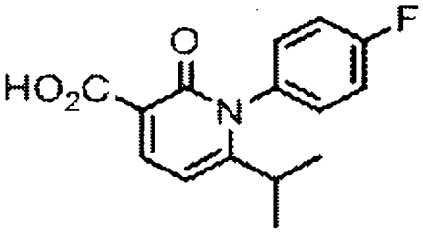

A mixture of (1E)-1-methoxy-4-methylpenta-1-en-3-one (508 mg, 3.96 mmol), 2-cyano-N-(4-fluorophenyl)acetamide (847 mg, 4.75 mmol), 1,4-diazabicyclo[2.2.2]octane (444 mg, 3.96 mmol) and 2-(2-methoxyethoxy)ethanol (10 mL) was stirred at 130°C for 6 hr. After cooling to room temperature, the mixture was diluted with ethyl acetate, washed with 1N hydrochloric acid, water (×2) and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (ethyl

acetate/hexane=0/100→60/40) and silica gel column chromatography (NH silica gel, ethyl acetate/hexane=0/100→60/40) to give the title compound (604 mg, 59%) as a yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.08 (6H, d, J = 6.8 Hz), 2.34 - 2.45 (1H, m), 6.52 (1H, d, J = 7.7 Hz), 7.34 - 7.57 (4H, m), 8.21 (1H, d, J = 7.7 Hz).

Reference Example 62

Production of 1-(4-fluorophenyl)-6-(1-methylethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid

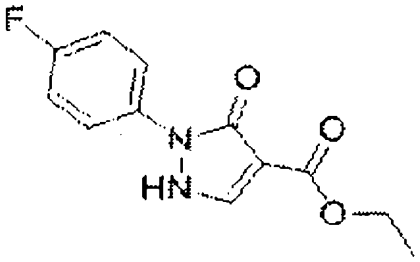


To a mixture of 1-(4-fluorophenyl)-6-(1-methylethyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (604 mg, 2.35 mmol) and water (5 mL) was added conc. sulfuric acid (5 mL) at 0°C, and the mixture was stirred at 100°C for 14 hr. After cooling to 0°C, the mixture was basified (pH 11) with 8N aqueous sodium hydroxide solution and washed with ethyl acetate. The aqueous layer was acidified (pH 4) with 5N hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure to give the title compound (425 mg, 65%) as a pale-yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.12 (6H, d, J = 6.8 Hz), 2.42 - 2.53 (1H, m), 6.85 (1H, d, J = 7.7 Hz), 7.40 - 7.49 (2H, m), 7.53 - 7.61 (2H, m), 8.46 (1H, d, J = 7.7 Hz), 14.22 (1H, s).

Reference Example 63

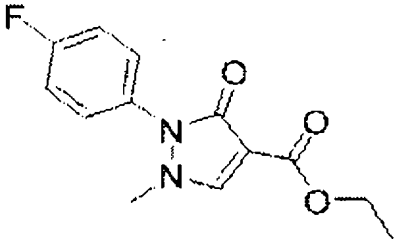
Production of ethyl 2-(4-fluorophenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate



To a suspension of (4-fluorophenyl)hydrazine·hydrochloride (3 g, 18 mmol) and water (75 mL) were added potassium carbonate (5.6 g, 40 mmol) and diethyl ethoxymethylenemalonate (4.8 g, 22 mmol), and the mixture was heated under reflux for 7 hr. After cooling to room temperature, the mixture was washed with ethyl acetate. 6N Aqueous hydrochloric acid solution was added to the separated aqueous layer under ice-cooling. The precipitated solid was collected by filtration, washed with water and ethyl acetate/hexane (1/10), and dried under reduced pressure to give the title compound (2.2 g, 48%) as a yellow solid.
$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.28 (3H, t, J = 6.5 Hz), 4.10 - 4.34 (2H, m), 7.25 - 7.44 (2H, m), 7.71 (2H, br s), 7.82 (1H, br s), 12.31 (1H, br s).

Reference Example 64

Production of ethyl 2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate



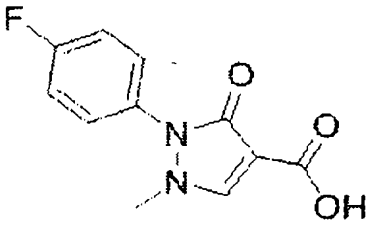
A mixture of ethyl 2-(4-fluorophenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (2.2 g, 8.9 mmol) and methyl trifluoromethanesulfonate (3 mL) was stirred at 80°C for 40 min. The mixture was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=70/30→100/0) to give the title compound (1.6 g,

67%) as a pale-yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.23 (3H, t, J = 7.1 Hz), 3.39 (3H, s), 4.15 (2H, q, J = 7.2 Hz), 7.34 - 7.47 (4H, m), 8.51 (1H, s).

Reference Example 65

Production of 2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid

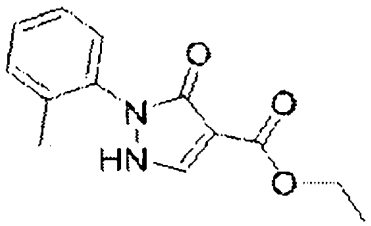



To a solution of ethyl 2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (1.6 g, 5.9 mmol) in tetrahydrofuran (6 mL)/methanol (5 mL) was added 4N aqueous sodium hydroxide solution (9 mL), and the mixture was stirred at 60°C for 1 hr. Tetrahydrofuran and methanol were evaporated under reduced pressure. 6N Aqueous hydrochloric acid solution was added to the residue with stirring, and the precipitated solid was collected by filtration. The filtrate was washed with water and ethyl acetate/hexane (1/5), and dried under reduced pressure to give the title compound (1.1 g, 79%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 3.41 (3H, s), 7.35 - 7.54 (4H, m), 8.52 (1H, s), 11.85 (1H, br s).

Reference Example 66

Production of ethyl 2-(2-methylphenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate



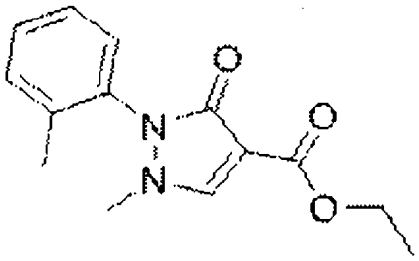

In the same manner as in Reference Example 63 and using

(2-methylphenyl)hydrazine·hydrochloride (5 g, 32 mmol), water (100 mL), potassium carbonate (9.7 g, 70 mmol) and diethyl ethoxymethylenemalonate (8.3 g, 38 mmol) as starting materials, the title compound (6.8 g, 87%) was obtained as a brown solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.28 (3H, t, J = 7.2 Hz), 2.07 (3H, s), 4.22 (2H, q, J = 7.2 Hz), 7.23 - 7.43 (4H, m), 7.79 (1H, s).

Reference Example 67

Production of ethyl 1-methyl-2-(2-methylphenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate

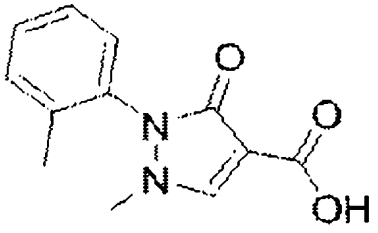


In the same manner as in Reference Example 64 and using ethyl 2-(2-methylphenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (3.1 g, 12 mmol) and methyl trifluoromethanesulfonate (2.5 mL) as starting materials, the title compound (2.1 g, 66%) was obtained as a pale-yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.23 (3H, t, J = 7.1 Hz), 2.10 (3H, s), 3.29 (3H, s), 4.09 - 4.20 (2H, m), 7.27 (1H, d, J = 7.6 Hz), 7.33 - 7.46 (3H, m), 8.49 (1H, s).

Reference Example 68

Production of 1-methyl-2-(2-methylphenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid



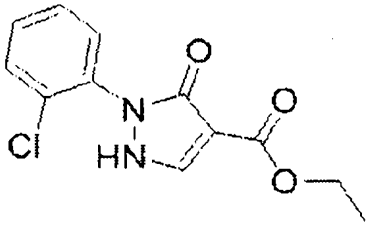
In the same manner as in Reference Example 65 and using

ethyl 1-methyl-2-(2-methylphenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (2.1 g, 8.2 mmol), tetrahydrofuran (6 mL), methanol (4 mL) and 4N aqueous sodium hydroxide solution (9 mL) as starting materials, the title compound (750 mg, 40%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.11 (3H, s), 3.29 (3H, s), 7.26 - 7.48 (4H, m), 8.42 (1H, s).

Reference Example 69

Production of ethyl 2-(2-chlorophenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate

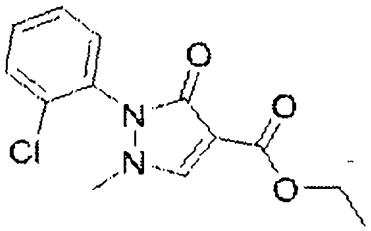


In the same manner as in Reference Example 63 and using (2-chlorophenyl)hydrazine·hydrochloride (5 g, 28 mmol), water (100 mL), potassium carbonate (8.5 g, 62 mmol) and diethyl ethoxymethylenemalonate (7.3 g, 34 mmol) as starting materials, the title compound (5.8 g, 78%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.28 (3H, t, J = 7.0 Hz), 4.22 (2H, q, J = 7.0 Hz), 7.48 - 7.60 (3H, m), 7.65 - 7.70 (1H, m), 7.81 (1H, s), 12.13 (1H, br s).

Reference Example 70

Production of ethyl 2-(2-chlorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate

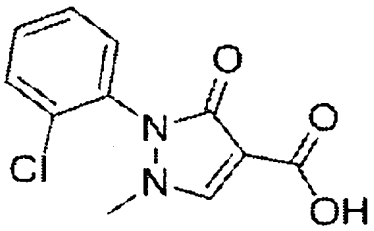


In the same manner as in Reference Example 64 and using ethyl 2-(2-chlorophenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (3.4 g, 12 mmol) and methyl

trifluoromethanesulfonate (3 mL) as starting materials, the title compound (2.8 g, 81%) was obtained as a white solid.
$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.23 (3H, t, J = 7.1 Hz), 3.32 (3H, s), 4.15 (2H, q, J = 7.1 Hz), 7.51 - 7.66 (3H, m), 7.70 - 7.75 (1H, m), 8.53 (1H, s).

Reference Example 71

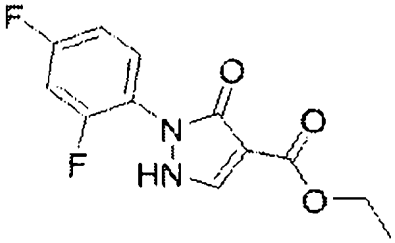
Production of 2-(2-chlorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid



In the same manner as in Reference Example 65 and using ethyl 2-(2-chlorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (2.8 g, 9.9 mmol), tetrahydrofuran (6 mL), methanol (5 mL) and 4N aqueous sodium hydroxide solution (8 mL) as starting materials, the title compound (2.3 g, 91%) was obtained as a white solid.
$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 3.34 (3H, s), 7.52 - 7.68 (3H, m), 7.72 - 7.77 (1H, m), 8.53 (1H, s), 11.75 (1H, s).

Reference Example 72

Production of ethyl 2-(2,4-difluorophenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate



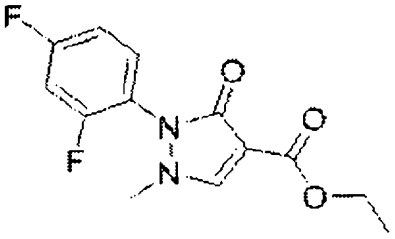
In the same manner as in Reference Example 63 and using (2,4-difluorophenyl)hydrazine·hydrochloride (5.1 g, 28 mmol), water (100 mL), potassium carbonate (8.6 g, 62 mmol) and diethyl ethoxymethylenemalonate (7.4 g, 34 mmol) as starting materials, the title compound (5.0 g, 66%) was obtained as a

pale-yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.27 (3H, t, J = 7.0 Hz), 4.22 (2H, q, J = 7.0 Hz), 7.22 - 7.31 (1H, m), 7.49 - 7.66 (2H, m), 7.83 (1H, s), 12.26 (1H, br s).

Reference Example 73

Production of ethyl 2-(2,4-difluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate

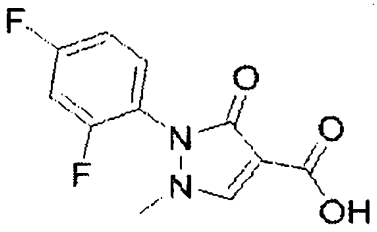


In the same manner as in Reference Example 64 and using ethyl 2-(2,4-difluorophenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (3.6 g, 13 mmol) and methyl trifluoromethanesulfonate (3 mL) as starting materials, the title compound (2.4 g, 65%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.23 (3H, t, J = 7.1 Hz), 3.38 (3H, s), 4.09 - 4.20 (2H, m), 7.26 - 7.35 (1H, m), 7.54 - 7.70 (2H, m), 8.54 (1H, s).

Reference Example 74

Production of 2-(2,4-difluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid

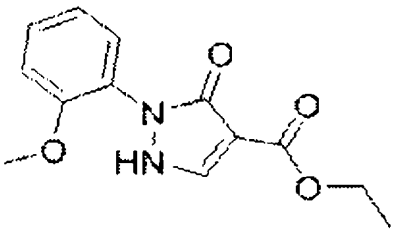


In the same manner as in Reference Example 65 and using ethyl 2-(2,4-difluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (2.4 g, 8.7 mmol), tetrahydrofuran (6 mL), methanol (5 mL) and 4N aqueous sodium hydroxide solution (8 mL) as starting materials, the title compound (1.8 g, 83%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 3.38 (3H, s), 7.26 - 7.37 (1H, m), 7.54 - 7.74 (2H, m), 8.53 (1H, s), 11.77 (1H, br s).

Reference Example 75

Production of ethyl 2-(2-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate

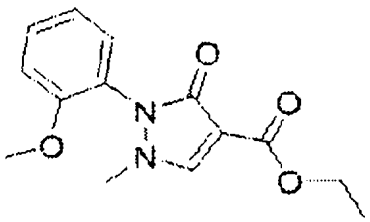


In the same manner as in Reference Example 63 and using (2-methoxyphenyl)hydrazine·hydrochloride (5.3 g, 30 mmol), water (100 mL), potassium carbonate (9.1 g, 66 mmol) and diethyl ethoxymethylenemalonate (7.8 g, 36 mmol) as starting materials, the title compound (6.1 g, 78%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.27 (3H, t, J = 7.0 Hz), 3.75 (3H, s), 4.21 (2H, q, J = 7.0 Hz), 7.02 - 7.09 (1H, m), 7.20 (1H, dd, J = 8.3, 1.1 Hz), 7.29 (1H, dd, J = 7.7, 1.7 Hz), 7.44 - 7.52 (1H, m), 7.74 (1H, s), 11.56 (1H, br s).

Reference Example 76

Production of ethyl 2-(2-methoxyphenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate

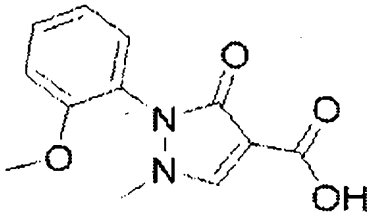


In the same manner as in Reference Example 64 and using ethyl 2-(2-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (3.6 g, 14 mmol) and methyl trifluoromethanesulfonate (3 mL) as starting materials, the title compound (2.5 g, 66%) was obtained as a pale-yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.22 (3H, t, J = 7.1 Hz), 3.28 (3H, s), 3.77 (3H, s), 4.08 - 4.18 (2H, m), 7.06 - 7.15 (1H, m), 7.23 (1H, dd, J = 8.4, 1.0 Hz), 7.34 (1H, dd, J = 7.7, 1.7 Hz), 7.49 - 7.58 (1H, m), 8.41 (1H, s).

Reference Example 77

Production of 2-(2-methoxyphenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid

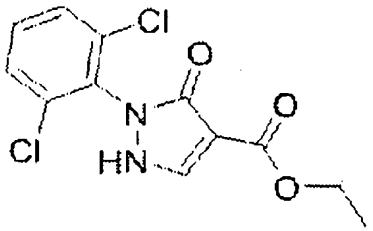


In the same manner as in Reference Example 65 and using ethyl 2-(2-methoxyphenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (2.5 g, 9.2 mmol), tetrahydrofuran (6 mL), methanol (5 mL) and 4N aqueous sodium hydroxide solution (8 mL) as starting materials, the title compound (1.9 g, 85%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 3.33 (3H, s), 3.79 (3H, s), 7.08 - 7.16 (1H, m), 7.26 (1H, dd, J = 8.4, 1.0 Hz), 7.41 (1H, dd, J = 7.7, 1.7 Hz), 7.53 - 7.62 (1H, m), 8.47 (1H, s), 11.79 (1H, s).

Reference Example 78

Production of ethyl 2-(2,6-dichlorophenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate



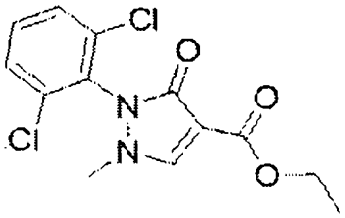
In the same manner as in Reference Example 63 and using (2,6-dichlorophenyl)hydrazine·hydrochloride (4.8 g, 23 mmol), water (100 mL), potassium carbonate (6.9 g, 50 mmol) and diethyl ethoxymethylenemalonate (5.9 g, 27 mmol) as starting

materials, the title compound (5.0 g, 73%) was obtained as a pale-yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.28 (3H, t, J = 7.0 Hz), 4.22 (2H, q, J = 7.0 Hz), 7.57 - 7.63 (1H, m), 7.68 - 7.73 (2H, m), 7.87 (1H, s), 12.37 (1H, br s).

Reference Example 79

Production of ethyl 2-(2,6-dichlorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate

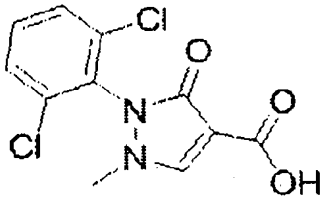


In the same manner as in Reference Example 64 and using ethyl 2-(2,6-dichlorophenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (3.7 g, 12 mmol) and methyl trifluoromethanesulfonate (3 mL) as starting materials, the title compound (3.4 g, 87%) was obtained as a pale-yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.24 (3H, t, J = 7.2 Hz), 3.35 (3H, s), 4.15 (2H, q, J = 7.2 Hz), 7.63 - 7.70 (1H, m), 7.74 - 7.78 (2H, m), 8.59 (1H, s).

Reference Example 80

Production of 2-(2,6-dichlorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid



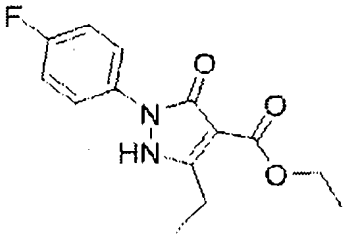
In the same manner as in Reference Example 65 and using ethyl 2-(2,6-dichlorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (3.4 g, 11 mmol), tetrahydrofuran (6 mL), methanol (5 mL) and 4N aqueous sodium hydroxide solution (8 mL) as starting materials, the title compound (2.8 g, 90%)

was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 3.35 (3H, s), 7.63 - 7.71 (1H, m), 7.74 - 7.80 (2H, m), 8.57 (1H, s), 11.79 (1H, br s).

Reference Example 81

Production of ethyl 5-ethyl-2-(4-fluorophenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate

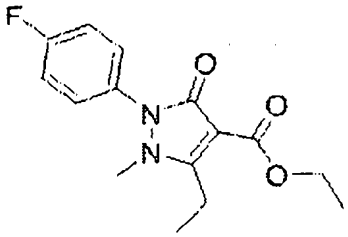


To a solution of (4-fluorophenyl)hydrazine (5.5 g, 43 mmol) in acetic acid (70 mL) was added diethylpropanoylpropanedionate (11 g, 52 mmol), and the mixture was stirred at 60°C for 3.5 hr. The solvent was evaporated under reduced pressure, and hexane was added to the residue. The mixture was filtered to remove insoluble materials. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=10/90→50/50) to give the title compound (3.7 g, 31%) as a pale-yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.19 (3H, t, J = 7.6 Hz), 1.29 (3H, t, J = 7.2 Hz), 2.74 (2H, q, J = 7.6 Hz), 4.24 (2H, q, J = 7.2 Hz), 7.26 - 7.40 (2H, m), 7.64 - 7.75 (2H, m).

Reference Example 82

Production of ethyl 5-ethyl-2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate



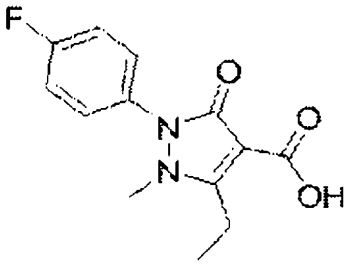
In the same manner as in Reference Example 64 and using ethyl 5-ethyl-2-(4-fluorophenyl)-3-oxo-2,3-dihydro-1H-

pyrazole-4-carboxylate (3.1 g, 11 mmol) and methyl trifluoromethanesulfonate (3.7 mL) as starting materials, the title compound (1.9 g, 57%) was obtained as a pale-yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.14 - 1.26 (6H, m), 2.99 (2H, q, J = 7.6 Hz), 3.31 (3H, s), 4.15 (2H, q, J = 7.1 Hz), 7.38 (4H, d, J = 6.8 Hz).

Reference Example 83

Production of 5-ethyl-2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid

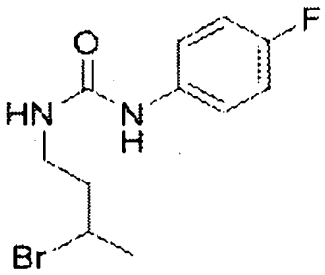


In the same manner as in Reference Example 65 and using ethyl 5-ethyl-2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (1.9 g, 6.4 mmol), tetrahydrofuran (4 mL), methanol (4 mL) and 4N aqueous sodium hydroxide solution (5 mL) as starting materials, the title compound (1.5 g, 92%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.20 (3H, t, J = 7.6 Hz), 3.02 (2H, q, J = 7.6 Hz), 3.39 (3H, s), 7.37 - 7.49 (2H, m), 7.49 - 7.59 (2H, m), 12.23 (1H, br s).

Reference Example 84

Production of 1-(3-bromobutyl)-3-(4-fluorophenyl)urea



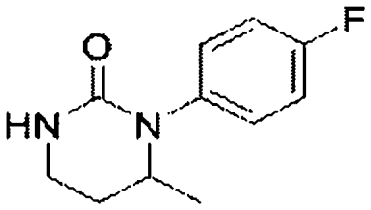
To a solution of 3-bromobutane-1-aminehydrobromide (2270

mg, 9.7 mmol) in pyridine (18 mL) was slowly added 1-fluoro-4-isocyanatobenzene (1600 mg, 12 mmol) under ice-cooling, and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure, ethyl acetate/tetrahydrofuran and 0.5N aqueous hydrochloric acid solution were added to the residue, and the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×3). The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was washed with ethyl acetate/hexane (=1/1) to give the title compound (1750 mg, 62%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.70 (3H, d, J = 6.6 Hz), 1.89 - 2.01 (2H, m), 3.06 - 3.19 (1H, m), 3.22 - 3.32 (1H, m), 4.25 - 4.37 (1H, m), 6.23 (1H, t, J = 5.8 Hz), 7.00 - 7.08 (2H, m), 7.35 - 7.42 (2H, m), 8.47 (1H, s).

Reference Example 85

Production of 1-(4-fluorophenyl)-6-methyltetrahydropyrimidin-2(1H)-one



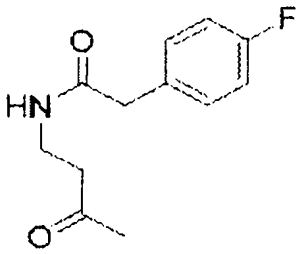

To a solution of 1-(3-bromobutyl)-3-(4-fluorophenyl)urea (1750 mg, 6.1 mmol) in N,N-dimethylformamide (30 mL) was added potassium tert-butoxide (920 mg, 7.0 mmol), and the mixture was stirred at 50°C for 6 hr. The solvent was evaporated under reduced pressure, and ethyl acetate/tetrahydrofuran and 6N aqueous hydrochloric acid solution were added to the residue. The aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×3). The combined organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica

gel column chromatography (NH silica gel, ethyl acetate/hexane=50/50→100/0) to give the title compound (490 mg, 39%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.02 (3H, d, J = 6.4 Hz), 1.66 - 1.81 (1H, m), 1.96 - 2.13 (1H, m), 3.14 - 3.31 (2H, m), 3.85 - 3.96 (1H, m), 6.57 (1H, br s), 7.10 - 7.26 (4H, m).

Reference Example 86

Production of 2-(4-fluorophenyl)-N-(3-oxobutyl)acetamide

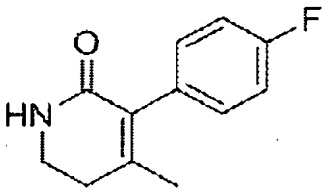


To a solution of 4-aminobutan-2-one hydrochloride (2.95 g, 24 mmol) in N,N-dimethylacetamide (50 mL) was slowly added (4-fluorophenyl)acetylchloride (4.90 g, 29 mmol) under ice-cooling, and the mixture was stirred at room temperature for 2 hr. Triethylamine (4.80 g, 48 mmol) was added to the mixture, and the mixture was stirred at room temperature for 17 hr. Ethyl acetate/tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the mixture, and the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×3). The combined organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=50/50→100/0) to give the title compound (2.10 g, 39%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.07 (3H, s), 2.58 (2H, t, J = 6.7 Hz), 3.17 - 3.25 (2H, m), 3.36 (2H, s), 7.05 - 7.16 (2H, m), 7.21 - 7.30 (2H, m), 8.04 (1H, br. s.).

Reference Example 87

Production of 3-(4-fluorophenyl)-4-methyl-5,6-dihydropyridin-2(1H)-one

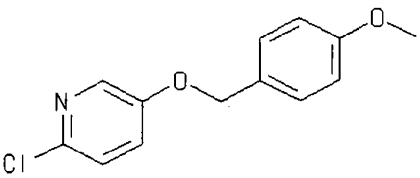


To a solution of 2-(4-fluorophenyl)-N-(3-oxobutyl)acetamide (1.95 g, 8.7 mmol) in ethanol (120 mL) was added 20 wt% sodium ethoxide/ethanol solution (6.54 g, 19 mmol), and the mixture was stirred at 80°C for 8 hr. The solvent was evaporated under reduced pressure, ethyl acetate/tetrahydrofuran and 1N aqueous hydrochloric acid solution were added to the residue, and the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×3). The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was washed with ethyl acetate/hexane (1/10) to give the title compound (1.36 g, 76%) as a brown solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.73 (3H, s), 2.39 (2H, t, J = 7.0 Hz), 3.28 (2H, td, J = 7.0, 2.7 Hz), 7.14 (4H, d, J = 7.6 Hz), 7.45 (1H, br s).

Reference Example 88

Production of 2-chloro-5-[(4-methoxybenzyl)oxy]pyridine



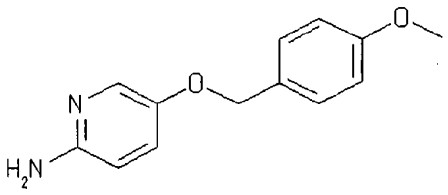
To a solution of 2-chloro-5-hydroxypyridine (50 g, 0.386 mol) and potassium carbonate (80 g, 0.579 mol) in N,N-dimethylformamide (300 mL) was added p-methoxybenzyl chloride (66.5 g, 0.425 mol), and the mixture was stirred at 80°C for 4 hr. Ethyl acetate and water were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and

filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with methanol to give the title compound (61.3 g, 64%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 3.76 (3H, s), 5.10 (2H, s), 6.82 - 7.06 (2H, m), 7.34 - 7.46 (3H, m), 7.50 - 7.59 (1H, m), 8.17 (1H, d, J = 2.6 Hz).

Reference Example 89

Production of 5-[(4-methoxybenzyl)oxy]pyridin-2-amine

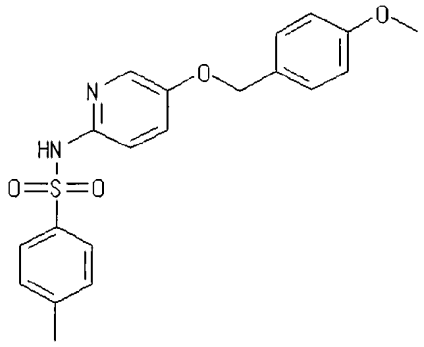


To a solution of 2-chloro-5-[(4-methoxybenzyl)oxy]pyridine (45 g, 180 mmol), tris(dibenzylideneacetone)dipalladium(0) (5 g, 5.46 mmol) and (2-biphenyl)dicyclohexylphosphine (5.1 g, 14.56 mmol) in tetrahydrofuran (500 mL) was added dropwise bis(trimethylsilyl)amidelithium (1.6 mol/L tetrahydrofuran solution, 170 mL, 273.2 mmol) at room temperature, and the mixture was stirred at 80°C for 4 hr under a nitrogen atmosphere. 2N Hydrochloric acid (300 mL, 600 mmol) was added to the reaction mixture, and the mixture was stirred at room temperature for 1 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with water and twice with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with methanol to give the title compound (34.4 g, 82%) as a yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 3.75 (3H, s), 4.90 (2H, s), 5.45 (2H, s), 6.40 (1H, d, J = 8.9 Hz), 6.86 - 6.98 (2H, m), 7.14 (1H, dd, J = 8.9, 3.0 Hz), 7.28 - 7.38 (2H, m), 7.67 (1H, d, J = 2.6 Hz).

Reference Example 90

Production of N-{5-[(4-methoxybenzyl)oxy]pyridin-2-yl}-4-methylbenzenesulfonamide

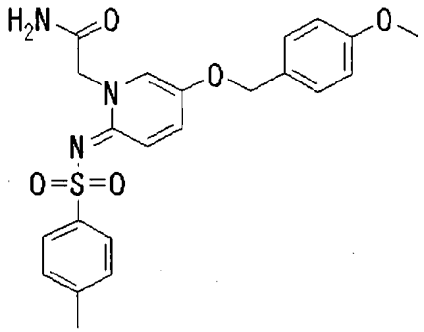


To a solution of 5-[(4-methoxybenzyl)oxy]pyridin-2-amine (24 g, 104 mmol) in pyridine (210 mL) was added 4-methylbenzenesulfonyl chloride (20.9 g, 110 mmol) at 0°C, and the mixture was stirred at room temperature for 4 hr. The reaction mixture was concentrated, the residue was washed with saturated aqueous sodium hydrogen carbonate solution and ethyl acetate to give the title compound (37 g, 93%) as a pale-red solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.34 (3H, s), 3.75 (3H, s), 4.98 (2H, s), 6.82 - 7.00 (2H, m), 7.07 (1H, d, J = 8.9 Hz), 7.26 - 7.46 (5H, m), 7.66 - 7.77 (2H, m), 7.91 (1H, d, J = 2.6 Hz), 10.74 (1H, br s).

Reference Example 91

Production of 2-[5-[(4-methoxybenzyl)oxy]-2-{[(4-methylphenyl)sulfonyl]imino}pyridin-1(2H)-yl]acetamide



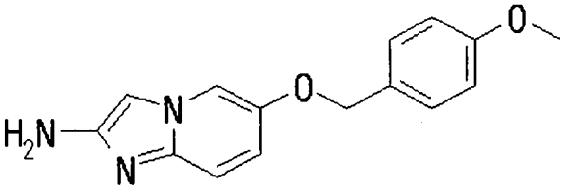
To a suspension of N-{5-[(4-methoxybenzyl)oxy]pyridin-2-yl}-4-methylbenzenesulfonamide (10.0 g, 26.0 mmol) in N,N-

dimethylformamide (85 mL) were added N,N-diisopropylethylamine (6.8 mL, 39.0 mmol) and iodoacetamide (5.77 g, 31.0 mmol), and the mixture was stirred at 60°C for 5 hr. After cooling to room temperature, ethyl acetate and water were added, and the mixture was extracted 3 times with a mixed solution of ethyl acetate and tetrahydrofuran. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (34.4 g, 75%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.33 (3H, s), 3.75 (3H, s), 4.82 (2H, s), 4.89 (2H, s), 6.81 - 7.03 (2H, m), 7.20 - 7.41 (6H, m), 7.60 - 7.69 (3H, m), 7.76 (1H, d), 7.92 (1H, d, J = 3.0 Hz).

Reference Example 92

Production of 6-[(4-methoxybenzyl)oxy]imidazo[1,2-a]pyridin-2-amine



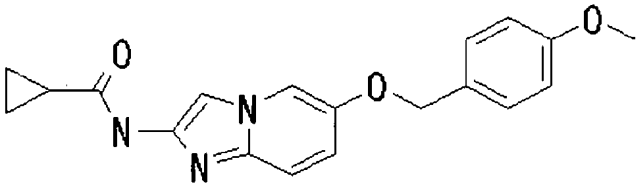
To a suspension of 2-[5-[(4-methoxybenzyl)oxy]-2-{[(4-methylphenyl)sulfonyl]imino}pyridin-1(2H)-yl]acetamide (20.8 g, 47.1 mmol) in tetrahydrofuran (200 mL) was added trifluoroacetic acid anhydride (49.5 g, 235.5 mmol) at 0°C, and the mixture was stirred for 1 hr. Methanol (100 mL) was added to the reaction mixture, 8N aqueous sodium hydroxide solution was added until pH reached 12 to 13, and the mixture was stirred at room temperature for 3 hr. Water and ethyl acetate were added to the reaction mixture, and the mixture was extracted 4 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated

under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (8.6 g, 68%) as a brown solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 3.76 (3H, s), 4.90 (2H, s), 4.93 (2H, s), 6.81 (1H, dd, J = 9.5, 2.4 Hz), 6.88 - 7.00 (3H, m), 7.08 (1H, d, J = 9.6 Hz), 7.32 - 7.44 (2H, m), 8.12 (1H, d, J = 1.7 Hz).

Reference Example 93

Production of N-{6-[(4-methoxybenzyl)oxy]imidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide

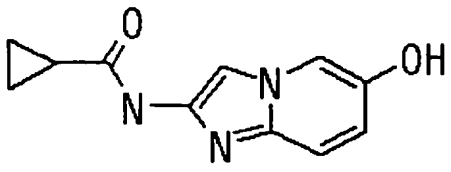


To a solution of 6-[(4-methoxybenzyl)oxy]imidazo[1,2-a]pyridin-2-amine (8.5 g, 31.6 mmol) in N,N-dimethylacetamide (80 mL) was added a solution of cyclopropanecarbonyl chloride (3.43 mL, 37.9 mmol) in N,N-dimethylacetamide (20 mL) at 0°C, and the mixture was stirred at 0°C for 3 hr. The reaction mixture was diluted with water, and the precipitate was collected by filtration and washed with water and ethyl acetate to give the title compound (8.9 g, 83%) as a gray solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.62 - 0.89 (4H, m), 1.87 - 1.96 (1H, m), 3.76 (3H, s), 4.96 (2H, s), 6.89 - 6.99 (2H, m), 7.02 (1H, dd, J = 9.6, 2.3 Hz), 7.32 (1H, d, J = 9.6 Hz), 7.37 - 7.45 (2H, m), 7.96 (1H, s), 8.36 (1H, d, J = 1.7 Hz), 10.88 (1H, s).

Reference Example 94

Production of N-(6-hydroxyimidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide

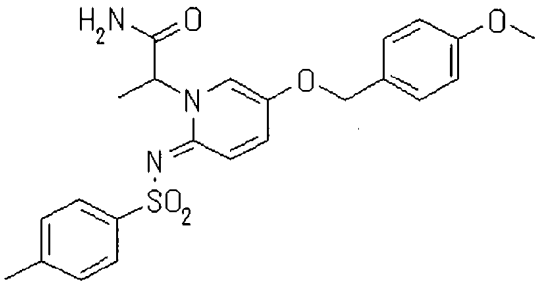


To a solution of N-{6-[(4-methoxybenzyl)oxy]imidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide (10.1 g, 29.9 mmol) and anisole (25.97 mL, 239.2 mmol) in trifluoromethylbenzene (200 mL) was added trifluoroacetic acid (40.4 mL), and the mixture was stirred at room temperature for 3 hr. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted 5 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (5.7 g, 88%) as a pale-brown solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.67 - 0.86 (4H, m), 1.83 - 1.97 (1H, m), 6.89 (1H, dd, J = 9.6, 2.3 Hz), 7.25 (1H, d, J = 9.4 Hz), 7.91 (1H, s), 7.96 - 8.00 (1H, m), 9.43 (1H, br s), 10.81 (1H, s).

Reference Example 95

Production of 2-[5-[(4-methoxybenzyl)oxy]-2-{[(4-methylphenyl)sulfonyl]imino}pyridin-1(2H)-yl]propanamide



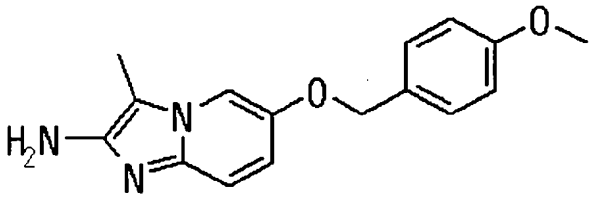
To a solution of N-{5-[(4-methoxybenzyl)oxy]pyridin-2-yl}-4-methylbenzenesulfonamide (3 g, 7.80 mmol) in N,N-dimethylformamide (30 mL) were added 2-bromopropanamide (2.82 g, 18.4 mmol) and N,N-diisopropylethylamine (4.04 mL, 23.4 mmol), and the mixture was stirred at room temperature for 2 days. Ethyl acetate and water were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine,

dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=3/1→ethyl acetate alone) to give the title compound (2.64 g, 74%) as a colorless oil.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.65 (3H, d, J = 7.4 Hz), 2.33 (3H, s), 3.75 (3H, s), 4.83 - 5.12 (2H, m), 5.80 (1H, q, J = 7.2 Hz), 6.86 - 6.98 (2H, m), 7.19 - 7.47 (6H, m), 7.59 - 7.83 (5H, m).

Reference Example 96

Production of 6-[(4-methoxybenzyl)oxy]-3-methylimidazo[1,2-a]pyridin-2-amine



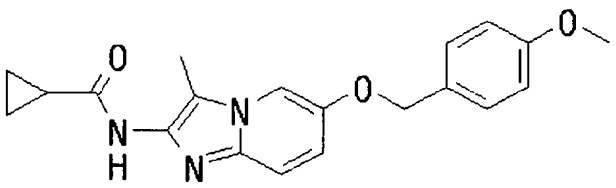
To a suspension of 2-[5-[(4-methoxybenzyl)oxy]-2-{[(4-methylphenyl)sulfonyl]imino}pyridin-1(2H)-yl]propanamide (2.6 g, 5.71 mmol) in tetrahydrofuran (25 mL) was added trifluoroacetic acid anhydride (2.35 mL, 17.1 mmol) at 0°C, and the mixture was stirred at room temperature for 1 hr. 8N Aqueous sodium hydroxide solution was added to the reaction mixture until it reached pH 12 to 13, and the mixture was stirred at 50°C for 5 hr. Water and ethyl acetate were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (1.0 g, 68%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.26 (3H, s), 3.76 (3H, s), 4.81 (2H, s), 5.01 (2H, s), 6.80 (1H, dd, J = 9.4, 2.3 Hz), 6.91 - 6.99 (2H, m), 7.09 (1H, d, J = 9.4 Hz), 7.31 - 7.48 (2H, m),

7.67 (1H, d, J = 2.1 Hz).

Reference Example 97

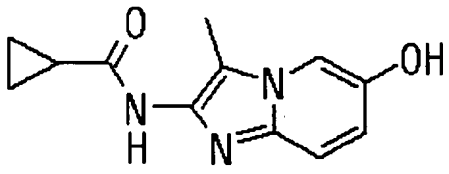
Production of N-{6-[(4-methoxybenzyl)oxy]-3-methylimidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide



To a solution of 6-[(4-methoxybenzyl)oxy]-3-methylimidazo[1,2-a]pyridin-2-amine (1.0 g, 3.53 mmol) in N,N-dimethylacetamide (10 mL) was added cyclopropanecarbonyl chloride (352 μL, 3.88 mmol), and the mixture was stirred at 0°C for 2 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (750 mg, 60%) as a slightly-yellow solid. $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.64 - 0.93 (4H, m), 1.80 - 1.89 (1H, m), 2.28 (3H, s), 3.76 (3H, s), 5.06 (2H, s), 6.91 - 7.08 (3H, m), 7.34 - 7.48 (3H, m), 7.91 (1H, d, J = 1.9 Hz), 10.12 (1H, s).

Reference Example 98

Production of N-(6-hydroxy-3-methylimidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide



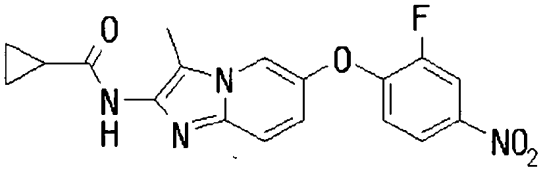
To a solution of N-{6-[(4-methoxybenzyl)oxy]-3-methylimidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide (700 mg, 1.99 mmol) and anisole (1.73 mL, 15.9 mmol) in

trifluoromethylbenzene (7 mL) was added trifluoroacetic acid (1.4 mL), and the mixture was stirred at room temperature for 2 hr. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted 4 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate to give the title compound (65 mg, 14%) as a slightly-yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.70 - 0.82 (4H, m), 1.73 - 1.90 (1H, m), 2.21 (3H, s), 6.87 - 6.98 (1H, m), 7.32 (1H, d, J = 9.6 Hz), 7.58 (1H, d, J = 1.9 Hz), 9.51 (1H, br s), 10.06 (1H, s).

Reference Example 99

Production of N-[6-(2-fluoro-4-nitrophenoxy)-3-methylimidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide



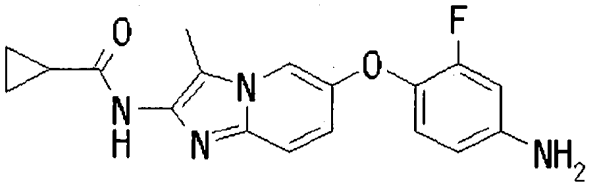
To a solution of N-(6-hydroxy-3-methylimidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide (65 mg, 0.281 mmol) and 1,2-difluoro-4-nitrobenzene (37 μL, 0.337 mmol) in dimethyl sulfoxide (1 mL) was added cesium carbonate (137 mg, 0.422 mmol), and the mixture was stirred overnight at room temperature. Ethyl acetate and saturated aqueous ammonium chloride solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=1/1→ethyl acetate alone) to give the title

compound (80 mg, 77%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.68 - 0.91 (4H, m), 1.76 - 1.92 (1H, m), 2.29 (3H, s), 7.12 - 7.28 (2H, m), 7.60 (1H, d, J = 9.4 Hz), 7.96 - 8.11 (1H, m), 8.37 (1H, dd, J = 10.9, 2.7 Hz), 8.53 (1H, d, J = 1.9 Hz), 10.27 (1 H, br s).

Reference Example 100

Production of N-[6-(4-amino-2-fluorophenoxy)-3-methylimidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide

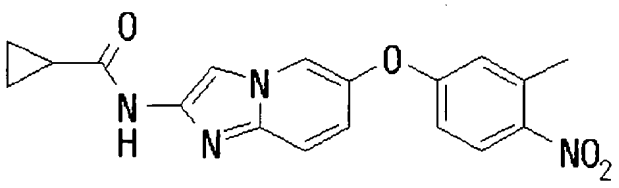


A mixed solution of N-[6-(2-fluoro-4-nitrophenoxy)-3-methylimidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (80 mg, 0.216 mmol), reduced iron (64 mg, 1.08 mmol) and ammonium chloride (116 mg, 2.16 mmol) in ethanol (2 mL)/water (0.5 mL) was stirred at 80°C for 3 hr. The reaction mixture was diluted with ethyl acetate and filtered through celite. Water was added to the filtrate, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure to give the title compound (60 mg, 82%) as a slightly yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.77 (4H, d, J = 5.9 Hz), 1.80 - 1.91 (1H, m), 2.22 (3H, s), 5.33 (2H, s), 6.33 - 6.42 (1H, m), 6.49 (1H, dd, J = 13.4, 2.6 Hz), 6.88 - 7.04 (2H, m), 7.45 (1H, d, J = 9.8 Hz), 7.85 (1H, d, J = 2.1 Hz), 10.17 (1H, br s).

Reference Example 101

Production of N-[6-(3-methyl-4-nitrophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide

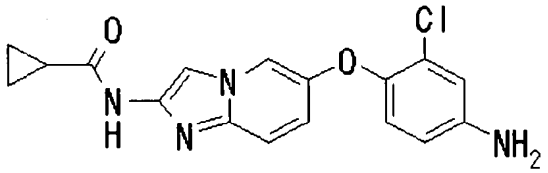


To a solution of N-(6-hydroxyimidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide (200 mg, 0.92 mmol) and 4-fluoro-2-methyl-1-nitrobenzene (171.3 mg, 1.1 mmol) in dimethyl sulfoxide (2 mL) was added cesium carbonate (450 mg, 1.38 mmol), and the mixture was stirred at room temperature for 6 hr. Ethyl acetate and saturated aqueous ammonium chloride solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The residue was washed with ethyl acetate and collected by filtration to give the title compound (232 mg, 72%) as a brown solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.74 - 0.88 (4H, m), 1.88 - 1.97 (1H, m), 2.52 (3H, s), 7.03 (1H, dd, J = 9.1, 2.8 Hz), 7.09 - 7.18 (2H, m), 7.52 (1H, d, J = 9.4 Hz), 7.99 - 8.16 (2H, m), 8.68 (1H, dd, J = 2.5, 0.8 Hz), 11.02 (1H, s).

Reference Example 102

Production of N-[6-(4-amino-2-chlorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide

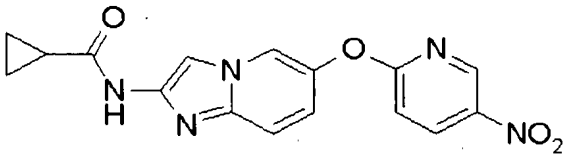


To a solution of N-(6-hydroxyimidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide (200 mg, 0.921 mmol) and 4-fluoro-3-chloro-1-nitrobenzene (193 mg, 1.11 mmol) in dimethyl sulfoxide (2 mL) was added cesium carbonate (450 mg, 1.38 mmol), and the mixture was stirred at room temperature for 6 hr. Ethyl acetate and saturated aqueous ammonium chloride

solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, and the solvent was evaporated under reduced pressure. A mixed solution of the obtained residue, reduced iron (271 mg, 4.61 mmol) and ammonium chloride (493 mg, 9.21 mmol) in ethanol (2 mL)/tetrahydrofuran (2 mL)/water (1 mL) was stirred at 80°C for 7 hr. The reaction mixture was diluted with ethyl acetate and tetrahydrofuran, and filtered through celite. Water was added to the filtrate, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=2/1→ethyl acetate alone) to give the title compound (177.5 mg, 56%) as a white solid. $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.67 - 0.89 (4H, m), 1.82 - 1.96 (1H, m), 5.33 (2H, s), 6.54 (1H, dd, J = 8.7, 2.6 Hz), 6.72 (1H, d, J = 2.6 Hz), 6.93 (1H, d, J = 8.7 Hz), 6.99 (1H, dd, J = 9.6, 2.5 Hz), 7.38 (1H, d, J = 9.6 Hz), 8.00 (1H, s), 8.17 (1H, d, J = 1.9 Hz), 10.89 (1H, s).

Reference Example 103

Production of N-{6-[(5-nitropyridin-2-yl)oxy]imidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide



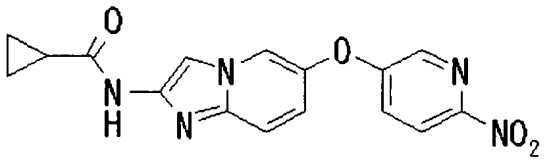
To a solution of N-(6-hydroxyimidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide (200 mg, 0.921 mmol) and 2-chloro-5-nitropyridine (175 mg, 1.1 mmol) in dimethyl sulfoxide (3 mL) was added cesium carbonate (450 mg, 1.38 mmol), and the mixture was stirred at room temperature for 3 hr. Ethyl acetate, tetrahydrofuran and water were added to the reaction mixture, and the mixture was extracted 3 times with ethyl

acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (111 mg, 36%) as a brown solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.67 - 0.91 (4H, m), 1.90 - 1.98 (1H, m), 7.19 (1H, dd, J = 9.6, 2.3 Hz), 7.37 (1H, d, J = 9.1 Hz), 7.50 (1H, d, J = 9.6 Hz), 8.08 (1H, s), 8.65 (1H, dd, J = 9.1, 2.8 Hz), 8.69 - 8.74 (1H, m), 9.05 (1H, d, J = 2.3 Hz), 11.02 (1H, s).

Reference Example 104

Production of N-{6-[(6-nitropyridin-3-yl)oxy]imidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide

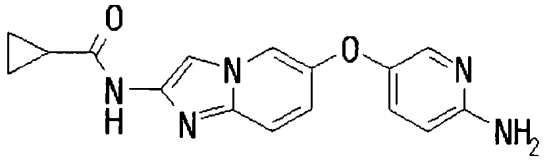


Using N-(6-hydroxyimidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide (200 mg, 0.921 mmol), 5-chloro-2-nitropyridine (218.8 mg, 1.38 mmol), dimethyl sulfoxide (5 mL) and cesium carbonate (450 mg, 1.38 mmol), and in the same manner as in the production method of N-[6-(3-methyl-4-nitrophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (Reference Example 101), the title compound (190 mg, 61%) was obtained as a yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.70 - 0.88 (4H, m), 1.88 - 1.98 (1H, m), 7.22 (1H, dd, J = 9.6, 2.3 Hz), 7.55 (1H, d, J = 9.6 Hz), 7.74 (1H, dd, J = 9.0, 2.9 Hz), 8.09 (1H, s), 8.33 (1H, d, J = 9.4 Hz), 8.50 (1H, d, J = 2.5 Hz), 8.76 (1H, dd, J = 2.5, 0.8 Hz), 11.02 (1H, s).

Reference Example 105

Production of N-{6-[(6-aminopyridin-3-yl)oxy]imidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide

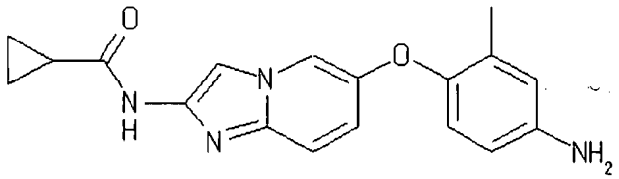


A mixed solution of N-{6-[(6-nitropyridin-3-yl)oxy]imidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide (184 mg, 0.542 mmol), reduced iron (173 mg, 2.95 mmol) and ammonium chloride (315 mg, 5.89 mmol) in ethanol (2 mL) and water (0.5 mL) was stirred at 80°C for 1 hr. The reaction mixture was diluted with ethyl acetate, and filtered through celite. Water was added to the filtrate, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate→ethyl acetate/methanol=95/5) to give the title compound (75 mg, 45%) as a yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.70 - 0.87 (4H, m), 1.84 - 1.94 (1H, m), 5.87 (2H, s), 6.48 (1H, d, J = 8.9 Hz), 7.04 (1H, dd, J = 9.6, 2.5 Hz), 7.24 (1H, dd, J = 8.9, 3.0 Hz), 7.39 (1H, d, J = 9.6 Hz), 7.79 (1H, d, J = 2.5 Hz), 8.00 (1H, s), 8.29 (1H, dd, J = 2.5, 0.8 Hz), 10.91 (1H, s).

Reference Example 106

N-[6-(4-amino-2-methylphenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide



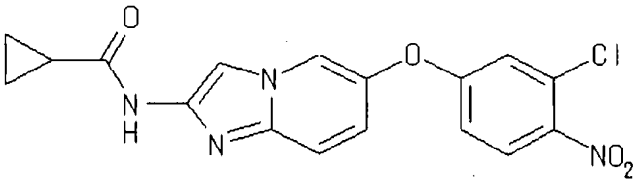
To a solution of N-(6-hydroxyimidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide (300 mg, 1.38 mmol) and 4-fluoro-3-methyl-1-nitrobenzene (279 mg, 1.80 mmol) in dimethyl sulfoxide (3 mL) was added cesium carbonate (674 mg, 2.07 mmol), and the mixture was stirred at room temperature for 24

hr. Ethyl acetate, tetrahydrofuran and water were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, and the solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration. A mixed solution of the obtained solid, reduced iron (406 mg, 6.9 mmol) and ammonium chloride (738 mg, 13.8 mmol) in ethanol (5 mL)/tetrahydrofuran (3 mL)/water (2 mL) was stirred at 80°C for 6 hr. The reaction mixture was diluted with ethyl acetate and tetrahydrofuran, and filtered through celite. Water was added to the filtrate, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=2/1→ethyl acetate alone) to give the title compound (190 mg, 43%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.60 - 0.92 (4H, m), 1.79 - 1.93 (1H, m), 2.06 (3H, s), 4.93 (2H, s), 6.35 - 6.44 (1H, m), 6.48 (1H, d, J = 2.3 Hz), 6.69 (1H, d, J = 8.5 Hz), 6.97 (1H, dd, J = 9.6, 2.3 Hz), 7.36 (1H, d, J = 9.6 Hz), 7.97 (1H, s), 8.03 - 8.06 (1H, m), 10.87 (1H, s).

Reference Example 107

Production of N-[6-(3-chloro-4-nitrophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide



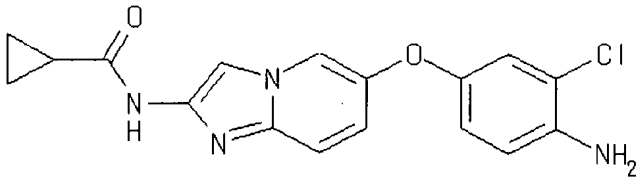
Using N-(6-hydroxyimidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide (200 mg, 0.92 mmol), 4-fluoro-2-chloro-1-nitrobenzene (315 mg, 1.79 mmol), dimethyl sulfoxide (4 mL) and cesium carbonate (675 mg, 2.07 mmol), and in the

same manner as in Reference Example 101, the title compound (382 mg, 74%) was obtained as a yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.68 - 0.92 (4H, m), 1.88 - 1.97 (1H, m), 7.13 - 7.24 (2H, m), 7.44 (1H, d, J = 2.6 Hz), 7.53 (1H, d), 8.04 - 8.20 (2H, m), 8.64 - 8.81 (1H, m), 11.02 (1H, s).

Reference Example 108

Production of N-[6-(4-amino-3-chlorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide

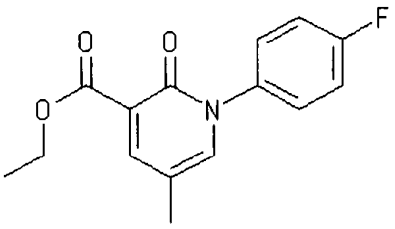


Using N-[6-(3-chloro-4-nitrophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (300 mg, 0.805 mmol), reduced iron (237 mg, 4.02 mmol), ammonium chloride (430 mg, 8.05 mmol), ethanol (2 mL), tetrahydrofuran (2 mL) and water (0.5 mL), and in the same manner as in Reference Example 105, the title compound (166 mg, 60%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.58 - 0.94 (4H, m), 1.85 - 1.97 (1H, m), 5.20 (2H, s), 6.73 - 6.91 (2H, m), 6.96 - 7.06 (2H, m), 7.40 (1H, d, J = 9.6 Hz), 8.01 (1H, s), 8.34 (1H, d, J = 1.5 Hz), 10.91 (1H, s).

Reference Example 109

Production of ethyl 1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate



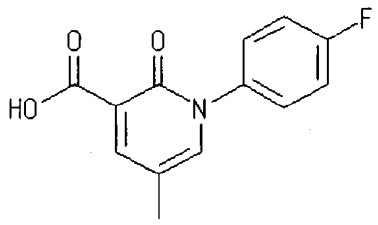
To a solution (30 mL) of diethyl[(2E)-3-ethoxy-2-methylprop-2-en-1-ylidene]propanedionate (160 mg, 0.467 mmol) and piperidine (0.2 mL) in ethanol was added 4-fluoroaniline

(1.12 mL, 11.7 mmol) was added, and the mixture was stirred at 80°C for 17 hr. The reaction mixture was concentrated, and the obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=1/2→1/1) to give a brown solid. The brown solid was washed with diethyl ether and collected by filtration to give the title compound (1.2 g, 37%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.25 (3H, t, J = 7.1 Hz), 2.09 (3H, s), 4.21 (2H, q, J = 7.2 Hz), 7.26 - 7.41 (2H, m), 7.43 - 7.54 (2H, m), 7.76 (1H, dd, J = 2.6, 0.9 Hz), 7.98 (1H, d, J = 2.6 Hz).

Reference Example 110

Production of 1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

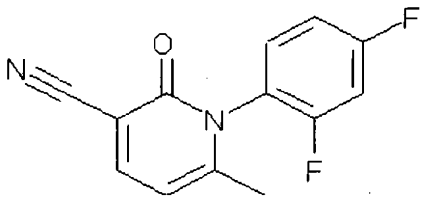


To a solution of ethyl 1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (1.2 g, 4.36 mmol) in methanol (12 mL) was added 1N aqueous sodium hydroxide solution (10 mL, 10 mmol), and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated, and the obtained residue was diluted with ethyl acetate and water and extracted with water. The aqueous layer was treated with 1N hydrochloric acid (20 mL, 20 mmol), and the precipitate was collected by filtration to give a white solid. The white solid was washed with water to give the title compound (730 mg, 68%).

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.20 (3H, s), 7.31 - 7.52 (2H, m), 7.55 - 7.67 (2H, m), 8.07 (1H, dd, J = 2.6, 0.9 Hz), 8.39 (1H, d, J = 2.5 Hz), 14.48 (1H, br s).

Reference Example 111

Production of 1-(2,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile

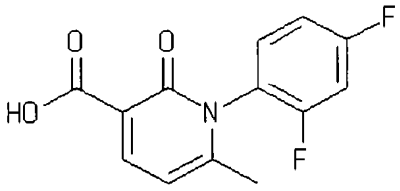


To a solution of 2-cyano-N-(2,4-difluorophenyl)acetamide (5.5 g, 28 mmol) and (3E)-4-methoxybut-3-en-2-one (3.65 g, 36.5 mmol) in dimethyleneglycol monomethylether (50 mL) was added 1,4-diazabicyclo[2.2.2]octane (3.14 g, 28 mmol), and the mixture was stirred at 120°C for 12 hr. The reaction mixture was diluted with 2N hydrochloric acid, tetrahydrofuran and ethyl acetate, and extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate to give a slightly yellow solid. The slightly yellow solid was suspended in tetrahydrofuran at 80°C, and the suspension was stirred for 30 min. The suspension was filtrated, and the obtained solid was washed with tetrahydrofuran to give the title compound (650 mg, 9.4%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.07 (3H, s), 6.38 - 6.75 (1H, m), 7.17 - 7.39 (1H, m), 7.53 - 7.74 (2H, m), 8.05 - 8.39 (1H, m).

Reference Example 112

Production of 1-(2,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid



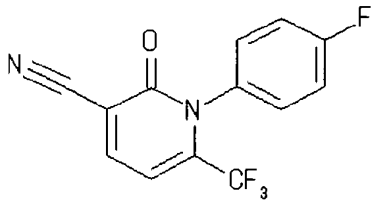
A solution of 1-(2,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (600 mg, 2.44 mmol) in conc. sulfuric acid (3 mL)/water (3 mL) was stirred at 120°C for 17

hr. The reaction solution was allowed to cool to room temperature, and alkalified with 8N aqueous sodium hydroxide solution. The aqueous layer was washed with ethyl acetate. The aqueous layer was acidified with 2N hydrochloric acid and the precipitate was collected by filtration and washed with water to give the title compound (600 mg, 93%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.15 (3H, s), 6.83 (1H, d, J = 8.1 Hz), 7.28 - 7.43 (1H, m), 7.56 - 7.82 (2H, m), 8.44 (1H, d, J = 7.6 Hz), 13.74 (1 H, br s).

Reference Example 113

Production of 1-(4-fluorophenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

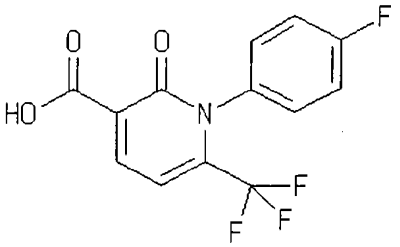



To a solution of 2-cyano-N-(4-fluorophenyl)acetamide (2 g, 11.2 mmol) and (3E)-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (2.26 g, 13.4 mmol) in dimethyleneglycol monomethylether (20 mL) was added 1,4-diazabicyclo[2.2.2]octane (1.26 g, 11.2 mmol), and the mixture was stirred at 120°C for 6 hr. The reaction mixture was diluted with 1N hydrochloric acid and ethyl acetate, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=1/2→1/1) to give a white solid. The white solid was washed with ethyl acetate and collected by filtration to give the title compound (230 mg, 7.2%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 7.13 (1H, d, J = 7.6 Hz), 7.32 - 7.46 (2H, m), 7.49 - 7.60 (2H, m), 8.44 (1H, d, J = 7.4 Hz).

Reference Example 114

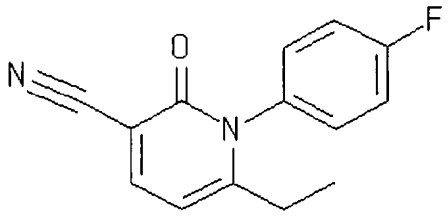
Production of 1-(4-fluorophenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3-carboxylic acid



A solution of 1-(4-fluorophenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile (200 mg, 0.709 mmol) in conc. sulfuric acid (1.5 mL)/water (1.5 mL) was stirred at 120°C for 17 hr. The reaction solution was allowed to cool to room temperature, 6N aqueous sodium hydroxide solution was added, and the aqueous layer was washed with ethyl acetate. 1N Hydrochloric acid was added to the aqueous layer, and the precipitate was filtered and washed with water to give the title compound (160 mg, 75%) as a white solid.
$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 7.24 (1H, d, J = 7.6 Hz), 7.35 - 7.48 (2H, m), 7.51 - 7.65 (2H, m), 8.40 (1H, d, J = 7.6 Hz), 13.62 (1H, br s).

Reference Example 115

Production of 6-ethyl-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile



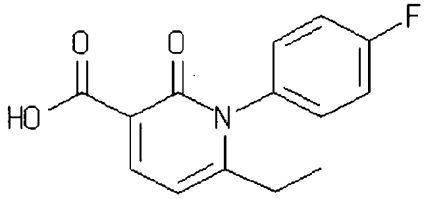
To a solution of 2-cyano-N-(4-fluorophenyl)acetamide (1.7 g, 10.6 mmol) in dimethyleneglycol monomethylether (20 mL) were added 1,4-diazabicyclo[2.2.2]octane (1.2 g, 10.6 mmol) and (1E)-1-methoxypent-1-en-3-one (1.82 g, 15.9 mmol), and the mixture was stirred at 120°C for 12 hr. The reaction mixture was diluted with 1N hydrochloric acid and ethyl

acetate, and extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=50/50→100/0) to give a white solid. The white solid was washed with ethyl acetate to give the title compound (410 mg, 16%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.00 (3H, t, J = 7.4 Hz), 2.25 (2H, q, J = 7.4 Hz), 6.44 (1H, d, J = 7.6 Hz), 7.35 - 7.49 (4H, m), 8.20 (1H, d, J = 7.6 Hz).

Reference Example 116

Production of 6-ethyl-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid

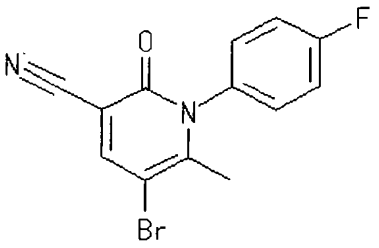


A solution of 6-ethyl-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (410 mg, 1.69 mmol) in conc. sulfuric acid (2 mL)/water (2 mL) was stirred at 120°C for 17 hr. The reaction solution was allowed to cool to room temperature, 6N aqueous sodium hydroxide solution was added, and the aqueous layer was washed with ethyl acetate. 1N Hydrochloric acid was added to the aqueous layer, and the precipitate was collected by filtration and washed with water to give the title compound (345 mg, 78%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.05 (3H, t, J = 7.4 Hz), 2.33 (2 H, q, J = 7.4 Hz), 6.76 (1H, d, J = 7.7 Hz), 7.37 - 7.62 (4H, m), 8.45 (1H, d, J = 7.7 Hz), 14.17 (1H, br s).

Reference Example 117

Production of 5-bromo-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile

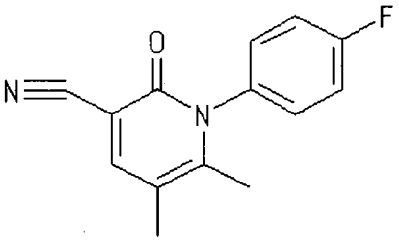


To a solution of 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (1 g, 4.05 mmol) in acetonitrile (10 mL)/tetrahydrofuran (5 mL) was added N-bromosuccinimide (792 mg, 4.46 mmol), and the mixture was stirred at 60°C overnight. After cooling to room temperature, saturated aqueous sodium hydrogen carbonate solution and ethyl acetate were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was washed with diethyl ether and collected by filtration to give the title compound (1.07 g, 86%) as a slightly yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.12 (3H, s), 6.95 - 7.77 (4H, m), 8.55 (1H, s).

Reference Example 118

Production of 1-(4-fluorophenyl)-5,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile



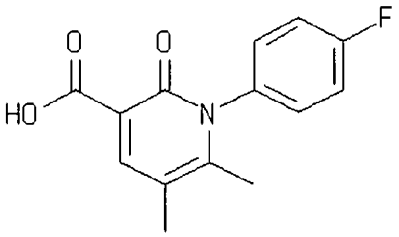
To a solution of 5-bromo-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (200 mg, 0.651 mmol) in N,N-dimethylformamide (2 mL) were added tetramethyltin (582 mg, 3.255 mmol) and tetrakistriphenylphosphinepalladium(0) (22.3 mg, 0.019 mmol), and the mixture was stirred at 120°C for 17 hr. Water and ethyl acetate were added to the reaction

mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, and the solvent was evaporated under reduced pressure. The obtained residue was washed with diethyl ether and collected by filtration to give the title compound (94 mg, 60%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.94 (3H, s), 2.10 (3H, s), 7.27 - 7.52 (4H, m), 8.13 (1H, s).

Reference Example 119

Production of 1-(4-fluorophenyl)-5,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

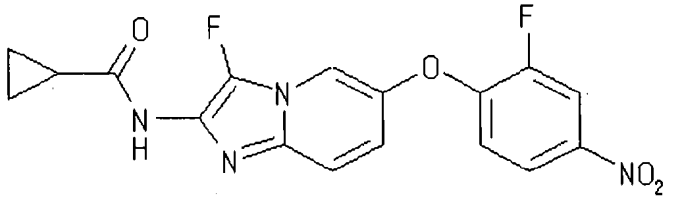


A solution of 1-(4-fluorophenyl)-5,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (90 mg, 0.324 mmol) in conc. sulfuric acid (0.5 mL) and water (0.5 mL) was stirred at 120°C for 8 hr. The reaction solution was allowed to cool to room temperature and diluted with water. The precipitate was collected by filtration and washed with water to give the title compound (90 mg, 93%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.03 (3H, s), 2.23 (3H, s), 7.37 - 7.52 (4H, m), 8.37 (1H, s), 14.44 (1H, br s).

Reference Example 120

Production of N-[3-fluoro-6-(2-fluoro-4-nitrophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide



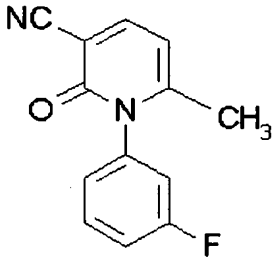
To a solution of N-[6-(2-fluoro-4-

nitrophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (121.6 mg, 0.341 mmol) in acetonitrile (0.5 mL)/tetrahydrofuran (0.5 mL) was added 1-fluoro-2,6-dichloropyridine triflate (129 mg, 0.409 mmol), and the mixture was stirred at room temperature for 2 hr. Tetrahydrofuran, ethyl acetate and 1N hydrochloric acid were added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=1/2→1/1) to give the title compound (15.2 mg, 12%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.69 - 0.89 (4H, m), 1.77 - 1.94 (1H, m), 7.10 - 7.37 (2H, m), 7.58 (1H, d, J = 1.9 Hz), 7.94 - 8.16 (1H, m), 8.37 (1H, dd, J = 10.9, 2.7 Hz), 8.56 (1H, d, J = 2.3 Hz), 10.58 (1H, s).

Reference Example 121

1-(3-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile



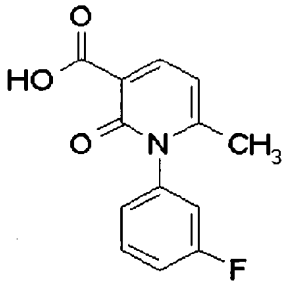

A solution (50 mL) of 2-cyano-N-(3-fluorophenyl)acetamide (6.60 g, 37.0 mmol), (3E)-4-methoxybut-3-en-2-one (5.60 g, 56.0 mmol) and 1,4-diazabicyclo[2.2.2]octane (6.20 g, 56.0 mmol) in 2-(2-methoxyethoxy)ethanol was stirred at 120°C for 12 hr. The reaction solution was divided into two layers with ethyl acetate and water and subjected to extraction (3 times) with ethyl acetate. The organic layer was washed with water and

saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (2.60 g, 31%) as a brown solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.03 (3H, s), 6.50 (1H, d, J = 7.6 Hz), 7.24 (1H, ddd, J = 7.4, 1.1 0.9 Hz), 7.34 - 7.46 (2H, m), 7.54 - 7.71 (1H, m), 8.17 (1H, d, J = 7.6 Hz).

Reference Example 122

1-(3-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

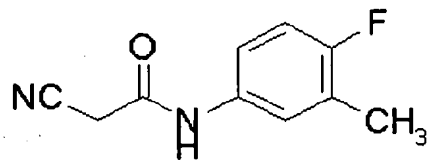


1-(3-Fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (2.60 g, 11.0 mmol) was suspended in aqueous sulfuric acid solution (98% sulfuric acid 13 mL, water 13 mL), and the mixture was stirred at 130°C for 10 hr. The reaction solution was allowed to cool to room temperature, water was added, and the precipitate was collected by filtration. The obtained solid was washed with ethyl acetate to give the title compound (2.20 g, 78%) as a brown solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.12 (3H, s), 6.81 (1H, dd, J = 7.6, 0.8 Hz), 7.32 (1H, ddd, J = 7.9, 1.9, 0.9 Hz), 7.38 - 7.53 (2H, m), 7.66 (1H, td, J = 8.1, 6.4 Hz), 8.41 (1H, d, J = 7.6 Hz).

Reference Example 123

2-cyano-N-(4-fluoro-3-methylphenyl)acetamide

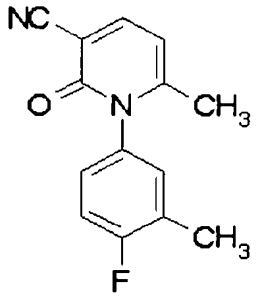


A mixture of 4-fluoro-3-methylaniline (2.50 g, 20.0 mmol) and ethyl cyanoacetate (2.70 g, 24.0 mmol) was stirred at 180°C for 14 hr. After cooling to room temperature, the obtained solid was washed with hexane and collected by filtration to give the title compound (3.60 g, 95%) as a brownish-red solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.22 (3H, s), 3.88 (2H, s), 7.10 (1H, t, J = 9.2 Hz), 7.28 - 7.55 (2H, m), 10.27 (1H, br s).

Reference Example 124

1-(4-fluoro-3-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile

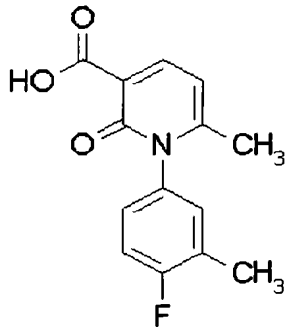



A solution (30 mL) of 2-cyano-N-(4-fluoro-3-methylphenyl)acetamide (3.60 g, 19.0 mmol), (3E)-4-methoxybut-3-en-2-one (2.80 g, 28.0 mmol) and 1,4-diazabicyclo[2.2.2]octane (3.20 g, 28.0 mmol) in 2-(2-methoxyethoxy)ethanol was stirred at 120°C for 12 hr. After cooling to room temperature, the reaction solution was divided into two layers with ethyl acetate and water and subjected to extraction (3 times) with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (1.60 g, 34%) as a brown solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.02 (3H, s), 2.27 (3H, d, J = 1.9 Hz), 6.43 - 6.53 (1H, m), 7.17 - 7.38 (3H, m), 8.14 (1H, d, J = 7.4 Hz).

Reference Example 125

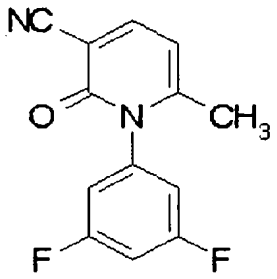
1-(4-fluoro-3-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid



1-(4-Fluoro-3-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (1.60 g, 6.60 mmol) was suspended in aqueous sulfuric acid solution (98% sulfuric acid 8 mL, water 8 mL), and the mixture was stirred at 130°C for 10 hr. The reaction solution was cooled to room temperature, water was added, and the precipitated solid was collected by filtration. The obtained solid was washed with ethyl acetate to give the title compound (1.00 g, 58%) as a brown solid. $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.11 (3H, s), 2.29 (3H, d, J = 1.9 Hz), 6.80 (1H, d, J = 7.6 Hz), 7.27 - 7.48 (3H, m), 8.40 (1H, d, J = 7.6 Hz).

Reference Example 126

1-(3,5-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile



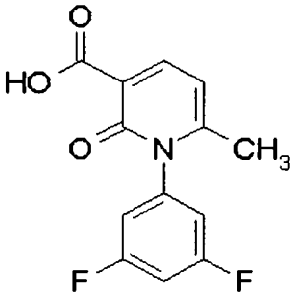
A solution (30 mL) of 2-cyano-N-(3,5-difluorophenyl)acetamide (3.10 g, 16.0 mmol), (3E)-4-methoxybut-3-en-2-one (2.40 g, 24.0 mmol) and 1,4-diazabicyclo[2.2.2]octane (2.70 g, 24.0 mmol) in 2-(2-methoxyethoxy)ethanol was stirred at 130°C for 12 hr. After

cooling to room temperature, the reaction solution was divided into two layers with ethyl acetate and water and subjected to extraction (3 times) with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (1.60 g, 40%) as a brown solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.07 (3H, s), 6.51 (1H, dd, J = 7.6, 0.8 Hz), 7.24 - 7.42 (2H, m), 7.49 (1H, tt, J = 9.4, 2.4 Hz), 8.18 (1H, d, J = 7.6 Hz).

Reference Example 127

1-(3,5-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

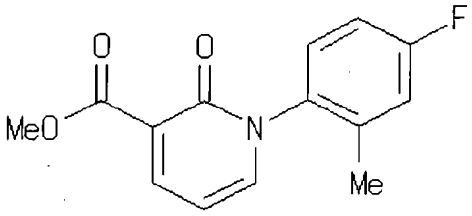


1-(3,5-Difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (1.50 g, 6.20 mmol) was suspended in aqueous sulfuric acid solution (98% sulfuric acid 8 mL, water 8 mL), and the mixture was stirred at 120°C for 10 hr. The reaction solution was cooled to room temperature and poured into water, and the precipitate was collected by filtration. The obtained solid was washed with ethyl acetate to give the title compound (1.00 g, 61%) as a brown solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.15 (3H, s), 6.80 (1H, dd, J = 7.6, 0.8 Hz), 7.35 - 7.47 (2H, m), 7.53 (1H, tt, J = 9.4, 2.4 Hz), 8.42 (1H, d, J = 7.6).

Reference Example 128

Production of methyl 1-(4-fluoro-2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

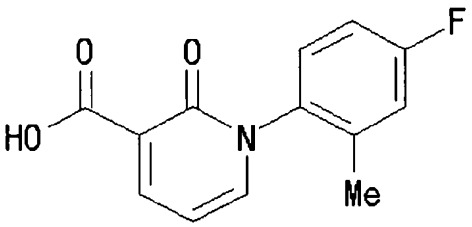


To a solution of methyl 2-oxo-2H-pyran-3-carboxylate (3 g, 19.5 mmol) in N,N-dimethylformamide (18 mL) was added 4-fluoro-2-methylaniline (2.44 g, 19.5 mmol), and the mixture was stirred at room temperature for 3 hr. 4-Dimethylaminopyridine (119 mg, 0.974 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.48 g, 23.4 mmol) were added to the reaction mixture, and the mixture was further stirred at room temperature for 16 hr. 2N Hydrochloric acid was added to the reaction solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=1/1), and the obtained solid was washed with hexane/ethyl acetate (=1/1) and collected by filtration to give the title compound (0.40 g, 8%) as a yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.04 (3H, s), 3.75 (3H, s), 6.43 (1H, t, J = 6.9 Hz), 7.15 - 7.23 (1H, m), 7.27 - 7.37 (2H, m), 7.86 (1H, dd, J = 7.1, 2.4 Hz) 8.16 (1H, dd, J = 7.1, 2.4 Hz).

Reference Example 129

Production of 1-(4-fluoro-2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid



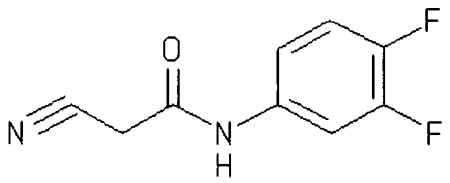
To a suspension of methyl 1-(4-fluoro-2-methylphenyl)-2-

oxo-1,2-dihydropyridine-3-carboxylate (0.40 g, 1.53 mmol) in methanol (9 mL) was added 2N aqueous sodium hydroxide solution (1.15 mL), and the mixture was stirred at room temperature for 3 hr. 6N Hydrochloric acid (0.5 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with hexane/ethyl acetate (=1/1) to give the title compound (704 mg, 85%) as a yellow solid.

$^1$H-NMR (300 MHz, DMSO-$d_6$) δ 2.07 (3H, s), 6.81 (1H, t, J = 6.9 Hz), 7.20 - 7.29 (1H, m), 7.32 - 7.38 (1H, m), 7.46 - 7.52 (1H, m), 8.13 (1H, dd, J = 6.9, 2.1 Hz), 8.51 (1H, dd, J= 6.9, 2.1 Hz), 14.16 (1H, br s).

Reference Example 130

Production of 2-cyano-N-(3,4-difluorophenyl)acetamide



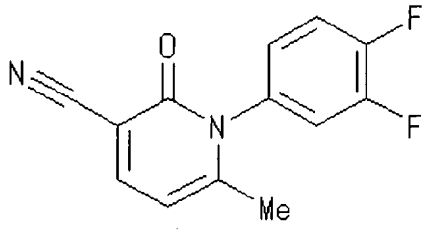

A mixed solution of 3,4-difluoroaniline (10 g, 77.5 mmol) and ethyl cyanoacetate (10.5 g, 92.9 mmol) was heated to 180°C and stirred for 8 hr. After cooling to room temperature, the mixture was dissolved in ethyl acetate/tetrahydrofuran and washed with water and saturated brine in this order. The mixture was dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (7.6 g, 56%) as a yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 3.92 (2H, s), 7.22 - 7.28 (1H, m), 7.36 - 7.47 (1H, m), 7.68 - 7.75 (1H, m), 10.53 (1H, s).

Reference Example 131

Production of 1-(3,4-difluorophenyl)-6-methyl-2-oxo-1,2-

dihydropyridine-3-carbonitrile

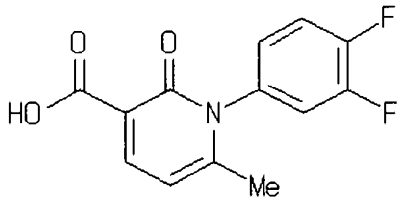


A mixture of 2-cyano-N-(3,4-difluorophenyl)acetamide (6.0 g, 30.6 mmol), (3E)-4-methoxybut-3-en-2-one (4.29 g, 42.8 mmol) and 2-(2-methoxyethoxy)ethanol (60 mL) was stirred at 90°C for 20 min. 1,4-Diazabicyclo[2.2.2]octane (3.77 g, 33.6 mmol) was added, and the mixture was stirred at 125°C for 5 hr. After cooling to room temperature, the mixture was adjusted to pH 5 with 2N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with ethyl acetate/hexane (=1/1) and collected by filtration to give the title compound (3.69 g, 49%) as a pale-yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.05 (3H, s), 6.48 - 6.51 (1H, m), 7.25 - 7.35 (1H, m), 7.61 - 7.73 (2H, m), 8.17 (1H, d, J = 7.5 Hz).

Reference Example 132

Production of 1-(3,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid



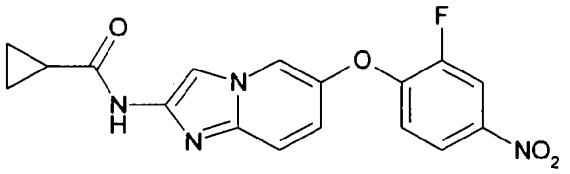
Water (7.2 mL) and conc. sulfuric acid (7.2 mL) were added to 1-(3,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (3.6 g, 14.6 mmol), and the mixture was stirred at 100°C for 20 hr. The mixture was basified (pH 10) with 8N aqueous sodium hydroxide solution at

0°C and washed with ethyl acetate. The aqueous layer was acidified (pH 3) with 6N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with ethyl acetate/hexane (=1/1) and collected by filtration to give the title compound (2.49 g, 64%) as a thin-yellow powder.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.13 (3H, s), 6.80 (1H, d, J = 8.1 Hz), 7.34 - 7.43 (1H, m), 7.65 - 7.80 (2H, m), 8.41 (1H, d, J = 7.5 Hz), 14.06 (1H, br s).

Reference Example 133

Production of N-[6-(2-fluoro-4-nitrophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide

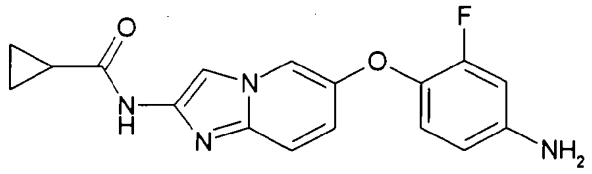


To a solution of N-(6-hydroxyimidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide (30 g, 138 mmol) and 1,2-difluoro-4-nitrobenzene (24.2 g, 152 mmol) in dimethyl sulfoxide (180 mL) was added cesium carbonate (58.5 g, 180 mmol), and the mixture was stirred at room temperature for 5 hr under an argon atmosphere. Water (1080 mL) was added to the reaction mixture, and the mixture was stirred for 20 min. The precipitate was collected by filtration and washed with water and ethyl acetate. After air drying for one day, the mixture was dried under reduced pressure at 100°C for 5 hr to give the title compound (46.5 g, 95%) as a yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.76 - 0.84 (4H, m), 1.88 - 1.99 (1H, m), 7.22 (1H, d, J = 9.5 Hz), 7.21 - 7.27 (1H, m), 7.54 (1H, d, J = 9.5 Hz), 8.01 - 8.08 (1H, m), 8.08 (1H, s), 8.36 (1H, dd, J = 11.1, 2.9 Hz), 8.74 (1H, d, J = 1.8 Hz), 11.02 (1H, s).

Reference Example 134

Production of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide

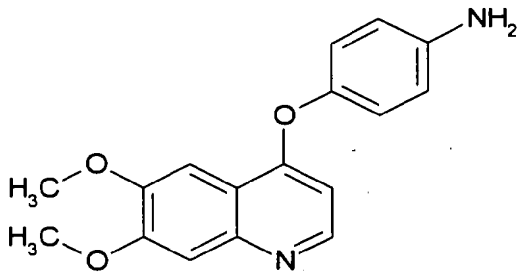


To a suspension of N-[6-(2-fluoro-4-nitrophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (10 g, 28.1 mmol) in tetrahydrofuran (80 mL)/methanol (80 mL) were added iron chloride·hexahydrate (0.5 g), hydrazine·monohydrate (8.2 mL, 168 mmol) and activated carbon (1.0 g), and the mixture was heated under reflux for 16 hr. After cooling to 40°C, the mixture was filtered through celite and washed with methanol. The solvent of the filtrate was evaporated under reduced pressure, and the precipitate was washed with water/methanol (=10/1) and collected by filtration to give the title compound (8.4 g, 92%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.75 - 0.81 (4H, m), 1.85 - 1.96 (1H, m), 5.34 (2H, s), 6.34 - 6.40 (1H, m), 6.49 (1H, dd, J = 135.5, 2.7 Hz), 7.00 - 7.05 (1H, m), 7.38 (1H, d, J = 9.5 Hz), 8.00 (1H, s), 8.21 (1H, d, J = 2.1 Hz), 10.88 (1H, s).

Reference Example 135

Production of 4-[(6,7-dimethoxyquinolin-4-yl)oxy]aniline

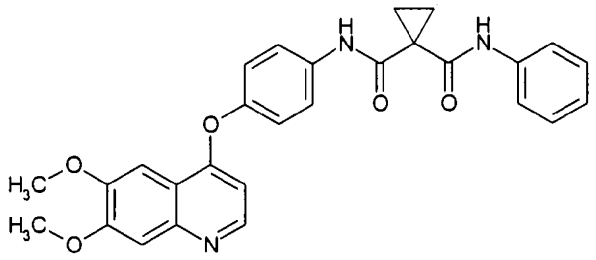


A suspension of 4-chloro-6,7-dimethoxyquinoline (1566 mg, 7.00 mmol), 4-aminophenol (917 mg, 8.40 mmol) and cesium carbonate (4561 mg, 14.0 mmol) in dimethyl sulfoxide (14 ml)

was stirred at 100°C for 18 hr. Water was added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate/tetrahydrofuran (=1/1). The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate→ethyl acetate/methanol=60/40). Ethyl acetate was added to the obtained residue and the mixture was filtrated to give the title compound (1267 mg, 61%) as a white powder.
$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 3.93 (6H, s), 5.16 (2H, s), 6.37 (1H, d, J = 5.4 Hz), 6.67 (2H, d, J = 8.7 Hz), 6.93 (2H, d, J = 8.7 Hz), 7.36 (1H, s), 7.50 (1H, s), 8.43 (1H, d, J = 5.4 Hz).

Reference Example 136

Production of N-{4-[(6,7-dimethoxyquinolin-4-yl]phenyl}-N'-phenylcyclopropanedicarboxamide



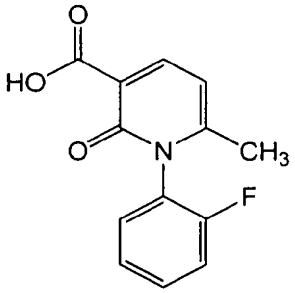
To a solution of 1-(phenylcarbamoyl)cyclopropanecarboxylic acid (237 mg, 1.04 mmol) in tetrahydron (10 mL) were added N,N-dimethylformamide (1 drop) and oxalyl chloride (178 μL, 2.08 mmol), and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure, N,N-dimethylacetamide (3 ml) and 4-[(6,7-dimethoxyquinolin-4-yl)oxy]aniline (213 mg, 1.04 mmol) were added to the obtained residue, and the mixture was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (ethyl acetate→ethyl

acetate/methanol=75/25). The obtained powder was recrystallized from ethyl acetate/diisopropyl ether to give the title compound (286 mg, 74%) as white crystals.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 1.49 (4H, s), 3.93 (3H, s), 3.95 (3H, s), 6.43 (1H, d, J = 5.3 Hz), 7.07 (1H, t, J = 7.4 Hz), 7.23 (2H, d, J = 9.2 Hz), 7.27 - 7.35 (2H, m), 7.39 (1H, s), 7.51 (1H, s), 7.63 (2H, d, J = 7.4 Hz), 8.47 (1H, d, J = 5.3 Hz), 10.05(1H, brs), 10.26 (1H, brs).

Reference Example 137

Production of 1-(2-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

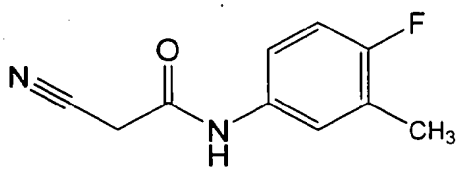


An aqueous solution (98% sulfuric acid 3 mL, water 3 mL) of 1-(2-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (660 mg, 3.08 mmol) in sulfuric acid was stirred at 130°C for 6 hr. The reaction solution was cooled to room temperature, water was added, and the precipitated solid was collected by filtration. The obtained solid was washed with ethyl acetate to give the title compound (550 mg, 72%) as a brown solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.14 (3H, s), 6.84 (1H, d, J = 8.1 Hz), 7.41 - 7.70 (4H, m), 8.45 (1H, d, J = 7.6 Hz), 13.87 (1H, br s).

Reference Example 138

Production of 2-cyano-N-(4-fluoro-3-methylphenyl)acetamide

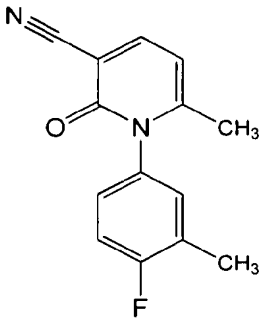


A mixture of 4-fluoro-3-methylaniline (2.50 g, 20.0 mmol) and ethyl cyanoacetate (2.70 g, 24.0 mmol) was stirred at 180°C for 14 hr. After the reaction, the mixture was cooled to room temperature, and the obtained solid was washed with hexane and collected by filtration to give the title compound (3.60 g, 95%) as a brownish-red solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.22 (3H, s), 3.88 (2H, s), 7.10 (1H, t, J = 9.2 Hz), 7.28 - 7.55 (2H, m), 10.27 (1H, br s).

Reference Example 139

Production of 1-(4-fluoro-3-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile

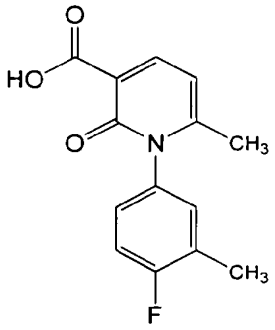



A solution (30 mL) of 2-cyano-N-(4-fluoro-3-methylphenyl)acetamide (3.60 g, 19.0 mmol), (3E)-4-methoxybut-3-en-2-one (2.80 g, 28.0 mmol) and 1,4-diazabicyclo[2.2.2]octane (3.20 g, 28.0 mmol) in 2-(2-methoxyethoxy)ethanol was stirred at 120°C for 12 hr. After cooling to room temperature, the reaction solution was divided into two layers with ethyl acetate and water and subjected to extraction (3 times) with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (1.60 g, 34%) as a brown solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.02 (3H, s), 2.27 (3H, d, J = 1.9 Hz), 6.43 - 6.53 (1H, m), 7.17 - 7.38 (3H, m), 8.14 (1H, d, J = 7.4 Hz).

Reference Example 140

Production of 1-(4-fluoro-3-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

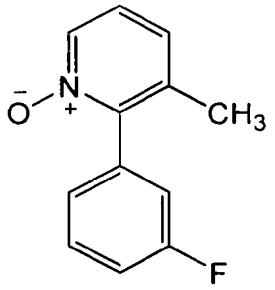


An aqueous solution (98% sulfuric acid 8 mL, water 8 mL) of 1-(4-fluoro-3-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (1.60 g, 6.60 mmol) in sulfuric acid was stirred at 130°C for 10 hr. The reaction solution was cooled to room temperature, water was added, and the precipitated solid was collected by filtration. The obtained solid was washed with ethyl acetate to give the title compound (1.00 g, 58%) as a brown solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.11 (3H, s), 2.29 (3H, d, J = 1.9 Hz), 6.80 (1H, d, J = 7.6 Hz), 7.27 - 7.48 (3H, m), 8.40 (1H, d, J = 7.6 Hz).

Reference Example 141

Production of 2-(3-fluorophenyl)-3-methylpyridine 1-oxide



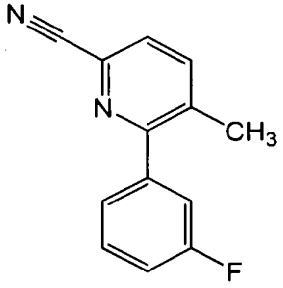
To a solution (100 mL) of 2-(3-fluorophenyl)-3-methylpyridine (4.83 g, 25.8 mmol) in ethyl acetate was added 3-chloroperbenzoic acid (7.1 g, 28.4 mmol), and the mixture was stirred at 50°C for 5 hr. The disappearance of 3-chloroperbenzoic acid was confirmed using potassium iodide

starch paper (manufactured by ADVANTEC MFS, INC), and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (4.26 g, 81%).

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.05 (3H, s), 7.17 (1H, dt, J = 7.6, 1.2 Hz), 7.21 - 7.40 (4H, m), 7.54 (1H, td, J = 7.8, 5.9 Hz), 8.20 (1H, dd, J = 5.4, 1.6 Hz).

Reference Example 142

Production of 6-(3-fluorophenyl)-5-methylpyridine-2-carbonitrile



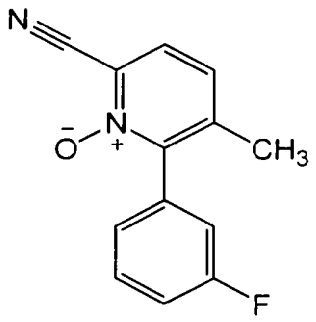

A solution (40 mL) of 2-(3-fluorophenyl)-3-methylpyridine 1-oxide (4.26 g, 21.0 mmol), dimethylcarbamic acid chloride (2.94 g, 27.3 mmol) and trimethylsilanecarbonitrile (2.71 g, 27.3 mmol) in tetrahydrofuran was heated under reflux, and the mixture was stirred for 2 hr. After cooling to room temperature, the reaction solution was divided into two layers with ethyl acetate and saturated aqueous sodium hydrogen carbonate solution and subjected to extraction (3 times) with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography to give the title compound (4.42 g, 99%).

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.41 (3H, s), 7.27 - 7.39 (1H, m), 7.39 - 7.48 (2H, m), 7.50 - 7.62 (1H, m), 7.93 - 8.09 (2H, m).

Reference Example 143

Production of 6-(3-fluorophenyl)-5-methylpyridine-2-

carbonitrile 1-oxide

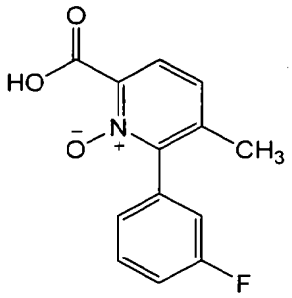


To a solution (50 mL) of 6-(3-fluorophenyl)-5-methylpyridine-2-carbonitrile (4.42 g, 20.8 mmol) in acetonitrile were added trifluoroacetic acid anhydride (17.6 g, 62.4 mmol) and sodium percarbonate (6.5 g, 41.6 mmol) at 0°C, and the mixture was stirred at 0°C for 1 hr and at room temperature overnight. The reaction solution was divided into two layers with ethyl acetate and saturated aqueous sodium hydrogen carbonate solution and subjected to extraction (3 times) with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The disappearance of sodium percarbonate was confirmed, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography to give the title compound (1.4 g, 29%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.11 (3H, s), 7.23 (1H, dt, J = 7.7, 1.2 Hz), 7.29 - 7.39 (2H, m), 7.48 - 7.53 (1H, m), 7.53 - 7.64 (1H, m), 8.05 (1H, d, J = 8.3 Hz).

Reference Example 144

Production of 6-(3-fluorophenyl)-5-methylpyridine-2-carboxylic acid 1-oxide

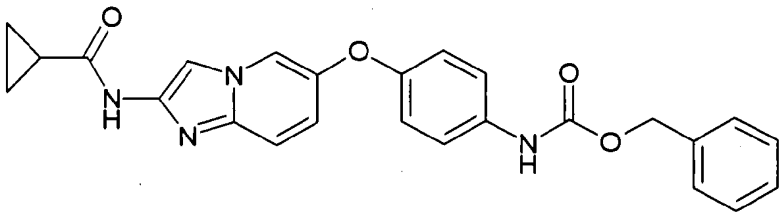


An aqueous solution (98% sulfuric acid 6 mL, water 6 mL) of 6-(3-fluorophenyl)-5-methylpyridine-2-carbonitrile 1-oxide (1.4 g, 6.13 mmol) in sulfuric acid was stirred at 120°C for 10 hr. The reaction solution was cooled to room temperature and added to water, and the precipitated solid was collected by filtration. The obtained solid was washed with ethyl acetate to give the title compound (1.07 g, 71%) as a brown solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 2.18 (3H, s), 7.26 - 7.47 (3H, m), 7.54 - 7.73 (1H, m), 7.87 - 8.01 (1H, m), 8.31 (1H, d, J = 8.3 Hz).

Example 1

Production of benzyl [4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]carbamate



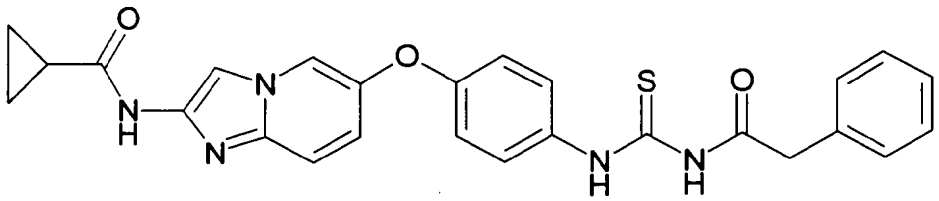
To a solution of benzylcarbamate {4-[(2-aminoimidazo[1,2-a]pyridin-6-yl)oxy]phenyl}carbamate (8.7 g, 22.2 mmol) in N,N-dimethylacetamide (70 mL) was added cyclopropanecarbonyl chloride (2.21 mL, 24.4 mmol) at room temperature, and the mixture was stirred at room temperature for 1 hr. Saturated aqueous sodium hydrogen carbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was

washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/ethyl acetate (=1/1) and collected by filtration to give the title compound (8.5 g, 87%) as a thin-brown solid.

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.76 - 0.82 (4H, m), 1.85 - 1.95 (1H, m), 5.14 (2H, s), 6.97 - 7.09 (3H, m), 7.27 - 7.50 (8H, m), 8.03 (1H, s), 8.44 (1H, d, J = 1.8 Hz), 9.75 (1H, s), 10.97 (1H, s).

Example 2

Production of N-[6-(4-{[(phenylacetyl)carbamothioyl]amino}phenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide



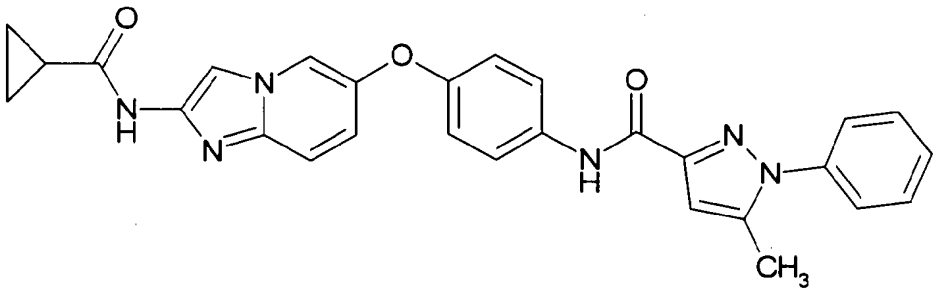
To a solution of phenylacetyl chloride (422 mg, 2.59 mmol) in acetonitrile (8 mL) was added potassium thiocyanate (317 mg, 3.24 mmol), and the mixture was stirred at 50°C for 1 hr. The reaction solution was cooled to room temperature, saturated aqueous sodium hydrogen carbonate was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The obtained residue was dissolved in toluene (2 mL)/ethanol (2 mL), N-[6-(4-aminophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (200 mg, 649 μmol) was added, and the mixture was stirred at room temperature for 1 hr. Saturated aqueous sodium hydrogen carbonate was added to the reaction solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N aqueous sodium

hydroxide solution, water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane) and recrystallized from ethanol/water to give the title compound (98 mg, 31%) as a pale-yellow powder.

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.68-0.93 (4H, m), 1.82 - 2.05 (1H, m), 3.81 (2H, s), 7.02 (2H, d, J = 8.9 Hz), 7.08 (1H, dd, J = 9.6, 2.1 Hz), 7.22 - 7.41 (5H, m), 7.46 (1H, d, J = 9.6 Hz), 7.57 (2H, d, J = 8.9 Hz), 8.05 (1H, s), 8.57 (1H, d, J = 2.1 Hz), 10.97 (1H, s), 11.69 (1H, s), 12.30 (1H, s).

Example 3

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-5-methyl-1-phenyl-1H-pyrazole-3-carboxamide



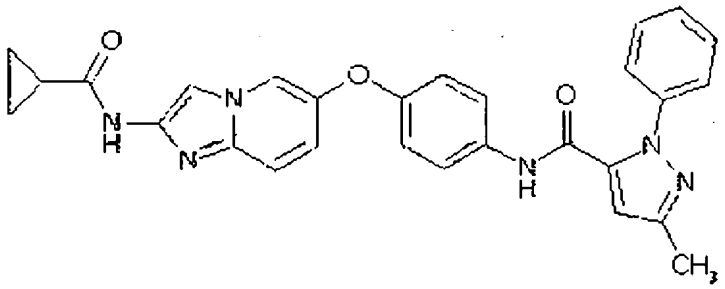
To a solution of 5-methyl-1-phenyl-1H-pyrazole-3-carboxylic acid (197 mg, 973 μmol) in tetrahydrofuran (2 mL) were added oxalyl chloride (80 μL, 973 μmol) and N,N-dimethylformamide (2 drops) under ice-cooling, and the mixture was stirred at room temperature for 1 hr. A solution of N-[6-(4-aminophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (200 mg, 649 μmol) in N,N-dimethylacetamide (2 mL) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Saturated aqueous sodium hydrogen carbonate was added to the reaction solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N aqueous sodium

hydroxide solution, water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The obtained residue was recrystallized from ethanol/water to give the title compound (187 mg, 39%) as a white powder.

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.75 - 0.86 (4H, m), 1.86 - 1.98 (1H, m), 2.30 (3H, s), 6.83 (1H, s), 7.03 (2H, d, J = 9.1 Hz), 7.02 - 7.08 (1H, m), 7.31 - 7.50 (6H, m), 7.65 (2H, d, J = 9.1 Hz), 8.04 (1H, s), 8.48 (1H, d, J = 1.7 Hz), 10.53 (1H, s), 10.95 (1H, s).

Example 4

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-3-methyl-1-phenyl-1H-pyrazole-5-carboxamide



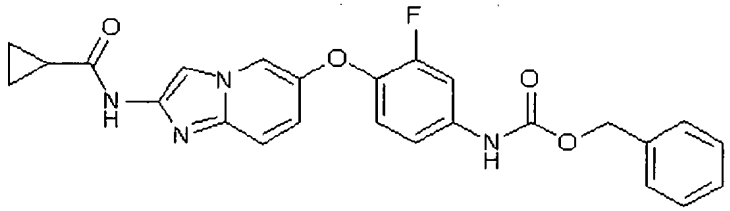
To a solution of 3-methyl-1-phenyl-1H-pyrazole-5-carboxylic acid (197 mg, 973 μmol) in tetrahydrofuran (2 mL) were added oxalyl chloride (80 μL, 973 μmol) and N,N-dimethylformamide under ice-cooling, and the mixture was stirred at room temperature for 1 hr. A solution of N-[6-(4-aminophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (200 mg, 649 μmol) in N,N-dimethylacetamide (2 mL) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Saturated aqueous sodium hydrogen carbonate was added to the reaction solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N aqueous sodium hydroxide solution, water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The obtained

residue was recrystallized from ethanol/water to give the title compound (138 mg, 29%) as a white powder.

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.74 - 0.87 (4H, m), 1.83 - 2.05 (1H, m), 2.36 (3H, s), 6.79 (1H, s), 7.02 (2H, d, J = 9.1 Hz), 7.07 (1H, dd, J = 9.6, 2.2 Hz), 7.45 (1H, d, J = 9.6 Hz), 7.47 - 7.68 (5H, m), 7.82 (2H, d, J = 8.9 Hz), 8.05 (1H, s), 8.49 (1H, d, J = 1.7 Hz), 10.08 (1H, s), 10.95 (1H, s).

Example 5

Production of benzyl [4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]carbamate

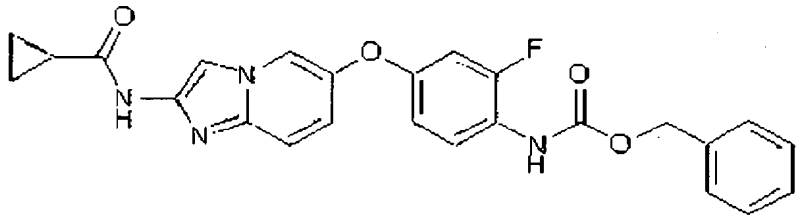


To a solution of benzyl {4-[(2-aminoimidazo[1,2-a]pyridin-6-yl)oxy]-3-fluorophenyl}carbamate (10.0 g, 25.5 mmol) in N,N-dimethylacetamide (100 mL) was added cyclopropanecarbonyl chloride (2.77 mL, 30.6 mmol) at 0°C, and the mixture was stirred at room temperature for 2 hr. Water and saturated aqueous sodium hydrogen carbonate were added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate and collected by filtration to give the title compound (9.2 g, 78%) as a thin-brown solid.

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.76 - 0.81 (4H, m), 1.85 - 1.96 (1H, m), 5.17 (2H, s), 7.05 - 7.25 (4H, m), 7.30 - 7.45 (5H, m), 7.52 - 7.60 (1H, m), 8.01 (1H, s), 8.38 (1H, d, J = 2.1 Hz), 10.02 (1H, s), 10.93 (1H, s).

Example 6

Production of benzyl [4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-2-fluorophenyl]carbamate

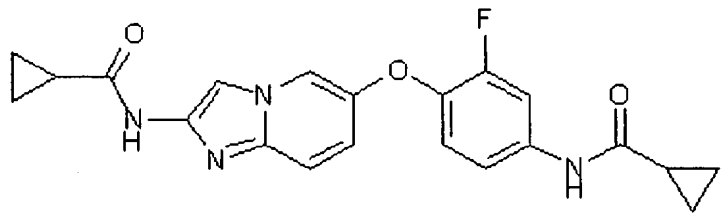


To a solution of benzyl {4-[(2-aminoimidazo[1,2-a]pyridin-6-yl)oxy]-2-fluorophenyl}carbamate (12.1 g, 30.9 mmol) in N,N-dimethylacetamide (84.7 mL) was added cyclopropanecarbonyl chloride (3.36 mL, 37.0 mmol) at 0°C, and the mixture was stirred at room temperature for 2 hr. Water and saturated aqueous sodium hydrogen carbonate were added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate and collected by filtration to give the title compound (9.7 g, 68%) as a thin-brown solid.

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.77 - 0.83 (4H, m), 1.86 - 1.96 (1H, m), 5.14 (2H, s), 6.81 - 6.86 (1H, m), 6.97 - 7.11 (2H, m), 7.31 - 7.56 (7H, m), 8.05 (1H, s), 8.57 (1H, d, J = 1.5 Hz), 9.37 (1H, br s), 10.97 (1H, s).

Example 7

Production of N-(6-{4-[(cyclopropylcarbonyl)amino]-2-fluorophenoxy}imidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide

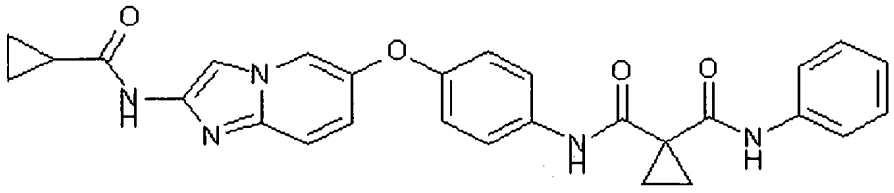


To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol) in N,N-dimethylacetamide (1.5 mL) was added cyclopropanecarbonyl chloride (50.1 μL, 0.55 mmol) at room temperature, and the mixture was stirred at room temperature for 30 min. Saturated aqueous sodium hydrogen carbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=40/60→0/100). The obtained powder was washed with ethyl acetate and collected by filtration to give the title compound (150 mg, 83%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.76 - 0.84 (8H, m), 1.71 - 1.80 (1H, m), 1.86 - 1.96 (1H, m), 7.09 (1H, dd, J = 9.6, 2.4 Hz), 7.16 (1H, d, J = 9.0 Hz), 7.24 - 7.30 (1H, m), 7.43 (1H, d, J = 9.6 Hz), 7.78 (1H, dd, J = 13.5, 2.4 Hz), 8.02 (1H, s), 8.41 (1H, d, J = 2.1 Hz), 10.41 (1H, s), 10.93 (1H, s).

Example 8

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-N'-phenylcyclopropane-1,1-dicarboxamide



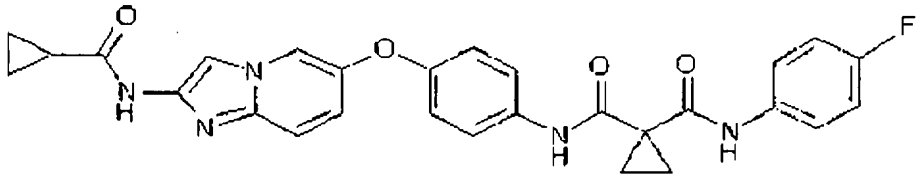
To a solution of N-[6-(4-aminophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (142 mg, 0.461 mmol) in N,N-dimethylacetamide (2.8 mL) were added 1-(phenylcarbamoyl)cyclopropanecarboxylic acid (142 mg, 0.691

mmol), HATU (263 mg, 0.691 mmol) and N,N-diisopropylethylamine (120 μL, 0.691 mmol), and the mixture was stirred at room temperature for 4 hr. Saturated aqueous sodium hydrogen carbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=40/60→0/100), washed with hexane/ethyl acetate and collected by filtration to give the title compound (130 mg, 57%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.75 - 0.82 (4H, m), 1.46 (4H, s), 1.86 - 1.96 (1H, m), 6.96 - 7.09 (4H, m), 7.27 - 7.33 (2H, m), 7.44 (1H, d, J = 9.6 Hz), 7.57 - 7.62 (4H, m), 8.04 (1H, s), 8.47 (1H, d, J = 1.5 Hz), 10.00 (1H, br s), 10.07 (1H, br s), 10.94 (1H, s).

Example 9

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide



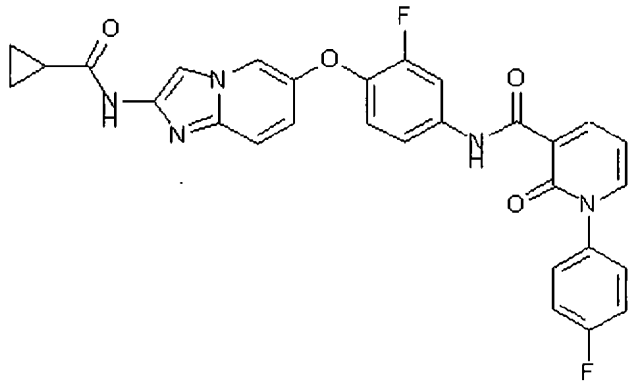
Using N-[6-(4-aminophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.486 mmol), N,N-dimethylacetamide (3.0 mL), 1-[(4-fluorophenyl)carbamoyl]cyclopropanecarboxylic acid (163 mg, 0.730 mmol), HATU (277 mg, 0.730 mmol) and N,N-diisopropylethylamine (127 μL, 0.730 mmol) and in the same manner as in Example 8, the title compound (111 mg, 44%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.75 - 0.82 (4H, m), 1.44 (4H, s),

1.86 - 1.96 (1H, m), 6.96 - 7.17 (5H, m), 7.44 (1H, d, J = 9.6 Hz), 7.57 - 7.65 (4H, m),8.03 (1H, s), 8.47 (1H, d, J = 1.8 Hz), 10.03 (1H, br s), 10.06 (1H, br s), 10.94 (1H, s).

Example 10

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide



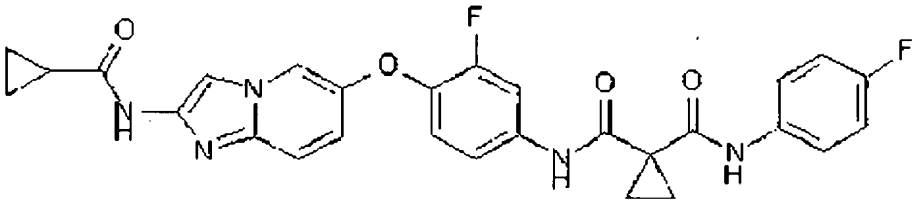
To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.460 mmol) in N,N-dimethylacetamide (3.0 mL) were added 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (161 mg, 0.689 mmol), HATU (262 mg, 0.689 mmol) and N,N-diisopropylethylamine (120 μL, 0.689 mmol), and the mixture was stirred at room temperature for 2 hr. Water and saturated aqueous sodium hydrogen carbonate were added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate and collected by filtration to give the title compound (269 mg, 81%) as a pale-yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.76 - 0.81 (4H, m), 1.85 - 1.96 (1H, m), 6.69 - 6.75 (1H, m), 7.08 - 7.19 (2H, m), 7.34 - 7.45 (4H, m), 7.58 - 7.63 (2H, m), 7.94 - 7.99 (1H, m),8.03 (1H, s),

8.10 - 8.14 (1H, m), 8.47 (1H, d, J = 1.8 Hz), 8.57 (1H, dd, J = 7.4, 2.3 Hz), 10.94 (1H, br s), 12.03 (1H, s).

Example 11

N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

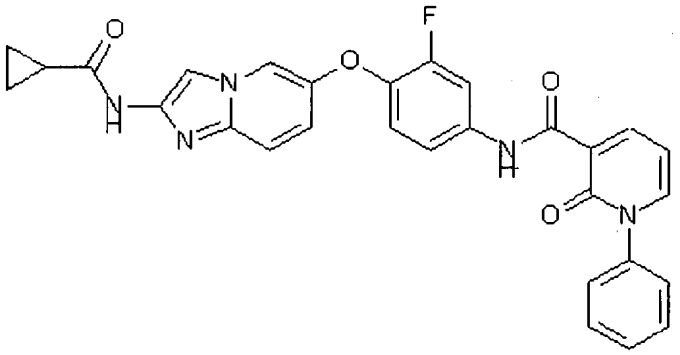


To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.460 mmol) in N,N-dimethylacetamide (3.0 mL) were added 1-[(4-fluorophenyl)carbamoyl]cyclopropanecarboxylic acid (154 mg, 0.689 mmol), HATU (262 mg, 0.689 mmol) and N,N-diisopropylethylamine (120 μL, 0.689 mmol), and the mixture was stirred at room temperature for 4 hr. Saturated aqueous sodium hydrogen carbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=40/60→0/100), washed with hexane/ethyl acetate and collected by filtration to give the title compound (99 mg, 41%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.76 - 0.81 (4H, m), 1.42 - 1.47 (4H, m), 1.86 - 1.96 (1H, m), 7.05 - 7.18 (4H, m), 7.33 - 7.45 (2H, m), 7.60 - 7.66 (2H, m), 7.81 (1H, dd, J = 13.8, 2.4 Hz),8.02 (1H, s), 8.43 (1H, d, J = 2.1 Hz), 9.99 (1H, br s), 10.24 (1H, br s), 10.93 (1H, s).

Example 12

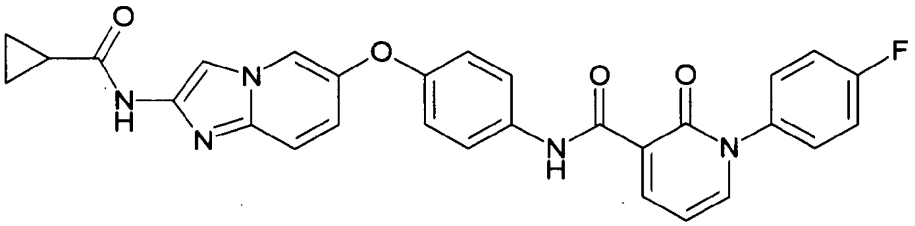
Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide



Using N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.460 mmol), N,N-dimethylacetamide (3.0 mL), 2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid (138 mg, 0.644 mmol), HATU (262 mg, 0.689 mmol) and N,N-diisopropylethylamine (120 μL, 0.689 mmol) and in the same manner as in Example 10, the title compound (171 mg, 71%) was obtained as a pale-yellow solid. $^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.75 - 0.82 (4H, m), 1.85 - 1.96 (1H, m), 6.70 - 6.75 (1H, m), 7.08 - 7.20 (2H, m), 7.34 - 7.61 (7H, m), 7.94 - 8.00 (1H, m), 8.02 (1H, s), 8.10 - 8.15 (1H, m), 8.46 (1H, d, J = 1.8 Hz), 8.56 - 8.60 (1H, m), 10.93 (1H, s), 12.06 (1H, s).

Example 13

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-2-oxo-1-(4-fluorophenyl)-1,2-dihydropyridine-3-carboxamide

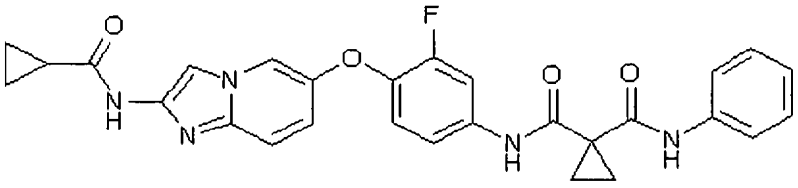


Using N-[6-(4-aminophenoxy)imidazo[1,2-a]pyridin-2-

yl]cyclopropanecarboxamide (150 mg, 0.486 mmol), N,N-dimethylacetamide (3.0 mL), 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (170 mg, 0.729 mmol), HATU (277 mg, 0.729 mmol) and N,N-diisopropylethylamine (127 μL, 0.729 mmol) and in the same manner as in Example 10, the title compound (181 mg, 71%) was obtained as a white solid.
$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.76 - 0.82 (4H, m), 1.85 - 1.96 (1H, m), 6.68 - 6.74 (1H, m), 7.00 - 7.10 (3H, m), 7.37 - 7.48 (3H, m), 7.56 - 7.72 (4H, m), 8.04 (1H, s), 8.08 - 8.12 (1H, m), 8.50 - 8.51 (1H, m), 8.54 - 8.58 (1H, m), 10.95 (1H, s), 11.89 (1H, s).

Example 14

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-N'-phenylcyclopropane-1,1-dicarboxamide



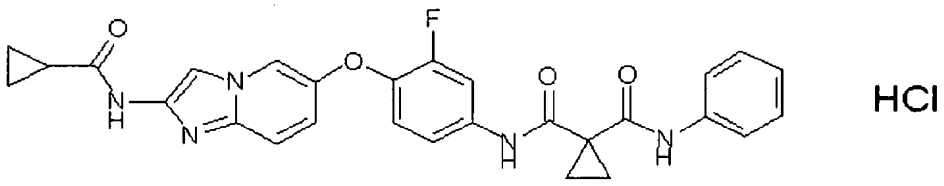
To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (400 mg, 1.23 mmol) in N,N-dimethylacetamide (4.0 mL) were added 1-(phenylcarbamoyl)cyclopropanecarboxylic acid (352 mg, 1.72 mmol), HATU (699 mg, 1.84 mmol) and N,N-diisopropylethylamine (320 μL, 1.84 mmol), and the mixture was stirred at room temperature for 3 hr. Water and saturated aqueous sodium hydrogen carbonate were added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl

acetate=40/60→0/100). The obtained powder was recrystallized from methyl ethyl ketone/water (=20/1) to give the title compound (294 mg, 47%) as white crystals.

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.75 - 0.83 (4H, m), 1.43 - 1.48 (4H, m), 1.85 - 1.96 (1H, m), 7.02 - 7.18 (3H, m), 7.26 - 7.46 (4H, m), 7.62 (2H, dd, J = 8.6, 1.1 Hz), 7.81 (1H, dd, J = 13.5, 2.7 Hz), 8.03 (1H, s), 8.42 - 8.44 (1H, m), 9.98 (1H, br s), 10.22 (1H, s), 10.94 (1H, s).

Example 15

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-N'-phenylcyclopropane-1,1-dicarboxamide hydrochloride




HCl

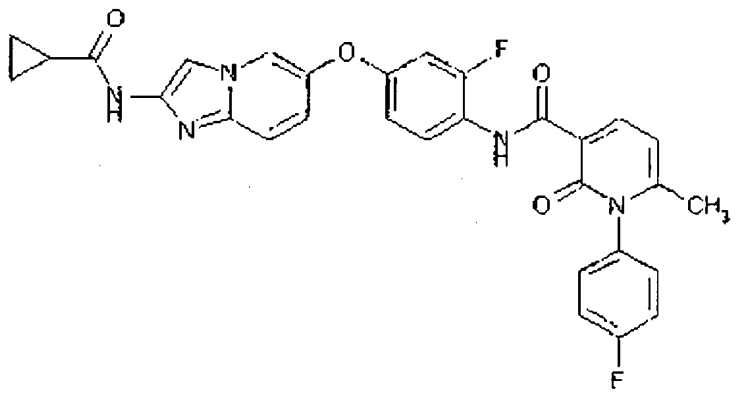
A suspension of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-N'-phenylcyclopropane-1,1-dicarboxamide (960 mg, 1.87 mmol) in methyl ethyl ketone (9.6 mL) was stirred with heating at 60°C, and 6N hydrochloric acid was added. The mixture was cooled to room temperature and left standing for 20 hr. The precipitate was filtered and washed with methyl ethyl ketone to give the title compound (697 mg, 68%) as white crystals.

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.85 - 0.94 (4H, m), 1.44 - 1.51 (4H, m), 1.90 - 1.99 (1H, m), 7.03 - 7.10 (1H, m), 7.21 - 7.34 (3H, m), 7.41 - 7.52 (2H, m), 7.60 - 7.64 (2H, m), 7.70 (1H, d, J = 9.6 Hz), 7.82 - 7.87 (1H, m), 8.06 (1H, s), 8.57 (1H, d, J = 1.8 Hz), 9.99 (1H, s), 10.32 (1H, s), 11.66 (1H, s).

Example 16

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-2-

fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



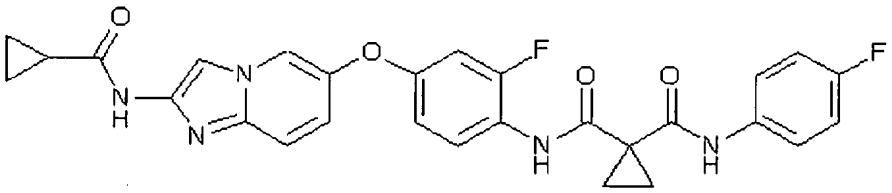
To a solution of N-[6-(4-amino-3-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol) in N,N-dimethylacetamide (3.0 mL) were added 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (170 mg, 0.689 mmol), HATU (262 mg, 0.689 mmol) and N,N-diisopropylethylamine (120 μL, 0.689 mmol), and the mixture was stirred at room temperature for 20 hr. Saturated aqueous sodium hydrogen carbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate and collected by filtration to give the title compound (208 mg, 81%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.77 - 0.81 (4H, m), 1.86 - 1.96 (1H, m), 2.07 (3H, s), 6.70 (1H, d, J = 8.1 Hz), 6.86 - 6.92 (1H, m), 7.06 - 7.12 (2H, m), 7.40 - 7.52 (5H, m), 8.04 (1H, s), 8.37 - 8.56 (3H, m), 10.97 (1H, s), 12.04 (1H, s).

Example 17

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-2-

fluorophenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

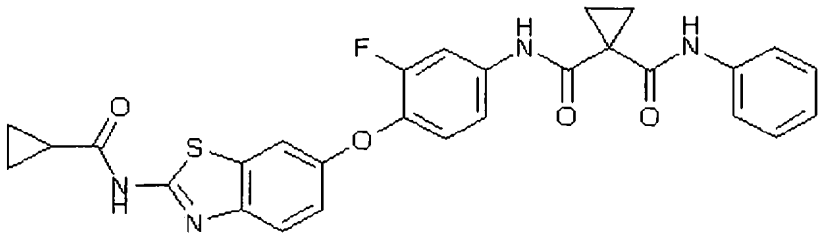


To a solution of N-[6-(4-amino-3-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol) in N,N-dimethylacetamide (3.0 mL) were added 1-[(4-fluorophenyl)carbamoyl]cyclopropanecarboxylic acid (170 mg, 0.689 mmol), HATU (262 mg, 0.689 mmol) and N,N-diisopropylethylamine (120 μL, 0.689 mmol), and the mixture was stirred at room temperature for 20 hr. Saturated aqueous sodium hydrogen carbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate alone). The obtained powder was washed with hexane/ethyl acetate and collected by filtration to give the title compound (115 mg, 47%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.77 - 0.82 (4H, m), 1.51 - 1.59 (4H, s), 1.87 - 1.96 (1H, m), 6.82 - 6.88 (1H, m), 7.00 - 7.20 (4H, m), 7.47 (1H, d, J = 9.6 Hz), 7.56 - 7.63 (2H, m), 7.72 - 7.80 (1H, m), 8.05 (1H, s), 8.57 (1H, d, J = 1.5 Hz), 10.00 (1H, s), 10.37 (1H, s), 10.97 (1H, s).

Example 18

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]-1,3-benzothiazol-6-yl}oxy)-3-fluorophenyl]-N'-phenylcyclopropane-1,1-dicarboxamide

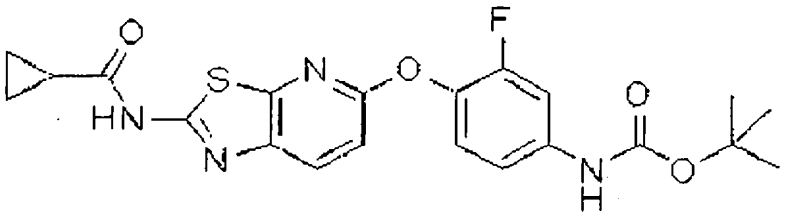


To a solution of 1-(phenylcarbamoyl)cyclopropanecarboxylic acid (214 mg, 1.04 mmol) in tetrahydrofuran (2 mL) were added oxalyl chloride (178 μL, 2.08 μmol) and N,N-dimethylformamide (2 drops) under ice-cooling, and the mixture was stirred at room temperature for 3 hr. The solvent was evaporated under reduced pressure. To a solution of the obtained residue in N,N-dimethylacetamide (5 mL) was added N-[6-(4-amino-2-fluorophenoxy)-1,3-benzothiazol-2-yl]cyclopropanecarboxamide (275 mg, 0.80 mmol), and the mixture was stirred at room temperature for 18 hr. Water was added to the reaction solution, and the mixture was extracted with ethyl acetate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=80/20→20/80, NH silica gel, hexane/ethyl acetate=50/50→0/100) and recrystallized from ethyl acetate to give the title compound (241 mg, 57%) as white crystals.

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.89 - 0.97 (4H, m), 1.44 - 1.47 (4H, m), 1.95 - 2.06 (1H, m), 7.03 - 7.19 (3H, m), 7.25 - 7.43 (3H, m), 7.56 (1H, d, J = 2.7 Hz), 7.60 - 7.64 (2H, m), 7.70 (1H, d, J = 8.7 Hz), 7.81 (1H, dd, J = 13.5, 2.4 Hz), 9.99 (1H, s), 10.24 (1H, s), 12.59 (1H, s).

Example 19

Production of tert-butyl [4-({2-[(cyclopropylcarbonyl)amino][1,3]thiazolo[5,4-b]pyridin-5-yl}oxy)-3-fluorophenyl]carbamate

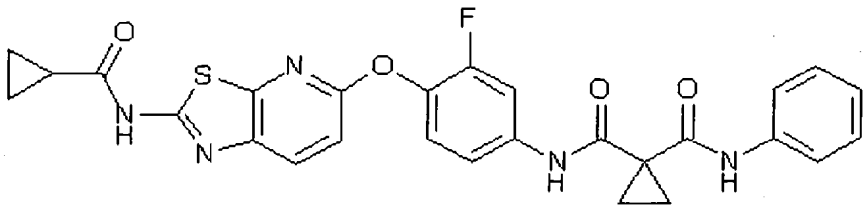


To a solution of tert-butyl {4-[(2-amino[1,3]thiazolo[5,4-b]pyridin-5-yl)oxy]-3-fluorophenyl}carbamate (2.02 g, 5.37 mmol) in N,N-dimethylacetamide (20.2 mL) were added cyclopropanecarbonyl chloride (0.97 mL, 10.7 mmol) and triethylamine (2.24 mL, 16.1 mmol), and the mixture was stirred at room temperature for 24 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, methanol (20 mL) and 5% aqueous sodium carbonate solution (10 mL) were added to the residue, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/ethyl acetate(=1/1) and collected by filtration to give the title compound (1.33 g, 56%).

$^1$H-NMR (DMSO-$d_6$, 300MHz) $\delta$ 0.92 - 0.99 (4H, m), 1.49 (9H, s), 1.85 - 1.95 (1H, m), 7.16 (1H, d, J = 8.7 Hz), 7.24 - 7.27 (2H, m), 7.50 - 7.58 (1H, m), 8.16 (1H, d, J = 8.7 Hz), 9.63 (1H, s), 12.67 (1H, br s).

Example 20

Production of N-[4-({2-[(cyclopropylcarbonyl)amino][1,3]thiazolo[5,4-b]pyridin-5-yl}oxy)-3-fluorophenyl]-N'-phenylcyclopropane-1,1-dicarboxamide

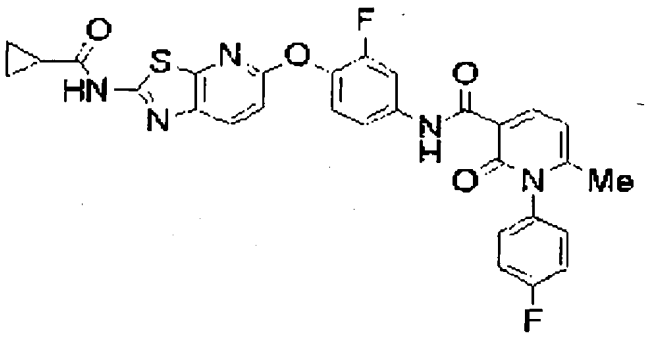


To a solution of N-[5-(4-amino-2-fluorophenoxy)[1,3]thiazolo[5,4-b]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.436 mmol) in N,N-dimethylacetamide (3.0 mL) were added 1-(phenylcarbamoyl)cyclopropanecarboxylic acid (134 mg, 0.653 mmol), HATU (248 mg, 0.653 mmol) and N,N-diisopropylethylamine (114 μL, 0.653 mmol), and the mixture was stirred at room temperature for 2 hr. Saturated aqueous sodium hydrogen carbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate alone). The obtained powder was washed with hexane/ethyl acetate and collected by filtration to give the title compound (175 mg, 76%).

$^1$H-NMR (DMSO-$d_6$, 300MHz) δ 0.89 - 0.98 (4H, m), 1.47 (4H, s), 1.94 - 2.03 (1H, m), 7.03 - 7.09 (1H, m), 7.18 (1H, d, J = 8.9 Hz), 7.25 - 7.34 (3H, m), 7.40 - 7.46 (1H, m), 7.61 - 7.65 (2H, m), 7.79 (1H, dd, J = 13.1, 2.3 Hz), 8.17 (1H, d, J = 8.9 Hz), 10.01 (1H, s), 10.26 (1H, s), 12.68 (1H, br s).

Example 21

Production of N-[4-({2-[(cyclopropylcarbonyl)amino][1,3]thiazolo[5,4-b]pyridin-5-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide

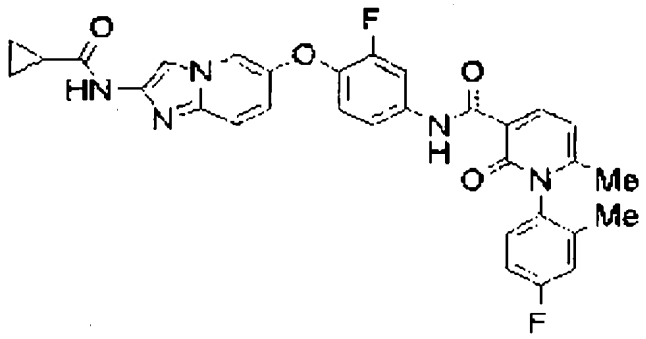


N-[5-(4-Amino-2-fluorophenoxy)[1,3]thiazolo[5,4-b]pyridin-2-yl]cyclopropanecarboxamide (240 mg, 0.70 mmol), 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (190 mg, 0.77 mmol) and HATU (340 mg, 0.91 mmol) were suspended in N,N'-dimethylformamide (3.0 mL), and N,N-diisopropylethylamine (0.24 mL, 1.4 mmol) was added. After stirring at room temperature for 8 hr, the mixture was diluted with ethyl acetate (5.0 mL) and tetrahydrofuran (5.0 mL). The mixture was washed twice with saturated aqueous sodium hydrogen carbonate solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and ethyl acetate was added to the residue. The resulting precipitate was collected by filtration to give the title compound (350 mg, 0.61 mmol, 88%) as a pale-yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.89 - 0.99 (4H, m), 1.93 - 2.03 (1H, m), 2.08 (3H, s), 6.71 (1H, d, J=8.3 Hz), 7.19 (1H, d, J=8.7 Hz), 7.32 (1H, t, J=8.8 Hz), 7.40 - 7.55 (5H, m), 7.95 (1H, dd, J=12.9, 2.4 Hz), 8.17 (1H, d, J=8.7 Hz), 8.50 (1H, d, J=7.6 Hz), 12.03 (1H, s), 12.69 (1H, s).

Example 22

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide

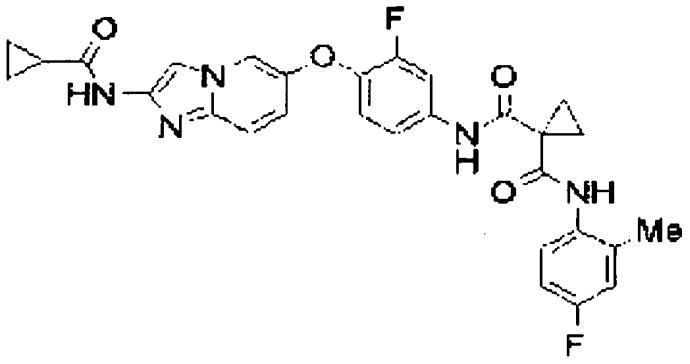


N-[6-(4-Amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol), 1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (130 mg, 0.51 mmol) and HATU (230 mg, 0.60 mmol) were suspended in N,N-dimethylformamide (3.0 mL), and N,N-diisopropylethylamine (0.16 mL, 0.92 mmol) was added. After stirring at room temperature for 8 hr, the reaction mixture was diluted with ethyl acetate (5.0 mL) and tetrahydrofuran (5.0 mL). The mixture was washed twice with saturated aqueous sodium hydrogen carbonate solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, ethyl acetate was added to the residue, and the resulting precipitate was collected by filtration. The obtained precipitate was recrystallized from ethanol/water to give the title compound (130 mg, 50%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) $\delta$ 0.74-0.83 (4H, m), 1.86 - 1.97 (1H, m), 2.00 (3H, s), 2.03 (3H, s), 6.75 (1H, d, J = 8.1 Hz), 7.07 - 7.18 (2H, m), 7.21 - 7.30 (1H, m), 7.33 - 7.47 (4H, m), 7.97 (1H, dd, J = 13.3, 2.4 Hz), 8.02 (1H, s), 8.45 (1H, d, J = 1.9 Hz), 8.51 (1H, d, J = 7.6 Hz), 10.93 (1H, s), 11.97 (1H, s).

Example 23

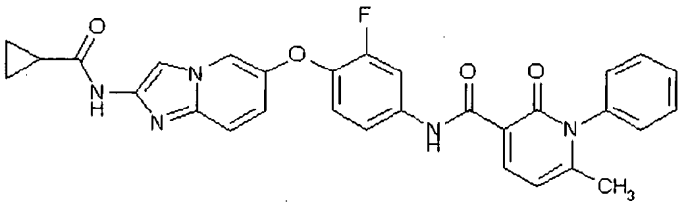
Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-N'-(4-fluoro-2-methylphenyl)cyclopropane-1,1-dicarboxamide



N-[6-(4-Amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol), 1-[(4-fluoro-2-methylphenyl)carbamoyl]cyclopropanecarboxylic acid (120 mg, 0.51 mmol) and HATU (230 mg, 0.60 mmol) were suspended in N,N-dimethylformamide (3.0 mL), and N,N-diisopropylethylamine (0.16 mL, 0.92 mmol) was added. After stirring at room temperature for 8 hr, the reaction mixture was diluted with ethyl acetate (5.0 mL) and tetrahydrofuran (5.0 mL). The mixture was washed twice with saturated aqueous sodium hydrogen carbonate solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, ethyl acetate was added to the residue, and the resulting precipitate was collected by filtration. The obtained precipitate was recrystallized from ethanol/water to give the title compound (110 mg, 45%) as a white solid.
$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.74 - 0.84 (4H, m), 1.52 (4H, s), 1.85 - 1.97 (1H, m), 2.20 (3H, s), 6.97 - 7.19 (4H, m), 7.34 - 7.40 (1H, m), 7.41 - 7.50 (2H, m), 7.75 - 7.85 (1H, m), 8.03 (1H, s), 8.44 (1H, d, J=1.9 Hz), 9.73 (1H, s), 10.41 (1H, s), 10.94 (1H, s).

Example 24

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide

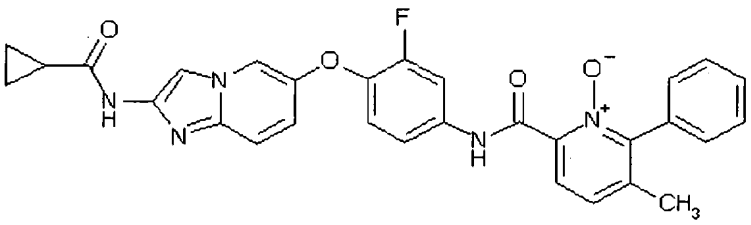


To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (70 mg, 0.215 mmol) and 6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid (59.1 mg, 0.258 mmol) in N,N-dimethylformamide (1.0 mL) were added HATU (98 mg, 0.258 mmol) and N,N-diisopropylethylamine (74 μL, 0.43 mmol), and the mixture was stirred at room temperature for 17 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate) to give a pale-yellow solid. The obtained pale-yellow solid was washed with ethyl acetate and collected by filtration to give the title compound (66 mg, 57%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.70 - 0.85 (4H, m), 1.86 - 1.96 (1H, m), 2.06 (3H, s), 6.71 (1H, d, J = 8.3 Hz), 7.07 - 7.17 (2H, m), 7.32 - 7.65 (7H, m), 7.96 (1H, dd, J = 13.4, 2.5 Hz), 8.02 (1H, s), 8.42 - 8.52 (2H, m), 10.93 (1H, s), 12.02 (1H, s).

Example 25

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-5-methyl-6-phenylpyridine-2-carboxamide 1-oxide

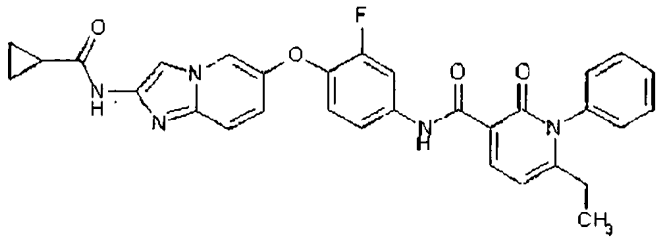


To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (98.8 mg, 0.303 mmol) and 5-methyl-6-phenylpyridine-2-carboxylic acid 1-oxide (83.1 mg, 0.363 mmol) in N,N-dimethylformamide (1.0 mL) were added HATU (150 mg, 0.394 mmol) and N,N-diisopropylethylamine (104 μL, 0.606 mmol), and the mixture was stirred at room temperature for 3.5 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate) to give a white solid. The obtained solid was washed with ethyl acetate to give the title compound (100 mg, 61%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.72 - 0.86 (4H, m), 1.85 - 1.98 (1H, m), 2.12 (3H, s), 7.05 - 7.21 (2H, m), 7.36 - 7.61 (7H, m), 7.70 (1H, d, J = 8.9 Hz), 7.98 (1H, dd, J = 13.0, 2.5 Hz), 8.03 (1H, s), 8.31 (1H, d, J = 8.3 Hz), 8.49 (1 H, d, J = 1.7 Hz), 10.94 (1H, s), 13.79 (1H, s).

Example 26

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-ethyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide

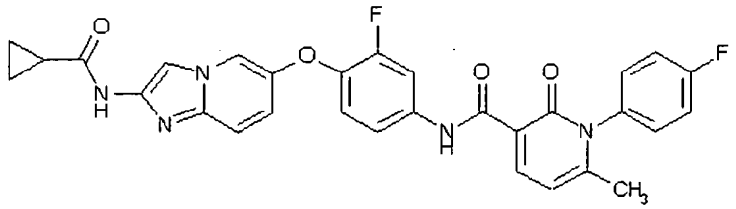


To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (100 mg, 0.306 mmol) and 6-ethyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid (89 mg, 0.366 mmol) in N,N-dimethylformamide (1.0 mL) were added HATU (151 mg, 0.397 mmol) and N,N-diisopropylethylamine (105 μL, 0.612 mmol), and the mixture was stirred at room temperature for 17 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate) to give a white solid. The obtained white solid was washed with ethyl acetate to give the title compound (100 mg, 59%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.73 - 0.85 (4H, m), 1.05 (3H, t, J = 7.4 Hz), 1.82 - 2.01 (1H, m), 2.30 (2H, q, J= 7.4 Hz), 6.68 (1H, d, J = 7.7 Hz), 7.05 - 7.21 (2H, m), 7.31 - 7.48 (4H, m), 7.49 - 7.66 (3H, m), 7.97 (1H, dd, J = 13.2, 2.5 Hz), 8.02 (1H, s), 8.45 (1H, d, J = 1.7 Hz), 8.53 (1H, d, J = 7.7 Hz), 10.94 (1H, s), 12.02 (1H, s).

Example 27

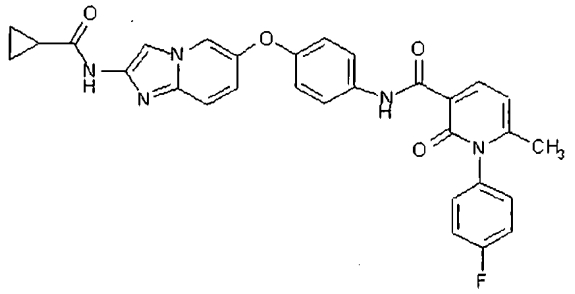
Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (100 mg, 0.306 mmol) and 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (90.8 mg, 0.367 mmol) in N,N-dimethylformamide (1.0 mL) were added HATU (151 mg, 0.397 mmol) and N,N-diisopropylethylamine (105 μL, 0.612 mmol), and the mixture was stirred at room temperature for 20 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate) to give a white solid. The obtained white solid was washed with ethyl acetate to give the title compound (131 mg, 77%) as a white solid.
$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.66 - 0.92 (4H, m), 1.87 - 1.93 (1H, m), 2.07 (3H, s), 6.70 (1H, d, J = 7.6 Hz), 7.01 - 7.18 (2H, m), 7.26 - 7.56 (6H, m), 7.97 (1H, d, J = 13.4 Hz), 8.02 (1H, s), 8.40 - 8.54 (2H, m), 10.93 (1H, s), 11.98 (1H, s).

Example 28

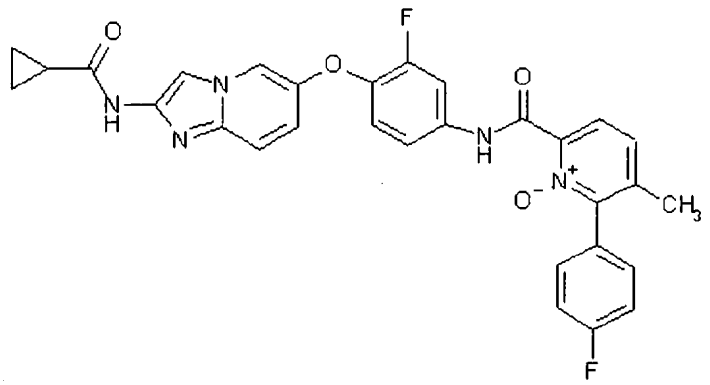
Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



To a solution of N-[6-(4-aminophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (100 mg, 0.324 mmol) and 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (96.1 mg, 0.389 mmol) in N,N-dimethylformamide (1.0 mL) were added HATU (147.8 mg, 0.389 mmol) and N,N-diisopropylethylamine (111.6 μL, 0.648 mmol), and the mixture was stirred at room temperature for 20 hr. Tetrahydrofuran, ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with tetrahydrofuran and collected by filtration to give the title compound (154 mg, 88%) as a white solid.
$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.68 - 0.86 (4H, m), 1.89 - 1.95 (1H, m), 2.06 (3H, s), 6.60 - 6.76 (1H, m), 6.93 - 7.12 (3H, m), 7.37 - 7.53 (5H, m), 7.63 - 7.73 (2H, m), 8.03 (1H, s), 8.40 - 8.54 (2H, m), 10.94 (1H, s), 11.83 (1H, s).

Example 29

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide



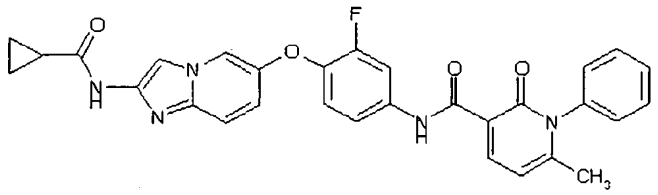
To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (100 mg, 0.306 mmol) and 6-(4-fluorophenyl)-5-methylpyridine-2-carboxylic acid 1-oxide (98.9 mg, 0.367 mmol) in N,N-dimethylformamide (1.0 mL) were added HATU (140 mg, 0.368 mmol) and N,N-diisopropylethylamine (105 μL, 0.612 mmol), and the mixture was stirred at room temperature for 3 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate) to give a white solid. The obtained white solid was washed with ethyl acetate to give the title compound (80 mg, 47%) as white crystals.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.66 - 0.89 (4H, m), 1.87 - 1.97 (1H, m), 2.13 (3H, s), 7.07 - 7.22 (2H, m), 7.33 - 7.55 (6H, m), 7.69 (1H, d, J = 8.9 Hz), 7.98 (1H, dd, J = 13.0, 2.5 Hz), 8.03 (1H, s), 8.31 (1H, d, J = 8.3 Hz), 8.48 (1H, d, J = 1.7 Hz), 10.94 (1H, s), 13.73 (1H, s).

Example 30

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-

carboxamide hydrochloride




HCl

To a suspension of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide (464 mg, 0,864 mmol) in ethanol was added and dissolved therein 6N hydrochloric acid (86.4 μL, 1.04 mmol). The solution was concentrated to a half amount, and left standing for 17 hr. The precipitate was collected by filtration and washed with ethanol to give a pale-yellow solid (458 mg).

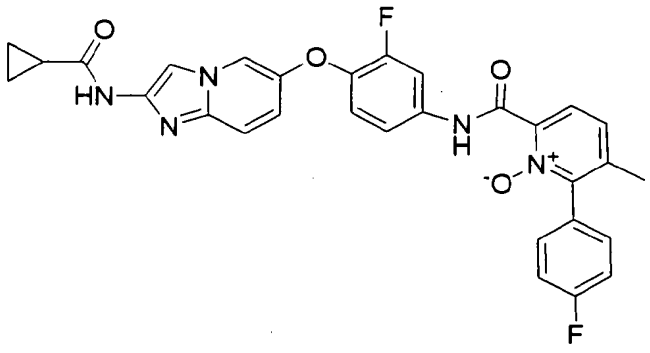
A suspension of pale-yellow solid (100 mg) in methyl ethyl ketone (10 mL) was stirred at 60°C for 17 hr. The precipitate was filtered, washed with methyl ethyl ketone and collected by filtration to give the title compound (80 mg).

To the title compound (80 mg) was added a pale-yellow solid (358 mg), after which methyl ethyl ketone (4 mL) was added, and the mixture was stirred at 60°C for 6 hr. The precipitate was collected by filtration to give the title compound (330 mg, 67%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.80 - 0.93 (4H, m), 1.88 - 2.00 (1H, m), 2.07 (3H, s), 6.72 (1H, d, J= 8.3 Hz), 7.24 (1H, t, J = 9.1 Hz), 7.37 - 7.75 (8H, m), 8.01 (1H, dd, J = 13.2, 2.5 Hz), 8.06 (1H, s), 8.49 (1H, d, J = 7.6 Hz), 8.59 (1H, d, J = 2.1 Hz), 11.65 (1 H, br s), 12.07 (1H, s).

Example 31

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide hydrochloride



HC l

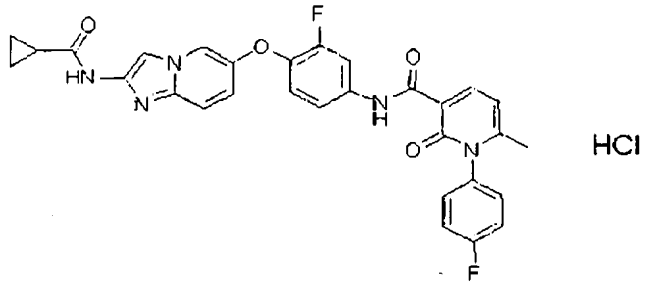
To a suspension of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide (1.54 g, 2.77 mmol) in ethanol (15 mL) was added and dissolved therein 6N hydrochloric acid (554 μL, 3.32 mmol), and the mixture was left standing at room temperature overnight. The precipitate was collected by filtration and washed with ethanol to give a white powder. The white powder was dissolved in ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The residue was suspended in ethanol (30 mL) and heated to 80°C. 6N Hydrochloric acid (370 μL, 2.22 mmol) was added dropwise and dissolved therein. The solution was allowed to gradually cool to 50°C, and the mixture was stirred for 6 hr. The precipitate was collected by filtration and washed with ethanol to give a white solid. The white solid was suspended in methyl ethyl ketone (10 mL), and the suspension was stirred at 50°C overnight. The precipitate was collected by filtration and washed with methyl ethyl ketone to give the title compound (747 mg, 46%) as white crystals.

$^1$H-NMR (300 MHz, DMSO-$d_6$) δ 0.80 - 0.97 (4H, m), 1.88 - 2.06 (1H, m), 2.13 (3H, s), 7.20 - 7.44 (3H, m), 7.46 - 7.82 (6H, m), 8.03 (1H, dd, J = 13.1, 2.4 Hz), 8.09 (1H, s), 8.31 (1H, d,

J= 8.3 Hz), 8.66 (1H, d, J = 1.7 Hz), 11.91 (1H, s), 13.77 (1H, s).

Example 32

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide hydrochloride



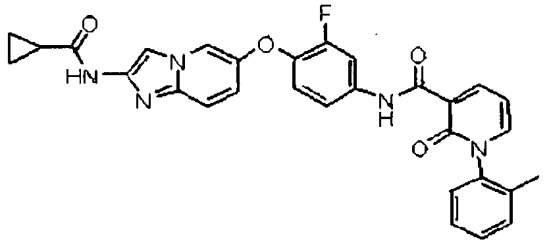

To a suspension of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (1.42 g, 2.55 mmol) in ethanol (14 mL) and water (2 mL) was added and dissolved therein 6N hydrochloric acid (510 μL, 3.06 mmol), and the solution was concentrated to a half amount, and left standing for 1 hr. The precipitate was collected by filtration to give white crystals. The white crystals were suspended in ethanol (50 mL) again, 6N hydrochloric acid (205 μL, 1.53 mmol) was added, and the mixture was dissolved at 70°C. The solution was left standing at room temperature for 6 hr. The precipitate was collected by filtration to give a white solid. The white solid (850 mg) was dissolved in ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The residue was suspended in ethanol (20 mL), heated to 80°C and dissolved by dropwise addition of 6N hydrochloric acid (358 μL, 2.15 mmol).

The solution was allowed to gradually cool to 50°C, and the mixture was stirred overnight. The precipitate was collected by filtration and washed with ethanol to give a white solid. The white solid was suspended in methyl ethyl ketone (10 mL), and the mixture was stirred at 50°C overnight. The precipitate was collected by filtration and washed with methyl ethyl ketone to give the title compound (590 mg, 39%) as white crystals.

$^1$H-NMR (300 MHz, DMSO-$d_6$) δ 0.83 - 0.97 (4H, m), 1.90 - 2.03 (1H, m), 2.08 (3H, s), 6.71 (1H, d, J = 8.1 Hz), 7.25 (1H, t, J = 9.1 Hz), 7.35 - 7.61 (6H, m), 7.75 (1H, d, J = 9.8 Hz), 8.02 (1H, dd, J = 13.2, 2.5 Hz), 8.08 (1H, s), 8.49 (1H, d, J= 7.6 Hz), 8.62 (1H, d, J = 1.9 Hz), 11.85 (1H, s), 12.03 (1H, s).

Example 33

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide



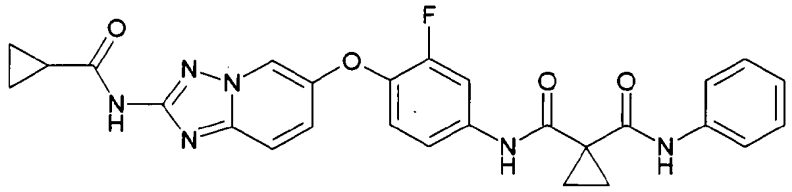
Using N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (200 mg, 0.613 mmol), 1-(2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (169 mg, 0.735 mmol), N,N-dimethylformamide (2 mL), N,N-diisopropylethylamine(211 µL, 1.23 mmol) and HATU (280 mg, 0.735 mmol) and in the same manner as in Example 24, the title compound (177 mg, 54%) was obtained as pale-yellow crystals.

$^1$H-NMR (300 MHz, DMSO-$d_6$) δ 0.61 - 0.95 (4H, m), 1.87 - 1.95 (1H, m), 2.08 (3H, s), 6.64 - 6.83 (1H, m), 7.04 - 7.24 (2H, m), 7.33 - 7.53 (6H, m), 7.91 - 8.09 (3H, m), 8.46 (1H, d, J =

1.7 Hz), 8.61 (1H, dd, J = 7.3, 2.2 Hz), 10.94 (1H, s), 12.07 (1H, s).

Example 34

Production of N-[4-({2-[(cyclopropylcarbonyl)amino][1,2,4]triazolo[1,5-a]pyridin-6-yl}oxy)-3-fluorophenyl]-N'-phenylcyclopropane-1,1-dicarboxamide

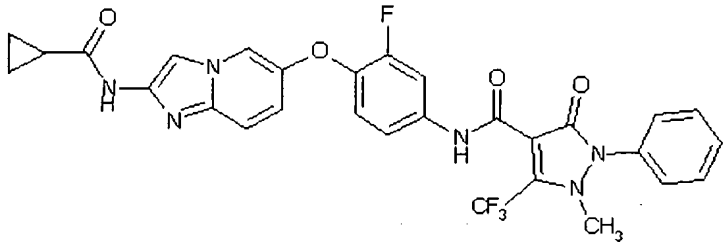


Using N-[6-(4-amino-2-fluorophenoxy)[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide (120 mg, 0.367 mmol), 1-(phenylcarbamoyl)cyclopropanecarboxylic acid (90.4 mg, 0.440 mmol), N,N-dimethylformamide (1 mL), N,N-diisopropylethylamine (126 μL, 0.733 mmol) and HATU (209 mg, 0.550 mmol) and in the same manner as in Example 24, the title compound (151 mg, 80%) was obtained as white crystals.

$^1$H-NMR (300 MHz, DMSO-$d_6$) δ 0.71 - 0.86 (4H, m), 1.43 - 1.50 (4H, m), 1.97 - 2.09 (1H, m), 7.03 - 7.10 (1H, m), 7.19 (1H, t, J = 9.2 Hz), 7.26 - 7.41 (3H, m), 7.51 (1H, dd, J = 9.6, 2.3 Hz), 7.58 - 7.65 (2H, m), 7.71 (1H, d, J = 9.6 Hz), 7.82 (1H, dd, J = 13.5, 2.4 Hz), 8.78 (1H, d, J = 1.7 Hz), 9.98 (1H, s), 10.24 (1H, s), 11.03 (1H, s).

Example 35

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-methyl-3-oxo-2-phenyl-5-(trifluoromethyl)-2,3-dihydro-1H-pyrazole-4-carboxamide

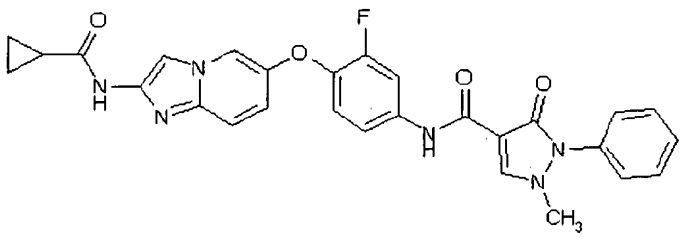


A mixture of 1-methyl-3-oxo-2-phenyl-5-(trifluoromethyl)-2,3-dihydro-1H-pyrazole-4-carboxylic acid (450 mg, 1.6 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (360 mg, 1.1 mmol), HATU (590 mg, 1.6 mmol), diisopropylethylamine (430 mg, 3.3 mmol) and N,N-dimethylformamide (7 mL) was stirred at room temperature for 13 hr. Ethyl acetate/tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the mixture, and the aqueous layer was extracted 4 times with ethyl acetate/tetrahydrofuran. The combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=40/60→100/0) to give the title compound (320 mg, 48%) as a pale-yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.75 - 0.84 (4H, m), 1.85 - 1.97 (1H, m), 3.52 (3H, s), 7.11 (1H, dd, J = 9.6, 2.5 Hz), 7.17 (1H, t, J = 9.0 Hz), 7.26 - 7.32 (1H, m), 7.44 (1H, d, J = 9.6 Hz), 7.53 - 7.69 (5H, m), 7.88 (1H, dd, J = 13.1, 2.4 Hz), 8.03 (1H, s), 8.45 (1H, d, J = 1.7 Hz), 10.93 (1H, s), 10.97 (1H, s).

Example 36

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide

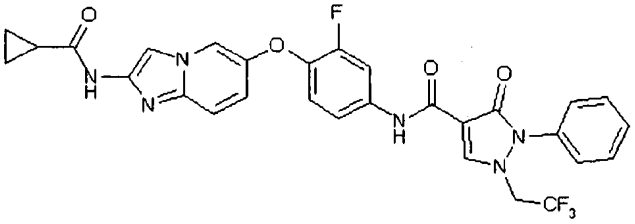


Using 1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic acid (220 mg, 0.99 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (220 mg, 0.66 mmol), HATU (380 mg, 0.99 mmol), diisopropylethylamine (260 mg, 2.0 mmol) and N,N-dimethylformamide (6 mL) as starting materials and in the same manner as in Example 35, the title compound (50 mg, 15%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.74 - 0.84 (4H, m), 1.86 - 1.97 (1H, m), 3.48 (3H, s), 7.11 (1H, dd, J = 9.6, 2.5 Hz), 7.16 (1H, t, J = 9.0 Hz), 7.21 - 7.27 (1H, m), 7.43 (1H, d, J = 9.6 Hz), 7.46 - 7.64 (5H, m), 7.90 (1H, dd, J = 13.3, 2.5 Hz), 8.02 (1H, s), 8.44 (1H, d, J = 1.9 Hz), 8.62 (1H, s), 10.45 (1H, s), 10.93 (1H, s).

Example 37

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-3-oxo-2-phenyl-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-pyrazole-4-carboxamide



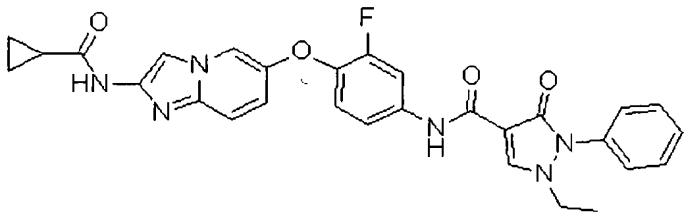
Using 3-oxo-2-phenyl-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-pyrazole-4-carboxylic acid (210 mg, 0.72 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (170 mg, 0.52 mmol), HATU (280 mg, 0.72 mmol), diisopropylethylamine (200 mg, 1.6 mmol) and N,N-

dimethylformamide (6 mL) as starting materials and in the same manner as in Example 35, the title compound (240 mg, 77%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.74 - 0.84 (4H, m), 1.87 - 1.97 (1H, m), 4.90 (2H, q, J = 8.5 Hz), 7.11 (1H, dd, J = 9.6, 2.3 Hz), 7.17 (1H, t, J = 9.0 Hz), 7.27 - 7.33 (1H, m), 7.40 - 7.46 (3H, m), 7.50 - 7.65 (3H, m), 7.89 (1H, dd, J = 13.1, 2.3 Hz), 8.03 (1H, s), 8.46 (1H, d, J = 1.9 Hz), 8.87 (1H, s), 10.26 (1H, s), 10.94 (1H, s).

Example 38

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-ethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide

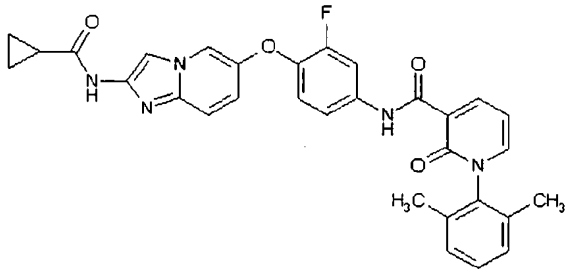


Using 1-ethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic acid (270 mg, 1.2 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (260 mg, 0.79 mmol), HATU (450 mg, 1.2 mmol), diisopropylethylamine (300 mg, 2.4 mmol) and N,N-dimethylformamide (6 mL) as starting materials and in the same manner as in Example 35, the title compound (140 mg, 34%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.75 - 0.83 (4H, m), 1.07 (3H, t, J = 7.2 Hz), 1.87 - 1.96 (1H, m), 3.88 (2H, q, J = 7.2 Hz), 7.11 (1H, dd, J = 9.7, 2.4 Hz), 7.16 (1H, t, J = 8.9 Hz), 7.22 - 7.28 (1H, m), 7.40 - 7.66 (6H, m), 7.90 (1H, dd, J = 13.3, 2.4 Hz), 8.02 (1H, s), 8.44 (1H, d, J = 1.7 Hz), 8.71 (1H, s), 10.43 (1H, s), 10.93 (1H, s).

Example 39

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(2,6-dimethylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

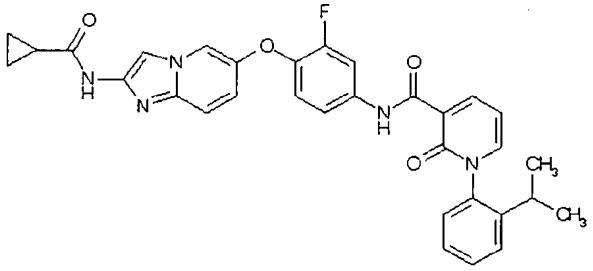


1-(2,6-Dimethylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (120 mg, 0.51 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol) and HATU (340 mg, 0.91 mmol) were suspended in N,N-dimethylformamide (3.0 mL), and N,N-diisopropylethylamine (0.16 mL, 0.92 mmol) was added. After stirring at room temperature overnight, the mixture was diluted with ethyl acetate (5.0 mL) and tetrahydrofuran (5.0 mL). The mixture was washed twice with saturated aqueous sodium hydrogen carbonate solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=65/35→85/15). The fractions containing the object product were mixed. The solvent was evaporated under reduced pressure, and a small amount of hexane/ethyl acetate was added. The resulting precipitate was collected by filtration to give the title compound (130 mg, 49%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.80 (4H, d, J = 2.3 Hz), 1.86 - 1.97 (1H, m), 2.02 (6H, s), 6.81 (1H, d, J = 7.0 Hz), 7.07 - 7.19 (2H, m), 7.24 - 7.41 (4H, m), 7.44 (1H, d, J = 9.6 Hz), 7.93-8.04 (3H, m), 8.46 (1H, d, J = 1.9 Hz), 8.64 (1H, dd, J = 7.3, 2.2 Hz), 10.94 (1H, s), 12.07 (1H, s).

Example 40

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-[2-(1-methylethyl)phenyl]-2-oxo-1,2-dihydropyridine-3-carboxamide



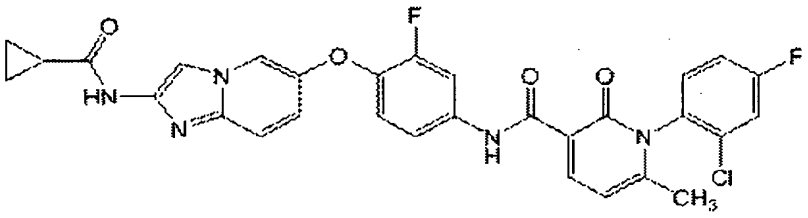
1-[2-(1-Methylethyl)phenyl]-2-oxo-1,2-dihydropyridine-3-carboxylic acid (100 mg, 0.39 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (120 mg, 0.35 mmol) and HATU (170 mg, 0.45 mmol) were suspended in N,N-dimethylformamide (3.0 mL), and N,N-diisopropylethylamine (0.12 mL, 0.71 mmol) was added. After stirring at room temperature overnight, the mixture was diluted with ethyl acetate (5.0 mL) and tetrahydrofuran (5.0 mL). The mixture was washed twice with saturated aqueous sodium hydrogen carbonate solution, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=65/35→85/15). The fractions containing the object product were mixed. The solvent was evaporated under reduced pressure, and a small amount of hexane/ethyl acetate (=2/1) was added. The resulting precipitate was collected by filtration to give the title compound (53 mg, 27%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.79 (4H, d, J = 2.5 Hz), 1.12 (3H, d, J = 6.8 Hz), 1.16 (3H, d, J=7.2 Hz), 1.86 - 1.97 (1H, m), 2.52 - 2.62 (1H, m), 6.75 (1H, d, J = 7.2 Hz), 7.06 - 7.21 (2H, m), 7.31 - 7.47 (4H, m), 7.48 - 7.60 (2H, m), 7.97 (1H, dd, J

= 13.2, 2.5 Hz), 8.02 (1H, s,), 8.10 (1H, dd, J = 6.5, 2.2 Hz,), 8.45 (1H, d, J = 1.9 Hz), 8.62 (1H, dd, J = 7.3, 2.2 Hz), 10.94 (1H, s), 12.08 (1H, s).

Example 41

Production of 1-(2-chloro-4-fluorophenyl)-N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



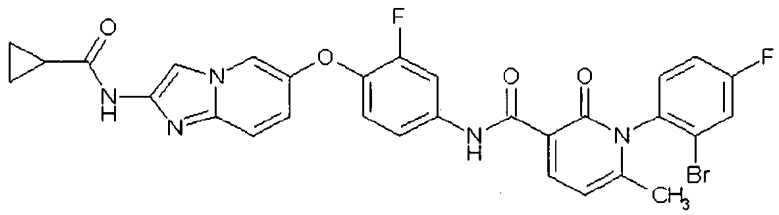
A mixture of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.459 mmol), 1-(2-chloro-4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (168 mg, 0.597 mmol), HATU (262 mg, 0.689 mmol), N,N-diisopropylethylamine (160 μL, 0.919 mmol) and N,N-dimethylformamide (3 mL) was stirred at room temperature for 18 hr. After dilution with ethyl acetate, the mixture was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (NH silica gel, 30 g, ethyl acetate/hexane=2/98→100/0), silica gel column chromatography (30 g, ethyl acetate/hexane=0/100→100/0) and preparative HPLC (acetonitrile/water=40/60→50/50, containing 0.1% trifluoroacetic acid) to give the title compound (101 mg, 37%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.74 - 0.83 (4H, m), 1.86 - 1.97 (1H, m), 2.07 (3H, s), 6.75 - 6.80 (1H, m), 7.07 - 7.18 (2H, m), 7.35 - 7.41 (1H, m), 7.44 (1H, d, J = 9.6 Hz), 7.47 - 7.55 (1H, m), 7.71 - 7.78 (1H, m), 7.83 (1H, dd, J = 8.5, 2.8 Hz), 7.97 (1H, dd, J = 13.4, 2.4 Hz), 8.02 (1H, s), 8.46 (1H, dd, J

= 2.4, 0.6 Hz), 8.54 (1H, d, J = 7.5 Hz), 10.95 (1H, s), 11.81 (1H, s).

Example 42

Production of 1-(2-bromo-4-fluorophenyl)-N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



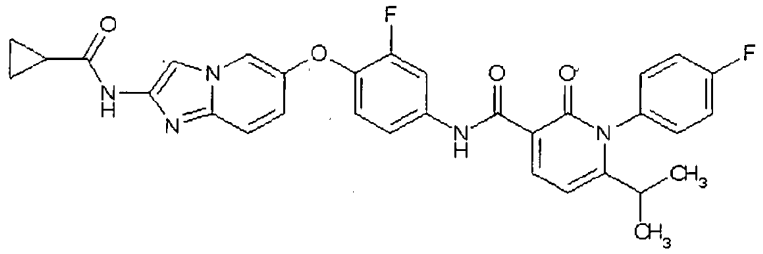
A mixture of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.459 mmol), 1-(2-bromo-4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (146 mg, 0.448 mmol), HATU (262 mg, 0.689 mmol), N,N-diisopropylethylamine (160 μL, 0.919 mmol) and N,N-dimethylformamide (3 mL) was stirred at room temperature for 3 days. After dilution with ethyl acetate, the mixture was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (NH silica gel, 30 g, ethyl acetate/hexane=2/98→100/0) and preparative HPLC (acetonitrile/water =40/60→50/50, containing 0.1% trifluoroacetic acid) to give the title compound (152 mg, 52%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.75 - 0.82 (4H, m), 1.86 - 1.97 (1H, m), 2.06 (3H, s), 6.75 - 6.80 (1H, m), 7.07 - 7.18 (2H, m), 7.35 - 7.47 (2H, m), 7.50 - 7.58 (1H, m), 7.69 - 7.76 (1H, m), 7.90 - 8.01 (2H, m), 8.02 (1H, s), 8.44 - 8.47 (1H, m), 8.54 (1H, d, J = 7.5 Hz), 10.94 (1H, s), 11.84 (1H, s).

Example 43

Production of N-[4-({2-

[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-(1-methylethyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

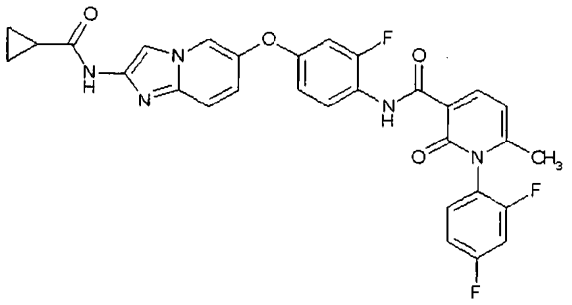


A mixture of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.459 mmol), 1-(4-fluorophenyl)-6-(1-methylethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (151 mg, 0.551 mmol), HATU (262 mg, 0.689 mmol), N,N-diisopropylethylamine (240 μL, 1.37 mmol) and N,N-dimethylformamide (3 mL) was stirred at room temperature for 4 days. After dilution with ethyl acetate, the mixture was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (NH silica gel, 30 g, ethyl acetate/hexane=2/98→80/20) to give the title compound (157 mg, 58%) as a white powder.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.74 - 0.82 (4H, m), 1.12 (6H, d, J = 6.8 Hz), 1.87 - 1.97 (1H, m), 2.44 - 2.56 (1H, m), 6.76 (1H, d, J = 7.9 Hz), 7.07 - 7.18 (2H, m), 7.33 - 7.39 (1H, m), 7.39 - 7.49 (3H, m), 7.49 - 7.57 (2H, m), 7.97 (1H, dd, J = 13.2, 2.4 Hz), 8.02 (1H, s), 8.45 (1H, dd, J = 2.4, 0.6 Hz), 8.54 (1H, d, J = 7.9 Hz), 10.93 (1H, s), 11.97 (1H, s).

Example 44

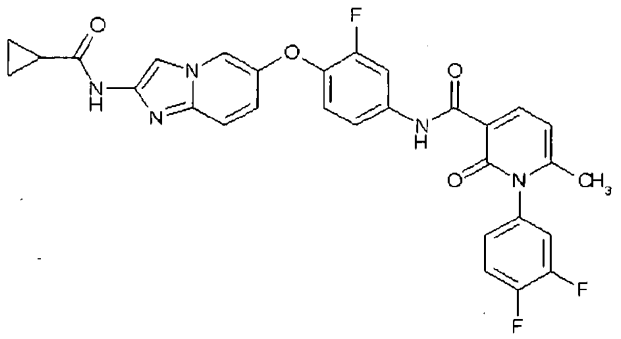
Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-2-fluorophenyl]-1-(2,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (200 mg, 0.613 mmol) and 1-(2,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (244 mg, 0.919 mmol) in N,N-dimethylacetamide (2.0 mL) were added HATU (350 mg, 0.919 mmol) and N,N-diisopropylethylamine (160 μL, 0.919 mmol), and the mixture was stirred at room temperature for 3 hr. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (284 mg, 81%) as a white solid.
$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.77 - 0.81 (4H, m), 1.86 - 1.99 (1H, m), 2.12 (3H, s), 6.76 (1H, d, J = 8.4 Hz), 6.87 - 6.94 (1H, m), 7.07 - 7.13 (2H, m), 7.31 - 7.40 (1H, m), 7.46 (1H, d, J = 9.9 Hz), 7.58 - 7.76 (2H, m), 8.04 (1H, s), 8.39 (1H, t, J = 9.2 Hz), 8.51 - 8.56 (2H, m), 10.96 (1H, s), 11.84 (1H, d, J = 1.8Hz).

Example 45

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(3,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide

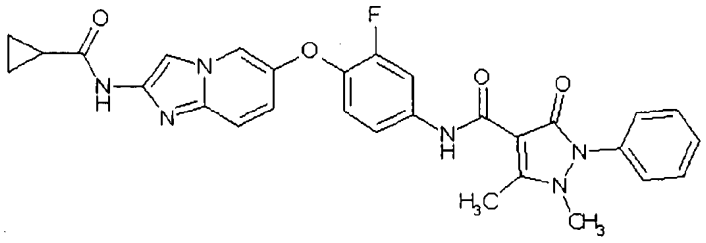


Using a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (200 mg, 0.613 mmol) and 1-(3,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (244 mg, 0.919 mmol) in N,N-dimethylacetamide (2.0 mL), HATU (350 mg, 0.919 mmol) and N,N-diisopropylethylamine (160 μL, 0.919 mmol) and in the same manner as in Example 44, the title compound (301 mg, 86%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.76 - 0.80 (4H, m), 1.87 - 1.97 (1H, m), 2.10 (3H, s), 6.71 (1H, d, J = 7.8 Hz), 7.08 - 7.14 (2H, m), 7.33 - 7.46 (3H, m), 7.64 - 7.74 (2H, m), 7.94 - 7.97 (1H, m), 8.02 (1H, s), 8.44 - 8.50 (2H, m), 10.93 (1H, s), 11.91 (1H, d, J = 1.8Hz).

Example 46

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide



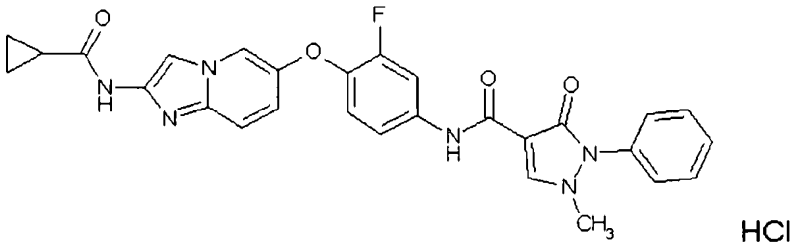
A mixture of 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic acid (279 mg, 1.2 mmol), N-[6-(4-amino-

2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (265 mg, 0.81 mmol), HATU (460 mg, 1.2 mmol), N,N-diisopropylethylamine (320 mg, 2.4 mmol) and N,N-dimethylformamide (9 mL) was stirred at room temperature for 18 hr. Ethyl acetate/tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the mixture, and the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×3). The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=40/60→100/0) to give the title compound (300 mg, 69%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.75 - 0.83 (4H, m), 1.86 - 1.97 (1H, m), 2.70 (3H, s), 3.36 (3H, s), 7.07 - 7.24 (3H, m), 7.40 - 7.46 (3H, m), 7.47 - 7.63 (3H, m), 7.90 (1H, dd, J = 13.4, 2.3 Hz), 8.03 (1H, s), 8.44 (1H, d, J = 1.9 Hz), 10.86 (1H, s), 10.93 (1H, s).

Example 47

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide·hydrochloride



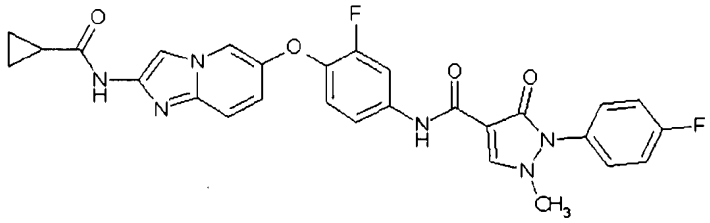

To a suspension of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (480 mg, 0.92 mmol) in methyl ethyl ketone (7

mL) was slowly added 6N aqueous hydrochloric acid solution (4 mL) and then water (4 mL), and the mixture was stirred at 80°C for 5 min. The mixture was cooled to room temperature and stirred at room temperature for 3 hr. The precipitated solid was collected by filtration, washed with methyl ethyl ketone and dried under reduced pressure to give the title compound (410 mg, 79%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.83 - 0.93 (4H, m), 1.90 - 2.00 (1H, m), 3.49 (3H, s), 7.22 - 7.33 (2H, m), 7.45 - 7.64 (6H, m), 7.70 (1H, d, J = 9.6 Hz), 7.95 (1H, dd, J = 13.4, 1.9 Hz), 8.06 (1H, s), 8.57 (1H, d, J = 1.9 Hz), 8.64 (1H, s), 10.50 (1H, s), 11.65 (1H, s).

Example 48

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide



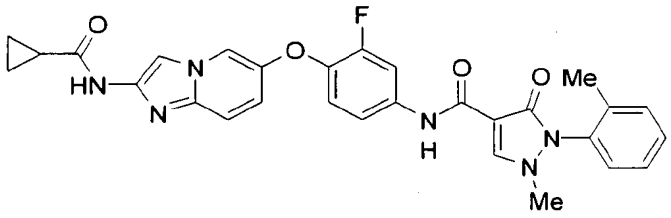
In the same manner as in Example 46 and using 2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid (280 mg, 1.2 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (260 mg, 0.80 mmol), HATU (460 mg, 1.2 mmol), N,N-diisopropylethylamine (310 mg, 2.4 mmol) and N,N-dimethylformamide (6 mL) as starting materials, the title compound (350 mg, 81%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.72 - 0.85 (4H, m), 1.86 - 1.97 (1H, m), 3.48 (3H, s), 7.11 (1H, dd, J = 9.6, 2.3 Hz), 7.16 (1H, t, J = 8.9 Hz), 7.21 - 7.27 (1H, m), 7.40 - 7.50 (3H, m), 7.52 - 7.60 (2H, m), 7.90 (1H, dd, J = 13.2, 2.3 Hz), 8.02 (1H,

s), 8.44 (1H, d, J = 1.9 Hz), 8.62 (1H, s), 10.43 (1H, s), 10.94 (1H, s).

Example 49

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-methyl-2-(2-methylphenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide

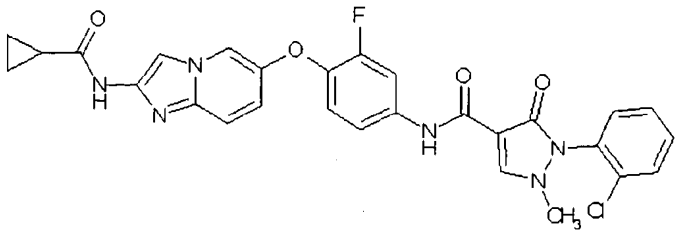



In the same manner as in Example 46 and using 1-methyl-2-(2-methylphenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid (370 mg, 1.6 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (260 mg, 0.80 mmol), HATU (610 mg, 1.6 mmol), N,N-diisopropylethylamine (410 mg, 3.2 mmol) and N,N-dimethylformamide (12 mL) as starting materials, the title compound (300 mg, 70%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.72 - 0.84 (4H, m), 1.86 - 1.96 (1H, m), 2.14 (3H, s), 3.38 (3H, s), 7.08 - 7.19 (2H, m), 7.20 - 7.25 (1H, m), 7.38 - 7.54 (5H, m), 7.91 (1H, dd, J = 13.3, 2.4 Hz), 8.02 (1H, s), 8.44 (1H, d, J = 1.7 Hz), 8.62 (1H, s), 10.47 (1H, s), 10.94 (1H, s).

Example 50

Production of 2-(2-chlorophenyl)-N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide

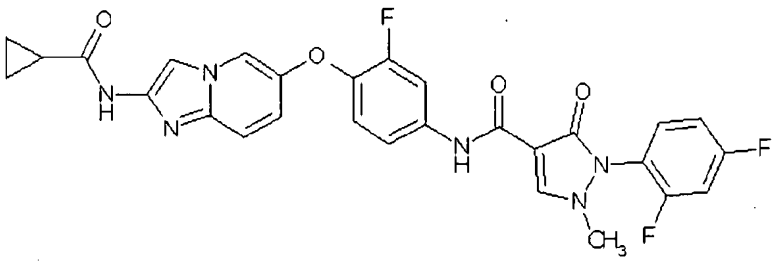


In the same manner as in Example 46 and using 2-(2-chlorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid (330 mg, 1.3 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (250 mg, 0.77 mmol), HATU (490 mg, 1.3 mmol), N,N-diisopropylethylamine (340 mg, 2.6 mmol) and N,N-dimethylformamide (15 mL) as starting materials, the title compound (260 mg, 60%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.71 - 0.85 (4H, m), 1.86 - 1.96 (1H, m), 3.41 (3H, s), 7.08 - 7.20 (2H, m), 7.21 - 7.27 (1H, m), 7.44 (1H, d, J = 9.6 Hz), 7.57 - 7.73 (3H, m), 7.78 (1H, dd, J = 7.8, 1.4 Hz), 7.90 (1H, dd, J = 13.2, 2.5 Hz), 8.03 (1H, s), 8.44 (1H, d, J = 1.9 Hz), 8.66 (1H, s), 10.33 (1H, s), 10.93 (1H, s).

Example 51

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-2-(2,4-difluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide



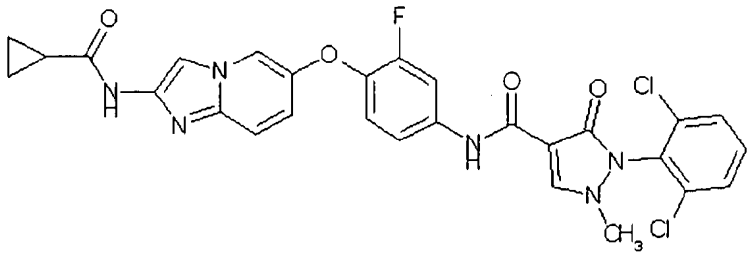
In the same manner as in Example 46 and using 2-(2,4-difluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid (330 mg, 1.3 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-

yl]cyclopropanecarboxamide (250 mg, 0.77 mmol), HATU (490 mg, 1.3 mmol), N,N-diisopropylethylamine (340 mg, 2.6 mmol) and N,N-dimethylformamide (15 mL) as starting materials, the title compound (330 mg, 76%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.72 - 0.84 (4H, m), 1.87 - 1.97 (1H, m), 3.47 (3H, s), 7.08 - 7.20 (2H, m), 7.22 - 7.28 (1H, m), 7.33 - 7.41 (1H, m), 7.44 (1H, d, J = 9.6 Hz), 7.61 - 7.70 (1H, m), 7.72 - 7.81 (1H, m), 7.89 (1H, dd, J = 13.2, 2.5 Hz), 8.02 (1H, s), 8.44 (1H, d, J = 1.7 Hz), 8.66 (1H, s), 10.27 (1H, s), 10.93 (1H, s).

Example 52

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-2-(2,6-dichlorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide



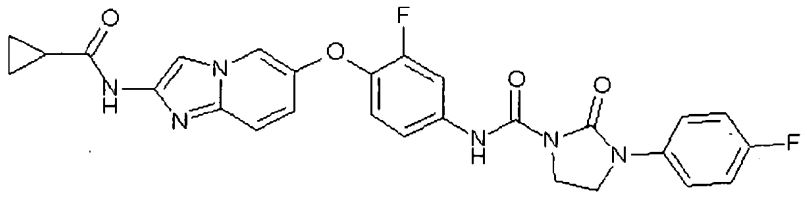
In the same manner as in Example 46 and using 2-(2,6-dichlorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid (370 mg, 1.3 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (250 mg, 0.77 mmol), HATU (490 mg, 1.3 mmol), N,N-diisopropylethylamine (340 mg, 2.6 mmol) and N,N-dimethylformamide (15 mL) as starting materials, the title compound (330 mg, 72%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.71 - 0.84 (4H, m), 1.86 - 1.98 (1H, m), 3.44 (3H, s), 7.07 - 7.20 (2H, m), 7.23 - 7.29 (1H, m), 7.44 (1H, d, J = 9.6 Hz), 7.69 - 7.76 (1H, m), 7.79 - 7.84 (2H, m), 7.89 (1H, dd, J = 13.3, 2.4 Hz), 8.03 (1H, s), 8.44 (1H, d, J = 1.9 Hz), 8.73 (1H, s), 10.18 (1H, s), 10.94 (1H,

s).

Example 53

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-3-(4-fluorophenyl)-2-oxoimidazolidine-1-carboxamide



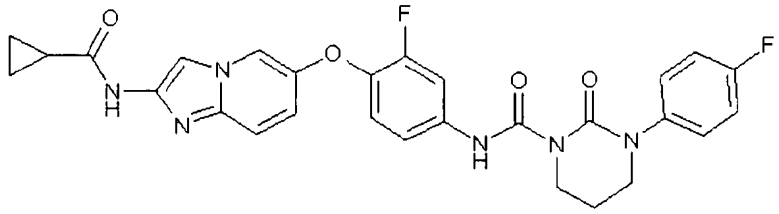
To a solution of 1-(4-fluorophenyl)imidazolidin-2-one (280 mg, 1.5 mmol) in tetrahydrofuran (5 mL) was added bis(trichloromethyl) carbonate (270 mg, 0.92 mmol), and the mixture was stirred at 70°C for 5 hr. The mixture was cooled to room temperature, a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (250 mg, 0.77 mmol) in tetrahydrofuran (5 mL) and N,N-diisopropylethylamine (300 mg, 2.3 mmol) were added to the mixture, and the mixture was stirred at room temperature for 40 min. Ethyl acetate/tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the mixture, and the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×3). The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=50/50→90/10) to give the title compound (120 mg, 30%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.74 - 0.84 (4H, m), 1.85 - 1.97 (1H, m), 3.86 - 4.00 (4H, m), 7.10 (1H, dd, J = 9.6, 2.5 Hz), 7.16 (1H, t, J = 9.1 Hz), 7.23 - 7.32 (3H, m), 7.44 (1H, d, J = 9.6 Hz), 7.61 - 7.67 (2H, m), 7.75 (1H, dd, J = 13.2, 2.5

Hz), 8.03 (1H, s), 8.45 (1H, d, J = 1.7 Hz), 10.42 (1H, s), 10.93 (1H, s).

Example 54

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-3-(4-fluorophenyl)-2-oxotetrahydropyrimidine-1(2H)-carboxamide



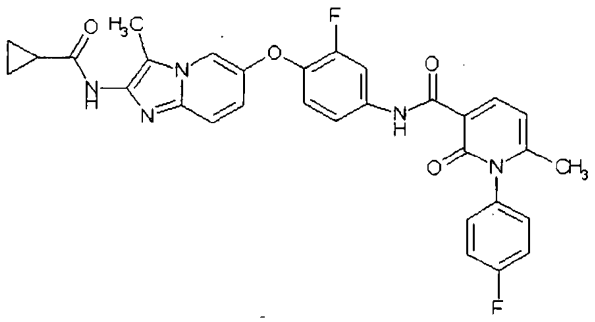
To a solution of 1-(4-fluorophenyl)tetrahydropyrimidin-2(1H)-one (360 mg, 1.8 mmol) in tetrahydrofuran (5 mL) was added bis(trichloromethyl) carbonate (330 mg, 1.1 mmol), and the mixture was stirred at 70°C for 3.5 hr. The mixture was cooled to room temperature, a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (300 mg, 0.92 mmol) in tetrahydrofuran (8 mL) and N,N-diisopropylethylamine (360 mg, 2.8 mmol) were added to the mixture, and the mixture was stirred at room temperature for 30 min. Ethyl acetate/tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the mixture, and the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×3). The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=40/60→90/10) to give the title compound (250 mg, 49%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.73 - 0.85 (4H, m), 1.86 - 1.98 (1H, m), 2.06 - 2.16 (2H, m), 3.66 (2H, t, J = 5.9 Hz), 3.85 - 3.96 (2H, m), 7.06 - 7.15 (2H, m), 7.15 - 7.32 (3H, m), 7.38 -

7.48 (3H, m), 7.71 (1H, dd, J = 13.3, 2.4 Hz), 8.02 (1H, s), 8.44 (1H, d, J = 1.7 Hz), 10.94 (1H, s), 11.78 (1H, s).

Example 55

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]-3-methylimidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



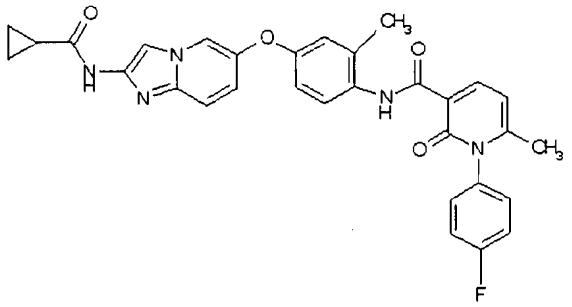
To a solution of 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (56.7 mg, 0.229 mmol) and N-[6-(4-amino-2-fluorophenoxy)-3-methylimidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (60 mg, 0.176 mmol) in N,N-dimethylformamide (1 mL) were added N,N-diisopropylethylamine (61 μL, 0.352 mmol) and HATU (87 mg, 0.229 mmol), and the mixture was stirred at room temperature for 17 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate alone) to give a yellow oil. The obtained oil was dissolved in ethyl acetate (1 mL) and left standing at room temperature for 17 hr. The precipitated solid was collected by filtration, washed with diethyl ether and collected by filtration to give the title compound (76 mg, 75%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.78 (4H, m), 1.74 - 1.91 (1H, m), 2.07 (3H, s), 2.26 (3H, s), 6.61 - 6.79 (1H, m), 7.01 - 7.15

(2H, m), 7.28 - 7.37 (1H, m), 7.38 - 7.54 (5H, m), 7.97 (1H, dd, J = 13.2, 2.5 Hz), 8.19 (1H, d, J = 1.9 Hz), 8.48 (1 H, d, J = 7.6 Hz), 10.21 (1H, br s), 11.97 (1H, s).

Example 56

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-2-methylphenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



A mixed solution of N-[6-(3-methyl-4-nitrophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (200 mg, 0.568 mmol), reduced iron (166.9 mg, 2.84 mmol) and ammonium chloride (303 mg, 5.68 mmol) in ethanol (2 mL) and water (0.5 mL) was stirred at 80°C for 6 hr. The reaction mixture was diluted with ethyl acetate and tetrahydrofuran, and filtered through celite. Water was added to the filtrate, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=50/50→100/0) to give a white solid.

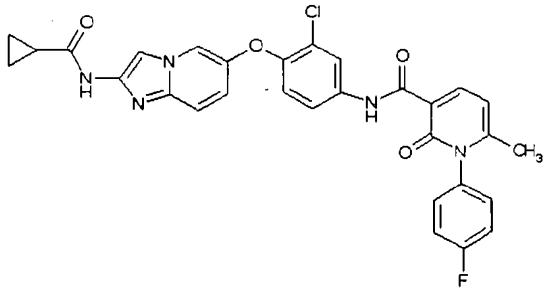
To a solution of the obtained white solid and 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (45 mg, 0.182 mmol) in N,N-dimethylformamide (1 mL) were added N,N-diisopropylethylamine (48 μL, 0.28 mmol) and HATU (69 mg, 0.182 mmol), and the mixture was stirred at room

temperature for 2 hr. Ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate alone) to give a yellow solid. The obtained solid was washed with ethyl acetate and collected by filtration to give the title compound (33 mg, 41%) as a slightly yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.68 - 0.91 (4H, m), 1.89 - 1.96 (1H, m), 2.06 (3H, s), 2.19 (3H, s), 6.70 (1H, d, J = 8.3 Hz), 6.83 - 6.97 (2H, m), 7.05 (1H, dd, J = 9.6, 2.3 Hz), 7.35 - 7.56 (5H, m), 8.03 (1H, s), 8.23 (1H, d, J = 8.9 Hz), 8.45 - 8.53 (2H, m), 10.94 (1H, s), 11.67 (1H, s).

Example 57

Production of N-[3-chloro-4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



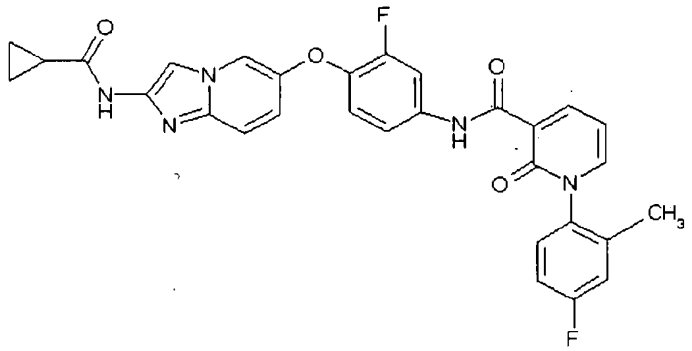
To a solution of N-[6-(4-amino-2-chlorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (100 mg, 0.292 mmol) and 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (94 mg, 0.38 mmol) in N,N-dimethylformamide (1 mL) were added N,N-diisopropylethylamine (100 μL, 0.583 mmol) and HATU

(144 mg, 0.380 mmol), and the mixture was stirred at 60°C for 4 hr. Ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate alone) to give a white solid. The obtained solid was washed with ethyl acetate and collected by filtration to give the title compound (120.2 mg, 72%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.67 - 0.90 (4H, m), 1.85 - 1.96 (1H, m), 2.07 (3H, s), 6.71 (1H, d, J = 8.3 Hz), 6.99 - 7.14 (2H, m), 7.35 - 7.57 (6H, m), 8.02 (1H, s), 8.16 (1H, d, J = 2.5 Hz), 8.40 - 8.51 (2H, m), 10.94 (1H, s), 11.96 (1H, s).

Example 58

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluoro-2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide



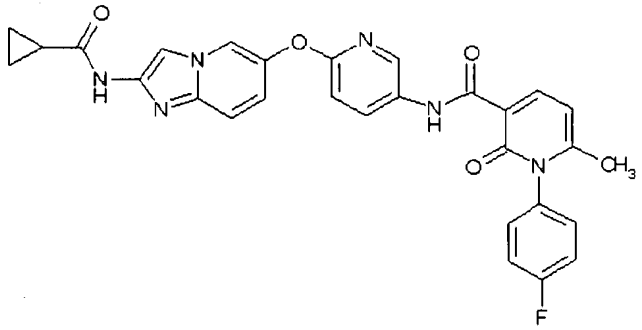
To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (100 mg, 0.306 mmol) and 1-(4-fluoro-2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (98 mg, 0.398 mmol) in N,N-dimethylformamide (2 mL) were

added N,N-diisopropylethylamine (105 μL, 0.612 mmol) and HATU (151 mg, 0.398 mmol), and the mixture was stirred at room temperature for 4 hr. Ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (140 mg, 82%) as a slightly yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.69 - 0.85 (4H, m), 1.86 - 1.96 (1H, m), 2.08 (3H, s), 6.67 - 6.81 (1H, m), 7.06 - 7.52 (7H, m), 7.88 - 8.11 (3H, m), 8.46 (1H, d, J = 1.7 Hz), 8.61 (1 H, dd, J = 7.3, 2.2 Hz), 10.94 (1H, s), 12.02 (1H, s).

Example 59

Production of N-[6-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)pyridin-3-yl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



A mixed solution of N-{6-[(5-nitropyridin-2-yl)oxy]imidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide (111 mg, 0.327 mmol), reduced iron (96 mg, 1.64 mmol) and ammonium chloride (175 mg, 3.27 mmol) in ethanol (2 mL) and water (0.5 mL) was stirred at 70°C for 1.5 hr. The reaction mixture was diluted with ethyl acetate and filtered through celite. Water was added to the filtrate, and the mixture was extracted twice

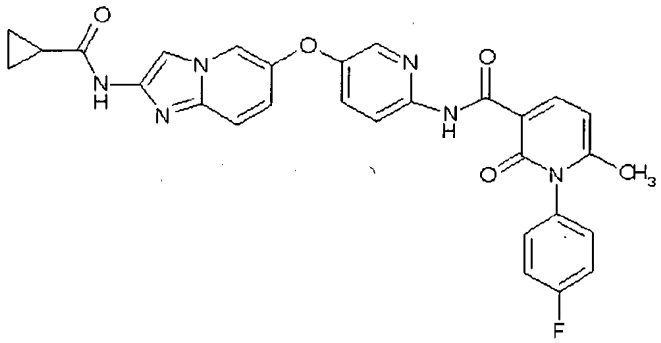
with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give a yellow solid.

To a solution of the obtained yellow solid and 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (76.8 mg, 0.311 mmol) in N,N-dimethylformamide (1 mL) were added N,N-diisopropylethylamine (89 μL, 0.518 mmol) and HATU (128 mg, 0.337 mmol), and the mixture was stirred at room temperature for 7 hr. Ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (70 mg, 40%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.64 - 0.91 (4H, m), 1.87 - 1.96 (1H, m), 2.08 (3H, s), 6.70 (1H, d, J = 8.3 Hz), 7.03 - 7.18 (2H, m), 7.34 - 7.56 (5H, m), 8.04 (1H, s), 8.24 (1H, dd, J = 8.9, 2.8 Hz), 8.42 (1H, d, J = 2.3 Hz), 8.47 (1H, d, J = 7.6 Hz), 8.56 - 8.61 (1H, m), 10.96 (1H, s), 11.85 (1H, s).

Example 60

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)pyridin-2-yl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide

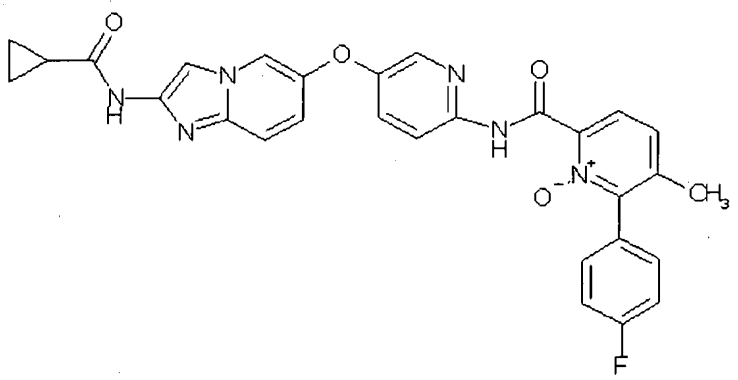


To a solution of N-{6-[(6-aminopyridin-3-yl)oxy]imidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide (75 mg, 0.242 mmol) and 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (78 mg, 0.315 mmol) in N,N-dimethylformamide (1 mL) were added N,N-diisopropylethylamine (83 μL, 0.484 mmol) and HATU (120 mg, 0.315 mmol), and the mixture was stirred at room temperature for 17 hr. Ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (116 mg, 89%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.70 - 0.88 (4H, m), 1.85 - 1.96 (1H, m), 2.07 (3H, s), 6.66 - 6.75 (1H, m), 7.12 (1H, dd, J = 9.6, 2.5 Hz), 7.38 - 7.52 (5H, m), 7.58 (1H, dd, J = 9.1, 3.0 Hz), 8.03 (1H, s), 8.16 (1H, d, J = 2.5 Hz), 8.29 (1 H, d, J = 9.6 Hz), 8.46 - 8.56 (2H, m), 10.95 (1H, s), 12.22 (1H, s).

Example 61

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)pyridin-2-yl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide

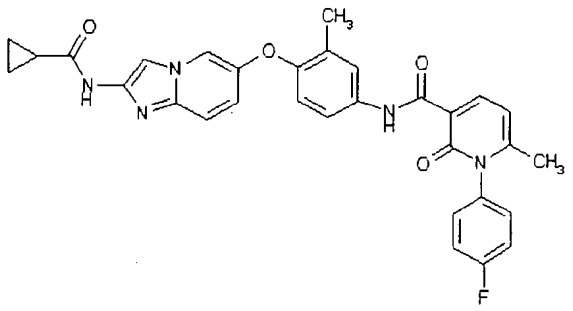


To a solution of N-{6-[(6-aminopyridin-3-yl)oxy]imidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide (100 mg, 0.323 mmol) and 6-(4-fluorophenyl)-5-methylpyridine-2-carboxylic acid 1-oxide (103.8 mg, 0.42 mmol) in N,N-dimethylformamide (1 mL) were added N,N-diisopropylethylamine (111 μL, 0.646 mmol) and HATU (160 mg, 0.42 mmol), and the mixture was stirred at room temperature for 4 hr. Ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (140 mg, 80%) as a slightly yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.60 - 0.87 (4H, m), 1.86 - 1.96 (1H, m), 2.13 (3H, s), 7.14 (1H, dd, J = 9.5, 2.4 Hz), 7.33 - 7.55 (5H, m), 7.62 (1H, dd, J = 9.1, 3.0 Hz), 7.69 (1H, d, J = 8.9 Hz), 8.04 (1H, s), 8.21 (1H, d, J = 2.5 Hz), 8.26 - 8.37 (2H, m), 8.57 (1H, dd, J = 2.5, 0.8 Hz), 10.97 (1H, s), 13.99 (1H, s).

Example 62

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-methylphenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide

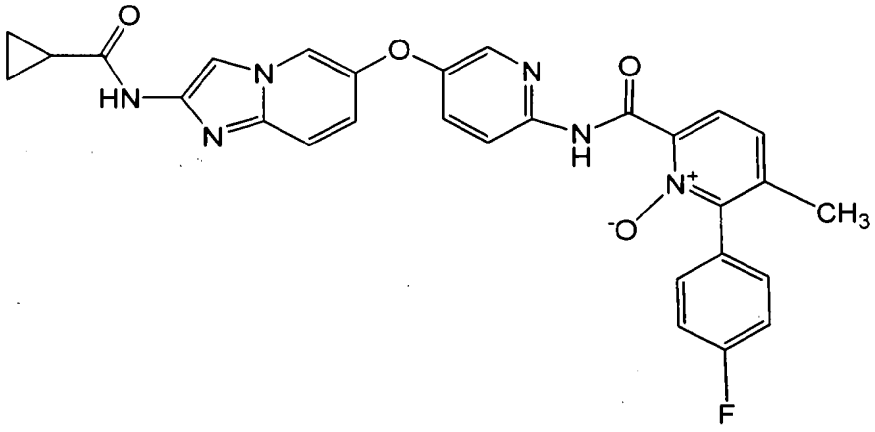


Using N-[6-(4-amino-2-methylphenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (100 mg, 0.31 mmol), 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (99.7mg,0.403 mmol), N,N-dimethylformamide (1 mL), N,N-diisopropylethylamine (107 μL, 0.620 mmol) and HATU (153 mg, 0.403 mmol) and in the same manner as in Example 57, the title compound (125.7 mg, 74%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.67 - 0.88 (4H, m), 1.86 - 1.95 (1H, m), 2.07 (3H, s), 2.23 (3H, s), 6.69 (1H, d, J = 8.1 Hz), 6.85 (1H, d, J = 8.9 Hz), 7.03 (1H, dd, J = 9.6, 2.3 Hz), 7.37 - 7.68 (7H, m), 8.01 (1H, s), 8.32 (1H, d, J = 1.7 Hz), 8.46 (1H, d, J = 7.6 Hz), 10.92 (1H, s), 11.85 (1H, s).

Example 63

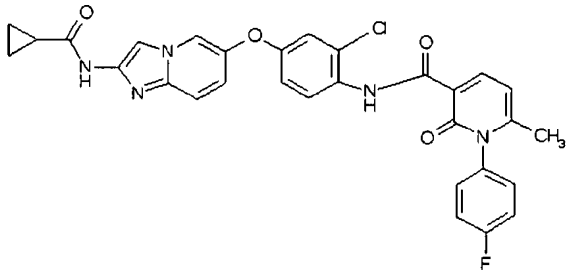
Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)pyridin-2-yl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide·hydrochloride·monohydrate



To a suspension of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)pyridin-2-yl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide (530 mg, 0.984 mmol) in ethanol (8 mL) were added 6N hydrochloric acid (0.984 mL, 5.9 mmol) and water (0.984 mL) at 80°C. The reaction solution was stirred at 70°C for 7 hr, and the precipitate was collected by filtration to give the title compound (197.6 mg, 34%) as a white solid.
$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.79 - 0.98 (4H, m), 1.86 - 2.01 (1H, m), 2.14 (3H, s), 7.28 - 7.57 (5H, m), 7.61 - 7.77 (3H, m), 8.06 (1H, s), 8.26 (1H, d, J = 2.5 Hz), 8.29 - 8.37 (2H, m), 8.67 (1H, d, J = 1.7 Hz), 11.48 (1H, br s), 14.02 (1H, s).

Example 64

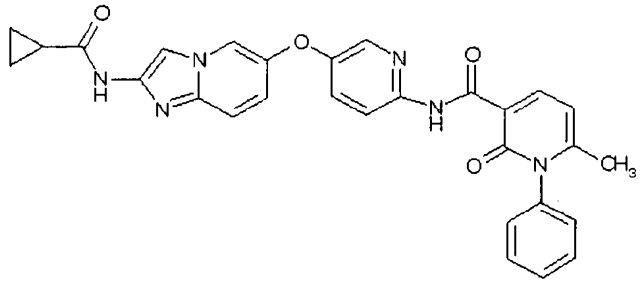
Production of N-[2-chloro-4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



Using N-[6-(4-amino-3-chlorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (160 mg, 0.467 mmol), 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (150 mg, 0.607 mmol), N,N-dimethylformamide (2 mL), N,N-diisopropylethylamine (161 μL, 0.934 mmol) and HATU (230.8 mg, 0.607 mmol) and in the same manner as in Example 60, the title compound (250 mg, 94%) was obtained as a white solid.
$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.74 - 0.86 (4H, m), 1.86 - 1.97 (1H, m), 2.06 (3H, s), 6.64 - 6.77 (1H, m), 7.02 - 7.14 (2H, m), 7.24 (1H, d, J = 3.0 Hz), 7.38 - 7.54 (5H, m), 8.04 (1H, s), 8.43 - 8.58 (3H, m), 10.96 (1H, s), 12.15 (1H, s).

Example 65

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)pyridin-2-yl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide

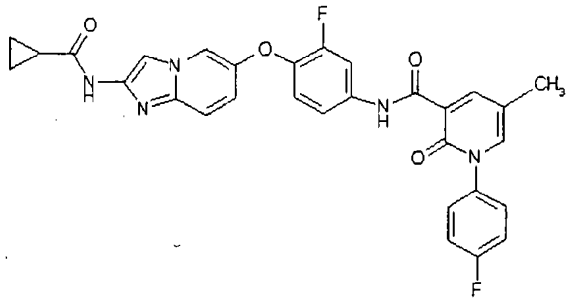


To a solution of N-{6-[(6-aminopyridin-3-yl)oxy]imidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide (200 mg, 0.647 mmol) and 6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid (178 mg, 0.776 mmol) in N,N-dimethylformamide (3 mL) were added N,N-diisopropylethylamine (233 μL, 1.29 mmol) and HATU (320 mg, 0.841 mmol), and the mixture was stirred at room temperature for 6 hr. Ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration. The obtained white solid was suspended in methyl ethyl ketone (2 mL), and the mixture was stirred at 80°C for 17 hr. The suspension was collected by filtration to give the title compound (175 mg, 52%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.72 - 0.84 (4H, m), 1.86 - 1.98 (1H, m), 2.06 (3H, s), 6.70 (1H, d, J = 8.3 Hz), 7.12 (1H, dd, J = 9.6, 2.5 Hz), 7.29 - 7.70 (7H, m), 8.03 (1H, s), 8.16 (1H, d, J = 2.5 Hz), 8.29 (1H, d, J = 9.1 Hz), 8.45 - 8.55 (2H, m), 10.95 (1H, s), 12.24 (1H, s).

Example 66

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



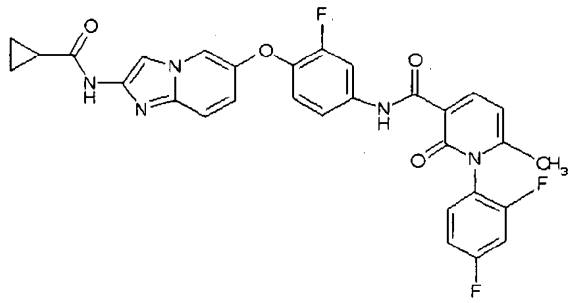
To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (100 mg, 0.306 mmol) and 1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (90.8 mg, 0.367 mmol) in N,N-dimethylformamide (1 mL) were added N,N-diisopropylethylamine (105 μL, 0.612 mmol) and HATU (151 mg, 0.40 mmol), and the mixture was stirred at room temperature for 6 hr. Ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration. The obtained slightly yellow solid was suspended in methanol (3 mL), and the mixture was stirred at 70°C for 10 min. The suspension was collected by filtration, and the obtained solid was washed with methanol to give the title compound (122 mg, 72%) as a slightly yellow solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.71 - 0.85 (4H, m), 1.92 (1H, m), 2.20 (3H, s), 7.02 - 7.23 (2H, m), 7.30 - 7.50 (4H, m), 7.53 -

7.67 (2H, m), 7.88 - 8.06 (3H, m), 8.46 (2H, s), 10.93 (1H, s), 12.16 (1H, s).

Example 67

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(2,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide

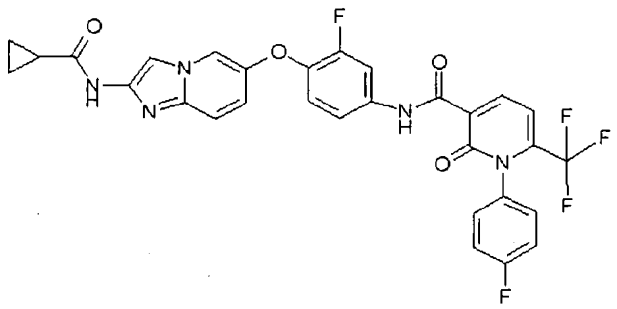


Using N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide(100mg, 0.306 mmol), 1-(2,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (97.4 mg, 0.367 mmol), N,N-dimethylformamide (1 mL), N,N-diisopropylethylamine (105 μL, 0.612 mmol) and HATU (151 mg, 0.40 mmol) and in the same manner as in Example 65, the title compound (115 mg, 66%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.67 - 0.83 (4H, m), 1.85 - 1.96 (1H, m), 2.13 (3H, s), 6.71 - 6.86 (1H, m), 7.04 - 7.22 (2H, m), 7.30 - 7.48 (3H, m), 7.57 - 7.79 (2H, m), 7.96 (1H, dd, J = 13.2, 2.5 Hz), 8.02 (1H, s), 8.46 (1H, d, J = 1.9 Hz), 8.52 (1H, d, J = 7.6 Hz), 10.93 (1H, s), 11.76 (1H, s).

Example 68

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3-carboxamide

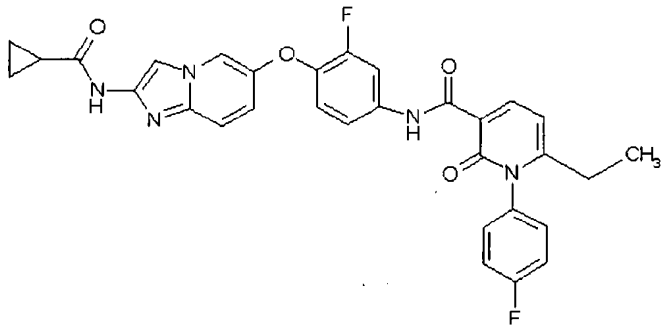


To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (90 mg, 0.276 mmol) and 1-(4-fluorophenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3-carboxylic acid (100 mg, 0.331 mmol) in N,N-dimethylformamide (2 mL) were added N,N-diisopropylethylamine (95 μL, 0.552 mmol) and HATU (126 mg, 0.331 mmol), and the mixture was stirred at room temperature for 6 hr. Ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration. The obtained slightly yellow solid was suspended in ethanol (3 mL), and the mixture was stirred at 70°C for 17 hr. The suspension was collected by filtration and washed with ethanol to give the title compound (32.7 mg, 19%) as a slightly yellow solid.
$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.61 - 0.91 (4H, m), 1.86 - 1.97 (1H, m), 7.04 - 7.20 (2H, m), 7.31 (1H, d, J = 7.7 Hz), 7.38 - 7.48 (4H, m), 7.57 (2H, d, J = 4.5 Hz), 7.97 (1H, dd, J = 13.0, 2.5 Hz), 8.02 (1H, s), 8.47 (1H, d, J = 1.7 Hz), 8.63 (1H, d, J = 7.6 Hz), 10.93 (1H, s), 11.66 (1H, s).

Example 69

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-

fluorophenyl]-6-ethyl-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

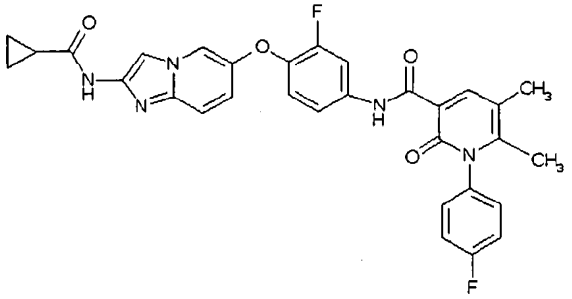


Using N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (100 mg, 0.306 mmol), 6-ethyl-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (95.9mg,0.367 mmol), N,N-dimethylformamide (1 mL), N,N-diisopropylethylamine (105 μL, 0.612 mmol) and HATU (151 mg, 0.40 mmol) and in the same manner as in Example 68, the title compound (64.1 mg, 37%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.70 - 0.87 (4H, m), 1.06 (3H, t, J = 7.3 Hz), 1.81 - 2.01 (1H, m), 2.30 (2H, q, J = 7.5 Hz), 6.68 (1H, d, J = 7.7 Hz), 7.01 - 7.22 (2H, m), 7.30 - 7.56 (6H, m), 7.87 - 8.06 (2H, m), 8.45 (1H, d, J = 1.7 Hz), 8.53 (1H, d, J = 7.7 Hz), 10.93 (1H, s), 11.98 (1H, s).

Example 70

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-5,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide

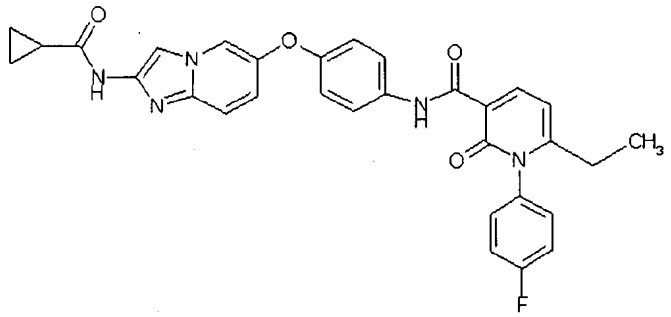


To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (83 mg, 0.255 mmol) and 1-(4-fluorophenyl)-5,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (80 mg, 0.306 mmol) in N,N-dimethylformamide (1 mL) were added N,N-diisopropylethylamine (88 μL, 0.51 mmol) and HATU (116 mg, 0.306 mmol), and the mixture was stirred at room temperature for 6 hr. Ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate alone) to give a white solid. The obtained solid was suspended in methyl ethyl ketone, stirred at 80°C and collected by filtration to give the title compound (90 mg, 62%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.69 - 0.85 (4H, m), 1.82 - 1.96 (1H, m), 2.01 (3H, s), 2.23 (3H, s), 7.05 - 7.20 (2H, m), 7.30 - 7.50 (6H, m), 7.91 - 8.08 (2H, m), 8.35 - 8.48 (2H, m), 10.93 (1H, s), 12.11 (1H, s).

Example 71

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-6-ethyl-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

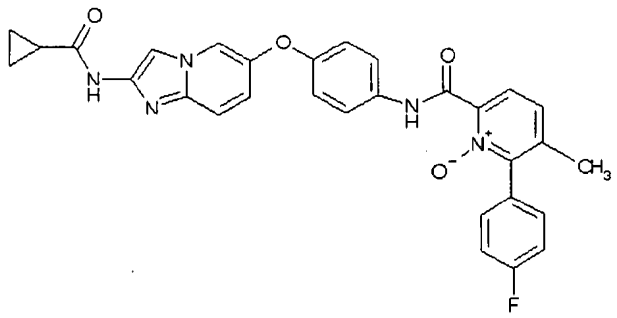


Using N-[6-(4-aminophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (100 mg, 0.324 mmol), 6-ethyl-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (101.5mg,0.389 mmol), N,N-dimethylformamide (1 mL), N,N-diisopropylethylamine (111 μL, 0.648 mmol) and HATU (148 mg, 0.389 mmol) and in the same manner as in Example 57, the title compound (133 mg, 74%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.68 - 0.87 (4H, m), 1.05 (3H, t, J = 7.4 Hz), 1.86 - 1.96 (1H, m), 2.30 (2H, q, J = 7.4 Hz), 6.66 (1H, d, J = 7.9 Hz), 6.93 - 7.16 (3H, m), 7.36 - 7.55 (5H, m), 7.63 - 7.75 (2H, m), 8.03 (1H, s), 8.44 - 8.59 (2H, m), 10.94 (1H, s), 11.83 (1H, s).

Example 72

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide



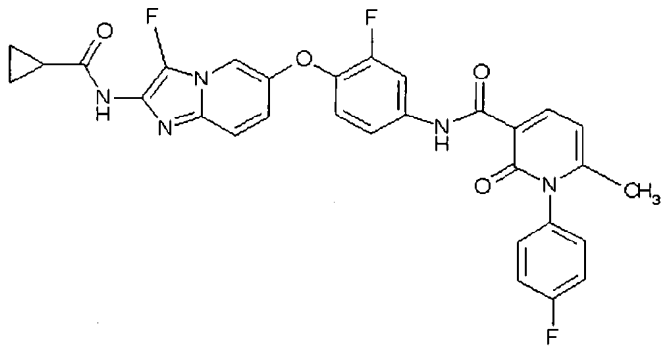
Using N-[6-(4-aminophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (200 mg, 0.649 mmol), 6-(4-fluorophenyl)-5-methylpyridine-2-carboxylic acid 1-oxide (192.5 mg, 0.779 mmol), N,N-dimethylformamide (2 mL), N,N-diisopropylethylamine (224 μL, 1.30 mmol) and HATU (296 mg, 0.779 mmol) and in the same manner as in Example 58, the title compound (254 mg, 73%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.70 - 0.87 (4H, m), 1.86 - 1.98 (1H, m), 2.12 (3H, s), 6.94 - 7.15 (3H, m), 7.32 - 7.56 (5H, m), 7.65 - 7.80 (3H, m), 8.04 (1H, s), 8.31 (1H, d, J = 8.3

Hz), 8.50 - 8.56 (1H, m), 10.95 (1H, s), 13.60 (1H, s).

Example 73

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]-3-fluoroimidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



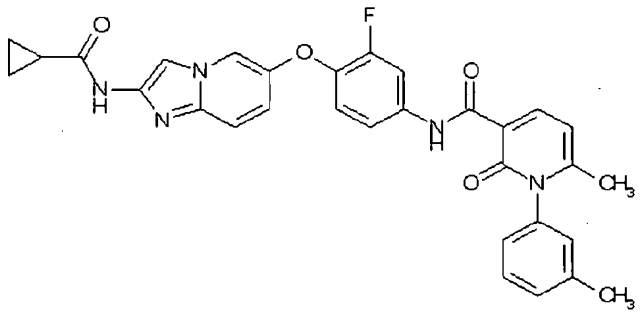
A mixed solution of N-[3-fluoro-6-(2-fluoro-4-nitrophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (15.2 mg, 0.041 mmol), reduced iron (12.1 mg, 0.205 mmol) and ammonium chloride (21.9 mg, 0.41 mmol) in ethanol (1 mL) and water (0.2 mL) was stirred at 90°C for 5 hr. The reaction mixture was diluted with ethyl acetate and saturated aqueous ammonium chloride solution and extracted twice with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. To a solution of the obtained residue and 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (12.2 mg, 0.0492 mmol) in N,N-dimethylformamide (1 mL) were added N,N-diisopropylethylamine (14 μL, 0.082 mmol) and HATU (18.7 mg, 0.0492 mmol), and the mixture was stirred at room temperature for 17 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The

obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=2/1→ethyl acetate alone) to give a white solid. The obtained solid was washed with ethyl acetate and collected by filtration to give the title compound (8 mg, 34%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.68 - 0.90 (4H, m), 1.77 - 1.93 (1H, m), 2.07 (3H, s), 6.66 - 6.78 (1H, m), 7.07 - 7.25 (2H, m), 7.32 - 7.59 (6H, m), 7.97 (1H, dd, J = 13.3, 2.4 Hz), 8.13 (1H, d, J = 2.3 Hz), 8.48 (1H, d, J = 7.6 Hz), 10.51 (1H, s), 11.99 (1H, s).

Example 74

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-1-(3-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide



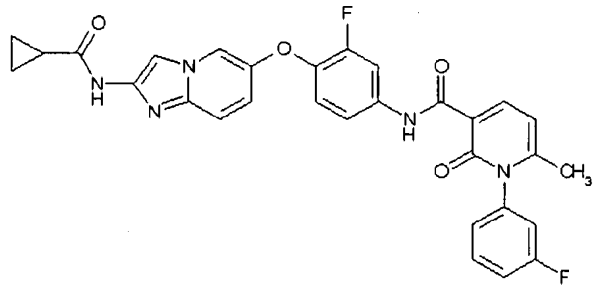
To a solution (3 mL) of 6-methyl-1-(3-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (120 mg, 0.50 mmol) in tetrahydrofuran were added oxalyl dichloride (130 mg,1.0 mmol) and N,N-dimethylformamide (1 drop), and the mixture was stirred at room temperature for 1 hr. The mixture was concentrated under reduced pressure, and the solvent was evaporated. N,N-Dimethylformamide (3,0 mL) and a solution (2.0 mL) of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (130 mg, 0.40 mmol) in N,N-dimethylformamide were successively added, and the mixture was stirred at room temperature for 5 hr. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction

solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (150 mg, 69%) as a brown solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.70 - 0.86 (4H, m), 1.85 - 1.96 (1H, m), 2.07 (3H, s), 2.38 (3H, s), 6.69 (1H, d, J = 8.1 Hz), 7.05 - 7.55 (8H, m), 7.96 (1H, dd, J = 13.2, 2.5 Hz), 8.02 (1H, s), 8.43 - 8.53 (2H, m), 10.93 (1H, s), 12.03 (1H, s).

Example 75

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(3-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



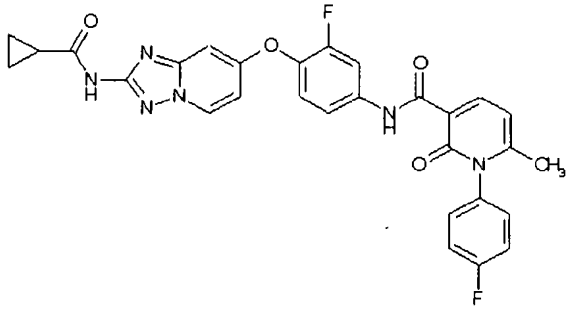
A solution (5 mL) of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (130 mg, 0.40 mmol), 1-(3-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (120 mg, 0.48 mmol), HATU (180 mg, 0.48 mmol) and N,N-diisopropylethylamine (100 mg, 0.80 mmol) in N,N-dimethylformamide was stirred at room temperature for 5 hr. The reaction solution was divided into two layers with tetrahydrofuran (10 mL) and saturated aqueous sodium hydrogen carbonate solution (10 mL) and the aqueous layer was subjected to extraction (3 times) with ethyl acetate (15 mL). The combined organic layer was washed with water (15 mL) and

saturated brine (15 mL), dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (80 mg, 35%) as a brown solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.77 - 0.93 (4H, m), 1.88 - 1.98 (1H, m), 2.10 (3H, s), 6.72 (1H, d, J = 8.3 Hz), 7.22 (1H, t, J = 9.1 Hz), 7.30 (1H, dt, J = 7.8, 1.0 Hz), 7.35 - 7.52 (4H, m), 7.65 (2H, d, J = 8.7 Hz), 8.00 (1H, dd, J = 13.2, 2.5 Hz), 8.05 (1H, s), 8.49 (1H, d, J = 7.6 Hz), 8.57 (1H, d, J = 2.1 Hz), 11.52 (1H, br s), 11.98 (1H, s).

Example 76

Production of N-[4-({2-[(cyclopropylcarbonyl)amino][1,2,4]triazolo[1,5-a]pyridine-7-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



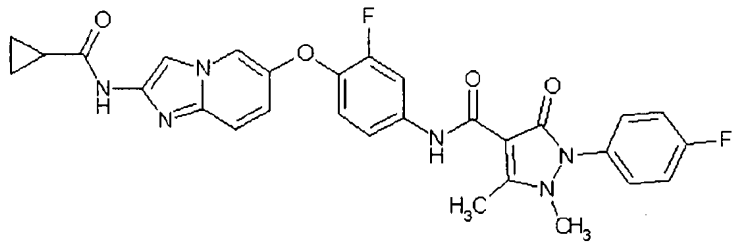
To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.458 mmol) and 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (170 mg, 0.687 mmol) in N,N-dimethylacetamide (3.0 mL) were added HATU (261 mg, 0.687 mmol) and N,N-diisopropylethylamine (120 μL, 0.687 mmol), and the mixture was stirred at room temperature for 16 hr. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The extract was washed with

saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=25/75→100/0) and the obtained solid was washed with ethyl acetate and collected by filtration to give the title compound (111 mg, 44%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.78 - 0.83 (4H, m), 1.98 - 2.07 (1H, m), 2.08 (3H, s), 6.72 (1H, d, J = 8.4 Hz), 6.84 (1H, d, J = 2.7 Hz), 6.91 - 6.96 (1H, m), 7.34 - 7.54 (6H, m), 8.03 (1H, dd, J = 12.9, 2.4 Hz), 8.50 (1H, d, J = 7.5 Hz), 8.80 (1H, d, J = 6.9 Hz), 10.99 (1H, s), 12.08 (1H, s).

Example 77

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-2-(4-fluorophenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide



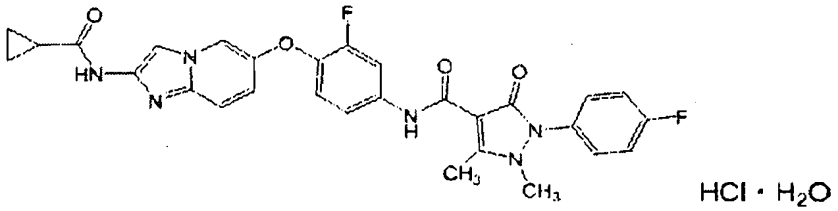
To a solution of 2-(4-fluorophenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid (1130 mg, 4.5 mmol) in tetrahydrofuran (75 mL) were added N,N-dimethylformamide (6 drops) and oxalyl dichloride (780 μL, 9.1 mmol), and the mixture was stirred at room temperature for 1 hr. The solvent was evaporated under reduced pressure, and the obtained residue was dissolved in N,N-dimethylacetamide (10 mL). The solution was added to a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (1230 mg, 3.8 mmol) in N,N-dimethylacetamide (30 mL), and the mixture was stirred at room

temperature for 4 hr. Ethyl acetate/tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the mixture, and the aqueous layer was extracted 4 times with ethyl acetate/tetrahydrofuran. The combined organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate and collected by filtration to give the title compound (1640 mg, 67%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.75 - 0.84 (4H, m), 1.86 - 1.97 (1H, m), 2.69 (3H, s), 3.35 (3H, s), 7.05 - 7.24 (3H, m), 7.38 - 7.55 (5H, m), 7.90 (1H, dd, J = 13.4, 2.3 Hz), 8.02 (1H, s), 8.44 (1H, d, J = 1.9 Hz), 10.84 (1H, s), 10.94 (1H, s).

Example 78

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-2-(4-fluorophenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide hydrochloride monohydrate



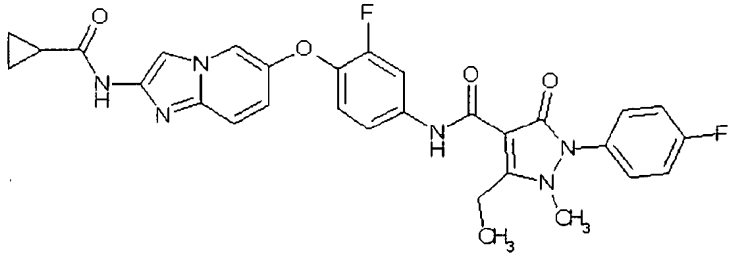

To a suspension of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-2-(4-fluorophenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide (400 mg, 0.72 mmol) in methyl ethyl ketone (7 mL) and water (5 mL) was slowly added 6N aqueous hydrochloric acid solution (240 μL), and the mixture was stirred at room temperature for 1 hr. The precipitated solid was collected by filtration, washed with methyl ethyl ketone and suspended in ethanol (5 mL), and the suspension was stirred at 70°C for 10 min. The solid was collected by filtration, washed with ethanol and dried under

reduced pressure to give the title compound (120 mg, 27%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.84 - 0.95 (4H, m), 1.90 - 2.01 (1H, m), 2.69 (3H, s), 3.36 (3H, s), 7.25 - 7.28 (2H, m), 7.41 - 7.54 (4H, m), 7.57 (1H, dd, J = 9.6, 2.1 Hz), 7.75 (1H, d, J = 9.6 Hz), 7.90 - 7.99 (1H, m), 8.08 (1H, s), 8.61 (1H, d, J = 2.1 Hz), 10.89 (1H, s), 11.85 (1H, s).

Example 79

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-5-ethyl-2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide



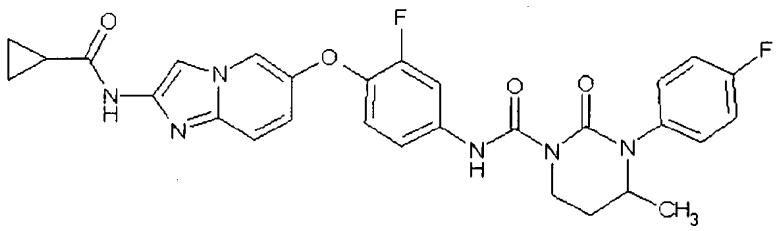
In the same manner as in Example 77 and using 5-ethyl-2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid (250 mg, 0.94 mmol), tetrahydrofuran (9 mL), N,N-dimethylformamide (1 drop), oxalyl dichloride (160 μL, 1.9 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (250 mg, 0.78 mmol) and N,N-dimethylacetamide (12 mL) as starting materials, the title compound (210 mg, 47%) was obtained as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.75 - 0.83 (3H, m), 1.20 - 1.29 (4H, m), 1.85 - 1.96 (1H, m), 3.15 (2H, q, J = 7.5 Hz), 3.39 (3H, s), 7.06 - 7.23 (3H, m), 7.39 - 7.48 (3H, m), 7.49 - 7.58 (2H, m), 7.91 (1H, dd, J = 13.4, 2.3 Hz), 8.03 (1H, s), 8.42 - 8.47 (1H, m), 10.87 (1H, s), 10.94 (1H, s).

Example 80

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-

fluorophenyl]-3-(4-fluorophenyl)-4-methyl-2-oxotetrahydropyrimidine-1(2H)-carboxamide



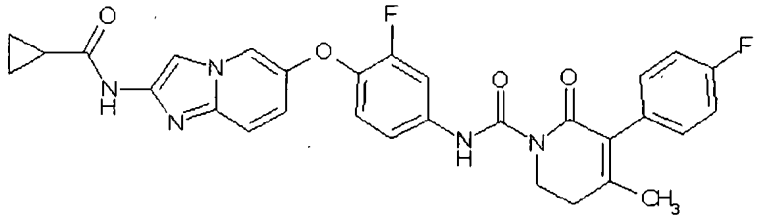
To a solution of 1-(4-fluorophenyl)-6-methyltetrahydropyrimidin-2(1H)-one (240 mg, 1.1 mmol) in tetrahydrofuran (5 mL) was added bis(trichloromethyl) carbonate (170 mg, 0.57 mmol), and the mixture was stirred at 70°C for 3.5 hr. The mixture was cooled to room temperature, a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (250 mg, 0.76 mmol) in tetrahydrofuran (8 mL) and N,N-diisopropylethylamine (300 mg, 2.3 mmol) were added to the mixture, and the mixture was stirred at room temperature for 1 hr. Ethyl acetate/tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the mixture, and the aqueous layer was extracted 3 times with ethyl acetate/tetrahydrofuran. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=50/50→100/0) to give the title compound (29 mg, 7%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.69 - 0.86 (4H, m), 1.07 (3H, d, J = 6.4 Hz), 1.84 - 1.97 (2H, m), 2.19 - 2.36 (1H, m), 3.74 - 3.88 (1H, m), 3.91 - 4.13 (2H, m), 7.04 - 7.15 (2H, m), 7.17 - 7.31 (3H, m), 7.33 - 7.46 (3H, m), 7.65 - 7.77 (1H, m), 8.02 (1H, s), 8.41 - 8.47 (1H, m), 10.94 (1H, s), 11.81 (1H, s).

Example 81

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-

fluorophenyl]-5-(4-fluorophenyl)-4-methyl-6-oxo-3,6-dihydropyridine-1(2H)-carboxamide



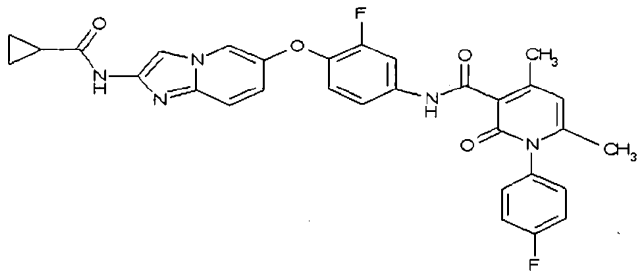
To a solution of bis(trichloromethyl) carbonate (127 mg, 0.43 mmol) in tetrahydrofuran (4 mL) were slowly added a solution of 3-(4-fluorophenyl)-4-methyl-5,6-dihydropyridin-2(1H)-one (240 mg, 1.2 mmol) and triethylamine (240 mg, 2.3 mmol) in tetrahydrofuran (2 mL) under ice-cooling, and the mixture was stirred at 0°C for 40 min and at room temperature for 15 min. A solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (250 mg, 0.78 mmol) in tetrahydrofuran (4 mL) and triethylamine (79 mg, 0.78 mmol) were added to the mixture, and the mixture was stirred at room temperature for 2 hr. Ethyl acetate/tetrahydrofuran and saturated brine were added to the mixture, and the aqueous layer was extracted 3 times with ethyl acetate/tetrahydrofuran. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=40/60→90/10) to give the title compound (170 mg, 39%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.72 - 0.85 (4H, m), 1.82 (3H, s), 1.87 - 1.96 (1H, m), 2.60 (2H, t, J = 6.5 Hz), 4.02 (2H, t, J = 6.5 Hz), 7.06 - 7.17 (2H, m), 7.19 - 7.32 (5H, m), 7.43 (1H, d, J = 9.6 Hz), 7.74 (1H, dd, J = 13.3, 2.5 Hz), 8.02 (1H, s), 8.45 (1H, d, J = 1.7 Hz), 10.94 (1H, s), 11.51 (1H, s).

Example 82

Production of N-[4-({2-

[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide



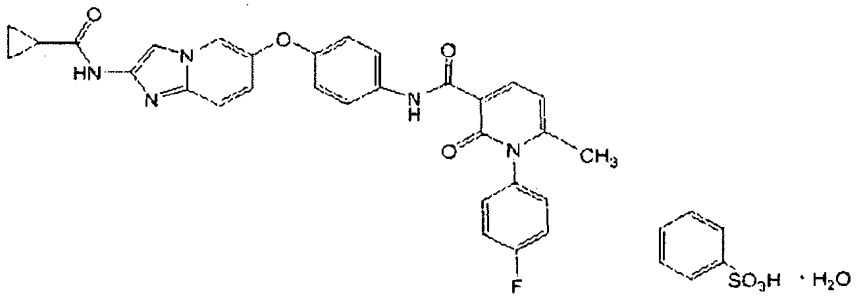
To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (116 mg, 0.357 mmol) and 1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (112 mg, 0.429 mmol) in N,N-dimethylformamide (1 mL) were added N,N-diisopropylethylamine (123 μL, 0.714 mmol) and HATU (163 mg, 0.428 mmol), and the mixture was stirred at room temperature for 4 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate) to give a white solid. The obtained solid was washed with ethyl acetate and collected by filtration to give the title compound (110 mg, 54%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.38 - 1.08 (4H, m), 1.54 - 2.17 (4H, m), 2.36 (3H, s), 6.37 (1H, s), 6.91 - 7.24 (2H, m), 7.24 - 7.58 (6H, m), 7.88 (1H, dd, J = 13.4, 2.5 Hz), 8.02 (1H, s), 8.42 (1H, d, J = 1.9 Hz), 10.93 (1H, s), 11.11 (1H, s).

Example 83

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-

yl}oxy)phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide benzenesulfonate monohydrate

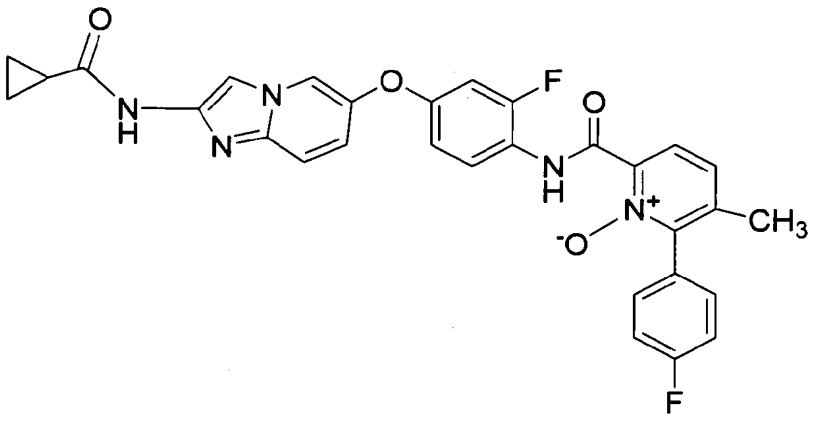


To a solution (90 mL) of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (400 mg, 0.744 mmol) in tetrahydrofuran was added benzenesulfonic acid monohydrate (197 mg, 1.12 mmol) at 80°C. The mixture was filtered, and the filtrate was gradually cooled to room temperature. The solution at room temperature was distilled off at 110°C to evaporate tetrahydrofuran to about half, and gradually cooled again to room temperature. The precipitate was collected by filtration, and the solid was washed with tetrahydrofuran and dried to give the title compound (309 mg, 58%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.78 - 0.99 (4H, m), 1.90 (1H, s), 2.07 (3H, s), 6.70 (1H, d, J = 8.3 Hz), 7.01 - 7.16 (2H, m), 7.25 - 7.35 (3H, m), 7.38 - 7.53 (5H, m), 7.56 - 7.64 (2H, m), 7.65 - 7.78 (3H, m), 8.05 (1H, s), 8.48 (1H, d, J = 7.6 Hz), 8.60 (1H, d, J = 1.7 Hz), 11.43 (1H, s), 11.88 (1H, s).

Example 84

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-2-fluorophenyl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide

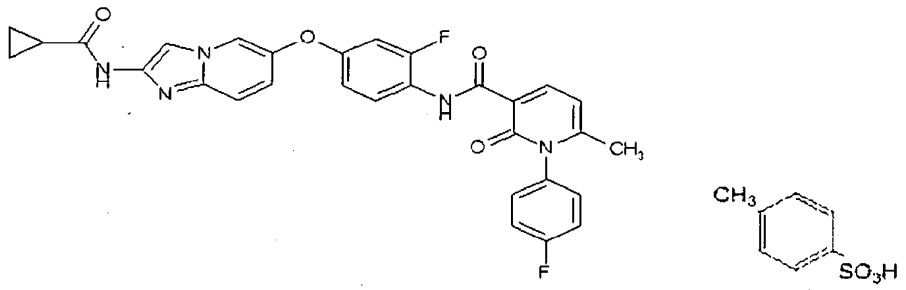


To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (200 mg, 0.613 mmol) and 6-(4-fluorophenyl)-5-methylpyridine-2-carboxylic acid 1-oxide (212 mg, 0.858 mmol) in N,N-dimethylacetamide (2.0 mL) were added HATU (350 mg, 0.919 mmol) and N,N-diisopropylethylamine (160 μL, 0.919 mmol), and the mixture was stirred at room temperature for 6 hr. Ethyl acetate/tetrahydrofuran was added and the mixture was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure and the obtained residue was recrystallized from tetrahydrofuran to give the title compound (109 mg, 32%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.78 - 0.82 (4H, m), 1.88 - 1.97 (1H, m), 2.13 (3H, s), 6.90 - 6.95 (1H, m), 7.08 - 7.16 (2H, m), 7.28 - 7.52 (5H, m), 7.70 - 7.73 (1H, m), 8.05 (1H, s), 8.30 - 8.40 (2H, m), 8.58 (1H, s), 10.97 (1H, s), 14.01 (1H, s).

Example 85

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-2-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide p-toluenesulfonate

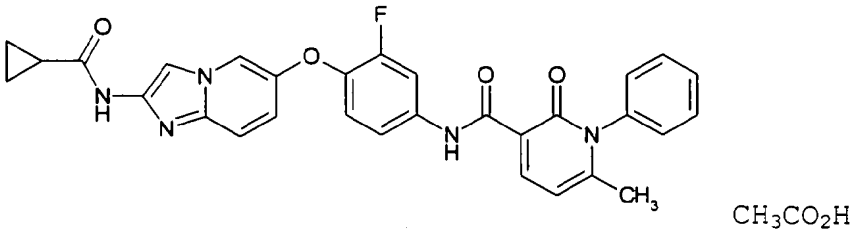


To N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-2-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (300 mg, 0.54 mmol) was added tetrahydrofuran (15 mL), and the mixture was dissolved by heating at 60°C. p-Toluenesulfonic acid monohydrate (123.3 mg, 0.65 mmol) was added. The mixture was stirred at 50°C for 1 hr and at 40°C for 12 hr. After cooling to room temperature, the precipitate was collected by filtration, washed with tetrahydrofuran and dried at 100°C for 3 hr under reduced pressure to give the title compound (259 mg, 66%) as a white powder.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.85 - 0.90 (4H, m), 1.86 - 1.94 (1H, m), 2.07 (3H, s), 2.29 (3H, s), 6.71 (1H, d, J = 8.1 Hz), 6.95 - 7.00 (1H, m), 7.11 (2H, d, J = 7.8 Hz), 7.13 - 7.18 (1H, m), 7.40 - 7.52 (7H, m), 7.66 (1H, d, J = 9.6Hz), 8.05 (1H, s), 8.42 - 8.50 (2H, m), 8.66 (1H, s), 11.35 (1H, s), 12.09 (1H, s).

Example 86

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide acetate



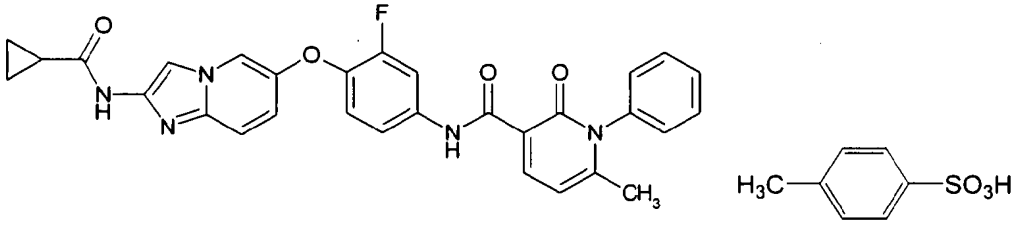
To a solution of N-[4-({2-

[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide (500 mg, 0.93 mmol) in acetic acid (3 ml) was added diisopropyl ether (15 ml) at room temperature. The reaction solution was stirred at 70°C for 3 hr, and the precipitate was collected by filtration and washed with diisopropyl ether to give a white solid (420 mg). To a solution (4 ml) of the white solid (400 mg) in acetic acid was added water (3 ml) at 80°C, and the mixture was cooled to room temperature and stirred for 17 hr. The precipitate was collected by filtration and washed with water to give the title compound (330 mg, 59%) as white crystals.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.80 (4H, m), 1.91 (4H, s), 2.06 (3H, s), 6.71 (1H, d, J = 7.4 Hz), 6.89 - 7.25 (2H, m), 7.25 - 7.48 (4H, m), 7.48 - 7.74 (3H, m), 7.74 - 8.15 (2H, m), 8.15 - 8.66 (2H, m), 10.93 (1H, s), 12.02 (2H, s).

Example 87

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide p-toluenesulfonate



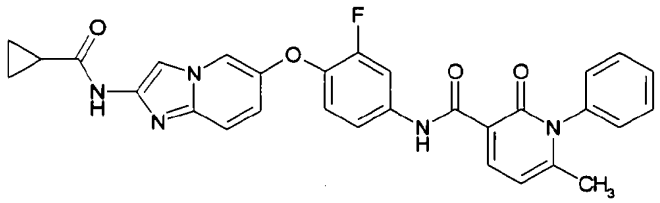

To a suspension of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide (650 mg, 1.21 mmol) in ethanol (6.5 ml) was added p-toluenesulfonic acid monohydrate (276 mg, 1.45 mmol) at 70°C. The reaction solution was stirred at 70°C for 1 hr, and the precipitate was collected by filtration and washed with ethanol to give the title compound (702 mg, 82%) as white

crystals.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.48 - 0.96 (4H, m), 1.90 (1H, br s), 2.07 (3H, s), 2.29 (3H, s), 6.71 (1H, d, J = 7.9 Hz), 6.98 - 7.26 (3H, m), 7.27 - 7.73 (10H, m), 7.83 - 8.15 (2H, m), 8.27 - 8.69 (2H, m), 11.23 (1H, br s), 12.05 (1H, s).

Example 88

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide hydrochloride



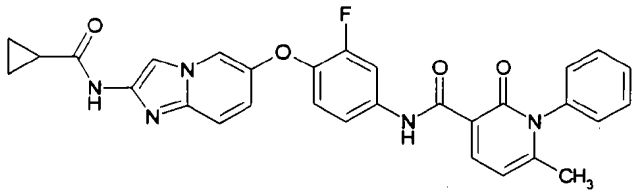
HCl

A solution (5 to 10%) of hydrogen chloride/methanol was heated to 50°C, and N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide (500 mg, 0.93 mmol) was added. The mixture was stirred for 5 min and at room temperature for 30 min. The precipitate was collected by filtration and washed with methanol to give the title compound (420 mg, 79%) as white crystals.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.35 - 1.61 (4H, m), 1.77 - 2.04 (1H, m), 2.07 (3H, s), 6.72 (1H, d, J = 8.3 Hz), 7.04 - 7.36 (1H, m), 7.36 - 7.49 (4H, m), 7.49 - 7.80 (4H, m), 7.93 - 8.26 (2H, m), 8.49 (1H, d, J = 7.6 Hz), 8.56 (1H, d, J = 1.9 Hz), 11.49 (1H, br s), 12.06 (1H, s).

Example 89

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide methanesulfonate



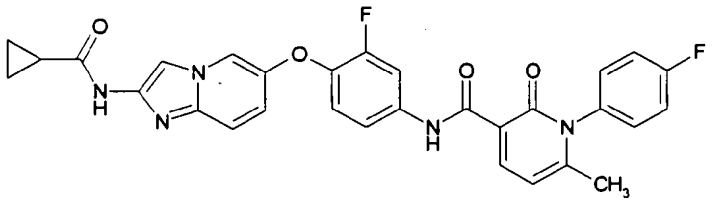
$CH_3SO_3H$

A suspension (3 mL) of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide (500 mg, 0.93 mmol) in ethanol was heated to 80°C, and a solution (1 mL) of methanesulfonic acid (107 mg, 1.12 mmol) in ethanol was added. The mixture was cooled to room temperature, diethyl ether was added dropwise, and the obtained solid was collected by filtration to give the title compound (550mg, 93%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.82 - 0.98 (4H, m), 1.83 - 1.97 (1H, m), 2.07 (3H, s), 2.37 (3H, s), 6.72 (1H, d, J = 8.1 Hz), 7.27 (1H, t, J = 9.0 Hz), 7.36 - 7.47 (3H, m), 7.50 - 7.66 (4H, m), 7.75 (1H, d, J = 1.2 Hz), 7.96 - 8.13 (2H, m), 8.49 (1H, d, J = 7.6 Hz), 8.61 (1H, d, J = 1.9 Hz), 11.56 (1H, s), 12.08 (1H, s).

Example 90

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide acetate



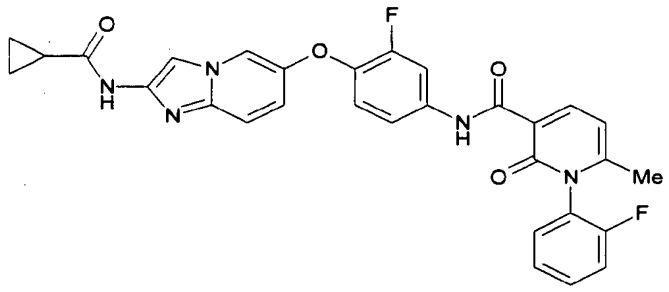
$CH_3CO_2H$

To N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (700 mg, 1.26 mmol) was added acetic acid (3.5 mL), and the mixture was

heated to 60°C. Methylethylketone (2.1 mL) and water (3.5 mL) were added, and the mixture was cooled to room temperature and stirred at room temperature for 16 hr. The precipitate was collected by filtration and washed with water to give the title compound (512 mg, 66%) as white crystals.
$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.75 - 0.82 (4H, m), 1.85 - 1.96 (1H, m), 1.91 (3H, s), 2.07 (3H, s), 6.75 (1H, d, J = 8.1 Hz), 7.10 - 7.17 (2H, m), 7.34 - 7.53 (6H, m), 7.97 (1H, dd, J = 13.2, 2.7 Hz), 8.02 (1H, s), 8.45 - 8.50 (2H, m), 10.94 (1H, s), 11.99 (1H, s).

Example 91

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(2-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



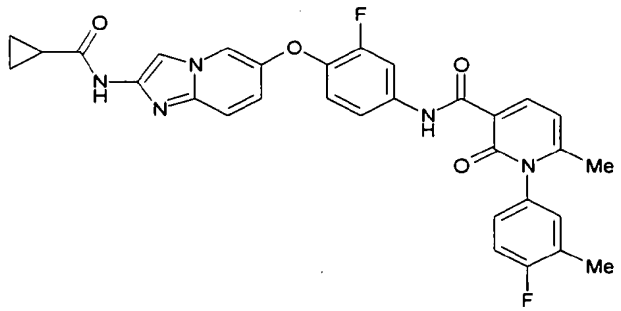

A solution (5 mL) of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (131 mg, 0.40 mmol), 1-(2-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (119 mg, 0.48 mmol), HATU (183 mg, 0.48 mmol) and N,N-diisopropylethylamine (103 mg, 0.80 mmol) in N,N-dimethylformamide was stirred at room temperature for 5 hr. The reaction solution was divided into two layers with tetrahydrofuran and sodium hydrogen carbonate saturated aqueous solution and the aqueous layer was subjected to extraction (3 times) with ethyl acetate. The combined organic layer was washed with water and saturated brine, dried over

anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (basic silica) and recrystallized from ethanol to give the title compound (80 mg, 36%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.68 - 0.89 (4H, m), 1.83 - 1.98 (1H, m), 2.12 (3H, s), 6.71 - 6.82 (1H, m), 7.07 - 7.19 (2H, m), 7.35 - 7.68 (6H, m), 7.96 (1H, dd, J = 13.2, 2.5 Hz), 8.02 (1H, s), 8.46 (1H, d, J = 1.7 Hz), 8.53 (1H, d, J = 7.6 Hz), 10.94 (1H, s), 11.81 (1H, s).

Example 92

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluoro-3-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



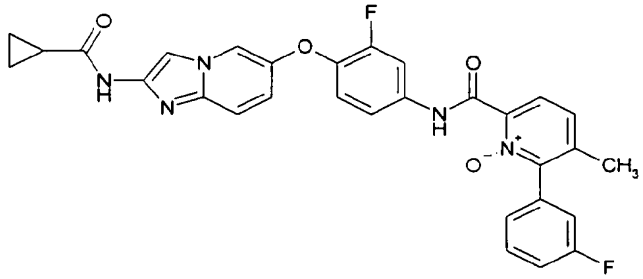
A solution (5 mL) of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (131 mg, 0.40 mmol), 1-(4-fluoro-3-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (125 mg, 0.48 mmol), HATU (183 mg, 0.48 mmol) and N,N-diisopropylethylamine (103 mg, 0.80 mmol) in N,N-dimethylformamide was stirred at room temperature for 5 hr. The reaction solution was divided into two layers with tetrahydrofuran and sodium hydrogen carbonate saturated aqueous solution and the aqueous layer was subjected to extraction (3 times) with ethyl acetate. The combined organic layer was washed with water and saturated brine, dried over

anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (basic silica) and recrystallized from ethanol to give the title compound (100 mg, 44%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.69 - 0.87 (4H, m), 1.84 - 1.98 (1H, m), 2.09(3H, s), 2.29 (3H, d, J = 1.5 Hz), 6.70 (1H, d, J = 8.3 Hz), 7.05 - 7.19 (2H, m), 7.24 - 7.41 (4H, m), 7.43 (1H, d, J = 9.6 Hz), 7.97 (1H, dd, J = 13.2, 2.5 Hz), 8.02 (1H, s), 8.35 - 8.57 (2H, m), 10.94 (1H, s), 12.00 (1H, s)

Example 93

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-(3-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide



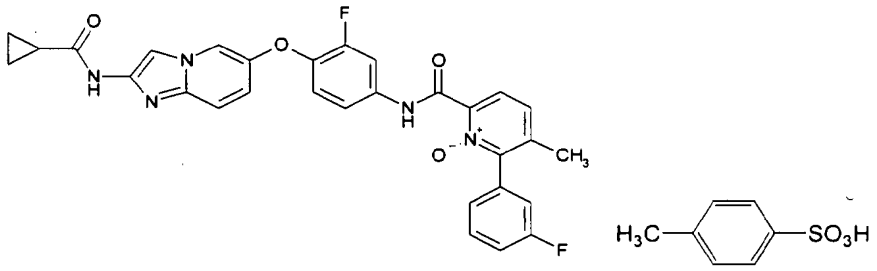
A solution (5 mL) of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (196 mg, 0.60 mmol), 6-(3-fluorophenyl)-5-methylpyridine-2-carboxylic acid 1-oxide (178 mg, 0.72 mmol), HATU (273 mg, 0.72 mmol) and N,N-diisopropylethylamine (155 mg, 1.20 mmol) in N,N-dimethylformamide was stirred at room temperature for 5 hr. The reaction solution was divided into two layers with tetrahydrofuran and sodium hydrogen carbonate saturated aqueous solution and the aqueous layer was subjected to extraction (3 times) with ethyl acetate. The combined organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was

evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (basic silica) and recrystallized from ethanol/water to give the title compound (250 mg, 75%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.74 - 0.85 (4H, m), 1.85 - 1.98 (1H, m), 2.13 (3H, s), 7.08 - 7.21 (2H, m), 7.24 - 7.30 (1H, m), 7.30 - 7.40 (2H, m), 7.41 - 7.52 (2H, m), 7.54 - 7.65 (1H, m), 7.71 (1H, d, J = 9.1 Hz), 7.98 (1H, dd, J = 13.0, 2.5 Hz), 8.03 (1H, s), 8.32 (1H, d, J = 8.3 Hz), 8.49 (1H, d, J = 1.7 Hz), 10.94 (1H, s), 13.69 (1H, s).

Example 94

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-(3-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide p-toluenesulfonate



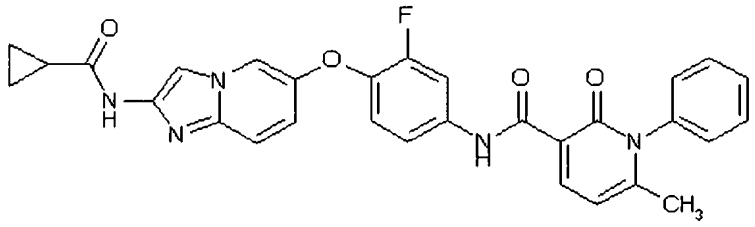
An ethanol (20 mL) suspension containing N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-(3-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide (833 mg, 1.50 mmol) was heated to 90°C, and p-toluenesulfonic acid monohydrate (314 mg, 1.65 mmol) was added. When the mixture became a uniform transparent solution, the precipitated solid was collected by filtration and washed with ethanol to give the title compound (870 mg, 80%) as a white solid.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.79 - 0.96 (4H, m), 1.83 - 1.97 (1H, m), 2.14 (3H, s), 2.29 (3H, s), 7.11 (2H, d, J = 7.7 Hz), 7.21 - 7.41 (4H, m), 7.43 - 7.66 (5H, m), 7.66 - 7.76 (2H, m), 7.96 - 8.10 (2H, m), 8.33 (1H, d, J = 8.3 Hz), 8.60 (1H, d, J

= 1.9 Hz), 11.42 (1H, s), 13.73 (1H, s).

Example 95

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide



To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (1.0 g, 3.06 mmol) and 6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid (843 mg, 3.68 mmol) in N,N-dimethylacetamide (10 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (822 mg, 4.29 mmol), 1-hydroxybenzotriazole (580 mg, 4.29 mmol) and triethylamine (854 μL, 6.13 mmol), and the mixture was stirred at room temperature for 16 hr. Water (60 mL) was added to the reaction mixture, and the mixture was stirred for 20 min. The precipitate was collected by filtration and washed with water and ethyl acetate. The obtained powder was recrystallized from methyl ethyl ketone/water to give the title compound (1.08 g, 66%) as white crystals.

$^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 0.70 - 0.85 (4H, m), 1.86 - 1.96 (1H, m), 2.06 (3H, s), 6.71 (1H, d, J = 8.3 Hz), 7.07 - 7.17 (2H, m), 7.32 - 7.65 (7H, m), 7.96 (1H, dd, J = 13.4, 2.5 Hz), 8.02 (1H, s), 8.42 - 8.52 (2H, m), 10.93 (1H, s), 12.02 (1H, s).

**Formulation Example 1**

A pharmaceutical agent containing the compound of the present invention as an active ingredient can be produced, for example, according to the following formulation.

1. capsule

| | |
|---|---|
| (1) compound obtained in Example 2 | 40 mg |
| (2) lactose | 70 mg |
| (3) crystalline cellulose | 9 mg |
| (4) magnesium stearate | 1 mg |
| 1 capsule | 120 mg |

(1), (2), (3) and 1/2 of (4) are blended, granulated and the rest of (4) is added thereto. The whole mixture is sealed in a gelatin capsule.

2. tablet

| | |
|---|---|
| (1) compound obtained in Example 2 | 40 mg |
| (2) lactose | 58 mg |
| (3) cornstarch | 18 mg |
| (4) crystalline cellulose | 3.5 mg |
| (5) magnesium stearate | 0.5 mg |
| 1 tablet | 120 mg |

(1), (2), (3), 2/3 of (4), and 1/2 of (5) are blended and granulated. The rest of (4) and (5) are added to the granules. The mixture is compression-formed into a tablet.

**Formulation Example 2**

The compound (50 mg) obtained Example 2 is dissolved in Japanese Pharmacopoeia distilled water for injection (50 mL), and the Japanese Pharmacopoeia distilled water for injection is added to 100 mL. This solution is filtrated under sterile conditions. The solution (1 mL) is taken, filled in a vial for injection under sterile conditions, freeze-dried and sealed.

**Experimental Example 1**

Cloning of human vascular endothelial growth factor receptor 2 (VEGFR2) gene and preparation of recombinant baculovirus

Human vascular endothelial growth factor receptor 2 (hereinafter to be referred to as VEGFR2) gene was cloned by PCR using cDNA Libraries Human Placenta (Clontech) as a template. The primer used for PCR was prepared from base sequence (Genbank Accession AF035121) information of VEGFR2 gene by adding a base

sequence encoding flag peptide and a recognition sequence of the restriction enzyme to a base sequence (2671-4374 of Genbank Accession AF035121) encoding the VEGFR2 intracellular domain region, so that the protein contains an N-terminal Flag tag. The primer base sequence is shown below.

VEGFR2-U:

5′-
AATTAAGTCGACATGGACTACAAGGATGACGATGACAAGAAGCGGGCCAATGGAGGGGAACTGA
AGACA-3′ (SEQ ID NO: 1)

and

VEGFR2-L:

5′-AATTAAGCATGCTTAAACAGGAGGAGAGCTCAGTGTGGTCCC-3′ (SEQ ID NO: 2)

The base sequence of primer VEGFR2-U is shown in SEQUENCE LISTING SEQ ID NO: 1, and the base sequence of primer VEGFR2-L is shown in SEQUENCE LISTING SEQ ID NO: 2.

The PCR reaction was conducted using a KOD-plus kit (TOYOBO). The obtained PCR product was electrophoresed on agarose gel (1%), the DNA fragment amplified by PCR was recovered from the gel, and then digested with restriction enzymes Sal I and Sph I. The DNA treated with the restriction enzymes was electrophoresed on agarose gel (1%), and the obtained DNA fragment was recovered and ligated to plasmid pFASTBAC1 (Invitrogen) digested with restriction enzymes Sal I and Sph I to give expression plasmid pFB-VEGFR2. The base sequence of the insert fragment was confirmed and found to be identical with the base sequence (2671-4374 of Genbank Accession AF035121) of VEGFR2 intracellular domain. Furthermore, using BAC-TO-BAC Baculovirus Expression System (Invitrogen), virus stock BAC-VEGFR2 of recombinant baculovirus was prepared.

**Experimental Example 2**

Preparation of vascular endothelial growth factor receptor 2 (VEGFR2) intracellular domain protein

SF-21 cells were sown at $1\times10^6$ cells/mL to Sf-900II SFM medium (1 L, Invitrogen) containing 10% fetal bovine serum

(trace), 50 mg/L Gentamicin (Invitrogen) and 0.1% Pluronic F-68 (Invitrogen), and shaking culture was performed using a 2 L volume Erlenmeyer flask at 27°C, 100 rpm. After culturing for 24 hrs, recombinant baculovirus BAC-VEGFR2 (13.4 mL) was added to the mixture, and the mixture was further cultured for 3 days. The culture medium was centrifuged at 2,000 rpm for 5 min to give virus-infected cells. The infected cells were washed with a phosphate buffered saline (Invitrogen), centrifuged under the same conditions, and the cells were preserved at -80°C. The cryopreserved cells were thawed in ice, suspended in buffer A (50 mM Tris buffer (30 mL, pH 7.4) containing 20% glycerol, 0.15 M NaCl) supplemented with Complete Protease Inhibitor (Boehringer), and ruptured 3 times with a Polytron homogenizer (Kinematica) at 20,000 rpm for 30 sec. The ruptured medium was clarified by centrifugation at 40,000 rpm for 30 min and filtered with a 0.45 μm filter. The filtrate was passed through a column packed with Anti-FLAG M2 Affinity Gel (4 mL, Sigma) at a flow rate of about 0.5 mL/min. The column was washed with buffer A, and eluted with buffer A containing 100 μg/mL of FLAG peptide. The eluate was concentrated with Vivaspin 20 (Vivascience) having a molecular weight cut off of 30K. The buffer of this concentrate was exchanged using NAP™ 25 column (Amersham Bioscience) equilibrated with buffer A. The fractions containing intracellular domain protein of VEGFR2 were collected, glycerol was added to the final concentration of 50% and cryopreserved at -80°C.

**Test Example 1**

Determination of vascular endothelial growth factor receptor 2 (VEGFR2) kinase inhibitory activity

A test compound dissolved in dimethyl sulfoxide (DMSO) was diluted with a buffer (50 mM Tris-HCl (pH 7.5), 5 mM $MgCl_2$, 5 mM $MnCl_2$, 2 mM dithiothreitol, 0.01% Tween-20). To this compound solution (5 μL) was added a buffer (10 μL) containing 50 ng/mL of VEGFR2 intracellular domain protein and 250 ng/mL of biotin

labeled polypeptide biotinyl-poly-Glu:Tyr (4:1) (CIS bio International). To the obtained mixture was added a buffer (10 μL) containing ATP (25 μM), the mixture was allowed to react at 25°C for 5 min and the reaction was quenched with 25 μL of a stop solution (100 mM EDTA disodium salt, 62.5 mM HEPES buffer (pH 7.4), 250 mM NaCl, 0.1% bovine serum albumin, 10 μg/mL AlphaScreen assay streptavidin donor beads (Streptavidin Donor beads: PerkinElmer), 10 μg/mL AlphaScreen assay anti-phosphotyrosine recognition antibody PY-100 binding acceptor beads (Anti-phosphotyrosine (P-Tyr-100) Acceptor beads: PerkinElmer)). The reaction solution was allowed to stand at 25°C for 16 hrs, and the wells were counted using a plate reader (Fusion™ (PerkinElmer)). The kinase inhibitory rate (%) of the test compound was calculated by the following formula:

Inhibitory rate (%)=(1-(count of test compound - blank)÷(control - blank))×100

The count of the solution reacted without addition of the compound was used as a "control", and the count of the solution without the compound and ATP was used as a "blank".

As shown in Table 1, the inhibitory rates of the compounds of Examples 10, 11, 14, 18, 20, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 at 1 μM were not less than 70%.

In addition, the $IC_{50}$ values of the compounds of Examples 10, 11, 14, 18, 20, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 were not more than 1 μM.

Table 1

| Example | inhibitory rate (%) at 1 μM |
|---|---|
| 10 | 97 |
| 11 | 99 |
| 14 | 99 |
| 18 | 91 |
| 20 | 73 |
| 24 | 100 |
| 27 | 100 |
| 28 | 96 |
| 29 | 100 |
| 32 | 100 |
| 45 | 99 |
| 46 | 100 |
| 53 | 92 |
| 57 | 100 |
| 60 | 98 |
| 61 | 99 |
| 66 | 100 |
| 70 | 99 |
| 72 | 100 |
| 75 | 100 |
| 76 | 99 |
| 77 | 100 |
| 80 | 100 |
| 81 | 99 |
| 82 | 100 |
| 84 | 99 |
| 86 | 100 |
| 87 | 100 |
| 88 | 100 |
| 90 | 100 |
| 93 | 100 |
| 94 | 100 |

**Test Example 2**

Vascular endothelial cell proliferation inhibitory test

Human umbilical vein-derived vascular endothelial cells (HUVEC purchased from KURABO INDUSTRIES LTD.) were cultured in an incubator at 37°C, 5% carbon dioxide in a vascular endothelial cell medium (Invitrogen) containing 3% bovine fetal serum and 2.5 ng/mL basic fibroblast growth factor. To be specific, HUVEC was suspended in a vascular endothelial cell medium containing the aforementioned 3% bovine fetal serum and plated on a 96 well flat bottom plate by 50 μL (3000 cells) each well. After culture overnight, various concentrations of the test substance and 120 ng/mL of vascular endothelial growth factor (VEGF) were dissolved in a vascular endothelial cell medium containing 3% bovine fetal serum and added to each well by 50 μL. After 5 days of culture, a Cell counting kit-8 reagent (DOJINDO LABORATORIES) was added to each well by 10 μL, and the mixture was reacted in an incubator at 37°C, 5% carbon dioxide for 2-3 hr. The absorbance at 450 nm was measured by a microtiter plate reader and the cell proliferation inhibitory activity was determined. Using the absorbance with addition of a test substance at each concentration and based on the nonlinear least-squares analysis using a logistic curve of SAS system NLIN procedure, the concentration of the test substance ($IC_{50}$ value) necessary for showing 50% of the value obtained without addition of the test substance was calculated.

The inhibitory rates of the compounds of Example 10, 11, 14, 18, 20, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 at 1 μM were not less than 40%.

In addition, the $IC_{50}$ values of the compounds of Examples 10, 11, 14, 18, 20, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 were not more than 2 μM.

Table 2

| Example | inhibitory rate (%) at 1 μM |
|---|---|
| 10 | 92 |
| 11 | 92 |
| 14 | 92 |
| 18 | 87 |
| 20 | 48 |
| 24 | 83 |
| 27 | 89 |
| 28 | 85 |
| 29 | 87 |
| 32 | 87 |
| 45 | 89 |
| 46 | 80 |
| 53 | 89 |
| 57 | 83 |
| 60 | 89 |
| 61 | 89 |
| 66 | 94 |
| 70 | 90 |
| 72 | 91 |
| 75 | 91 |
| 76 | 83 |
| 77 | 91 |
| 80 | 88 |
| 81 | 88 |
| 82 | 88 |
| 84 | 91 |
| 86 | 88 |
| 87 | 88 |
| 88 | 99 |
| 90 | 89 |
| 93 | 91 |
| 94 | 86 |

**Test Example 3**

Determination of hepatocyte growth factor receptor (c-Met) kinase inhibitory activity

A test compound dissolved in dimethyl sulfoxide (DMSO) was diluted with a buffer (50 mM Tris-HCl (pH 7.5), 5 mM $MgCl_2$, 5 mM $MnCl_2$, 2 mM dithiothreitol, 0.01% Tween-20). To this compound solution (5 μL) was added a buffer (10 μL) containing 2.5 ng/ml of c-Met intracellular domain protein (Millipore) and 250 ng/mL of biotin labeled polypeptide biotinyl-poly-Glu:Tyr (4:1) (CIS bio International). At 5 min after mixing kinase enzyme and the compound and biotin labeled polypeptide, to the obtained mixture was added a buffer (10 μL) containing ATP (5 μM), the mixture was allowed to react at 25°C for 10 min and the reaction was quenched with 25 μL of a stop solution (100 mM EDTA disodium salt, 62.5 mM HEPES buffer (pH 7.4), 250 mM NaCl, 0.1% bovine serum albumin, 10 μg/mL AlphaScreen assay streptavidin donor beads (Streptavidin Donor beads: PerkinElmer), 10 μg/mL AlphaScreen assay anti-phosphotyrosine recognition antibody PT-66 binding acceptor beads (Anti-phosphotyrosine (PT-66) Acceptor beads: PerkinElmer)). The reaction solution was allowed to stand at 25°C for 16 hrs, and the wells were counted using a plate reader (Fusion™ (PerkinElmer)). The kinase inhibitory rate (%) of the test compound was calculated by the following formula:

Inhibitory rate (%)=(1-(count of test compound - blank)÷(control - blank))×100

The count of the solution reacted without addition of the compound was used as a "control", and the count of the solution without the compound and ATP was used as a "blank".

As shown in Table 3, the inhibitory rates of the compounds of Examples 10, 11, 14, 18, 20, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93, and 94 at 1 μM were not less than 80%.

In addition, the $IC_{50}$ values of the compounds of Examples

10, 11, 14, 18, 20, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 were not more than 1 μM.

Table 3

| Example | inhibitory rate (%) at 1 μM |
|---|---|
| 10 | 99 |
| 11 | 100 |
| 14 | 100 |
| 18 | 100 |
| 20 | 98 |
| 24 | 100 |
| 27 | 100 |
| 28 | 100 |
| 29 | 100 |
| 32 | 100 |
| 45 | 100 |
| 46 | 100 |
| 53 | 100 |
| 57 | 100 |
| 60 | 99 |
| 61 | 100 |
| 66 | 100 |
| 70 | 100 |
| 72 | 100 |
| 75 | 100 |
| 76 | 100 |
| 77 | 100 |
| 80 | 100 |
| 81 | 100 |
| 82 | 100 |
| 84 | 100 |
| 86 | 100 |
| 87 | 100 |
| 88 | 100 |
| 90 | 100 |
| 93 | 100 |
| 94 | 100 |

**Test Example 4**

Human gastric cancer cell line MKN-45 growth inhibitory test

Human gastric cancer cell line MKN-45 (RIKEN BioResource Center) was cultured in RPMI1640 (Invitrogen) containing 10% bovine fetal serum in a gas incubator at 37°C, 5% $CO_2$. MKN-45 cells were treated with trypsin/EDTA and recovered. The cells were suspended in RPMI1640 containing 0.3% bovine fetal serum, plated on a 96 well flat bottom plate at a cells density of 3000 cells/50 μL per well. After culturing overnight, various concentrations of test substance were dissolved in RPMI1640 containing 0.3% bovine fetal serum and added to each well by 50 μL. After culture for 3 days, a Cell counting kit-8 reagent (DOJINDO LABORATORIES) was added to each well by 10 μL, and reacted in an incubator at 37°C, 5% $CO_2$ for 2-3 hr. After the reaction, the absorbance of each well at 450 nm was measured by a microtiter plate reader. The concentration of a test substance necessary for inhibiting the growth by 50% ($IC_{50}$ value) was calculated using a cell proliferation rate with addition of the test substance at each concentration and according to the nonlinear regression analysis using GraphPad Prism [Sigmoidal dose response (variable slope)]. The cell proliferation rate (%) with addition of a test substance at each concentration was calculated by the following formula. As a positive control (100% growth), dimethyl sulfoxide was added instead of a test substance. As a negative control (0% growth), the compound of Reference Example 136 (WO2005/030140, Entry 104), which is a known c-Met inhibitor, was added in large excess (10 μM) instead of a test substance.

As shown in Table 4, the inhibitory rates of the compounds of Examples 10, 11, 14, 18, 20, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 at 1 μM were not less than 80%.

In addition, the $IC_{50}$ values of the compounds of Examples

10, 11, 14, 18, 20, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 were not more than 1 μM.

Table 4

| Example | inhibitory rate (%) at 1 μM |
|---|---|
| 10 | 100 |
| 11 | 100 |
| 14 | 100 |
| 18 | 96 |
| 20 | 99 |
| 24 | 91 |
| 27 | 100 |
| 28 | 100 |
| 29 | 100 |
| 32 | 97 |
| 45 | 99 |
| 46 | 100 |
| 53 | 97 |
| 57 | 98 |
| 60 | 100 |
| 61 | 100 |
| 66 | 88 |
| 70 | 97 |
| 72 | 99 |
| 75 | 96 |
| 76 | 99 |
| 77 | 92 |
| 80 | 82 |
| 81 | 89 |
| 82 | 100 |
| 84 | 93 |
| 86 | 100 |
| 87 | 100 |
| 88 | 93 |
| 90 | 95 |
| 93 | 99 |
| 94 | 99 |

**Test Example 5**

Antitumor test (MKN-45 and MV-4-11)

Cancer cells were cultured in a culture medium containing 10% bovine fetal serum in an incubator at 37°C, 5% $CO_2$. MKN-45 cells were treated with trypsin/EDTA and isolated. MKN-45 and MV-4-11 cells were washed with HBSS (HANK's Balanced Saline Solution). When MKN-45 cells were transplanted, they were adjusted with HBSS to a cell density of $1.2 \times 10^8$ cells/mL, and transplanted by subcutaneous injection of 0.05 mL of a mixed suspension ($3 \times 10^6$ cells) of the cell suspension and the same amount of Matrigel into the abdomen of 6 or 7-week-old female nude mouse (BALB/c nu/nu, CLEA Japan, Inc.). When MV-4-11 cells were transplanted, they were adjusted with HBSS to a cell density of $1.2 \times 10^8$ cells/mL, and transplanted by subcutaneous injection of 0.05 mL of a mixed suspension ($3 \times 10^6$ cells) of the cell suspension and the same amount of Matrigel into the abdomen of 7-week-old female nude mouse (BALB/c nu/nu, CLEA Japan, Inc.). When the average tumor volume reached 100-250 $mm^3$, the mice were grouped, and various doses of test substance were orally administered for 14 consecutive days starting from the next day. The length of the major axis and the length of the minor axis of the tumor were measured over time and the tumor volume was calculated by tumor volume = major axis length × minor axis length × minor axis length × 0.5. The ratio of an increase in the average tumor volume of the control group to an increase in the average tumor volume of the drug administration group was taken as the tumor growth rate (%) of the drug administration group. Table 5 showned MKN-45 tumor growth rate (%) and table 6 showned MV-4-11 tumor growth rate (%).

Table 5

| Example | dose (mg/kg) | tumor growth rate(%) |
|---|---|---|
| 15 | 2 | 85 |
| 32 | 2 | 14 |
| 63 | 1 | 24 |
| 87 | 2 | 17 |
| 88 | 2 | 17 |

Table 6

| Example | dose (mg/kg) | tumor growth rate (%) |
|---|---|---|
| 15 | 2 | 17 |
| 32 | 2 | <0 |
| 63 | 2 | <0 |
| 87 | 2 | <0 |
| 88 | 2 | <0 |

**Test Example 6**

Determination of Fms Like Tyrosine Kinase 3 (FLT3) kinase inhibitory activity

A test compound dissolved in dimethyl sulfoxide (DMSO) was diluted with a buffer (50 mM Tris-HCl (pH 7.5), 5 mM $MgCl_2$, 5 mM $MnCl_2$, 2 mM dithiothreitol, 0.01% Tween-20). To this compound solution (5 μL) was added a buffer (10 μL) containing 7.5 ng/ml of FLT3 intracellular domain protein (Millipore) and 250 ng/mL of biotin labeled polypeptide biotinyl-poly-Glu:Tyr (4:1) (CIS bio International). At 5 min after mixing kinase enzyme and the compound and biotin labeled polypeptide, to the obtained mixture was added a buffer (10 μL) containing ATP (5 μM), the mixture was allowed to react at 25°C for 10 min and the reaction was quenched with 25 μL of a stop solution (100 mM EDTA disodium salt, 62.5 mM HEPES buffer (pH 7.4), 250 mM NaCl, 0.1% bovine serum albumin, 10 μg/mL AlphaScreen assay streptavidin donor beads (Streptavidin Donor Beads: PerkinElmer), 10 μg/mL AlphaScreen assay anti-phosphotyrosine recognition antibody Y-

100 binding acceptor beads (Anti-phosphotyrosine (P-Tyr-100) Acceptor beads: PerkinElmer)). The reaction solution was allowed to stand at 25°C for 16 hrs, and the wells were counted using a plate reader (Envision™ (PerkinElmer)). The kinase inhibitory rate (%) of the test compound was calculated by the following formula:

Inhibitory rate (%)=(1-(count of test compound - blank)÷(control - blank))×100

The count of the solution reacted without addition of the compound was used as a "control", and the count of the solution without the compound and ATP was used as a "blank".

As shown in Table 7, the inhibitory rates of the compounds of Examples 10, 11, 14, 18, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 at 1 μM were not less than 50%.

In addition, the $IC_{50}$ values of the compounds of Examples 10, 11, 14, 18, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 were not more than 1 μM.

Table 7

| Example | inhibitory rate (%) at 1 μM |
|---|---|
| 10 | 63 |
| 11 | 88 |
| 14 | 88 |
| 18 | 55 |
| 24 | 87 |
| 27 | 73 |
| 28 | 63 |
| 29 | 96 |
| 32 | 75 |
| 45 | 93 |
| 46 | 92 |
| 53 | 66 |
| 57 | 93 |
| 60 | 89 |
| 61 | 71 |
| 66 | 75 |
| 70 | 94 |
| 72 | 91 |
| 75 | 92 |
| 76 | 86 |
| 77 | 96 |
| 80 | 93 |
| 81 | 90 |
| 82 | 79 |
| 84 | 96 |
| 86 | 97 |
| 87 | 96 |
| 88 | 96 |
| 90 | 69 |
| 93 | 93 |
| 94 | 94 |

**Test Example 7**

Determination of TIE2 kinase inhibitory activity

A test compound dissolved in dimethyl sulfoxide (DMSO) was diluted with a buffer (50 mM Tris-HCl (pH 7.5), 5 mM $MgCl_2$, 5 mM $MnCl_2$, 2 mM dithiothreitol, 0.01% Tween-20). A buffer (10 μL) containing 50 ng/mL of Tie2 intracellular domain protein (Millipore) and 250 ng/mL of biotin labeled polypeptide biotinyl-poly-Glu:Tyr (4:1) (CIS bio International) was added to the compound solution (5 μL). At 5 min from the mixing of the kinase enzyme, the compound and the biotin labeled polypeptide, a buffer (10 μL) containing 5 μM ATP was added, and the mixture was reacted at 25°C for 10 min. The reaction was quenched by the addition of 25 μL of a stop solution (100 mM EDTA disodium salt, 62.5 mM HEPES buffer (pH 7.4), 250 mM NaCl, 0.1% bovine serum albumin, 10 μg/mL AlphaScreen assay streptavidin donor beads (Streptavidin Donor beads: PerkinElmer), 10 μg/mL AlphaScreen assay anti-phosphotyrosine recognition antibody PT-66 binding acceptor beads (Anti-phosphotyrosine (PT-66) Acceptor beads: PerkinElmer)). The reaction solution was allowed to stand at 25°C for 16 hrs, and the cells were counted using a plate reader (Fusion™ (PerkinElmer)). The kinase inhibitory rate (%) of the test compound was calculated by the following formula:

Inhibitory rate (%)=(1-(count of test compound - blank)÷(control - blank))×100

The count of the solution reacted without addition of the compound was used as a "control", and the count of the solution without the compound and ATP was used as a "blank".

As shown in Table 8, the inhibitory rates of the compounds of Examples 10, 11, 14, 18, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 at 1 μM were not less than 50%.

In addition, the $IC_{50}$ values of the compounds of Examples

10, 11, 14, 18, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 were not more than 1 μM.

Table 8

| Example | inhibitory rate (%) at 1 μM |
|---|---|
| 10 | 99 |
| 11 | 100 |
| 14 | 98 |
| 18 | 77 |
| 24 | 100 |
| 27 | 100 |
| 28 | 100 |
| 29 | 100 |
| 32 | 99 |
| 45 | 100 |
| 46 | 100 |
| 53 | 56 |
| 57 | 100 |
| 60 | 100 |
| 61 | 99 |
| 66 | 100 |
| 70 | 99 |
| 72 | 100 |
| 75 | 100 |
| 76 | 100 |
| 77 | 100 |
| 80 | 100 |
| 81 | 100 |
| 82 | 100 |
| 84 | 100 |
| 86 | 100 |
| 87 | 100 |
| 88 | 100 |
| 90 | 100 |
| 93 | 100 |
| 94 | 100 |

**Test Example 8**

Human blood cell cancer cell line MV-4-11 growth inhibitory test

Human blood cell cancer cell line MV-4-11 (ATCC) was cultured in IMDM (Invitrogen) containing 10% bovine fetal serum in an incubator at 37°C, 5% $CO_2$. MV-4-11 cells were treated with trypsin/EDTA and recovered. The cells were suspended in IMDM containing 10% bovine fetal serum, plated on a 96 well flat bottom plate at a cells density of 30,000 cells/50 μL per well. After culturing overnight, various concentrations of test substance were dissolved in IMDM containing 10% bovine fetal serum and added to each well by 50 μL. After culture for 3 days, a Cell counting kit-8 reagent (DOJINDO LABORATORIES) was added to each well by 10 μL, and reacted in an incubator at 37°C, 5% $CO_2$ for 2-3 hr. After the reaction, the absorbance of each well at 450 nm was measured by a microtiter plate reader. The concentration of a test substance necessary for inhibiting the growth by 50% ($IC_{50}$ value) was calculated using a cell proliferation rate with addition of the test substance at each concentration and according to the nonlinear regression analysis using GraphPad Prism [Sigmoidal dose response (variable slope)].

As shown in Table 9, the inhibitory rates of the compounds of Examples 10, 11, 14, 18, 20, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 at 1 μM were not less than 90%.

The $IC_{50}$ values of the compounds of Examples 10, 11, 14, 18, 20, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 were not more than 1 μM.

Table 9

| Example | inhibitory rate (%) at 1 μM |
|---|---|
| 10 | 96 |
| 11 | 97 |
| 14 | 97 |
| 18 | 96 |
| 20 | 96 |
| 24 | 98 |
| 27 | 96 |
| 28 | 97 |
| 29 | 97 |
| 32 | 92 |
| 45 | 97 |
| 46 | 97 |
| 53 | 97 |
| 57 | 97 |
| 60 | 97 |
| 61 | 97 |
| 66 | 98 |
| 70 | 98 |
| 72 | 97 |
| 75 | 97 |
| 76 | 97 |
| 77 | 97 |
| 80 | 97 |
| 81 | 98 |
| 82 | 97 |
| 84 | 98 |
| 86 | 91 |
| 87 | 92 |
| 88 | 91 |
| 90 | 92 |
| 93 | 91 |
| 94 | 92 |

SEQUENCE LISTING free text

[SEQ ID NO: 1]

Designed oligonucleotide primer to amplify DNA encoding human VEGFR2

[SEQ ID NO: 2]

Designed oligonucleotide primer to amplify DNA encoding human VEGFR2

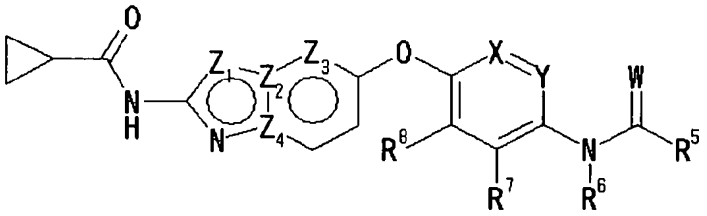
**Industrial Applicability**

The compound of the present invention show superior inhibitory activity on kinases such as vascular endothelial growth factor receptor, hepatocyte growth factor receptor, angiopoietin receptor (TIE2), Fms Like Tyrosine Kinase 3 (FLT3) and the like. Therefore, a clinically useful agent for the prophylaxis or treatment of diseases related to the action of vascular endothelial growth factor, hepatocyte growth factor, angiopoietin, FLT3 ligand (FL) in the living body (e.g., cancer etc.) can be provided. Moreover, since the compound of the present invention are also superior in efficacy expression, pharmacokinetics, solubility, interaction with other pharmaceutical products, safety and stability, they are useful as pharmaceutical agents.

This application is based on patent application Nos. 2008-122789 and 2008-306661 filed in Japan, the contents of which are incorporated in full herein by this reference.

## CLAIMS

1. A compound represented by the formula (I):



wherein $Z_1$, $Z_2$, $Z_3$ and $Z_4$ are in the following combination:

$(Z_1, Z_2, Z_3, Z_4) = (CR^1, N, CR^2, C)$,

$(N, N, CR^2, C)$,

$(N, C, CR^2, N)$,

$(S, C, CR^2, C)$, or

$(S, C, N, C)$;

$R^1$ and $R^2$ are the same or different and each is

(1) a hydrogen atom,

(2) a halogen atom,

(3) a group bonded via a carbon atom,

(4) a group bonded via a nitrogen atom,

(5) a group bonded via an oxygen atom, or

(6) a group bonded via a sulfur atom;

W is O or S;

X is $CR^3$ ($R^3$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl), or N;

Y is $CR^4$ ($R^4$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl), or N;

$R^5$ is

(1) $C_{3-6}$ cycloalkyl optionally having one $C_{6-10}$ aryl-aminocarbonyl optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl,

(2) $C_{1-6}$ alkyl-carbonylamino optionally having one $C_{6-10}$ aryl,

(3) $C_{1-6}$ alkoxy optionally having one $C_{6-10}$ aryl, or

(4) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from

(a) $C_{6-10}$ aryl optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl,

(b) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and

(c) oxo;

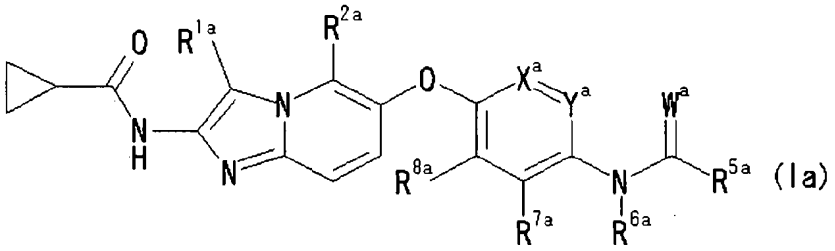
$R^6$ is a hydrogen atom;

$R^7$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl; and

$R^8$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl,

or a salt thereof.

2. A compound represented by the formula



(Ia)

wherein $R^{1a}$ and $R^{2a}$ are the same or different and each is

(1) a hydrogen atom,

(2) a halogen atom,

(3) a group bonded via a carbon atom,

(4) a group bonded via a nitrogen atom,

(5) a group bonded via an oxygen atom, or

(6) a group bonded via a sulfur atom;

$W^a$ is O or S;

$X^a$ is $CR^{3a}$ ($R^{3a}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl), or N;

$Y^a$ is $CR^{4a}$ ($R^{4a}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl), or N;

$R^{5a}$ is

(1) $C_{3-6}$ cycloalkyl optionally having one $C_{6-10}$ aryl-aminocarbonyl optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl,

(2) $C_{1-6}$ alkyl-carbonylamino optionally having one $C_{6-10}$ aryl,

(3) $C_{1-6}$ alkoxy optionally having one $C_{6-10}$ aryl, or

(4) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from

(a) $C_{6-10}$ aryl optionally having 1 to 3 substituents selected from a halogen atom and $C_{1-6}$ alkyl,

(b) $C_{1-6}$ alkyl optionally having 1 to 3 halogen atoms, and

(c) oxo;

$R^{6a}$ is a hydrogen atom;

$R^{7a}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl;

$R^{8a}$ is a hydrogen atom, a halogen atom or $C_{1-6}$ alkyl,

or a salt thereof.

3. The compound of claim 2 wherein

$R^{1a}$ is a hydrogen atom, a fluorine atom or methyl;

$R^{2a}$ is a hydrogen atom;

$W^a$ is O or S;

$X^a$ is CH, CF, CCl, $C(CH_3)$ or N;

$Y^a$ is CH, CF, CCl, $C(CH_3)$ or N;

$R^{5a}$ is

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom, a chlorine atom, a bromine atom, methyl and isopropyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms,

(d) isopropyl, and

(e) oxo;

$R^{6a}$ is a hydrogen atom;
$R^{7a}$ is a hydrogen atom; and
$R^{8a}$ is a hydrogen atom.

4. N-[4-({2-[(Cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-N'-phenylcyclopropane-1,1-dicarboxamide or a salt thereof.

5. N-[4-({2-[(Cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide or a salt thereof.

6. N-[4-({2-[(Cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide or a salt thereof.

7. N-[5-({2-[(Cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)pyridin-2-yl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide or a salt thereof.

8. A prodrug of the compound of claim 1.

9. A pharmaceutical agent comprising the compound of claim 1 or a prodrug thereof.

10. The pharmaceutical agent of claim 9, which is a kinase inhibitor.

11. The pharmaceutical agent of claim 9, which is an agent for the prophylaxis or treatment of cancer.

12. A method for the prophylaxis or treatment of cancer, which comprises administering an effective amount of the compound of claim 1 or a prodrug thereof to the mammal.

13. Use of the compound of claim 1 or a prodrug thereof for the production of an agent for the prophylaxis or treatment of cancer.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2009/058962

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D277/82 C07D471/04 C07D513/04 A61P35/00 A61K31/429
A61K31/437 A61K31/496 A61K31/444

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)
C07D A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | WO 02/44156 A (GLAXO GROUP LTD [GB]; GLAXOSMITHKLINE K K [JP]; CHEUNG MUI [US]; HARRI) 6 June 2002 (2002-06-06) claims 1,74 | 1-13 |
| Y | WO 2008/016192 A (TAKEDA PHARMACEUTICAL [JP]; SAKAI NOZOMU [JP]; IMAMURA SHINICHI [JP];) 7 February 2008 (2008-02-07) claims 1,10,15,21 | 1-13 |
| P,X | WO 2008/150015 A (TAKEDA PHARMACEUTICAL [JP]; OGURO YUYA [JP]; IMAMURA SHINICHI [JP]; CA) 11 December 2008 (2008-12-11) claims 1,21,32 | 1-13 |

☐ 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 document 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 |
|---|---|
| 13 July 2009 | 29/07/2009 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Miniejew, Catherine |

Form PCT/ISA/210 (second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/JP2009/058962

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 0244156 A | 06-06-2002 | AU 3243902 A | 11-06-2002 |
| | | EP 1341771 A2 | 10-09-2003 |
| | | JP 2004517080 T | 10-06-2004 |
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| | | CL 22612007 A1 | 02-05-2008 |
| | | CR 10607 A | 12-03-2009 |
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| WO 2008150015 A | 11-12-2008 | US 2009163488 A1 | 25-06-2009 |

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 13984559 |
| **Filing Date:** | 20-Mar-2014 |
| **Title of Invention:** | PROCESSES FOR PREPARING QUINOLINE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH COMPOUNDS |
| **First Named Inventor/Applicant Name:** | Jo Ann Wilson |
| **Filer:** | Heid Marie Berven/Charles Gregg-Geist |
| **Attorney Docket Number:** | 224990/10-039C-US/343999 |

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($) |
|---|---|---|---|---|
| **Miscellaneous:** | | | | |
| RCE- 2nd and Subsequent Request | 2820 | 1 | 850 | 850 |
| | | **Total in USD ($)** | | **850** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 25549838 |
| **Application Number:** | 13984559 |
| **International Application Number:** | |
| **Confirmation Number:** | 6725 |
| **Title of Invention:** | PROCESSES FOR PREPARING QUINOLINE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH COMPOUNDS |
| **First Named Inventor/Applicant Name:** | Jo Ann Wilson |
| **Customer Number:** | 91684 |
| **Filer:** | Heid Marie Berven/Charles Gregg-Geist |
| **Filer Authorized By:** | Heid Marie Berven |
| **Attorney Docket Number:** | 224990/10-039C-US/343999 |
| **Receipt Date:** | 20-APR-2016 |
| **Filing Date:** | 20-MAR-2014 |
| **Time Stamp:** | 17:06:08 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $850 |
| RAM confirmation Number | 4177 |
| Deposit Account | 503145 |
| Authorized User | BERVEN, HEIDI M. |

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 | | EX10-039C-US_RCE.pdf | 2600674<br>970a21321b1ff19af0447d992377a6719b83a46d | yes | 16 |

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

| Document Description | Start | End |
|---|---|---|
| Transmittal Letter | 1 | 2 |
| Miscellaneous Incoming Letter | 3 | 3 |
| Claims | 4 | 6 |
| Applicant Arguments/Remarks Made in an Amendment | 7 | 10 |
| Request for Continued Examination (RCE) | 11 | 12 |
| Information Disclosure Statement (IDS) Form (SB08) | 13 | 15 |
| Transmittal Letter | 16 | 16 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 2 | Foreign Reference | WO2009136663A1.PDF | 12623477<br>4d4b466297604a28fb793626cb651c667601afb5 | no | 340 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 3 | Fee Worksheet (SB06) | fee-info.pdf | 30867<br>66cbda02e43fd646cdc67f3aab50cf4785d1f369 | no | 2 |

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**Information:**

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| **Total Files Size (in bytes):** | 15255018 |

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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.**

HONIGMAN

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Attorneys and Counselors

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*Via EFS*

April 20, 2016

Commissioner for Patents
United States Patent and Trademark Office
P. O. Box 1450
Alexandria, VA 22313

***Re:*** ***Application No.: 13/984,559***
***Inventor: Jo Ann Wilson***
***Filing Date: March 20, 2014***
***Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds***
***Confirmation No.: 6725***
***Attorney Docket No.: 224990/10-039C-US/343999***

Dear Sir or Madam:

Enclosed for filing please find the following documents:

1. This Cover Letter to the Commissioner for Patents;
2. Request for Continued Examination under 37 C.F.R. § 1.114;
3. Request for Continued Examination Transmittal (PTO/SB/30);
4. Information Disclosure Statement (PTO/SB/08A);
5. Foreign Patent Document (1); and
6. Certificate of Transmission under 37 C.F.R. § 1.8(a).

The Applicant notes that the filing of the enclosed Information Disclosure Statement shall not be construed to be an admission that the information cited in the statement qualifies as prior art under 35 U.S.C. §§ 102 or 103, or is considered to be material to patentability as defined in 37 C.F.R § 1.56(b).

It is believed that due for this submission is the $850.00 fee set forth in 37 C.F.R. § 1.17(e)(2) for a small entity filing a second Request for Continued Examination under § 1.114. The Applicant authorizes the Office to charge this $850.00 to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C-US/343999. It is believed that no additional fees are due at this time. However, if there are any other fees required for this submission, or any credits, please apply them to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C-US/343999.

Very truly yours,

HONIGMAN MILLER SCHWARTZ AND COHN LLP

Heidi M. Berven, Ph.D.
Reg. No. 48,951

HMB/ewg

Enclosures