

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 10275-0161-00304	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/US2020/046116	International filing date (day/month/year) 13.08.2020	Priority date (day/month/year) 14.08.2019	
International Patent Classification (IPC) or national classification and IPC INV. C07D207/08			
Applicant Vertex Pharmaceuticals Incorporated			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>7</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ (sent to the applicant and to the International Bureau) a total of <u>25</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions). ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2). ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)). b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in the form of an Annex C/ST.25 text file, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3ter of Annex C of the Administrative Instructions).			
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☒ Box No. II Priority ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement ☒ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application ☐ Box No. VIII Certain observations on the international application			
Date of submission of the demand 08.06.2021		Date of completion of this report 26.07.2021	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465		Authorized officer Bakboord, Joan Telephone No. +49 89 2399-2168	



Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the **elements*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

Description, Pages

1-198 as originally filed

Claims, Numbers

1-37 filed in electronic form on

08-06-2021

- ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
5. ☐ This report has been established:
- ☐ taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
 - ☐ without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2020/046116

6. ☒ With regard to top-up searches (Rules 66.1 *ter* and 70.2(f)):
- ☐ A top-up search was carried out by this Authority on (all discovered documents are listed in the Supplemental Box Relating to Top-up Search).
 - ☐ Additional relevant documents have been discovered during the top-up search.
 - ☒ No top-up search was carried out by this Authority because it would serve no useful purpose.
7. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

* If item 4 applies, some or all of those sheets may be marked "superseded".

Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
 - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

see separate sheet

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-37</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-37</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-37</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

**INTERNATIONAL PRELIMINARY REPORT
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Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)
and / or
2. Non-written disclosures (Rule 70.9)
see separate sheet

Re Item II

Priority

The priority document has been filed and the priority has been validly claimed.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- 1 The present application relates to a process for the preparation of compound I.

Compound I is a modulator of cystic fibrosis transmembrane conductance regulator (CFTR) and as such useful in the treatment of cystic fibrosis.
- 2 Reference is made to the following documents:
 - D1 NEWKOME G.R. ET AL: "Nicotinic Acid Crown Ethers. Synthesis, Reactions, and Complexation of Nicotinonitrile macrocycles", JOURNAL OF ORGANIC CHEMISTRY, vol. 44, no. 15, 1 January 1979, pages 2639-2697, XP55732460,
 - D2 REWCASTLE G W ET AL: "TYROSINE KINASE INHIBITORS. 10. ISOMERIC 4-Ú(3-BROMOPHENYL)AMINO3?4 PYRIDOÚD3?4-PYRIMIDINES ARE POTENT ATP BINDING SITE INHIBITORS OF THETYROSINE KINASE FUNCTION OF THE EPIDERMAL GROWTH FACTOR RECEPTOR", JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, no. 9, 26 April 1996, pages 1823-1835, XP000671261
 - D3 ARTEM YU. CHEREPAKHA ET AL: "Hetaryl Bromides Bearing the SO 2 F Group - Versatile Substrates for Palladium-Catalyzed C-C Coupling Reactions", EUROPEAN JOURNAL OF ORGANIC CHEMISTRY, vol. 2018, no. 47, 19 December 2018, pages 6682-6692, XP0055733124
 - D4 NISHIDA HARUYUKI ET AL: "Exploration of pyrrole derivatives to find an effective potassium-competitive acid blocker with moderately long-lasting suppression of gastric acid secretion", BIOORGANIC & MEDICINAL CHEMISTRY, vol. 25, no. 13, 27 April 2017, pages 3447-3460, XP085037327

- D5 PRASHANTHA GUNAGA ET AL: "Selective I Kur Inhibitors for the Potential Treatment of Atrial Fibrillation: Optimization of the Phenyl Quinazoline Series Leading to Clinical Candidate 5-[5-Phenyl-4-(pyridin-2-ylmethylamino)quinazolin-2-yl]pyridine-3-sulfonamide", JOURNAL OF MEDICINAL CHEMISTRY, vol. 60, no. 9, 28 April 2017, pages 3795-3803, XP055733118
- D6 WO 2019/195739 A1 (ABELA ALEXANDER RUSSELL ET AL) 10 October 2019
- D7 WO 2019/200246 A1 (ABELA ALEXANDER RUSSELL ET AL) 17 October 2019
- D8 US 2018/162839 A1
- D9 WO 2019/161078 A1 (VERTEX PHARMA [US]) 22 August 2019
- D10 WO 2020/102346 A1 (VERTEX PHARMA [US]) 22 May 2020

Documents D6, D7, D9 and D10 were published after the priority date. The priority has been validly claimed and these documents are not regarded as prior art.

3 Novelty

Document D1 discloses a compound of formula VII.

Document D2 discloses a compound of formula VII.

Document D3 discloses a compound of formula V.

Document D4 discloses a compound of formula V.

Document D5 discloses a compound of formula V.

It is noted that document D6 discloses a compound of formula VII.

It is noted that document D7 discloses a compound of formula VII.

Document D8 discloses modulators of cystic fibrosis transmembrane conductance regulator differing from compound I in that they do not have a macrocyclic structure.

It is noted that document D9 discloses the synthesis of compound I by closing the bond between the pyrrolidine ring and the pyridine ring as the last step.

It is noted that document D10 discloses the synthesis of compound I by closing the bond between the pyrrolidine ring and the pyridine ring as the last step.

Compound I is not disclosed in the cited prior art. A method for the preparation of compound I is novel by consequence.

Claims 1-36 therefore fulfil the requirements of Art 33(2) PCT.

A compound as described in claim 37 is not disclosed in the cited prior art. Claim 37 therefore fulfils the requirements of Art 33(2) PCT.

4 Inventive step

Starting from document D8 the problem to be solved by the present application may be regarded to be the provision of a further modulator of CFTR. The solution of the applicant resides in compound I. The applicant shows in paragraph [0009] that compound I is indeed a modulator of CFTR. As the structural modifications have not been made obvious by the cited prior art the solution of the applicant may be regarded to involve an inventive step. A method for the preparation of compound I is inventive by consequence. Claims 1-37 therefore fulfil the requirements of Art 33(3) PCT.

Re Item VI

Certain documents cited

WO 2019/195739 A1

WO 2019/200246 A1

WO 2019/161078 A1

WO 2020/102346 A1

IN THE EUROPEAN PATENT OFFICE

Applicant: Vertex Pharmaceuticals Incorporated

International Application No.: PCT/US2020/046116

International Filing date: 13 August 2020

European Patent Office
P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
The Netherlands

Attn: Authorized Officer Joan Bakboord

**ARTICLE 34 AMENDMENTS -
LETTER ACCOMPANYING REPLACEMENT SHEETS AND INDICATION OF
THE BASIS OF THE AMENDMENTS**

This is a request to amend the claims of the international application under PCT Article 34. The following is an explanation of the amendments:

- (i) Claims 1 to 36 are unchanged.
- (ii) Claim 37 is amended to remove Formulas V and VII.

All amendments are made without prejudice or disclaimer. These amendments and the below arguments should not be considered as a waiver of any subject matter disclosed in the application, or as an admission over the prior art.

Support for these amendments can be found in the as-filed specification. These amendments do not add any new matter.

REPLY TO WRITTEN OPINION

In response to the PCT WRITTEN OPINION mailed 16 October 2020, Applicant submits the following remarks in response to the Novelty and Inventive Step objections. Applicant requests that the Examiner consider the attached amended claims and explanatory comments before issuing a substantive examination report.

The Examiner contends that pending claim 37 lacks novelty and inventive step over D1-D5 because of the recitation of Formulas V and VII in that claim. Written Opinion at Section "Re Item V." Without acquiescing to the propriety of the rejection, and solely to expedite prosecution, Applicant amends claim 37 to remove Formulas V and VII. Applicant respectfully asserts that none of the cited references teaches or suggests the subject matter encompassed by the amended claims.

Accordingly, the amended claims are novel and inventive over the cited references. Applicant requests withdrawal of all objections, reconsideration of the objected claim, and issuance of a favorable examination report.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

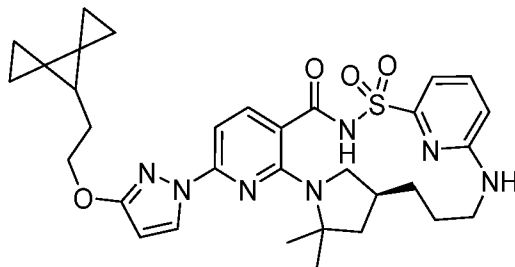
Dated: 8 June 2021

By: /Leslie A. McDonell/
Leslie A. McDonell
(617) 646-1650

Enclosures - Replacement sheets (clean and marked)

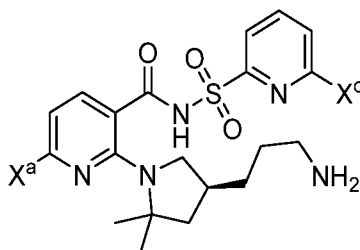
CLAIMS

1. A method of preparing Compound **I**:



Compound **I**,

or a pharmaceutically acceptable salt thereof, comprising converting a compound of Formula **(I)**:



(I),

or a salt thereof, into Compound **I**, or a pharmaceutically acceptable salt thereof, wherein:

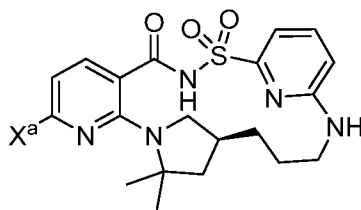
X^a is selected from F, Cl, Br, I, and $-\text{OSO}_2\text{R}$;

R is selected from $-\text{C}_{1-10}$ alkyl, $-\text{C}_{1-10}$ haloalkyl, and aryl optionally substituted with $-\text{C}_{1-10}$ alkyl, $-\text{C}_{1-10}$ haloalkyl, halo, or nitro; and

X^c is selected from F, Cl, Br, and I.

2. The method of claim 1, wherein the conversion of the compound of Formula **(I)**, or a salt thereof, into Compound **I**, or a pharmaceutically acceptable salt thereof, comprises the steps of:

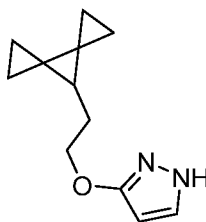
1) combining the compound of Formula **(I)**, or a salt thereof, with at least one first base to produce a compound of Formula **(II)**:



(II),

or a salt thereof; and

2) combining the compound of Formula (II), or a salt thereof, with compound 1:



1,

or a salt thereof,

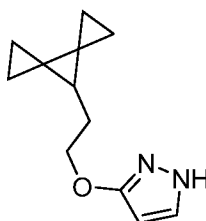
and at least one second base to produce Compound I, or a pharmaceutically acceptable salt thereof,

wherein in the compound of Formula (II), or a salt thereof:

X^a is selected from F, Cl, Br, I, and $-OSO_2R$; and

R is selected from $-C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, and aryl optionally substituted with $-C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, halo, or nitro.

3. The method of claim 1, wherein the conversion of the compound of Formula (I), or a salt thereof, into Compound I, or a pharmaceutically acceptable salt thereof, comprises combining the compound of Formula (I), or a salt thereof, with compound 1:



1,

or a salt thereof, and at least one third base to produce Compound I, or a pharmaceutically acceptable salt thereof,

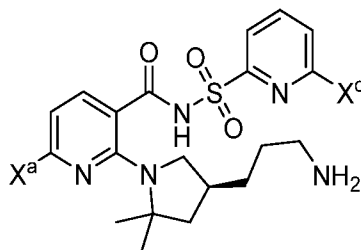
wherein in the compound of Formula (I), or a salt thereof:

X^a is selected from F, Cl, Br, I, and $-OSO_2R$;

R is selected from -C₁₋₁₀ alkyl, -C₁₋₁₀ haloalkyl, and aryl optionally substituted with -C₁₋₁₀ alkyl, -C₁₋₁₀ haloalkyl, halo, or nitro; and

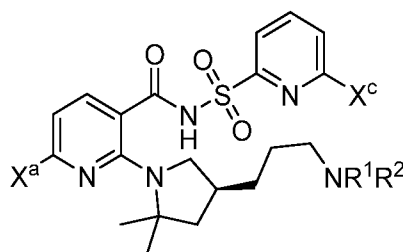
X^c is selected from F, Cl, Br, and I.

4. The method of claim 1, wherein the compound of Formula **(I)**:



(I),

or a salt thereof, is prepared by converting a compound of Formula **(III)**:



(III),

or a salt thereof, into the compound of Formula **(I)**, or a salt thereof, wherein in the compound of Formula **(III)**, or a salt thereof:

X^a is selected from F, Cl, Br, I, and -OSO₂R;

R is selected from -C₁₋₁₀ alkyl, -C₁₋₁₀ haloalkyl, and aryl optionally substituted with -C₁₋₁₀ alkyl, -C₁₋₁₀ haloalkyl, halo, or nitro;

X^c is selected from F, Cl, Br, and I; and

wherein:

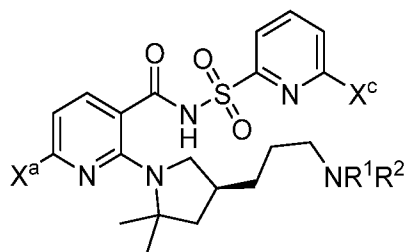
R¹ is hydrogen and R² is a monovalent nitrogen protecting group;

R¹ and R² are independently selected from monovalent nitrogen protecting groups;

or

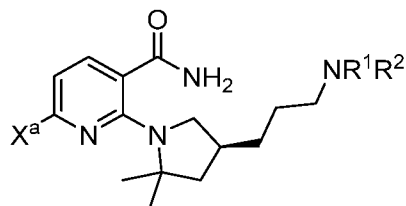
R¹ and R², together with the atoms to which they are attached, form a nitrogen protecting group.

5. The method of claim 4, wherein the compound of Formula **(III)**:



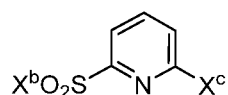
(III),

or a salt thereof, is prepared by combining a compound of Formula (IV):



(IV),

or a salt thereof, with a compound of Formula (V):

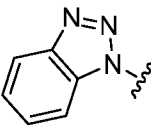
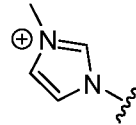


(V),

or a salt thereof, to produce the compound of Formula (III), or a salt thereof, wherein:

X^a is selected from F, Cl, Br, I, and $-\text{OSO}_2\text{R}$;

R is selected from $-\text{C}_{1-10}$ alkyl, $-\text{C}_{1-10}$ haloalkyl, and aryl optionally substituted with $-\text{C}_{1-10}$ alkyl, $-\text{C}_{1-10}$ haloalkyl, halo, or nitro

X^b is selected from Cl, F, $-\text{OC}_6\text{F}_5$, , and  ;

X^c is selected from F, Cl, Br, and I; and

wherein:

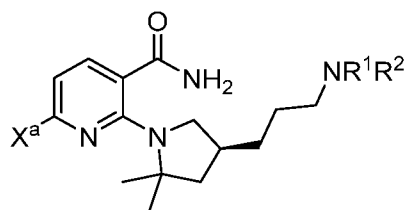
R^1 is hydrogen and R^2 is a monovalent nitrogen protecting group;

R^1 and R^2 are independently selected from monovalent nitrogen protecting groups;

or

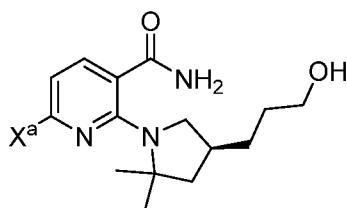
R^1 and R^2 , together with the atoms to which they are attached, form a nitrogen protecting group.

6. The method of claim 5, wherein the compound of Formula (IV):



(IV),

or a salt thereof, is prepared by converting a compound of Formula (VI):



(VI),

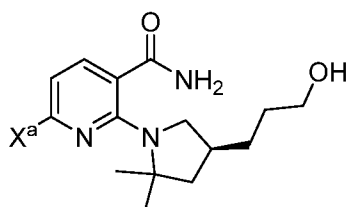
or a salt thereof, into the compound of Formula (IV), or a salt thereof,

wherein in the compound of Formula (VI), or a salt thereof:

X^a is selected from F, Cl, Br, I, and $-\text{OSO}_2\text{R}$; and

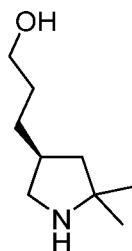
R is selected from $-\text{C}_{1-10}$ alkyl, $-\text{C}_{1-10}$ haloalkyl, and aryl optionally substituted with $-\text{C}_{1-10}$ alkyl, $-\text{C}_{1-10}$ haloalkyl, halo, or nitro.

7. The method of claim 6, wherein the compound of Formula (VI):



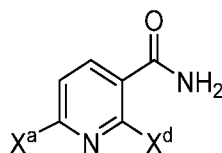
(VI),

or a salt thereof, is prepared by combining compound 2:



2,

or a salt thereof, with a compound of Formula (VII):



(VII),

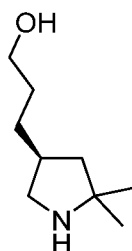
or a salt thereof, to produce the compound of Formula (VI), or a salt thereof, wherein in the compound of Formula (VII), or a salt thereof:

X^a is selected from F, Cl, Br, I, and $-\text{OSO}_2\text{R}$;

R is selected from $-\text{C}_{1-10}$ alkyl, $-\text{C}_{1-10}$ haloalkyl, and aryl optionally substituted with $-\text{C}_{1-10}$ alkyl, $-\text{C}_{1-10}$ haloalkyl, halo, or nitro; and

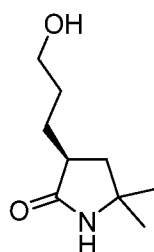
X^d is selected from F, Cl, Br, and I.

8. The method of claim 7, wherein compound 2:



2,

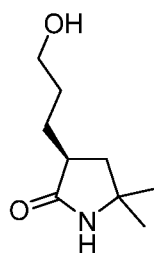
or a salt thereof, is prepared by converting compound 3:



3,

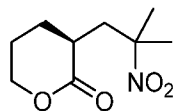
or a salt thereof, into compound 2, or a salt thereof.

9. The method of claim 8, wherein compound 3:



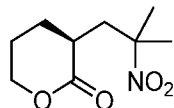
3,

or a salt thereof, is prepared by converting compound 4:

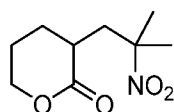
**4,**

or a salt thereof, into compound **3**, or a salt thereof.

10. The method of claim 9, wherein compound **4**:

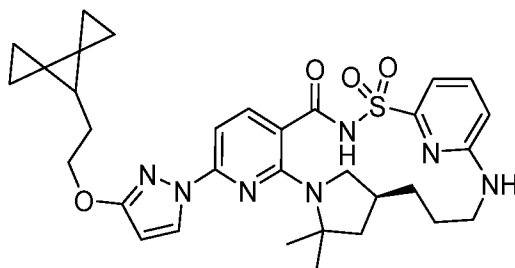
**4,**

or a salt thereof, is prepared by chiral resolution of compound ($\pm$)-**4**:

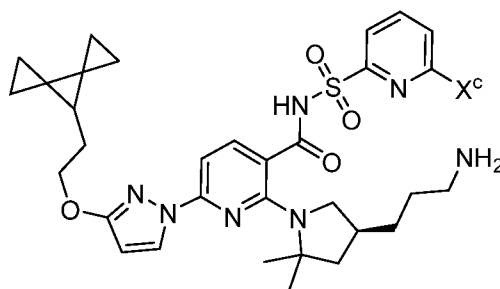
**($\pm$)-4,**

or a salt thereof.

11. A method of preparing Compound **I**:

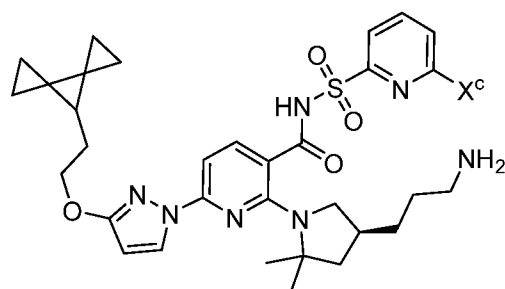
Compound **I**,

or a pharmaceutically acceptable salt thereof, comprising converting a compound of Formula (**VIII**):

**(VIII),**

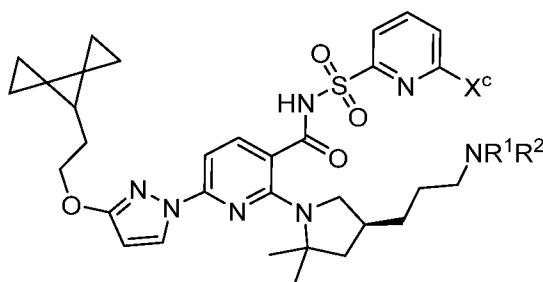
or a salt thereof, into Compound **I**, or a pharmaceutically acceptable salt thereof, wherein in the compound of Formula (**VIII**), or a salt thereof, X^c is selected from F, Cl, Br, and I.

12. The method of claim 11, wherein the compound of Formula **(VIII)**:



(VIII),

or a salt thereof, is prepared by converting a compound of Formula **(IX)**:



(IX),

or a salt thereof, into the compound of Formula **(VIII)**, or a salt thereof, wherein in the compound of Formula **(IX)**, or a salt thereof:

X^c is selected from F, Cl, Br, and I; and

wherein:

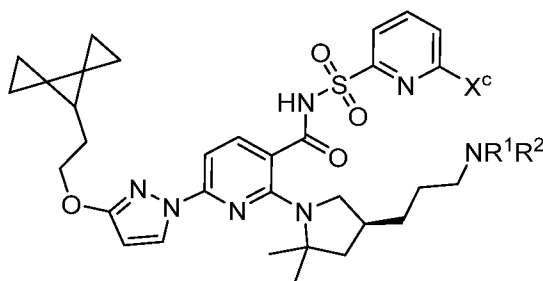
R¹ is hydrogen and R² is a monovalent nitrogen protecting group;

R¹ and R² are independently selected from monovalent nitrogen protecting groups;

or

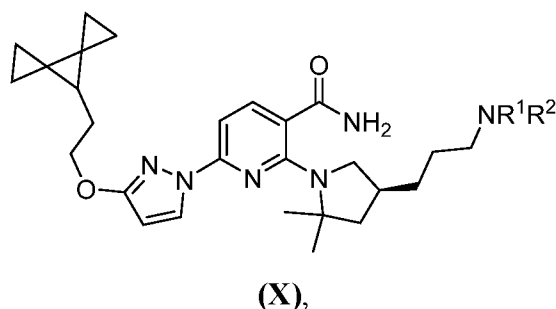
R¹ and R², together with the atoms to which they are attached, form a nitrogen protecting group.

13. The method of claim 12, wherein the compound of Formula **(IX)**:

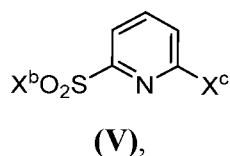


(IX),

or a salt thereof, is prepared by combining a compound of Formula (X):



or a salt thereof, with a compound of Formula (V):



or a salt thereof, to produce the compound of Formula (IX), or a salt thereof, wherein in the compound of Formula (X), or a salt thereof:

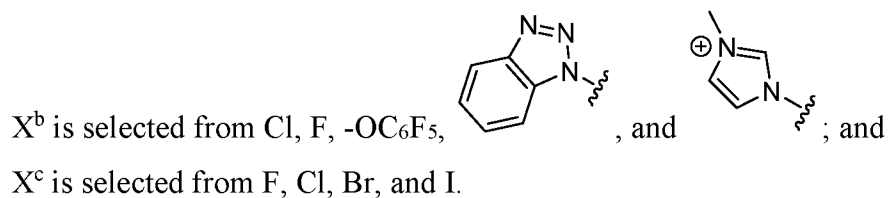
R^1 is hydrogen and R^2 is a monovalent nitrogen protecting group;

R^1 and R^2 are independently selected from monovalent nitrogen protecting groups;

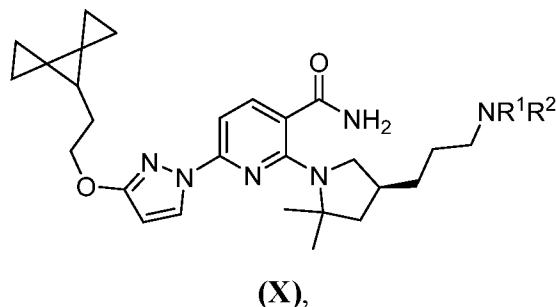
or

R^1 and R^2 , together with the atoms to which they are attached, form a nitrogen protecting group; and

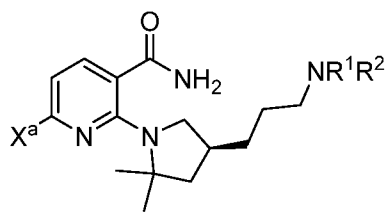
wherein in the compound of Formula (V), or a salt thereof:



14. The method of claim 13, wherein the compound of Formula (X):

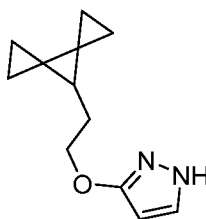


or a salt thereof, is prepared by combining a compound of Formula (IV):



(IV),

or a salt thereof, with compound **1**:

**1**

or a salt thereof, to produce the compound of Formula (X), or a salt thereof, wherein in the compound of Formula (IV), or a salt thereof:

X^a is selected from F, Cl, Br, I, and $-\text{OSO}_2\text{R}$;

R is selected from $-\text{C}_{1-10}$ alkyl, $-\text{C}_{1-10}$ haloalkyl, and aryl optionally substituted with $-\text{C}_{1-10}$ alkyl, $-\text{C}_{1-10}$ haloalkyl, halo, or nitro; and wherein:

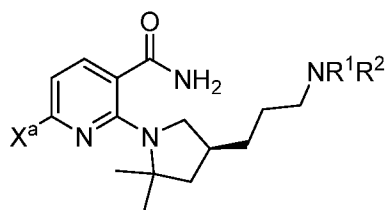
R^1 is hydrogen and R^2 is a monovalent nitrogen protecting group;

R^1 and R^2 are independently selected from monovalent nitrogen protecting groups;

or

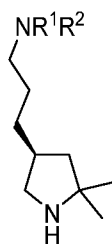
R^1 and R^2 , together with the atoms to which they are attached, form a nitrogen protecting group.

15. The method of claim 14, wherein the compound of Formula (IV):



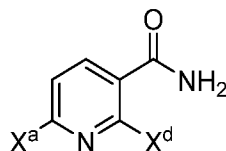
(IV),

or a salt thereof, is prepared by combining a compound of Formula (XI):



(XI),

or a salt thereof, with a compound of Formula (VII):



(VII),

or a salt thereof, to produce the compound of Formula (IV), or a salt thereof,

wherein in the compound of Formula (XI), or a salt thereof:

R^1 is hydrogen and R^2 is a monovalent nitrogen protecting group;

R^1 and R^2 are independently selected from monovalent nitrogen protecting groups;

or

R^1 and R^2 , together with the atoms to which they are attached, form a nitrogen protecting group; and

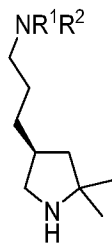
wherein in the compound of Formula (VII), or a salt thereof:

X^a is selected from F, Cl, Br, I, and $-\text{OSO}_2\text{R}$;

R is selected from $-\text{C}_{1-10}$ alkyl, $-\text{C}_{1-10}$ haloalkyl, and aryl optionally substituted with $-\text{C}_{1-10}$ alkyl, $-\text{C}_{1-10}$ haloalkyl, halo, or nitro; and

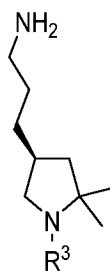
X^d is selected from F, Cl, Br, and I.

16. The method of claim 15, wherein the compound of Formula (XI):



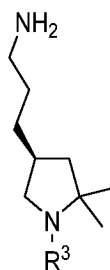
(XI),

or a salt thereof, is prepared by converting a compound of Formula (XII):

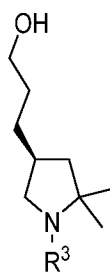
**(XII),**

or a salt thereof, into the compound of Formula **(XI)**, or a salt thereof, wherein in the compound of Formula **(XII)**, or a salt thereof, R^3 is a monovalent nitrogen protecting group.

17. The method of claim 16, wherein the compound of Formula **(XII)**:

**(XII),**

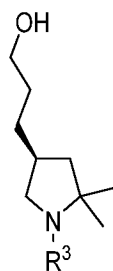
or a salt thereof, is prepared by converting the compound of Formula **(XV)**:

**(XV),**

or a salt thereof, into the compound of Formula **(XII)**, or a salt thereof, wherein in the compound of Formula **(XV)**, or a salt thereof, R^3 is a monovalent nitrogen protecting group.

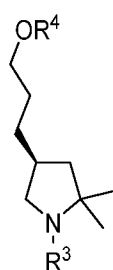
18. The method of claim 17, wherein the conversion of the compound of Formula **(XV)**, or a salt thereof, into the compound of Formula **(XII)**, or a salt thereof, comprises the steps of:

1) converting the compound of Formula **(XV)**:



(XV),

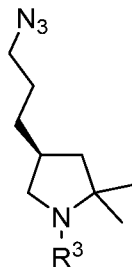
or a salt thereof, into the compound of Formula (XIV):



(XIV),

or a salt thereof;

2) converting the compound of Formula (XIV), or a salt thereof, into the compound of Formula (XIII):



(XIII),

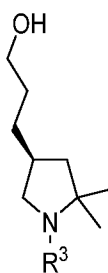
or a salt thereof; and

3) converting the compound of Formula (XIII), or a salt thereof, into the compound of Formula (XII), or a salt thereof, wherein in the compounds of Formulae (XIII)-(XV), or a salt thereof, R^3 is a monovalent nitrogen protecting group; and wherein in the compound of Formula (XIV), or a salt thereof:

R^4 is $-SO_2R$; and

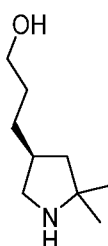
R is selected from $-C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, and aryl optionally substituted with $-C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, halo, or nitro.

19. The method of claim 18, wherein the compound of Formula **(XV)**:



(XV),

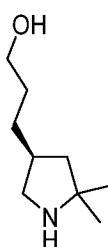
or a salt thereof, is prepared by converting compound **2**:



2,

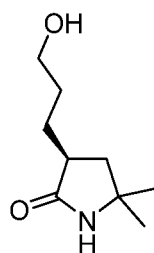
or a salt thereof, into the compound of Formula **(XV)**, or a salt thereof.

20. The method of claim 19, wherein compound **2**:



2,

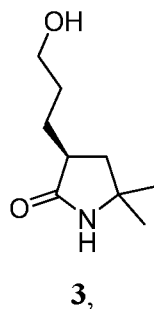
or a salt thereof, is prepared by converting compound **3**:



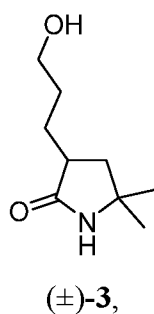
3,

or a salt thereof, into compound **2**, or a salt thereof.

21. The method of claim 20, wherein compound **3**:

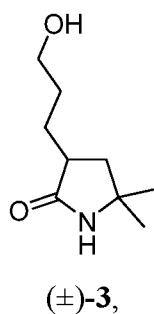


or a salt thereof, is prepared by chiral resolution of compound ($\pm$)-**3**:

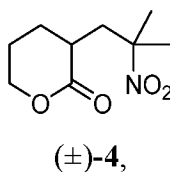


or a salt thereof.

22. The method of claim 21, wherein compound ($\pm$)-**3**:

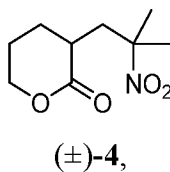


or a salt thereof, is prepared by converting compound ($\pm$)-**4**:

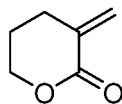


or a salt thereof, into compound ($\pm$)-**3**, or a salt thereof.

23. The method of claim 22, wherein compound ($\pm$)-**4**:



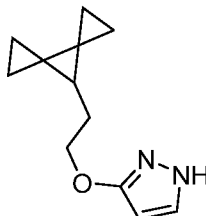
or a salt thereof, is prepared by combining compound **5**:



5,

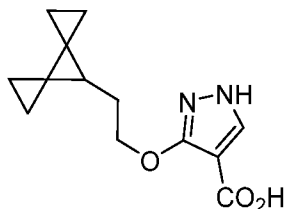
or a salt thereof, with 2-nitropropane to produce compound ($\pm$)-4, or a salt thereof.

24. The method of claim 2, wherein compound 1:



1,

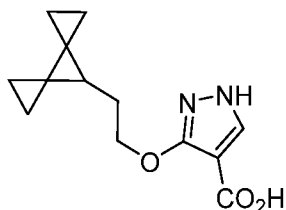
or a salt thereof, is prepared by converting compound 6:



6,

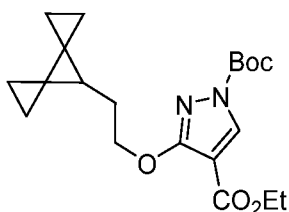
or a salt thereof, into compound 1, or a salt thereof.

25. The method of claim 24, wherein compound 6:



6,

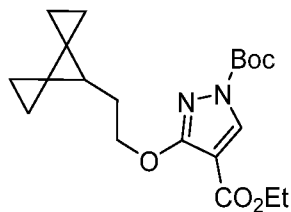
or a salt thereof, is prepared by converting compound 7:



7,

or a salt thereof, into compound 6, or a salt thereof.

26. The method of claim 25, wherein compound 7:



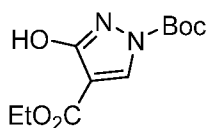
7,

or a salt thereof, is prepared by combining compound **8**:



8,

or a salt thereof, with compound **9**:



9,

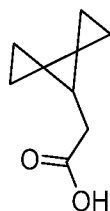
or a salt thereof, to produce compound **7**, or a salt thereof.

27. The method of claim 26, wherein compound **8**:



8,

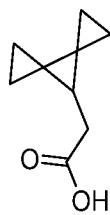
or a salt thereof, is prepared by converting compound **10**:



10,

or a salt thereof, into compound **8**, or a salt thereof.

28. The method of claim 27, wherein compound **10**:

**10,**

or a salt thereof, is prepared by converting compound **11**:

**11,**

or a salt thereof, into compound **10**, or a salt thereof.

29. The method of claim 28, wherein compound **11**:

**11,**

or a salt thereof, is prepared by converting compound **12**:

**12,**

or a salt thereof, into compound **11**, or a salt thereof.

30. The method of claim 29, wherein compound **12**:

**12,**

or a salt thereof, is prepared by converting compound **13**:

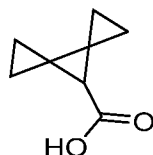
**13,**

or a salt thereof, into compound **12**, or a salt thereof.

31. The method of claim 30, wherein compound **13**:

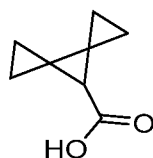
**13,**

or a salt thereof, is prepared by converting compound **14**:

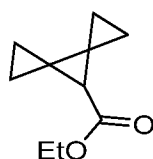
**14,**

or a salt thereof, into compound **13**, or a salt thereof.

32. The method of claim 31, wherein compound **14**:

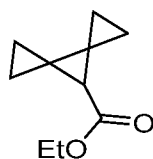
**14,**

or a salt thereof, is prepared by converting compound **15**:

**15,**

or a salt thereof, into compound **14**, or a salt thereof.

33. The method of claim 32, wherein compound **15**:

**15,**

or a salt thereof, is prepared by converting compound **16**:



16,

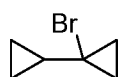
or a salt thereof, into compound **15**, or a salt thereof.

34. The method of claim 33, wherein compound **16**:



16,

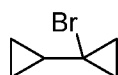
or a salt thereof, is prepared by converting compound **17**:



17,

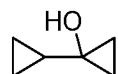
or a salt thereof, into compound **16**, or a salt thereof.

35. The method of claim 34, wherein compound **17**:



17,

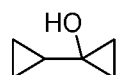
or a salt thereof, is prepared by converting compound **18**:



18,

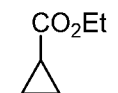
or a salt thereof, into compound **17**, or a salt thereof.

36. The method of claim 35, wherein compound **18**:



18,

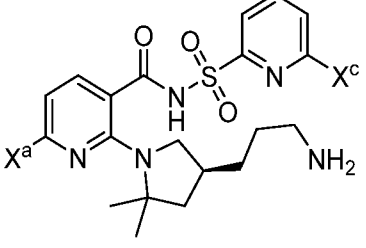
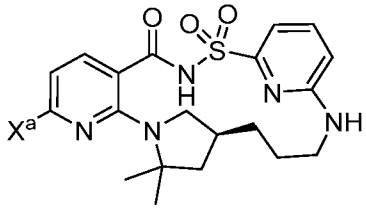
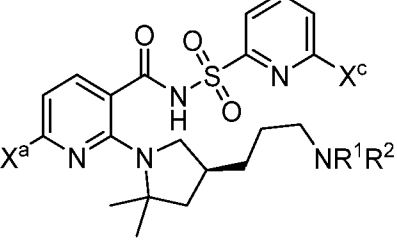
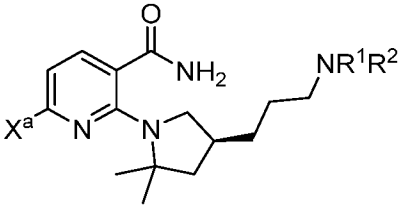
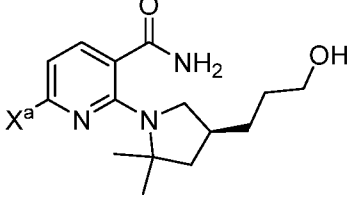
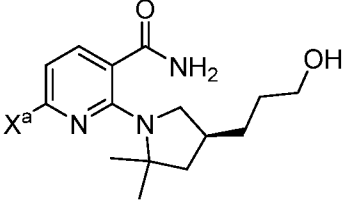
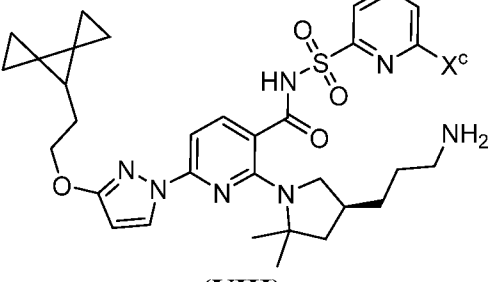
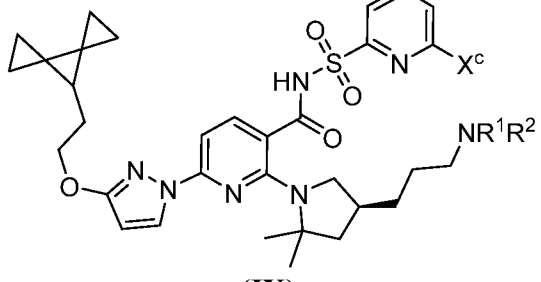
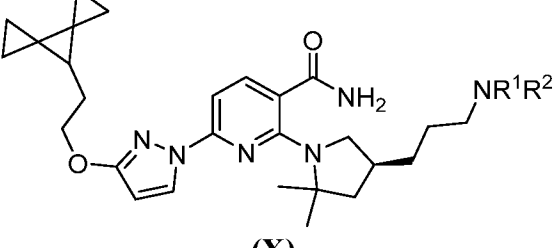
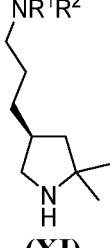
or a salt thereof, is prepared by converting compound **19**:

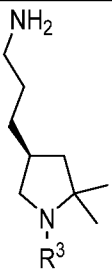
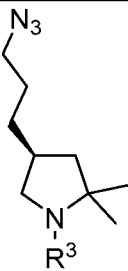
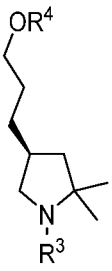
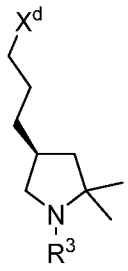
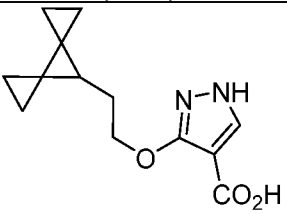
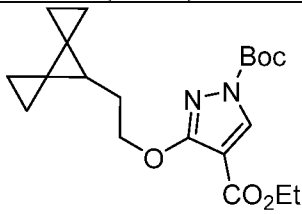


19,

or a salt thereof, into compound **18**, or a salt thereof.

37. A compound selected from:

 (I),	 (II),
 (III),	 (IV),
	 (VI),
 (VI),	
 (VIII),	 (IX),
 (X),	 (XI),

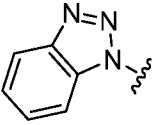
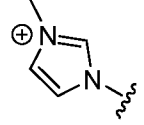
 (XII),	 (XIII),
 (XIV),	 (XIVa),
 6, and	 7,

and salts thereof,

wherein:

X^a is selected from F, Cl, Br, I, and $-\text{OSO}_2\text{R}$;

R is selected from $-\text{C}_{1-10}$ alkyl, $-\text{C}_{1-10}$ haloalkyl, and aryl optionally substituted with $-\text{C}_{1-10}$ alkyl, $-\text{C}_{1-10}$ haloalkyl, halo, or nitro;

X^b is selected from Cl, F, $-\text{OC}_6\text{F}_5$, , and ;

X^c is selected from F, Cl, Br, and I;

X^d is selected from F, Cl, Br, and I;

R^3 is a monovalent nitrogen protecting group;

R^4 is $-\text{SO}_2\text{R}$; and

R is selected from $-\text{C}_{1-10}$ alkyl, $-\text{C}_{1-10}$ haloalkyl, and aryl optionally substituted with $-\text{C}_{1-10}$ alkyl, $-\text{C}_{1-10}$ haloalkyl, halo, or nitro; and
wherein:

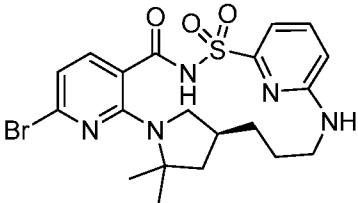
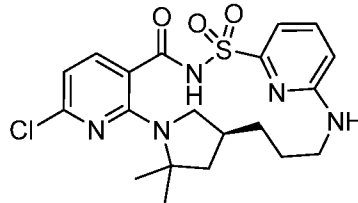
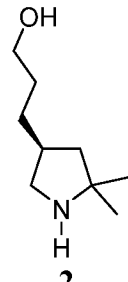
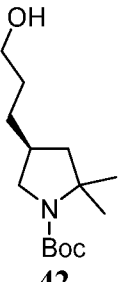
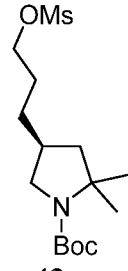
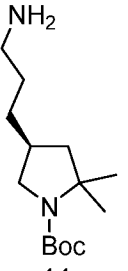
R^1 is hydrogen and R^2 is a monovalent nitrogen protecting group;

R^1 and R^2 are independently selected from monovalent nitrogen protecting groups;

or

R^1 and R^2 , together with the atoms to which they are attached, form a nitrogen protecting group; and

wherein the compound is not:

 40,	 41,
 2,	 42,
 43, or	 44,

or a salt thereof.