

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference V0286.70021	FOR FURTHER ACTION		See item 4 below
International application No. PCT/US2015/021464	International filing date (<i>day/month/year</i>) 19 March 2015 (19.03.2015)	Priority date (<i>day/month/year</i>) 19 March 2014 (19.03.2014)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant VIAMET PHARMACEUTICALS, INC.			

<p>1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).</p> <p>2. This REPORT consists of a total of 18 sheets, including this cover sheet.</p> <p>In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.</p>																								
<p>3. This report contains indications relating to the following items:</p> <table border="0"> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. I</td> <td>Basis of the report</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table> <p>4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).</p>	<input checked="" type="checkbox"/>	Box No. I	Basis of the report	<input type="checkbox"/>	Box No. II	Priority	<input checked="" type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input type="checkbox"/>	Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input type="checkbox"/>	Box No. VI	Certain documents cited	<input type="checkbox"/>	Box No. VII	Certain defects in the international application	<input checked="" type="checkbox"/>	Box No. VIII	Certain observations on the international application
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<input checked="" type="checkbox"/>	Box No. VIII	Certain observations on the international application																						

<p align="center">The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No. +41 22 338 82 70</p>	<p>Date of issuance of this report 20 September 2016 (20.09.2016)</p>
	<p>Authorized officer</p> <p align="center">Simin Baharlou</p> <p>e-mail: pt09.pct@wipo.int</p>

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To: HSI, JEFFREY D. LOCKE LORD LLP P.O. BOX 55874 BOSTON MA 02205 USA
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Date of mailing (day/month/year) 14 July 2015 (14.07.2015)
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Applicant's or agent's file reference 95003WO(305005)	FOR FURTHER ACTION See paragraph 2 below
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International application No. PCT/US2015/021464	International filing date (day/month/year) 19 March 2015 (19.03.2015)	Priority date(day/month/year) 19 March 2014 (19.03.2014)
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International Patent Classification (IPC) or both national classification and IPC C07D 413/06(2006.01)i, C07D 295/215(2006.01)i, C07D 405/06(2006.01)i, A61P 31/04(2006.01)i
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Applicant VIAMET PHARMACEUTICALS, INC.
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1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/KR International Application Division Korean Intellectual Property Office 189 Cheongsu-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea Facsimile No. +82-42-472-7140	Date of completion of this opinion 14 July 2015 (14.07.2015)	Authorized officer LEE KI CHEUL Telephone No. +82-42-481-3491
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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US2015/021464

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of :
 - the international application in the language in which it was filed
 - a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
2. This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. forming part of the international application as filed:
 - in the form of an Annex C/ST.25 text file.
 - on paper or in the form of an image file.
 - b. furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. furnished subsequent to the international filing date for the purposes of international search only:
 - in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2015/021464

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

the entire international application

claims Nos. 45-48, 70-74

because:

the said international application, or the said claims Nos. _____
relate to the following subject matter which does not require an international search (*specify*):

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 45-48, 70-74
are so unclear that no meaningful opinion could be formed (*specify*):

Claims 45-48 are worded in reference to compound 13 or 13a of claim 39. However, said compound 13 or 13a has not been worded in claim 39.

Claims 70-74 are worded in reference to morpholine amide 7 of claim 68. However, said morpholine amide 7 has not been worded in claim 68.

the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed (*specify*):

no international search report has been established for said claims Nos. 45-48, 70-74

a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

See Supplemental Box for further details.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2015/021464

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	<u>1-44,49-69,75-89</u>	YES
	Claims	<u>NONE</u>	NO
Inventive step (IS)	Claims	<u>1-33,40-44,49-56,63-69,75-89</u>	YES
	Claims	<u>34-39,57-62</u>	NO
Industrial applicability (IA)	Claims	<u>1-44,49-69,75-89</u>	YES
	Claims	<u>NONE</u>	NO

2. Citations and explanations :

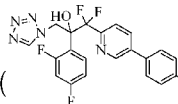
The present invention relates to processes to prepare compounds of formula X or Xa and their intermediates (claims 1-32, 36-44, 59-69, 75), and compounds of formula X or Xa and their intermediates (claims 33-35, 49-58, 76-89).

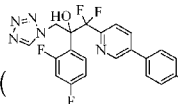
Reference is made to the following documents:

D1: WO 2013-109998 A1 (VIAMET PHARMACEUTICALS, INC.) 25 July 2013

D2: WO 2013-110002 A1 (VIAMET PHARMACEUTICALS, INC.) 25 July 2013

D3: WO 2011-133875 A2 (VIAMET PHARMACEUTICALS, INC.) 27 October 2011



D1-D3 disclose tetrazole compounds () as a metalloenzyme inhibitor and processes to prepare tetrazole compounds (see abstract, scheme 1, examples 1-58 and claims 1-14 in D1; abstract, scheme 1 and examples 1-58 in D2; abstract, scheme 1, examples 1-28 and claims 1-14 in D3).

1. Novelty and Inventive Step

1.1. Claim 1

The subject matter of claim 1 relates to processes to prepare morpholine amides (2b).

D1-D3 disclose processes for preparing tetrazole compounds. However, the processes comprising amidation of ester 2 in the present invention are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claim 1 is considered to be novel and to involve an

Continued on Supplemental Box

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2015/021464

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The substituent "R3" in claims 26-27, 44, 53, 56-57, 59, 63, 67-68, 72-75 is not described in the alternative. Therefore, claims 26-27, 44, 53, 56-57, 59, 63, 67-68, 72-75 are not clear (PCT Article 6).

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inventive step under PCT Article 33(2) and 33(3).

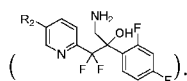
1.2. Claim 2

The subject matter of claim 2 relates to processes to prepare ketones 3 comprising aryl substitution of morpholine **amide** 2b.

D1-D3 disclose processes for preparing tetrazole compounds. However, the processes comprising aryl substitution of morpholine amides 2b in the present invention are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claim 2 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

1.3. Claim 3

The subject matter of claim 3 relates to processes to prepare compounds of formula II



D1-D3 disclose processes for preparing tetrazole compounds. However, the processes comprising epoxide opening of compounds of formula I in the present invention are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claim 3 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

1.4. Claim 4

The subject matter of claim 4 relates to processes to prepare amino alcohols 1-6 or 1-7.

D1-D3 disclose processes for preparing tetrazole compounds. However, the processes comprising arylation of pyridines 4b or 4c in the present invention are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claim 4 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

1.5. Claims 5-12

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The subject matter of claim 5 relates to processes of enriching the enantiomeric purity of enantiomeric compound mixtures.

D1-D3 disclose processes for preparing tetrazole compounds. However, the processes using resolving agents in the present invention are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claim 5 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

Claims 6-12 are dependent on claim 5 and therefore are considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

1.6. Claims 13-18, 23, 30, 40-43

The subject matter of claim 13 relates to processes to prepare a **compound 1** or 1a.

D1-D3 disclose processes for preparing tetrazole compounds. However, the processes comprising converting morpholine **amide 2** in the present invention are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claim 13 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

Claims 14-18, 23, 30, 40-43 are dependent on claim 13 and therefore are considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

1.7. Claims 19-20

The subject matter of claims 19-20 relates to processes to prepare epoxide 5.

D1-D3 disclose processes for preparing tetrazole compounds. However, the processes comprising forming the epoxide of aryl-**pyridines 1-4** in the present invention are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claims 19-20 are considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

1.8. Claims 21-22, 24-25

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The subject matter of claims 21-22, 24-25 relates to processes to prepare enantio-enriched amino-alcohols 1-6* or 1-7*.

D1-D3 disclose processes for preparing tetrazole compounds. However, the processes comprising enriching the enantiomeric purity of amino-alcohols in the present invention are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claims 21-22, 24-25 are considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

1.9. Claims 26-29

The subject matter of claims 26-27 relates to processes to prepare enantio-enriched amino-alcohol XV or XVa.

D1-D3 disclose processes for preparing tetrazole compounds. However, the processes comprising enriching the enantiomeric purity of amino-alcohols in the present invention are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claims 26-27 are considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

Claims 28-29 are dependent on any one of claims 26-27 and therefore are considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

1.10. Claim 31

The subject matter of claim 31 relates to processes to prepare a **compound 1** or 1a.

D1-D3 disclose processes for preparing tetrazole compounds. However, the processes comprising epoxide-opening of compounds of formula I, VII or VIIa in the present invention are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claim 31 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

1.11. Claim 32

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The subject matter of claim 32 relates to processes to prepare a **compound 1** or **1a**.

D1-D3 disclose processes for preparing tetrazole compounds. However, the processes comprising the arylation of substituted pyridines 4b or 4c in the present invention are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claim 32 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

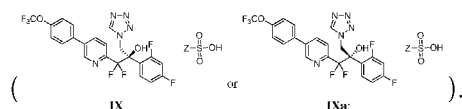
1.12. Claim 33

The subject matter of claim 33 relates to a compound that is 2-(5-bromopyridin-2-yl)2,2-difluoro-1-morpholinoethanone (2b).

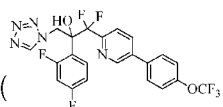
D1-D3 disclose tetrazole compounds and their intermediates. However, the claimed compound is not disclosed in D1-D3. Furthermore, it is not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claim 33 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

1.13. Claims 34-35

The subject matter of claim 34 relates to compounds of formula IX or IXa



D1, which is considered to represent the most relevant state of the art, discloses

enantiomers of a compound of formula () as a metalloenzyme inhibitor (see abstract, example 7 and claims 1-14).

D1 is silent about acid salts of the cited compound. However, D1 discloses a free base of the cited compound and its salt, and it is obvious **for a person** skilled in the art to configure the claimed salts by regular compound design process based on the cited document. In addition, the present invention does not demonstrate that the claimed compounds produce an unexpected effect compared with the cited compound.

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Therefore, claim 34 is novel over D1 under PCT Article 33(2), but considered to lack an inventive step under PCT Article 33(3).

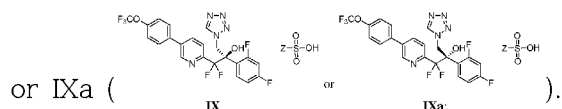
Claim 35 practically dependent on claim 34, discloses the compounds limited by acid.

The claimed compounds are not unique, as the claimed compounds belong to the compounds of claim 34, which are not inventive as described above.

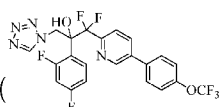
Therefore, claim 35 is novel over D1 under PCT Article 33(2), but considered to lack an inventive step under PCT Article 33(3).

1.14. Claims 36-39

The subject matter of claim 36 relates to processes to prepare **compounds** of formula IX



D1, which is considered to represent the most relevant state of the art, discloses

enantiomers of a compound of formula () as a metalloenzyme inhibitor and processes to prepare tetrazole compounds (see abstract, example 7 and claims 1-14).

D1 is silent about processes to prepare acid salts of the cited compound. However, D1 discloses processes to prepare a free base of the cited compound and its salt, and it is obvious for a person skilled in the art to configure the claimed processes by regular chemical synthesis based on the cited document. In addition, the present invention does not demonstrate that the claimed processes produce an unexpected effect compared with the cited processes.

Therefore, claim 36 is novel over D1 under PCT Article 33(2), but considered to lack an inventive step under PCT Article 33(3).

Claims 37-39 practically dependent on claim 36, disclose the processes limited by acid or

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solvent.

The claimed processes are not unique, as the claimed processes belong to the processes of claim 36, which are not inventive as described above.

Therefore, claims 37-39 are novel over D1 under PCT Article 33(2), but considered to lack an inventive step under PCT Article 33(3).

1.15. Claim 44

The subject matter of claim 44 relates to processes to prepare **compounds** 13 or 13a.

D1-D3 disclose processes for preparing tetrazole compounds. However, the processes enriching the enantiomeric purity of alcohols in the present invention are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claim 44 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

1.16. Claim 49

The subject matter of claim 49 relates to compounds of formula 18.

D1-D3 disclose tetrazole compounds and their intermediates. However, the claimed compounds are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claim 49 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

1.17. Claims 50-52

The subject matter of claim 50 relates to compounds of formula 11 or 11a.

D1-D3 disclose tetrazole compounds and their intermediates. However, the claimed compounds are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claim 50 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

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Claims 51-52 are dependent on claim 50 and therefore are considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

1.18. Claims 53-55

The subject matter of claim 53 relates to compounds of formula 12 or 12a.

D1-D3 disclose tetrazole compounds and their intermediates. However, the claimed compounds are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claim 53 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

Claims 54-55 are dependent on claim 53 and therefore are considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

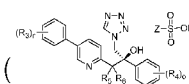
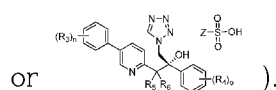
1.19. Claim 56

The subject matter of claim 56 relates to compounds of formula 14.

D1-D3 disclose tetrazole compounds and their intermediates. However, the claimed compounds are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claim 56 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

1.20. Claims 57-58

The subject matter of claim 57 relates to compounds of formula X or Xa (



D1, which is considered to represent the most relevant state of the art, discloses

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In case the space in any of the preceding boxes is not sufficient.

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enantiomers of tetrazole compounds as a metalloenzyme inhibitor (see abstract, example 7 and claims 1-14).

D1 is silent about acid salts of the cited compounds. However, D1 discloses free bases of the cited compounds and their salts, and it is obvious for a person skilled in the art to configure the claimed salts by regular compound design process based on the cited document. In addition, the present invention does not demonstrate that the claimed compounds produce an unexpected effect compared with the cited compounds.

Therefore, claim 57 is novel over D1 under PCT Article 33(2), but considered to lack an inventive step under PCT Article 33(3).

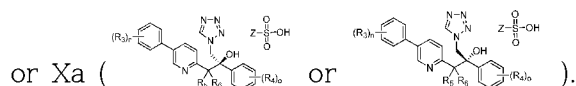
Claim 58 practically dependent on claim 57, discloses the compounds limited by acid.

The claimed compounds are not unique, as the claimed compounds belong to the compounds of claim 57, which are not inventive as described above.

Therefore, claim 58 is novel over D1 under PCT Article 33(2), but considered to lack an inventive step under PCT Article 33(3).

1.21. Claims 59-62

The subject matter of claim 59 relates to processes to prepare **compounds** of formula X



D1, which is considered to represent the most relevant state of the art, discloses enantiomers of tetrazole compounds as a metalloenzyme inhibitor and processes to prepare tetrazole compounds (see abstract, example 7 and claims 1-14).

D1 is silent about processes to prepare acid salts of the cited compounds. However, D1 discloses processes to prepare free bases of the cited compounds and their salts, and it is obvious for a person skilled in the art to configure the claimed processes by regular chemical synthesis based on the cited document. In addition, the present invention does not demonstrate that the claimed processes produce an unexpected effect compared with the cited processes.

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Therefore, claim 59 is novel over D1 under PCT Article 33(2), but considered to lack an inventive step under PCT Article 33(3).

Claims 60-62 practically dependent on claim 59, disclose the processes limited by acid or solvent.

The claimed processes are not unique, as the claimed processes belong to the processes of claim 59, which are not inventive as described above.

Therefore, claims 60-62 are novel over D1 under PCT Article 33(2), but considered to lack an inventive step under PCT Article 33(3).

1.22. Claims 63-64

The subject matter of claim 63 relates to processes to prepare **compounds 13** or 13a.

D1-D3 disclose processes for preparing tetrazole compounds. However, the processes comprising enriching the enantiomeric purity of alcohols in the present invention are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claim 63 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

Claim 64 is dependent on claim 63 and therefore is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

1.23. Claim 65

The subject matter of claim 65 relates to processes to prepare morpholine **amides 7**.

D1-D3 disclose processes for preparing tetrazole compounds. However, the processes comprising amidation of **ester 6** in the present invention are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claim 65 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

1.24. Claim 66

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The subject matter of claim 66 relates to processes to prepare **ketones 8**.

D1-D3 disclose processes for preparing tetrazole compounds. However, the processes comprising aryl substitution of morpholine **amides 7** in the present invention are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claim 66 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

1.25. Claim 67

The subject matter of claim 67 relates to processes to prepare compounds of formula XIII.

D1-D3 disclose processes for preparing tetrazole compounds. However, the processes comprising the epoxide opening of compounds of formula XII in the present invention are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claim 67 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

1.26. Claim 68

The subject matter of claim 68 relates to processes to prepare amino **alcohols 20** or 20a.

D1-D3 disclose processes for preparing tetrazole compounds. However, the processes comprising arylation of **pyridine 11** or 11a in the present invention are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claim 68 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

1.27. Claim 69

The subject matter of claim 69 relates to processes to prepare a **compound 1** or 1a.

D1-D3 disclose processes for preparing tetrazole compounds. However, the processes comprising converting morpholine **amide 7** in the present invention are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3

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taken alone or in combination. Therefore, claim 69 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

1.28. Claim 75

The subject matter of claim 75 relates to processes to prepare a **compound 1** or **1a**.

D1-D3 disclose processes for preparing tetrazole compounds. However, the processes comprising the arylation of substituted **pyridine 11** or **11a** to amino alcohol **12** or **12a** in the present invention are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claim 75 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

1.29. Claims 76-89

The subject matter of claim 76 relates to compounds of formula XXIV or XXIVa.

D1-D3 disclose tetrazole compounds and their intermediates. However, the claimed compounds are not disclosed in D1-D3. Furthermore, **they are** not obvious to a person skilled in the art over D1-D3 taken alone or in combination. Therefore, claim 76 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

Claims 77-89 are dependent on claim 50 and therefore are considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

2. Industrial Applicability

The subject matter of claims 1-44, 49-69, 75-89 appears to be industrially applicable under PCT Article 33(4).

** Note that the subject matter of claims 26-27, 44, 53, 56-57, 59, 63, 67-68, 72-75 is not clear for the following reasons:*

The substituent "R3" in claims 26-27, 44, 53, 56-57, 59, 63, 67-68, 72-75 is not described

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2015/021464

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in the alternative.

However, the search has been carried out and statement on novelty, inventive step, and industrial application has been established.