

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference see form PCT/ISA/220		FOR FURTHER ACTION See paragraph 2 below
International application No. PCT/EP2015/055823	International filing date (day/month/year) 19.03.2015	Priority date (day/month/year) 04.04.2014
International Patent Classification (IPC) or both national classification and IPC INV. A61K31/404 A61K31/4045 A61K31/405 A61K31/407 A61K31/4184 A61K31/4188 A61K31/423 A61K31/424 A61P31/00 A61P25/00 A61P35/00 A61P37/00 A61P43/00 A61K31/4355 A61K31/437		
Applicant IOMET PHARMA LTD		

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 usually 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:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Houyvet-Landriscina Telephone No. +49 89 2399-0
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Box No. I Basis of the 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:

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. 20, 23-27, 29-31, 34, 36-39(completely); 1-19, 21, 22, 28, 32, 33, 35(partially)

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. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ 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 the whole application or for said claims Nos. 20, 23-27, 29-31, 34, 36-39(completely); 1-19, 21, 22, 28, 32, 33, 35(partially)
- ☐ 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

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-19, 21, 22, 28, 32, 33, 35(all partially)

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)	Yes: Claims	<u>8, 15(all partially)</u>
	No: Claims	<u>1-7, 9-14, 16-19, 21, 22, 28, 32, 33, 35(all partially)</u>
Inventive step (IS)	Yes: Claims	<u>8, 15(all partially)</u>
	No: Claims	<u>1-7, 9-14, 16-19, 21, 22, 28, 32, 33, 35(all partially)</u>
Industrial applicability (IA)	Yes: Claims	<u>1-19, 21, 22, 28, 32, 33, 35(all partially)</u>
	No: Claims	

2. Citations and explanations

see separate sheet

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:

see separate sheet

Re Item IV

Lack of unity of invention

The subject-matter of the present application is not unitary in the sense of Rule 13 PCT for the following reasons :

The technical problem underlying the present application is the provision of compounds useful for the treatment of diseases selected from a cancer, an inflammatory condition, an infectious disease, a CNS disease or disorder, coronary heart disease, chronic renal failure, post anaesthesia cognitive dysfunction, a disease condition or disorder relating to female reproductive health and cataracts alternative to those already known in the art.

The proposed solution is to use a compound as defined in claim 1, and in particular an indole, benzimidazole, benzoxazole, 4-azaindole, 4-azabenzimidazole, 4-azabenzoxazole, 5-azaindole, 5-azabenzimidazole, 5-azabenzoxazole, 6-azaindole, 6-azabenzimidazole, 6-azabenzoxazole, 7-azaindole, 7-azabenzimidazole or 7-azabenzoxazole derivative as defined in claim 2.

In addition, for the specific treatment of cancer, the combinations as defined in claims 29-31 are proposed.

A further problem underlying the present application is the provision of particular indole, benzoxazole, 5-azaindole and 7-azaindole derivatives together with their method of synthesis. The solution to this problem being found in claims 36-39.

The only technical feature which all these solutions, i.e. claimed compounds, have in common is the chemical structure as defined in claim 1. Such technical feature can however not be regarded as "special technical feature" in the sense of Rule 13(1) and (2) PCT, because it is not novel. Indole-2-carboxamide derivatives for use in medicine, and in particular for use in the treatment of cancer, are indeed already known from D1-D4.

As to the mechanism of action underlying the present application, namely tryptophan-2,3-dioxygenase (TDO) and/or indoleamine-2,3-dioxygenase (IDO) inhibition, it can not serve as special technical feature distinguishing the presently claimed compounds from those already known in the art either. Such a mechanism, although not necessarily explicitly disclosed in each piece of prior art, is indeed necessarily present as a functional characteristic that is inherent to the product. In this regard, it merely represents an additional piece of information and does not automatically result, in a new, defined use or application for treatment of a pathological condition, and therefore does not actually represent a real technical contribution to the art which could be considered as a special technical feature within

the meaning of Rule 13(1) and (2) PCT. Accordingly the various claimed therapeutic uses as defined above can not form a single general inventive concept either.

Should the applicant nevertheless consider TDO and/or IDO inhibition as a distinguishing feature, an objection under Article 5 PCT is likely to arise since it would have to be concluded that the claimed formula covers compounds which are TDO/IDO inhibitors and others which are not, such as those known from the cited prior art. Consequently, it would be an undue burden for the skilled person to find the compounds covered by the claimed formula which indeed fulfill the claimed function, i.e. which are TDO/IDO inhibitors. In any case, it is furthermore to be noted that indole-2-carboxamide derivatives are already known as IDO inhibitors in D3-D4.

Concerning the various chemical structures as identified above, those do also not share any significant structural element, nor do they belong to the same recognized class of chemical compounds and no further technical feature is apparent that could be regarded as a special technical feature establishing a technical relationship among the above different solutions.

Finally, some of the compounds as defined in claim 36 are already known in the art (D1), such that the provision of these particular derivatives can not form an unifying concept linking them to their use in medicine on one hand and to their synthesis on the other hand.

Accordingly, the present application relates to a plurality of inventions, or groups of inventions, in the sense of Rule 13.1 PCT. Those have been divided as follows :

1. Claims 1-19, 21-22, 28, 32-33, 35 (all partially) : indole derivatives for use in the treatment of a cancer
2. Claims 1-20, 28, 32-33, 35 (all partially) : indole derivatives for use in the treatment of an inflammatory condition
3. Claims 1-19, 23, 28, 32-33, 35 (all partially) : indole derivatives for use in the treatment of an infectious disease
4. Claims 1-19, 24, 28, 32-33, 35 (all partially) : indole derivatives for use in the treatment of an CNS disease or disorder
5. Claims 1-19, 28, 32-33, 35 (all partially) : indole derivatives for use in the treatment of coronary heart disease
6. Claims 1-19, 28, 32-33, 35 (all partially) : indole derivatives for use in the treatment of chronic renal failure
7. Claims 1-19, 28, 32-33, 35 (all partially) : indole derivatives for use in the treatment of post anaesthesia cognitive dysfunction

8. Claims 1-19, 25, 28, 32-33, 35 (all partially) : indole derivatives for use in the treatment of an disease condition or disorder relating to female reproductive health
9. Claims 1-19, 28, 32-33, 35 (all partially) : indole derivatives for use in the treatment of cataracts
10. Claims 29-31, 34, 35 (all partially) : indole derivatives in combination with an anti-cancer agent for use in the treatment of cancer
11. Claims 26-27 (partially) : a pharmaceutical composition comprising an indole derivative
12. Claims 36, 38 (partially), 37 (completely): an indole compound
13. Claim 39 (partially) : a method of synthesis of an indole compound as defined in claims 36-38
14. Claims 1-4, 7-13, 15-16, 18-35 (all partially) : benzimidazole derivatives and their use in medicine
15. Claims 1-4, 7-13, 15-36, 38-39 (all partially) : benzoxazole derivatives and their use in medicine
15. Claims 1-4, 7-13, 15-16, 18-35 (all partially) : 4-azaindole derivatives and their use in medicine
17. Claims 1-4, 7-13, 15-16, 18-35 (all partially) : 4-azabenzimidazole derivatives and their use in medicine
18. Claims 1-4, 7-13, 15-16, 18-35 (all partially) : 4-azabenzoxazole derivatives and their use in medicine
19. Claims 1-4, 7-13, 15-36, 38-39 (all partially) : 5-azaindole derivatives and their use in medicine
20. Claims 1-4, 7-13, 15-16, 18-35 (all partially) : 5-azabenzimidazole derivatives and their use in medicine
21. Claims 1-4, 7-13, 15-16, 18-35 (all partially) : 5-azabenzoxazole derivatives and their use in medicine
22. Claims 1-4, 7-13, 15-36, 38-39 (all partially) : 6-azaindole derivatives and their use in medicine
23. Claims 1-4, 7-13, 15-16, 18-35 (all partially) : 6-azabenzimidazole derivatives and their use in medicine
24. Claims 1-4, 7-13, 15-16, 18-35 (all partially) : 6-azabenzoxazole derivatives and their use in medicine

25. Claims 1-4, 7-13, 15-36, 38-39 (all partially) : 7-azaindole derivatives and their use in medicine

26. Claims 1-4, 7-13, 15-16, 18-35 (all partially) : 7-azabenzimidazole derivatives and their use in medicine

27. Claims 1-4, 7-13, 15-16, 18-35 (all partially) : 7-azabenzoxazole derivatives and their use in medicine

The search has been restricted to the first invention and the present Written Opinion is accordingly restricted to said first invention, i.e. indole derivatives for use in the treatment of a cancer (claims 1-19, 21-22, 28, 32-33, 35 (all partially)).

Searching the additional subject-matters would have required MAJOR additional searching effort.

If the applicant pays additional fees for one (or more) not yet searched group(s) of invention(s), then the further search(es) may reveal further prior art that gives evidence of a further lack of unity 'a posteriori' within one (or more) of the not yet searched group(s). In such a case only the first invention in this (each of these) group(s) of inventions, which is considered to lack unity of invention, will be the subject of a search. No further invitation to pay further additional fees will be issued. This is because Article 17(3)(a) PCT stipulates that the ISA shall establish the International Search Report on those parts of the international application which relate to the invention first mentioned in the claims ('main invention') and for those parts which relate to inventions in respect of which the additional fees were paid. Neither the PCT nor the PCT guidelines provide a legal basis for further invitations to pay further additional search fees (W17/00, point 11 and W1/97, points 11-16). In such a case the non-searched claims may be the subject of one or more divisional applications after the application has entered the regional phase before the EPO (see W18/07, point 26).

Re Item V

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

Reference is made to the following documents:

D1 US 2011/136807 A1, cited in the application

- D2 TSOTINIS A ET AL: "C5,C6-disubstituted 1H-indole-2-carboxamides: Synthesis and cytotoxic activity in the human non-small lung cancer cell line NSCLC-N16-L16", LETTERS IN DRUG DESIGN AND DISCOVERY, vol. 3, no. 1, February 2006, pages 14-16
- D3 DOLUSIC EDUARD ET AL: "Discovery and preliminary SARs of keto-indoles as novel indoleamine 2,3-dioxygenase (IDO) inhibitors", EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 46, no. 7, July 2011 (2011-07), pages 3058-3065, cited in the application
- D4 KAMLENDRA S. BHADORIYA, SHAILESH V. JAIN, SANJAYKUMAR B. BARI, MANISH L. CHAVHAN, AND KULDEEP R. VISPUTE: "3D-QSAR Study of Indol-2-yl Ethanones Derivatives as Novel Indoleamine 2,3-Dioxygenase (IDO) Inhibitors", E-JOURNAL OF CHEMISTRY, vol. 9, no. 4, 2012, pages 1753-1759, Retrieved from the Internet: URL:<http://www.hindawi.com/journals/jchem/2012/368617/cta/>

Unless otherwise stated, reference is made to the relevant passages cited in the International Search Report for each of these documents.

Claims 32-35 relate to subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv)/67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment as correctly found in present claim 1 but not in claims 28 and 31. Can also be allowed dependent claims in the form : "composition ... for use according to claim §, wherein ...". Such formulation would apply to claims 2-25 and 29-30.

As for application and priority filings on or after the 28.01.2011, the EPO does also not recognize as patentable claims drafted according to the so-called Swiss-type format, if the claimed substance or composition is not novel per se.

V.2.1. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-7, 9-14, 16-19, 21-22, 28, 32-33 and 35 is not new in the sense of Article 33(2) PCT.

D1 and D2 both describe indole 2-carboxamide derivatives for use in the treatment of

cancer. In D1, the presently claimed compounds 29 and 51 as found in claim 17 are disclosed. Claims 1-7, 9-14, 16-19, 21-22, 28, 32-33 and 35 are not novel over D1 and claims 1-7, 9-14, 16, 18-19, 21-22, 28, 32-33 and 35 are not novel over D2.

D3 and D4 both describe another indole 2-carboxamide derivative, respectively compound 4 and 21, as IDO inhibitor for use in the treatment of cancer. Claims 1-7, 9, 13, 18-19, 21-22, 28, 32-33 and 35 are not novel over D3-D4.

Claims 8 and 15 appear partially novel over the cited prior art documents.

V.2.2. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-7, 9-14, 16-19, 21-22, 28, 32-33, 35 does not involve an inventive step in the sense of Article 33(3) PCT.

Claims 1-7, 9-14, 16-19, 21-22, 28, 32-33 and 35 not being novel, they can not be inventive either.

Concerning claim 8, only two indole compounds, namely compounds 52 and 57, with a X^{66} group ($X^{66} = CH_2$) and accordingly a R^{66} group as defined in claim 8, have been disclosed in the application. These compounds appear novel. For these two compounds only, it can be considered that the problem has been solved in view of the experimental data on file and is inventive (Article 33(3) PCT). For both these compounds however, $R^{66} = H$, whereas support and disclosure for the many other possible R^{66} groups as defined in claim 8 is not to be found in the whole specification (Article 5 PCT, see also item VIII, e) below). Accordingly, it is not credible that the problem has been solved over the whole scope of claim 8 (Article 33(3) PCT).

Concerning claim 15 : it appears that no indole bearing the different substituents as defined in said claim seem to be known in the art. Thus, based on the *in vitro* data presented in the application for the compounds falling within claim 15, it appears that the problem has been solved and claim 15 is therefore considered to involve an inventive step.

It is hereby reminded that the present written opinion is based on invention 1 as identified above. The problem to be solved is therefore the treatment of cancer with indole derivatives, and claims 8 (only for compounds 52 and 57) and 15 appear inventive only for this particular subject-matter.

Re Item VIII

Certain observations on the international application

- a) The scope of claims 11 and 16 appears broader than the scope of one of the claims on which they are dependent, respectively claims 10 and 15 (Article 6 PCT).
- b) Claim 8 can not be dependent on claims 6-7, and claim 19 is defined as independent claim (Article 6 PCT).
- c) The feature of claim 31 is not supported by the description as required by Article 6 PCT.
- d) Most of the cited references in the description are not complete (i.e. no journal, pages and/or volume given; Article 6 PCT).
- e) The present claims relate to an extremely large number of possible compounds, whereas support and disclosure in the sense of Article 6 and 5 PCT is to be found for only a very small proportion of the compounds claimed, namely those of claim 17. It is for example noted that, based on claim 3, no support is to be found for indole compounds bearing $X^{66} = 1,2$ when $R6 = (X^{66})_{0-2}-C(=O)N-$, no support is to be found for indole compounds bearing $X^{66} = 0$ when $R6 = (X^{66})_{0-1}-N-C(=O)-$, no support is to be found for indole compounds bearing $X^{66} = 0$ when $R6 = (X^{66})_{0-2}-SO_2N-$ and no support is to be found for indole compounds bearing $X^{66} = 1,2$ when $R6 = (X^{66})_{0-1}-NSO_2-$.