

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43*bis*.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/US2022/027304

International filing date (day/month/year)
02.05.2022

Priority date (day/month/year)
03.05.2021

International Patent Classification (IPC) or both national classification and IPC

INV. A61P35/00 C07D311/30 C07D405/04 C07D405/10 C07D405/12 C07D407/04 C07D413/10 C07D417/12
A61K31/352 A61K31/4155 A61K31/4433 A61K31/506 A61K31/4025 A61K31/427

Applicant

PETRA PHARMA CORPORATION

1. This opinion contains indications relating to the following items:

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

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will 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 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

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

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:



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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

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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. 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>1-74</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-74</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-74</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

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 V

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

1 Preliminary remarks

- 1.1 The subject-matter of claims 48-61 concerns a method of treatment and is therefore covered by the provisions 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 recognise 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.

Patentability, in particular novelty and inventive step, of claims 48-61 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

- 1.2 Claims 69-74 are Swiss-type claims which are now considered under EPC procedure as simply meaning "use of compounds for the preparation of a medicament". The applicant is therefore advised that they would be considered as redundant and superfluous in the European Phase.

2 Prior art

Reference is made to the following documents:

- D1 WO 2004/016607 A1 (KINACIA PTY LTD [AU]; JACKSON SHAUN P [AU] ET AL.) 26 February 2004 (2004-02-26)
- D2 WO 2017/156520 A1 (H LEE MOFFITT CANCER CT & RES [US]) 14 September 2017 (2017-09-14)
- D3 EP 0 341 104 A2 (LIPHA [FR]) 8 November 1989 (1989-11-08)
- D4 BARLAAM BERNARD ET AL: "Discovery of (R)-8-(1-(3,5-Difluorophenylamino)ethyl)- N , N -dimethyl-2-morpholino-4-oxo-4 H -chromene-6-carboxamide (AZD8186): A Potent and Selective Inhibitor of PI3Kβ and PI3Kδ for the Treatment of PTEN-Deficient Cancers", JOURNAL OF MEDICINAL CHEMISTRY, vol. 58, no. 2, 22 January 2015 (2015-01-22), pages 943-962,

XP055813284,

US

ISSN: 0022-2623, DOI: 10.1021/jm501629p

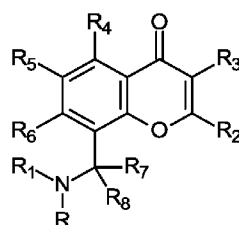
Retrieved from the Internet:

URL: <https://pubs.acs.org/doi/pdf/10.1021/jm501629p>

D5 US 2011/098271 A1 (BARLAAM BERNARD CHRISTOPHE [FR]
ET AL) 28 April 2011 (2011-04-28)

3 The present application concerns in claim 1:

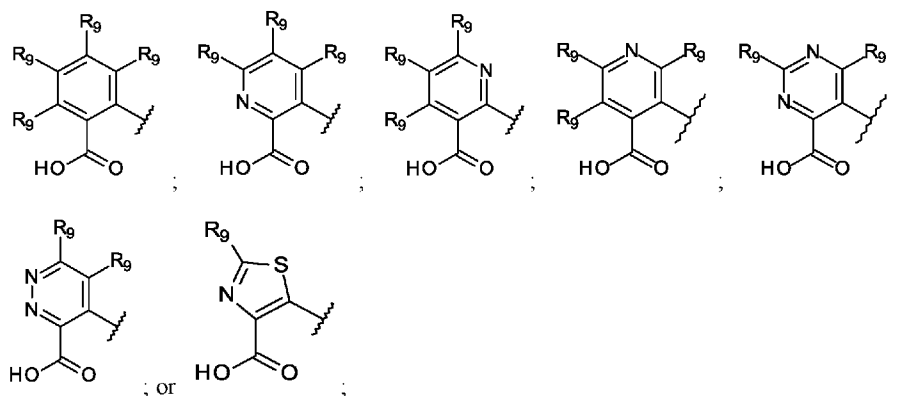
A compound of the Formula:



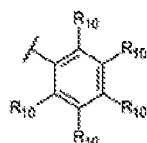
or pharmaceutically acceptable salt thereof, wherein:

R is -H or C_1 - C_3 alkyl;

*R*₁ is a group of the formula:



*R*₂ is a group of the formula:



*R*₃ is -H, halogen, -CN, -N(H)(C_1 - C_3 alkyl), -N(C_1 - C_3 alkyl)₂, -N(H)(CH₂CH₂CO₂H), -C(O) C_1 -

C₃ alkyl, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₃-Cs cycloalkyl, an optionally substituted heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or an optionally substituted heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S; wherein the optionally substituted heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

each of R₄, R₅ and R₆ is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₈ is -H or C₁-C₆ alkyl;

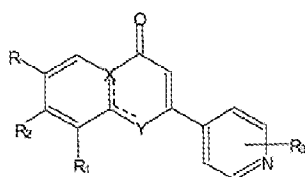
each R₉ is independently -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-Cs cycloalkyl;

each R₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -C(O)OC₁-C₃ alkyl, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, -OH, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-Cs cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, orthiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, C₁-C₃ alkoxy, or -CONR₁₁R₁₁; the optionally substituted C₃-Cs cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and

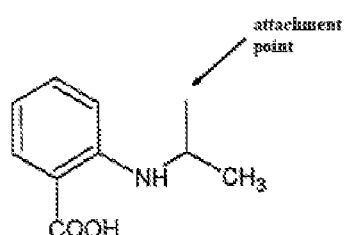
each R₁₁ is independently -H or C₁-C₃ alkyl.

4 Novelty (Art. 33(2) PCT)

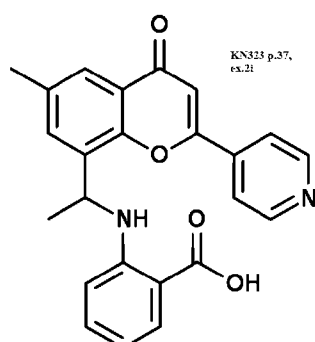
- 4.1 D1 is the closest prior art and discloses substituted chromenone derivatives of the general formula (III), that are claimed to be PI3K inhibitors and useful agents for the treatment of cancer, like the presently claimed compounds.



(III) see in claim 5 of D1, wherein X and Y can be C or O and R, R2, R3 and R1 are substitution groups which meanings overlap with the presently claimed substitution groups, in particular R1 can be a $\text{CHR}^{\text{R}3}\text{-NR}^{\text{R}3}\text{-aryl}$. R1, according to claim 8 of D1, can further be the group



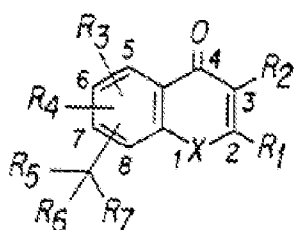
In particular the following single compound is disclosed in D1:



- 4.2 However, the subject-matter of claim 1 does not overlap with these known compounds on account of the substitution of a 4-yl-pyridine on the core chromenone whereas present claim 1 foresees an eventually substituted phenyl on the chromenone core.
- 4.3 No other document of the prior art discloses the presently claimed domain of compounds.
- 4.4 Therefore, the subject-matter of claim 1 is novel as well as dependent and medical application claims referring to it.

5 Inventive step Art. 33(3) PCT

- 5.1 The present compounds have been tested and show PI3K inhibition activity on a substantial part of the claimed scope (see examples). However, no comparative data has been provided concerning the 4-yl pyridine compounds disclosed in D1, therefore the problem to be solved by the present invention must be regarded as the provision of alternative PI3K inhibitors based on the chromenone core structure.
- 5.2 The solution proposed in claim 1 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons:
- 5.3 Numerous examples have been provided and show the required activity so that the technical problem appears to be credibly solved on the whole scope of the claims.
- 5.4 D1 encompasses PI3K inhibitors that are structurally very close to the present compounds (see above). However D1 clearly seems to focus on morpholine or 4-yl-pyridine substituted chromenone. D4 and D5 provide further morpholine-substituted chromenone derivatives.
- 5.5 D2 and D3 disclose phenyl-substituted chromenone that appear to show anti-cancer activity. In particular D3 discloses the following compounds of generic formula (I):



wherein R1 can be a phenyl eventually substituted and wherein the group C(R5)(R6)(R7) can form a COOH-substituted alkyl substituent. D3 however does not encompass a methylamino-cyclic group as presently described in claim 1. D2 encompasses only alkyl substitution at that position. Furthermore, neither D2 nor D3 discloses or suggest the inhibition of PI3K as a biological target.

A skilled person wishing to provide alternative PI3K inhibitors to the ones of D1 would have tried eventually pyridine or heterocycle analogs of the compounds of D1 but would have no reason to try a phenyl group as a replacement to pyridine or morpholine group.

Given the structural differences between claim 1 and D1, it cannot be said with any degree of accuracy that the skilled person, faced with the problem of providing further novel compounds useful as PI3K inhibitors, would have been

unambiguously led to prepare the compounds of the present application, which are phenyl-substituted and comprise the precise substitution group as defined in D1. Such structural changes would have been considered as highly unpredictable as far as the PI3K inhibition activity is concerned. Hence the present application involves an inventive step.

The corresponding dependent application claims that refer to compounds of claim 1 are also inventive by consequence.

Re Item VII

Certain defects in the international application

- 1 The closest prior art D1 as well as D2-D3 should be cited and briefly discussed.

Re Item VIII

Certain observations on the international application

- 1 Second medical use claims 48-50, 56, 63, 69 is not acceptable under Art.6 PCT. The therapeutic application is functionally defined by a mechanism of action which does not allow practical application in the form of a defined, real treatment of a pathological condition (disease) (G-II, 4.2). The objection could be overcome by either introducing in the claims a list of pathological conditions (diseases) cited in the application, or by showing that means are available which would allow the skilled person to recognise which additional condition(s) would fall within the functional definition (C-III, 6.5).

A claim directed to a method for *in vitro* inhibition of PI3K involving present compounds would be considered as acceptable.
- 2 In the last sentence of paragraph [37] on page 9, all cited prior art is considered as "incorporated herein by reference in their entireties", although it does not appear to be essential to the performance of the invention as required by Article 5 PCT. Thus, this phrase should be deleted unless any of the subject-matter is indeed considered to be essential; in which case it should be incorporated expressly in the description (see PCT Guidelines C-II, 4.17).