

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 136867-00120	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/US2023/019588	International filing date (<i>day/month/year</i>) 24.04.2023	Priority date (<i>day/month/year</i>) 25.04.2022	
International Patent Classification (IPC) or national classification and IPC INV. A61P35/00			
Applicant NESTED THERAPEUTICS, INC.			
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. ☒ a total of <u>12</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which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions).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 ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in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. ☐ a separate electronic file containing a sequence listing (<i>sent to the International Bureau only</i>)			
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 22.02.2024		Date of completion of this report 27.03.2024	
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 Marzi, Elena Telephone No. +49 89 2399-2199	



INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2023/019588

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

1-142 as originally filed

Claims, Numbers

1-8 filed with the demand for preliminary international examination

Drawings, Sheets

1-4 as originally filed

☐ 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. 9-27
 - ☐ 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/US2023/019588

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 11.03.2024 (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. 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>1-8</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-8</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-8</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item I

Basis of the report

The claims filed under Art. 34 PCT do not go beyond the disclosure as originally filed.

Re Item V

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

1. Reference is made to the following documents:

- D1 EP 1 982 982 A1 (CHUGAI PHARMACEUTICAL CO LTD [JP]; SAKAI TOSHIYUKI [JP]) 22 October 2008 (2008-10-22)
- D2 SUN JING ET AL: "Discovery of 3-benzyl-1,3-benzoxazine-2,4-dione analogues as allosteric mitogen-activated kinase kinase (MEK) inhibitors and anti-enterovirus 71 (EV71) agents",
BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER, AMSTERDAM, NL,
vol. 24, no. 16, 30 May 2016 (2016-05-30), pages 3472-3482,
XP029642285,
ISSN: 0968-0896, DOI: 10.1016/J.BMC.2016.05.055
- D3 WANG CHAO ET AL: "Hybrids of MEK inhibitor and NO donor as multitarget antitumor drugs",
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, ELSEVIER, AMSTERDAM, NL,
vol. 196, 9 April 2020 (2020-04-09), XP086153339,
ISSN: 0223-5234, DOI: 10.1016/J.EJMECH.2020.112271
[retrieved on 2020-04-09]
- D4 Aoki Toshihiro ET AL: "Optimizing the Physicochemical Properties of Raf/MEK Inhibitors by Nitrogen Scanning",
ACS MEDICINAL CHEMISTRY LETTERS,
vol. 5, no. 4, 24 January 2014 (2014-01-24), pages 309-314,
XP093007319,
US
ISSN: 1948-5875, DOI: 10.1021/ml400379x
- D5 CN 107 200 716 A (UNIV BEIJING) 26 September 2017 (2017-09-26)

- D6 GUO YALAN ET AL: "Novel Nitric Oxide Donors of Phenylsulfonylfuroxan and 3-Benzyl Coumarin Derivatives as Potent Antitumor Agents", ACS MEDICINAL CHEMISTRY LETTERS, vol. 9, no. 5, 20 April 2018 (2018-04-20), pages 502-506, XP093069414, US
ISSN: 1948-5875, DOI: 10.1021/acsmmedchemlett.8b00125
- D7 WO 2021/142144 A1 (IMMUNEERING CORP [US]) 15 July 2021 (2021-07-15)

2. Claim 8 relates to subject-matter considered by this Authority to be 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.

3. Novelty

The present compounds of formula (I) differ from the compounds disclosed in D5 on account of the present heterocyclic core.

There is overlap between present formula (I) and formula (I) of D1 and D7. However as D7 does not disclose any preferred subgroups or any specific compounds which have the same substitution pattern of the present compounds, the present formula (I) can be considered to be a novel selection from D1 and D7, the selection being characterized by the specific definition of R¹.

The present compounds of formula (I) are novel over the compounds disclosed in D4 on account of the definition of the present group R¹.

The present compounds are novel over the compounds disclosed in D2, D3 and D6 on account of the present group OR¹.

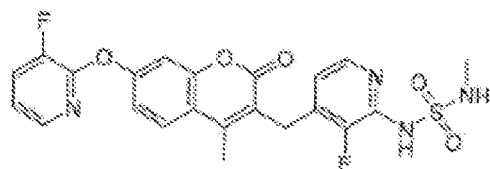
Novelty is acknowledged.

4. Inventive step

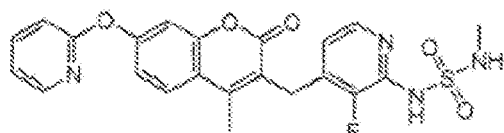
The present application relates to heterocyclic compounds and their use as MEK or ERK inhibitors for the treatment of cancer. The compounds of the application are associated with an increased CNS penetration and therefore can be used to treat metastasis in the brain (description, page 2, first paragraph).

D1 can be considered to represent the closest prior art as it discloses structurally similar compounds for the treatment of cancer.

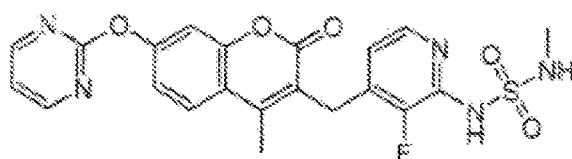
The application contains biological data (Table 2 on pages 122-123) wherein the blood penetration of a compound according to the claims (compound 35) has been compared to those of the compounds 1J-6-16-2 (reference compound 2) on page 169 and 1J-2-16-2 on page 149 (reference compound 1) of D1. Reference compounds 1 and 2 appear to be the structurally closest examples of the prior art as they differ from example 35 only in the distinguishing feature, i.e. the R¹ group.



Compound 35 (Claim 6)



Reference Compound 2



Reference Compound 1

Compound 35 has a $K_{p,uu}$ of 1.29, reference compound 2 has a $K_{p,uu}$ of 0.26 and reference compound 1 has a $K_{p,uu}$ of 0.18. The $K_{p,uu}$ value is a measure of the vrain penetration, the higher the value, the higher the brain penetration.

Hence the objective technical problem to be solved can be seen in the provision of compounds useful for the treatment of cancer with increased brain penetration.

The solution provided by the applicant consists of the compounds of present formula (I) which solves the problem as shown by the biological tests reported in the description.

All the compounds encompassed by the claims have the same group R¹ which appears to be responsible of the improved brain penetration.

It is considered that the present solution involves an inventive step as there was no hint in any of the documents cited that the present compounds could be associated with an increased brain penetration.

**IN THE EUROPEAN PATENT OFFICE
AS INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY
(IPEA/EP)**

International Application No.	: PCT/US2023/019588
International Filing Date	: 24 April 2023
Earliest Priority Date	: 25 April 2022
Applicant	: NESTED THERAPEUTICS, INC.
Title	: HETEROCYCLIC DERIVATIVES AS MITOGEN- ACTIVATED PROTEIN KINASE (MEK) INHIBITORS
IPC Number	: A61P 35/00 (2006.01)i; C07D 311/16 (2006.01)i; C07D 405/06 (2006.01)i; C07D 405/12 (2006.01)i; C07D 405/14 (2006.01)i; C07D 417/12 (2006.01)i; C07D 417/14 (2006.01)i; A61K 31/352 (2006.01)i

Attn: IPEA/EP
European Patent Office
P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
NETHERLANDS

RESPONSE TO THE WRITTEN OPINION AND ARTICLE 34 AMENDMENTS

Dear Sir:

The following remarks are in response to the Second Written Opinion (WO) mailed from the European Patent Office serving as the International Searching Authority (ISA), on 10 August 2023 in the above-identified international patent application. Also submitted herewith are amendments to the claims under PCT Article 34. Replacement Sheets for the claim amendments are enclosed herewith.

PCT Article 34 Amendments to the Claims begin at page 2.

Remarks begin on page 2.

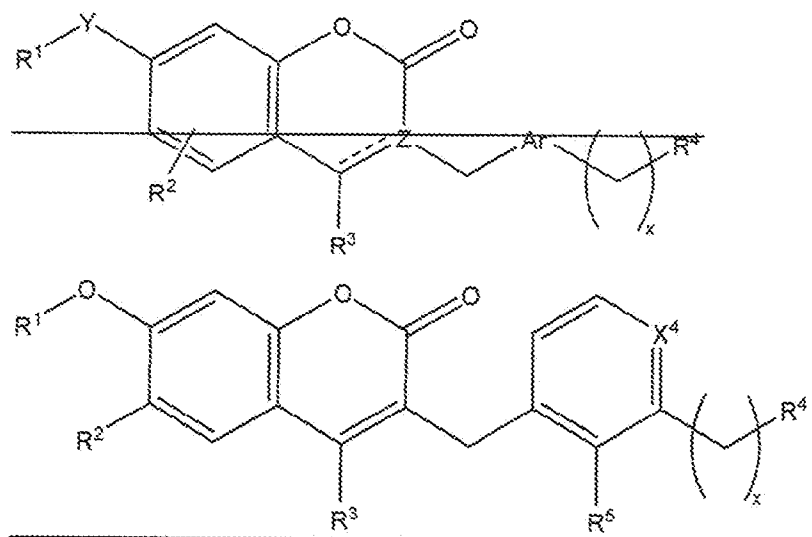
AMENDMENTS TO THE CLAIMS UNDER PCT ARTICLE 34

In accordance with PCT Article 34, Applicant encloses herewith an amended claim set in the form of replacement sheets containing the below described claim amendments without markings showing the changes. The following details the amendments to the claims:

CLAIMS

What is claimed is:

1. (Currently Amended) A compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein:

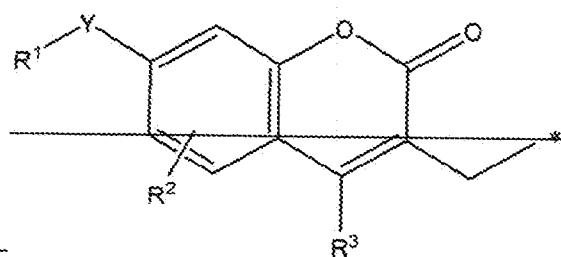
X⁴ is N or CH₃;

Z is C or N;

is a double bond or a single bond when Z is N or R³ is oxo;

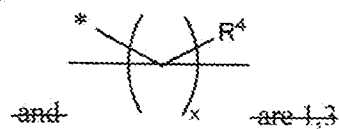
Y is a covalent bond or O;

Ar is phenyl, or 2-pyridinone, a five-membered heteroaryl or a six-membered heteroaryl, wherein the phenyl, the five-membered heteroaryl and the six-membered heteroaryl are each independently substituted with a group represented by R⁵ and

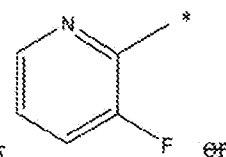


wherein

relative to each other on the group represented by Ar;



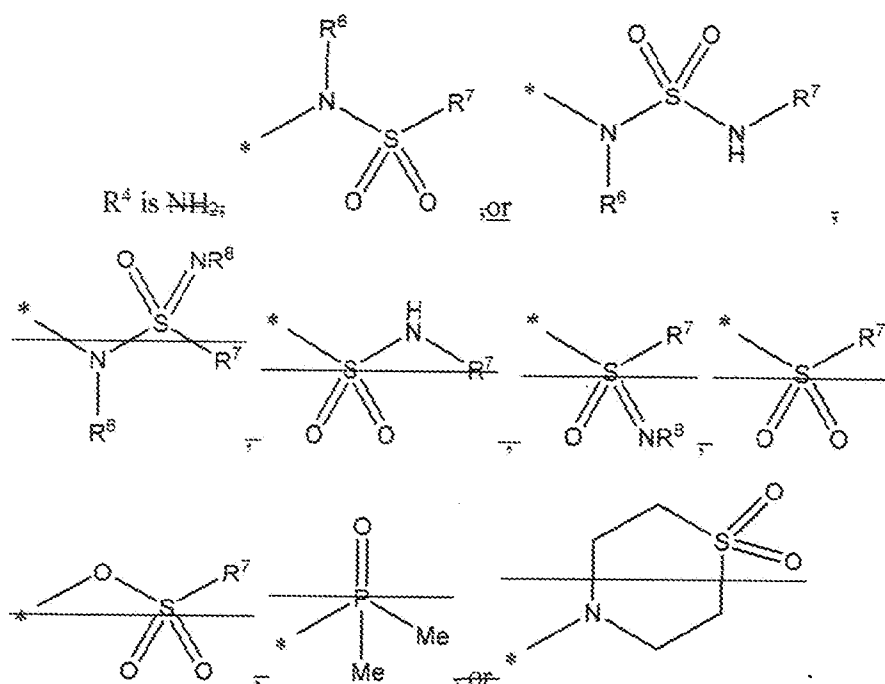
R¹ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl,



wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, and C₃₋₆ cycloalkyl optionally substituted with one or more groups selected from, halo, hydroxyl, and cycloalkyl;

R² is H or fluoro, halo, CH₂OR⁹, CH₂N(R⁹)₂, (CH₂)_nCN, (CH₂)_nC(O)R⁹, (CH₂)_nC(S)R⁹, (CH₂)_nC(O)N(R⁹)₂, (CH₂)_nNHC(O)R⁹, (CH₂)_nC(S)N(R⁹)₂, (CH₂)_nNHC(S)R⁹, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl;

R³ is methyl, H, halo, oxo (when — is a single bond), (CH₂)_nOR⁹, (CH₂)_nN(R⁹)₂, (CH₂)_nCN, (CH₂)_nC(O)R⁹, (CH₂)_nC(S)R⁹, (CH₂)_nC(O)N(R⁹)₂, (CH₂)_nNHC(O)R⁹, (CH₂)_nC(S)N(R⁹)₂, (CH₂)_nNHC(S)R⁹, C₁₋₆ alkyl, C₁₋₆ haloalkyl or C₃₋₆ cycloalkyl;



each R⁵ is independently H, halo, ~~methoxy or methyl~~C₁₋₆-alkoxy or C₁₋₆-alkyl;

R⁶ and R⁸ are independently selected from ~~is~~ H or methyl; or

R⁵ and R⁶ taken together are ~~C₁-C₄-alkylene~~;

R⁷ is H, methyl or ethylC₁₋₄-alkyl, C₂₋₆-alkenyl, C₃₋₈-cycloalkyl (optionally substituted with methyl), C₁₋₆-haloalkyl, or 4-6 membered heterocycle optionally substituted with methyl, wherein the C₁₋₆-alkyl group is optionally substituted with phenyl, cyano, hydroxy, C₁₋₆-alkoxy or N(R¹⁰)₂; or

R⁶ and R⁷ taken together are ~~C₂-C₄-alkylene or C(O)CH₂~~;

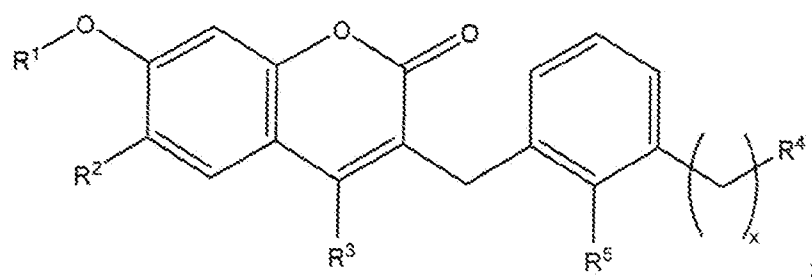
each R⁹ and each R¹⁰ are independently H or methyl;

n is 0 or 1; and

x is 0 or 1.

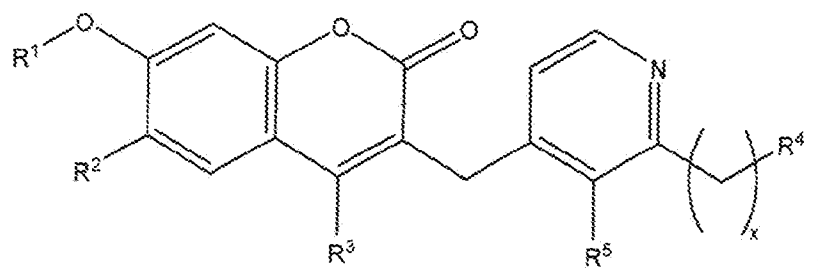
2-4. (Cancelled)

5. (Currently Amended) The compound of claim 1 or 2, represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

6. **(Currently Amended)** The compound of claim 1 ~~or 2~~, represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

- 7-16. **(Cancelled)**

17. **(Original)** The compound of any of claims 1, 5 or 6 ~~to 15~~ or a pharmaceutically acceptable salt thereof, wherein R⁵ is fluoro, methyl or methoxy.

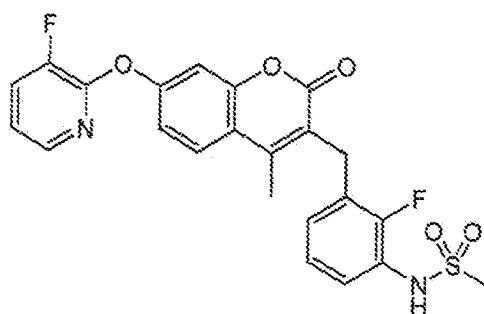
- 18-24. **(Cancelled)**

25. **(Currently Amended)** A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the compound of any one of claims 1, 5, 6, 17, 28 or 29 ~~[[24]]~~ or a pharmaceutically acceptable salt thereof.

26. **(Cancelled)**

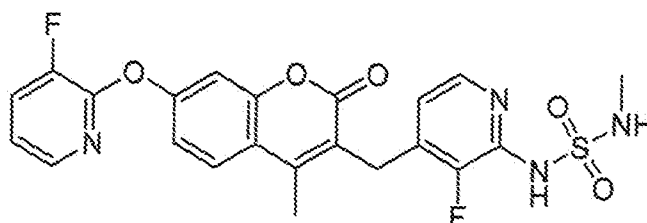
27. **(Currently Amended)** A method of treating a subject with cancer, comprising administering an effective amount of: i) the compound of any one of claims 1, 5, 6, 17, 28 or 29 ~~[[24]]~~ or a pharmaceutically acceptable salt thereof; or ii) the pharmaceutical composition of claim 25.

28. **(New)** The compound of claim 1, represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

29. (New) The compound of claim 1, represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

REMARKS

CLAIM STATUS

New claim 1 is a combination of original claim 1, claim 4 (the structure), claim 7 (definition of R¹), claim 23 (definition of R² and R³), claims 11 and 12 (definition of x and R⁴), claim 16 (definition of R⁵) and a selection of alternatives from claim 19 (definition of R⁷).

New claim 2 corresponds with original claim 5.

New claim 3 corresponds with original claim 6.

New claim 4 corresponds with original claim 17.

Support for new claim 5 is found in Example 3.

Support for new claim 6 is found in Example 35.

New claim 7 corresponds with original claim 25.

New claim 8 corresponds with original claim 27.

No new matter has been introduced by the foregoing amendments. Applicant respectfully requests that replacement sheets 143-145 enclosed herewith replace pages 143-151 of the originally filed application.

RESPONSE TO WRITTEN OPINION

Section 3 – Novelty

The International Preliminary Examination Authority (IPEA) asserts that claims “1, 3-5, 9, 12, 16-23 and 25-27 are not novel” (last line in Section 3), but acknowledges novelty for claims 2, 6-8, 10, 11, 13-15 and 24 (See Box V).

In response, the features of original claim 7 have been incorporated into new claim 1. The IPEA found original claim 1 to be novel. As such, new claims 1-8 are novel.

Section 4 – Inventive Step

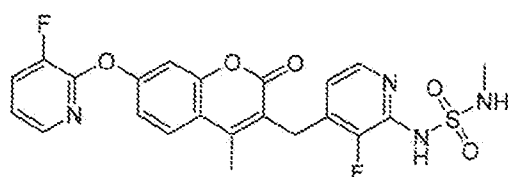
The IPEA states that the “compounds described in the present application are a selection of those by D7” (last paragraph on Sheet 3 of the Written Opinion). The IPEA states further that “other documents disclose structurally very close compounds which are encompassed by general formula (I) of D7 and have the desired anticancer activity or MEK activity (i.e., D1, D2, D4 and D5)” (last paragraph on Sheet 3 of the Written Opinion).

The IPEA acknowledges that the “application contains comparative data which show that the present compounds have been compared to reference examples 1-3”, however maintains that “these compounds are not the structurally closest compounds of the prior art” (sheet 4, second full paragraph of the Written Opinion). For reasons provides below, Applicant respectfully disagrees that these compounds are not the structurally closest prior art compounds.

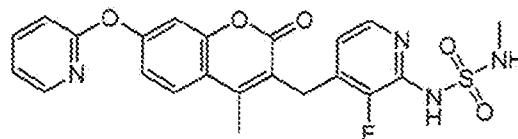
The IPEA is referred to Table 2 on page 122-23 of the present application. Table 2 shows the results of an experiment measuring the central nervous system penetration in laboratory rats by compounds of the invention and reference compounds 1-3. Central nervous system penetration is a feature not present in many anticancer agents, but is a feature that is essential for treating cancers of the brain and cancers that have metastasized to the brain. The IPEA is directed to the last column of Table 2, which is the $K_{p,uu}$ of each compound tested.

$K_{p, un}$ is unbound brain-to-plasma partition coefficient of each compound tested, and, accordingly, is a measure of central nervous system (CNS) penetration. A higher $K_{p, un}$ is indicative of greater CNS penetration.

Table 2 provides the $K_{p, un}$ for the Compound 35 of the present invention, which is the compound recited in claim 6, and Reference Compound 2. The structures of Compound 35 and Reference Compound 2 are shown below:



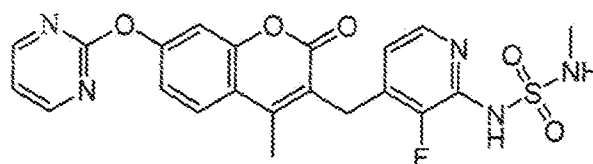
Compound 35 (Claim 6)



Reference Compound 2

Compound 35 differs from Reference Compound 2 solely by the presence of a single fluorine atom on the pyridyl group. As reported in the last column in Table 2, Compound 35 has a $K_{p, un}$ 1.29, whereas Reference Compound 2 has a $K_{p, un}$ of 0.26. Accordingly, Compound 35 has a $K_{p, un}$ that is five times greater than Reference Compound 2, i.e., Compound 35 has superior CNS penetration compared with Reference Compound 2.

Reference Compound 2 is disclosed as Compound Ij-6-16-2 in paragraph [0453] on page 169 of D1. It is respectfully submitted that this is the compound in the prior art that is closest structurally to Compound 35 (claim 6). Moreover, Reference Compound 1, whose structure is shown below, is an even poorer central nervous system penetrant than Reference Compound 2 ($K_{p, un}$ of 0.18 for Reference Compound 1 versus 0.26 for Reference Compound 2).



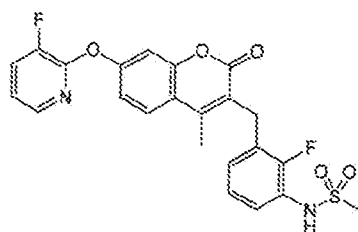
Reference Compound 1

VS-6766

Reference Compound 1 is also known as “VS-6766” and “avutometinib”, which is in clinical trials being developed as a cancer treatment (low grade serous ovarian cancer in combination

with dafactinib) by Chugai Pharmaceutical Co. (see <https://en.wikipedia.org/wiki/Avatometinib>). Reference Compound 1 is disclosed as compound Ij-2-16-2 in paragraph [0403] on pages 149-150 of D1. Accordingly, Compound 35 has superior CNS penetration relative to the compound in the prior that is closest structurally (Reference Compound 2) *and* to the compound which the skilled person would select as the one that is most promising to optimize (Reference Compound 1). None of the prior art cited in the Written Opinion teaches the structural modifications necessary to obtain a compound with superior CNS penetration. As such, Compound 35 is non-obvious over the prior art cited in the Written Opinion.

The superior CNS penetration shown by Compound 35 is shared by Compound 3, which is recited in Claim 5. The IPEA is again referred to Table 2 of the present application, which shows a $K_{p,uu}$ of 0.80 for Compound 3. The structure of Compound 3 is shown below:



Accordingly, Compound 3 also has superior CNS penetration over Reference Compounds 1 and 2 and therefore is also non-obvious over the prior art cited in the Written Opinion.

Compounds 3 and 35 both have a 3-fluoro-2-pyridyl group at the position corresponding to R^1 . This 3-fluoro-2-pyridyl accordingly seems to be a driver of the CNS penetrating properties of these compounds. Based on the structural differences between Compounds 3 and 35, the CNS penetrating properties also appear to be tolerant of minor structural modifications made at the position represented by R^7 and at the aromatic ring to which R^7 is attached. Accordingly, new claim 1 incorporates these structural differences and represents a reasonable extrapolation from Compounds 3 and 35. A favorable statement on inventive step is therefore requested.

CONCLUSION

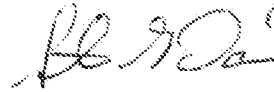
Applicant submits that, for the foregoing reasons, all pending claims including claims 1-8 fulfill the requirements of PCT Article 33(2) and 33(3), and respectfully requests the Examiner to reconsider and withdraw the novelty and inventive step objections.

PCT/US2023/019588

136867-00120

Dated: 22 February 2024

Respectfully submitted,

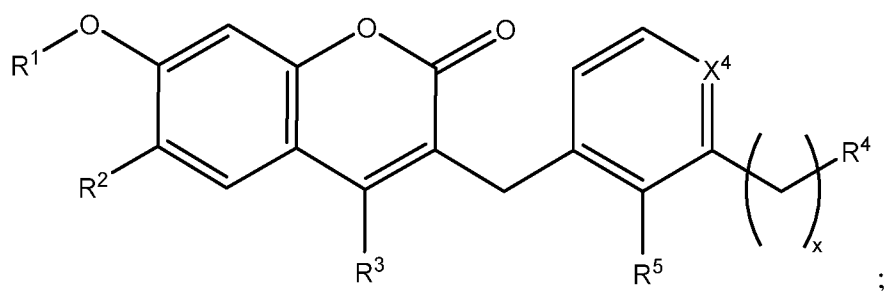
A handwritten signature in black ink, appearing to read 'S. G. Davis', is written over a horizontal line.

Steven G. Davis

Registration No.: 39,652
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Boston, Massachusetts 02110
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(617) 607-9200 (Fax)
Attorney/Agent For Applicant

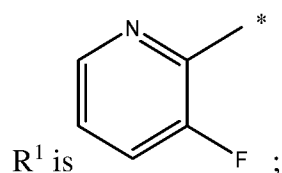
What is claimed is:

1. A compound represented by the following structural formula:



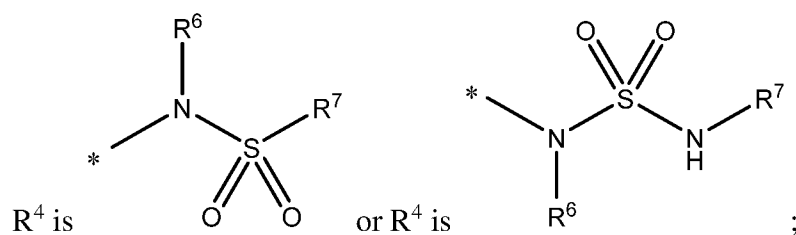
or a pharmaceutically acceptable salt thereof, wherein:

X^4 is N or CH;



R^2 is H or fluoro;

R^3 is methyl;



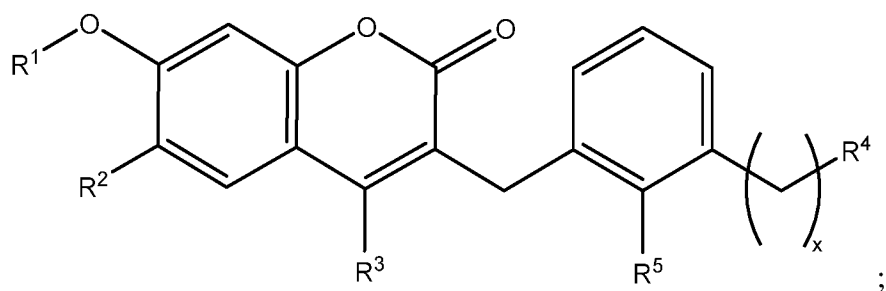
each R^5 is independently R^5 is H, halo, methoxy or methyl;

R^6 is H or methyl;

R^7 is H, methyl or ethyl; and

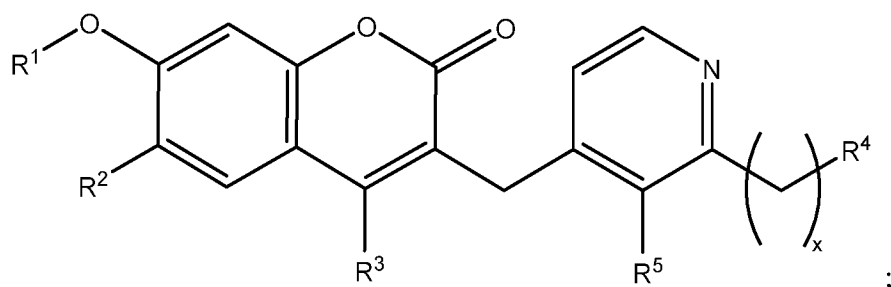
x is 0.

2. The compound of claim 1, represented by the following structural formula:



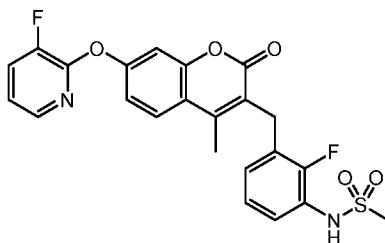
or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, represented by the following structural formula:



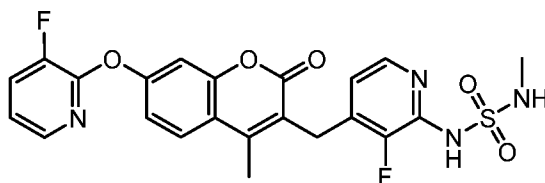
or a pharmaceutically acceptable salt thereof.

4. The compound of any of claims 1 to 3 or a pharmaceutically acceptable salt thereof, wherein R⁵ is fluoro, methyl or methoxy.
5. The compound of claim 1, represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1, represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the compound of any one of claims 1-6 or a pharmaceutically acceptable salt thereof.
8. A method of treating a subject with cancer, comprising administering an effective amount of: i) the compound of any one of claims 1-6 or a pharmaceutically acceptable salt thereof; or ii) the pharmaceutical composition of claim 7.