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(54) Title: INHIBITORS OF FIBROBLAST ACTIVATION PROTEIN

(57) Abstract: Compounds and compositions for modulating fibroblast activation protein (FAP) are described. The compounds and compositions may find use as therapeutic agents for the treatment of diseases, including hyperproliferative diseases.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 19/68189

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 10-15, 17-38
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
--see attached extra sheet--

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-4

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/US 19/68189

--BOX III - LACK OF UNITY--

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-9 and 16 directed to a compound of Formula (A) or a pharmaceutically acceptable salt thereof. The compound of Formula (A) will be searched to the extent that it encompasses the first species of claim 1, wherein R is hydrogen; RM is hydrogen; m is 1, n is 0, wherein m + n is 1, 2, 3 or 4; X is -C(=O)-; Y is the formula indicated wherein the wavyline represents the point of attachment to the rest of the molecule; s is 1; R11 and R12 are hydrogen; R13 is C1 alkyl. It is believed that claims 1-4 encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass the first species of claim 1. Applicant is invited to elect additional compounds of Formula (A), wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of claim 1, wherein R is C1 alkyl; RM is hydrogen; m is 1, n is 0, wherein m + n is 1, 2, 3 or 4; X is -C(=O)-; Y is the formula indicated wherein the wavyline represents the point of attachment to the rest of the molecule; s is 1; R11 and R12 are hydrogen; R13 is C1 alkyl (i.e. claims 1-4).

The groups of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique compound of Formula (A), which is not required by any other invention of Group I+.

Common technical features:

The inventions of Groups I+ share the technical feature of a compound having the structure of Formula (A).

These shared technical features, however, do not provide a contribution over the prior art, as being obvious over the article entitled "Extended Structure Activity Relationship and Pharmacokinetic Investigation of (4-Quinolinoyl)glycyl-2-cyanopyrrolidine Inhibitors of Fibroblast Activation Protein (FAP)" by Jansen et al. (hereinafter 'JANSEN').

Jansen teaches a compound of Formula (A) wherein R is hydrogen; RM is hydrogen; m is 1, n is 1, wherein m + n is 1, 2, 3 or 4; X is -C(=O)-; Y is the formula indicated wherein the wavyline represents the point of attachment to the rest of the molecule; R11 and R12 are hydrogen (abstract, formula 60), but Jansen does not teach wherein R13 is selected from the list of substructures indicated in the instant claim, thus Jansen does not teach wherein s is 1, 2, 3 or 4. However, it is known in the art that phosphonate moiety enhances permeability through biological membranes (as evidenced by separately attached supporting document entitled "Design, synthesis, in silico, and in vitro evaluation of novel pyrimidine phosphonates with cytotoxicity against breast cancer cells" by Yellapu et al.; see pg 2, col 1, para 2. The phosphonate moiety is highly potent, which readily penetrates biological membranes and enters the target organ. Phosphate esters are frequently used as a prodrug strategy, especially for water insoluble compounds, since the phosphate group enables following characteristic features to the xenobiotic-like decreases the adverse effects of the drugs, increases water solubility and thereby enables delivery of the drug parenterally). It would therefore have been obvious to a person having ordinary skill in the art to prepare the analog of the compound of Jansen wherein R13 is -P(O)(OR15)(OR16), R15 and R16 are hydrogen; and s is 1 by routine experimentation in order to develop and commercialize the invention of Jansen.

As said compound was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the inventions of Group I+.

The inventions of Group I+ thus lack unity under PCT Rule 13.

Note reg. item 4: Claims 10-15 and 17-38 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). These claims are therefore, not included in the above analysis.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 19/68189

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C07K 7/06; A61K 38/08; A61K 38/10 (2020.01)

CPC - A61K 38/08; A61K 38/10; A61K 38/1709; C07K 7/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/071454 A2 (GUILFORD PHARMACEUTICALS INC) 26 August 2004 (26.08.2004), entire document, especially: pg 29, ln 15-20, Scheme V, formula 20.	1-4
A	PubChem-CID-10376593, Create Date: 25 October 2006 (25.10.2006), pg 2, Fig.	1-4
A	JANSEN et al. "Extended Structure Activity Relationship and Pharmacokinetic Investigation of (4-Quinolinoyl)glycyl-2-cyanopyrrolidine Inhibitors of Fibroblast Activation Protein (FAP)", J. Med. Chem. 2014. Vol. 57, pp 3053-3074, entire document, especially: abstract, formula 60.	1-4
A	YELLAPU et al. "Design, synthesis, in silico, and in vitro evaluation of novel pyrimidine phosphonates with cytotoxicity against breast cancer cells", Medicinal Chemistry Research. 2013. Vol. 23(1), pp 317-328, entire document.	1-4
A	WO 2018/111989 A1 (PURDUE RESEARCH FOUNDATION) 21 June 2018 (21.06.2018), entire document.	1-4

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

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