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(54) Title: INHIBITING G PROTEIN COUPLED RECEPTOR 6 KINASE POLYPEPTIDES

(57) Abstract: This document relates to inhibitors of G protein coupled receptor 6 kinase (GRK6) polypeptides as well as methods and materials for using such inhibitors to treat hematological malignancies, inflammation diseases, and autoimmune disorders.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 2012/062206

A. CLASSIFICATION OF SUBJECT MATTER

(see extra sheet)

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)

C07D 249/12, 285/135, 401/10, 403/10, 413/10, A61K 31/4196, 31/433, 31/454, 31/496, 31/497, 31/506, 31/5377, A61P 29/00, 35/00, 37/00

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

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

Esp@cenet, RUPTO, USPTO, WIPO, EAPATIS, PatSearch, STN, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| X | MAZZONE, G. et al. "Synthesis of pharmaceutically significant 1-aryl-4H(R)-thiosemicarbazides, the corresponding 5-aryl-4H(R)-1,2,4-triazoline-3-thiones and some derivatives". Farmaco, Edizione Scientifica, 1981, vol. 36, no. 3, pp. 181-196 (abstract) [on-line] Retrieved from STN on the Web, DATABASE CA: 95:6695, compound of the formula II, compounds with RN 77803-55-5, 77803-57-7 | 1-10, 17-23 |
| X | PUGLISI, G. et al. "Antiinflammatory and analgesic activities of 3-(carboxymethylthio)-5-aryl-4-methyl- and -4-phenyl-4H-1,2,4-triazoles". Farmaco, Edizione Scientifica, 1982, vol. 37, no. 9, pp. 633-640 (abstract) [on-line] Retrieved from STN on the Web, DATABASE CA: 97:207757, compound of the formula I, compound with RN 58755-01-4D | 1-10, 17-23 |
| X | MAZZONE, G. et al. "Synthesis and biological evaluation of some 5-aryl-2-amino-1,3,4-oxa(thia)diazoles". Farmaco, Edizione Scientifica, 1982, vol. 37, no. 10, pp. 685-700 (abstract) [on-line] Retrieved from STN on the Web, DATABASE CA: 98:100754, compound of the formulae I, II, compounds with RN 35314-01-3, 83796-35-4 | 1-10, 17-23 |

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

| | |
|---|--|
| * Special categories of cited documents: | "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 |
| "A" document defining the general state of the art which is not considered to be of particular relevance | "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 |
| "E" earlier document but published on or after the international filing date | "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 |
| "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) | "&" document member of the same patent family |
| "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 | |

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 2012/062206

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| X | MATYSIAK, JOANNA, "QSAR of antiproliferative activity of N-substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles in various human cancer cells". QSAR & Combinatorial Science, 2008, vol. 27, no. 5, pp. 607-617 (abstract) [on-line] Retrieved from STN on the Web, DATABASE CA, compound with RN 117839-93-7, 312576-10-4 | 1-16 |
| X | WO 2005/092873 A2 (UNIWERSYTET MARI CURIE SKŁODOWSKIEJ et al.) 06.10.2005, abstract, p. 4-5, examples, claims 1-7 | 1-23 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 2012/062206

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.: 1-8, 13-23 (all partially)
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:

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty for the subject matter of independent claims 1, 13, 17, 23 and only few of them are cited in the search report. Furthermore, claims 1, 13, 17, 23 relate to an extreme large number of possible compounds. Support within the meaning of Articles 6 and disclosure in the meaning of Article 5 is to be found for a very small proportion of compounds. Therefore the search over the whole breadth of claims is impossible. The search was restricted to those compounds of the formula (4), which appear to be supported, namely, to compounds, wherein X, R¹, R² and R³ are as defined in claim 1, R³ and R⁴ are independently selected from the group consisting of H, (C₁-C₆)-alkyl or phenyl; m and n is an integer from 1 to 5.
Besides, in claims 1-12 the therapeutic application is functionally defined by a mechanism of action, which does not allow any practical application in the form of a defined therapeutic application and left a skilled person in a doubt as to real scope of protection (Article 6 PCT).
3. ☐ Claims Nos.:
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 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.: 1-23

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.

Continuation of Box. No. III

The present international application lacks unity *a priori* within the meaning of Rule 13 PCT. Claims of the invention comprise 38 groups of inventions, which are not so linked as to form a single general inventive concept. With respect to a group of inventions, unity exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features.

The first group of inventions comprises independent claims 1, 10, 13, 17 and 23. The unifying common special technical feature for this group of inventions is the use of a compound of the Formula (4) in the claimed methods of treatment.

The second group of inventions comprises independent claim 24. The special technical feature for this group of inventions is the use of a compound of the Formula (1).

The third group of inventions comprises independent claim 25. The special technical feature for this group of inventions is the use of a compound of the Formula (2).

The forth group of inventions comprises independent claim 26. The special technical feature for this group of inventions is the use of a compound of the Formula (3).

The fifth group of inventions comprises independent claim 27. The special technical feature for this group of inventions is the use of a compound of the Formula (5).

The sixth group of inventions comprises independent claim 28. The special technical feature for this group of inventions is the use of a compound of the Formula (6).

The seventh group of inventions comprises independent claim 29. The special technical feature for this group of inventions is the use of a compound of the Formula (7).

Independent claim 30 relates to a method providing the use of a compound selected from the group of 31 compounds defined in this claim. However, these compounds lack a common structural element, which is shared by all of the alternatives. Consequently, claim 30 comprises further 31 groups of inventions.

The compounds used in the methods of independent claims 1, 10, 13, 17, 23 and in the methods of independent claims 24-30 are not of similar nature and have no common chemical structure, which is essential to the common activity.

INTERNATIONAL SEARCH REPORT
Classification of subject matter

International application No.

PCT/US 2012/062206

CLASSIFICATION OF SUBJECT-MATTER

A61P 29/00 (2006.01)
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A61P 37/00 (2006.01)
C07D 249/12 (2006.01)
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