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(54) Title: COMPOUNDS AND METHODS FOR THE SELECTIVE INHIBITION OF ABCB1, ABCC1 AND ABCG2 TRANSPORTERS AND THE TREATMENT OF CANCERS, ESPECIALLY DRUG RESISTANT CANCERS AND HIGH THROUGH-PUT FLOW CYTOMETRY ASSAY TO DETECT SELECTIVE INHIBITORS

(57) Abstract: Compounds disclosed which inhibit ABCB1 transporter protein are useful for treating diseases in which ABCB1 transporter protein mediates the disease state, including numerous cancers, including hematopoietic cancers, including various leukemias, especially T-lineage acute lymphoblastic leukemia, as well as cancerous tumors, especially forms which exhibit multiple drug resistance. Pharmaceutical compositions which comprise an inhibitor of ABCB1 transporter protein and at least one additional anticancer agent, optionally in combination with a pharmaceutically acceptable carrier, additive or excipient are another aspect of the present invention. A flow cytometry based, high-throughput screening (HST) assay that quantifies ABCB1 efflux is also disclosed. Methods of identifying inhibitors of ABCB1, ABCG2 and ABCC1 transporter proteins are also disclosed.



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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/013209**A. CLASSIFICATION OF SUBJECT MATTER*****A61K 31/415(2006.01)i, A61K 31/12(2006.01)i, A61P 35/00(2006.01)i***

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)

IPC 8 A61K, A61P

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)

eKIPASS(KIPO internal), Delphion, PubMed, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- A	US 2006-0135445 A1 (YAMAZAKI, R. et al.) 22 June 2006 See compounds (1), (2), (4), claims 1, 2, paragraphs 4, 28, 31	26-31, 62-66 ----- 43-45, 52-54, 60, 61
X --- A	ROSS, D. D. et al. "Mining our ABCs: pharmacogenomic approach for evaluating transporter function in cancer drug resistance", Cancer Cell, 2004, Vol.6, No.2, 105-107 See abstract, page 105	26, 28-31 ----- 27, 43-45, 52-54, 60-66



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

"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 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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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2008/013209**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.: 1-25, 33-42
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 1-25, 33-42 pertain to methods for treatment of the human by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.
2. ☒ Claims Nos.: 10-14, 17, 22
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:
Claims 10-14, 17, 22 refer to claims which are not searchable due to not being drafted in accordance with the third sentence of Rule 6.4(a).
3. ☒ Claims Nos.: 5-9, 15, 16, 18-21, 32, 46-51, 55-59
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:

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 an additional fee, this Authority did not invite payment of any additional fee.
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.:

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/US2008/013209

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2006-0135445 A1	22.06.2006	CA 2515135 A	19.08.2004
		CN 1744887 A	08.03.2006
		EP 1591112 A1	02.11.2005
		EP 1591112 A4	14.06.2006
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