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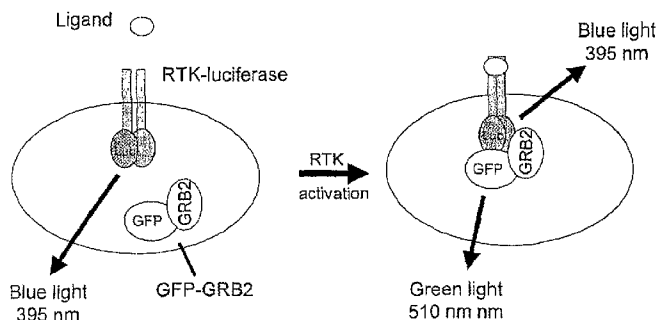
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: FUNCTIONAL BIOLUMINESCENCE ENERGY RESONANCE TRANSFER (BRET) ASSAY TO SCREEN, IDENTIFY AND CHARACTERIZE RECEPTOR TYROSINE KINASE LIGANDS

RTK BRET assay

BRET = bioluminescence resonance energy transfer



Ligand induced autophosphorylation of tyrosine residues on the intracellular domain of RTK's serve as docking sites for signaling molecules (e.g. GRB2)

(57) Abstract: Disclosed herein are methods of evaluating whether a test compound functions as a ligand for a receptor tyrosine kinase. Also provided are methods of making pharmaceutical compositions that include agonists, antagonists, or inverse agonists of receptor tyrosine kinases. Also provided are isolated cells that include a receptor tyrosine kinase and a second protein, wherein the receptor tyrosine kinase contains a fluorescent donor moiety and the second protein contains a fluorescent acceptor moiety.

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2006/007304

A. CLASSIFICATION OF SUBJECT MATTER
 INV. G01N33/542 G01N33/533 G01N33/50

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)

G01N

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 practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ISSAD T ET AL: "Looking for an insulin pill? Use the BRET methodology " DIABETES & METABOLISM. APR 2003, vol. 29, no. 2 Pt 1, April 2003 (2003-04), pages 111-117, XP002392109 ISSN: 1262-3636	1-4,7, 10-18, 31-38, 40-42, 45,47-56
Y	the whole document	5,6,8,9, 19-30, 39,43, 44,46, 62-65
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☒ 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 document 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

Date of the actual completion of the international search

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22/08/2006

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2006/007304

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BOUTE NICOLAS ET AL: "The use of resonance energy transfer in high-throughput screening: BRET versus FRET." TRENDS IN PHARMACOLOGICAL SCIENCES. AUG 2002, vol. 23, no. 8, August 2002 (2002-08), pages 351-354, XP004386171 ISSN: 0165-6147 the whole document	19-30,39
A	MINOR LISA K: "Assays to measure the activation of membrane tyrosine kinase receptors: focus on cellular methods." CURRENT OPINION IN DRUG DISCOVERY & DEVELOPMENT. SEP 2003, vol. 6, no. 5, September 2003 (2003-09), pages 760-765, XP008067040 ISSN: 1367-6733	1-56
Y	page 762, column 1, paragraph 2 page 764, column 1, paragraph 2 - page 765, column 1, paragraph 1 abstract; figure 3	62-65
Y	US 2004/214227 A1 (JOLY ERIK) 28 October 2004 (2004-10-28) paragraphs [0103], [0150], [0151]	5,6,8,9, 22,43, 44,46
Y	BUERGER CLAUDIA ET AL: "Sequence-specific peptide aptamers, interacting with the intracellular domain of the epidermal growth factor receptor, interfere with Stat3 activation and inhibit the growth of tumor cells." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 278, no. 39, 26 September 2003 (2003-09-26), pages 37610-37621, XP002392110 ISSN: 0021-9258 page 37610, column 1 - page 37611, column 1 abstract	62-65
A	ANONYMOUS: "EGF receptor"[Online] 12 March 2005 (2005-03-12), pages 1-4, XP002392111 Human Protein Reference Database Retrieved from the Internet: URL:http://www.hprd.org/protein/00579?selectedtab=INTERACTIONS> [retrieved on 2006-07-26] page 3	62-65

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/007304

Box 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.: 57-61
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:
see FURTHER INFORMATION sheet PCT/ISA/210
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 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.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 57-61

Present claims 61 relates to a pharmaceutical composition defined by reference to a desirable characteristic or property, namely making use of a compound being identifiable by any of the methods of claims 1-19. Present claims 57-60 relate to methods of making such a pharmaceutical composition or a pharmaceutical.

The description does not provide support and disclosure in the sense of Article 6 and 5 PCT for any such compounds having said properties or effects and there is no common general knowledge of this kind available to the person skilled in the art. This non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of the claim (PCT Guidelines 9.19 and 9.20). No search has been carried out for the subject-matter of claims 57-61.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/007304

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2004214227 A1	28-10-2004	AU 2137101 A WO 0146694 A2	03-07-2001 28-06-2001