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— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
17 November 2011

(54) Title: INHIBITORS OF RECEPTOR TYROSINE KINASES (RTK) AND METHODS OF USE THEREOF

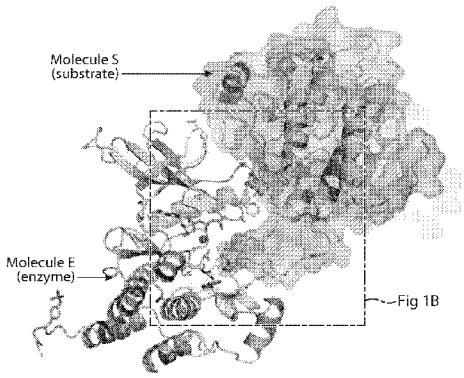

Fig. 1A

(57) Abstract: The present invention provides moieties that bind to the asymmetric contact interface of a receptor tyrosine kinase (RTK), wherein the moieties inhibit ligand induced trans autophosphorylation of the RTK. The present invention also provides methods of treating or preventing an RTK-associated disease and methods for identifying moieties that bind to an asymmetric contact interface of an RTK.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/21109

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/00; C07K 16/00 (2011.01)
USPC - 514/324; 514/388.15
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 38/00; C07K 16/00 (2011.01)
USPC - 514/324; 514/388.15

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)
PubWEST (PGPB, USPT, USOC, EPAB, JPAB); Google Scholar and PubMed: receptor tyrosine kinase, RTK, EGFR, FGFR, FGFR1, FGFR2, asymmet$, c-lobe, c-terminal lobe, inhibi$, small molecule, R577, arg577, 577, asp519, D519, D519$, scree$, small molecule inhibitor, achondroplasia, Crouzon, Saethre-Chotzen

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ADAMS, et al. Humanization of a Recombinant Monoclonal Antibody to Produce a Therapeutic HER Dimerization Inhibitor, Pertuzumab. Cancer Immunol Immunother 2005, 55:717-727; abstract; pg 718, col 2, para 1; pg 720, col. 1, para 2; pg 722, col 1, para 2; pg 724, col 2, para 4 to pg 725, col 1, para 1	1-10, 14-17, 20-23, 25-30, 45-46, 48-54, 58-59 and 61
Y	ZHANG, et al. An Allosteric Mechanism for Activation of the Kinase Domain of Epidermal Growth Factor Receptor. Cell 2006, 125:1137-1149; fig 4A, 4B, 5; abstract; pg 1138, col 2, para 2 to pg 1139, col 1, para 1; pg 1141, col 1, para 1 to col 2, para 2; pg 1142, col 2, para 2 to pg 1145, col 2, para 1; pg 1146, col 1, para 2-4, col 2, para 1	1-10, 14-17, 20-23, 25-30, 45-46, 48-54, 58-59 and 61
Y	CHEN, et al. A Crystallographic Snapshot of Tyrosine Trans-Phosphorylation in Action. PNAS. 2008, 105(50):19660-19665: fig 1D; abstract; pg 19661, col 1, para 1 to col 2, para 1; pg 19662, col 2, para 2 to pg 19663, col 1, para 1	9-10, 14-17, 23, 28, 30, 45-46, 53 and 59
Y	ZHANG, et al. Targeting Cancer with Small Molecule Kinase Inhibitors. Nature Reviews Cancer. January 2009, 9:28-39: abstract; pg 32, col 1, para 1	27-30, 58-59 and 61
Y	US 2009/0192133 A1 (HORTON et al.) 30 Jully 2009 (30.07.2009) para [0007], [0008], [0010]	53
A, P	BAE, et al. Asymmetric receptor contact is required for tyrosine autophosphorylation of fibroblast growth factor receptor in living cells. PNAS. 26 January 2010, 107(7):2866-2867	1-10, 14-17, 20-23, 25-30, 45-46, 48-54, 58-59 and 61

☐ Further documents are listed in the continuation of Box C. ☐

* 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 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	Date of mailing of the international search report
26 July 2011 (26.07.2011)	29 SEP 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/21109

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.:
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:
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.

Group I+: claims 1-54, 58-61, drawn to a moiety that binds to an asymmetric contact interface of a receptor tyrosine kinase (RTK), wherein the moiety inhibits ligand-induced trans autophosphorylation of the RTK. The first invention is restricted to FGFR1, a small molecule that binds to FGFR1's conformational epitope comprising R57. Should an additional fee(s) be paid, Applicant is invited to elect an additional FGFR(s), binding moiety, and/or specific epitope(s) to be searched. The exact claims searched will depend on Applicant's election.
[NOTE: Claims 11-13, 18-19, 24, 31-44, 47, 60 were excluded from the search, because they are drawn to a non-electe subject matter.]

Group II, claims 55-57, drawn to a method for identifying a moiety that binds to an asymmetric contact interface of a receptor tyrosine kinase (RTK) and inhibits ligand-induced trans autophosphorylation of the RTK.
**********Continued in Supplemental

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.:

claims 1-10, 14-17, 20-23, 25-30, 45-46, 48-54, 58-59 and 61

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 11/21109

********** Supplemental Box **********

Continuation of Box No. III - Observations where unity of invention is lacking:

The inventions listed as Groups I+ and II 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:

The inventions of Groups I+ do not include the inventive concept of a method for identifying a moiety that binds to an asymmetric contact interface of a receptor tyrosine kinase (RTK) and inhibits ligand-induced trans autophosphorylation of the RTK, as required by Group II.

The inventions of Group I+ share the technical feature of a moiety that binds to an asymmetric contact interface of a receptor 5 tyrosine kinase (RTK), wherein the moiety inhibits ligand-induced trans autophosphorylation of the RTK. However, this shared technical feature does not represent a contribution over prior art as being obvious over the article titled "Humanization of a Recombinant Monoclonal Antibody to Produce a Therapeutic HER Dimerization Inhibitor, Pertuzumab" by Adams, et al. (hereinafter "ADAMS") (Cancer Immunol Immunother. 2006, 55(6):717-27) in view of the article titled "An Allosteric Mechanism for Activation of the Kinase Domain of Epidermal Growth Factor Receptor" by Zhang, et al. (Cell 2006, 125(6):1137-49) (hereinafter "ZHANG") as follows:

ADAMS discloses a moiety that binds to dimerization domain of a receptor tyrosine kinase (RTK), wherein the moiety inhibits dimerization of said RTK (abstract-"2C4").
ADAMS does not disclose that said moiety binds to an asymmetrical contact surface of a RTK, wherein said mutation inhibits ligand-induced trans autophosphorylation of the RTK.
ZHANG discloses mutations of amino acids in an asymmetrical contact surface of a RTK, said mutations inhibit ligand-induced trans autophosphorylation of the RTK (fig 4A, 4B; abstract; pg 1141, col 1, para 1 to col 2, para 2; pg 1143, col 1, para 4 to pg 1145, col 2, para 1).
ZHANG further discloses that said asymmetrical contact surface is the surface for dimerization of said RTK and that said one or more mutations inhibits ligand-induced trans autophosphorylation by inhibiting ligand-induced dimerization (fig 4A, 4B; abstract; pg 1141, col 1, para 1 to col 2, para 2; pg 1143, col 1, para 4 to pg 1145, col 2, para 1). Therefore, it would have been obvious to one of ordinary skill in the art that a moiety designed to bind to the asymmetric contact interface of a RTK disclosed by ADAMS would inhibit said dimerization, thereby inhibiting ligand-induced trans autophosphorylation of said RTK. As said moiety agent was known at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Another special technical feature of the inventions listed as Group I+ is the specific RTK recited therein. As the claimed RTKs were known in the art at the time of the invention, no significant structural similarities can readily be ascertained among the RTKs, the inventions do not share a special technical feature. Without a shared special technical feature, the inventions lack unity with one another.

Another special technical feature of the inventions listed as Group I+ is the specific epitope recited therein. As amino acid sequences of the claimed RTKs were known in the art, no significant structural similarities can readily be ascertained among the epitopes, and therefore, the inventions do not share a special technical feature. Without a shared special technical feature, the inventions lack unity with one another.

Another special technical feature of the inventions listed as Group I+ is the specific moiety recited therein. As no significant structural similarities can readily be ascertained among moieties of different nature, i.e. small molecule, peptide, and an antibody, the inventions do not share a special technical feature. In addition, ADAMS discloses that the moiety is a peptidic molecule (abstract-"2C4") and an isolated antibody (abstract). Without a shared special technical feature, the inventions lack unity with one another.

Groups I+ and II therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.