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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *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))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) **Date of publication of the international search report**:
10 December 2015

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(54) **Title**: PEPTIDE INHIBITORS OF BCR-ABL OLIGOMERIZATION

(57) **Abstract**: In one aspect, the invention relates to peptides comprising the Bcr-Abl coiled-coil oligomerization domain and an alpha helix stabilizing moiety, mutant forms thereof, truncated forms thereof, derivatives thereof, and related peptides, which are useful as inhibitors of the Bcr-Abl chimeric protein; pharmaceutical compositions comprising the compounds; and methods of treating hyperproliferative disorders associated with Bcr-Abl using the compounds and compositions. This abstract is intended as a scanning tool for purposes of searching in the particular art and is not intended to be limiting of the present invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/22417

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/00, A61K 38/48 (2015.01)
CPC - A61K 38/00
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, A61K 38/48 (2015.01)
CPC- A61K 38/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 514/19.2, 514/21.1, 530/300 (keyword search, terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT, PGPB, EPAB, JPAB), Google Patents/Scholar
Search Terms Used: Bcr-Abl, oligomerization, coiled-coil, staple, hydrocarbon, alpha helix, alkenylglycine, alpha, alpha-disbustituted amino acid, peptidomimetic

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Guo et al. "Peptide containing the BCR oligomerization domain (AA1-160) reverses the transformed phenotype of p210bcr-abl positive 32D myeloid leukemia cells" Oncogene (1998) 17, 825-833; abstract, pg 826, col 2, para 3, pg 830, col 1, para 2	1, 127-130
Y	US 2014/0005118 A1 (Verdine et al.) 02 January 2014 (02.01.2014) abstract, para [0004], [0157], [0168], [0214], [0223], Figs. 3, 14	1, 127-130
Y	US 2003/0064061 A1 (Zhao et al.) 03 April 2003 (03.04.2003) para [0017], Fig. 1, SEQ ID NO: 3	1, 127-130
Y	Dixon et al. "IMPROVED COILED-COIL DESIGN ENHANCES INTERACTION WITH BCR-ABL AND INDUCES APOPTOSIS" Mol Pharm. 2012 January 1; 9(1): 187?195; abstract	1, 127-130

☐ 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
21 September 2015 (21.09.2015)	13 OCT 2015
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. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/22417

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.: 10-39, 44-114, 131-136
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. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

- Please see extra sheet for continuation -

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, 127-130, limited to SEQ ID NO: 1

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. Observations where unity of invention is lacking

Group I+: Claims 1-9, 127-130, directed to a peptide comprising a Bcr-Abl coiled-coil oligomerization domain comprises at least one alpha helix stabilizing moiety. The Bcr-Abl coiled-coil oligomerization domain will be searched to the extent that the oligomerization domain encompasses SEQ ID NO: 1. It is believed that claims 1, 127-130 encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass SEQ ID NO: 1. Additional oligomerization domain(s) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected oligomerization domain sequence(s). 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. An exemplary election would be SEQ ID NO: 2 (claim 1, 4, 127 -130)
[NOTE, SEQ ID NO: 7 comprises SEQ ID NO: 2; see instant Specification para [00169], For example, the mutated Bcr coiled-coil domain can have an Ala at position 38, an Arg at position 41, a Asp at position 45, an Arg at position 48, and a Glu at position 60 as shown for SEQ ID NO: 2.]
[NOTE, SEQ ID NOs: 4-8 are truncated version of SEQ ID NO: 1, see instant Specification, para [00170], a "truncated Bcr coiled-coil" refers to the peptide consisting essentially of the alpha helix domain of the wild-type Bcr coiled-coil, i.e. a peptide comprising 35-40 amino acids in the region from about position 23 to about position 65, inclusive, of SEQ ID NO: 1, SEQ ID NO:2, SEQ ID NO:3, or SEQ ID NO:7. Examples of suitable truncated Bcr coiled-coil peptides are given in SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO: 8.].

Group II: Claims 40-43, 115-126, directed to a nucleic acid capable of encoding a peptide and a recombinant cell comprising said peptide.

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:

Special Technical Features

Group I+ includes the special technical feature of a peptide comprising at least one alpha helix stabilizing moiety, not required by Group II.

Group II includes the special technical feature of a composition comprising nucleic acid and recombinant cells, not required by Group I+.

Another special technical feature of the inventions listed as Group I+ is the specific amino acid sequences recited therein. Each amino acid sequence is considered a distinct technical feature, because there is no significant structural similarities can readily be ascertained among these sequences. Furthermore, SEQ ID NO: 1 is disclosed by US 2003/0064061 A1 to Zhao et al. (hereinafter 'Zhao) (para [0017], The sequence of wild-type Bcr1-72 (SEQ ID NO: 3) is indicated in Fig. 1, wherein amino acid residues 1-70 of SEQ ID NO: 3 is 100% match to SEQ ID NO: 1 of instant claim 1).

Common Technical Features

The inventions of Groups I+ and II share the technical feature of a peptide comprising a Bcr-Abl coiled-coil oligomerization domain.

The inventions of Groups I+ share the technical feature of a peptide comprising a Bcr-Abl coiled-coil oligomerization domain comprises at least one alpha helix stabilizing moiety/hydorcarbon staple.

However, these shared technical feature do not represent a contribution over prior art in view of the article entitled "Peptide containing the BCR oligomerization domain (AA1-160) reverses the transformed phenotype of p210bcr-abl positive 32D myeloid leukemia cells" by Guo et al. (hereinafter 'Guo') and US 2012/0172311 A1 to Nash et al. (hereinafter 'Nash').

Guo teaches a peptide comprising a Bcr-Abl coiled-coil oligomerization domain (pg 826, col 2, para 3, we report that the over expression of a transcription unit, which encodes the bcr N-terminal oligomerization domain, leads to inhibition of the p210bcr-abl dependent growth factor and anchorage independent growth in a colony formation assay of p210bcr-abl transformed cells on methyl cellulose; pg 830, col 1, para 2, the plasmid transcription unit coding for the first 160 amino acids of the bcr (p210+BCR1-160), which contains the oligomerization domain, significantly suppresses the plating efficiency of the 32D cells (fourfold reduction of plating efficiency). Guo further suggest that these studies may be of eventual interest for those investigators whose goal is to design molecular therapeutic approaches to CML based on the use of peptidomimetic chemical functionalities, which mimic the structure and the inhibitory binding properties of the oligomerization domain containing fragment so as to inhibit the transforming function of the P210bcr-abl oncoprotein (abstract). Accordingly, it would have been obvious to one of ordinary skill in the art to have at least one alpha helix stabilizing moiety/hydorcarbon staple attached to the the Bcr-Abl oligomerization domain of Guo, because such an alpha helix stabilizing moiety/hydrocarbon staple is well known to one of ordinary skill in the art, as exemplified by Nash (abstract, para [0029], stapled peptide, para [0114]).

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Continuation from prior sheet

The inventions of Groups I+ further share the technical feature of a variant of Bcr-Abl coiled-coil oligomerization domain, wherein the Bcr -Abl inhibitory activity of the variant Bcr-Abl coiled-coil oligomerization domain is greater than that of it's parental domain.

However, this shared technical feature does not represent a contribution over prior art in view of the article entitled "IMPROVED COILED-COIL DESIGN ENHANCES INTERACTION WITH BCR-ABL AND INDUCES APOPTOSIS" by Dixon et al. (hereinafter 'Dixon'). Dixon teaches a variant of Bcr-Abl coiled-coil oligomerization domain, wherein the Bcr-Abl inhibitory activity of the variant Bcr-Abl coiled-coil oligomerization domain is greater than that of it's parental domain (abstract, We have
previously reported a modified version of this coiled-coil domain, CCmut2, which exhibits disruption of Bcr-Abl oligomeric complexes and results in decreased proliferation of CML cells and induction of apoptosis. major contributing factor to these enhanced capabilities is the destabilization of the CCmut2 homo-dimers, increasing the availability to interact with and inhibit Bcr-Abl. ... CCmut2 (C38A, S41R, L45D, E48R, Q60E)). As said technical feature was known in the art at the time of the invention, this cannot be considered special technical feature that would otherwise unify the groups.

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