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WO 02/016407 A3

(54) Title: SH2 DOMAIN BINDING INHIBITORS

(57) Abstract: Disclosed are compounds for SH2 domain binding inhibition. For example, disclosed is a compound of formula (I) wherein R1 is a lipophile; R2, in combination with the phenyl ring, is a phenylphosphate mimic group or a protected phenylphosphate mimic group; R3 is hydrogen, azido, amino, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, or alkylcarbonylamino, wherein the alkyl portion of R3 may be optionally substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, aminoalkyl, alkyl, alkoxy, and keto; R6 is a linker; AA is an amino acid; and n is 1 to 6; or a salt thereof. The compounds of the present invention have the advantage that their conformation is constrained to provide enhanced binding affinity with SH2 domain protein. Also disclosed are a pharmaceutical composition comprising a pharmaceutically or pharmacologically acceptable carrier and a compound of the present invention, a method for inhibiting an SH2 domain from binding with a phosphoprotein comprising contacting an SH2 domain with a compound of the present invention, a method of preventing or treating a disease, state, or condition by the use of one or more of these compounds, and a method for preparing the compounds of the present invention. The present invention further provides intermediates useful in the preparation of the compounds.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/26078

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K5/065 C07K5/087 C07F9/40 C07C211/30 A61K38/05
A61K38/06 G01N33/68 A61P35/00

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 7 C07K A61K 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)
CHEM ABS Data, MEDLINE, EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	GAO, Y. ET AL: "Macrocyclization in the design of a conformationally constrained Grb2 SH2 domain inhibitor" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS (2001), 11(14), 1889-1892, 23 July 2001 (2001-07-23), XP002211775 figure 1 ---	21-29
P,X	GAO, YANG ET AL: "Olefin Metathesis in the Design and Synthesis of a Globally Constrained Grb2 SH2 Domain Inhibitor" ORGANIC LETTERS (2001), 3(11), 1617-1620, 31 May 2001 (2001-05-31), XP002211776 schemes 1-4 figures 1-3 --- -/--	21-29

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in 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	Date of mailing of the international search report
28 August 2003	10 SEP 2003

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	FURET P ET AL: "Structure-based design and synthesis of high affinity tripeptide ligands of the Grb2-SH2 domain." JOURNAL OF MEDICINAL CHEMISTRY. UNITED STATES 27 AUG 1998, vol. 41, no. 18, 27 August 1998 (1998-08-27), pages 3442-3449, XP002211777 ISSN: 0022-2623 the whole document	21-30
X	GAO ET AL: "Inhibition of Grb2 SH2 Domain Binding by Non-Phosphate-Containing Ligands. 2. 4-(2-Malonyl)phenylalanine as a Potent Phosphotyrosyl Mimetic" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 43, no. 5, 2000, pages 911-920, XP002143953 ISSN: 0022-2623 tables 1,2	21-30
X	WO 97 08193 A (CARAVATTI GIORGIO ;CIBA GEIGY AG (CH); FRETZ HEINZ (CH); GARCIA EC) 6 March 1997 (1997-03-06) claims; examples	21-30
P,X	WO 00 56760 A (YAO ZHU JUN ;BURKE TERRENCE R JR (US); US COMMERCE (US); GAO YANG) 28 September 2000 (2000-09-28) claims; examples	21-30
X	WO 97 12903 A (PARA KIMBERLY SUZANNE ;SALTIEL ALAN ROBERT (US); SHAHRIPOUR AURASH) 10 April 1997 (1997-04-10) claims; examples	30

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/26078

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

As far as claims 32-33, 37-46 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] 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:

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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] 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.

[X] No protest accompanied the payment of additional search fees.

Continuation of Box I.2

Present claims 1-20 relate to an extremely large number of possible compounds/products. In fact, the claims contain so many options and variables, that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely claims 21-29.

Present claims 40-44 relate to a method defined by reference to a desirable characteristic or property, namely a method for 'inhibiting cell motility or angiogenesis' by adminstering compounds 'having ... inhibiting cell motiliy or cell angiogenesis activity'.
The claims cover all methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the method by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the methods in which compounds of claims 21-29 are imployed.

The applicant's attention is drawn to the fact that claims, or parts of 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-29, 45, 48-80 (completely), 40-44, 46-47, 31-39 (partially)

cyclic peptides having an phenylphosphate or phenylphosphate relating group and their uses and methodes for manufacturing them

2. Claims: 30 (completely), 40-44, 46-47, 31-39 (partially)

uncyclic peptides having an phenylphosphate or phenylphosphate relating group and their uses.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna | Application No
PCT/US 01/26078

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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