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- (81) **Designated States (unless otherwise indicated, for every kind of national protection available):** AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,

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**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:**  
13 December 2012



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(54) **Title:** ADIPONECTIN RECEPTOR AGONISTS AND METHODS OF USE

(57) **Abstract:** Short peptide mimetics of adiponectin suitable for development as pharmaceutical agonists in the treatment of cellular proliferative disorders such as cancer and atherosclerosis are provided.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/33099

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07K 4/00, 14/00; A61K 38/00 (2012.01)

USPC - 530/300; 514/19.3

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)

USPC: 530/300; 514/19.3

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC: 530/300; 514/19.3, 19.2 (text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Electronic data bases: PubWEST (USPT, EPAB, JPAB, PGPB); Google Scholar

Search terms: adiponectin (ADIPOQ, APM1, ACRP30), synthetic analog, mimetic peptide, agonist, cellular proliferative disease, epithelial cancer, atherosclerosis, pharmaceutical agent, therapeutic

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2010/0016216 A1 (COOPER et al.) 21 January 2010 (21.01.2010) abstract; Fig. 5; para [0005]; [0026]; [0175]; [0507]; [0564]; [0283]; [0289]; [0300]; [0310]; [0296];	1, 8, 10-15
Y	US 2006/0052292 A1 (RASMUSSEN et al.) 9 March 2006 (09.03.2006) abstract; para [0124]-[0126]	1, 8, 10-15
Y	US 2010/0189682 A1 (SCHELLENBERGER et al.) 29 July 2010 (29.07.2010) para [0005]; [0228]	1, 8, 10-15
Y	US 2008/0221305 A1 (CHEN et al.) 11 September 2008 (11.09.2008) para [0012]; [0850]	14, 15
X,P	OTVOS et al. Design and development of a peptide-based adiponectin receptor agonist for cancer treatment. BMC Biotechnol 5 October 2011 Vol 11 No 90 Pages 1-14. Especially abstract, pg 6 table 1.	1, 8, 10-15

 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

"&amp;" document member of the same patent family

Date of the actual completion of the international search

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01 OCT 2012

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/33099

Box No. 1 Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

a. (means)

on paper

in electronic form

b. (time)

in the international application as filed

together with the international application in electronic form

subsequently to this Authority for the purposes of search

2.  In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

GenCore ver 6.3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/33099

**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:  
Please see extra sheet

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, 8 and 10-15; limited as indicated.

- 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 III: Lack of Unity of Invention

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.

Groups I+: Claims 1-15, directed to a compound of Formula I:

X-M1-SEQ ID NO: 1-M2-Z (1); wherein:

SEQ ID NO: 1 is Xaa1-Ile-Pro-Xaa2-Leu-Tyr-Xaa3-Phe-Ala-Xaa4-Xaa5, wherein:

(a) Xaa1 is Asn or a non-natural amino acid;

(b) Xaa2 is Gly or a non-natural amino acid;

(c) Xaa3 is Tyr or a non-natural amino acid;

(d) Xaa4 is Tyr or a non-natural amino acid;

(e) Xaa5 is no amino acid, .beta.-Ala or .beta.-AlaNH.sub.2;

provided at least one of Xaa1, Xaa2, Xaa3, or Xaa4 is a non-natural amino acid;

X and Z are independently optionally present:

1-10 amino acid peptides

polymer molecules,

lipophilic compounds, or

peptide transduction domains;

M1 and M2 are independently optionally present single bonds or linking groups; and

wherein, when the compound of formula I comprises a C-terminal amino acid, said amino acid is optionally amidated; or a salt thereof;

limited to (based upon the listing of non-natural amino acids in the specification, as no limitation or listing of said amino acids was

specified in the claims): a 1-10 amino acid peptide; single bond: iodinated tyrosine-Ile-Pro-Gly-Leu-Tyr-Tyr-Phe-Ala-Tyr: single bond: 1-

10 amino acid peptide: NH.sub.2 (claims 1, 8 and 10-15) (applicants may opt for additional compounds to be searched by fully

specifying the sequence of said peptide, including the identity of the non-natural amino acids used, or the SEQ ID NO., and paying an

additional invention search fee for each elected compound).

The inventions listed as Groups I+ 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 special technical feature of the claims of Groups I+ claims is that they are directed to different specific amino acid-comprising compound sequences.

The common technical element shared by the above groups is that they are related to a compound of Formula I, as in claim 1. This common technical element does not represent an improvement over the combined prior art of US 2006/0128610 A1 to Cooper, US 2006/0052292 A1 to Rasmussen et al. (hereinafter "Rasmussen"), and US 2010/00189682 A1 to Schellenberger et al. (hereinafter "Schellenberger"). Although Cooper does not explicitly recite a compound (peptide or peptidomimetic or derivative thereof) according to formula I, Cooper teaches the digestion of denatured (two-dimensional gel electrophoresis...transferred to nitrocellulose; para [0219]) adiponectin using trypsin and isolation of the tryptic peptides (para [0220]-[0222]). Cooper further teaches wherein the sequence of adiponectin comprises the following sequence: Lys Phe His Cys Asn Ile Pro Gly Leu Tyr Tyr Phe Ala Tyr His Ile Thr Val Tyr Met Lys, which, as known to a person of skill in the art, upon digestion with trypsin, would have been cleaved to yield the following sequence: Phe His Cys Asn Ile Pro Gly Leu Tyr Tyr Phe Ala Tyr His Ile Thr Val Tyr Met Lys; wherein said peptide conforms to Formula I, wherein X is a 1-10 amino acid peptide, M1 comprises a bond (peptide), M2 also comprises a peptide bond, and Z is also a 1-10 amino acid peptide which is (optionally) not derivatized, with the exception that Cooper does not explicitly recite wherein the peptide comprises at least one non-natural amino acid in any of positions Xaa1, Xaa2, Xaa3, or Xaa4. However, in a related disclosure, Rasmussen teaches adiponectin conjugates comprising covalent attachment of a non-polypeptide moiety to adiponectin, or an analog thereof, wherein an amino acid residue has been introduced in a position that in the parent adiponectin is occupied by a surface exposed amino acid residue (abstract), including the potential substitution of residues in positions corresponding to Xaa1 and Xaa3 (N153, Y159; para [0124]-[0126]). Although Rasmussen does not explicitly recite wherein the residues are mutated to non-natural amino acids, it would have been obvious to a person skilled in the art that mutation to a non-natural amino acid would have enable the conjugation of a desired moiety, such as PEG, as taught by Schellenberger (para [0005]) and applied to adiponectin (para [0228]). It would have been obvious to a person skilled in the art to combine the teaching of Schellenberger with that of Rasmussen in order to utilize a single chemistry type to introduce non-peptide pendant moieties at desired locations in the adiponectin sequence, as taught by Rasmussen, and to screen the modified peptides using tryptic digestion, as taught by Cooper, in order to assess the effectiveness and efficiency of attachment of the desired moiety.

Therefore, the inventions of Groups I+ lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.