Title: METHODS OF TREATING OBESITY BY INHIBITING NICOTINAMIDE N-METHYL TRANSFERASE (NNMT)

Abstract: The present invention, in various embodiments, relates to methods of inhibiting NNMT production or activity in a cell, and methods of treating or preventing obesity or a related metabolic condition in a subject in need thereof, comprising administering a nicotinamide N-methyltransferase (NNMT) antagonist. The invention further provides methods of identifying NNMT antagonists useful for treating obesity and related metabolic disorders.
### A. CLASSIFICATION OF SUBJECT MATTER

**INV.** C12N15/113  A61K31/712  A61K31/7125

According to International Patent Classification (IPC) and both national classification and IPC

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbol)
- C12N
- A61K

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)
- EPO-Internal
- BIOSIS
- EMBASE
- Sequence Search
- EMBL
- WPI Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>the whole document</td>
<td>3, 62</td>
</tr>
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</table>

* Special categories of cited documents:
- **X** document defining the general state of the art which is not considered to be of particular relevance
- **Y** document referring to an oral disclosure, use, exhibition or other means

Further documents are listed in the continuation of Box C.

See patent family annex.

Date of the actual completion of the international search 6 September 2012

Date of mailing of the international search report 14/01/2013

Name and mailing address of the ISA/Authorized officer
- European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk
- Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016
- Bucka, Alexander
INTERNATIONAL SEARCH REPORT

<table>
<thead>
<tr>
<th>Box No. I</th>
<th>Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)</th>
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1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

   a. (means)
      - [ ] on paper
      - [x] in electronic form

   b. (time)
      - [x] in the international application as filed
      - [ ] together with the international application in electronic form
      - [ ] subsequently to this Authority for the purpose of search

2. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto 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:

Form PCT/ISA/21 0 (continuation of first sheet (1)) (July 2009)
### 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:

- See additional 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 an 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.:**
   - 6-11, 16-21, 31-36, 44-49, 54-59 (completely); 1-5, 13-15, 23-30, 38-43
   - 51-53, 61, 62 (partially)

**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.
<table>
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Form PCT/ISA/210 (continuation of second sheet) (April 2005)
### DOCUMENTS CONSIDERED TO BE RELEVANT

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<tr>
<td>CA 2720675 A1</td>
<td>22-10-2009</td>
<td>CN 102007213 A</td>
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</table>
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:


A method of inhibiting the expression or activity of a nicotinamide N-methyltransferase (NNMT) protein in a cell, comprising providing the cell with an effective amount of at least one NNMT antagonist, where n the NNMT antagonists inhibit production of NNMT protein, one or more activities of an NNMT protein, or a combination thereof, where n the NNMT antagonists is an anti sense oligonucleotide; methods to treat obesity using said antagonists; rel ated methods.

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A method of inhibiting the expression or activity of a nicotinamide N-methyltransferase (NNMT) protein in a cell, comprising providing the cell with an effective amount of at least one NNMT antagonist, where n the NNMT antagonists inhibit production of NNMT protein, one or more activities of an NNMT protein, or a combination thereof, where n the NNMT antagonists is an siRNA; methods to treat obesity using said antagonists; related methods.

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A method of inhibiting the expression or activity of a nicotinamide N-methyltransferase (NNMT) protein in a cell, comprising providing the cell with an effective amount of at least one NNMT antagonist, where n the NNMT antagonists inhibit production of NNMT protein, one or more activities of an NNMT protein, or a combination thereof, where n the NNMT antagonists is a microRNA; methods to treat obesity using said antagonists; related methods.

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A method of inhibiting the expression or activity of a nicotinamide N-methyltransferase (NNMT) protein in a cell, comprising providing the cell with an effective amount of at least one NNMT antagonist, where n the NNMT antagonists inhibit production of NNMT protein, one or more activities of an NNMT protein, or a combination thereof, where n the NNMT antagonists is an aptamer; methods to treat obesity using said antagonists; related methods.

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A method of inhibiting the expression or activity of a nicotine N-methyltransferase (NNMT) protein in a cell, comprising providing the cell with an effective amount of at least one NNMT antagonist, wherein the NNMT antagonist is an inhibitor of NNMT protein, or a combination thereof, wherein the NNMT antagonist is a ribozyme; methods to treat obesity using said antagonist; related methods.

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6. **Claims**: 12, 22, 37, 50, 60 (completely); 1-3, 13, 23-28, 38-41, 51, 61, 62 (partially)

A method of inhibiting the expression or activity of a nicotine N-methyltransferase (NNMT) protein in a cell, comprising providing the cell with an effective amount of at least one NNMT antagonist, wherein the NNMT antagonist is an inhibitor of NNMT protein, or a combination thereof, wherein the NNMT antagonist is an antibody; methods to treat obesity using said antagonist; related methods.

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