Abstract:

Title: NOVEL BIFUNCTIONAL METNASE/INTNASE INHIBITORS AND RELATED COMPOSITIONS AND METHODS OF TREATMENT OF CANCER

Abstract: This invention relates to novel cancer treatment compositions and associated therapeutic methods. More particularly, this invention relates in part to small chemical bifunctional inhibitors of DNA replication and repair proteins Metnase and/or Intnase (also termed Gypsy Integrase, Gypsy Integrase-1, Gypsy Retrasposon Integrase 1, or GIN-1) that simultaneously damage DNA, and to a therapeutic method that utilizes the inhibitors to increase the effectiveness of cancer treatment protocols, including radiation therapy. In preferred embodiments, compounds, compositions, methods and compositions of treatment of the invention are used to treat a patient suffering from leukemia (e.g. acute myeloid leukemia (AML) and related cancers. In certain aspects of such treatments, compounds, compositions and methods of treatment of the invention are administered as a monotherapy (in some cases, to patients who have exhibited resistance to Topo Ialpha inhibitors such as VP-16), or are co-administered with a Topo Ialpha inhibitor or other anti-cancer agents as otherwise described herein or in combination with radiation therapy.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

C07D 215/233(2006.01)i, C07D 401/04(2006.01)i, C07D 401/14(2006.01)i, A61K 31/47(2006.01)i, A61K 31/4709(2006.01)i, A61P 35/00(2006.01)i

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)

C07D 215/233; C07D 401/04; C04D 401/14; A61K 31/47; A61K 31/4709; A61P 35/00

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)

eKOMPASS (KIPO internal), NCBI (PubMed, MeSH)

**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>
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<tbody>
<tr>
<td>A</td>
<td>W00 03-084475 A2 (UNIVERSITY OF MARYLAND, BALTIMORE) 16 October 2003 See pp. 12-13 and 23-24; formula (IX); compound 24; abstract.</td>
<td>9,11-14,17-19,21,24-29,50,64-66</td>
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<td>X</td>
<td>US 5854227 A (JOHN F., HARTMANN et al.) 29 December 1998 See examples 8, 9, 11 and 12; abstract.</td>
<td>1-3,9,11-21,24-29</td>
</tr>
<tr>
<td>A</td>
<td>JUSTIN WRAY et al., 'Metnase meditates chromosome decatenation in acute leukemia cells', Blood, 2009, Vol. 114, No. 9, pp. 1852-1858, ISSN 0006-4971 See the whole document.</td>
<td>50,64-66</td>
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</tbody>
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* 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 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

10 OCTOBER 2011 (10.10.2011)

Date of mailing of the international search report

10 OCTOBER 2011 (10.10.2011)

Name and mailing address of the ISA/KR

Korean Intellectual Property Office
Government Complex-Daejeon, 189 Cheongsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea

Facsimile No. 82-42-472-7140

Authorized officer

SUNG Sun Young

Telephone No. 82-42-481-8405

Form PCT/ISA/210 (second sheet) (July 2009)
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.: 30-49**
   
   because they relate to subject matter not required to be searched by this Authority, namely:
   
   The claims pertain to methods for treatment of the human body by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(I) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. **Claims Nos.: 8, 22, 23, 45, 49, 57-59**
   
   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:
   
   Claims 8, 45, 49 and 57-59 are unsearchable, because they are worded in reference to multiple dependant claims.
   
   Claims 22 and 23 are unsearchable, because they rely on references to the figure instead of expressly stating a feature in the claims.

3. **Claims Nos.: 4-7, 10, 33-39, 43, 44, 46-48, 51-56, 60-63**
   
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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 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 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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<tr>
<th>Patent document cited in search report</th>
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<th>Patent family member(s)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>AU 2003-230705 B2</td>
<td>29.05.2008</td>
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<tr>
<td></td>
<td></td>
<td>AU 2003-230705 B9</td>
<td>17.07.2008</td>
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<td></td>
<td></td>
<td>CA 2480 194 A1</td>
<td>16.10.2003</td>
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<tr>
<td></td>
<td></td>
<td>EP 1539248 A2</td>
<td>15.06.2005</td>
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<td></td>
<td>JP 2006-508330 A</td>
<td>09.03.2006</td>
</tr>
<tr>
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<td></td>
<td>WO 03-084475 A3</td>
<td>16.10.2003</td>
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<td></td>
<td>DE 69633333 D1</td>
<td>14.10.2004</td>
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<td></td>
<td>EP 083 1845 A1</td>
<td>01.04.1998</td>
</tr>
<tr>
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<td></td>
<td>EP 083 1845 B1</td>
<td>08.09.2004</td>
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