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(88) Date of publication of the international search report:
22 January 2015

(54) Title: COMPOUNDS, COMPOSITIONS AND METHODS FOR THE TREATMENT OF DISEASES THROUGH INHIBITING TGF-β ACTIVITY

(57) Abstract: The present disclosure relates to compounds, compositions and methods for the treatment of diseases through inhibiting the activity of the transforming growth factor beta (TGF-β). More specifically, the disclosed compounds, compositions and methods are useful in the treatment of certain cancers (e.g., multiple myeloma, hematologic malignancies), diseases associated with excessive TGF-β activity including fibrosis, dermal scarring, immune dysfunction, and bone loss by inhibiting the conversion of latent TGF-β to active TGF-β. A method of preventing the activation of TGF-β in pathology is also provided, comprising administering an amount of the compounds sufficient to inhibit conversion of latent TGF-β to active TGF-β by thrombospondin 1 (TSP1), resulting in reduced TGF-β activity and reduced adverse effects such as fibrosis, bone loss, and immune dysfunction.

Figure 1: Compound No 1 (30 mg/kg) has anti-bone loss in the ECD/ED2 stage - hyper-Min model.
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/037 4 7 1

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/06 (2014.01)
CPC - A61K 38/06 (2014.10)

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, 38/06 (2014.01)
CPC - A61K 38/00, 38/06 (2014.10) (keyword delimited)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/2, 18, 19.3, 21.9; 530/331 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, STN, Google Patents, Google Scholar

Search terms used: tripeptide glycine alaninamide transforming growth factor

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>A</td>
<td>US 2012/0065144 A1 (INSA BORONAT et al) 15 March 2012 (15.03.2012) entire document</td>
<td>1, 7-9, 13, 15-24, 28</td>
</tr>
<tr>
<td>A</td>
<td>US 2004/01 10131 A1 (LAWLER) 10 June 2004 (10.06.2004) entire document</td>
<td>1, 7-9, 13, 15-24, 28</td>
</tr>
<tr>
<td>A</td>
<td>US 2012/0045462 A1 (LUGER) 23 February 2012 (23.02.2012) entire document</td>
<td>1, 7-9, 13, 15-24, 28</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

Date of the actual completion of the international search
06 November 2014

Date of mailing of the international search report
02 DEC 2014

Name and mailing address of the ISA/US
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Form PCT/ISA/210 (second sheet) (July 2009)
**INTERNATIONAL SEARCH REPORT**

**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:

Claims 1, 7-9, 13, 15-24, and 28 have been analyzed subject to the restriction that the claims read on the compound of Formula (I) as described in the Lack of Unity of Invention (See Extra Sheet). The claims are restricted to a compound of Formula (I); wherein designates a chiral center of R or S configuration when the carbon atom so marked carries at most one hydrogen substituent. Y1, R4, R5, and R6, are identical and are hydrogen; Y2 is hydrogen; R1 is hydrogen; R2 is C1-C6-alkyl which is substituted by 5- or 6-membered heterocycyl; R3 is optionally substituted C1-C6-alkyl; or a derivative thereof selected from the group consisting of pharmaceutically acceptable salts, prodrugs, deuterated forms, radio-actively labeled forms, stereo isomers, solvates and combination thereof.

<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, 7-9, 13, 15-24, 28

**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.

Form PCT/ISA.210 (continuation of first sheet (2)) (July 2009)
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 need to be paid.

Group I: Claims 1-29 are drawn to a compound having Formula (I); a derivative thereof, a pharmaceutical composition thereof, and a method of use thereof.

The first invention of Group I is restricted to a compound of Formula (I): wherein &* designates a chiral center of R or S configuration when the carbon atom so marked carries at most one hydrogen substituent, Y1, R4, R5, and R6, are identical and are hydrogen; Y2 is hydrogen; R1 is hydrogen; R2 is C1-C6-alkyl which is substituted by 5- or 6-membered heterocycl; R3 is optionally substituted C1-C6-alkyl; or a derivative thereof selected from the group consisting of pharmaceutically acceptable salts, prodrugs, deuterated forms, radio-actively labeled forms, stereo isomers, solvates and combination thereof. It is believed that claims 1, 7-9, 13, 15-24 and 2B read on this first named invention and these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be a compound of Formula (I): wherein &* designates a chiral center of R or S configuration when the carbon atom so marked carries at most one hydrogen substituent, Y1 is C1-C4-alkyl, R4, R5, and R6, are identical and are hydrogen; Y2 is hydrogen; R1 is hydrogen; R2 is C1-C6-alkyl which is substituted by 5- or 6-membered heterocycl; R3 is optionally substituted C1-C6-alkyl; or a derivative thereof selected from the group consisting of pharmaceutically acceptable salts, prodrugs, deuterated forms, radio-actively labeled forms, stereo isomers, solvates and combination thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on 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/examined.

The inventions listed in 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 Groups I formulae do not share a significant structural element, requiring the selection of alternatives for the compound variables Y1, R4, R5, R6, Y2, R1, R2, R3, and R7.

The Groups I share the technical features of a compound having a core structure of formula (I); a pharmaceutical composition thereof and a pharmaceutically acceptable carrier, a method of treating a patient suffering from a disease or dysfunction associated with abnormal and increased TGF-beta activity in a patient, an amount of at least one compound having the core structure of formula (I,a), and a method of reducing the activation of TGF-beta in a patient affected by abnormal and increased TGF-beta activity, which comprises administering to the patient at least one compound having the core structure of formula (I,a) in an amount sufficient to reduce or inhibit the activation of latent TGF-beta by thrombospondin. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2012/0065144 A1 to Insa Boronat et al. teach a compound having a core structure of formula (I); (Para. [0010]). Thus, one aspect of the invention refers to a TGF- beta 1 inhibitor peptide for use in the preventive or therapeutic treatment of skin tumors at early stages, in which the peptide is disintegrin or a derivative thereof. As evidenced by CID 9833938 to PubChem, disintegrin is a polypeptide containing the core structure of formula I, a pharmaceutical composition thereof and a pharmaceutically acceptable carrier (Para. [0011]). Another aspect of the invention refers to a pharmaceutical composition that comprises a therapeutically effective amount of the peptide defined above, together with at least one pharmaceutically acceptable carrier. . . . a method of treating a patient suffering from a disease or dysfunction associated with abnormal and increased TGF-beta activity in a patient, an amount of at least one compound having the core structure of formula (I,a) (Para. [0011]). Another aspect of the invention refers to a pharmaceutical composition that comprises a therapeutically effective amount of the peptide defined above, . . . for use in the preventive or therapeutic treatment of skin tumors at early stages; (Para. [0003]). Transforming growth factor beta 1 (TGF- beta 1) is a multi-functional cytokine that regulates a variety of cell processes, such as cell proliferation, differentiation, apoptosis, remodeling of tissue and angiogenesis; (Para. [0025]), and a method of reducing the activation of TGF-beta in a patient affected by abnormal and increased TGF-beta activity, which comprises administering to the patient at least one compound having the core structure of formula (I,a) (Para. [0017]). The term “disintegrin or disintegrin” includes mammalian fragments, analogues and homologues of the sequence SEQ ID NO: 1, provided that they maintain their capacity to inhibit the biological activity of TGF- beta 1; (Para. [0025]; Para. [0019]).

Further, US 2004/0101311 A1 to Lawler teaches a method of reducing the activation of TGF-beta in a patient affected by abnormal and increased TGF-beta activity, which comprises administering to the patient at least one compound having the core structure of formula (I,a) (Para. [0007], . . . polypeptides based on the amino acid sequence: . . . (Para. [0030]), in an amount sufficient to reduce or inhibit the activation of latent TGF-beta by thrombospondin (Para. [0030]).

The inventions listed in Groups I therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.