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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))

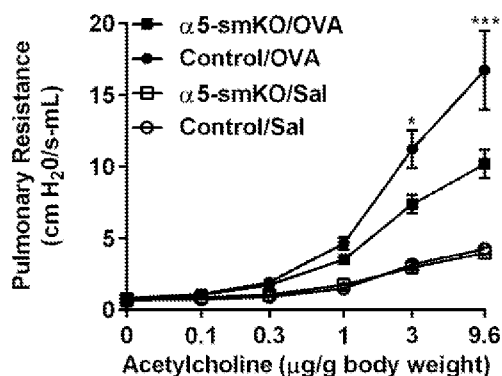
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09 November 2017 (09.11.2017)

(54) Title: INHIBITORS OF INTEGRIN ALPHA 5 BETA 1 AND METHODS OF USE

(57) Abstract: Disclosed herein, inter alia, are inhibitors of integrin alpha 5 beta 1 and methods of using the same.

FIG. 1B



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US17/25432

## A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 38/05; C07D 403/12, 413/12 (2017.01)

CPC - A61K 38/05; C07D 403/12, 413/12

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)

See Search History document

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

See Search History document

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

See Search History document

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                       | Relevant to claim No.                                                                                                                |
|-----------|----------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| Y         | WO 2015/048819 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 02 April 2015; paragraphs [0005]-[0007]  | 1, 3, 8-15, 20-22, 32-34, 37, 40, 59/1, 59/3, 59/8-15, 59/20-22, 59/32-34, 59/37, 59/40, 60-61, 65-72, 77-79, 89-91, 94, 97, 116-119 |
| Y         | US 2010/0179119 A1 (DEGRADO, WF et al.) 15 July 2010; paragraphs [0015]-[0019]                           | 1, 3, 8-15, 20-22, 32-34, 37, 40, 59/1, 59/3, 59/8-15, 59/20-22, 59/32-34, 59/37, 59/40, 60-61, 65-72, 77-79, 89-91, 94, 97, 116-119 |
| Y         | US 2007/0219252 A1 (CHEN, W et al.) 20 September 2007; paragraphs [0006], [0012], [0037]                 | 60-61, 65-72, 77-79, 89-91, 94, 97                                                                                                   |
| Y         | US 2012/0114667 A1 (EBERLEIN, CA et al.) 10 May 2012; abstract; paragraphs [0012]-[0013], [0060], [0100] | 116 119                                                                                                                              |

☐ Further documents are listed in the continuation of Box C.☐ See patent family 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 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

15 June 2017 (15.06.2017)

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US17/25432

## 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:

\*\*\*Continued Within the Next Supplemental Box\*\*\*

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, 3, 8-15, 20-22, 32-34, 37, 40, 59/1, 59/3, 59/8-15, 59/20-22, 59/32-34, 59/37, 59/40, 60-61, 65-72, 77-79, 89-91, 94, 97, 116-119

### 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.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US17/25432

\*\*\*Continued from Box No. III Observations where unity of invention is lacking \*\*\*

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 1-119 (in-part) and a compound of shown formula are directed toward a compound wherein R1 is halogen; L1 is a bond; Y is a bond; R2 is halogen; R3 is hydrogen; L2 is unsubstituted alkylene; L3 is a bond; L4 is alkylene; R5 is hydrogen; R6 is C(NH)NH<sub>2</sub>; z1 is 1; z2 is 1; and z3 is 0; and methods thereof.

The compound and methods will be searched to the extent they encompass a compound of the shown formula (exemplary compound structure). Applicant is invited to elect additional compound(s), with specified structural formula(ae) for each, to be searched. Additional compound(s) will be searched upon the payment of additional fees. It is believed that claims 1 (in-part), 3 (in-part), 8 (in-part), 9 (in-part), 10 (in-part), 11 (in-part), 12 (in-part), 13 (in-part), 14 (in-part), 15 (in-part), 20 (in-part), 21 (in-part), 22 (in-part), 32 (in-part), 33 (in-part), 34 (in-part), 37 (in-part), 40 (in-part), 59 (in-part), 60 (in-part), 61 (in-part), 65 (in-part), 66 (in-part), 67 (in-part), 68 (in-part), 69 (in-part), 70 (in-part), 71 (in-part), 72 (in-part), 77 (in-part), 78 (in-part), 79 (in-part), 89 (in-part), 90 (in-part), 91 (in-part), 94 (in-part), 97 (in-part), 116 (in-part), 117 (in-part), 118 (in-part), and 119 (in-part) encompass this exemplary named invention and thus these claims will be searched without fee to the extent that they encompass a compound of the shown formula (exemplary compound structure). Applicants must specify the claims that encompass any additionally elected compound(s). Applicants must further indicate, if applicable, the claims which encompass 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 exemplary claimed invention to be searched/examined.

Groups I+ share the technical features including a compound having the formula: as shown, wherein R1 is halogen; L1 is a bond; Y is a bond; R2 is halogen; R3 is hydrogen; R4 is hydrogen; L2 is unsubstituted alkylene; L3 is a bond; L4 is alkylene; R5 is hydrogen and R6 is C(NH)NH<sub>2</sub>; z1 is 1; z2 is 1; and z3 is 0.

However, these shared technical features are previously disclosed by WO 2015/048819 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) (hereinafter 'California') in view of US 2010/0179119 A1 to DeGrado, et al. (hereinafter 'DeGrado').

California discloses a compound having the formula: as shown (compound of formula I; paragraph [0007]), wherein R1 is halogen (formula I wherein R2 (R1) is halogen; paragraph [0005]); L1 is a bond (formula I wherein L1 is a bond; paragraph [0005]); Y is a bond (formula I wherein X (Y) is a bond; paragraph [0005]); R2 is halogen (formula I wherein R1 (R2) is halogen; paragraph [0005]); R3 is hydrogen (formula I (R3 is hydrogen); paragraph [0005]); R4 is hydrogen (formula I wherein Y is -NR4- wherein R4 is hydrogen; paragraph [0005]); L2 is unsubstituted alkylene (formula I wherein L2 is a C1-C10 alkylene; paragraph [0005]); L3 is a bond (formula I wherein L3 is C1-C10 alkylene (L3 is a bond); paragraph [0005]); L4 is alkylene (formula I wherein L3 is C1-C10 alkylene (L4 is alkylene); paragraph [0005]); R5 is hydrogen and R6 is C(NH)NH<sub>2</sub> (formula I wherein R3A (R5) is hydrogen and R3B (R6) is -C(NH)NH<sub>2</sub>; paragraph [0005]); z1 is 1 (formula I wherein z2 (z1) is 1; paragraph [0005]); z2 is 1 (formula I wherein z1 (z2) is 1; paragraph [0005]); and z3 is 0 (formula I wherein L3 is C1-C10 alkylene (z3 is 0); paragraph [0005]), but California does not disclose wherein the compound does not comprise a ring between the -NH- and alkylene moieties. However, DeGrado discloses wherein the compound does not comprise a ring between the -NH- and alkylene moieties (formula I wherein R0 is alkylene and R1 is NH(CO)R2 (not ring between NH and alkylene moieties); paragraphs [0015]-[0019]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the compound, as previously disclosed by California, in order to have provided wherein the compound does not comprise a ring between the -NH- and alkylene moieties, as previously disclosed by DeGrado, for providing pharmaceutical compounds capable of inhibiting alpha beta-1 integrins for use in the treatment of inflammatory diseases (DeGrado; paragraph [0039]).

Since none of the special technical features of the Groups I+ is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the California and DeGrado references, unity of invention is lacking.