

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization

International Bureau

(43) International Publication Date
07 September 2018 (07.09.2018)



(10) International Publication Number
WO 2018/160521 A3

(51) International Patent Classification:

C07D 401/12 (2006.01) C07D 471/04 (2006.01)

(21) International Application Number:

PCT/US2018/019838

(22) International Filing Date:

27 February 2018 (27.02.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/464,693 28 February 2017 (28.02.2017) US

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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, BN, BR, BW, BY, BZ,
CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO,
DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,
HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP,
KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,
OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,
SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,
UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,

EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

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))

(88) Date of publication of the international search report:

11 October 2018 (11.10.2018)

(54) Title: INHIBITORS OF (ALPHA-V)(BETA-6) INTEGRIN

(57) Abstract: Disclosed are small molecule inhibitors of $\alpha v \beta 6$ integrin, and methods of using them to treat a number of diseases and conditions.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US18/19838

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.: 7-34, 44-52
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 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.:
1, 3, 6/1, 6/3, 35, 39-41
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.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US18/19838

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C07D 401/12, 471/04 (2018.01)

CPC - C07D 401/12, 471/04

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	US 6,358,970 B1 (DUGGAN, ME et al.) 19 March 2002; column 9, lines 16-25, 51-53; column 10, lines 29-31; column 13, lines 4-8, 32-47	1, 3, 6/1, 6/3, 35, 39-41
Y	WO 93/10091 A2 (GLAXO GROUP LIMITED) 27 May 1993; page 1, lines 12-15, 22; page 2, line 2	1, 3, 6/1, 6/3
Y	US 2014/0038910 A1 (SAINT LOUIS UNIVERSITY) 06 February 2014; paragraphs [0011]-[0012]	1, 3, 6/1, 6/3, 35, 39-41
A	US 5,952,341 A (DUGGAN, ME et al.) 14 September 1999; entire document	1, 3, 6/1, 6/3

 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

"&" document member of the same patent family

Date of the actual completion of the international search

28 March 2018 (28.03.2018)

Date of mailing of the international search report

08 AUG 2018

Name and mailing address of the ISA/

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

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PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

-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 1-6 (in-part) and 35-43 (in-part); a compound of Formula (I), A-B-C, wherein A is the first recited moiety wherein each R1 is H; B is alkylene; C is the first recited moiety that is a 3-12 membered heterocycloalkylene unsubstituted; R2 is H; each Ra is H; and Rb is H (first exemplary compound structure).

The compound, compositions and methods will be searched to the extent the compound encompasses a compound of Formula (I), A-B-C, wherein A is the first recited moiety wherein each R1 is H; B is alkylene; C is the first recited moiety that is a 3-12 membered heterocycloalkylene unsubstituted; R2 is H; each Ra is H; and Rb is H (first exemplary compound structure). Applicant is invited to elect additional compound(s), with fully specified structure (e.g. no optional or variable atoms or substituents) 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), and 6 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass a compound of Formula (I), A-B-C, wherein A is the first recited moiety wherein each R1 is H; B is alkylene; C is the first recited moiety that is a 3-12 membered heterocycloalkylene unsubstituted; R2 is H; each Ra is H; and Rb is H (first exemplary compound structure). Applicants must specify the claims that encompass any additionally elected compound structure(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 first claimed invention to be searched/examined. An exemplary election would be a compound of Formula (I), A-B-C, wherein A is the second recited moiety wherein R is H; each R1 is H; B is alkylene; C is the first recited moiety that is a 3-12 membered heterocycloalkylene unsubstituted; R2 is H; each Ra is H; and Rb is H (first exemplary elected compound structure).

Groups I+ share the technical features including: a compound of Formula (I), A-B-C, wherein A is the first recited moiety wherein each R1 is H; B is alkylene; C is the first recited moiety that is a 3-12 membered heterocycloalkylene unsubstituted; R2 is H; each Ra is H; and Rb is H (first exemplary compound structure).

However, these shared technical features are previously disclosed by US 6,358,970 B1 to Duggan, et al. (hereinafter 'Duggan') in view of WO 93/10091 A2 (GLAXO GROUP LIMITED) (hereinafter 'Glaxo').

Duggan discloses a compound of Formula (I), A-B-C, wherein A is the first recited moiety wherein each R1 is H; B is alkylene; C is the first recited moiety that is a 3-12 membered heterocycloalkylene unsubstituted; and each Ra is H (compound of formula I wherein X is the third recited moiety in column 13 (A is first recited moiety) wherein R1 is H, Y is -(CH2)m- wherein m is 1 (B is alkylene), and a and a are both 2 (C is the first recited moiety that is a 6 membered heterocycloalkylene unsubstituted and each Ra is H); column 9, lines 16-25, 51-53; column 10, lines 29-31; column 13, lines 4-8, 32-47), but Duggan does not disclose wherein R2 is H; and Rb is H.

However, Glaxo discloses wherein R2 is H; and Rb is H (compound of formula I (Rb is H) wherein Z is N and R6 is hydrogen (R2 is H); page 1, lines 12-15, 22; page 2, line 2). 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 Duggan, in order to have provided wherein R2 is H; and Rb is H, as previously disclosed by Glaxo, for providing heterocyclic compounds useful as integrin receptor antagonists for the treatment of osteoporosis (Duggan; abstract; Glaxo; page 8, lines 3-6).

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