

(51) International Patent Classification:
A61K 31/12 (2006.01)(21) International Application Number:
PCT/US2013/042693(22) International Filing Date:
24 May 2013 (24.05.2013)

(25) Filing Language: English

(26) Publication Language: English

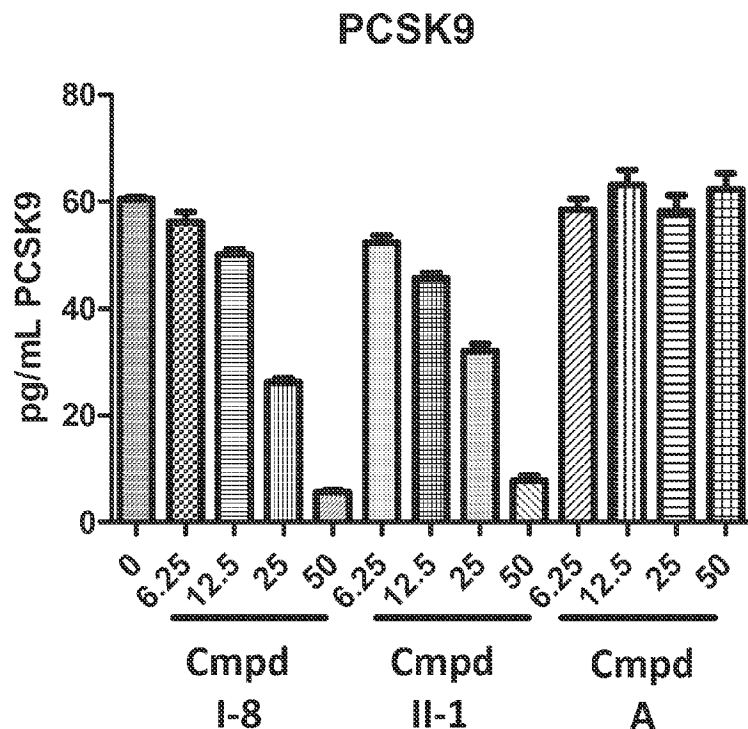
(30) Priority Data:
61/651,870 25 May 2012 (25.05.2012) US
61/697,104 5 September 2012 (05.09.2012) US
61/780,445 13 March 2013 (13.03.2013) US(71) Applicant: CATABASIS PHARMACEUTICALS, INC.
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trict of Columbia 20004 (US).(81) Designated States (unless 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, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,
KR, KZ, LA, LC, LK, LR, LS, LT, 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, 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, SZ, TZ,
UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,

[Continued on next page]

(54) Title: METHODS OF LOWERING PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 (PCSK9)

(57) Abstract: The invention relates to
new methods of modulating cholesterol by
inhibiting proprotein convertase
subtilisin/kexin type 9 (PCSK9) with fatty
acid derivatives; and new methods for
treating or preventing a metabolic disease
comprising the administration of an effective
amount of a fatty acid derivative. The
present invention is also directed to fatty
acid bioactive derivatives and their use in
the treatment of metabolic diseases.



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, ML, MR, NE, SN, TD, TG).

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))*

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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

13 March 2014

INTERNATIONAL SEARCH REPORT

~~57042693-16.01.2014~~

International application No.

PCT/US2013/042693

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/12 (2014.01)

USPC - 514/678

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 31/12, 31/121 (2014.01)

USPC - 514/678, 688

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

CPC - A61K 31/12, 31/121 (2013.01)

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

PatBase, Orbit, STN, PubChem, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2011/0009628 A1 (LIU et al) 13 January 2011 (13.01.2011) entire document	1-20
A	WO 2011/109681 A1 (MILNE et al) 09 September 2011 (09.09.2011) entire document	1-20
A	US 2011/0053990 A1 (MILNE et al) 03 March 2011 (03.03.2011) entire document	1-20
A	WO 2011/116312 A1 (VU et al) 22 September 2011 (22.09.2011) entire document	1-20

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


* 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

06 January 2014

Date of mailing of the international search report

16 JAN 2014

Name and mailing address of the ISA/US

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

Facsimile No. 571-273-3201

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PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2013/042693

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 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.:
1-20

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/US2013/042693

<Continuation of Box 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 need to be paid.

Group I+: Claims 1-98 are drawn to a method for treating a metabolic disease comprising inhibiting the production of or lowering serum levels of the proprotein convertase subtilisin/kexin type 9 (PCSK9) by administering to a patient in need thereof an effective amount of a fatty acid bioactive derivative.

The first invention of Group I+ is restricted to a compound of Formula II' or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, enantiomer or stereoisomer thereof wherein Rn is phenyl, W1 and W2 are each independently null; W3 is not present, R12 is not present, each m1 is not present, each a, b, c, and d is independently -H, each n, o, p, and q is independently 0, each L is independently null, R6 is not present, R5 is independently selected from the group consisting of -H; g and h are not present; m is 0; m2 is 0; k is not present, z is not present, R3, R4 and e are not present, each Z is -H with the proviso that there must be at least one first structure shown; r is 2, s is 3, t is 0, v is not present, R1 and R2 are not present and R is not present. It is believed that claims 1-20 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the first named invention.

Applicant is invited to elect additional formula(e) to be search in a specific combination by paying additional fee for each election. An exemplary election would be a compound of Formula II' or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, enantiomer or stereoisomer thereof wherein Rn is naphthyl, W1 and W2 are each independently null. W3 is not present, R12 is not present, each m1 is not present, each a, b, c, and d is independently -H, each n, o, p, and q is independently 0, each L is independently null, R6 is not present, R5 is independently selected from the group consisting of -H; g and h are not present; m is 0; m2 is 0; k is not present, z is not present, R3, R4 and e are not present, each Z is -H with the proviso that there must be at least one first structure shown; r is 2, s is 3, t is 0, v is not present, R1 and R2 are not present and R is not present. Additional formulae 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 responsible for a common property or function, requiring the selection of alternatives where Rn, W1, W2, W3, R12, a, b, c, d, n, o, p, q, L, R6, R5, g, h, m, m1, m2, k, z, R3, R4, e, Z, r, s, t, v, R1, R2 and R are each selected from a group of substitutions.

The Group I+ claims share the technical features of a method for treating a metabolic disease comprising inhibiting the production of or lowering serum levels of the proprotein convertase subtilisin/kexin type 9 (PCSK9) by administering to a patient in need thereof an effective amount of a fatty acid bioactive derivative; a fatty acid bioactive having a core structure of -C(=O)-W1-(Caa)n-(Cbb)o-(L)m-(Ccc)p-(Cdd)q-W2-Z, a pharmaceutical composition comprising a compound of the fatty acid bioactive and a pharmaceutically acceptable carrier.

However, these technical features do not represent a contribution over the prior art. Specifically, US 2011/0009628 A1 to Liu et al. discloses a method for treating a metabolic disease comprising inhibiting the production of or lowering serum levels of the proprotein convertase subtilisin/kexin type 9 (PCSK9) by administering to a patient in need thereof an effective amount of a fatty acid bioactive derivative (Abstract, ...inhibit PCSK9 expression...; Para. [0033]; Para. [0092], ...the compounds, disclosed herein reduce lipid levels... inhibiting the degradation of LDLR protein mediated through the proprotein convertase subtilisin/kexin type 9 (PCSK9)...; Para. [0002], ...compounds and compositions for modulating lipid levels, including treating...metabolic syndrome...; Para. [0003], ...Formula 1...; Para. [0243]. A compound of the present technology can also be modified, for example, by the covalent attachment of an organic moiety or conjugate...the conjugate can be a...fatty acid group...; Para. [0093], ...administering to a subject in need thereof a therapeutically effective amount of a compound or composition...; a pharmaceutical composition comprising a compound of the fatty acid bioactive and a pharmaceutically acceptable carrier (Para. [0023], ...lipid lowering agent of the present technology is part of a pharmaceutical composition containing one or more excipients, carriers or fillers...).

Further, US 2011/0053990 A1 to Milne et al. discloses a method for treating a metabolic disease by administering to a patient in need thereof an effective amount of a fatty acid bioactive derivative (Paras. [0006];[0007];[0036];[0037]); a fatty acid bioactive having a core structure of -C(=O)-W1-(Caa)n-(Cbb)o-(L)m-(Ccc)p-(Cdd)q-W2-Z (Para. [0008], Formula I; Para. [0269], Example 3); a pharmaceutical composition comprising a compound of the fatty acid bioactive and a pharmaceutically acceptable carrier (Paras. [0006];[0007];[0036];[0037]).

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

<End Box III: Observations where unity of invention is lacking>