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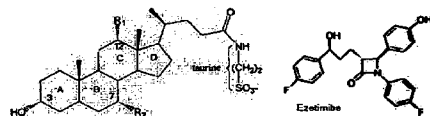
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, 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, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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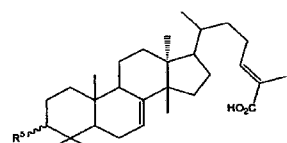
(54) Title: INHIBITORS OF PANCREATIC PHOSPHOLIPASE A2 FOR ALTERING CHOLESTEROL AND FAT UPTAKE

A.



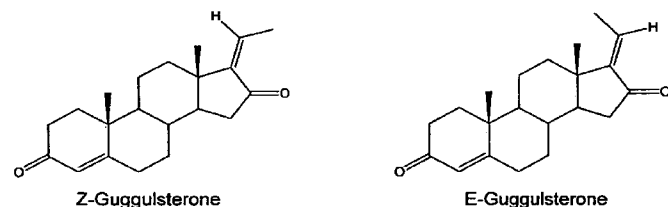
Bile Salt	3	7	12
Cholate (Chol)	OH	OH	OH
Deoxycholate (DOC)	OH	H	OH
Cheno-DOC	OH	OH	H
Urso-deoxycholate	OH	OH β	H

B.



Masticadienolic Acid/Masticadienoic Acid

C.



Z-Guggulsterone

E-Guggulsterone

(57) Abstract: Disclosed herein are methods for regulation of fat and/or cholesterol uptake from the gastrointestinal tract and/or regulation of plasma fat and/or cholesterol levels comprising administering to a mammal in need thereof an effective amount of a regulator of pancreatic IB PLA2 functionality. Also disclosed herein are methods of regulating the function of a polypeptide of interest comprising inserting of the 62-66 loop region of a pancreatic IB PLA2 amino acid sequence into the polypeptide of interest; and administering an effective amount of a regulatory molecule that effects its regulation through said amino acid sequence. Further disclosed are novel bile salt compounds that regulate pancreatic IB PLA2. Methods for detecting altered pancreatic IB PLA2 function and methods for identifying an agent suitable for regulating pancreatic IB PLA2 enzyme functionality are also disclosed.



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A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/015 A61K31/575 A61K45/06 C07K2/00 A61P3/06

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)

A61K

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 practical, search terms used)

EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WANG DAVID Q-H ET AL: "Feeding natural hydrophilic bile acids inhibits intestinal cholesterol absorption: studies in the gallstone-susceptible mouse." AMERICAN JOURNAL OF PHYSIOLOGY. GASTROINTESTINAL AND LIVER PHYSIOLOGY SEP 2003, vol. 285, no. 3, September 2003 (2003-09), pages G494-G502, XP002499684 ISSN: 0193-1857 page G489; figure 3 page G499, column 2, paragraph 3 page G501, column 1, paragraph 1 page G489; figure 3 page G500, column 1, paragraph 1 page G500, column 1, paragraph 1 ----- -/--	1-10, 18, 19, 22

☒ 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 document 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.

G document member of the same patent family

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International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	COHEN B I ET AL: "Sterol metabolism studies in the rat. Effects of primary bile acids (sodium taurochenodeoxycholate and sodium taurocholate) on sterol metabolism." JOURNAL OF LIPID RESEARCH MAR 1977; vol. 18, no. 2, March 1977 (1977-03), pages 223-231, XP002499685 ISSN: 0022-2275 page 226; tables 2,3 page 227, column 2 page 229, column 2, paragraph 3	1-6,8,9, 11,18, 19,22
X	SWERTFEGER D ET AL: "The impact of bile salt on pancreatic phospholipase A2 (p-PLA2) mediated cholesterol uptake by intestinal cells" FASEB JOURNAL, FED. OF AMERICAN SOC. FOR EXPERIMENTAL BIOLOGY, BETHESDA, MD, US, vol. 13, no. 5 PART 2, 15 March 1999 (1999-03-15), page A900, XP008097108 ISSN: 0892-6638 the whole document	1-6,8, 18,19,22
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X	US 2005/187204 A1 (KONDO TATSUHIITO [JP] ET AL) 25 August 2005 (2005-08-25) paragraphs [0003], [0004], [0021], [0012], [0069] - [0078], [0082] - [0098] -/--	1-7,9, 10,18, 22,23

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/018526

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OWSLEY ERIKA ET AL: "Guggulsterone antagonizes farnesoid X receptor induction of bile salt export pump but activates pregnane X receptor to inhibit cholesterol 7alpha-hydroxylase gene." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 304, no. 1, 25 April 2003 (2003-04-25), pages 191-195, XP002499687 ISSN: 0006-291X abstract page 191, column 2, paragraph 2 page 194, column 2, paragraph 1	1-5,7,9, 10,18,19
X	RICHMOND BONNIE L ET AL: "Compensatory phospholipid digestion is required for cholesterol absorption in pancreatic phospholipase A2-deficient mice" BIOSIS,, 1 January 1900 (1900-01-01), XP002500775 page 1193, column 2, paragraph 2 page 1196, column 1, paragraph 3 - column 2, paragraph 1 figure 1	1-3,7,9, 10
X	FRANCIS, JAYARAJ A. ET AL: "Bioactive terpenoids and guggulusteroids from Commiphora mukul gum resin of potential anti-inflammatory interest" CHEMISTRY & BIODIVERSITY , 1(11), 1842-1853 CODEN: CBHIAM; ISSN: 1612-1872, 2004, XP002499688 page 1842 page 1843 page 1844; compounds 1-4	9,10,18, 19,37
X	KOBAYASHI, MASARU ET AL: "Marine terpenes and terpenoids. VII. Minor cembranoid derivatives, structurally related to the potent anti-tumor-promoter sarcophytol A, from the soft coral Sarcophyton glaucum" CHEMICAL & PHARMACEUTICAL BULLETIN , 37(3), 631-6 CODEN: CPBTAL; ISSN: 0009-2363, 1989, XP008097507 page 631; figures chart,1	37

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/018526

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	YU BAO-ZHU ET AL: "Role of 57-72 loop in the allosteric action of bile salts on pancreatic IB phospholipase A(2): regulation of fat and cholesterol homeostasis." BIOCHIMICA ET BIOPHYSICA ACTA OCT 2007, vol. 1768, no. 10, 26 May 2007 (2007-05-26), pages 2478-2490, XP002499689 ISSN: 0006-3002 page 2479 page 2483, column 2, paragraph 2; figure 6	1-7, 18-22,37
P,X	PAN ET AL: "Structural Basis for Bile Salt Inhibition of Pancreatic Phospholipase A2" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB, vol. 369, no. 2, 6 May 2007 (2007-05-06), pages 439-450, XP022065192 ISSN: 0022-2836 page 445, column 1, paragraph 1 page 448, column 1, paragraph 1	1-7,18, 22
E	WO 2007/111992 A (HARVARD COLLEGE [US]; HOTAMISLIGIL GOKHAN S [US]; OZCAN UMUT [US]) 4 October 2007 (2007-10-04) page 18, line 1 - line 26 claims 1,4	9,10,18, 19,22
T	BAI, SHI ET AL: "1H and 13C assignments of five cembrenes from guggul" MAGNETIC RESONANCE IN CHEMISTRY, 46(8), 791-793 CODEN: MRCHEG; ISSN: 0749-1581, 2008, XP002499690 page 791, column 1, paragraph 1 page 792; figure 1	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/018526

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 additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an 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 reportcovers 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.:

see annex

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-11, 18-23, 37 completely

Use of a regulator of pancreatic IB PLA2 functionality in the manufacture of a medicament for the up or down regulation of fat and/or cholesterol uptake or for the regulation of plasma fat and/or cholesterol levels.
A pharmaceutical composition for the regulation of uptake of fat and/or cholesterol from the intestine or for the regulation of plasma fat and/or cholesterol levels comprising an isolated bile salt compound.
A compound according to claim 37.

2. claims: 12-17 completely

A method of regulating the function of a polypeptide of interest comprising:
(a) inserting a 62-66 loop region of a pancreatic IB PLA2 amino acid sequence into the polypeptide of interest to produce a modified polypeptide; and
(b) contacting the modified polypeptide with a regulatory molecule that effects its regulation through said 62-66 loop region.

3. claims: 24-32 completely

A method for determining activity or altered function of pancreatic IB PLA2 enzyme in a sample comprising:
(a) combining said sample with a regulator of pancreatic IB PLA2 functionality; and
(b) determining the amount or the effectiveness of pancreatic IB PLA2 present in said sample as a function of the ability of the enzyme to digest lipids in the presence of said regulator.

4. claims: 33-36 completely

A method for identifying an agent suitable for regulating pancreatic IB PLA2 enzyme functionality comprising:
(a) combining said agent with pancreatic IB PLA2; and
(b) determining the ability of the agent to regulate pancreatic IB PLA2 functionality as a function of the ability of the enzyme to digest lipids in the presence of said agent.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2007/018526

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2005187204	A1	25-08-2005	NONE
WO 2007111992	A	04-10-2007	AU 2007230989 A1 04-10-2007
		EP 2001484 A2	17-12-2008