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CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: SUBSTRATE REDUCTION THERAPY

(57) Abstract: The present invention provides a compound which is an inhibitor of sphingolipid biosynthesis for use in the treatment of a disease which has a secondary Niemann-Pick type C disease like cellular phenotype.

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2008/002207

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/195 A61K31/40 A61K31/42 A61K31/431 A61K31/445
A61K31/513 A61K31/52 A61K31/5375 A61K31/58 A61K31/6615
A61K31/675 A61K31/685 A61K31/7008 A61K31/7012 A61P43/00

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 A61P

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, EMBASE, BIOSIS, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZERVAS M ET AL: "Critical role for glycosphingolipids in Niemann-Pick disease type C." CURRENT BIOLOGY : CB 21 AUG 2001, vol. 11, no. 16, 21 August 2001 (2001-08-21), pages 1283-1287, XP007905921 ISSN: 0960-9822	1-32
Y	page 1286, left-hand column, lines 45-50	1-7, 12, 21, 28, 29, 32
X	EP 1 528 056 A (AZ UNIV AMSTERDAM [NL]) 4 May 2005 (2005-05-04) pages 1-2, paragraphs 1,7; compounds 4,7, 28-30 ----- -/--	1-12, 28, 29, 32

☒ 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 SEARCH REPORT

International application No
PCT/GB2008/002207

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 2006/037069 A (ALLERGAN INC [US]; SCHWEIGHOFFER FABIEN [FR]; DONELLO JOHN E [US]) 6 April 2006 (2006-04-06) claims 13,14,18-22	1-12, 28-32
X	WO 2004/007454 A (OXFORD GLYSCSCIENCES UK LTD [GB]; ALI MEZHER HUSSEIN [GB]; ORCHARD MIC) 22 January 2004 (2004-01-22) claims 1,18	1-11,28, 29,32
X	STURLEY S L ET AL: "The pathophysiology and mechanisms of NP-C disease" BIOCHIMICA AND BIOPHYSICA ACTA. MOLECULAR AND CELL BIOLOGY OF LIPIDS, ELSEVIER, AMSTERDAM, NL, vol. 1685, no. 1-3, 11 October 2004 (2004-10-11), pages 83-87, XP004590040 ISSN: 1388-1981 page 86, left-hand column, paragraph 3	1-32
X	NOREZ ET AL: "Rescue of functional delF508-CFTR channels in cystic fibrosis epithelial cells by the alpha-glucosidase inhibitor miglustat" FEBS LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 580, no. 8, 3 April 2006 (2006-04-03), pages 2081-2086, XP005413398 ISSN: 0014-5793 the whole document	1-12, 28-30,32
X	WO 2005/123055 A (MUSC FOUND FOR RES DEV [US]; SINGH INDERJIT [US]; SINGH AVTAR K [US]) 29 December 2005 (2005-12-29) pages 18-20, paragraphs 1.,2.,3.; claim 9 page 4, line 13	1-12, 28-30,32
X	page 4, line 23 - page 5, line 5	1-7,12, 21,28-32
X	US 2004/034019 A1 (TOMLINSON RONALD [US] ET AL) 19 February 2004 (2004-02-19) claims 1,21-24	1-11, 28-30,32
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INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2008/002207

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/62780 A (OXFORD GLYCOSCIENCES UK LTD [GB]; WALKLEY STEVEN [US]; HOLT GORDON D [US]) 26 October 2000 (2000-10-26) claims 1,5,8	1-12,28, 29,32
X	claims 1,6	1-7,12, 21,28, 29,32
X	----- WO 03/037338 A (VERTEX PHARMA [US]; BOTFIELD MARTYN [US]; MCDONALD FIONA [DE]; KRAETZS) 8 May 2003 (2003-05-08)	1-11, 28-30,32
Y	claims 1-3	31
Y	----- STEINER ROBERT D ET AL: "Sterol balance in the Smith-Lemli-Opitz syndrome: Reduction in whole body cholesterol synthesis and normal bile acid production" JOURNAL OF LIPID RESEARCH, vol. 41, no. 9, September 2000 (2000-09), pages 1437-1447, XP002500214 ISSN: 0022-2275 page 1438, left-hand column, paragraph 4	31
Y	----- WO 2005/009349 A (SUPERGEN INC [US]; LYONS JOHN [GB]; CHANG LUCY [US]) 3 February 2005 (2005-02-03) the whole document	31
A	----- MUKHERJEE S ET AL: "Lipid and cholesterol trafficking in NPC" BIOCHIMICA AND BIOPHYSICA ACTA. MOLECULAR AND CELL BIOLOGY OF LIPIDS, ELSEVIER, AMSTERDAM, NL, vol. 1685, no. 1-3, 11 October 2004 (2004-10-11), pages 28-37, XP004590035 ISSN: 1388-1981 the whole document	1-32
X	----- WO 93/02673 A (UNIV EMORY [US]; US AGRICULTURE [US]) 18 February 1993 (1993-02-18) page 12, paragraph 1; claims 1-3,6,9,11	1-7,24, 28,29,32
X	----- US 2005/182020 A1 (WORGALL TILLA S [US] ET AL) 18 August 2005 (2005-08-18) paragraphs [0008], [0073], [0077], [0082], [0086], [0087]; figures 3A,7	1-7,12, 21,24, 28,29,32
X	----- WO 2007/015175 A (UNIV FRIEDRICH ALEXANDER ER [DE]; STAMM STEFAN [DE]; NOVOYATLEVA TATYA) 8 February 2007 (2007-02-08) claims 3,6,8	1-7,24, 28-30,32
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INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2008/002207

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 720 184 B1 (MERRILL JR ALFRED H [US] ET AL) 13 April 2004 (2004-04-13) claims 1,2	1-7, 24, 28, 29, 32
X	----- ABE A ET AL: "Agents for the treatment of glycosphingolipid storage disorders" CURRENT DRUG METABOLISM 2001 NL, vol. 2, no. 3, 2001, pages 331-338, XP009116910 ISSN: 1389-2002	1-7, 12, 21, 28, 29, 32
Y	the whole document	1-7, 12, 21, 28, 29, 32
A	----- FOX T E ET AL: "The clinical potential of sphingolipid-based therapeutics" CMLS CELLULAR AND MOLECULAR LIFE SCIENCES, BIRKHÄUSER-VERLAG, BA, vol. 63, no. 9, 29 March 2006 (2006-03-29), pages 1017-1023, XP019419144 ISSN: 1420-9071 page 1018	1-32
P, X	----- WO 2008/012555 A (ISIS INNOVATION [GB]; CRISPIN MATTHEW DAVID MAX [GB]; SCANLAN CHRISTOP) 31 January 2008 (2008-01-31) the whole document	1-32
P, X	----- WO 2007/123403 A (ACADEMISCH MEDISCH CT [NL]; AERTS JOHANNES MARIA FRANCISCU [NL]; BOOT) 1 November 2007 (2007-11-01) claims 1, 4, 5, 10, 11 pages 11-12; table 1	1-12, 28-32
P, X	----- LLOYD-EVANS ET AL: "61. Smith-Lemli-Opitz syndrome: A closet lysosomal storage disease hiding within an inheritable metabolic disorder of cholesterol biosynthesis" MOLECULAR GENETICS AND METABOLISM, ACADEMIC PRESS, SAN DIEGO, CA, US, vol. 93, no. 2, 14 January 2008 (2008-01-14), page 29, XP022420694 ISSN: 1096-7192 paragraphs [0004], [0005]	1-32
P, X	----- WO 2008/006007 A (UNIV COLUMBIA [US]; WORGALL TILLA [US]) 10 January 2008 (2008-01-10) claim 8	1-12, 21, 24, 28-32

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: -

I. The present claims 1-12, 21, 24, 28-29 and 32 relates to an extremely large number of possible therapeutical uses, namely the treatment of disorders which are defined as a disease which has a secondary Niemann-Pick type C disease like cellular phenotype.

Here, the condition to be treated is defined in functional terms, e.g. disease having a cellular phenotype of a secondary Niemann-Pick type C disease, said claims can be regarded as clear only if instructions, in the form of experimental tests or any testable criteria, are available from the patent documents or from the common general knowledge allowing the skilled person to recognise which conditions fall within the functional definition and accordingly within the scope of the claims. As determining a list of disorders implied by these features might be difficult, a skilled person would not be able to ascertain the scope of the claim by considering this feature. The requirements of Art. 6 PCT are not met for these claims.

Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the disease claimed, namely those of claim 30 which appears to be clearly defined.

II. Present claim 30 fails to meet the requirements of Art. 6/5 PCT for the following reasons:

Claim 30 is directed to a further therapeutic application of a compound and the condition to be treated is defined in functional terms, e.g. any condition susceptible of being improved or prevented by altering the activity of an enzyme involved in cholesterol synthesis or homeostasis, said claim can be regarded as clear only if instructions, in the form of experimental tests or any testable criteria, are available from the patent documents or from the common general knowledge allowing the skilled person to recognise which conditions fall within the functional definition and accordingly within the scope of the claim. As determining a list of disorders implied by this feature might be difficult, a skilled person would not be able to ascertain the scope of the claim by considering this feature. The same would apply when considering the expression "an inborn error of cholesterol synthesis" as found claim 30.

It would appear that the Applicant intends the discovery of a mechanism of action, viz the inhibition of cholesterol synthesis, to form the basis of the claimed medical use. This is not allowable since no instruction allowing the skilled person to recognise which conditions fall within the functional definition and accordingly within the scope of the claim has been provided. Requirements of Art. 5/6 PCT are therefore not met. It should be noted that scientific discoveries are excluded from patentable subject-matter in many countries and the ISA/IPEA does not need to consider such matter (Rule 67.1(i) PCT).

The non-compliance with the substantive provisions is to such an extent,

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

that the search was performed taking into consideration the non-compliance in determining the extent of the search of claims 1-12, 21, 24, 28-29 and 32 (PCT Guidelines 9.19, 9.23 and 9.24).

The search of claims 1-12, 21, 24, 28-30 and 32 was restricted to those claimed uses in therapy which appear to be sufficiently clear, supported and disclosed, namely the treatment of Smith-Lemli-Opitz Syndrome (SLOS), CHILD syndrome, XLD chondrodysplasia punctata type 2, Conradi-Hünermann-Happle syndrome, HEM dysplasia, Tangier disease, Huntington's disease, Cystic Fibrosis, Pelizaeus-Merzbacher disease, Mucopolidosis II (Icell), variant late infantile-Neuronal Ceroid Lipofuscinosis, and autism.

III. The combination therapy of claim 31 comprises the administration of a so-called "inhibitor of de novo cholesterol biosynthesis". This definition does not enable the skilled man to clearly define the compounds used in the combination therapies intended to be protected. Because said claims seeks to define the scope of protection by a desirable result to be achieved/property/function rather than by a technical feature, a skilled person would not be able to determine the compounds encompassed by the definition of claim 31 which is not clear (Art. 6 PCT).

Since the use of this expression in claim 31 refers to an extremely large number of possible combination therapies and since sufficient support and disclosure is only to be found for the co-administration of statin, for instance simvastatin, pravastatin, lovastatin, fluvastatin, cerivastatin or atorvastatin as suggested by page 94, lines 17-19, claim 31 does not meet the requirements of Articles 6 and 5 PCT.

The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search (PCT Guidelines, 9.19 and 9.24).

The extent of the search of claim 31 was consequently limited to the combination therapies which are clearly defined in the description, namely those involving the co-administration of statin, for instance simvastatin, pravastatin, lovastatin, fluvastatin, cerivastatin or atorvastatin as suggested by page 94, lines 17-19.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
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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:
see FURTHER INFORMATION sheet PCT/ISA/210
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 report covers only those claims for which fees were paid, specifically claims Nos.:
1-8(in part), 9-10, 11-12 (in part), 21, 24 (in part), 28-32 (in part)
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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-8 (in part), 9-10, 11-12 (in part), 28-32 (in part)

use of sphingolipid biosynthesis inhibitor of formula I,
wherein X=N, n=0 or 1, Y=C for the preparation of a
medicament for the treatment of a disease which has a
secondary Niemann-Pick type C disease cell like phenotype.

2. claims: 1-8 (in part), 11-12 (in part), 28-32 (in part)

use of sphingolipid biosynthesis inhibitor of formula I,
wherein X=N, n=1, Y=0 or S for the preparation of a
medicament for the treatment of a disease which has a
secondary Niemann-Pick type C disease cell like phenotype.

3. claims: 1-8 (in part), 13-16 (each all), 28-32 (in part)

use of sphingolipid biosynthesis inhibitor of formula I,
wherein X=0 or S, n=0 or 1, Y=C for the preparation of a
medicament for the treatment of a disease which has a
secondary Niemann-Pick type C disease cell like phenotype.

4. claims: 1-8 (in part), 28-32 (in part)

use of sphingolipid biosynthesis inhibitor of formula I,
wherein X=0 or S, n= 1, Y=0 or S for the preparation of a
medicament for the treatment of a disease which has a
secondary Niemann-Pick type C disease cell like phenotype.

5. claims: 1-8 (in part), 17-18, 28-32 (in part)

use of sphingolipid biosynthesis inhibitor of formula II for
the preparation of a medicament for the treatment of a
disease which has a secondary Niemann-Pick type C disease
cell like phenotype.

6. claims: 1-8 (in part), 19-20, 28-32 (in part)

use of sphingolipid biosynthesis inhibitor of formula III
for the preparation of a medicament for the treatment of a
disease which has a secondary Niemann-Pick type C disease
cell like phenotype.

7. claims: 1-7 (in part), 21, 28-32 (in part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

use of sphingolipid biosynthesis inhibitor of formula IV for the preparation of a medicament for the treatment of a disease which has a secondary Niemann-Pick type C disease cell like phenotype.

8. claims: 1-7 (in part), 22-23, 28-32 (in part)

use of sphingolipid biosynthesis inhibitor of formula V for the preparation of a medicament for the treatment of a disease which has a secondary Niemann-Pick type C disease cell like phenotype.

9. claims: 1-7 (in part), 24(part), 28-32 (in part)

use of sphingolipid biosynthesis inhibitor of formula XII for the preparation of a medicament for the treatment of a disease which has a secondary Niemann-Pick type C disease cell like phenotype.

10. claims: 1-7 (in part), 24 (in part), 28-32 (in part)

use of sphingolipid biosynthesis inhibitor of formula IX for the preparation of a medicament for the treatment of a disease which has a secondary Niemann-Pick type C disease cell like phenotype.

11. claims: 1 (in part), 25, 28-32 (in part)

use of a sphingolipid biosynthesis inhibitor such as RNA for the preparation of a medicament for the treatment of a disease which has a secondary Niemann-Pick type C disease cell like phenotype.

12. claims: 1(in part), 26-27, 28-32 (in part)

use of sphingolipid biosynthesis inhibitor which is an inhibitor of ceramide degradation for the preparation of a medicament for the treatment of a disease which has a secondary Niemann-Pick type C disease cell like phenotype.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2008/002207

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008006007	A	10-01-2008	NONE