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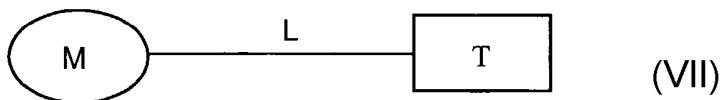
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(54) Title: USE OF CELL-SPECIFIC CONJUGATES FOR TREATMENT OF INFLAMMATORY DISEASES OF THE GASTROINTESTINAL TRACT



(57) Abstract: The present invention is directed to methods for the prevention and treatment of inflammatory diseases, disorders, and conditions of gastrointestinal tract by administering to a patient in need of such treatment, conjugate compounds of Formula (VII) having low oral bioavailability, or pharmaceutically acceptable salts, prodrugs, or solvate thereof: wherein M represents a macrolide subunit possessing the property of accumulation in inflammatory cells, T represents an anti-inflammatory subunit that can be a steroid or nonsteroid (nonsteroidal moiety) derived from a non-steroid drug with anti-inflammatory, analgesic and/or antipyretic activity (NSAID) and L represents a linker covalently linking M and T. The present disclosure is also directed to pharmaceutical compositions containing conjugate compounds of Formula (VII) having low oral-bioavailability.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/002406A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/48 A61P29/00 A61P1/00

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, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/005310 A (PLIVA D.D; MERCEP, MLADEN; MESIC, MILAN; TOMASKOVIC, LINDA; MARKOVIC,) 15 January 2004 (2004-01-15) cited in the application pag. 47 line 4 and pag. 48 lines 24-28; claims 8-47, 49-54	1-5,7,8, 22-27
X	WO 03/070173 A (SYMPORE GMBH; BURNET, MICHAEL; GUSE, JAN-HINRICH; KIM, GENE; BECK, ALB) 28 August 2003 (2003-08-28) pag. 46 lines 6-24; example 25 pag. 108, 109, 111, 112; compound 52 pag. 81; comp-compound 58 pag. 87; compound 59 pag. 88; compound 106 pag. 128 ----- -/--	1-9, 22-27

 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
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- *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

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INTERNATIONAL SEARCH REPORT

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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	WO 03/070174 A (SYMPORE GMBH; BURNET, MICHAEL; GUSE, JAN-HINRICH; GUTKE, HANS-JURGEN;) 28 August 2003 (2003-08-28) Example 25 pag. 107, 108, 110, 111; pag. 47 lines 1-3; claims 21-26; Compound 52 pag. 80-comp. 60 pag. pag. 88	1-9, 22-27
X	WO 2004/005313 A (PLIVA D.D; MERCEP, MLADEN; MESIC, MILAN; TOMASKOVIC, LINDA; MARKOVIC,) 15 January 2004 (2004-01-15) claims 1-8,14,16-19,37-42	1-9, 22-27
X	WO 02/055531 A (PLIVA D.D; MERCEP, MLANDEN; MESIC, MILAN; TOMASKOVIC, LINDA; KOMAC, MA) 18 July 2002 (2002-07-18) claims 1-3,12,45-47	1-8,11, 22-27
Y		1-20, 22-27
X	WO 2004/005309 A (PLIVA D.D; MERCEP, MLADEN; MESIC, MILAN; TOMASKOVIC, LINDA; MARKOVIC,) 15 January 2004 (2004-01-15) cited in the application Claims 1-4, 8, 17, 28, 32, 37	1-9,12, 14,18, 22-27
P,X	WO 2004/094449 A (PLIVA PHARMACEUTICAL INDUSTRY, INC; MERCEP, MLADEN; MESIC, MILAN; TOMA) 4 November 2004 (2004-11-04) claims 1-32,35,37	1-10, 22-27
Y	ROMO D ET AL: "Total Synthesis and Immunosuppressive Activity of (-)-Pateamine A and Related Compounds: Implementation of beta-Lactam Based Macrocyclization" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 120, no. 47, 1998, pages 12237-12254, XP002200620 ISSN: 0002-7863 Scheme 12	1-20, 22-27
Y	WO 03/070254 A (SYMPORE GMBH; BURNET, MICHAEL; GUSE, JAN-HINRICH; KIM, GENE) 28 August 2003 (2003-08-28) Example 1 pag. 28- Example 4 pag. 40	1-20, 22-27
Y	GRIFFITH E C ET AL: "Yeast three-hybrid system for detecting ligand-receptor interactions" METHODS IN ENZYMOLOGY, ACADEMIC PRESS INC, SAN DIEGO, CA, US, vol. 328, 2000, pages 89-103, XP001181421 ISSN: 0076-6879 page 96; figure 4	1-20, 22-27

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/002406

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	COSTA A M ET AL: "Hybrids of macrolides and nucleobases or nucleosides" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 41, no. 18, April 2000 (2000-04), pages 3371-3375, XP004198041 ISSN: 0040-4039 cited in the application 3371 first 2 paragraphs	1-20, 22-27
A	PATENT ABSTRACTS OF JAPAN vol. 017, no. 567 (C-1120), 14 October 1993 (1993-10-14) & JP 05 163293 A (D D S KENKYUSHO:KK), 29 June 1993 (1993-06-29) abstract	1-20, 22-27
A.	BUDAVARI S. ET AL.: "The Merck Index" 1996, MERCK RESEARCH LABORATORIES, WHITEHOUSE STATION NJ, XP002401458 Pag. THER-2, THER-12, THER-15, THER-23	1-20, 22-27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/002406

Box 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:

Although claims 1-23, 25-27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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 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 all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
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.:

1-9, 22-27 in part; 10-20 completely
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.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 1-23, 25-27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 10, 11, 19, completely; 1-8, 22-27 in part

A method for the maintenance treatment of an inflammatory disease, disorder or condition of the gastrointestinal tract comprising administering to a human or non human mammalian subject in need thereof an effective amount of conjugate of present formula VII wherein T is a steroidal anti-inflammatory subunit (i. e. cortisol, cortison...triamcinolone); except the subject matter of inventions 2-18

2. claims: 12, 13, 16, 18 completely ; 1-9, 22-27 in part

A method for the maintenance treatment of an inflammatory disease, disorder or condition of the gastrointestinal tract comprising administering to a human or non human mammalian subject in need thereof an effective amount of conjugate of present formula VII wherein T is a nonsteroidal anti-inflammatory arylcarboxylic acid (e. g. cinmetacine, tolmetin, protizinic acid, xenbucin, tinoridine); except the subject matter of inventions 1, 3-18

3. claims: 1-9, 22-27 in part

A method for the maintenance treatment of an inflammatory disease, disorder or condition of the gastrointestinal tract comprising administering to a human or non human mammalian subject in need thereof an effective amount of conjugate of present formula VII wherein T is an antipyretic (e. g. naproxen); except the subject matter of inventions 1, 2, 4-18

4. claims: 1-9, 22-27 in part

A method for the maintenance treatment of an inflammatory disease, disorder or condition of the gastrointestinal tract comprising administering to a human or non human mammalian subject in need thereof an effective amount of conjugate of present formula VII wherein T is an analgesic (e. g. perisoxal); except the subject matter of inventions 1-3, 5-18.

5. claims: 1-9, 22-27 in part

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method for the maintenance treatment of an inflammatory disease, disorder or condition of the gastrointestinal tract comprising administering to a human or non human mammalian subject in need thereof an effective amount of conjugate of present formula VII wherein T is an immunosuppressant (e. g. azathioprine); except the subject matter of inventions 1-4, 6-18.

6. claims: 1-9, 22-27 in part

A method for the maintenance treatment of an inflammatory disease, disorder or condition of the gastrointestinal tract comprising administering to a human or non human mammalian subject in need thereof an effective amount of conjugate of present formula VII wherein T is a compound selected from the group comprising bisabolol, ditazol, bendazac, parsalimid, oxaceprol, fepradinol, tomoxiprol; except the subject matter of inventions 1-5, 7-18.

7. claims: 14, 15 completely; 1-9, 22-27 in part

A method for the maintenance treatment of an inflammatory disease, disorder or condition of the gastrointestinal tract comprising administering to a human or non human mammalian subject in need thereof an effective amount of conjugate of present formula VII wherein T is a nonsteroidal anti-inflammatory subunit belonging to the group comprising acetylsalicylic acid, salicylamide, salicylsulfuric acid, mesalazine, acetaminosalol, salicin, salsalate diflunisal, flunixin, fendosal; except the subject matter of inventions 1-6, 8-18.

8. claims: 1-9, 22-27 in part

A method for the maintenance treatment of an inflammatory disease, disorder or condition of the gastrointestinal tract comprising administering to a human or non human mammalian subject in need thereof an effective amount of conjugate of present formula VII wherein T is a nonsteroidal anti-inflammatory subunit belonging to the group of immunomodulators (e. g. thalidomid); except the subject matter of inventions 1-7, 9-18.

9. claims: 1-9, 22-27 in part

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method for the maintenance treatment of an inflammatory disease, disorder or condition of the gastrointestinal tract comprising administering to a human or non human mammalian subject in need thereof an effective amount of conjugate of present formula VII wherein T is the phosphodiesterase inhibitor cipamfylline; except the subject matter of inventions 1-9, 10-18.

10. claims: 20 completely; claims 1-9, 22-27 in part

A method for the maintenance treatment of an inflammatory disease, disorder or condition of the gastrointestinal tract comprising administering to a human or non human mammalian subject in need thereof an effective amount of conjugate of present formula VII wherein T is a COX-2 inhibitor (e. g. rofecoxib and celecoxib); except the subject matter of inventions 1-9, 11-18.

11. claims: 17 completely; claims 1-9, 22-27 in part

A method for the maintenance treatment of an inflammatory disease, disorder or condition of the gastrointestinal tract comprising administering to a human or non human mammalian subject in need thereof an effective amount of conjugate of present formula VII wherein T is a nonsteroidal anti-inflammatory aminocarboxylic acid (e. g. mefenamic acid and flufenamic acid); except the subject matter of inventions 1-10, 12-18.

12. claims: 1-9, 22-27 in part

A method for the maintenance treatment of an inflammatory disease, disorder or condition of the gastrointestinal tract comprising administering to a human or non human mammalian subject in need thereof an effective amount of conjugate of present formula VII wherein T is the nonsteroidal anti-inflammatory thiazinecarboxiamide meloxicam; except the subject matter of inventions 1-11, 13-18.

13. claims: 1-9, 22-27 in part

A method for the maintenance treatment of an inflammatory disease, disorder or condition of the gastrointestinal tract comprising administering to a human or non human mammalian subject in need thereof an effective amount of conjugate of present formula VII wherein T is an antirheumatic or an antiarthritic (i. e. methotrexate and leflunomide); except the subject matter of inventions 1-12, 14-18.

14. claims: 1-9, 22-27 in part

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method for the maintenance treatment of an inflammatory disease, disorder or condition of the gastrointestinal tract comprising administering to a human or non human mammalian subject in need thereof an effective amount of conjugate of present formula VII wherein T is an antiasthmatic (i. e. zafirlukast and montelukast); except the subject matter of inventions 1-13, 15-18.

15. claims: 1-9, 22-27 in part

A method for the maintenance treatment of an inflammatory disease, disorder or condition of the gastrointestinal tract comprising administering to a human or non human mammalian subject in need thereof an effective amount of conjugate of present formula VII wherein T is a gastrointestinal nonsteroidal anti-inflammatory subunit (i. e. sulfasalazine and olsalazine); except the subject matter of inventions 1-14, 16-18.

16. claims: 1-9, 22-27 in part

A method for the maintenance treatment of an inflammatory disease, disorder or condition of the gastrointestinal tract comprising administering to a human or non human mammalian subject in need thereof an effective amount of conjugate of present formula VII wherein T is a nonsteroidal anti-inflammatory pyrazolone (i. e. oxyphenbutazone and suxibutazone); except the subject matter of inventions 1-15, 17, 18.

17. claims: 1-9, 22-27 in part

A method for the maintenance treatment of an inflammatory disease, disorder or condition of the gastrointestinal tract comprising administering to a human or non human mammalian subject in need thereof an effective amount of conjugate of present formula VII wherein T is teophylline; except the subject matter of inventions 1-16, 18.

18. claims: Claim 21 completely; claims 1-9, 22-27 in part

A method for the maintenance treatment of an inflammatory disease, disorder or condition of the gastrointestinal tract comprising administering to a human or non human mammalian subject in need thereof an effective amount of conjugate of present formula VII wherein T is 4,5,6,7-tetrafluoro-isoindole-1,3-dione; except the subject matter of inventions 1-17.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2005/002406

Patent document cited in search report		Publication date	Patent family member(s)	Publication date			
WO 2004005310	A	15-01-2004	AU 2003255851 A1	23-01-2004			
			BR 0312634 A	10-05-2005			
			CA 2489402 A1	15-01-2004			
			CN 1692123 A	02-11-2005			
			EP 1521764 A2	13-04-2005			
			JP 2005535654 T	24-11-2005			
			NZ 537717 A	28-04-2006			
WO 03070173	A	28-08-2003	AU 2003215245 A1	09-09-2003			
			EP 1483579 A2	08-12-2004			
			HR 20040849 A2	31-08-2005			
WO 03070174	A	28-08-2003	AU 2003219770 A1	09-09-2003			
			CA 2476423 A1	28-08-2003			
			EP 1483277 A2	08-12-2004			
			HR 20040850 A2	31-08-2005			
WO 2004005313	A	15-01-2004	AU 2003264917 A1	23-01-2004			
			CN 1665831 A	07-09-2005			
			EP 1551865 A2	13-07-2005			
			HR 20050002 A2	31-03-2006			
			JP 2005538070 T	15-12-2005			
WO 02055531	A	18-07-2002	BG 108073 A	31-05-2005			
			BR 0206347 A	10-02-2004			
			CA 2434009 A1	18-07-2002			
			CN 1491230 A	21-04-2004			
			CZ 20031825 A3	12-11-2003			
			EE 200300293 A	15-10-2003			
			EP 1351973 A1	15-10-2003			
			HR 20010018 A2	31-12-2002			
			JP 2004518670 T	24-06-2004			
			PL 363478 A1	15-11-2004			
			SK 9792003 A3	08-01-2004			
			US 2004198677 A1	07-10-2004			
			WO 2004005309	A	15-01-2004	AU 2003255849 A1	23-01-2004
						BR 0312584 A	12-04-2005
CA 2489398 A1	15-01-2004						
CN 1665829 A	07-09-2005						
EP 1521763 A2	13-04-2005						
JP 2005536488 T	02-12-2005						
WO 2004094449	A	04-11-2004				AU 2004232546 A1	04-11-2004
			BR PI0410490 A	13-06-2006			
			CA 2523081 A1	04-11-2004			
			CN 1777619 A	24-05-2006			
			EP 1633771 A1	15-03-2006			
			HR 20030324 A2	28-02-2005			
			IS 8141 A	22-11-2005			
			MX PA05011359 A	12-05-2006			
			US 2005080003 A1	14-04-2005			
			WO 03070254	A	28-08-2003	AU 2003211113 A1	09-09-2003
CA 2476448 A1	28-08-2003						
EP 1482957 A1	08-12-2004						
JP 05163293	A	29-06-1993	JP 2076093 C	25-07-1996			

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2005/002406

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 05163293 A		JP 7103148 B	08-11-1995
<hr/>			