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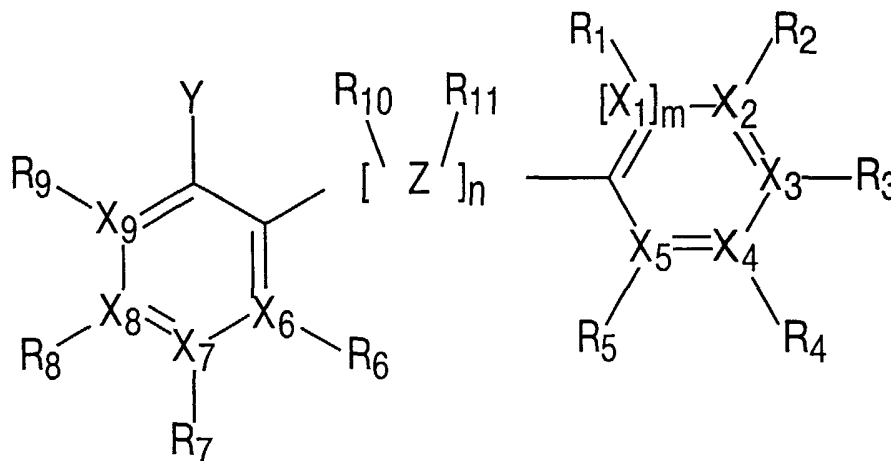
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MUCIN SYNTHESIS INHIBITORS



(57) Abstract: The claimed invention relates to methods of modulating mucin synthesis and the therapeutic application of compounds in controlling mucin over-production associated with diseases such as chronic obstructive pulmonary diseases (COPD) including asthma and chronic bronchitis, inflammatory lung diseases, cystic and acute or chronic respiratory infectious diseases.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/21315

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/443 A61K31/192 A61K31/435 A61K31/54 A61K31/4706
A61P11/00

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)

IPC 7 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, WPI Data, PAJ, EMBASE, BIOSIS, CHEM ABS Data, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 97/03659 A (JUERGENS UWE) 6 February 1997 (1997-02-06) page 4, line 15 - page 5, line 10 page 6, line 4 - line 8 claims 1,7 ----- -/--	1-5, 7-10, 20, 34-37, 40, 41, 46, 48-55, 59-62, 68, 69, 71

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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.

"&" document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No

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X	JACKSON R H ET AL: "New therapy in bronchial asthma. An evaluation of ponstel (mefenamic acid) in chronic bronchial asthma and pulmonary emphysema." THE JOURNAL OF THE KANSAS MEDICAL SOCIETY. UNITED STATES OCT 1968, vol. 69, no. 10, October 1968 (1968-10), pages 474-478, XP008020211 ISSN: 0022-8699 abstract page 474, left-hand column page 477, left-hand column -----	1-5, 7-11, 16-19, 32, 34-37, 41, 48-55, 68,70-72
X	MELICA A ET AL: "A new anti-inflammatory, analgesic, antipyretic drug, morniflumate, for chronic relapsing bronchitis" EUROPEAN REVIEW FOR MEDICAL AND PHARMACOLOGICAL SCIENCES 1991 ITALY, vol. 13, no. 1-2, 1991, pages 51-60, XP008020214 ISSN: 0392-291X abstract page 51, right-hand column, paragraph 3 page 53, right-hand column, last paragraph page 54, left-hand column, paragraph 1 page 56, left-hand column, paragraph 2 - right-hand column, paragraph 1 -----	1-5, 7-11, 16-19, 32, 34-37, 41, 48-55, 68,70-72
X	WO 97/03678 A (SOD CONSEILS RECH APPLIC ;CHABRIER DE LASSAUNIERE PIERRE (FR); BRO) 6 February 1997 (1997-02-06) abstract page 1, paragraph 1 - paragraph [0002] page 2, line 18 - line 38 page 4, line 25 - page 5, line 9 page 5, line 31 - page 6, line 5 table 1 claims 1-4 ----- -/--	1-5,16, 19, 34-37, 48,49, 54,55, 68,70

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/21315

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X	US 4 515 980 A (BAILEY DENIS M) 7 May 1985 (1985-05-07) column 2, line 14 - line 31 column 3, line 1 - line 19 column 9, paragraphs 3,5	1-5
X	US 4 552 899 A (LASKA EUGENE M ET AL) 12 November 1985 (1985-11-12) abstract column 1, paragraph 1 column 1, last paragraph - column 2, paragraph 1 column 3, paragraph 2 column 3, line 43 - line 45 example 1	20,22-28
A		1-5, 7-19,32, 34-37, 40,41, 46, 48-55, 59-73
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X	EP 0 174 006 A (RICHARDSON VICKS INC) 12 March 1986 (1986-03-12) abstract page 2, paragraph 1 - paragraph [0002] page 3, line 22 - line 23 page 3, line 29 - page 5, line 26 claims 1,9	1,13-15

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/21315

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	US 5 875 776 A (VAGHEFI FARID) 2 March 1999 (1999-03-02) column 10, line 63 - column 14, line 6 -----	29
A	EP 0 935 964 A (PANACEA BIOTEC LTD) 18 August 1999 (1999-08-18) paragraphs [0006], [0015] -----	1,65,72
A	WIDDICOMBE J H ET AL: "Regulation of airway mucosal ion transport." INTERNATIONAL ARCHIVES OF ALLERGY AND APPLIED IMMUNOLOGY. SWITZERLAND 1991, vol. 94, no. 1-4, 1991, pages 56-61, XP008020298 ISSN: 0020-5915 abstract page 56 -----	1-5
A	WAGNER J A ET AL: "MOLECULAR STRATEGIES FOR THERAPY OF CYSTIC FIBROSIS" ANNUAL REVIEW OF PHARMACOLOGY AND TOXICOLOGY, ANNUAL REVIEW INC., PALO ALTO, CA, US, vol. 35, no. 35, 1995, pages 257-276, XP000905581 ISSN: 0362-1642 abstract page 258, line 3 - line 6 page 258, paragraph 2 - paragraph [0003] table 1 page 259, paragraph 1 page 261, paragraph 2 page 265, paragraph 4 -----	1-5
A	GABRIEL S E ET AL: "Permeabilization via the P2X7 purinoreceptor reveals the presence of a Ca ²⁺ -activated Cl- conductance in the apical membrane of murine tracheal epithelial cells." THE JOURNAL OF BIOLOGICAL CHEMISTRY. UNITED STATES 10 NOV 2000, vol. 275, no. 45, 10 November 2000 (2000-11-10), pages 35028-35033, XP002249625 ISSN: 0021-9258 abstract ----- -/--	1-5

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/21315

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WINPENNY J P ET AL: "Calcium-activated chloride conductance in a pancreatic adenocarcinoma cell line of ductal origin (HPAF) and in freshly isolated human pancreatic duct cells." PFLUGERS ARCHIV: EUROPEAN JOURNAL OF PHYSIOLOGY. GERMANY MAY 1998, vol. 435, no. 6, May 1998 (1998-05), pages 796-803, XP002249626 ISSN: 0031-6768 abstract page 796, right-hand column - page 797, left-hand column, paragraph 1 page 801, right-hand column, last paragraph page 802, right-hand column, line 7 - line 12	1-5
A	----- CUTHBERT, ALAN W.: "Assessment of CFTR chloride channel openers in intact normal and cystic fibrosis murine epithelia" BRITISH JOURNAL OF PHARMACOLOGY (2001), 132(3), 659-668, XP002249627 abstract page 659	1-3
A	----- MCCARTY, N. A. ET AL: "Voltage-dependent block of the cystic fibrosis transmembrane conductance regulator chloride channel by two closely related arylaminobenzoates" JOURNAL OF GENERAL PHYSIOLOGY (1993), 102(1), 1-23, XP002249628 abstract page 2 figure 1	1-3
A	----- CHAO A C ET AL: "Niflumic and flufenamic acids are potent inhibitors of chloride secretion in mammalian airway." LIFE SCIENCES. ENGLAND 1992, vol. 51, no. 18, 1992, pages 1453-1457, XP008020257 ISSN: 0024-3205 abstract page 1453 ----- -/--	1-5

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/21315

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	WO 01/054685 A (NICOLAIDES NICHOLAS C ;JONES STEVE (US); MCLANE MIKE (US); ZHOU YU) 2 August 2001 (2001-08-02) abstract page 1, line 13 - line 17 page 2, line 27 - page 3, line 13 page 4, line 7 - page 7, line 27 examples 1-7 figures 1-19	1-5, 7-20, 22-28, 32, 34-37, 40,41, 46, 48-55, 59-73
P,X	WO 01/085146 A (THONG KAM WAH ;ASTRAZENECA AB (SE)) 15 November 2001 (2001-11-15) abstract page 1, line 3 - line 4 page 1, line 28 - page 2 page 5, line 11 - line 18 page 5, lines 24-27 claims 1-8	1-5, 7-20, 22-28, 32, 34-37, 40,41, 48-55, 59-73

INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 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 1-19, 30, 32-38, 40-43, 46-48, 50-57, and 59-73 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 II Observations where unity of invention is lacking (Continuation of item 2 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.:
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.:
6,21,30,33,38,42-45,47,56,57, and partially 1-5,7-20,22-29,32,34-37,40,41
46,48-55,59-73

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 I.2

Claims Nos.: -

The definition of the therapeutic application by a mechanism of action (treatment of a "disease characterized by the production of mucin") in claims 1-15, 30, 32-38, 40-43, 48-67, and 71-73 is considered to lack clarity within the meaning of Article 6 PCT because it is unclear which pathological conditions (diseases) do fall within this definition and which do not.

The expression "acute or chronic infectious disease" in claims 16, and 68 is considered to lack clarity as well because it is unclear which infectious diseases other than those explicitly disclosed within the application are considered to fall within the scope of the claims and which not.

Consequently, as far as the therapeutic applications are concerned, the search for the first invention has been limited to the treatment of those pathological conditions (diseases) which appear to be clearly defined within the claims or the description, namely to the treatment of chronic obstructive pulmonary disease (COPD), including emphysema, chronic bronchitis, and asthma, to the treatment of inflammatory lung diseases, of cystic fibrosis (CF) and of its associated gastrointestinal complications (malabsorption syndrome, steatorrhea, diarrhea; page 6, lines 26-27 and page 12, lines 8-17), and to the treatment of chronic sinusitis (claim 46).

Present claims 1-3, 11-19, 34, 35, 40, 41, 46, 48-53, and 59-73 encompass a genus of compounds defined only by their function, i.e. their ability to decrease mucin synthesis or (mucin) levels in the subject, wherein the relationship between the structural features of the members of the genus and said function has not been defined. In the absence of such a relationship either disclosed in the as-filed application or recognisable by one skilled in the art based upon information readily available, the skilled artisan would not know how to make and use compounds that lack a structural definition.

Moreover, the above claims relate to compounds defined by reference to desirable characteristics or properties, namely their ability to decrease mucin synthesis or (mucin) levels in the subject, to (additionally) inhibit a cyclooxygenase enzyme, and to specifically inhibit cyclooxygenase 2.

The claims cover all compounds having this characteristic or property,

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds.

In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved, namely the reduction of mucin synthesis or levels in a subject. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

The so-called "derivatives of anthranilic acid" according to the Markush formula of figure 11 encompass a very large number of compounds.

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible.

The expressions "analogues" and "derivatives" in claims 4-6, 20, 21, 36-38, and 54-56 are considered to be unclear pursuant to Article 6 PCT, as it is not clear in which aspect the compounds are considered to be analogs or by which method they are derived from the parent compounds, respectively.

The expression "prodrug" in claims 4-6, 20, 21, 36-38, and 54-56 is also considered to be unclear, as it is not clear which compounds are converted by or in the body of a subject to be treated to compounds of the present invention.

Consequently, as far as therapeutic agents is concerned, the search for the first invention has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to:

a) the following derivatives of anthranilic acid: flufenamic acid, mefenamic acid, tolfenamic acid, meclofenamic acid (page 17, lines 30-32),

b) the following derivatives of nicotinic acid:

niflumic acid, talniflumate, the NFA prodrug morniflumate (page 11, lines 11-12), and the so-called analogs of talniflumate (according to figure 21), namely MSI-2214, MSI-2215, MSI-2216, and MSI-2217.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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: 6, 21, 30, 33, 38, 42-45, 47, 56, 57, and partially 1-5, 7-20, 22-29, 32, 34-37, 40, 41, 46, 48-55, 59-73

Use of analogues and derivatives of anthranilic acid and of analogues and derivatives of 2-amino-nicotinic acid for the treatment of diseases characterised by the production of mucin, and an inhalation device comprising a therapeutic composition comprising analogues and derivatives of anthranilic acid and/or analogues and derivatives of 2-amino-nicotinic acid.

2. claims: 1-4, 7-19, 29, 32, 34-36, 40, 41, 46, 48-54, 59-73 (all partially)

Use of analogues and derivatives of 2-amino-phenylacetic acid for the treatment of diseases characterised by the production of mucin, and an inhalation device comprising a therapeutic composition comprising analogues and derivatives of 2-amino-phenylacetic acid.

3. claims: 1-5, 7-19, 29, 32, 34-37, 40, 41, 46, 48-55, 59-73 (all partially)

Use of bendroflumethiazide for the treatment of diseases characterised by the production of mucin, and an inhalation device comprising a therapeutic composition comprising bendroflumethiazide.

4. claims: 31, 39, 58, and partially 1-5, 7-20, 22-29, 32, 34-37, 40, 41, 46, 48-55, 59-73

Use of analogues and derivatives of aminoquinolines for the treatment of diseases characterised by the production of mucin, and an inhalation device comprising a therapeutic composition comprising analogues and derivatives of aminoquinolines.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/21315

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