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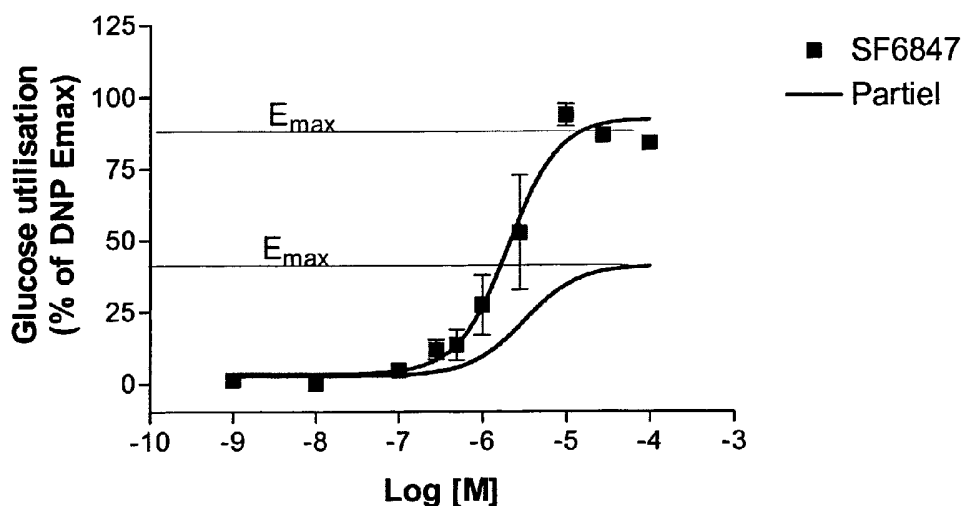
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[Continued on next page]

(54) Title: SAFE CHEMICAL UNCOUPLERS FOR THE TREATMENT OF OBESITY

Hep-G2 cells



(57) Abstract: This invention relates to chemical uncouplers with a broader safety window making the use of them in treating obesity and, consequently, in the treatment of obesity related dis-eases and conditions such as atherosclerosis, hypertension, diabetes, especially type 2 dia-betes (NIDDM (non-insulin dependent diabetes mellitus)), impaired glucose tolerance, dyslip-idemia, coronary heart disease, gallbladder disease, osteoarthritis and various types of can-cer such as endometrial, breast, prostate and colon cancers and the risk for premature death as well as other conditions, such as diseases and disorders, which conditions are improved by an increase in mitochondrial respiration, more attractive.

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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 03/00742

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/04 A61K31/06 C12Q1/00 C07C205/12 G01N33/50
 C12N5/00

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 C12Q C07C G01N C12N

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, MEDLINE, 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	ROBERT M. DRUMMOND ET AL: "Release of Ca ²⁺ from the sarcoplasmic reticulum increases mitochondrial (Ca ²⁺) in rat pulmonary artery smooth muscle cells" JOURNAL OF PHYSIOLOGY, vol. 516, no. 1, 1999, pages 139-147, XP002271195 Results, figures 2-4	1-17,20
X	ROLF ALTENBURGER ET AL: "Predictability of the toxicity of multiple chemical mixtures to vibrio fischeri: mixtures composed of similarly acting chemicals" ENVIRONMENTAL TOXICOLOGY AND CHEMISTRY, vol. 19, no. 9, 2000, pages 2341-2347, XP002271196 figures 1-4; tables 1-3	1-17,20
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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

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INTERNATIONAL SEARCH REPORT

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	WO 00/06143 A (ROY WOODIE ;TEXAS PHARM INC (US); BACHYNSKY NICHOLAS (US)) 10 February 2000 (2000-02-10) claims 1-54	1-17,20
X	WO 01/51923 A (MITOKOR ;MURPHY ANNE N (US); STOUT AMY K (US)) 19 July 2001 (2001-07-19) claims 1-96	1-17,20
X	WOO L W ET AL: "Steroidal and nonsteroidal sulfamates as potent inhibitors of steroid sulfatase." JOURNAL OF MEDICINAL CHEMISTRY. UNITED STATES 26 MAR 1998, vol. 41, no. 7, 26 March 1998 (1998-03-26), pages 1068-1083, XP002271197 ISSN: 0022-2623 figures 5,6	1-17,20
X	US 5 240 962 A (NAKATSU TETSUO ET AL) 31 August 1993 (1993-08-31) Formula I	1-17,20
X	GB 2 284 153 A (RADOPATH LTD) 31 May 1995 (1995-05-31) claims 1-33	1-17,20
X	GB 2 312 375 A (RADOPATH LTD) 29 October 1997 (1997-10-29) claims 1-33	1-17,20
X	US 4 673 691 A (BACHYNSKY NICHOLAS) 16 June 1987 (1987-06-16) claims 1-8	1-17,20
Y	HUANG SHU-GUI: "Development of a high throughput screening assay for mitochondrial membrane potential in living cells." JOURNAL OF BIOMOLECULAR SCREENING: THE OFFICIAL JOURNAL OF THE SOCIETY FOR BIOMOLECULAR SCREENING. UNITED STATES AUG 2002, vol. 7, no. 4, August 2002 (2002-08), pages 383-389, XP002271198 ISSN: 1087-0571 page 388 second column	1-17,20
Y	US 2001/046664 A1 (MURPHY ANNE N ET AL) 29 November 2001 (2001-11-29) claims 1-96	1-17,20
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00742

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>TERADA H ET AL: "Structural requirements of salicylanilides for uncoupling activity in mitochondria: quantitative analysis of structure-uncoupling relationships."----- BIOCHIMICA ET BIOPHYSICA ACTA. NETHERLANDS 7 DEC 1988, vol. 936, no. 3, 7 December 1988 (1988-12-07), pages 504-512, XP002271199 ISSN: 0006-3002 tables I,II</p>	1-17,20
P,A	<p>----- SABU KURUVILLA ET AL: "Effects of Minimally Toxic Levels of Carbonyl Cyanide P-(Trifluoromethoxy) Phenylhydrazone (FCCP), Elucidated through differential Gene Expression with Biochemical and Morphological Correlations" TOXICOLOGICAL SCIENCES, vol. 73, 2003, pages 348-361, XP002271200 figure 10</p>	1-17,20
A	<p>----- US 6 183 948 B1 (MARBAN EDUARDO ET AL) 6 February 2001 (2001-02-06) claims 1-31; example 1 -----</p>	1-17,20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 03/00742

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.: 1-11
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. Claims Nos.: 12-15
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.:
17 and 20 and part of claims 1-16

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.1

Claims Nos.: 1-11

Claims 1-11 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practised on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for those claims. The search has been based on the alleged effects of the compounds or medicaments.

Continuation of Box I.2

Claims Nos.: 12-15

Carbonyl-cyanide p-trifluoromethoxy-phenylhydrazone (FCCP) is a lipid-soluble weak acid which is a very powerful mitochondrial uncoupling agent related to CCCP and DNP according to the closest prior art in documents WO 01/51923A2 and WO 00/06143A1.

FCCP belongs to the group of uncouplers used in screen methods to detect agents (compounds) that bind to mitochondrial calcium uniporter and may also detect modulators of mitochondrial respiration.

Present claims 12-15 relate to a method of screening for compounds, wherein a mitochondrial uncoupling agent is used as a reference. The method is only defined by reference to the following equation:

$$P1: X_n = (Y_2 - Y_0) / (Y_1 - Y_0)$$

The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. Methods of screening in similar manners are described in

WO 01/51923A2, WO 00/06143A1, Drummond et al (Journal of Physiology(1999), 516.1 pp139-147) and Altenburger et al (Environmental Toxicology and Chemistry, Vol19 No9 pp2341-2347 (2000)).

The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to:
The parts relating to the compounds mentioned in the description on pages 110-112 (Table 1).

Claim 16

Present claim 16 relates to an extremely large number of possible variations. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the variations claimed. 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Consequently, the search has been restricted to:
The parts relating to the compounds mentioned in the description on pages 110-112 (Table 1).

The applicant's attention is drawn to the fact that claims, or parts of 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. Claims: 17 and 20 and part of claims 1-16

Use of a compound of the general formula III according to claims 17 and 20 and part of claims 1-16.

2. Claims: 18-19 and part of claims 1-16

Use of a compound of the general formula II according to claims 18-19 and part of claims 1-16.

- ~~3. Claims: 21-22 and part of claims 1-16~~

~~Use of a compound of the general formula IV according to claims 21-22 and part of claims 1-16.~~

4. Claims: 23-24 and part of claims 1-16

Use of a compound of the general formula V according to claims 23-24 and part of claims 1-16.

5. Claims: 25-26 and part of claims 1-16

Use of a compound of the general formula VI according to claims 25-26 and part of claims 1-16.

6. Claims: 27-28 and part of claims 1-16

Use of a compound of the general formula VII according to claims 27-28 and part of claims 1-16.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/DK 03/00742

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No PCT/DK 03/00742

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