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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: COMPOSITIONS COMPRISING INHIBITORS OF DPP-IV AND NEP ENZYMES FOR THE TREATMENT OF DIABETES

(57) Abstract: The present invention is related to a method and composition for treatment of diabetes, hypertension, chronic heart failure and fluid retentive states comprising administering inhibitors of the enzymes NEP and DPP-IV to individuals suffering from one or more of those conditions. Inhibition of the activity of the two enzymes will potentiate the insulin releasing activity of endogenous GLP-1 and other DPP-IV substrates like GIP.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 03/00017

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/30 C07D277/04 C07K5/06 C07K5/08 A61K31/426
A61K38/05 A61P3/10

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 C07D C07C C07K

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, WPI Data, PAJ, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02 059343 A (BROWN NANCY J ;UNIV VANDERBILT (US)) 1 August 2002 (2002-08-01) figure 2 ---	1-18
Y	US 2002/137120 A1 (BROWN NANCY J) 26 September 2002 (2002-09-26) figure 4A ---	1-18
A	MOTWANI J G ET AL: "Natriuretic response to neutral endopeptidase inhibition is blunted by enalapril in healthy men." HYPERTENTION, vol. 25, 1995, pages 637-642, XP002902889 American heart association Inc. the whole document --- -/--	1-18

[X] Further documents are listed in the continuation of box C.

[X] 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)

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"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	Date of mailing of the international search report
3 November 2003	29. 04. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	FERNANDO FARIETA /EÖ

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 03/00017

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KIRK J E ET AL: "Renal effects of concurrent E-24.11 and ACE inhibition in the aorto-venocaval fistula rat." BRITISH JOURNAL OF PHARMACOLOGY, vol. 119, 1996, pages 943-948, XP002902890 Stockton press 1996 ISBN: 0007-1188 the whole document	1-18
A	EP 0 274 234 A (PFIZER LTD) 13 July 1988 (1988-07-13) claims 1-5	1-18
A	HOLST J J ET AL: "Inhibition of the activity of dipeptidyl-peptidase IV as a treatment for type 2 diabetes." DIABETES. UNITED STATES NOV 1998, vol. 47, no. 11, November 1998 (1998-11), pages 1663-1670, XP002260039 ISSN: 0012-1797 the whole document	1-18
P,A	POSPISILIK J ANDREW ET AL: "Dipeptidyl peptidase IV inhibitor treatment stimulates beta-cell survival and islet neogenesis in streptozotocin-induced diabetic rats." DIABETES. UNITED STATES MAR 2003, vol. 52, no. 3, March 2003 (2003-03), pages 741-750, XP002260040 ISSN: 0012-1797 figures 1-6	1-18
P,A	US 2002/193562 A1 (ROBL JEFFREY A) 19 December 2002 (2002-12-19) the whole document	1-18
P,A	US 6 380 398 B1 (CHRISTIANSEN LISE BROWN ET AL) 30 April 2002 (2002-04-30) claims 1-17	1-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 03/00017

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. [X] Claims Nos.: 10-18
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.:
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 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:

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.:

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.: 10-18

Claims 10-18 relates 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 these claims. The search has been based on the alleged effects of the compounds or compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK 03/00017

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02059343 A	01-08-2002	US 2002137120 A1	26-09-2002
		WO 02059343 A2	01-08-2002
		US 2003180828 A1	25-09-2003
US 2002137120 A1	26-09-2002	US 2003180828 A1	25-09-2003
		WO 02059343 A2	01-08-2002
EP 0274234 A	13-07-1988	AT 67178 T	15-09-1991
		AU 595082 B2	22-03-1990
		AU 8240787 A	07-07-1988
		CA 1328264 C	05-04-1994
		CN 87107371 A ,B	06-07-1988
		CY 1723 A	06-05-1994
		DD 273831 A1	29-11-1989
		DE 3772950 D1	17-10-1991
		DK 648487 A	19-08-1988
		EG 18361 A	30-12-1992
		EP 0274234 A2	13-07-1988
		ES 2031523 T3	16-12-1992
		FI 875413 A ,B,	12-06-1988
		GR 3002739 T3	25-01-1993
		HK 65893 A	16-07-1993
		HU 45487 A2	28-07-1988
		HU 202482 B	28-03-1991
		IE 60304 B1	29-06-1994
		IL 84757 A	16-02-1992
		JP 1832862 C	29-03-1994
		JP 5041627 B	24-06-1993
		JP 63165353 A	08-07-1988
		KR 9103335 B1	27-05-1991
		MX 9715 A	01-09-1993
		NO 875169 A ,B,	13-06-1988
		NZ 222848 A	27-10-1989
		PH 25058 A	28-01-1991
		PL 269336 A1	08-12-1988
		PT 86316 A ,B	01-01-1988
		SG 50593 G	09-07-1993
		SU 1612996 A3	07-12-1990
		US 5030654 A	09-07-1991
		US 5192800 A	09-03-1993
		YU 223987 A1	28-02-1989
		ZA 8709247 A	26-07-1989
US 2002193562 A1	19-12-2002	NONE	
US 6380398 B1	18-10-2001	US 2001031780 A1	18-10-2001
		US 2002103384 A1	01-08-2002
		AU 2830901 A	07-08-2001
		WO 0155105 A1	02-08-2001
		EP 1254113 A1	06-11-2002
		JP 2003520849 T	08-07-2003
		AU 3362201 A	03-09-2001
		WO 0162266 A2	30-08-2001
		EP 1259246 A2	27-11-2002
		JP 2003523396 T	05-08-2003
		US 2001025023 A1	27-09-2001