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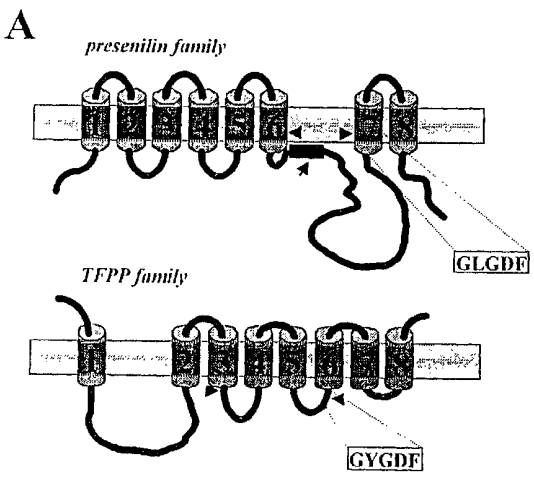
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[Continued on next page]

(54) Title: ASPARTYLPROTEASE



B

PS1	Hs	KLGLGDFI
PS2	Hs	KLGLGDFI
PS1	Bt	KLGLGDFI
PS2	Bt	KLGLGDFI
PS1	Rn	RLGLGDFI
PS2	Rn	KLGLGDFI
PS1	Mm	KLGLGDFI
PS2	Mm	KLGLGDFI
PS1	Xl	KLGLGDFI
PS2	Xl	KLGLGDFI
PS1	Dr	KLGLGDFI
PS	Dm	KLGLGDFI
PS	At	KLGLGDFI
sel-12	Ce	KLGFGDFY
hop-1	Ce	RLGMGDFY
spe-4	Ce	RLGFGDFV
Consensus		KLGLGDFI
TcpJ	Vc	VMGYGDIK
BfpP	Ec	VFAGGDIA
ComC	Bs	GVGGGDIK
FimP	Dn	GMGYGDFK
GspO	Bp	GIGYGDLK
HofD	Ss	GMGDGDPK
HopD	Ec	GLGYGDVK
OutO	Ec	ALGYGDFK
PilD	Aa	GLGFGDVI
Pph	Cl	GIGGGDLK
PulO	Kp	ALGYGDFK
TapD	Ah	GMGYGDFK
VcpD	Vc	GMGYGDFK
VvpD	Vv	GMGYGDFK
XpsO	Xc	GMGHGDFK
Consensus		GMGYGDFK

Consensus protease
Active site motif

G(A)X'GDX''

(57) Abstract: The invention relates to proteins, peptides or aspartyl-proteases comprising specified consensus motifs and nucleic acids encoding said proteins, peptides or aspartyl-proteases. The invention further relates to methods of screening for substances capable of inhibiting said aspartyl-proteases, substances identifiable with said method and pharmaceutical compositions comprising said substances.

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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.

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/EP 01/07512

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/55 C12N9/52 C12N9/64 G01N33/68

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 C12N G01N

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)
WPI Data, EPO-Internal, PAJ, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 34099 A (ROMMENS JOHANNA M ;FRASER PAUL E (CA); HSC RES DEV LP (CA); UNIV T) 31 October 1996 (1996-10-31)	1,2,4,6, 13
Y	page 3, line 21 -page 12, line 6 page 20, line 18 -page 44, line 36 page 73, line 24 -page 76, line 14 page 74, line 5 -page 80, line 29 claims 1-14,59-69,83-86,91	8,9,11, 12,14-24

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 January 2002	25/01/2002

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	van de Kamp, M

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	LEIMER UWE ET AL: "Zebrafish (Danio rerio) presenilin promotes aberrant amyloid beta-peptide production and requires a critical aspartate residue for its function in amyloidogenesis." BIOCHEMISTRY, vol. 38, no. 41, 12 October 1999 (1999-10-12), pages 13602-13609, XP002186843 ISSN: 0006-2960 cited in the application	1,2,4,6, 13
Y	abstract figure 1 page 13607, left-hand column, line 11-14 page 13607, right-hand column, line 19-44	8,9,11, 12,14-24
Y	DE STROOPER BART: "Closing in on gamma-secretase" NATURE (LONDON), vol. 405, 8 June 2000 (2000-06-08), pages 627-628, XP002186844 ISSN: 0028-0836 cited in the application the whole document	8,9,11, 12,14-24
Y	LI YUE-MING ET AL: "Photoactivated gamma-secretase inhibitors directed to the active site covalently label presenilin 1." NATURE (LONDON), vol. 405, no. 6787, 8 June 2000 (2000-06-08), pages 689-694, XP002186845 ISSN: 0028-0836 cited in the application the whole document	8,9,11, 12,14-24
Y	ESLER WILLIAM P ET AL: "Transition-state analogue inhibitors of gamma-secretase bind directly to presenilin-1." NATURE CELL BIOLOGY, vol. 2, no. 7, July 2000 (2000-07), pages 428-434, XP001042318 ISSN: 1465-7392 cited in the application the whole document	8,9,11, 12,14-24

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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	LAPOINTE CHRISTIAN F ET AL: "The type 4 prepilin peptidases comprise a novel family of aspartic acid proteases." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 275, no. 2, 14 January 2000 (2000-01-14), pages 1502-1510, XP002186846 ISSN: 0021-9258 cited in the application abstract page 1503, left-hand column, line 31-36 figure 2 ---	1,3,5,7, 8,10-14, 22
X	EP 0 778 266 A (SQUIBB BRISTOL MYERS CO) 11 June 1997 (1997-06-11) page 2, line 3-7 examples 20,50 claims 1,2,4-6,9-12 ---	25-28
A	WOLFE MICHAEL S ET AL: "Are presenilins intramembrane-cleaving proteases? Implications for the molecular mechanism of Alzheimer's disease." BIOCHEMISTRY, vol. 38, no. 35, 31 August 1999 (1999-08-31), pages 11223-11230, XP002186847 ISSN: 0006-2960 cited in the application the whole document ---	1,2,8,9, 11,14-24
A	WOLFE MICHAEL S ET AL: "Two transmembrane aspartates in presenilin-1 required for presenilin endoproteolysis and gamma-secretase activity." NATURE (LONDON), vol. 398, no. 6727, 8 April 1999 (1999-04-08), pages 513-517, XP002186848 ISSN: 0028-0836 cited in the application abstract ---	1,2,8,9, 11,14-24
A	KIMBERLY W TAYLOR ET AL: "The transmembrane aspartates in presenilin 1 and 2 are obligatory for gamma-secretase activity and amyloid beta-protein generation." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 275, no. 5, 4 February 2000 (2000-02-04), pages 3173-3178, XP002186849 ISSN: 0021-9258 cited in the application abstract --- -/--	1,2,8,9, 11,14-24

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INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/EP 01/07512

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 41443 A (KARRAN ERIC H ;DAVIS JOHN B (GB); GRAY CAROL (GB); WARD ROBIN V (G) 6 November 1997 (1997-11-06) page 2, line 10-28 examples 1,2 claim 1 ---	14,16, 20,21,23
A	WO 98 15828 A (SCIOS INC ;CORDELL BARBARA (US); HIGAKI JEFFREY N (US)) 16 April 1998 (1998-04-16) page 4, line 14 -page 5, line 15 examples 1,2 claim 1 ---	14,15, 17-19,24
P,X	STEINER HARALD ET AL: "Glycine 384 is required for presenilin-1 function and is conserved in bacterial polytopic aspartyl proteases." NATURE CELL BIOLOGY, vol. 2, no. 11, November 2000 (2000-11), pages 848-851, XP001035005 ISSN: 1465-7392 the whole document ---	1-24
P,X	WO 01 04277 A (DARTMOUTH COLLEGE ;TAYLOR RONALD K (US); LAPOINTE CHRISTIAN F (US)) 18 January 2001 (2001-01-18) the whole document page 5, line 1 -page 7, line 7 claims 1-12 -----	1,3,5,7, 8,10-14, 22

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 25-28 relate to a substance defined by reference to a desirable characteristic or property, namely that it is capable of specifically inhibiting the proteolytic cleavage of a gamma-secretase substrate. The claims cover all substances having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such substances. 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 substances by reference to a result to be achieved. 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. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the substance which has been depicted on p.11 l.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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 01/07512

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