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(54) Title: (HYDROXYETHYL)UREAS AS INHIBITORS OF ALZHEIMER'S BETA-AMYLOID PRODUCTION

(57) Abstract: Novel (hydroxyethyl)ureas are described. These compounds are effective inhibitors of certain aspartyl proteases, notably secretases involved in the enzymatic cleavage of amyloid precursor protein (APP) to yield amyloid- $\beta$  peptide. Methods are provided for administering the novel compounds to treat  $\beta$ -amyloid-associated diseases, notably Alzheimer's disease.

INTERNATIONAL SEARCH REPORT

International Application No  
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A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07C275/04 A61K31/17

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 C07C 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)

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	<p>WO 92 08698 A (MONSANTO CO) 29 May 1992 (1992-05-29)</p> <p>claims 1,74,78 page 2, line 12-34 examples 12,13,46-50; tables 4,5,16-20 --- -/--</p>	<p>1, 2, 4-8, 14, 16, 18, 19, 21-24, 26, 49-54, 60, 64, 68, 69</p>

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
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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

Date of the actual completion of the international search

18 February 2002

Date of mailing of the international search report

01/03/2002

Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

Inter. Patent Application No

PCT/US 01/25267

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 36 43 977 A (SQUIBB & SONS INC) 2 July 1987 (1987-07-02)  claim 1; examples 1D,E,2A,3A,B,4D-F,5A,7D,8A,B,E,23,28 page 17, line 14 - line 32 ---	1-7,16, 18-23, 49-53, 62,63, 68,69
X	DE 36 35 907 A (MERCK PATENT GMBH) 28 April 1988 (1988-04-28) abstract; examples 1,4,5 ---	1,2,4,5, 18,19,21
X	KICK E K ET AL: "STRUCTURE-BASED DESIGN AND COMBINATORIAL CHEMISTRY YIELD LOW NANOMOLAR INHIBITORS OF CATHEPSIN D" CHEMISTRY AND BIOLOGY, CURRENT BIOLOGY, LONDON, GB, vol. 4, no. 4, 1997, pages 297-307, XP002065985 ISSN: 1074-5521 page 297 -page 298; table 2 cpd. fbb ---	18,19, 21,22, 49,51, 52, 62-64, 68,69
X	US 4 599 198 A (HOOVER, DENNIS J.) 8 July 1986 (1986-07-08)  column 2, line 26 -column 4, line 47 examples 2,5-23 ---	18-22, 49,51, 52,62, 63,68,69
X	CHASE, B.H. ET AL.: J. PHARM. PHARMACOL., vol. 16, 1964, pages 163-173, XP001040339 example X; table 1 ---	1,18
X	US 2 331 926 A (OLIN, JOHN F.) 19 October 1943 (1943-10-19) example X ---	1,18
X	US 2 344 259 A (DAVIS MCLEOD EARLE ET AL) 14 March 1944 (1944-03-14) example 13 ---	18
X	GB 1 046 045 A (A WANDER S A DR) 19 October 1966 (1966-10-19) examples 12,21,37 ---	1,3,18, 20
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 14, no. 7, 1971, pages 600-614, XP001053530 page 610 ---	1,18
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INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 01/25267

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	<p>WO 01 66564 A (MERCK SHARP &amp; DOHME ; STEVENSON GRAEME IRVINE (GB); CASTRO PINEIRO) 13 September 2001 (2001-09-13)</p> <p>claims 1,4-8; examples 1-28 page 13, line 18 -page 15, line 24 -----</p>	<p>1-6, 16-22, 26,27, 49-52, 62-65, 67-69</p>
E	<p>WO 02 02518 A (UPJOHN CO ;ELAN PHARM INC (US)) 10 January 2002 (2002-01-10)</p> <p>claims 15,35,64-75,99-108; example 5 page 101, line 5 -page 108, line 12 -----</p>	<p>1-6, 16-22, 26,27, 49-52, 62-64, 66-69</p>

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-6,16-22,26,27,49-52,62-69 relate to an extremely large number of possible compositions and methods. 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 claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). 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 compositions and methods 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. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compositions and methods of claims 7-15, 23-25, 53-61 and compounds of general formula I with a combination of R1 = R60(CO) and NHR4 = residue of an alpha-amino acid (peptidyl).

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.

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International Application No PCT/US 01/25267
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