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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

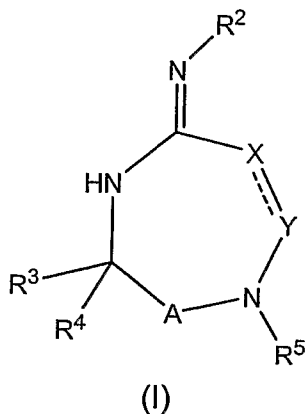
Published:

- with international search report

(88) Date of publication of the international search report:  
8 March 2007

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: THE PREPARATION AND USE OF COMPOUNDS AS ASPARTYL PROTEASE INHIBITORS



(57) Abstract: Disclosed are compounds of the formula I (Chemical formula should be inserted here as it appears on abstract in paper form) (I) or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof, wherein A is a bond, -C(O)-, or -C(R<sup>3</sup>)(R<sup>4</sup>)-; X is -N(R<sup>1</sup>)- or -C(R<sup>6</sup>)(R<sup>7</sup>)-; Y is -S(O)<sub>2</sub>-, -C(=O)-, -PO(OR<sup>9</sup>) or -C(R<sup>6</sup>)(R<sup>7</sup>)-; is a single or double bond and R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> are as defined in the specification; and pharmaceutical compositions comprising the compounds of formula I. Also disclosed is the method of inhibiting aspartyl protease, and in particular, the methods of treating cardiovascular diseases, cognitive and neurodegenerative diseases, and the methods of inhibiting of Human Immunodeficiency Virus, plasmepsins, cathepsin D and protozoal enzymes. Also disclosed are methods of treating cognitive or neurodegenerative diseases using the compounds of formula I in combination with a cholinesterase inhibitor or a muscarinic antagonist.

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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2006/022920A. CLASSIFICATION OF SUBJECT MATTER  
INV. C07D251/10 A61K31/53 A61P9/00

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)  
C07D

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, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002407972 retrieved from STN Database accession no. 1929:36029 compounds 38261-39-1, 38261-40-4, 847488-67-9 & OSTROGOVICH, ADRIANO ET AL: "Some new aryliminoxy-.gamma.-triazidinic derivatives. I" GAZZETTA CHIMICA ITALIANA , 59, 181-98 CODEN: GCITA9; ISSN: 0016-5603, 1929,	1,2
X	DATABASE BEILSTEIN [Online] XP002407973 Database accession no. 6091897 compounds 7949141, 7951514, 7952631, 7954201 -/--	1,2

 Further documents are listed in the continuation of Box C. See patent family 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.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

21 November 2006

Date of mailing of the international search report

12/12/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
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Grassi, Damian

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2006/022920

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	& VOVK, M. V.; TSYMBAL, I. F.: CHEM.HETEROCYCL.COMPD.(ENGL.TRANSL.), vol. 33, no. 5, 1997, page 614-618, ----- WO 2006/065277 A (SCHERING CORP [US]; PHARMA COPIA DRUG DISCOVERY IN [US]; ZHU ZHAONING) 22 June 2006 (2006-06-22) claim 1 -----	1
A	WENDELL W. WILKERSON ET AL.: "HIV Protease Inhibitory Bis-benzamide Cyclic Ureas: A Quantitative Structure-Activity Relationship Analysis" J. MED. CHEM., vol. 39, no. 21, 1996, page 4299 - 4312, XP002407903 example 31 -----	1-7, 16, 24

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

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 1 may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, the search was performed taking into consideration the non-compliance in determining the extent of the search of the claims.

The search was restricted to compounds according to claims 1-2 (part), 3, 4 (part) 5, 6 (part), 7, 16 and 17-24 (part).

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.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2006/022920

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 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:
  
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 III Observations where unity of invention is lacking (Continuation of item 3 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.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/022920

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006065277 A	22-06-2006	AR 050160 A1	04-10-2006
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