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60/216,808 7 July 2000 (07.07.2000) US
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**WO 02/004451 A3**

(54) Title: METHODS FOR STIMULATION OF SYNTHESIS OF SYNAPTOPHYSIN IN THE CENTRAL NERVOUS SYSTEM

(57) Abstract: A method of increasing the synthesis and/or secretion of synaptophysin comprises administering to a patient with a neurological disease or a patient at risk of developing a neurological disease an effective quantity of a purine derivative of analogue, a tetrahydroindolone derivative or analogue, or a pyrimidine derivative or analogue. If the compound is a purine derivative, the purine moiety can be guanine or hypoxanthine. The neurological disease can be a neurodegenerative disease such as Alzheimer's disease or a neurodevelopmental disorder such as Down's syndrome. Typically, the compound can pass through the blood-brain barrier. The purine moiety can be hypoxanthine or guanine. A particularly preferred purine derivative is N-4-carboxyphenyl-3-(6-oxohypurin-9-yl) propanamide.

# INTERNATIONAL SEARCH REPORT

International Application No  
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<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 7 A61K31/52 A61K31/405 A61K31/505		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K 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) CHEM ABS Data, BEILSTEIN Data, BIOSIS, EPO-Internal, PAJ, WPI Data		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 91 14434 A (A.J. GLASKY) 3 October 1991 (1991-10-03)  page 7, lines 30-35; page 42, lines 15-18; pages 44-59 idem	1-15, 107-116, 120-131, 133,134
A	idem	36,37
X	--- D.K. LAHIRI ET AL: "Annals of the New York Academy of Sciences, Vol. 903, pages 387-393" April 2000 (2000-04), NEW YORK ACADEMY OF SCIENCES, NEW YORK, US; XP001040392 page 391, lines 11-24 idem	1-9,111, 112,115, 120,133, 134
A	idem	36,37
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <span style="margin-left: 200px;"><input checked="" type="checkbox"/> Patent family members are listed in annex.</span>		
° 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	
Date of the actual completion of the international search	Date of mailing of the international search report	
14 May 2002	22. 08. 2002	
Name and mailing address of the ISA 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	Authorized officer  Van Amsterdam, L	

## 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.
A	B.R. BAKER ET AL: J. PHARM. SCI., vol. 54, no. 11, 1965, pages 1609-1616, XP001076681  table I, compounds XV, XVIII; scheme I, compounds XVI, XXII-XXVII, XXIX ---	1,3,36, 49-51, 107,108, 111,112, 115-117, 120,121
A	B.R. BAKER ET AL: J. PHARM. SCI., vol. 54, no. 12, 1965, pages 1774-1781, XP001076680  table I, compounds VIII, XXVI, XXVII ---	1,3,36, 107,108, 111,112, 115,120
A	WO 96 20711 A (UNIVERSITY OF MASSACHUSETTS MEDICAL CENTER) 11 July 1996 (1996-07-11)  page 3, lines 1-23; page 4, lines 14-29; page 5, line 25; page 8, lines 24-32 ---	1,3,16, 36,37, 48,107, 108
A	M.A. PEETERS ET AL: JOURNAL OF NEUROLOGICAL SCIENCES, vol. 133, 1995, pages 31-41, XP001040393 the whole document ---	133-136
P,X	WO 01 29039 A (NEOTHERAPEUTICS INC) 26 April 2001 (2001-04-26)  whole document, in particular formulae I-VII, X, XIII-XIV, XVIII, XXVI-XXVII, XXX, XXXII, XXXV, XL idem -----	1-3, 16-35, 107,108, 111,112, 115-117, 120-131, 133,134
A		36,37

# INTERNATIONAL SEARCH REPORT

International application No.  
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## 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.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 1-136 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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 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.:  
  
1-2, 104-136 (in part); 3-73

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

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

1. Claims: 1-2, 104-136 (in part); 3-73

Compounds of the formula A-L-B of claim 1, wherein A is selected from the group consisting of a purine moiety and a purine analogue, for use in the treatment of neurological diseases.

2. Claims: 1-2, 104-136 (in part); 74-79

Compounds of the formula A-L-B of claim 1, wherein A is selected from the group consisting of a tetrahydroindolone moiety and a tetrahydroindolone analogue, for use in the treatment of neurological diseases.

3. Claims: 1-2, 104-136 (in part); 80-103

Compounds of the formula A-L-B of claim 1, wherein A is selected from the group consisting of a pyrimidine moiety and a pyrimidine analogue, for use in the treatment of neurological diseases.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1 and 36 relate to extremely large numbers of possible compounds for use in the treatment of neurological diseases. In fact, the claims contain so many variables and options that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be sufficiently clear and concise, namely those parts relating to compounds of formula A-L-B of claim 1, wherein

A is a substituted or unsubstituted purine moiety covered by formula X of claim 36 for A7 is N and A8 is C and having any of the structures of formulae XI, XII or XIII (see claims 37, 49 or 54, respectively), an unsubstituted hypoxanthine moiety (see claim 4) or an unsubstituted guanine moiety (see claim 16);

L is a -(C1-6 straight or branched chain alkylene)-C(0)- linking group (see claims 6, 12, 14, 18, 22, 25, 28, 30, 34, 58-73) attached to N9 of the purine, hypoxanthine or guanine moiety (see claim 36, page 42, (f)), and

B is -OZ wherein Z is hydrogen or alkyl (see claims 108-110), or -N(Y1)-D wherein Y1 is hydrogen or alkyl (see claims 112-114) and D is as defined in claims 116-131 or is any of the D groups present in the compounds of claims 6, 12, 14, 18, 22, 25, 28, 30, 34, 58-73.

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/US 01/21385

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