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(81) Designated States (unless otherwise indicated, for every kind of national protection available):

AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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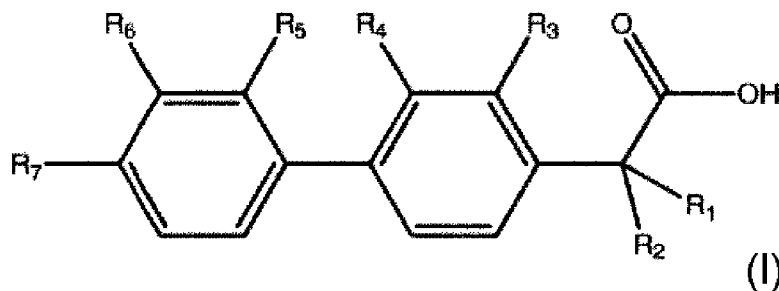
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(54) Title: INHIBITION OF THE TOXIC EFFECTS OF ISLET AMYLOID FORMATION BY FLURIPROFEN AND FLURIPROFEN DERIVATIVES



(57) Abstract: The subject invention provides a method of reducing the presence of toxic intermediates of amyloidosis from islet amyloid polypeptide (IAPP) in a patient, comprising administering a compound to the patient a compound having the structure: (Formula I) wherein R1 and R2 are each independently hydrogen, methyl, ethyl, propyl, butyl, pentyl or hexyl, or R1 and R2 are linked so as to form a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl ring; wherein R3, R4, R5, R6 are each independently hydrogen, fluorine or chlorine; and wherein R7 is hydrogen, phenyl, fluorine, chlorine, bromine, hydroxyl, amine, carboxylic acid, C1-C6 alkyl carboxylate, amide, methyl, ethyl, propyl, butyl, pentyl or hexyl, or a pharmaceutically acceptable salt or ester thereof, so as to thereby reduce the presence of toxic intermediates of amyloidosis from islet amyloid polypeptide (IAPP) in the patient.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 2014/025072

A. CLASSIFICATION OF SUBJECT MATTER				
<i>A61K 31/192 (2006.01)</i> <i>A61P 1/18 (2006.01)</i> <i>A61P 3/10 (2006.01)</i> <i>C07C 63/333 (2006.01)</i>				
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)				
A61K 31/19, 31/192, 31/185, A61P 3/10, C07C 63/333				
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 practicable, search terms used)				
EAPATIS, RUPAT, Patentscope, DWPI, NCBI (PubMed), SpringerLink				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X Y	PERETTO, Ilaria et al. Synthesis and biological activity of flurbiprofen analogues as selective inhibitors of β -amyloid(1)-(42) secretion. Journal of Medicinal Chemistry, 2005, 48(18), pp. 5705-5720	1-3 4-13		
X Y	KUKAR T. et al. Chronic administration of R-flurbiprofen attenuates learning impairments in transgenic amyloid precursor protein mice. BMC Neurosci., 2007, 8:54 (abstract) [online] Retrieved from the Internet: <URL: http://bsalud.org/portal/resource/pt/mdl-17650315	1-3 4-13		
X Y	ERIKSEN, Jason L. et al. NSAIDs and enantiomers of flurbiprofen target γ -secretase and lower A β 42 in vivo. J. Clin. Invest., 2003, 112(3): 440-449	1-3 4-13		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.				
* Special categories of cited documents: <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;"> "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 </td> <td style="width: 50%; border: none;"> "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 </td> </tr> </table>			"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
"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		
27 May 2014 (27.05.2014)		25 September 2014 (25.09.2014)		
Name and mailing address of the ISA/RU: FIPS, Russia, 123995, Moscow, G-59, GSP-5, Berezhkovskaya nab., 30-1 Facsimile No. +7 (499) 243-33-37		Authorized officer M. Trakhanova Telephone No. 8(495)531-64-81		

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 2014/025072

Box No. 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:

3. Claims Nos.: 14-36
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. 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 additional fees, this Authority did not invite payment of additional fees.
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 and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 2014/025072

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ODETTI, P. et al. Plasma levels of insulin and amyloid beta 42 are correlated in patients with amnesic Mild Cognitive Impairment. <i>J. Alzheimer's Dis.</i> , 2005, 8(3), pp. 243-245 (abstract) [online] Retrieved from PubMed, PMID: 16340082	4-8
Y	WESTERMARK, P. et al. Islet amyloid polypeptide, islet amyloid, and diabetes mellitus. <i>Physiol. Rev.</i> , 2011, 91(3): 795-826 (abstract) [online] Retrieved from PubMed, PMID: 21742788	9-13