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- (81) **Designated States (national):** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.
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(54) **Title:** LINEAR γ -CARBOXYGLUTAMATE RICH CONOTOXINS

(57) **Abstract:** The invention relates to linear γ -carboxyglutamate rich conotoxins, derivatives or pharmaceutically acceptable salts thereof, and uses thereof, including the treatment of neurologic and psychiatric disorders, such as anticonvulsant agents, as neuro-protective agents, as neuroprotective agents or for the management of pain. The invention further relates to nucleic acid sequences encoding the conopeptides and encoding propeptides, as well as the propeptides.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/06863

A. CLASSIFICATION OF SUBJECT MATTER																						
IPC(7) : A61K 38/10, 38/00, 38/02; C07K 5/00, 7/00																						
US CL : 530/326, 324, 325; 514/12, 13, 14																						
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) U.S. : 530/326, 324, 325; 514/12, 13, 14																						
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) Please See Continuation Sheet																						
C. DOCUMENTS CONSIDERED TO BE RELEVANT																						
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.																				
Y	WO 98/03189 (COGNETIX, INC.) 29 January 1998 (20.01.1998), page 6, line 27-page 8, line 14; page 10, line 9-page 11, line 9; page 19, line 29-page 21, line 23; Examples 6-	6-9																				
Y	US 5,844,077 (SAYDOFF) 1 December 1998 (1.12.1998), column 2 lines 44-67, Example.	6 and 7																				
A	OLIVERA, et al., Conotoxins, in Retrospect, Toxicon January 2001, Vol. 39, No. 1, pages 7-14. See whole document.	1, 2 and 5-9																				
A	LIRAZAN et al., The Spasmodic Peptide Defines a New Conotoxin Superfamily. Biochemistry February 2000, Vol. 39, No. 7, pages 1583-1588, See whole document.	1, 2 and 5-9																				
☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.																						
* Special categories of cited documents: <table border="0"> <tr> <td>"A"</td> <td>document defining the general state of the art which is not considered to be of particular relevance</td> <td>"T"</td> <td>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</td> </tr> <tr> <td>"E"</td> <td>earlier application or patent published on or after the international filing date</td> <td>"X"</td> <td>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</td> </tr> <tr> <td>"L"</td> <td>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)</td> <td>"Y"</td> <td>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</td> </tr> <tr> <td>"O"</td> <td>document referring to an oral disclosure, use, exhibition or other means</td> <td>"&"</td> <td>document member of the same patent family</td> </tr> <tr> <td>"P"</td> <td>document published prior to the international filing date but later than the priority date claimed</td> <td></td> <td></td> </tr> </table>			"A"	document defining the general state of the art which is not considered to be of particular relevance	"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	"E"	earlier application or patent published on or after the international filing date	"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	"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)	"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	"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family	"P"	document published prior to the international filing date but later than the priority date claimed		
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"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family																			
"P"	document published prior to the international filing date but later than the priority date claimed																					
Date of the actual completion of the international search 28 July 2002 (28.07.2002)		Date of mailing of the international search report 28 AUG 2002																				
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230		Authorized officer Chih-Min Kam Telephone No. (703) 308-0196																				

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/06863

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim 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. ☐ Claim 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:
Please See Continuation 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 and 5-9, in part

Remark on Protest

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☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/06863

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This International Search Authority has found 384 inventions claimed in the International Application covered by the claims indicated below:

Group 1-32, claims 1, 2 and 5-9, in part drawn to one of 32 Conotoxin peptides, respectively, the corresponding propeptide and a method for treating or preventing a neurologic disorders or a psychiatric disorder in which pathophysiology involves excessive excitation of nerve cells, comprising administering to a patient one of Conotoxin peptides, wherein the neurologic disorder is seizure. For group 1, the claims will be searched to extent that they read upon Conotoxin-Af6 and the corresponding propeptide. If group 2 is elected, the claims will be searched to extent that they read upon Conotoxin-Bt1 and the corresponding propeptide.

Group 33-64, claims 3 and 4, in part drawn to a nucleic acid encoding one of 32 conopeptide propeptide, respectively. For group 33, the claims will be searched to extent that they read upon the nucleic acid encoding the propeptide of Conotoxin-C1. If group 34 is elected, the claims will be searched to extent that they read upon the nucleic acid encoding the propeptide of Conotoxin-C2.

Group 65-96, claims 6, 7, 10 and 11, in part drawn to a method for treating or preventing a neurologic disorder in which pathophysiology involves excessive excitation of nerve cells, comprising administering to a patient one of Conotoxin peptides, wherein the neurologic disorder is neurotoxic injury associated with conditions of hypoxia, anoxia or ischemia. For group 65, the claims will be searched to extent that they read upon Conotoxin-Af6. If group 66 is elected, the claims will be searched to extent that they read upon Conotoxin-Bt1.

Group 97-128, claims 6, 7 and 12-14, in part drawn to a method for treating or preventing a neurologic disorder in which pathophysiology involves excessive excitation of nerve cells, comprising administering to a patient one of Conotoxin peptides, wherein the neurologic disorder is neurodegeneration. For group 97, the claims will be searched to extent that they read upon Conotoxin-Af6. If group 98 is elected, the claims will be searched to extent that they read upon Conotoxin-Bt1.

Group 129-160, claims 6, 7 and 15-16, in part drawn to a method for treating or preventing a neurologic disorder in which pathophysiology involves excessive excitation of nerve cells, comprising administering to a patient one of Conotoxin peptides, wherein the neurologic disorder is pain. For group 129, the claims will be searched to extent that they read upon Conotoxin-Af6. If group 130 is elected, the claims will be searched to extent that they read upon Conotoxin-Bt1.

Group 161-192, claims 6, 7 and 17-18, in part drawn to a method for treating or preventing a neurologic disorder in which pathophysiology involves excessive excitation of nerve cells, comprising administering to a patient one of Conotoxin peptides, wherein the neurologic disorder is chemical toxicity. For group 161, the claims will be searched to extent that they read upon Conotoxin-Af6. If group 162 is elected, the claims will be searched to extent that they read upon Conotoxin-Bt1.

Group 193-224, claims 6, 7 and 19-20, in part drawn to a method for treating or preventing a neurologic disorder in which pathophysiology involves excessive excitation of nerve cells, comprising administering to a patient one of Conotoxin peptides, wherein the neurologic disorder is dystonia, urinary incontinence, muscle relaxation or sleep disorder. For group 193, the claims will be searched to extent that they read upon Conotoxin-Af6. If group 194 is elected, the claims will be searched to extent that they read upon Conotoxin-Bt1.

Group 225-256, claims 6, 7 and 21-22, in part drawn to a method for treating or preventing a psychiatric disorder in which pathophysiology involves excessive excitation of nerve cells, comprising administering to a patient one of Conotoxin peptides, wherein the psychiatric disorder is anxiety, major depression, manic-depressive illness, obsessive-compulsive disorder, schizophrenia or mood disorder. For group 225, the claims will be searched to extent that they read upon Conotoxin-Af6. If group 226 is elected, the claims will be searched to extent that they read upon Conotoxin-Bt1.

Group 257-288, claim 23, in part drawn to a method for treating memory or cognitive deficits, comprising administering to a patient one of Conotoxin peptides. For group 257, the claims will be searched to extent that they read upon Conotoxin-Af6. If group 258 is elected, the claims will be searched to extent that they read upon Conotoxin-Bt1.

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Group 289-320, claim 23, in part drawn to a method for treating HIV infection, comprising administering to a patient one of Conotoxin peptides. For group 289, the claims will be searched to extent that they read upon Conotoxin-Af6. If group 290 is elected, the claims will be searched to extent that they read upon Conotoxin-Bt1.

Group 321-352, claim 23, in part drawn to a method for treating ophthalmic indications, comprising administering to a patient one of Conotoxin peptides. For group 321, the claims will be searched to extent that they read upon Conotoxin-Af6. If group 322 is elected, the claims will be searched to extent that they read upon Conotoxin-Bt1.

Group 353-384, claim 24, in part drawn to a method for controlling nematodes or parasitic worms, comprising applying to the locus one of Conotoxin peptides. For group 353, the claims will be searched to extent that they read upon Conotoxin-Af6. If group 354 is elected, the claims will be searched to extent that they read upon Conotoxin-Bt1.

The inventions listed as Groups 1-384 do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The special technical features of Groups 1-32 are the specific 32 Conotoxin peptides, the specific corresponding propeptides and the specific method for treating or preventing a neurologic disorder of seizure using the Conotoxin peptides claimed therein. In contrast, the special technical features of Groups 33-64 are the particular nucleic acids encoding 32 conopeptide propeptides claimed therein; the special technical features of Groups 65-96 are the particular method for treating or preventing a neurologic disorder of neurotoxic injury associated with conditions of hypoxia, anoxia or ischemia using the Conotoxin peptides claimed therein; the special technical features of Groups 97-128 are the particular method for treating or preventing a neurologic disorder of neurodegeneration using the Conotoxin peptides claimed therein; the special technical features of Groups 129-160 are the particular method for treating or preventing a neurologic disorder of pain using the Conotoxin peptides claimed therein; the special technical features of Groups 161-192 are the particular method for treating or preventing a neurologic disorder of chemical toxicity using the Conotoxin peptides claimed therein; the special technical features of Groups 193-224 are the particular method for treating or preventing a neurologic disorder of dystonia, urinary incontinence, muscle relaxation or sleep disorder using the Conotoxin peptides claimed therein; the special technical features of Groups 225-256 are the particular method for treating or preventing the psychiatric disorder of anxiety, major depression, manic-depressive illness, obsessive-compulsive disorder, schizophrenia or mood disorder using the Conotoxin peptides claimed therein; the special technical features of Groups 257-288 are the particular method for treating memory or cognitive deficits using the Conotoxin peptides claimed therein; the special technical features of Groups 289-320 are the particular method for treating HIV infection using the Conotoxin peptides claimed therein; the special technical features of Groups 321-352 are the particular method for treating ophthalmic indications using the Conotoxin peptides claimed therein; and the special technical features of Groups 353-384 are the particular method for controlling nematodes or parasitic worms using the Conotoxin peptides claimed therein. The 32 Conotoxin peptides, the corresponding propeptides and the nucleic acids encoding the propeptides are unrelated, each to the other. Each peptide or nucleic acid is unrelated and does not share a special technical feature with the other. Additionally, the claimed methods produce different results which are not coextensive and which do not share the same technical feature. Since the special technical feature of Group 1 is not present in the claims of Groups 2-384, and the special technical features of Groups 2-384 are not present in the claims of Group 1. Thus, unity of invention is lacking.

Continuation of B. FIELDS SEARCHED Item 3:

EAST search on USPAT, DERWENT, EPO JPO, USGPUB; STN search on MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA. Search terms: conotoxin, conopeptide, conantokin, gamma-carboxyglutamate, neurological disorder, psychiatric disorder, seizure, epilepsy. Amino acid sequence search on SEQ ID NO:133.