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(54) Title: NEUROPROTECTIVE BICYCLIC COMPOUNDS AND METHODS FOR THEIR USE IN TREATING AUTISM SPECTRUM DISORDERS AND NEURODEVELOPMENTAL DISORDERS

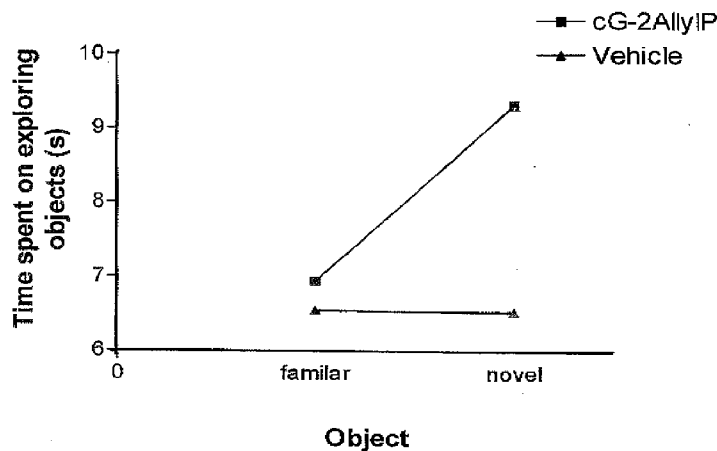


Figure 2

(57) Abstract: Embodiments of this invention provide compositions and methods for therapeutic use of diketopiperazines including cyclic G-2-Allyl Proline and other cyclic Glycyl Proline compounds to treat symptoms of Autism Spectrum Disorders and Neurodevelopmental Disorders as well as manufacture of medicaments including tablets, capsules, liquid formulations, gels, injectable solutions, and other formulations that are useful for treatment of such conditions.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/047801

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/499 (2015.01)

CPC - A61K 31/498 (2015.01)

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(8) - A61K 9/12, 31/50, 31/495, 31/498, 31/499, 31/4985, 38/00; A61P 25/28; C07D 241/36, 471/00, 487/00 (2015.01)

CPC - A61K 9/0019, 9/0085, 9/06, 9/107, 9/127, 31/401, 31/498, 31/4985, 38/06, 45/06 (2015.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

CPC - A61K 9/0019, 9/0085, 9/06, 9/107, 9/127, 31/401, 31/498, 31/4985, 38/06, 45/06 (2015.01) (keyword delimited)

USPC - 424/45; 514/1.1, 8.4, 9, 249; 544/349

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, Google Patents, PubMed, SureChEMBL

Search terms used: cG "2" AllylP (cyclic Glycyl "2" Allyl proline) OR (cyclic G 2AllylP) autism* OR spectrum OR asperger OR angelman OR Disintegrative OR (Pathological Demand Avoidance)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/0201614 A1 (BICKERDIKE) 18 August 2011 (18.08.2011) entire document	1-3, 6-8, 11, 12, 20, 22, 34
Y		4, 5, 9, 10
Y	WO 2012/102832 A1 (NEUREN PHARMACEUTICALS LIMITED) 02 August 2012 (02.08.2012) entire document	4, 5, 10
Y	US 2011/0217288 A1 (SHEN et al) 08 September 2011 (08.09.2011) entire document	9
A	US 2010/0247483 A1 (TRAN) 30 September 2010 (30.09.2010) entire document	1-12, 20, 22, 34
A	GUDASHEVA et al. "Identification of a novel endogenous memory facilitating cyclic dipeptide cyclo-prolylglycine in rat brain," FEBS Letters, 05 August 1996 (05.08.1996), Vol. 391, Iss. 1-2, Pgs. 149-152. entire document	1-12, 20, 22, 34

☐ Further documents are listed in the continuation of Box C.

* 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 application or patent 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

18 February 2015

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/047801

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.:
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:

See Extra Sheet(s).

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.:
1-12, 20, 22, and 34 to the extent that they read on cyclic glycyl-2-allyl proline (cG-2-allylP).

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/US2014/047801

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-12, 22-24, and 34-37 and in part claims 19-21 and 25-33 are drawn to a method for treating a symptom of an Autism Spectrum Disorder (ASD) or Neurodevelopmental Disorder (NDD) in an animal suffering from such a disorder, comprising administering to the animal, a pharmaceutically effective amount of cyclic glycyl-2-allyl proline (cG-2-allylP), or cyclic cyclohexyl-G-2MeP, or cyclic cyclopentyl-G-2MeP.

Group II: claim 13 and in part claims 19-21 and 25-33 are drawn to a method for treating a symptom of an Autism Spectrum Disorder (ASD) or Neurodevelopmental Disorder (NDD) in an animal suffering from such a disorder, comprising administering to the animal, a compound has the formula shown in claim 13.

Group III: claim 14 and in part claims 19-21 and 25-33 are drawn to a method for treating a symptom of an Autism Spectrum Disorder (ASD) or Neurodevelopmental Disorder (NDD) in an animal suffering from such a disorder, comprising administering to the animal, a compound has the formula shown in claim 14.

Group IV: claim 15 and in part claims 19-21 and 25-33 are drawn to a method for treating a symptom of an Autism Spectrum Disorder (ASD) or Neurodevelopmental Disorder (NDD) in an animal suffering from such a disorder, comprising administering to the animal, a compound has the formula shown in claim 15.

Group V: claim 16 and in part claims 25-33 are drawn to a method for treating a symptom of an Autism Spectrum Disorder (ASD) or Neurodevelopmental Disorder (NDD) in an animal suffering from such a disorder, comprising administering to the animal, a compound has the formula shown in claim 16.

Group VI: claims 17 and in part claims 19, 20, and 25-33 are drawn to a method for treating a symptom of an Autism Spectrum Disorder (ASD) or Neurodevelopmental Disorder (NDD) in an animal suffering from such a disorder, comprising administering to the animal, a compound has the formula shown in claim 17.

Group VII: claim 18 and in part claims 25-33 are drawn to a method for treating a symptom of an Autism Spectrum Disorder (ASD) or Neurodevelopmental Disorder (NDD) in an animal suffering from such a disorder, comprising administering to the animal, a compound has the formula shown in claim 18.

The first invention of Group I+ is restricted to a method for treating a symptom of an Autism Spectrum Disorder (ASD) or Neurodevelopmental Disorder (NDD) in an animal suffering from such a disorder, comprising administering to the animal, a pharmaceutically effective amount of a compound, wherein the compound is selected to be cyclic glycyl-2-allyl proline (cG-2-allylP). It is believed that claims 1-12, 20, 22, and 34 read on this first named invention and thus these claims will be searched without fee to the extent that they read on cG-2-allylP.

Applicant is invited to elect additional compounds with specified chemical structure for each method to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be a method for treating a symptom of an Autism Spectrum Disorder (ASD) or Neurodevelopmental Disorder (NDD) in an animal suffering from such a disorder, comprising administering to the animal, a pharmaceutically effective amount of a compound, wherein the compound is selected to be cyclic cyclohexyl-G-2MeP. Additional compounds will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ and II-VII do not relate to a single general 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 I+, a compound of cyclic glycyl-2-allyl proline (cG-2-AllylP), or cyclic cyclohexyl-G-2MeP, or cyclic cyclopentyl-G-2MeP, are not present in Groups II-VII; the special technical features of Group II, a compound having the formula shown in claim 13, are not present in Groups I+ and II-VII; the special technical features of Group III, a compound having the formula shown in claim 14, are not present in Groups I+, II, and IV-VII; the special technical features of Group IV, a compound having the formula shown in claim 15, are not present in Groups I+, II, III and V-VII; the special technical features of Group V, a compound having the formula shown in claim 16, are not present in Groups I+, II-IV, VI, and VII; the special technical features of Group VI, a compound having the formula shown in claim 17, are not present in Groups I+, II-V, and VII; the special technical features of Group VII, a compound having the formula shown in claim 18, are not present in Groups I+ and II-VI;

The Groups I+ formulas do not share a significant structural element for treating a symptom of an Autism Spectrum Disorder (ASD) or Neurodevelopmental Disorder (NDD), requiring the selection of alternatives for the compound or a pharmaceutically acceptable salt or hydrate thereof, where "pharmaceutically effective amount of cyclic Glycyl-2-Allyl Proline (cG-2-AllylP), or cyclic cyclohexyl-G-2MeP, or cyclic cyclopentyl-G-2MeP to said mammal".

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/047801

The Groups I+ share the technical features of a method for treating a symptom of an Autism Spectrum Disorder (ASD) or Neurodevelopmental Disorder (NDD) in an animal suffering from such a disorder, comprising administering to the animal, a pharmaceutically effective amount of cyclic glycyl-2-Allyl proline (cG-2-AllylP), or cyclic cyclohexyl-G-2MeP, or cyclic cyclopentyl-G-2MeP to said mammal and where said symptom is a deficit in executive function, or anxiety, or abnormal fear conditioning, or abnormal social behavior, or repetitive behavior. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2011/0201614 A1 to Bickerdike discloses a method for treating a symptom of an Autism Spectrum Disorder (ASD) or Neurodevelopmental Disorder (NDD) in an animal suffering from such a disorder, comprising administering to the animal, a pharmaceutically effective amount of cyclic glycyl-2-Allyl proline (cG-2-AllylP), or cyclic cyclohexyl-G-2MeP, or cyclic cyclopentyl-G-2MeP to said mammal and where said symptom is a deficit in executive function, or anxiety, or abnormal fear conditioning, or abnormal social behavior, or repetitive behavior (this invention provides methods of treating an animal having a cognitive impairment, comprising administration to that animal an effective amount of a composition comprising cyclic G-2-AllylP, Para. [0017]; cyclic G-2AllylP in modes of cognitive deficit and affective state anxiety, Para. [0123]).

Additionally, Groups I+ and II-VII share the technical features of a method for treating a symptom of an Autism Spectrum Disorder (ASD) or Neurodevelopmental Disorder (NDD) in an animal suffering from such a disorder, comprising administering to the animal, a compound or a pharmaceutically acceptable salt or hydrate thereof. However, these shared technical features do not represent a contribution over the prior art. Specifically, US 2011/0201614 A1 to Bickerdike discloses a method for treating a symptom of an Autism Spectrum Disorder (ASD) or Neurodevelopmental Disorder (NDD) in an animal suffering from such a disorder, comprising administering to the animal, a compound or a pharmaceutically acceptable salt or hydrate thereof (this invention provides methods of treating an animal having a cognitive impairment, comprising administration to that animal an effective amount of a composition comprising cyclic G-2-AllylP, Para. [0017]; cyclic G-2AllylP in modes of cognitive deficit and affective state anxiety, Para. [0123]).

Further, Groups I+ and II-VII share the technical features of a compound having the basic structure of octahydropyrrolo[1,2-a]piperazine-1,4-dione and/or octahydropyrrolo[1,2-a]piperazin-1-one. However, these shared technical features do not represent a contribution over the prior art. Specifically, US 2011/0201614 A1 to Bickerdike discloses a compound having the basic structure of octahydropyrrolo[1,2-a]piperazine-1,4-dione and/or octahydropyrrolo[1,2-a]piperazin-1-one (certain embodiments of this invention include novel derivatives of cPG having structures as described below (Formula 1), Para. [0052]; where X1 is NR' and R' is H.).

The inventions listed in Groups I+ and II-VII therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.